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Bent Aromatic Rings in Naphthalene Derivatives

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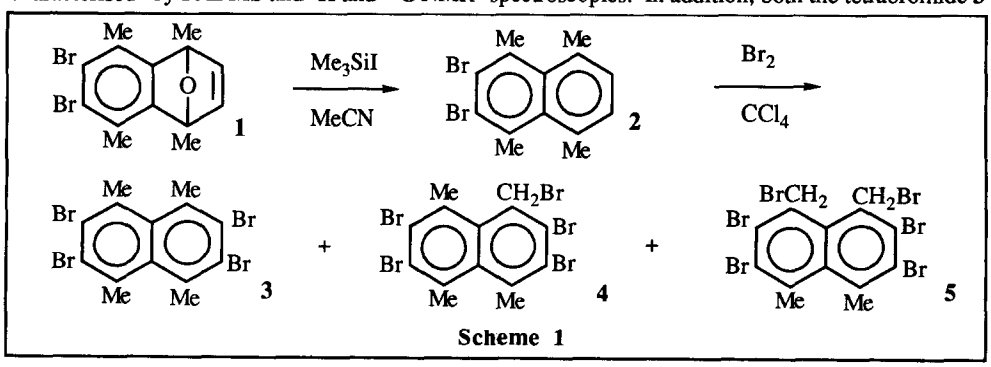
Abstract: X-Ray crystallography and dynamic ^{1}H NMR spectroscopy have revealed that 1,4,5,8-tetramethyl-, 1-bromomethyl-4,5,8-trimethyl-, and 1,8-bis(bromomethyl)-4,5-dimethyl-2,3,6,7-tetrabromonaphthalene – **3**, **4**, and **5**, respectively – have severely distorted naphthalene nuclei in the solid state that also correspond to the gross conformations that occupy appreciable ($\Delta G^{\ddagger}$ ~16 kcal mol^{-1}) energy wells in the solution state.

The development of synthetic methods, capable of producing nanosized molecular architectures,[1] is receiving more and more attention these days. In devising a molecular construction set,[2] which relies primarily upon repetitive Diels Alder reactions to build diastereoselectively macropolycycles with laterally-fused six-membered rings, we have become interested in altering the shapes – steric and electronic – and increasing the sizes of the internal voids of these belt-like molecules by introducing naphthalene, rather than benzene, units into their rigid toroidal frameworks. Thus, 2,3,6,7-tetrabromo-1,4,5,8-tetramethylnaphthalene[3] was identified as a bisaryne equivalent where the four methyl groups were incorporated to try and ensure that subsequent products did not become insoluble in organic solvents. Here, we describe the preparation (**Scheme 1**) of this tetrabromide **3**, along with the penta- and hexa-bromides **4** and **5**, resulting from benzylic as well as nuclear bromination of 2,3-dibromo-1,4,5,8-tetramethylnaphthalene **2**, obtained by deoxygenation from the known[4] endoxide **1**. The ^{1}H NMR spectra of **4** and **5** recorded in $CDCl_3$ solutions at room temperature revealed the presence of AB systems for the methylene protons associated with the bromomethyl substituents. These observations not only encouraged us to investigate the temperature dependences of the ^{1}H NMR spectra but they also prompted us to study the solid state structures of **3** and **5** by X-ray crystallography. Here, we report on our findings and their consequences for extending the range of the molecular construction set.[2]

Scheme 1 describes a more efficient synthesis of the tetrabromide **4** than that[3] previously reported. Deoxygenation[5,6] of the endoxide **1**, followed by bromination of the dibromide **2**, yielded a mixture of products from which the tetra-, penta-, and hexa-bromides **3**, **4**, and **5** were isolated[7] by silica gel chromatography. They were characterised[7] by FABMS and ^{1}H and ^{13}C NMR[8] spectroscopies. In addition, both the tetrabromide **3** and



Scheme 1

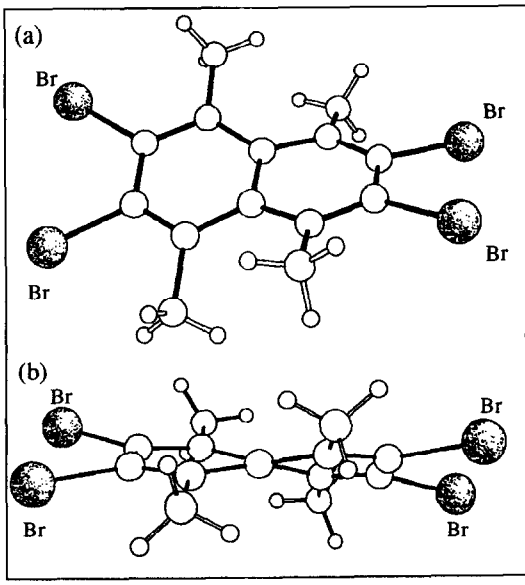


Figure 1

The solid state structure of the tetrabromide **3**

(a) viewed at an angle from above

(b) viewed along the C(9)-C(10) bond

(c) viewed along an axis bisecting the C(2)-C(3) and C(6)-C(7) bonds

the hexabromide **5** afforded good single crystals suitable for X-ray crystallography.[9] The tetrabromide **3** crystallises with two crystallographically independent molecules in the same asymmetric unit. Their gross conformations are virtually identical with a mean deviation of 0.05 Å for the least square fit of all the heavy atom centres and a maximum deviation of 0.08 Å for one of the bromine atoms. **Figure 1a** illustrates one of the pair of independent molecules. The presence of the two pairs of peri-methyl substituents results (**Figure 1b**) in a substantial twisting of the naphthalene nucleus such that the C(2)-C(3) and C(6)–C(7) bonds are inclined by *ca.* 28° to each other. The twisting is (**Figure 1c**) progressive through the nucleus, the mean torsional angle about the central C(9)–C(10) bond being *ca.* 22°. The solid state structure (**Figure 2a**) of the hexabromide **5** shows that the central naphthalene nucleus is once again

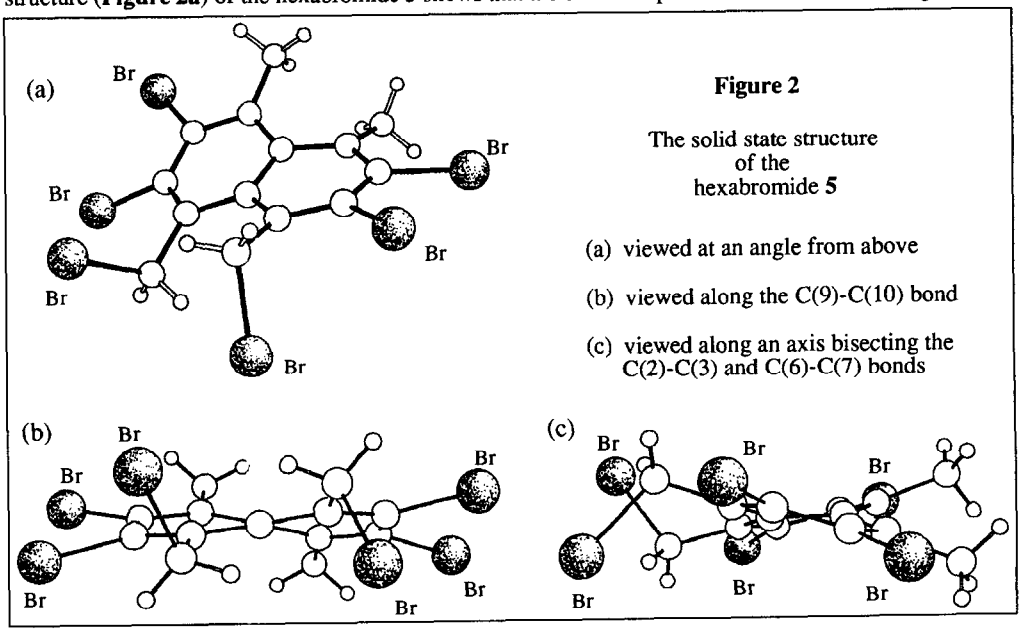


Figure 2

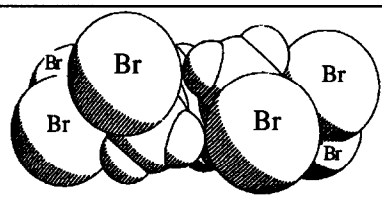
The solid state structure of the hexabromide **5**

(a) viewed at an angle from above

(b) viewed along the C(9)-C(10) bond

(c) viewed along an axis bisecting the C(2)-C(3) and C(6)-C(7) bonds

Figure 3
A space-filling representation of the solid state structure of the hexabromide **5**



severely twisted. The C(2)–C(3) and C(6)–C(7) bonds are inclined (**Figure 2b**) by *ca.* 30° to each other and the mean torsional angle of *ca.* 22° about the central C(9)-C(10) bond shows (**Figure 2c**) that the twisting is progressive throughout the naphthalene nucleus as expected. The space-filling representation (**Figure 3**) of the solid state structure of the hexabromide **5** shows how the two bromomethyl substituents interlock to reduce the peri-interaction, whilst the molecule avoids serious non-bonded interactions between nearest neighbour bromine atoms by distortion of the aromatic nucleus. A lot of research[10] has gone into the conformational analyses of substituted naphthalenes, particularly those with substituents at the 1 and 8 positions. The message that has come through from all of these investigations is that the relief of steric strain by both in-plane and out-of-plane distortions of the peri bonds has to be balanced against the loss of aromatic stabilisation on distortion of the naphthalene nucleus from planarity. Depending on the nature and the positioning of the substituents, both rotation and flipping processes have been revealed by variable temperature ^{1}H NMR spectroscopy in solution. Most relevant to **4** and **5** is the observation[11] that the free energy of activation ($\Delta G^{\ddagger}$ value) associated with site exchange for the methylene protons in 1,8-bis(bromomethyl)naphthalene is less than 8 kcal mol^{-1}. By contrast, dynamic ^{1}H NMR spectroscopic studies[12] on **4** and **5** in $CDCl_3$ revealed that the $\Delta G^{\ddagger}$ values for the same site-exchange processes are 15.6 and 16.6 kcal mol^{-1}, respectively. Clearly, the presence of bromine substituents at the 2,3,6, and 7 positions in **4** and **5** has raised appreciably the barrier(s) to rotation and/or flipping of the bromomethyl groups at the 1 and 8 positions. The diagrammatic representation (**Figure 4**) of the site exchange process for the methylene protons in **5** demonstrates that both rotation and flipping of the bromomethyl groups - as well as the consequent flipping of the bromine substituents - are required in order to exchange the sites (A and B) of the two pairs of methylene protons (H and H'). On the basis of the available evidence, we cannot identify whether rotation or flipping is the rate-determining step.

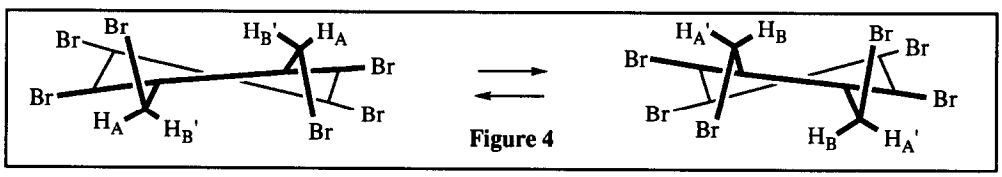


Figure 4

As to the incorporation of the 1,4,5,8-tetramethylnaphthalene nucleus into a molecular construction set during the synthesis of macropolycyclic belt-like compounds, the question of the influence of the peri interactions on subsequent synthetic steps remains to be answered.

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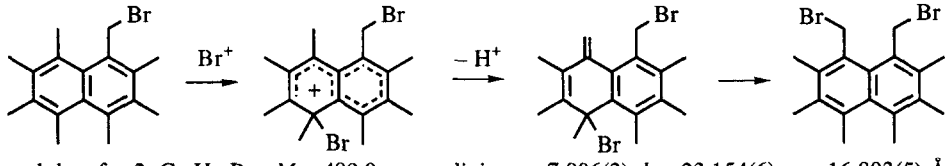
References and Footnotes

1. Wu, Z.; Lee, S.; Moore, J.S. *J. Am. Chem. Soc.* **1992**, *114*, 8730-8732.
2. Mathias, J.P.; Stoddart, J.F. *Chem. Soc. Revs.* **1992**, *21*, 215-225.
3. Sy, A.; Hart, H. *J. Org. Chem.* **1979**, *44*, 7-9. See also Hart, H.; Lai, C.; Nowokogu, G.C.; Shamouilian, S. *Tetrahedron* **1987**, *43*, 5203-5224.
4. Hart, H.; Bashir-Hashemi, A.; Luo, J.; Meador, M.A. *Tetrahedron* **1986**, *42*, 1641-1654.
5. Jung, K.-Y.; Koreeda, M. *J. Org. Chem.* **1989**, *54*, 5667-5675.
6. Preparation of **2**: Me_3SiCl (10.6 ml, 84 mmol) was added with stirring to a solution of **1** (10.0g, 28 mmol) and NaI (12.5g, 84 mmol) in dry MeCN (560 ml) maintained at room temperature under argon. After 3h, the reaction was quenched by the addition of 5% aqueous $Na_2S_2O_3$ solution (150 ml), extracted with Et_2O, and

the organic layer washed sequentially with NaCl and $Na_2S_2O_3$ solution before drying ($MgSO_4$). Concentration afforded a crude product, which was subjected to column chromatography (SiO_2:C_6H_{14}) to give a colourless solid, which was crystallised from C_6H_{14} and characterised as **2** (6.4g, 67%), m.p. 69°C [EIMS : *m/z* 340 (*M*)$^+$, 262 (*M*-Br)$^+$; ^{1}H NMR ($CDCl_3$) : δ = 2.69 (s, 6H), 2.87 (s, 6H), 7.15 (2H, s); ^{13}C NMR ($CDCl_3$) : δ = 25.5, 27.1, 126.9, 129.4, 132.8, 134.6, 136.0]

7. Preparation of **3**, **4**, and **5**: Br_2 (850 mg, 4.3 mmol) was added dropwise with stirring during 15 mins to a solution of **2** (500 mg, 1.5 mmol) in dry CCl_4 (5 ml) at room temperature. When the addition was complete, the reaction mixture was heated under reflux for 16 hr. On cooling, it was washed sequentially with 10% $Na_2S_2O_3$ solution to remove excess of Br_2 and $NaHCO_3$ solution. After drying ($MgSO_4$), the organic layer was concentrated to dryness to leave a crude product which, after chromatography (SiO_2 : C_6H_{14}) afforded three colourless solids, which were characterised as : (a) **3** (33 mg, 4.5%), m.p. 152°C, lit.[3] m.p. 150-152°C [EIMS : *m/z* 496 (M)$^+$; ^{1}H NMR ($CDCl_3$) : δ = 2.71; ^{13}C NMR ($CDCl_3$) : δ = 27.4, 127.7, 133.8, 136.5. (b) **4** (149 mg, 18%), m.p. 155°C, [EIMS : *m/z* 575 (*M*)$^+$; ^{1}H NMR ($CDCl_3$): δ = 2.70 (s, 3H), 2.72 (s, 3H), 3.02 (s, 3H), 4.87 and 5.02 (AB system, J_{AB} 10 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 27.3, 27.5, 28.0, 37.0, 128.6, 129.3 (x 2), 130.4, 132.1, 133.1, 134.2, 135.3, 136.8, 137.4. (c) **5** (57 mg, 5.9%); m.p. 210°C (decomp), [EIMS: *m/z* 654 (M$^+$); ^{1}H NMR ($CDCl_3$): δ = 2.72 (s, 6H), 4.98 and 5.58 (AB system, J_{AB} 12 Hz, 4H); ^{13}C-NMR ($CDCl_3$): δ = 28.2, 38.1, 129.5 (x 2), 131.5, 132.4, 137.0, 137.8. In the cases of **3** and **5**, crystals suitable for X-ray structural analyses were grown by slow evaporation from C_6H_{14} and C_6H_{14}/CH_2Cl_2 solutions, respectively.
8. It will be noted that there are *three* constitutionally-isomeric bis(bromomethyl)-dimethyl-2,3,6,7-tetrabromonaphthalenes. The isomers with the two bromomethyl groups 1,4 and 1,5 have *seven* heterotopic carbon atoms whereas the isomers with the two bromomethyl groups 1,8 have *eight* heterotopic carbon atoms. Since the ^{13}C NMR spectrum of the hexabromide showed (Ref. 7) *eight* resonances – assuming that one signal represents two overlapping resonances – the spectroscopic evidence favoured the constitutional assignment, 1,8-bis(bromomethyl)-4,5-dimethyl-2,3,6,7-tetrabromonaphthalene, *i.e.* **5**. Subsequently, this assignment was confirmed by X-ray crystallography. The regioselectivity which leads to the formation of the hexabromide **5** with the two bis(bromomethyl) groups 1,8 is in accordance with previous observations (Hart, H.; Reilly, J.L.; Jiang, J.B.-C. *J. Org. Chem.* **1977**, *42*, 2684-2689) on the electrophilic halogenation of octamethylnaphthalene where the following mechanistic pathway has been proposed by Hart *et al.* to account for the location of the second (peri)substitution:



9. Crystal data for **3**: $C_{14}H_{12}Br_4$, *M* = 499.9, monoclinic, *a* = 7.806(2), *b* = 23.154(6), *c* = 16.803(5) Å, β = 102.01(2)°, *V* = 2971 Å^3, space group $P2_1/n$, *Z* = 8 (two crystallographically independent molecules), ρ = 2.24 g cm^{-3}, μ(Cu-K_α) = 131 cm^{-1}, 4017 independent measured reflections (θ ≤ 58°) of which 3379 were considered to be observed [$|F_o| \geq 3\sigma(|F_o|)$]. Crystal data for **5**: $C_{14}H_{10}Br_6$, *M* = 657.7, monoclinic, *a* = 9.799(2), *b* = 16.019(3), *c* = 11.465(3) Å, β = 111.88(2)°, *V* = 1670 Å^3, space group $P2_1/c$, *Z* = 4, ρ = 2.62 g cm^{-3}, μ(Cu-K_α) = 175 cm^{-1}, 2257 independent reflections (θ ≤ 58°) of which 2154 were considered observed [$|F_o| \geq 3\sigma(|F_o|)$]. Data for both compounds were measured on a Nicolet R3m diffractometer with graphite-monochromated Cu-K_α radiation using ω-scans, In both cases, the data were corrected for absorption: maximum and minimum transmission factors for **3**, 0.391 and 0.106, and for **5**, 0.144 and 0.017. The structures were solved by direct methods and refined anisotropically to give for **3**, *R* = 0.046, R_w = 0.051, and for **5**, *R* = 0.039, R_w = 0.042. Computations were carried out using the SHELXTL and SHELXTL PLUS program systems. Further details of the crystal structures can be obtained from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.
10. For a comprehensive review, see Balasubramaniyan, V. *Chem. Revs.* **1966**, *66*, 567-641. For a representative paper from the 1970s, see Anderson, J.E.; Franck, R.W.; Mandella, W.L. *J. Am. Chem. Soc* **1972**, *94*, 4608-4614. For a recent communication, see Barth, T.; Krieger, C.; Neugebauer, F.A.; Staab, H.A. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1028-1032.
11. Robert, J.-B.; Sherfinski, J.S.; Marsh, R.E.; Roberts, J.D. *J. Org. Chem.* **1973**, *39*, 1152-1156.
12. Two methods were employed to obtain the $\Delta G^{\ddagger}$ values for the degenerate conformational change (shown in **Figure 4** for **5**) – namely the *coalescence method* (Sutherland, I.O. *Annu. Rep. NMR Spectrosc.* **1971**, *4*, 71-235) in the case of **4** and the *exchange method* (Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London 1982; Chapter 6) in the case of **5**.

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