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Synthesis and conformational behaviour of new intra-annularly linked cyclophane possessing a 1,6-dioxahexa-2,4-diyne spacer

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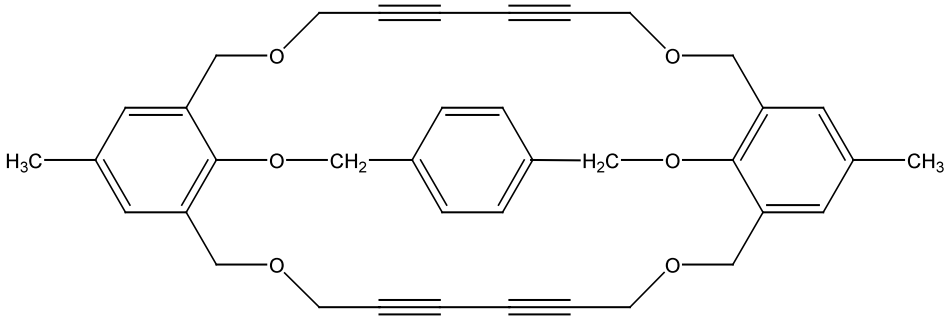
Abstract—The new intra-annularly linked cyclophane **1** was synthesized in five steps from *p*-cresol by intramolecular Eglington coupling of precyclophane **5**. From the ^{1}H NMR data, it was evident that the cyclophane **1** exists predominantly as conformer **1a** rather than **1b** at room temperature.

Cyclophanes are attractive synthetic targets due to their intriguing chemical, physicochemical, and biological properties.[1] The design and synthesis of cyclophanes possessing rigidly defined cavities and shape-persistent structures of molecular dimensions are of interest as molecular hosts in the area of host–guest chemistry.[2] Acetylenic units as bridges impart rigidity to the cyclophanes, and the number of acetylenic units in the bridge and their connectivity to the arene units control the size and shape of the cavity present in the cyclophane.[3] The synthesis of multiply bridged acetylenic thiacyclophanes,[4] [2.2.2]metacyclophane-1,9,17-triyne,[5] carbozolylacetylene-derived macrocycles,[6] twistophane ion sensors[7] and pyxophanes[8] have also been reported. Intermolecular acetylenic coupling leading to the synthesis of cyclophanes are reported mostly in poor yield.[9] Herein we wish to report the synthesis of intra-annularly linked cyclophane **1** by intramolecular Eglington coupling.

p-Cresol on treatment with formalin solution in the presence of aqueous NaOH (15%) for 5 days afforded 2,6-bis(hydroxymethyl)-4-methyl phenol **2** (80%).[10] The triol **2** was treated with *p*-xylenyl dibromide in K_2CO_3/acetone under reflux for 120 h to give the tetrol **3**[11] in 70% yield. Reaction of the tetrol **3** with 3 equiv. of PBr_3 in CH_2Cl_2 afforded the tetrabromide **4** in 80% yield. Precyclophane **5**[12] was obtained by the reaction of the tetrabromide **4** with sodium propargylate. The ^{1}H NMR spectrum of precyclophane **5** displayed a singlet at δ 2.34 corresponding to the methyl protons and another singlet at δ 2.44 corresponding to the acetylenic protons (Fig. 1). The methylene protons attached to the acetylenic carbon appeared as a singlet δ 4.20. The methylene protons attached to the arene unit appeared as a singlet at δ 4.63. The methylene protons present in the intra-annular tethering unit appeared as a singlet at δ 4.97. The aromatic protons present in the *p*-xylyl unit appeared as a singlet at δ 7.22. The aromatic protons



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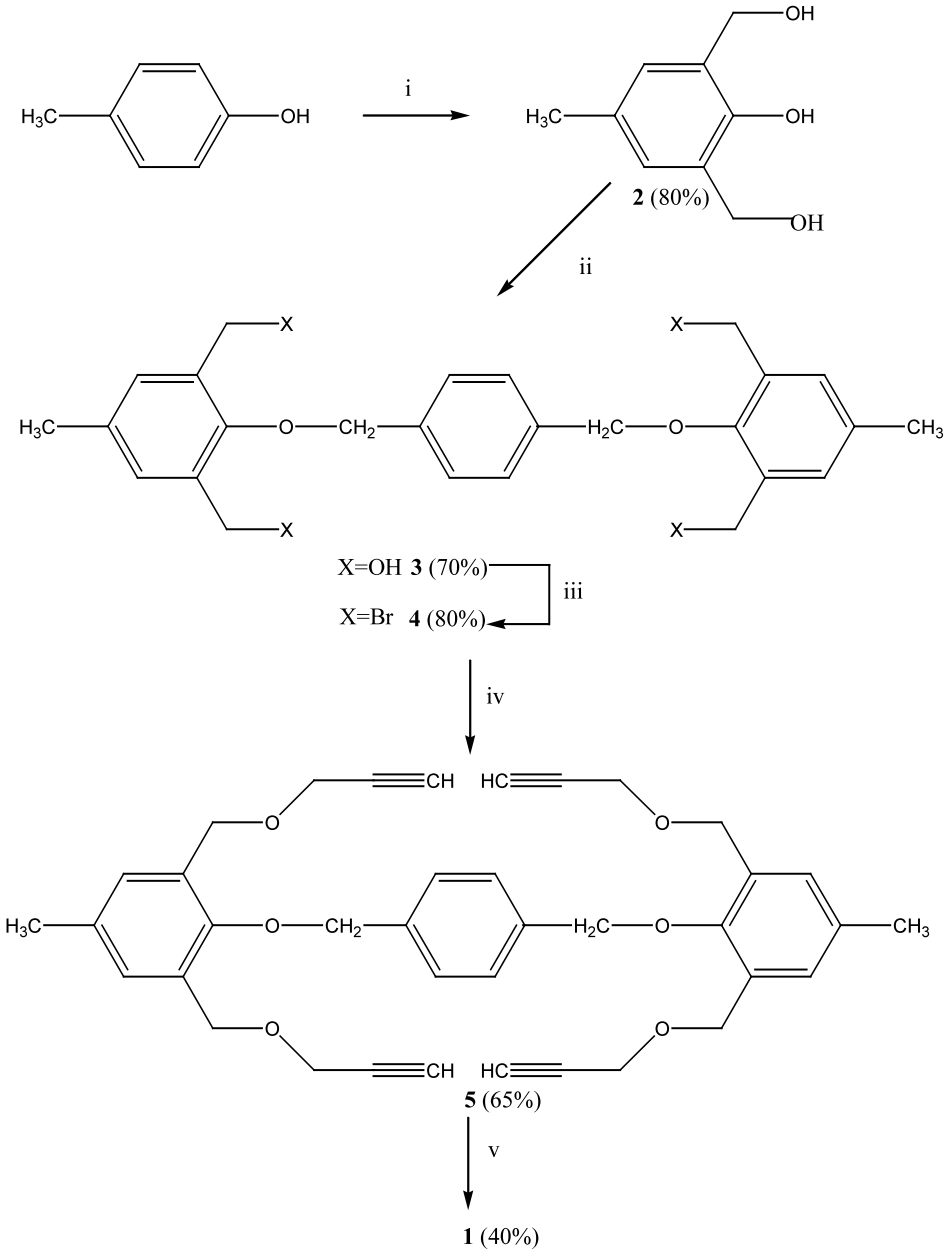
present in the *p*-cresol unit appeared as a singlet at δ 7.52. Application of the Eglington coupling to the precyclophane **5** in the presence of $Cu(OAc)_2$ in CH_3CN/pyridine (3:1) gave the intra-annularly linked diyne cyclophane **1**[13] in 40% yield. These reactions are shown in Scheme 1.

The ^1H NMR of cyclophane **1** showed a singlet at δ 2.23 corresponding to the methyl protons. The methylene protons attached to the acetylenic carbon appeared as a singlet at δ 4.27. The methylene protons attached to the arene unit also appeared as a singlet at δ 4.49. The aromatic protons present in the *p*-cresol unit appeared as a singlet at δ 7.56. It is interesting to note that the aromatic protons present in the *p*-xylyl unit appeared as two singlets δ 7.05 at δ 7.19 (Fig. 1). Although energy minimized calculations show the possibility of two conformers, the ^1H NMR data clearly indicate that the conformer **1a** is more favoured in $CDCl_3$ solution at room temperature (Scheme 2). If conformer **1b** was favoured then the aromatic protons in the *p*-xylyl unit should appear as two doublets. Since the ^1H NMR spectrum of cyclophane **1** shows two singlets for the *p*-xylenyl protons, the equilibrium is shifted towards conformer **1a** rather than **1b**. Furthermore, based on energy minimized calculations, (Fig. 2) conformer **1a** is preferred rather than (Fig. 3) **1b**.



Scheme 1. *Reagents and conditions*: (i) formalin solution, 15% NaOH, 5 days, rt; (ii) *p*-xylenyl dibromide, K_2CO_3, acetone, reflux, 5 days; (iii) PBr_3 (3 equiv.), CH_2Cl_2, rt, 12 h; (iv) NaH, propargyl alcohol, THF, reflux, 12 h; (v) $Cu(OAc)_2$, CH_3CN/pyridine (3:1), 80°C, 2 h.

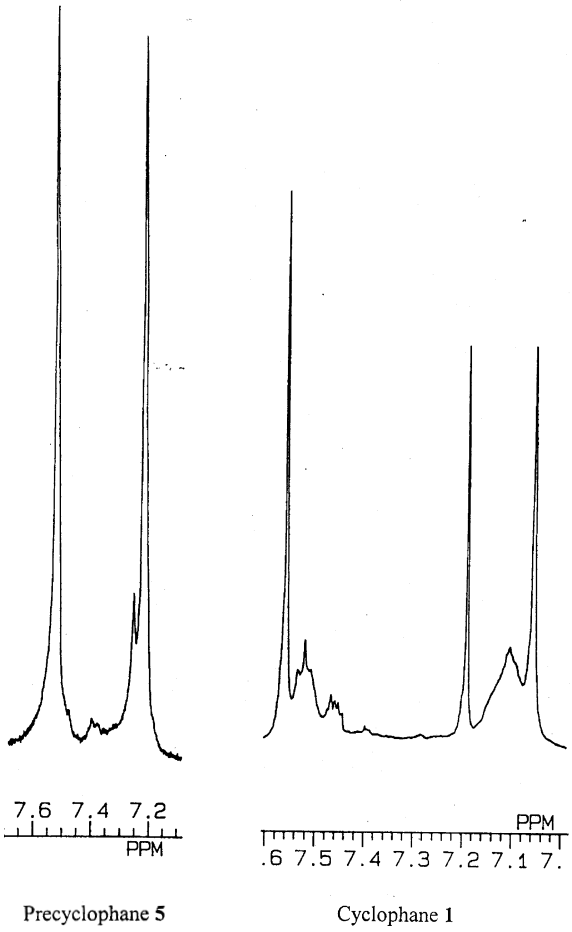


Figure 1. Comparison of the ^{1}H NMR of precyclophane **5** and cyclophane **1**.

In summary, we have synthesized a new intra-annularly linked cyclophane possessing a 1,6-dioxahexa-2,4-diyne spacer by intramolecular Eglington coupling. From the ^{1}H NMR data, it is evident that the cyclophane **1** exists mainly in conformation **1a** rather than **1b** (Scheme 2). The synthesis and conformational behaviour of other diyne cyclophanes with various tethering units instead of the *p*-xylenyl unit is under investigation.

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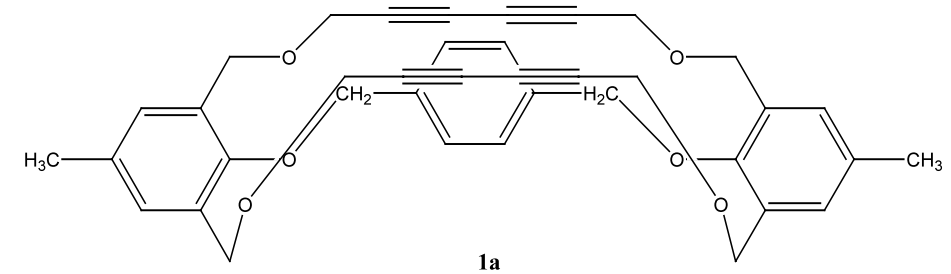
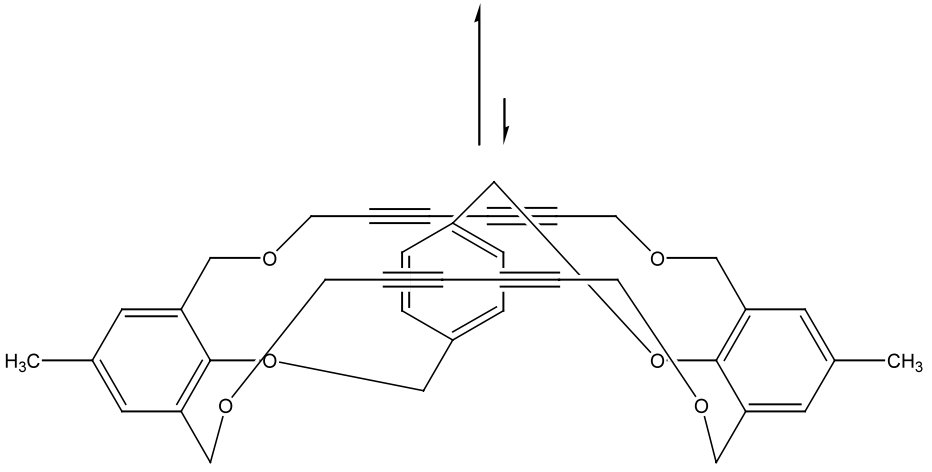


1a



1b

Scheme 2.

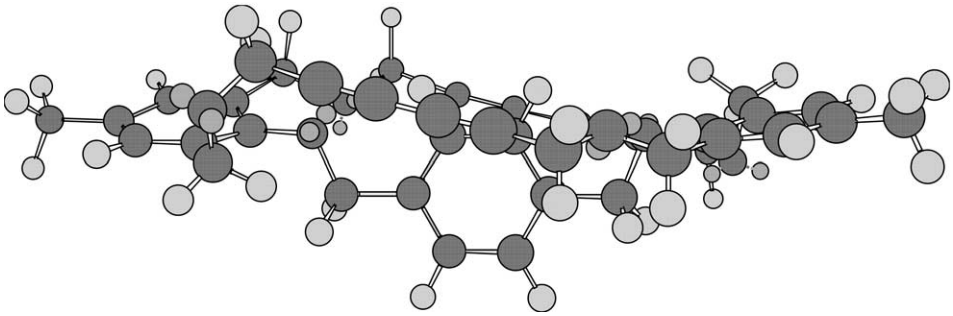


Figure 2. Conformer **1a** (MM2) energy 25.53 kcal/mol (total energy).

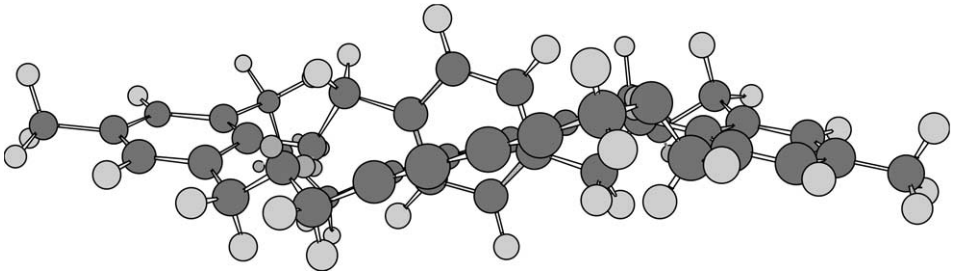


Figure 3. Conformer **1b** (MM2) energy 28.54 kcal/mol (total energy).

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11. Compound **3**: Yield 70%, melting point 185°C; IR (cm^{-1}) 3328, 2912, 1593, 1452, 1356, 1200, 1142, 1062, 1020, 979, 864, 796; ^1H NMR ($CDCl_3$/DMSO-d_6) 400 MHz δ 2.23 (s, 6H), 4.62 (s, 8H), 4.95 (s, 4H), 7.23 (s, 4H), 7.64 (s, 4H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) 100.4 MHz: 20.9, 58.7, 75.8, 127.9, 128.3, 132.9, 134.5, 137.3, 151.5; m/z: 438 (M^+). Anal. calcd for $C_{26}H_{30}O_6$: C, 71.21; H, 6.90. Found: C, 71.14, H 6.84%.
12. Compound **5**: Yield 65%, melting point 85°C; IR (cm^{-1}) 3296, 2922, 2860, 2359, 1618, 1469, 1352, 1259, 1207, 1078, 864, 661, 630; ^1H NMR ($CDCl_3$/DMSO-d_6) 400 MHz δ 2.34 (s, 6H), 2.44 (s, 4H), 4.20 (s, 8H), 4.62 (s, 8H), 4.96 (s, 4H), 7.22 (s, 4H), 7.52 (s, 4H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) 100.4 MHz: 20.8, 57.5, 66.8, 76.7, 74.8, 79.7, 127.9, 130.5, 131.2, 133.9, 137,3, 153.7; m/z: 590 (M^+). Anal. calcd for $C_{38}H_{38}O_6$: C, 77.26; H, 6.48. Found: C, 77.22; H, 6.44%.
13. Compound **1**: Yield 40%, melting point >300°C; IR (cm^{-1}) 2963, 2359, 1629, 1519, 1400, 1209, 1145, 1074, 993, 927, 866, 798, 661, 630; ^1H NMR ($CDCl_3$/DMSO-d_6) 400 MHz δ 2.23 (s, 6H), 4.27 (s, 8H), 4.49 (s, 8H), 5.02 (s, 4H), 7.06 (s, 2H), 7.19 (s, 2H), 7.56 (s, 4H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) 100.4 MHz: 22.9, 58.4, 68.2, 71.3, 75.9, 129.7, 130.7, 131.8, 132.1, 132.8, 133.9, 136.9, 153.4; m/z: 586 (M^+). Anal. calcd for $C_{38}H_{34}O_6$: C, 77.80; H, 5.84. Found: C, 77.77; H, 5.81%.