$1^2,5^2,9^2,13^2$-Tetranitro-1,5,9,13(1,3)-tetrabenzena-3,7,11,15(1,4)-tetrapiperazinacyclohexadecaphane,† a New Host Compound

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The new 36-membered macrocyclic host molecule $1^2,5^2,9^2,13^2$-tetranitro-1,5,9,13(1,3)-tetrabenzena-3,7,11,15(1,4)-tetrapiperazinacyclohexadecaphane, has been synthesised by a cyclisation reaction of 2,6-bis(bromomethyl)nitrobenzene and piperazine with Na_2CO_3 as a base under high dilution conditions; the macrocycle has an ellipsoidal non-polar cavity with a diameter of *ca.* 8 Å and has been characterized as a 1 : 1 inclusion complex with acetonitrile by X-ray diffraction and ^1H NMR.

Synthetic macrocyclic compounds have recently attracted much attention due to their ability to act as host or receptor molecules for ions or uncharged organic molecules.[1] The well-known and extensively studied families of such macrocycles are cyclodextrins[2] and calixarenes.[3,4] Unmodified cyclodextrins have a polar exterior due to the primary and secondary hydroxy groups, thus making them only sparingly soluble in non-polar solvents.[2] Simple calixarenes are less polar in nature and are soluble in non-polar solvents.[3,4] The 'receptor' site in cyclodextrins (CDs) is the apolar cavity, the diameter depending on the number of glucose units (*ca.* 5.7, 7.8 and 9.5 Å for α-, β- and γ-CD, respectively). Calixarenes possess a basket-shaped apolar cleft as a receptor site. Many studies have been published on the inclusion complexes of cyclodextrins and calixarenes or their derivatives with charged or neutral guest molecules.[2–4]

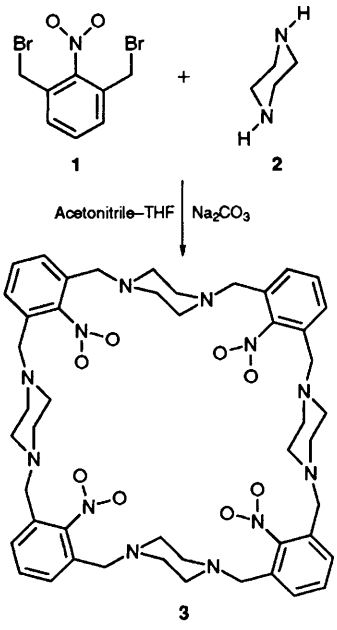
While searching building blocks for new macrocycles our attention was focused on piperazine, a water soluble cyclic diazine with rigid preorganized cyclohexane conformation.[5] As an amine, piperazine readily undergoes nucleophilic substitution reactions with proper halides. Piperazine is rarely used as a building block in macrocycles and only a few examples of macrocycles containing piperazine moieties have been reported.[6–8] Owing to the close overall structural similarity of piperazine and glucose, the macrocycle containing piperazine as an essential building block would be structurally similar to the cyclodextrins. Further the nitrogen atoms of piperazine can be easily protonated by treatment with acid, thus altering markedly the solubility of the macrocycle. Piperazine itself is achiral but the use of the easily available chiral piperazines as building blocks leads to chiral macrocycles. Therefore, piperazine is an excellent choice as a versatile building block for synthesisizing achiral or chiral macrocycles with convertable solubility.

The possibility of cyclising piperazine with various suitably substituted bis(bromomethyl)benzenes also relates the macrocycles produced to calixarenes. Macrocycles with piperazine and arene moieties would thus be structurally similar to cyclodextrins and in addition the arene unit is easily derivatizable just as in calixarenes.

We selected 2,6-bis(bromomethyl)nitrobenzene as the halide and cyclised‡ it with piperazine under dilution conditions in refluxing tetrahydrofuran (THF)–acetonitrile with sodium carbonate as a base (Scheme 1). The macrocycles obtained in this way are cyclic oligomers of the piperazine and the arene unit, thus, dimer, trimer, tetramer, pentamer *etc.* will be formed. In the present case the major product is a cyclic tetramer **3**.

† This macrocycle has been named using the forthcoming new, IUPAC approved, system for phane nomenclature due to be published in approximately one years time.

‡ *Synthesis* of **3**. Solutions of 2,6-bis(bromomethyl)nitrobenzene (7.6 g, 24.6 mmol) in 250 cm^3 of acetonitrile and piperazine (2.1 g, 24.6 mmol) in 250 cm^3 THF–acetonitrile (1 : 1.5) are simultaneously dropped into a refluxing, well stirred mixture of 400 cm^3 acetonitrile, 100 cm^3 THF and sodium carbonate (20 g, 189 mmol) over a period of 10 h. The inorganic residue is filtered off and the solvent is evaporated. The remaining yellow residue is chromatographically separated on silica gel using acetonitrile–ethanol (10 : 1 v/v) as eluent and gives **3** in 463 mg (8%) yield.



Scheme 1

The physical data§ indicate a highly symmetrical molecule. The compound was recrystallized from acetonitrile–ethanol for X-ray diffraction study.¶ The macrocycle was found to form an inclusion complex with acetonitrile (Fig. 1). The host : guest ratio was determined by ^{1}H NMR using the ratio of the acetonitrile methyl and CH_2-bridge integrated signals. The macrocycle has an ellipsoidal overall shape with parallel arene units. The non-polar (only the hydrogen atoms are pointing inwards) cavity is *ca.* 8 Å in diameter, which is very close to that of β-cyclodextrin. The acetonitrile is located not in the centre of the cavity but instead in a 'corner' or 'armpit', possibly due to some weak interactions between the C≡N bond and the benzene ring π-electrons.

§ *Physical and spectroscopic data* for **3**. R_f = 0.37 acetonitrile–ethanol (10 : 1 v/v); m.p. >300 °C; ^{1}H NMR (JEOL GSX, 270.2 MHz, $CDCl_3$, 30 °C, $SiMe_4$): δ 1.78 (s, 3H, MeCN), 2.31 (s, 32H, NCH_2), 3.43 (s, 16H, Ar-CH_2), 7.34 (s, 12H, Ar-H); ^{13}C NMR (JEOL GSX, 67.9 MHz, $CDCl_3$, 30 °C, $SiMe_4$): δ 52.50 (NCH_2), 57.55 (Ar-CH_2), 129.56, 129.93, 130.72, 151.44; FAB-MS (Kratos Concept 1 H), *m*-nitrophenol matrix: *m/z* (%) = 933(10) [M^+], 700 (100).

¶ *Crystal structure analysis* of **3**: colourless crystals, $C_{48}H_{60}N_{12}O_8$·MeCN (disordered over two identical sites), M_r = 974.13; monoclinic, space group $P2_1/c$ (no. 14); a = 13.286(1), b = 7.437(1), c = 27.985(12) Å, β = 97.95(2)°, V = 2738(1) Å^3, Z = 2; D_c = 1.181 g cm^{-3}; Mo-Kα (λ = 0.7107 Å); μ = 0.077 mm^{-1}; $F(000)$ = 1036; T = 296 ± 1 K; crystal dimensions: 0.20 × 0.30 × 0.35 mm; CAD4 diffractometer (Enraf-Nonius); corrections: Lorentz polarization, empirical absorption correction [DIFABS (N. Walker and D. Stuart, *Acta Crystallogr., Sect A*, 1983, **39**, 158) minimum and maximum correction coefficients 0.689 and 1.115]; 2θ = 4–50°; *hkl* range: h = 0 → 15, k = 0 → 8, l = = −33 → 33; 4797 measured and unique reflections, 1755 with $I > 3\sigma I$. The structure was solved by direct methods (SHELXS, G. M. Sheldrick, in *Crystallographic Computing 3*, ed. G. M. Sheldrick, C. Krüger and R. Goddard, Oxford University Press, Oxford, 1985, p. 175). Refinement by full-matrix least-squares analysis, R = 0.059, R_w = 0.045 {$w = w'$ [1.0 − $(\Delta F/6{\cdot}\sigma F)^2]^2$; where w' = Chebychev polynomial for F_c with five coefficients (2.76, −2.72, 0.399, −1.37, −1.29)}, non-hydrogen atoms refined anisotropically, the H atoms calculated to their idealized positions (C–H distance 1.00, 1.05 Å for acetonitrile) and refined as riding atoms with fixed isotropic temperature factors (U = 0.08 Å^2) (CRYSTALS program, D. Watkin, J. R. Carruthers and P. W. Betteridge, CRYSTALS, Chemical Crystallography Laboratory, Oxford, 1990). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

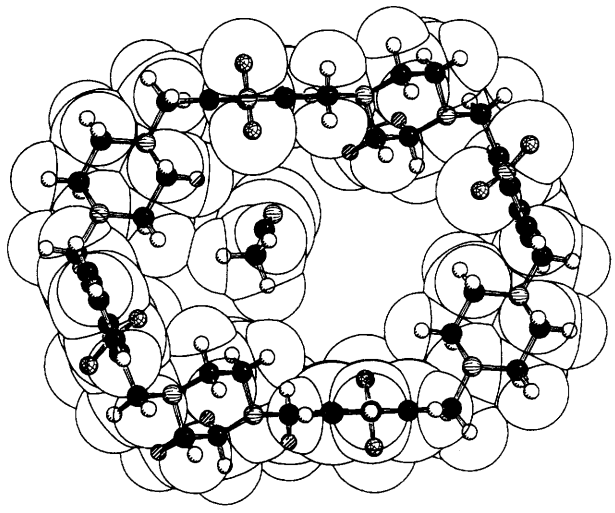


Fig. 1 A SCHAKAL[9] plot based on the X-ray study. The acetonitrile guest is distributed between two equally populated (0.5) sites, only one of which is shown occupied.

Molecular modelling studies‖ were performed in addition to the crystal structure analysis. The modelling for the acetonitrile complex gave an almost identical result to the X-ray analysis. Acetonitrile was then replaced by benzene in order to see if complexation and/or conformational changes occur. Benzene is located in the centre of the cavity and the overall conformation changes during the complexation. The modelling of the benzene inclusion complex thus suggests that the macrocycle is not completely rigid and that it is able to adapt itself (to some extent) according to the guest molecule (to prove this, complexing experiments between the macrocycle and benzene are currently in progress).

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‖ Molecular modelling studies were performed on a IRIS Indigo workstation using MacroModel version 3.5X software (F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Lispkamp, M. Lipton, C. Gaufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440). The coordinates from the crystal structure analysis were used as the starting geometry, which were then minimised and subjected to the modifications for the complexes as discussed in the text. The complex structures were also subjected to Monte Carlo conformational searching (G. Chang, W.C. Guida and W. C. Still, *J. Am. Chem. Soc.*, 1989, **111**, 4379) and the conformational space was thus mapped.