Synthesis and Crystal Structure of a New Large Cryptand encapsulating a Benzene Molecule

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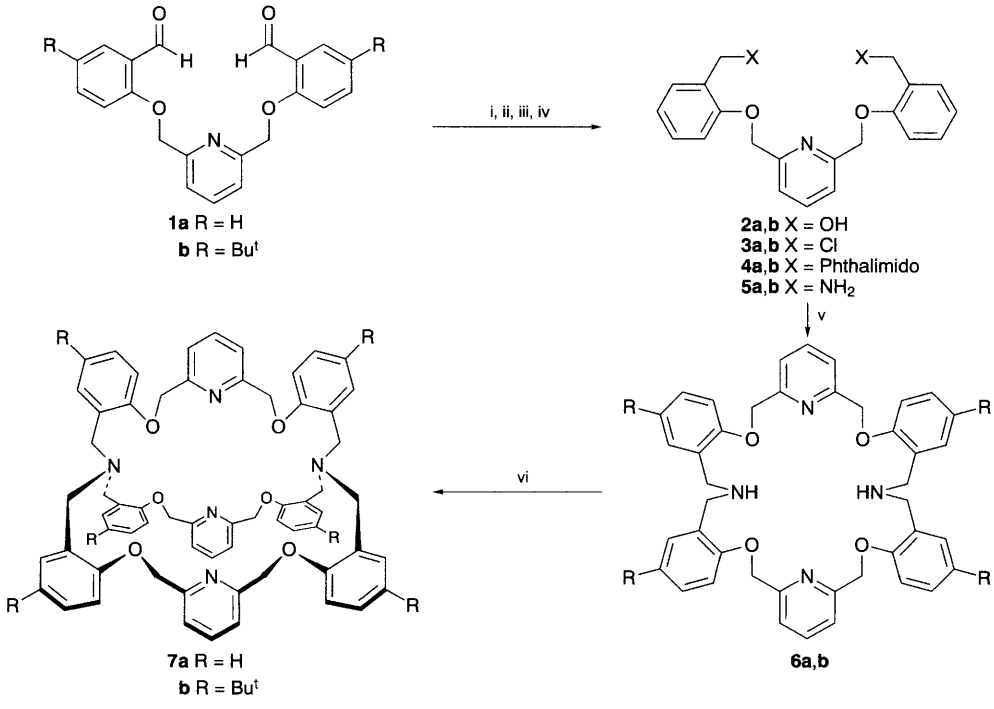
The synthesis of two new large cryptands **7a** and **7b** has been carried out and the X-ray structure of **7b** confirms that a benzene guest molecule is encapsulated centrally in its cavity.

Despite the large number of reports of the complexation of metal ions by cryptands,[1,2] there are fewer examples of corresponding complete encapsulation of neutral organic compounds. Notable exceptions are the cryptands incorporating bipyridyl[3] or other[4] 'straps' recently reported by Vögtle *et al.* We have synthesised two new moderately rigid cryptands whose cavity size is large enough to allow encapsulation of guest molecules up to approximately 8–9 Å in diameter. A feature of these cages is that the cavities are partially held open by the use of two tribenzylamine bridgehead moieties—thus incorporating an element of preorganization into the system. While the presence of preorganisation will generally enhance binding to a suitable guest, too rigid a structure may inhibit entry of the guest into the cavity. The new cages represent an attempt to provide a compromise between these opposing influences.

Both new cages were produced by the reaction sequence outlined in the Scheme 1. Dialdehyde **1b** was synthesised by alkylation of 5-*tert*-butylsalicylaldehyde[5] with 2,6-bis(chloromethyl)pyridine under phase transfer conditions (toluene/H_2O/NaOH/Bu_4NBr). This method proved to be more efficient than alkylation of the preformed sodium salt of the salicylaldehyde in DMF, the method used to produce **1a**.[6] Reduction of the dialdehyde with sodium borohydride and chlorination of the resulting diol **2**‡ with thionyl chloride in dichloromethane, afforded the dichloro derivative **3** in good yield. The diamine **5** was obtained from **3** by Gabriel methodology. Macrocyclisation of diamine **5** and dialdehyde **1** was conducted under conditions of moderate dilution, initially using sodium borohydride to reduce the Schiff base intermediate(s). In the case of macrocycle **6b**, a dramatically improved yield (82% *vs.* 45%) was obtained in the presence of powdered 4 Å molecular sieves, together with the use of sodium cyanoborohydride as a selective imine reductant.[7] This procedure avoids complications arising from reduction of free dialdehyde by sodium borohydride. The final cryptands were obtained by bis-*N*-alkylation of macrocycle **6** with the dichloro intermediate **3** in toluene, using excess caesium carbonate as the base. Although both **7a** and **7b** were synthesised, we have employed the *tert*-butyl derivative **7b** exclusively in subsequent studies because of its considerably enhanced solubility in chloroform and methylene chloride.

The X-ray structure§ of **7b**, crystallised from benzene, is illustrated in Fig. 1. The cage adopts a configuration in which both bridgehead nitrogens are *exo*. Molecular modelling studies (using a previously described molecular mechanics package)[8] suggest that the adoption of this nitrogen arrangement is dictated by steric constraints associated with the presence of three attached benzyl moieties. The cage has a *pseudo* threefold axis passing through the bridgehead nitrogens with the pyridyl rings aligned approximately parallel to this axis such that the pyridyl nitrogens do not point towards the central cavity. The mean distance of the pyridyl nitrogens from the centroid defined by all the nitrogens is 5.2 Å and that of the bridgehead nitrogens 4.6 Å. A single benzene molecule is a guest within the cavity.



Scheme 1 Synthesis of cage **7a** (**7b**). *Reagents and conditions*: i, $NaBH_4$, 95% EtOH, reflux 15 h, 97% (98%); ii, $SOCl_2$, CH_2Cl_2, reflux 8 h, 88% (94%); iii, potassium phthalimide, DMF, 120 °C 4 h, 99% (93%); iv, NH_2NH_2, EtOH then 2 Mol dm^{-3} HCl, 86% (98%); v, **1** 1 equiv., 4 Å molecular sieve, dry EtOH reflux 20 h then $NaCNBH_3$, reflux 20 h, (82%) or **1** 1 equiv., EtOH then $NaBH_4$, 30% (45%); vi, **3** 1 equiv., Cs_2CO_3 10 equiv., toluene, reflux 7 d, 41% (52%)

The centroid of the benzene overlays the centroid defined by the five nitrogen atoms, the plane of the benzene being perpendicular to the *pseudo* C_3-axis. The distance from the centroid of a pyridine ring to the nearest benzene proton is approximately 2.8 Å. This distance is well within the reported range for 'T' orientation π-stacking interactions,[9] suggesting that such interactions are important in binding (and orientating) the benzene guest in the present case.

Like the tris-bipyridyl cages[3] mentioned earlier, cryptand **7b** also selectively binds certain di- and tri-phenols. Thus, addition of resorcinol or phloroglucinol to a solution of the cryptand in $CDCl_3$ results in distinctive shifts in the ^1H NMR signals of both the host **7b** and the guest (resorcinol or phloroglucinol). These include for the cryptand, downfield shifts of the 3- and 4-pyridyl protons and corresponding (but smaller) upfield shifts of the benzylamine methylene protons. The ring protons of the guests appear at higher field in the complexes, consistent with increased electron density on the phenolic oxygens. The observed shifts are consistent with these guests being bound centrally within the cage *via* stereo-complementary H-bonds between the phenolic protons of the guest and the pyridyl nitrogens of the cage. A parallel experiment using catechol as the potential guest, produced no significant changes in the ^1H NMR signals of guest or host—attesting to the selectivity of the binding in the former cases.

Finally, the versatility of the present stepwise approach to cryptand synthesis should be emphasised. The ready availability of dialdehyde precursors related to **1** will allow us to produce a range of cryptand hosts—including unsymmetrical examples—suitable for binding other selected guests. Such a strategy has already been successful in producing the first member of a series of smaller mixed donor cages related to the present systems.[10]

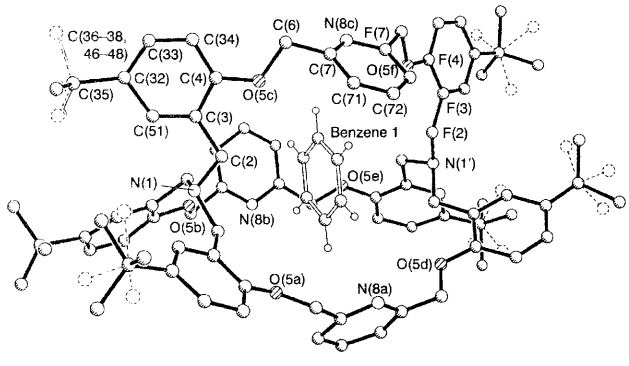


Fig. 1 X-ray crystal structure of **7b** containing an encapsulated benzene molecule

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Footnotes

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‡ For brevity, both the unsubstituted (**a**, R = H) and substituted (**b**, R = Bu^t) series of compounds are described together. Significant differences between the two series are noted in Scheme 1 or are discussed in the text. All compounds synthesised gave satisfactory NMR spectra, microanalysis and/or HRMS data.

§ *Crystal data* for $C_{87}H_{105}N_5O_6 \cdot \sim 6\ C_6H_6$, M 1785.4, monoclinic, $P2_1/c$, a = 22.406(8), b = 25.23(3), c = 19.78(1) Å, β = 102.95(4)°, Z = 4. Conventional R on $|F|$ at convergence was 0.15 for 4706 'observed' [$I > 2\sigma(I)$] out of 9144 unique diffractometer reflections ($2\theta_{max}$ = 40°; monochromatic Mo-Kα radiation, λ = 0.71073 Å; T = *ca.* 295 K; capillary mounted specimen). Crystals effloresced instantly on exposure to the air and were very susceptible to mechanical shock. Large block least squares refinement: isotropic thermal parameter forms for C, N, O; $(x, y, z, U_{iso})_H$ constrained at estimated values. The precision of the determination was adversely affected by disorder in five of the six *tert*-butyl groups, partial solvent occupancy of some lattice sites and high thermal motion. Solvent and *tert*-butyl groups were refined under rigid body constraints.

Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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