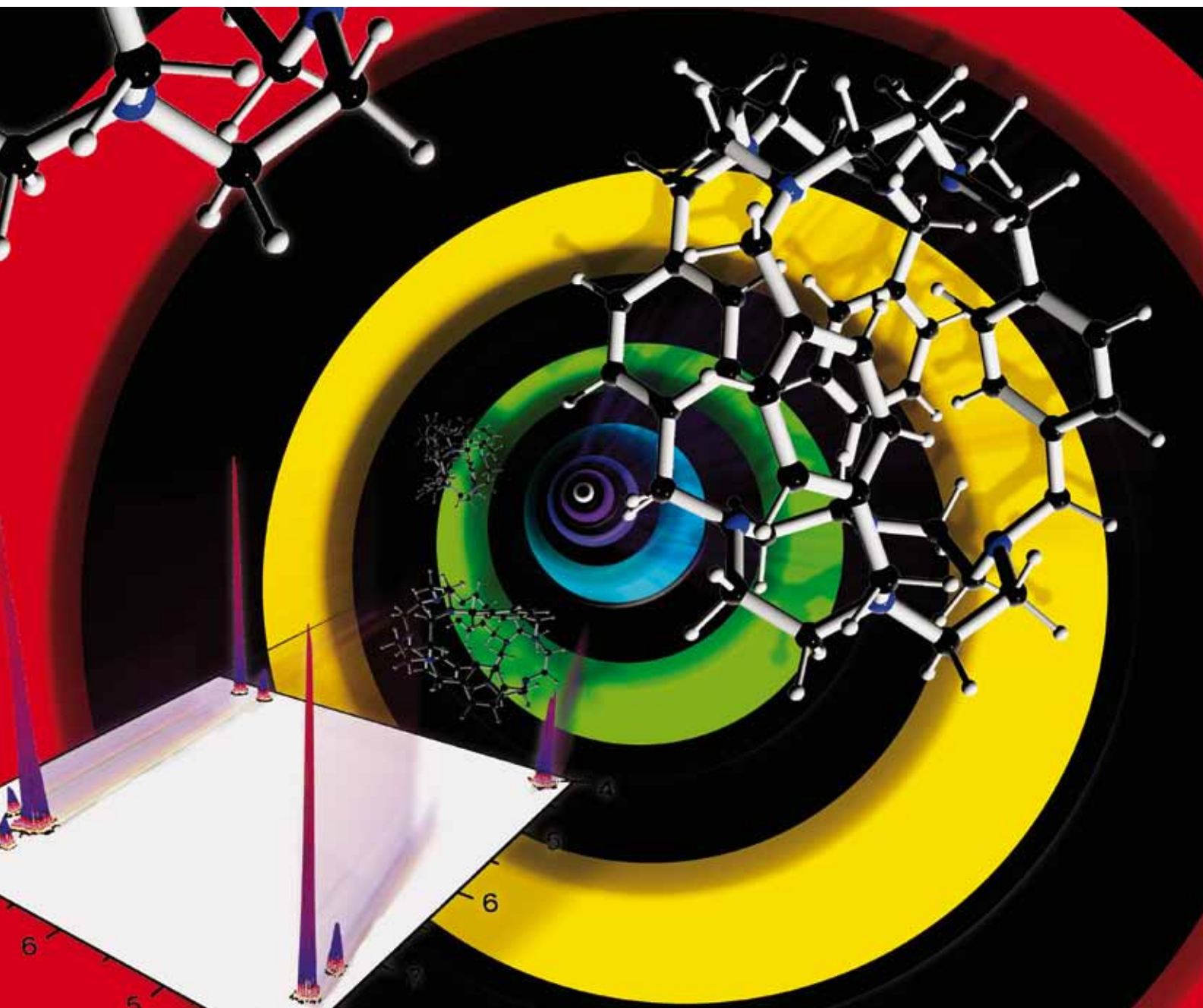


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with (Cl)Fe- and Mn porphyrins. A
theoretical study

Evidence for a ball-shaped cyclen cyclophane: an experimental and first principles study†

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Conformational isomerism of a ball-shaped cyclophane of cyclen was studied using NMR and computational methods with the most notable conformer containing a highly symmetric cyclic benzene tetramer.

Cyclophanes and nitrogen-containing cryptands are well-known for their oligomacrocyclic structures and reactivities especially in relation to their ability to bind guests.¹ In addition, the close intramolecular proximity of cyclophane components constrained by the cyclic or cage structures evidenced unusual features of these compounds.² In this work we were interested in studying molecules of ball-shaped morphology for their potential as complementary analogues or precursors of fullerenes.³ We chose to focus on the family of polyamine cages since a variety of these has already been synthesized suggesting a preparative accessibility for the proposed molecule, **1**.

Compound **1** (see Fig. 1a(i)) was prepared in one step by the dropwise mixing of solutions of 1,4,7,10-tetraazacyclododecane and α,α -dibromo-1,4-xylene (2 equivalents) in methanol and acetonitrile, respectively, in the presence of potassium carbonate.§ It is likely that the special reactivity of the amine groups in the 1,7 positions of cyclen assists in this synthesis possibly through the already reported macrotricyclic intermediate,⁴ containing two each of cyclen and 1,4-xylyl groups. Elemental analysis indicates a composition for **1** of C₄₈H₆₄N₈·8H₂O consistent with one hydrating water molecule per nitrogen atom. C:N ratio is also very close to that expected theoretically with an only 1% deviation. X-Ray powder diffraction measurement of a polycrystalline sample⁵ of **1** (see ESI†) was indexed⁶ to a monoclinic unit cell with

dimensions $a = 5.303$, $b = 13.292$, $c = 14.079$, $\beta = 113.847$, $V = 907.6$ Å³. Existence of the ‘doubly-strapped’ isomer of **1**, **1-4** (see Fig. 1) was discounted by molecular modeling and ¹H-NMR spectroscopy and only the ball-shaped isomer could be observed by STM imaging. ¹³C-NMR spectrum of **1** contains six non-equivalent aromatic carbon atoms and six carbons assigned to non-equivalent methylene groups. **1** exhibited a more complex than expected ¹H-NMR spectrum (see Fig. 2(a)) suggesting a molecular conformation different from the predicted stable structure **1-2** shown in Fig. 1(i), (ii). All chemical analytical data are consistent with the molecular structure of isomer **1-1** (Fig. 1b).

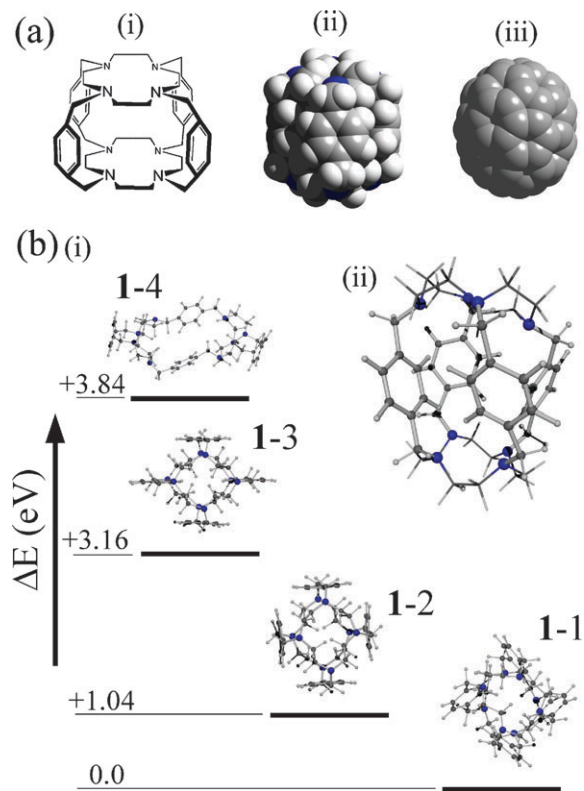


Fig. 1 (a) (i) Chemical structure of **1**; (ii) space-filling representation of the energy-minimized (MM2) structure of **1**; (iii) space-filling representation of fullerene C₇₀ for comparative purposes. (b) (i) Energy level diagram illustrating the relative stabilities of structural/conformational isomers of **1** obtained from molecular dynamics calculations, **1-1** (fylfot), **1-2** (box), **1-3** (sandwich), **1-4** (doubly-strapped); (ii) conformational isomer of **1** isolated after synthesis (**1-1**). Isomer **1-1** arbitrarily set at $E = 0$ eV; relative energies given in eV.

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† Electronic supplementary information (ESI) available: Synthetic procedure, chemical analysis, further NMR spectra, 2D NMR spectra, coordinates of calculated structures. See DOI: 10.1039/b822802g

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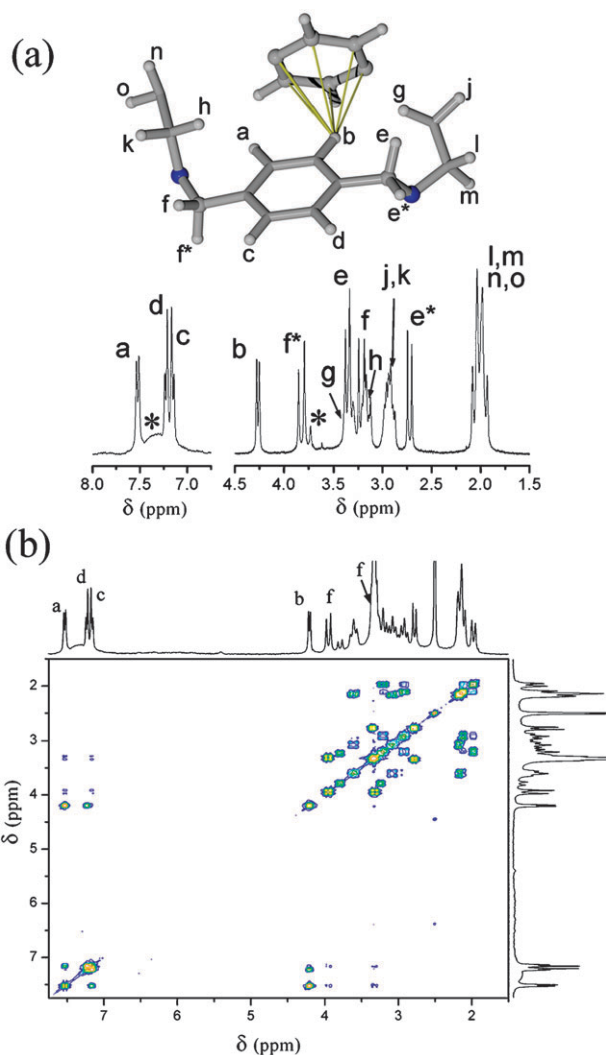


Fig. 2 (a) Composite ^1H -NMR spectrum of **1** (8.0–6.5 ppm: $\text{DMSO-}d_6$; 4.5–1.5 ppm: $\text{pyridine-}d_5$) and its assignment based on 1D and correlation spectroscopies. Structure shown is the repeating unit within **1**. Proton 'b' is that undergoing a $\text{CH}\cdots\pi$ interaction. Asterisk signifies peaks due to conformer **1-2**. (b) ^1H - ^1H COSY spectrum of compound **1** in $\text{DMSO-}d_6$ (not symmetrized). For further spectra see ESI † .

Car-Parrinello molecular dynamics simulations including empirical van der Waals corrections⁷ performed on **1** indicate several possible stable conformers (Fig. 1(b(i))) but only the mutually symmetrical positioning of phenyl groups in structure **1-1** is consistent with the multiplicity, coupling patterns and chemical shifts of its proton resonances. In particular, the substantial upfield shift of the resonance due to protons labeled 'b' in Fig. 2(a) is symptomatic of an edge-to-face $\text{CH}\cdots\pi$ interaction^{8,9} with an estimated distance of 3.19 Å separating the mean plane of the phenyl ring and the interacting proton (based on our model structure). The ^1H - ^1H COSY spectrum of **1** (see Fig. 2(b) and ESI †) confirms that all aromatic protons are connected at a single type of phenyl ring. Nuclear Overhauser enhancement (NOE) measurements also indicate which resonances are due to the methylene groups bonded directly to the phenyl rings. Proton resonances of cyclen are due to two non-identical ethylene groups, which

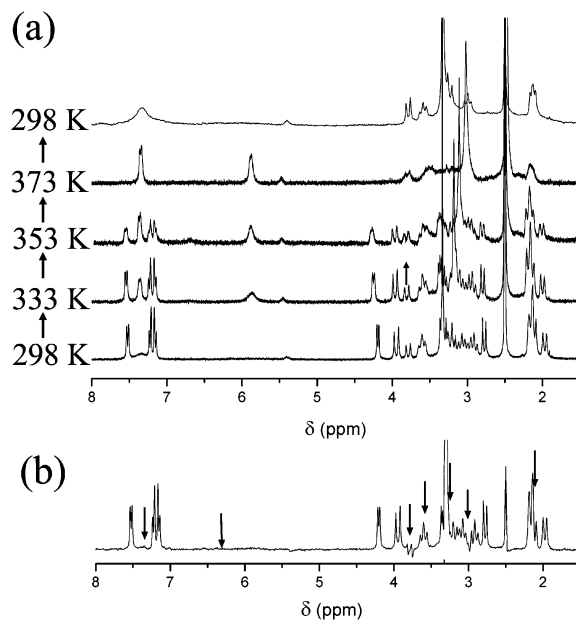


Fig. 3 (a) Variable temperature proton NMR spectra of **1** in $\text{DMSO-}d_6$. (b) Spectral subtraction of the spectrum obtained after cooling a solution of **1** in $\text{DMSO-}d_6$ from 373 K to 298 K. Arrows denote subtraction points.

could be assigned by considering NMR spectra (see ESI †). The unusually large upfield shift of one of the aromatic proton resonances and the symmetry of the molecule apparent from the low multiplicity of resonances are symptomatic of an intramolecularly cooperative $\text{CH}\cdots\pi$ interaction.¹⁰ To test the stability of this arrangement, variable temperature NMR spectroscopy (VT-NMR; see Fig. 3) was used. On heating of a solution of **1** in $\text{DMSO-}d_6$ from ambient temperature to 373 K, peaks assigned to **1-1** gradually disappear with intensification of peaks which are consistent with the box-like conformer **1-2**. Disappearance of peaks due to **1-1** is complete by 373 K and the new spectrum persists on cooling to ambient temperature. This suggests that the structure **1-1** occurs because of the particular conditions of its synthesis especially the solvent polarity although this parameter is thought not significantly to influence operation of the $\text{CH}\cdots\pi$ interaction. One peculiarity of the molecule obtained by heating is that at low temperature proton resonances of the cyclen moiety are relatively well resolved while those of the xylyl groups are broad and *vice versa* when the spectrum is measured again at high temperature. This reflects the variable motility of the molecules' components at different temperatures. Additionally, subtraction of the spectrum obtained at 373 K (attributed to isomer **1-2**) from that obtained at 298 K (see Fig. 3(b)) results in a spectrum containing resonances attributable solely to **1-1** with peak integrations also appropriate for **1-1**. This illustrates that samples are partly composed of box-like conformer **1-2** even at 298 K although its presence is most likely due to the brief warming of the sample applied in order to obtain a homogeneous solution. No evidence for the existence of 'sandwich' conformer **1-3** was found.

Scanning tunneling microscopy (STM) of compound **1** at the Cu(111) surface (Fig. 4) revealed an unusual quasi-hexagonal packing of the molecules with reduced symmetry.

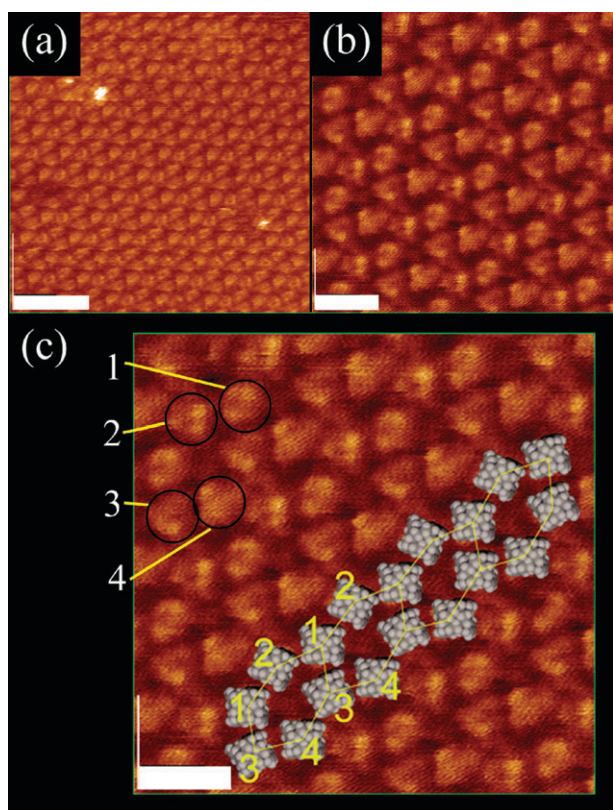


Fig. 4 (a) and (b) STM images of **1** on a Cu(111) surface illustrating its ball-like morphology; $V_t = 0.93$ V, $I_t = 80$ pA. Scale bars: (a): 5 nm; (b): 2 nm. (c) Model illustrating the basic edge-sharing hexagonal structure and 4 different STM profiles contained within the structure. Scale bar: 2 nm.

Four distinct STM profiles of **1** are presented in the images presumably due to a combination of intermolecular and molecule–surface interactions. Clearly, the shape and dimensions obtained by STM reveal the ball-like structure of **1** although the STM profiles are complex. We are currently attempting to model these STM profiles in order to better understand the intermolecular interactions responsible for this unusual 2-dimensional packing motif.

Car–Parrinello simulations at finite temperature were essential in identifying the most likely conformational isomers of **1**. Static DFT calculations of **1** resulted in the stable box-like **1–2**, but the $^1\text{H-NMR}$ spectrum is inconsistent with that form. On the other hand, first-principles dynamical simulations started from either the box-like **1–2** or the **1–3** conformers evolved spontaneously to **1–1**. The molecule was heated up from 300 to 600 K and, after about 10 ps equilibration, it was further raised to 800 K. After allowing the system to equilibrate at this temperature, an annealing was performed to reduce the temperature. The simulations were performed using an isolated¹¹ cubic cell with a lateral size of 16 Å. A BLYP^{12,13} functional was used to account for the electrons exchange–correlation interaction and the plane-wave basis set expansion was truncated at 70 Ry. In order to account for weak long-range interactions we included the empirical Elstner correction.¹⁴ Finite temperature simulations,¹⁵ followed by a final annealing, were performed using a fictitious electronic mass of 380 a.u. and a time step of 4.0 a.u.

We observed that structures **1–2** and **1–3** evolved to structure **1–1**, indicating that both **1–2** and **1–3** are, at very best, shallow local minima from which the system can escape thermodynamically, whereas **1–1**, lower in energy by ~ 1 eV, is the stable global minimum.¹⁶

Intuitively, a compact molecule such as **1** is expected to exhibit unusual phenomena based on the proximity of the components. Thus, **1–1** (see Fig. 5) exhibits enhanced stability in part due to internal $\text{CH}\cdots\pi$ interactions although these interactions can be overcome by heating a solution of **1–1**. The improved stability of **1–1** over other conformers is in line with entropic gains expected from $\text{CH}\cdots\pi$ interactions and the cooperative effect of four intramolecular points of interaction.^{9a} The $\text{CH}\cdots\pi$ hydrogen bonding interaction has been observed as one important factor in stabilizing certain proteins' conformations.¹⁷ Coincidentally, it has also been invoked during the study of small clusters of benzene molecules.¹⁸ In the latter, intermolecular $\text{CH}\cdots\pi$ interactions apparently determine the structure of higher order clusters, being preferred over extensive intermolecular π – π stacking. In our case stability is due to different effects like internal steric forces, hydrogen bonds, dipole effects, *etc.*, all these effects add up to produce energy differences of the order of eV. These energy scales are an indication that *ab initio* MD DFT based simulation is able to describe the system accurately.¹⁹ It must be stressed that the use of DFT for weak interactions and CH – π related effects is somewhat problematic. With this in mind the following points are important:

- (1) To take into account long-range correlations we included an empirical van der Waals correction.¹⁴
- (2) A full account of these effects would only be possible with the use of an improved exchange–correlation functional such as that proposed by Hooper *et al.*²⁰ However, this is not currently reasonable for large molecules and long simulation times.
- (3) As already mentioned, the order of magnitude of the energy differences found is so large that clearly other effects, rather than only weak $\text{CH}\cdots\pi$ interactions, play a major role in selecting the most stable structure, although the final geometry can to some extent be affected by the contribution of weaker interactions.

Several examples of intramolecularly occurring benzene ‘clusters’ have been reported most notably the self-assembled porphyrin trimer of Furuta *et al.*,²¹ which is apparently

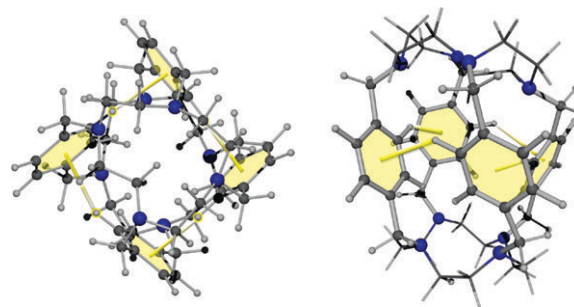


Fig. 5 Calculated structures of conformer **1–1** illustrating the intermolecular $\text{CH}\cdots\pi$ hydrogen bonding. Planes of aromatic moieties are colored pale yellow while points of interaction are indicated by yellow ‘bonds’.

substantially stabilized through CH $\cdots\pi$ interactions. Similar trimer formation was also found for a cyclophanyl-type compound. Interestingly, in that case an upfield shift of the interacting protons similar to that found in the case of **1**–**1** was observed, and corresponded to a proton–arene distance of 2.70 Å.²² In our model, a distance of 3.19 Å is obtained for the corresponding distance although the systems described are somewhat different in terms of their overall structures. Of course, in the case of **1**–**1**, cyclen groups will also influence the structure of the global minimum of **1** although simplicity of resonances due to these groups indicates their high symmetry.

In summary, we have examined a prototype ball-shaped molecule with dimensions similar to the common fullerenes. The highly constrained nature of the components of this ball-shaped compound results in several potential conformations, which we assessed using DFT-based dynamical simulations. The isolated molecule possesses a stable and highly symmetrical conformation with the resulting formation of a cyclic benzene tetramer. The similarity with the gaseous phase benzene tetramer although indicative of the same symmetry situation, should not be overextended, since the types of interactions, as well as the energy scales, are very different. We are currently investigating the properties of more highly functionally substituted derivatives of **1** and we predict that these derivatives will make up a significant new family of quasi-spherical molecules even as precursors of higher heterofullerenes.²³

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Notes and references

§ **Synthesis.** **1**: Solutions of 1,4,7,10-Tetraazacyclododecane (0.86 g, 5 mmol) in methanol (100 mL) and α,α -dibromo-1,4-xylene (2.63 g, 10 mmol) in acetonitrile (100 mL) were separately added dropwise to a rapidly stirred suspension of potassium carbonate (3 g, ~22 mmol) in acetonitrile (100 mL) over a period of 30 min. Stirring was continued at room temperature overnight (18 h) then the reaction mixture was filtered. Solvents were evaporated from the supernatant solution yielding a solid, which was triturated with water (100 mL). The suspension was subsequently filtered and dried in a vacuum at room temperature for 48 h giving **1** as a pale yellow powder. Yield: 80 mg, 4.25 %. ¹H-NMR (DMSO-*d*₆, 20 °C, 300 MHz): δ = 7.52 (d, 4H, ³*J* = 7.7 Hz), 7.21 (d, 4H, ³*J* = 7.52 Hz), 7.14 (d, 4H, ³*J* = 7.52 Hz), 4.37 (d, 4H, ³*J* = 7.34 Hz), 3.95 (d, 4H, ²*J* = 17.61 Hz), 3.60 (t, 4H, *J* = 13.20 Hz), 3.37–3.20 (m, obscured by HOD), 3.08 (t, *J* = 12.29 Hz), 2.19 (t, 4H, *J* = 12.66 Hz), 2.77 (d, 4H, ²*J* = 13.2 Hz), 2.14 (m, 12H), 1.97 (d, 4H, *J* = 14.49 Hz) ppm. ¹³C-NMR (DMSO-*d*₆, 20 °C, 300 MHz): δ = 140.4, 135.5, 129.4, 129.2, 128.7, 127.7, 58.7, 55.4, 52.7, 51.5, 49.6, 48.7 ppm. FT-IR (KBr pellet): ν = 2971 (m, aromatic C–H(str)), 2942 (m, aromatic C–H(str)), 2796 (s, methylene C–H(str)), 1510 (w, C=C(str)), 1458 (m, C–H(def)), 1437 (m, C–H(def)), 1417 (m, C–H(def)), 1369 (s, C–H(def)), 1307 (w), 1282 (w), 1255 (w), 1210 (w), 1170 (w), 1102 (s, C–N(str)), 1082 (m, C–N(str)), 1023 (w), 1009 (w), 992 (w), 968 (w), 894 (m), 841 (w), 821 (m), 781 (w), 762 (m), 712 (w), 583 (w), 513 (m) cm^{–1}. MALDI-TOF-MS (dithranol): calcd.

for C₄₈H₆₄N₈, 752.5332; found 753.5712 ([M + H]⁺). Elemental analysis: calculated for C₄₈H₆₄N₈·8H₂O: %C 64.26, %H 7.19, %N 12.49; found %C 65.04, %H 7.63, %N 12.50.

Calculations. First-principles molecular dynamics simulations, within the Car–Parrinello framework⁷ were performed on **1**.^{7,16} The Becke¹² (exchange) and Lee–Yang–Parr¹³ (correlation) functionals were employed. The core-valence interaction was described by norm-conserving Troullier–Martins pseudopotentials.²⁴ Valence electrons were expanded on a plane-wave basis set with an energy cut-off = 70 Ry and damped outside the simulation cell according to the Barnett–Landman scheme for isolated systems.¹¹ The ionic temperature was controlled with a Nosé–Hoover thermostat.¹⁵ The simulations were performed on the ICYS Linux Cluster Shizuwo.

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