Criteria to judge Preorganisation in the Study of Known and the Design of New Thiocrown Ethers†

George A. Forsyth and Joyce C. Lockhart
Department of Chemistry, Bedson Building, The University of Newcastle upon Tyne, Newcastle upon Tyne, NE1 7RU, UK

The structural preorganisation hypothesis has been considered in the light of current criteria and additional criteria have been proposed which enable *a priori* design of organised macrocycles. Molecular dynamics simulations have been performed on a series of 1,4,8,11-tetrathiacyclotetradecane molecules, with no, one and two sets of *gem*-dimethyl substituents on the central carbons of their trimethylene bridges; these molecules are known to have stronger complexation with copper or nickel as substitution increases. With the insights thus gained into the effect of the substitution, these studies are used to set new criteria which are then employed in the *a priori* design of novel conformationally locked 1,4,7-trithiacyclononane ligands, with a set of endodentate sulfurs, capable of co-ordinating to a metal ion simultaneously, without reorganisation.

The insight of Cram and co-workers[1,2] into the complexation of spherands with lithium ions led to the statement of the concept of preorganisation: 'the more highly hosts and guests are organised for binding and low solvation *prior* to their complexation, the more stable will be their complexes'.[1] Implicit are the assumptions that contributions neither from the thermodynamic energy nor the activation energy of reorganisation would be required for the complexation process, where crystal structures equate. Thus a preorganised ligand should have competitive advantage over a less organised one in certain thermodynamic and kinetic events. The original concept is often used as a rationalisation of known structures and is not helpful for design purposes, since it implies that the structure of the (relevant) metal–ligand complex must be known beforehand, hence alternative and readily applicable criteria are needed. Also relevant is the donor quality of the donor atom. The use of lanthanide shift reagents (bulky Lewis acids, likely to co-ordinate one or two potential donor atoms of a macrocycle) has been advocated[3] to determine relevant thermodynamic donor capacities of individual donors. This has established for example that the basicity of oxygen in $ROCH_2$ (R = aryl) is less than that of CH_2OCH_2 in the same crown. As for kinetics, is it likely that the crystal structure conformer can survive long enough in solution for reaction with a metal ion *i.e.* is the life-time of the preorganised conformation in solution longer than the pre-collision life-time for a metal ion and ligand (probably around 10^{-7}–10^{-9} s for typical metal ions)? This paper seeks to consider these matters to inform debate about preorganisation and to set supplementary criteria which do not require the initial structural information necessitated by the Cram hypothesis.

Central to our examination of preorganisation is the technique of molecular dynamics (MD) which conveniently simulates torsional movement on the picosecond to nanosecond timescale and so can be used to interrogate aspects of the potential-energy surface of small macrocycles. In earlier work, we looked at ways to lock propeller crowns, but the lock developed extended only over a portion of the molecular framework, and the ether segments remained fully mobile at the temperatures studied, which necessitated that we add a simulation technique.[4] We have explored a range of thioethers using simulation procedures[5,6] and have found that the ligand 1,4,7-trithiacyclononane (L^1), which would be preorganised according to Cram's criterion, is actually mobile, with the SCCS torsion inverting roughly every 60 ps (at 450 K). Literature searches revealed experimental information on complexation of a series of 1,4,8,11-tetrathiacyclotetradecane (L^2) macrocycles[7–10] [see equation (1)]. It was suggested that the enthalpic

$$M^{n+1} + L \rightleftharpoons [ML]^{n+1} \quad (1)$$

benefit seen when L is changed from L^2 to 6,6-dimethyl-1,4,8,11-tetrathiacyclotetradecane (L^3) and 6,6,13,13-tetramethyl-1,4,8,11-tetrathiacyclotetradecane (L^4) stems from the changed conformational preference induced by each dimethyl addition.[9] These molecules provided a key set of structures and data for molecular dynamics and simulations in an attempt to quantify the effect each addition had on the macrocycle backbone. These new computational experiments combined with the experimental information taken from refs. 8–11 provided supplementary criteria for future *a priori* designs of thiamacrocycles. We have also made an *a priori* design for a rigid derivative of L^1, which should prove a considerable challenge to the thiocrown ether community. The future synthetic implementation of this design will provide a further test of the criteria proposed in this paper. Elsewhere, we have considered other means of locking macrocycles, by ring fusion.[11] It has been shown that in thiocrown ethers built from SCH_2CH_2S segments the sulfurs on each unit generally occupy the *anti* conformation.[9,12] Most thiocrowns require rearrangement to their eventual complexed form. It would be advantageous to have a method of forcing the sulfur on an SCCS segment into a *gauche* relation, as has happened with L^1. Attempts to force a ECCCE (trimethylene) residue to have *endo* donors (E) have been made in addition to the substitutions on L^2 by Gellman and co-workers,[7–10] *e.g.* by Setzer *et al.*[13] using –SCC(O)CS– and Dale *et al.*,[14] using $-OCCMe_2CO-$ as structural elements of a macrocycle; Yamamoto and co-workers[15] suggest that Bu^t groups act as conformational locks on a –C(OR)CC(OR)– segment.

† *Supplementary data available* (No. SUP 57018, 15 pp.): Movement of SCCS torsions and plots of metal–sulfur distances *versus* steric energy. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1994, Issue 1, pp. xxiii–xxviii.

Non-SI unit employed: cal ≈ 4.184 J.

Method

The coordinates of the structure of L^2 [16] were taken from the Cambridge Crystallographic Database,[17] those for L^3 and L^4 were not available from this source, and the crystal structure conformations were constructed from the geometric parameters supplied in the publication of their crystal structures,[9] using the molecular editor of QUANTA.[18] The conformation behaviour of L^2–L^4 was studied by MD simulations at 470 K, a temperature we feel increases the rate of torsional movement (if any), thus reducing the required length of simulation to observe this motion, without supplying enough energy to induce unlikely torsional movements. The length of simulation used was 610 ps.

The crystal structure of L^1 [19] indicates two enantiomers, which may be defined by the sign of their SCCS torsion angles. The two carbons on each SCCS segment are thus different. The enantiomer with a minus torsion was used as the building block for ligands L^5 and L^6, which were then created by substituting methyls at the relevant positions using the molecular editor of QUANTA.[18] One methyl was added to each SCH_2CH_2S segment stereospecifically to give (2*R*,5*R*,8*R*)-2,5,8-trimethyl-1,4,7-trithiacyclononane (L^5) and (3*R*,6*R*,9*R*)-3,6,9-trimethyl-1,4,7-trithiacyclononane (L^6). Since (2*S*,5*S*,8*S*)-2,5,8- and (3*S*,6*S*,9*S*)-3,6,9-trimethyl-1,4,7-trithiacyclononane (L^7 and L^8) are mirror images of L^6 and L^5, respectively, neither of these compounds was investigated.

The conformational space of the proposed trimethyl-substituted ligands L^5 and L^6 was explored using a prolonged high temperature (2000 K) molecular dynamics simulation. The conformational behaviour of each conformation of interest was investigated by heating to 450 K and simulating for 500 ps. The macrocycle cavity size of each new species was investigated using the method devised by Drew *et al.*[20]

Computational Details.—All calculations and visual analyses were carried out on a Silicon Graphics IRIS 4D20 workstation; computational calculations were done using version 21.3 of CHARMm.[21] Charges were assigned as described previously.[5] Conformations used to initiate dynamics simulations were initially minimised by the adopted-basis Newton–Raphson (ABNR) minimiser until convergence was reached (when the first derivative of the energy was 0.1 kcal mol^{-1}). Non-bonded parameters were assigned as described before.[5]

The species L^2–L^4, each given a 470 K simulation, were initially heated for 9.4 ps, equilibrated for a further 10 ps, and then given a 610 ps simulation, saving conformations every 1 ps.

To calculate the available conformations of the new ligands L^5 and L^6 they were heated for 20 ps, to 2000 K, equilibrated for 50 ps, then given a 1000 ps simulation. Snapshot conformations were isolated from the trajectory every 1 ps, minimised using 50 steps of the steepest descents minimiser, then by the ABNR minimiser until the convergence criteria were reached. Conformations investigated by lower temperature (450 K) simulations were heated for 4.5 ps to attain the desired temperature, equilibrated for 3 ps then simulated for 500 ps. The CHARMm parameters used for the MD simulations are listed in Table 1.

In calculating the macrocycle cavity size, a metal–sulfur bond-stretching force constant of the order of ten times the expected value is used; in these calculations, this was 2500 kcal mol^{-1} $Å^{-2}$. Thus, it becomes the predominant term in energy calculations. Upon minimising, the macrocycle must readjust to meet the input ideal bond length. The minimised steric energy is an indication of the strain induced in the macrocycle by fitting with the enforced bond length. Thus, by varying the bond length and minimising each time, it is possible to deduce which M–S distance causes least strain in the macrocycle. In these minimisations, the bond length was increased from 1.8 to 2.5 Å in steps of 0.1 Å, and in the region of least strain (2.0–2.3 Å), minimisations were performed at 0.05 Å intervals. Calculations were performed for L^2–L^4 in a square-planar environment. For

Table 1 The CHARMm parameters for molecular dynamics simulations

	T/K		
	2000	450	470
CHARMm term (heating)			
IHTFRQ	50	100	200
TEMINC	5	10	10
NSTEP	20 000	4500	9400
FIRSTT	0.0	0.0	0.0
FINALT	2000.0	450.0	470.0
(equilibration)			
IEQFRQ	20	100	20
NSTEP	50 000	3000	10 000
(simulation)			
NSTEP	1 000 000	500 000	610 000

L^1, L^5 and L^6, an octahedral co-ordinating environment was assumed, in the following pairwise combinations of ligands: 2 × L^5; 2 × L^6; L^5 + L^6, L^5 + L^7, L^5 + L^8 and L^6 + L^7. Other possible combinations are mirror images of examples in the above list.

Results and Discussion

Investigation of L^2–L^4.—Gellman and co-workers [7–10] and Cooper and co-workers [12] state that *gem*-dimethyl substitution on the middle carbon of the SCCCS unit alters the conformational preference of the CSCC torsion from *gauche* in $CSCC(H_2)$ to *anti* in $CSCC(Me_2)$. This forces the sulfurs from *exo* in L^2 to *endo* in L^4. Further, this substitution is also said to favour 'conformations in which the sulfur atoms are pre-organised for metal ion chelation'.[9] Considering ligand L^4, in which the CSCC torsions are *anti*, and the sulfurs *endo*, the macrocycle must still undergo conformational rearrangement to chelate Ni^{II}, the ligand adopting a so-called *anti* conformation, or to chelate Cu^{II}, to form both the *syn* and *anti* complexes. Thus, in the Cram sense, this ligand is not preorganised for chelation, although the amount of conformational change necessary for L^4 to chelate is less than that for L^3, which in turn must undergo fewer changes to chelate than L^2. Our MD investigations of L^2–L^4 were undertaken to reveal the effect of *gem*-dimethyl substitution on the overall rigidity of these ligands; although the effect on conformational *preference* has already been studied [7–10,12] no information on the frequency of torsional movements of the $CSCC(Me_2)$ units of L^3 and L^4 was known. This information could be a guide to the extent of preorganisation of these ligands.

The simulation of L^2 revealed a large number of conformations available to this ligand. The SCCS torsions were in constant motion between *gauche* minus and *gauche* plus conformers, with brief periods in the *anti* state. In the crystal structure of L^4 the SCCS torsions are *gauche*, but the MD simulations of L^3 and L^4 show no inhibition of the fluctuation between *gauche* and *anti* caused by *gem*-dimethyl substitution on the middle carbon of the SCCCS segment. The average temperatures for each of these simulations were: 455 K (L^2), 451 K (L^3) and 473 K (L^4). No significantly prolonged deviation from the average temperatures of each simulation occurred. Sachleben and Burns [22] investigated the interatomic ethylene and propane 'bite' donor-atom ··· donor-atom distances in free and (lithium-) complexed dibenzo-14-crown-4 (6*H*,15*H*,7,8,16,17-tetrahydrodibenzo[*b*,*i*][1,4,8,11]tetraoxacyclotetradecine) species, showing that these O ··· O separations were almost identical in the free and complexed forms. This could be construed as a test of the preorganisation of a ligand. We monitored the change in the S ··· S distances of each ethylene bite for L^2–L^4, shown in Figs. 1 and 2. It can be seen that these distances switch between 3 and 4.4 Å, which

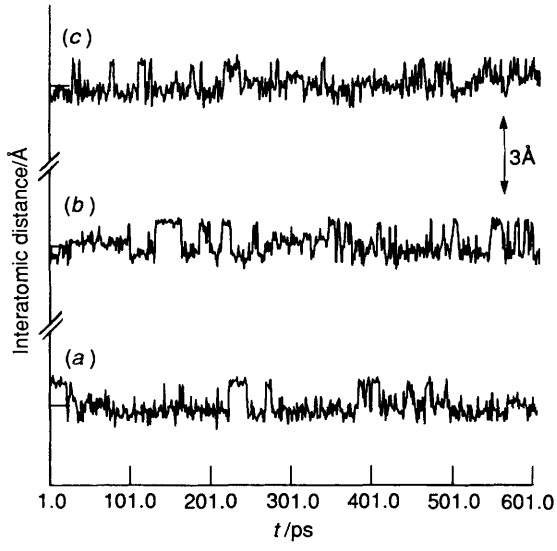

Fig. 1 Time evolution of the S(1) · · · S(4) ethylene bite distance during MD simulation of L^2 (*a*), L^3 (*b*) and L^4 (*c*), each centred on 3.5 Å

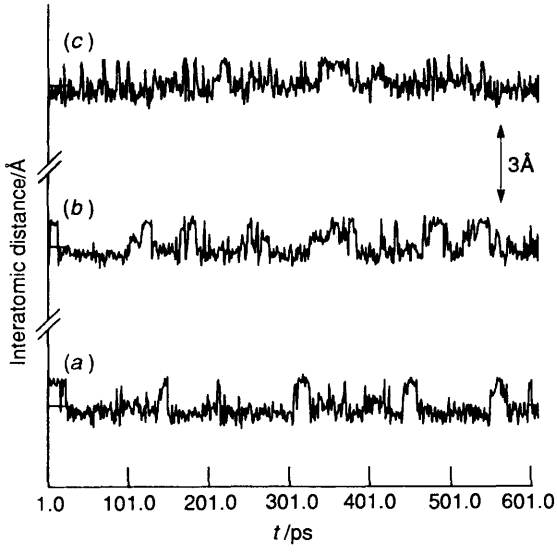

Fig. 2 Time evolution of the S(8) · · · S(11) ethylene bite distance during MD simulation of L^2 (*a*), L^3 (*b*) and L^4 (*c*), each centred on 3.5 Å

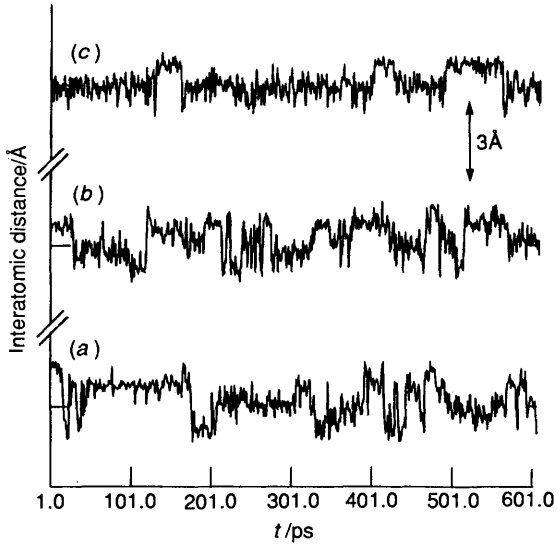

Fig. 3 Time evolution of the non-bonded S(1) · · · S(11) propane bite distance during MD simulation of L^2 (*a*), L^3 (*b*) and L^4 (*c*), each centred on 4 Å

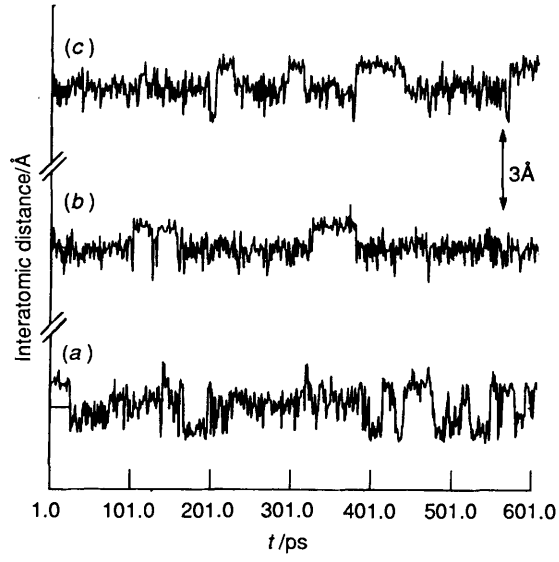

Fig. 4 Time evolution of the non-bonded S(4) · · · S(8) propane bite distance during MD simulation of L^2 (*a*), L^3 (*b*) and L^4 (*c*), each centred on 4 Å

corresponds to a *gauche* to *anti* flip. The effect of methyl substitution in L^3 and L^4 can thus be seen to have had no significant effect on this movement. Similar torsional behaviour was seen for each SCCC and CCCS torsion in L^2. In the crystal structures of L^3 and L^4, the $SCC(Me_2)C$ and $CC(Me_2)CS$ torsions are *gauche*, whereas in the crystal structure of L^2, the $SCC(H_2)C$ and $CC(H_2)CS$ torsions are *anti*, and one $SCC(H_2)C$ torsion of L^3 is *anti*. However, our MD simulations show that in each of L^2–L^4, the SCCC/CCCS torsions obviously prefer *gauche*, although the dimethyl groups radically slow down the transitions that occur, but fail to stop them completely. The effect of the *gem*-dimethyl substitution can be seen in the propane bite S · · · S distances, Figs. 3 and 4. This reveals, in L^3, the difference in movements of the SCCC (and CCCS) torsions of the dimethyl-substituted and un-substituted SCCCS segments; the S · · · S distance can be seen to have a greater movement in the SCCCS segment [Fig. 3(*b*)], as opposed to the $SCC(Me)_2CS$ segment [Fig. 4(*b*)]. When the CSCC/CCSC torsions of L^2–L^4 are studied, the traces show that L^2 prefers an *anti* conformation. Although flipping does occur to *gauche* conformations, the frequency and magnitude of motion are much reduced by the dimethyl groups in L^3 and L^4. This contradicts the conformational evidence in the relevant crystal structures. Substitution is said to alter the preference from *gauche* in a $CSCC(H_2)$ torsion to *anti* in $CSCC(Me_2)$. Thus, in macrocyclic poly(thioethers), it appears that there is very little energy barrier to $CSCC(H_2)$ adopting an *anti* conformation. Even more instructive is to monitor the cross-ring S · · · S interatomic distance (Figs. 5 and 6). This shows the negligible effect substitution has had on immobilising the sulfurs: in each ligand, these S · · · S distances fluctuate between *ca.* 2.5 and 7.5 Å. This means that, in relation to the macrocyclic ring, the sulfur atoms are periodically adopting *exo* positions as well as the *endo* conformation required for co-ordinating a single metal ion.

Considering the CSCCCSC segment in the three ligands investigated here, the simulations show that *gem*-dimethyl substitution greatly slows down any torsional movement in that segment.

These MD simulations have shown that, although *gem*-dimethyl substitution has an effect on the conformational preference of the ligand, and a noticeable effect on the torsional movements of $SCC(Me_2)C$, it has very little effect on the mobility of the sulfur atoms. This is probably because the

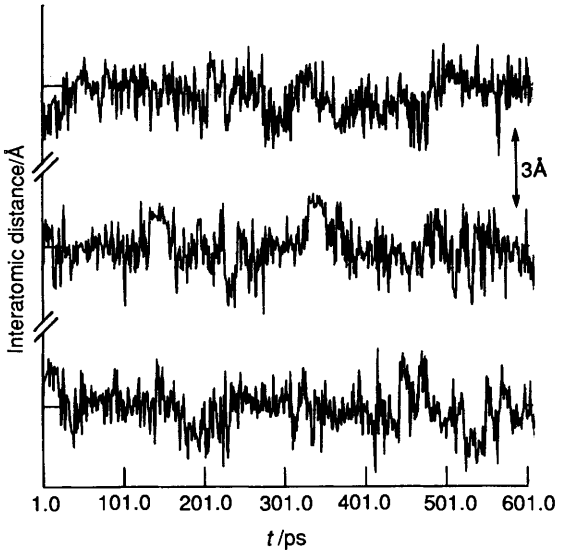

Fig. 5 Time evolution of the non-bonded S(1)···S(8) cross-ring distance during MD simulation of L^2 (*a*), L^3 (*b*) and L^4 (*c*), each centred on 5.5 Å

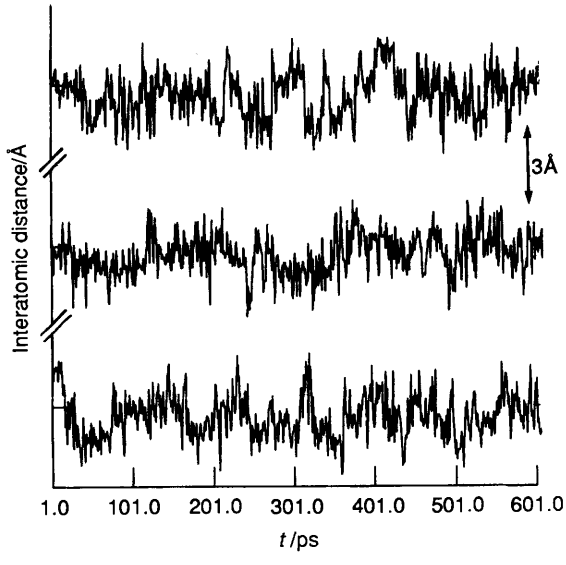

Fig. 6 Time evolution of the non-bonded S(4)···S(11) cross-ring distance during MD simulation of L^2 (*a*), L^3 (*b*) and L^4 (*c*), each centred on 5.5 Å

substituted methyl groups are too distant from the SCCS units to have any marked effect. Using the behaviour of L^2 as a guide we note that (*i*) each Me_2 substitution decreased the ΔH of complexation,[10] (*ii*) each Me_2 substitution altered the structure of the ligand observed in the crystal towards a more favourable co-ordinating conformation,[7–10] and (*iii*) although simulations showed that the structures were still fluxional on the picosecond timescale, each Me_2 substitution produced slower movements in the relevant substitution sections of L^3 and L^4.

There is a sufficient level of preorganisation in a substituted SCCCS unit to manifest itself in thermodynamic terms, even though torsional fluctuations can still be observed on a picosecond to nanosecond scale, albeit slower than in the unsubstituted SCCCS unit. Thus, it is not necessary for the observation of a thermodynamic effect, in this instance, that torsional movement should cease, as might be required for full preorganisation. We propose as provisional new criteria, which can be established by calculation before synthesis, that ligands can be considered preorganised if (*i*) torsional movements are slowed at least partly on a picosecond timescale, and (*ii*) where

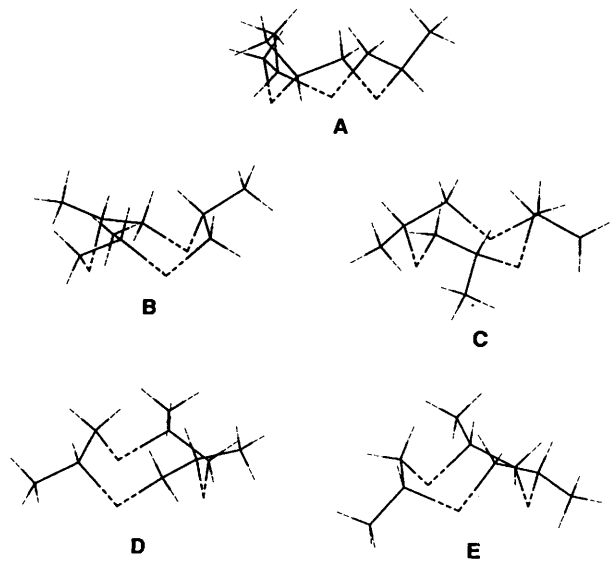

Fig. 7 The lowest energy conformers of ligand L^5 (**A**) and the four lowest energy conformations of L^6 (**B–E**)

relevant* cross-ring separations (other than bite distances) between donor atoms remain within certain bounds, these bounds defining the required separation in the metal complex. These criteria are open to test and subsequent modification in light of results.

For the design of a new and preorganised thiocrown based on these criteria, we turned our attention to a thiocrown with ethylene linked sulfur atoms, specifically 1,4,7-trithiacyclononane.

Conformational Searching for New Ligands L^5 *and* L^6.—1,4,7-Trithiacyclononane (L^1) has been shown by crystallography,[19] electron diffraction[23] and by NMR solution spectroscopy[5] to have all three sulfurs endodentate, and thus to be capable of facial co-ordination to appropriate metal ions. In the most recent update of the Cambridge Crystallographic Database,[17] crystal structures of 64 complexes of this ligand are recorded in 55 of which the nonane acts as a tridentate ligand, uniquely able of showing facial co-ordination to metal ions. Yet the ligand is under strain by reason of the unfavourable SCCS torsions. The special qualities of all-oxygen crown ethers stem in part from their more favourable preferred *gauche* OCCO conformations. Cram *et al.*[1,2] have suggested that ligands which are preorganised for complexation can be produced, where the ligand in its free form is in the same conformation as it adopts with the appropriate substrate. For this eventuality it can be expected that the complex will be thermodynamically favoured: this is likely to be at a kinetic cost. We wanted to design a derivative of L^1 that would lock the sulfurs in this endodentate conformation, and thus investigated the effect of methyl substitution on L^1, after noting the effect of methyl substitution on L^2 described above.

The high-temperature simulations of each species accessed many regions of conformational space. Each SCCS torsion was observed to fluctuate wildly, and assume a range of values (*anti*, *gauche* minus, eclipsed, *gauche* plus) although the *gauche* conformations occur most frequently. Thus, it seems possible to assume that every available conformation of each species was accessed by the simulations. After minimisation, it was apparent that from each simulation both isomers were being generated; the temperature of the simulations was high enough to cause a ring inversion. In the lowest energy conformations of these trimethyl-substituted thiocrowns, **A** (L^5, Fig. 7) and **B** (L^6,

* Not applicable to tridentate macrocycles.

Table 2 Geometrical features of low energy conformers of L^5 and L^6

Isomer conformation	Energy/ kcal mol^{-1}	Torsion angle/°			Distance/Å		
		S(1)C(2)C(3)S(4)	S(4)C(5)C(6)S(7)	S(7)C(8)C(9)S(9)	S(1)···S(4)	S(4)···S(7)	S(7)···S(1)
L^5, **A**	−0.153	−49	−49	−49	3.213	3.213	3.213
L^6, **B**	−0.124	−47	−47	−47	3.178	3.178	3.178
L^6, **C**	0.814	49	49	49	3.206	3.206	3.206
L^6, **D**	2.399	−37	−40	48	3.159	3.212	3.067
L^6, **E**	2.736	39	42	−46	3.184	3.186	3.082

Fig. 7), the sulfurs are all equivalent by symmetry and in an endodentate conformation, and the methyl groups are directed away from the ring. Some geometrical features of the lower energy conformations of L^5 and L^6 are shown in Table 2. Each SCCS torsion in the lowest energy conformation of L^5 (−0.153 kcal mol^{-1}) is −49, and −47° in L^6 (−0.124 kcal mol^{-1}). The parent macrocycle L^1 is chiral, and fluctuates[5] between *gauche* plus and *gauche* minus conformations; in the *gauche* minus conformation the SCCS torsions, which are all equivalent by symmetry, are −48°.[19] The interatomic S···S distances are 3.213 in L^5, and 3.178 Å in L^6, slightly greater than seen in L^1 (3.120 Å). There are three other all-*endo* conformations of the ligand L^6 (**C**, **D** and **E**, Fig. 7), which have energies of 0.814, 2.399 and 2.736 kcal mol^{-1}. In **C**, the SCCS torsions are all *gauche* plus, at 49°, and the S···S distances are 3.206 Å. The methyl groups are pointing down and towards the sulfur atoms, forming a shield of hydrogen atoms that seem to be protecting the sulfurs from potentially co-ordinating to a metal ion. The next conformation, **D**, has two *gauche* minus SCCS torsions (−37 and −40°) and one *gauche* plus (48°). The interatomic S···S distances vary from 3.067 to 3.212 Å. In the last *endo* conformation, **E**, two SCCS torsions are *gauche* plus (39° and 42°) and the other *gauche* minus, −46°. The S···S distances range from 3.082 to 3.186 Å.

Molecular dynamics simulations of conformers **A** *and* **B**. The MD simulations employed to calculate the accessible conformations of L^5 and L^6 established that in the lowest energy conformation of each the sulfurs are all endodentate, which was the desired result. It is apparent from the trace of each SCCS torsion (available as supplementary data, No. SUP 57018) for **A** that it is effectively locked in an *endo* conformation. An initial simulation of 500 ps on this *gauche* minus conformer of L^5 showed very little movement. The SCCS torsions are all *gauche* minus, and each angle only deviates slightly from −49° (between −80 and −20°). We decided to extend this simulation greatly, to 10 nanoseconds, still saving conformations every 1 ps. This extensive simulation (with little significant deviation from the average temperature 469 K) did not result in any significant change in the ligand: very occasionally one SCCS torsion would adopt a value that deviated by more than 35° from the value seen in the lowest energy conformation, but over the whole simulation, this was seen only 14 times, and only one torsion at a time showed such a deviation, so that overall, the ligand L^5 could be said to have an *endo* conformation.

Thus the methyl groups have raised the torsional barrier in each SCCS segment and prevented the switch to *gauche* plus, which was seen in the MD simulations of L^1,[5] and the sulfurs of this isomer of the macrocycle could be said to be preorganised in an *endo* conformation. Another guide to this preorganisation was seen in the difference in energies of the two lowest energy conformations of L^5. The global minimum is −0.153 kcal mol^{-1} and the next minimum occurs at 3.047 kcal mol^{-1}. This latter conformation does not have the SCCS torsions *gauche* plus, which occurs in the second-lowest energy conformation of L^6 (conformer **C**), but instead has one sulfur *exo* to the ring, and the two other sulfurs *endo*.

In the MD simulation at 450 K (average temperature of simulation 441 K, with no significant deviation) of the lowest

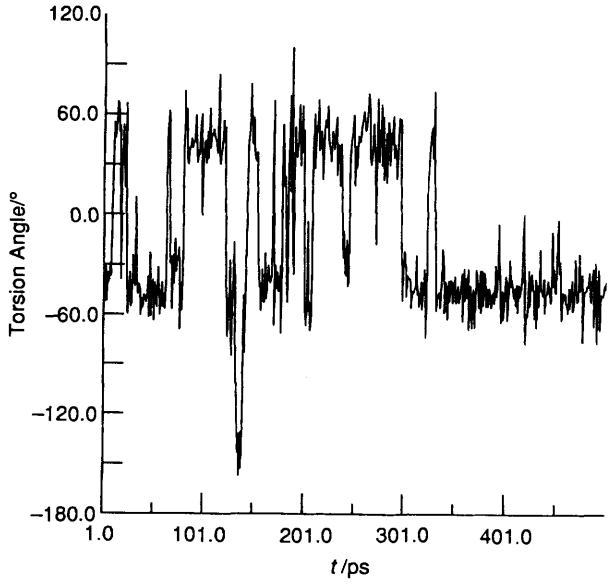

Fig. 8 Movement of the S(1)C(2)C(3)S(4) torsion for conformer **B** of L^6 at 450 K over 500 ps

energy conformer, **B**, of L^6, several conformational changes are found. Each SCCS torsion switches from *gauche* minus to *gauche* plus and back, except for S(1)C(2)C(3)S(4) briefly flipping from *gauche* minus to *anti*, and thus the sulfur atom S(4) becomes *exo*, from 120 ps to 135 ps. One SCCS trace is shown in Fig. 8 (other traces may be consulted in the supplementary data). After 300 ps each SCCS seems to settle to a *gauche* minus conformation, except for the S(4)C(5)C(6)S(7) torsion, which briefly adopts a *gauche* plus state after 300 ps. Thus, in these simulations the sulfurs are predominantly in all-*endo* conformations, potentially suitable for tridentate co-ordination to a single metal ion. Inspection of the *gauche* plus and *gauche* minus conformers of L^6 (**B** and **C**, Fig. 7) shows that there are no major steric hindrances to this switch. It also shows why a similar change was not observed for L^5: if the appropriate hydrogen atoms on **C** are replaced by methyl groups, and the existing methyls replaced by hydrogens, the *gauche* plus isomer of L^6 has been created. The geometric requirements of the chiral carbons are such that the methyl groups in this new structure are in very close proximity to each other. This was confirmed by constructing this conformer of L^5 in exactly the way described above using the molecular editor of QUANTA. Clearly it is not possible for such a conformer to exist in a minimised state, and indeed, upon minimisation the methyl groups were forced apart: in the resulting conformation, the SCCS torsions were all approximately 10°, *i.e.* nearly eclipsed. The energy of this conformer was 17.220 kcal mol^{-1} which is 17.373 kcal mol^{-1} above the ground state, and so rarely an observable component in the thermodynamic ensemble.

Macrocycle hole size. For the series of ligands L^2–L^4 and the new ligands based on L^1 the optimum metal–sulfur bond lengths were calculated, as described in the Method section. The calculations on L^2–L^4 used the minimised co-ordinating

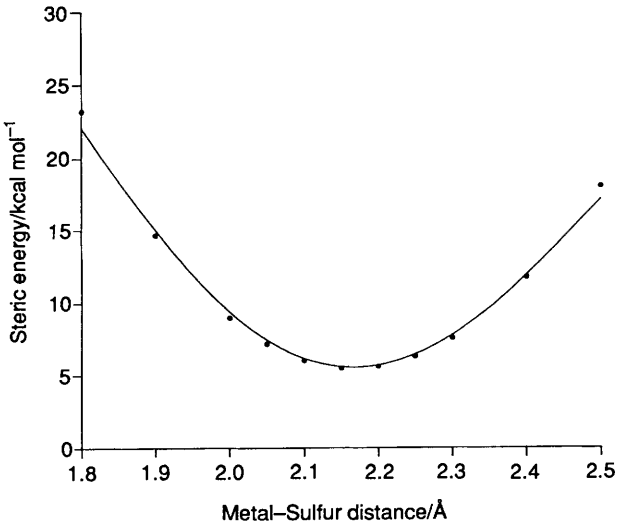

Fig. 9 Plot of metal–sulfur distance *versus* steric energy for ligand L^2 in a square-planar environment

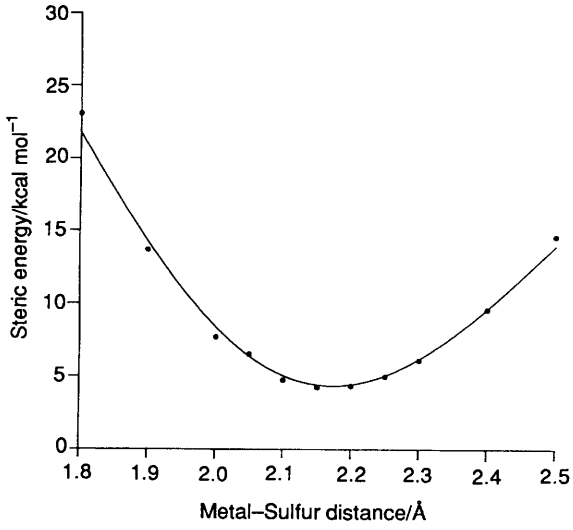

Fig. 10 Plot of metal–sulfur distance *versus* steric energy for ligand L^5 in an octahedral environment

conformation of that ligand. From the series of minimisations performed, the optimum M–S bond length of L^2 and the *gem*-dimethyl species L^3 was calculated to be 2.17 Å; for the *anti* form of L^4 it was 2.13 Å. A typical plot of metal–sulfur distance *versus* steric energy is shown in Fig. 9 (additional plots are available as supplementary data). It is thus apparent that *gem*-dimethyl substitution has little or no significant effect on the optimum M–S bond lengths of L^2, L^3 or L^4, when each ligand adopts an *anti* configuration. Given the predominance for octahedral complexes of 1,4,7-trithiacyclononane, and the new ligands being preorganised with *endo* sulfurs, the calculations assumed an octahedral co-ordination environment. Because there are four possible isomers which have equivalent chiral carbons L^5–L^8 and the ligand itself is chiral, there are six possible combinations of these isomers in an octahedral complex, *viz.* $2 \times L^5$, $2 \times L^6$, $L^5 + L^6$, $L^5 + L^7$, $L^5 + L^8$ and $L^6 + L^7$. Cavity size calculations were performed for each of the above species. The global minimum conformation of each isomer was used for the calculations. The ligand L^7 was constructed by inverting the *z* coordinates of the minimum of L^5 using the appropriate function within QUANTA, and L^8 was similarly constructed from the minimum of L^6. A typical plot of M–S distance *versus* steric energy is shown in Fig. 10 (additional plots are available as supplementary data). The $[ML^6_2]$ and $[ML^6L^8]$ complexes have an ideal M–S distance of 2.13 Å; the remaining complexes have an ideal distance of 2.17 Å. The energies of the ligands in complexed conformation at the ideal M–S distances were also calculated, and are listed in Table 3. These energies were calculated by removing the metal and one ligand, and calculating the CHARMm energy of the remaining ligand in its metal bound conformation. These calculations show that in the $[ML^6_2]$ the overall steric energy is lower than in any other complex and that in its complexed conformation the isomer L^6 in $[ML^6_2]$ is the least strained of the isomers on complexation.

The optimum M–S bond length for L^1 has been calculated to be 2.27[24] or 2.31 Å.[25] Substituting methyl groups stereospecifically has significantly shortened this distance, which could aid in the selectivity for certain first-row transition metals, such as cobalt or iron.

Dimethyl groups were also substituted on one carbon of each SCH_2CH_2S segment, to create 2,2,5,5,8,8- and 3,3,6,6,9,9-hexamethyl-1,4,7-trithiacyclononane (L^9 and L^{10}). We postulated that if an octahedral complex of L^9 and/or L^{10} was constructed, steric clashes between the two co-ordinated macrocycles would result in the macrocyclic backbone adopting energetically unfeasible conformations. This turned out to be the case, so neither was modelled further.

Table 3 Steric energies of complexed ligand * in an octahedral environment

Complex	Isomer	Steric energy/ kcal mol^{-1}	Isomer	Steric energy/ kcal mol^{-1}
$[ML^5_2]$	L^5	3.014	L^5	3.014
$[ML^6_2]$	L^6	2.064	L^6	2.064
$[ML^5L^6]$	L^5	3.012	L^6	2.060
$[ML^5L^7]$	L^5	3.004	L^7	3.044
$[ML^5L^8]$	L^5	2.989	L^8	2.088
$[ML^6L^8]$	L^6	2.040	L^8	2.082

* Defined in text.

Conclusion

The thermodynamic effect of methyl substitution in 1,4,8,11-tetrathiacyclotetradecane in improving the complexation of Ni^{II} or Cu^{II} was originally attributed to the preorganisation of the ligands. Simulations with molecular dynamics have shown that while the number of conformers accessed was clearly reduced by methyl substitution, this applied only to the CSCCCSC sections which were substituted. New criteria relating to the slowing of torsional movement, determinable by molecular dynamics, and cross-ring donor-atom interatomic separations, have been proposed as a guide to the preorganisation of a ligand. The new ligands L^5 and L^6 were computationally designed, and L^5 was shown to be fully preorganised with all three sulfurs atoms *endo* in a potential metal-chelating configuration.

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