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New cage and linked macrocyclic systems for metal ion and small molecule binding

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Abstract. Stepwise synthetic procedures have been developed for producing families of large cyclic ligand systems that include new oxygen-nitrogen donor cages as well as tri-linked macrocyclic species containing mixed nitrogen-sulfur donors. The crystal structure of a cage of the above type incorporating six phenoxy oxygens and two tribenzylamine (bridgehead) nitrogens reveals that the nitrogens adopt *exo-exo* configurations. Semiempirical MO calculations have been employed to investigate the topological rigidity of this hexabenzo cage relative to related aliphatic systems. The constraining of the bridgehead nitrogens (through the presence of tribenzylamine groups) has a significant effect on the overall flexibility of the system and appears to be largely responsible for inhibiting the inclusive coordination of metal ions by this cage. In contrast to the aliphatic 2,2,2-cryptand, which readily adopts an *endo-endo* arrangement, the present cage shows negligible affinity for sodium ions - as judged from comparative sodium picrate extraction experiments (water/ chloroform). New 'super' cages related to the above system but incorporating three additional pyridyl nitrogens in their heteroatom set have also been synthesised. Once again, the rigidity associated with the tribenzylamine bridgeheads introduces a measure of preorganisation into these cages. The X-ray structure of one system recrystallised from benzene shows that a benzene guest is encapsulated centrally in the cavity, seemingly held in position by 'T' orientation π-stacking interactions. In deutero-chloroform, this cage selectively binds phloroglucinol although it also shows significant affinity for resorcinol. Two new tri-linked S_2N_2-donor macrocycles incorporating three 16-membered rings connected by spacer groups to a phloroglucinol 'core' have been synthesised. Using an NMR titration procedure, these systems have been demonstrated to undergo stepwise interaction with silver(I), with the final product showing a 3:1(metal:ligand) stoichiometry.

INTRODUCTION

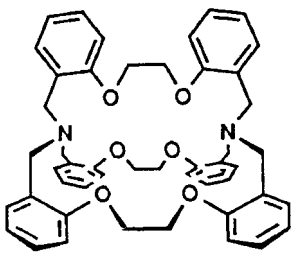
As an extension of our studies involving mixed-donor macrocycles incorporating oxygen, nitrogen and/or sulfur donors (1, 2), we have recently developed simple and efficient procedures for obtaining related new ligands showing both cage and tri-linked macrocyclic architectures. Results from our investigations of selected examples of these new systems are now presented.

New Mixed Donor Cages

Relative to monocyclic ligands, macrobicyclic 'cages' have the potential to provide a more closely defined coordination cavity for both small molecules and ions. The classic study by Lehn *et al.* (3) in which a range of aza-capped polyether cages were demonstrated to show cavity size selectivity towards particular alkali and alkaline earth ions illustrates well the use of such systems as selective receptors. Cages of this type incorporate flexible 'links' in their structure and hence are able to undergo a degree of 'accommodation' to best suit the requirements of an included guest. While a

higher degree of rigidity will lead to an increasing element of preorganisation, which may aid the thermodynamics of complexation for particular guests, it may also play an unfavourable role in that it may inhibit the entry of the guest into the cavity.

We have investigated the properties of the new cage **1** incorporating six phenoxy-ether and two nitrogen heteroatoms (4). The latter represents the first member of a series of cages prepared by related step-wise synthetic procedures based on a 'building block' approach.



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The X-ray structure of **1** (Fig. 1) shows that the cage adopts a three-bladed propeller-shaped arrangement in the solid. The polyhedron defined by the six oxygen donors approaches a trigonal prism, with the twist angle between the triangular faces being 2.7°. The bridgehead nitrogens have their lone electron pairs orientated *exo-exo* with these atoms separated by 5.44 Å. The mean distance between opposing oxygen atoms in this present cage (defining the coordination cavity) is 6.83 Å. Thus, the bridgehead atoms "intrude" somewhat into the cavity.

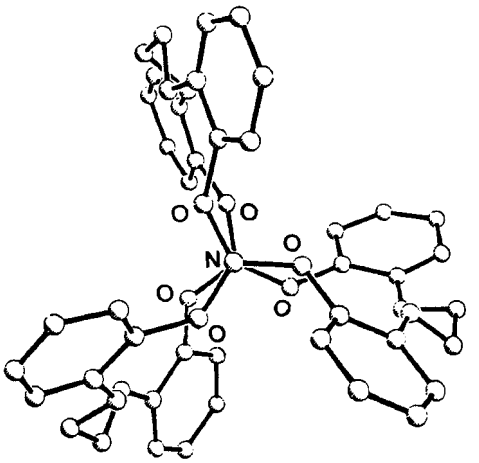


Fig. 1. End-on view of the X-ray structure of ***1****.*

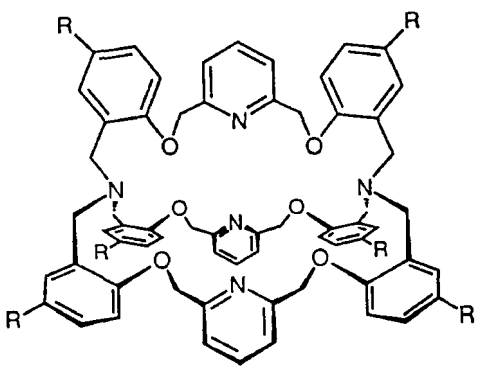
In contrast, the published X-ray structure of the aliphatic 2.2.2-cage shows an *endo-endo* arrangement with a N...N separation of 6.87 Å (5) . It is of significance to the present study that subsequent semiempirical (CNDO2) calculations performed on the optimised 2.2.2 (isomeric) structures indicate that the most elongated cavity occurs in the *endo-endo* form (6). That is, inversion of both nitrogens of the *endo-endo* cage produces an *exo-exo* arrangement which shows a *shorter* nitrogen-nitrogen distance. The presence of such a 'truncated' cavity in our hexabenzo cage clearly also appears to be a direct consequence of the steric imposition of an *exo-exo* arrangement in this system.

Semiempirical MO level (MOPAC AMI) calculations were undertaken in order to investigate the effect of the above bridgehead nitrogen configurations on the overall cage conformation (and flexibility) of the present system. While a minimised geometry corresponding to the X-ray (*exo-exo*) arrangement was obtained, initially no corresponding minimum was found for the analogous *endo-endo* arrangement - in accord with the latter being unstable for the present system. However, when the system was constrained to be *endo-endo* then minimised, a high energy local minimum (*c.* 117 kJ mol^{-1} higher than for the *exo-exo* form) was detected; the *endo-endo* arrangement is clearly unstable. This situation contrasts with that for the corresponding 2.2.2 cryptand for which molecular mechanics coupled with the semiempirical CNDO2 calculations (6) indicate that *endo* and *exo* forms

are of similar energies with interconversion between the forms predicted to occur readily. What is the major cause of the configurational and associated conformational inflexibility just discussed for **1**? Undoubtedly, this is imposed by the presence of three benzyl moieties attached to each nitrogen bridgehead - giving rise to somewhat rigid N-C-C-C torsion angles. Further calculations indicated that when the twist angle between the triangular faces defined by the six oxygen atoms was increased to 30° and the structure minimised, a new minimum with relatively low energy was obtained. This result is in accordance with the interconversion between rotamers (about the N...N axis) being facile.

Perhaps not surprisingly, attempts to form a sodium complex of **1** were unsuccessful - when a chloroform solution of **1** was shaken with an aqueous sodium picrate solution (at pH 7), no extraction of the latter into the organic phase was observed. Under similar conditions, the 2.2.2 cryptand is quite an efficient extractor of sodium picrate. Thus, in part, the different behaviour may be attributed to the forced *exo-exo* arrangement in the case of **1** which also appears to have methylene protons directed inwards in the vicinity of each of the nitrogen caps - this further restricting ingress of a spherical host into the cage. In this regard, the analogous more flexible, tetrabenzo (O_4N_2-donor) monocycle, for which the amine lone pairs are available for sodium complexation, also extracts sodium picrate into chloroform - as do the 'hybrid' cages in which one or two -$CH_2CH_2OCH_2$-$CH_2OCH_2CH_2$- moieties replace individual dibenzo arms in **1**.

Based on the above studies, we have synthesised the new 'super' cages **2a** and **2b** (7); in the case of **2b**, the presence of *tert*-butyl substituents results in significantly greater solubility of this cage in solvents of low polarity such as chloroform. A feature of both these cages is that the rigidity associated with the tribenzylamine bridgeheads once again introduces a measure of preorganisation into the respective systems. The resulting moderately rigid cages appear capable of including a guest having a maximum diameter of about 8-9Å. These new cages represent an attempt to provide a compromise between the existence of too great a degree of preorganisation and the presence of sufficient flexibility to allow entry of a suitable guest into the cavity.



2a R = H, **2b** R = *t*-butyl

Recrystallisation of **2b** from benzene results in inclusion of one benzene molecule in the cavity. This guest is orientated centrally (Fig. 2) such that it lies perpendicular to the pseudo three-fold axis that passes through the bridgehead nitrogens. The centroid of the benzene moiety is coincidental with

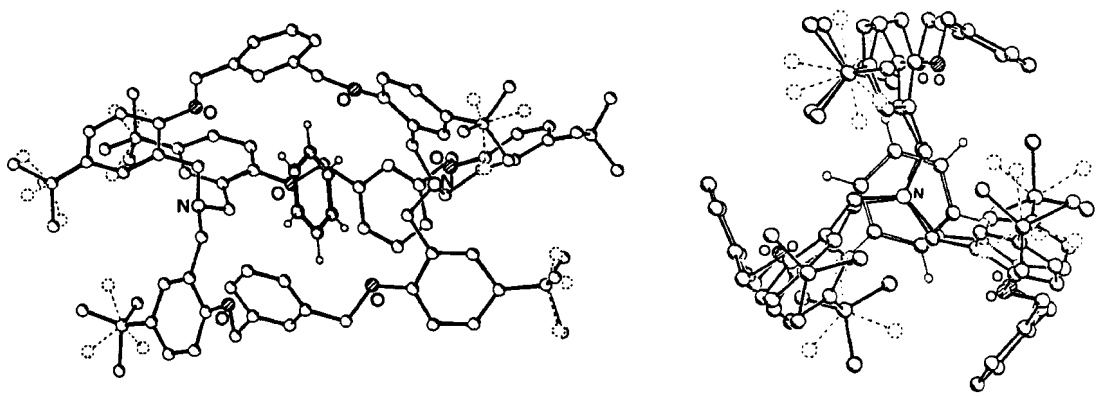
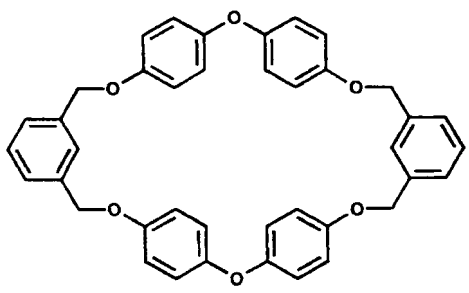


Fig. 2. Views of the X-ray structure of the benzene inclusion complex of ***2b****.*

the centroid defined by the five nitrogen heteroatoms. As expected, the host cage has its bridgehead nitrogens arranged *exo-exo*, while the pyridyl groups lie approximately "parallel" to the pseudo three fold axis such that their nitrogens do not point towards the centre of the cage. In this configuration, the mean distance of the above centroid from the pyridyl nitrogens is 5.2 Å while it is 4.6Å from the bridgehead nitrogens.

In the above structure the centroid of each pyridyl ring lies within 2.8 Å of a benzene proton - in accordance with the presence of 'T' orientated π-interactions. The latter appear to play a major role in binding and positioning the benzene with respect to the cavity. The situation in the above adduct resembles that found by Stoddart *et al.* (8) in the 1:1 host-guest complex between the hexaoxacyclophane **3** (incorporating six benzo groups) and benzene. In this case, aromatic ring interactions of the edge-to-face type also hold and orientate the guest in the molecular cavity.



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Molecular modelling using the semiempirical AM1 program suggested that **2b** should bind a tri-phenol such as phloroglucinol via complementary hydrogen bonds between the phenolic protons of the guest and the pyridyl nitrogens of the host. The predicted (minimised) structure is shown in Fig. 3. Accordingly, addition of phloroglucinol to a deutero-chloroform solution of the cryptand resulted in ^{1}H NMR shifts for both host and guest which were in accord with 1:1 complex formation in which the tri-phenol is held symmetrically in the cage. In addition to phloroglucinol, this cage has also been demonstrated to exhibit preferential binding for resorcinol (relative to a number of other simple mono-, di-, and tri-phenol derivatives).

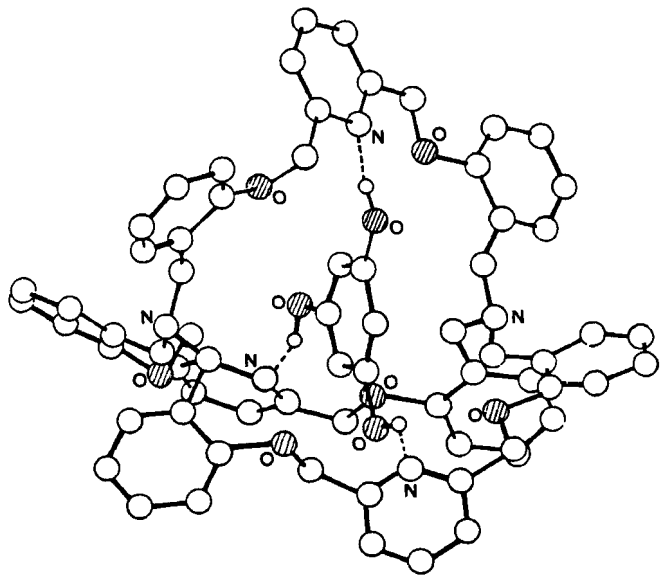
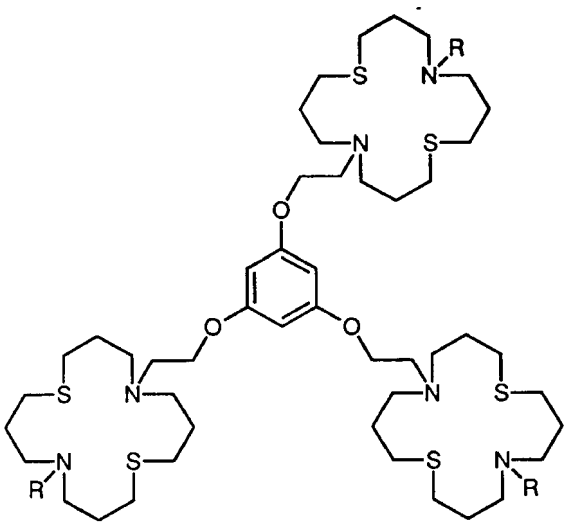


Fig. 3. Predicted structure of the phloroglucinol host-guest complex of ***2b****.*

New Tri-linked Macrocyclic Systems

New tri-linked S_2N_2-donor macrocycles of type **4**, incorporating three 16-membered rings connected by spacer groups to a phloroglucinol 'core', have also been synthesised - starting from the parent single rings incorporating differentially protected nitrogen donors (9).

Using an NMR titration technique, silver(I) nitrate has been shown to undergo stepwise interaction with both **4a** and **4b** in DMSO-d_6/$CDCl_3$, such that the final product has a 3:1 (metal:ligand) stoichiometry in each case. Silver(I) was selected to illustrate the ability of these systems to undergo metal ion binding since this 'soft' metal had been well documented previously to show affinity for a number of other nitrogen-sulfur donor, single-ring macrocycles (2, 10). While the titration of **4a** yielded a sharp 3:1 end point, that for the N,N,N-tribenzyl derivative **4b** was much less distinct. The latter is in keeping with the well documented observation that the presence of bulky N-substituents normally reduces the metal-ion binding strength of a ligand relative to that for the corresponding unsubstituted system (11). Analysis of the titration curve proved possible in this case (12), yielding values for the respective step-wise stability constants of log K_1 = 3.7, log K_2 = 3.3 and log K_3 = 2.3 at 25 °C. The corresponding speciation curves are shown in Fig. 4.



4a R = H, **4b** R = benzyl

Finally, the 'building block' approach (employing selectively protected S_2N_2-donor macrocycles) used to obtain **4a** and **4b** is readily extendable to the synthesis of other linked systems. In ongoing studies, we plan to incorporate the above and similar macrocyclic rings into a range of molecular architectures - these include both simple linked oligomeric systems as well as higher order dendrimers. Our projected synthesis of such dendritic macrocyclic systems capable of binding heavy metal ions represents entry into a novel and interesting class of organometallic materials whose properties at this time are not able to be fully predicted.

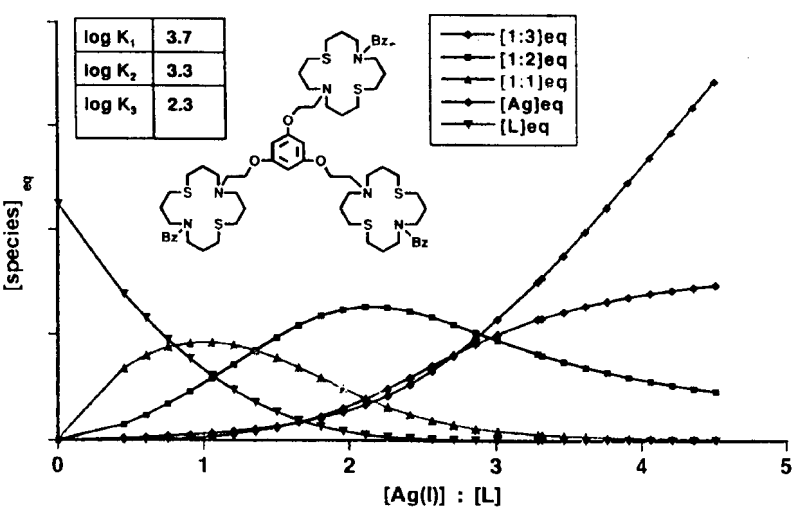


*Fig. 4. Speciation diagram for the interaction of **4** with silver(I) in DMSO-d_6/$CDCl_3$ (1:1) at 25 °C.*

Acknowledgment

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