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Synthesis of Functionalised Cyclophanes with Cage Structure; Via An Unusual Termolecular Collision[1]

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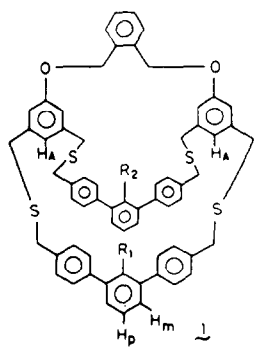
Abstract : Coupling of the tetrathiol **11** with two equivalents of the dibromide **6**,**7** & **8** under high dilution technique in the presence of KOH in benzene - ethanol afforded the cyclophanes **1a**, **1c** & **1b** respectively. Similarly cyclophane **1d** was obtained from the tetrathiol **11** and tetrabromide **9**.

Complexation of guest molecules as well as metal ions by cyclophane hosts has been reported as early as 1974[2]. However the synthesis of such cyclophanes & other functionalised cyclophanes[3] has gained additional impetus recently[4]. We wish to report the synthesis of novel functionalised cyclophanes **1** & **13** by a simple route. Cyclophane **1** has the cage structure and forms metal ion complexes.



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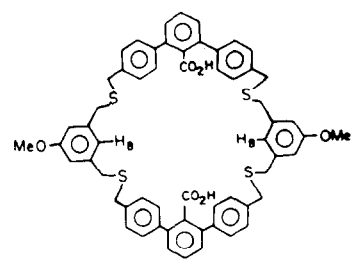
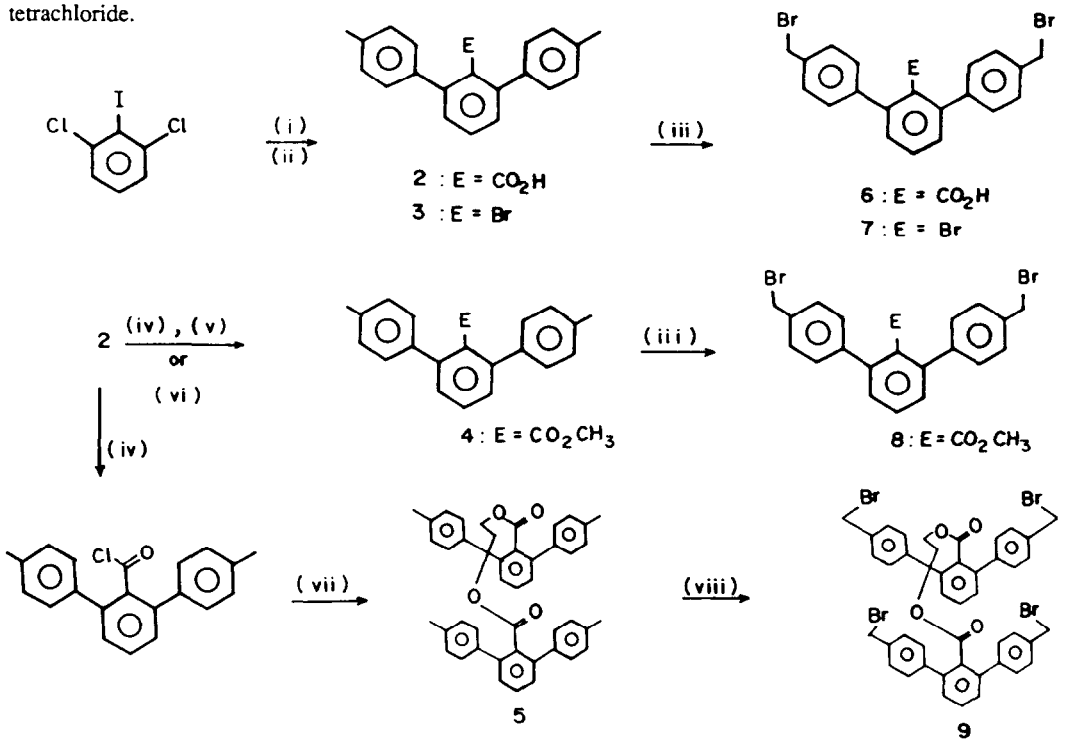


13

The m-terphenyl frame work in **1** is obtained by the known tandem aryne sequence[5]. Addition of three equivalents of p-tolylmagnesium bromide to 2,6-dichloroiodobenzene followed by quenching with CO_2 or Br_2 resulted in the formation of **2** or **3** in excellent yields (Scheme 1). **2** on treatment with either CH_2N_2 or $SOCl_2$ followed by refluxing in excess methanol afforded **4** quantitatively. Reaction of the disodium salt of ethylene glycol with the acid chloride of **2** gave the ethylene glycol ester **5** (mp 238°; 35%). Two fold radical bromination of **2**, **3** & **4** with NBS in CCl_4 gave **6** (mp 175°), **7**[6] and **8** (mp 110°) in 65%, 75% & 60% respectively. Four fold radical bromination on the ester **5** with NBS in CCl_4 afforded the tetrabromide **9** in 50% yield.

Bisalkylation of o-xylene-α,α'-dibromide with ethyl-5-hydroxyisophthalate in K_2CO_3/DMF afforded the tetraester **10** (mp 82°; 80%). The tetrathiol **11** (mp 58°) was obtained in a overall yield of 40% from the tetraester **10** by the application of the conventional route[7]. LAH reduction of **10** in THF gave the

corresponding tetraalcohol which on reaction with $SOCl_2$ in CH_2Cl_2 in the presence of pyridine gave the tetrachloride. The tetrathiol **11** was obtained by the hydrolysis of the thiouronium salt derived from the tetrachloride.



(i) p-tolylmagnesium bromide (3 eq.), THF, Δ; (ii) E, H_3^+O (E=CO_2, Br^+); (iii) NBS(2eq.), CCl_4,Δ; (iv) $SOCl_2$, Py, CH_2Cl_2; (v) CH_3OH,Δ; (vi) CH_2N_2, THF; (vii) $HOCH_2CH_2OH$, NaH, DMF; (viii) NBS(4 eq.), CCl_4,Δ.

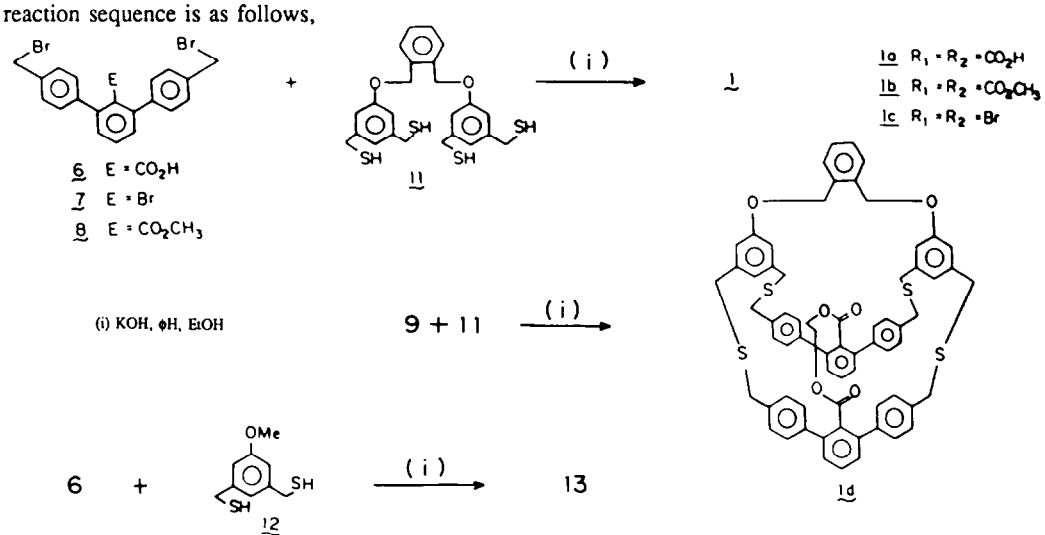
Scheme 1

Coupling of the tetrathiol **11** with two equivalents of the dibromide **6** under high dilution technique in the presence of KOH in benzene-ethanol afforded the cyclophane **1a** (mp 232° dec; 40%) (Scheme 2). The high polarity of **1a** in TLC and in column chromatography could be due to the presence of two carboxylic acid group in **1a**. The ^{1}H NMR[8] spectrum of **1a** showed two singlets for eight protons each at δ 3.31 & 3.70 and another singlet for four benzylic protons at δ5.01. In the aromatic region two broad singlets are observed at δ6.30 & 6.93 for four protons and two protons (H_A) respectively for the aromatic ring that had the thiol unit. In order to rule out the other possible mode of coupling involving the dibromide **6** with the dithiol groupfrom the same aromatic ring system, the diacid **1a** was treated with NaOMe. The chemical shift of H_A in unaffected in the ^{1}HNMR spectrum of the sodium salt of **1a**. Structure **1a** is further substantiated by ^{13}CNMR[9]. Further the four benzylic protons of the sodium salt of **1a** appeared at δ4.6 showing the shielding effect of the carboxylate anion on these protons. The ^{1}HNMR the sodium salt of **1a** displayed a triplet at δ6.87 and a

doublet at δ6.47 for H_p and H_m protons respectively. Another distinct change is the variation of the chemical shift of one of the ABquartet at δ7.07 & 7.09. In order to further confirm this mode of coupling, the dibromide **6** was coupled with the 3,5-bis(mercaptomethyl)anisole **12**[10]. The high polarity and high mp of **13** could be due to the presence of two carboxylic acid functionality. The ^{1}HNMR[11] spectrum of **13** showed two broad siglets at δ6.60 for four protons and at δ6.76 for two proton (H_B) for the aromatic protons derived from the thiol unit. The shielding effect observed on the H_B proton of **13** could be due to the electron releasing effect of OMe group. The chemical shift of the H_B protons are not affected in the disodium salt of **13**, thus favouring the dimeric structure. The presence of molecular ion at m/z 996 in FAB MS further supported the dimeric structure **13**.

Similarly coupling of the tetrathiol **11** with two equivalents of the dibromide **8** gave the cyclophane **1b** (mp 285° dec ; 50%). **1a** has been also converted into **1b** by the following two different routes. The cyclophane **1a** on treatement with CH_2N_2 in THF afforded quantitatively the dimethyl ester **1b** as evidenced by ^{1}H & ^{13}CNMR[12]. Alternatively **1b** (80%) was prepared by the reaction of the cyclophane **1a** with $SOCl_2$ in CH_2Cl_2 in the presence of few drops of pyridine followed by refluxing in CH_3OH . Further coupling of the tetrathiol **11** with two equivalents of the dibromide **7** gave the cyclophane **1c**[13] (mp 260° dec; 35%). The bromocyclophane **1c** when treated with two equivalents of n-BuLi at -78° for 2hr followed by quenching with CO_2 (dry CO_2 bubbled through the reaction mixture for 10-12 hr) afforded the **1a** (40%). The generation of dilithium salt has the scope of introducing various other functionality at C_2. position of the m-terphenyl frame work.

With a view to synthesis a cage cyclophane the tetrathiol **11** was coupled with one equivalent of the tetrabromide **9** to yield the cyclophane **1d** (mp 295°dec ; 35%) as evidenced by the ^{1}HNMR & ^{13}CNMR[14].The reaction sequence is as follows,



Scheme 2

Synthesis of such cage cyclophanes with functionalised cavity and its complexing activity with guest molecules is under further investigation.

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References and Notes

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8. ^{1}HNMR (DMSO-d_6, 400MHz) for **1a** (gave satisfactory elemental analysis) : ∂ 3.3 (s.8H), 3.7 (s 8H), 5.0 (s,4H), 6.3 (s, 4H), 6.93 (s, 2H), 7.15 (ABq, 8H, J =8.8 Hz), 7.26 (ABq, 8H, J=8.8 Hz), 7.31-7.33 (m,4H), 7.37 (d, 4H, J=8 Hz), 7.52 (t, 2H, J=8 Hz), 12.6 (bs, 2H).
9. ^{13}C NMR (DMSO-d_6, 100MHz) for **1a** : 34.400 (-CH_2S-), 35.235 (- SCH_2-), 67.805 (-OCH_2-), 114.484, 121.903, 128.237, 128.525, 128.565, 128.692, 129.193, 129.233, 135.015, 135.492, 138.088, 138.771, 138.862, 139.955, 158.413(15Ar-C), 170.343 (-CO_2H).
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11. ^{1}H NMR (DMSO-d_6, 400 MHz) for 13 (gave satisfactory elemental analysis); Δ 3.58 (s, 8H), 3.62 (s,8H), 3.69 (s, 6H), 6.6 (s, 2H), 6.76 (s, 4H), 7.16-7.25 (m, 20H), 7.37 (t, 2H, J=8.34 Hz) 12.62(bs,2H).
12. ^{1}H NMR ($CDCl_3$, 400MHz) for **1b** (gave satisfactory elemental analysis) : δ3.2 (s, 8H), 3.7 (s, 14H), 5.0 (s, 4H), 6.35(s, 4H), 7.0 (s, 2H), 7.2-7.5(m, 26H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ34.396 (-CH_2S-), 35.747 (-SCH_2-), 51.700 (-CO_2CH_3-), 67.805 (-OCH_2-), 114.602, 121.903, 128.050, 128.263, 128.475, 128.991, 129.037, 129.265, 133.773, 135.139, 137.568, 139.010, 139.556, 139.799, 158.591 (15Ar-C), 169.520(-CO_2CH_3-).
13. ^{13}C NMR ($CDCl_3$, 100MHz) for **1c** (gave satisfactory elemental analysis) : δ 35.045 (-CH_2S-), 35.880 (-SCH_2-), 66.769 (-OCH_2-), 114.325, 121.626, 126.848, 127.516, 127.744, 128.563, 129.277, 129.656, 130.278, 134.756, 137.443, 139.598, 140.494, 143.423, 158.316 (15Ar-C).
14. ^{1}H NMR (DMSO-d_6, 400MHz) for **1d** (gave satisfactory elemental analysis); Δ3.66 (ABq, 4H, J = 10), 3.72 (s, 4H), 3.77 (ABq, 4H, J=10 Hz), 3.85 (ABq, 4H, J=16 Hz), 3.96 (ABq, 4H, J=16 Hz), 5.1 (s,4H), 6.6 (s, 4H), 6.95 (s, 2H), 7.05 (ABq, 8H, J=8.8 Hz), 7.17 (ABq, 8H, J=8.8 Hz), 7.20-7.25 (m, 4H), 7.35 (d, 4H, J=8 Hz), 7.52 (5, 2H, J=8,8 Hz).^{13}C NMR ($CDCl_3$, 100MHz), (: δ35.534 (-CH_2S-), 35.792 (-SCH_2-), 61.883 (-OCH_2CH_2O-), 68.867(-OCH_2-), 114.222, 121.994, 126.381, 126.624, 126.684, 128.020, 128.354, 128.597, 129.037, 129.553, 137.795, 138.994, 139.753, 139.966, 158.257 (15Ar-C), 169.778 (CO).

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