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Synthesis and Self-association Properties of Diethynylbenzene Macrocycles

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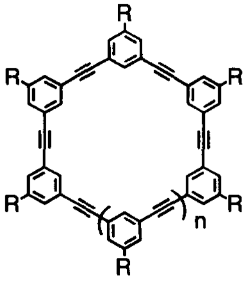
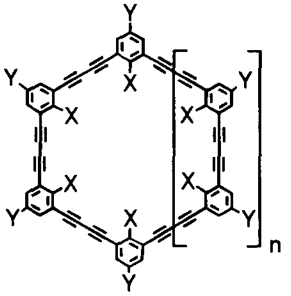
Abstract: We synthesized diethynylbenzene macrocycles (DBMs), cyclic oligomers of diethynylbenzene, having functional groups in the periphery of the macrocyclic framework and investigated their self-association properties in solution resulting from π-π stacking interaction. The tetrakis-DBM having hexadecyl ester groups showed dimerization behavior not only in chloroform-*d*, but also in *o*-dichlorobenzene-d_4. Copyright © 1996 Elsevier Science Ltd

During the last several years, conformationally rigid and shape-persistent macrocycles have attracted a great deal of interest because of their potential as functional molecules.[1] Recently, Moore et al. reported the synthesis of the phenylacetylene macrocycles, PAMs **1** (n = 0, 1, 2), and their interesting properties such as (i) self-association in solution,[2] (ii) organization to discotic liquid crystal phases,[3] and (iii) formation of organic zeolite structures in crystal.[4,5] These properties can be readily modified by the size and shape of macrocycles and the nature of the functional groups attached to the periphery of the macrocyclic framework. As a new member of this class of compounds, we designed the diethynylbenzene macrocycles (DBMs) of general formula **2**, butadiyne-bridged [4n]metacyclophanes.[6]



1 n = 0, 1, 2



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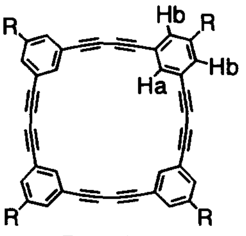
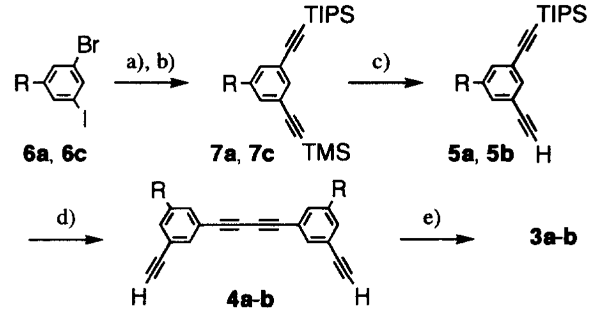


3a R = *t*-Bu
3b R = $CO_2C_{16}H_{33}$

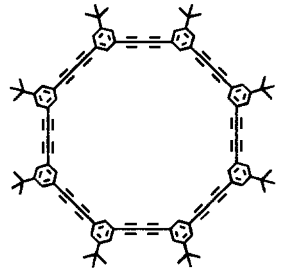
Like the acetylene-bridged counterparts **1**, the macrocycles **2** would exhibit intriguing properties due to self-organization. In particular, we were interested in the capability of the butadiyne-bridge to take part in π-π interaction between the triple bonds in addition to the aromatic-aromatic interaction. Moreover, topochemically controlled polymerization of the diyne unit of **2** in the crystalline phase would give rise to structurally ordered polyacetylene.[7] We report herein the synthesis of the diethynylbenzene macrocycles **3a-b** with a [4_4]metacyclophane framework and the self-association behavior of **3b** in solution resulting from π-π stacking interaction.

The synthetic route for **3a**-**b** is illustrated in Scheme 1. Two successive Pd^0-catalyzed couplings of bromoiodobenzene **6a** and **6c**[8] with TMS-acetylene and TIPS-acetylene gave doubly-protected monomer units **7a** (69%) and **7c** (70%), respectively. Selective deprotection of the TMS-group of **7a** with dilute LiOH yielded the monomer unit **5a** (98%). Hexadecyl ester **5b** was derived from ethyl ester **7c** by hydrolysis followed by esterification (44% for the 2 steps). Eglinton-coupling of **5a**-**b** and subsequent removal of the TIPS-group gave the dimer units **4a** (86%) and **4b** (39%). Eglinton-coupling of **4a**-**b** under high-dilution conditions gave the corresponding tetrakis-DBMs **3a**-**b**[10,11] (dimers of **4a**-**b**) in 25% and 17% yields, respectively. In the case of *t*-butyl derivative **4a**, octakis-DBM **8**[12] (tetramer of **4a**) was also obtained (13%). At this moment, however, we are not able to isolate any hexakis-DBMs (trimer of **4a**-**b**) under these conditions. We have no explanation for the absence (or very low yield, if any) of hexakis-DBMs, probably the most thermodynamically stable product. Such anomalous behavior has been frequently observed, however, in the copper-mediated oxidative coupling reactions.[7e,13] Tetrakis-DBM **3a** was also prepared by intramolecular coupling of the linear precursor **9** (Scheme 2). Pd^0-catalyzed hetero-coupling[14] of **4a** with bromoacetylene **10**, which was obtained by bromination of **7a**, gave **9** (27% for 3 steps), after removal of the TIPS-groups. High-dilution Eglinton coupling of **9** yielded **3a** in 73% yield, together with **8** (12%). DBMs **3a**-**b** and **8** are colorless solids while they darken gradually upon standing. *t*-Butyl derivatives **3a** and **8** are moderately soluble in aromatic solvents and chloroform. Hexadecyl ester **3b** is soluble in chloroform or halogenated aromatic solvents but less soluble in aromatic hydrocarbons.[15]

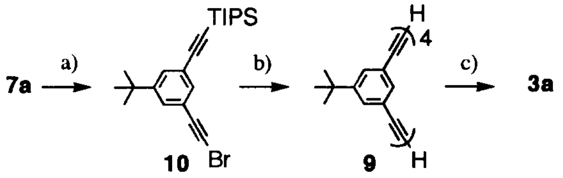


Scheme 1

a: R = t-butyl, **b**: R = $CO_2C_{16}H_{33}$, **c**: R = $CO_2C_2H_5$.
a) TMS-acetylene, $Pd(dba)_2$, CuI, PPh_3, NEt_3, 70°C; b) TIPS-acetylene, $Pd(dba)_2$, CuI, PPh_3, NEt_3, 70°C; c) LiOH, THF, H_2O, rt, 1h for **5a**; (i) LiOH, THF, H_2O, rt, 18h; (ii) $SOCl_2$, (iii) $C_{16}H_{33}OH$, Et_3N, Et_2O-benzene, 40°C for **5b**; d) (i) $Cu(OAc)_2$, pyridine, 50°C, (ii) Bu_4NF, THF, rt; e) $Cu(OAc)_2$, pyridine-benzene (3:2, 2×10^{-3} mol l^{-1}), rt.



8



Scheme 2

a) NBS, $AgNO_3$, acetone, rt; b) (i) **4a**, $Pd_2(dba)_3$, CuI, 1,2,2,6,6-pentamethylpyperidine, LiI, HMPA, benzene, rt; (ii) Bu_4NF, THF, rt; c) $Cu(OAc)_2$, pyridine-benzene (3:2, 1.0×10^{-3} mol l^{-1}), rt.

While **3a** and **8** did not exhibit concentration dependence in the ^{1}H-NMR spectra, hexadecyl ester **3b** showed obvious concentration-dependent chemical shifts of the aromatic protons. At 20°C, chemical shifts in

$CDCl_3$ of the two anisochronous aromatic protons Ha and Hb of **3b** varied from δ 8.09 to 7.96 and δ 8.06 to 7.88, respectively, as the concentration changed from 2.0×10^{-5} to 7.88×10^{-3} mol l^{-1}. This phenomenon may well be attributed to the self-association resulting from π-π stacking interactions, because there is no functionality that can engage in hydrogen bonding and only the protons directly attached to the aromatic ring show significant concentration-dependent chemical shifts. Assuming that monomer-dimer equilibrium is the predominant process of this self-association,[16] we can determine the dimerization constant K_{assoc} from the ^{1}H-NMR measurements at different concentrations, using the literature procedure.[17] By this method, K_{assoc} was found to be 38 mol^{-1} l at 20°C. Thermodynamic data were obtained from the van't Hoff plot; ΔG (293 K) = -2.1 ± 0.1 kcal mol^{-1}, $\Delta H = -5.8 \pm 0.1$ kcal mol^{-1}, and $\Delta S = -12.5 \pm 0.6$ cal mol^{-1} K^{-1}. It should be pointed out that the enthalpy of self-association for DBM **3b** is similar to that of the corresponding hexakis-PAM (**1**; n = 1, R = CO_2Bu) having six phenylacetylene units,[2] despite the fact that **3b** has only four aromatic rings. Pentakis-PAM (**1**; n = 0, R = CO_2Bu) having five aromatic rings is reported to have smaller ΔH values (-1.4 kcal mol^{-1}).[2] These results strongly suggest that the butadiyne units of **3b** take part in self-aggregation through π-π interaction between the triple bonds. While it has been reported that the ^{1}H-NMR spectra of PAMs did not exhibit concentration-dependence in an aromatic solvent (C_6D_6),[2] we found that the ^{1}H-NMR spectra of **3b** showed concentration-dependence in aromatic solvents. For example, assuming that the dimerization process is predominant, we estimate K_{assoc} to be 170 ± 40 mol^{-1} l in *o*-dichlorobenzene-d_4 at 30°C. The unexpectedly large K_{assoc} values relative to those determined in chloroform, is presumably due to unfavorable solvation to the butadiyne units by the aromatic solvent.

Thus, we have developed an efficient synthetic route to DBMs **3a-b**, the smallest members of a new class of macrocyclic compounds, and found the remarkable self-association of **3b**. Synthesis and properties of the other members, including hexakis-DBMs, are under investigation in our laboratories.

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8. Bromoiodobenzene **6a** was prepared by (i) monobromination of 4-*t*-butylacetanilide with bromine, (ii) deacetylation, (iii) iodination with benzyltrimethyammonium dichloroiodate,[9] and (iv) deamination (56% for the 4 steps). Ethyl ester **6c** was prepared by (i) monobromination of ethyl 4-aminobenzoate with NBS, (ii) iodination with ICl, and (iii) deamination (82% for the 3 steps).
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10. **3a**: colorless solid; decomposed at ca. 175°C; ^{1}H-NMR ($CDCl_3$, 270 MHz): δ = 7.79 (t, 4H, J = 1.5 Hz), 7.42 (d, 8H, J = 1.5 Hz), 1.31 (s, 36H); ^{13}C-NMR ($CDCl_3$, 67.5 MHz): δ = 152.1 (s), 138.7 (d), 128.3 (d), 122.2 (s), 83.0 (s), 75.1 (s), 34.9 (s), 31.1 (q); UV ($CHCl_3$): λ_{max} (log ε) = 339 (5.41), 315 (5.54), 296 (5.27), 281 (4.92) nm; FAB MS: m/z (relative intensity, %) 800 (100) [M^++C_6H_6+H], 721 (40) [M^+].

    3b: colorless solid; mp 133-134°C; ^{1}H-NMR ($CDCl_3$, 270 MHz, 3.0×10^{-5} mol l^{-1}): δ = 8.08 (t, 4H, J = 1.6 Hz), 8.05 (d, 8H, J = 1.6 Hz), 4.33 (t, 8H, J = 6.7 Hz), 1.78 (quintet, 8H, J = 6.7 Hz), 1.26 (s, 104H), 0.87 (t, 12H, J = 6.7 Hz); ^{13}C-NMR ($CDCl_3$, 67.5 MHz): δ = 164.5 (s), 144.7 (d), 131.6 (s), 131.2 (d), 122.8 (s), 81.9 (s), 76.2 (s), 65.9 (t), 31.9 (t), 29.7 (t), 29.7 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.3 (t), 28.6 (t), 26.0 (t), 22.7 (t), 14.1 (q); UV ($CHCl_3$): λ_{max} (log ε) = 339 (5.15), 315 (5.31), 296 (5.02), 281 (4.73) nm; FD MS: m/z 1570 [M^+].
11. So far, we have not been able to obtain single crystals of **3a** or **3b** suitable for X-ray diffraction study. According to the AM1 calculations, the triple bond of the parent hydrocarbon (tetrakis-DBM) is deformed from linearity by 12.4° ($\angle$sp-sp-sp = 173.7°, $\angle$sp-sp-sp^2 = 173.9°).
12. **8**: colorless solid; decomposed at ca. 180°C; ^{1}H-NMR ($CDCl_3$, 270 MHz): δ = 7.55 (d, 16H, J = 1.5 Hz), 7.51 (t, 8H, J = 1.5 Hz), 1.32 (s, 72H); ^{13}C-NMR ($CDCl_3$, 67.5 MHz): δ = 152.0 (s), 133.3 (d), 130.6 (d), 122.0 (s), 81.1 (s), 74.0 (s), 34.8 (s), 31.0 (q); UV ($CHCl_3$): λ_{max} (log ε) = 338 (5.10), 315 (5.15), 296 (5.01), 271 (5.07) nm; FAB MS: m/z 1441 [M^+].
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15. We also prepared tetrakis-DBM having ethyl ester groups from **7c** in a similar manner. However, we encountered difficulties in handling it because of its low solubility in most organic solvents.
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