Synthesis of thiophenophanes with ethyne and ethene spacers

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Abstract
Synthesis of thiophenophanes with ethyne and ethene spacers has been achieved by *O*-alkylation, Glaser-Eglinton and McMurry coupling techniques.

Keywords: Electron rich cyclophanes, Glaser-Eglinton coupling, Sonogashira coupling, stilbenophanes

Introduction

Remarkable advances have been made in the area of cyclophanes having acetylenic linkages in recent decades. The ability of the alkyne unit(s) in generating the cyclophane cavity with shape persistence[1] has often reflected its ability to complex metal ions or organic molecules,[2] or to self-aggregate in some cases.[3,4] The advantage of using acetylene linkage is the linearity of the ethynic bond, which turns the molecule more rigid and creates non-collapsible cavity.[5,6] Further the molecules will possess molecular co-planarity due to the presence of *sp* hybridised carbon atoms. The cavity size of a macrocycle can be altered by increasing or decreasing the number of acetylene linkages in the molecule.[7] Owing to the well-ordered structures and infinite conjugation of these macrocycles, they possess interesting optical, electronic, and magnetic properties and can be ideal materials in organic light-emitting diodes, (OLEDs),[8] organic field-effect transistors (OFETs),[9]nonlinear optics (NLOs)[10] and organic solar cells.[11] Cyclophanes with excess non-bonding electrons or dense π-electron clouds could be regarded as electron rich cyclophanes.[12] Electron rich cyclophanes like stilbenophanes[13]are important class of supramolecular structures in the cyclophane family since they can undergo functional group transformations and interesting photoisomerization.

Herein we report the synthesis of thiophenophanes **1**, **2**, **3** and **3a** with ethyne spacers and **4** with ethene spacer(Figure 1).

Results and discussion

2,5-Bis(4-(bromomethyl)phenyl)thiophene **5**[14] on *O*-alkylation with 2.1 equiv. of propargyl alcohol **6** in the presence of NaH in refluxing THF afforded 2,5-bis(4-((prop-2-ynyloxy)methyl)phenyl)thiophene **7** in 63 % yield. The ^{1}H NMR spectrum of 2,5-bis(4-((prop-2-ynyloxy)methyl)phenyl)thiophene **7** displayed a singlet at δ 2.40 corresponding to the acetylenic hydrogens. The methylene hydrogens attached to the acetylenic carbon appeared as a singlet at δ 4.13 and the methylene hydrogens attached to the phenyl unit appeared as a singlet at δ 4.58. The eight hydrogens in the benzene ring appeared as an AB quartet at δ 7.41 – 7.61 (J = 8.0 Hz). The two hydrogens in the thiophene ring appeared as singlet at δ 7.29. In the ^{13}C NMR spectrum, bispropargylated precyclophane **7** showed the *O*-methylene carbon signals at δ 56.2 and 70.1 along with eight signals of carbon in the aromatic region.

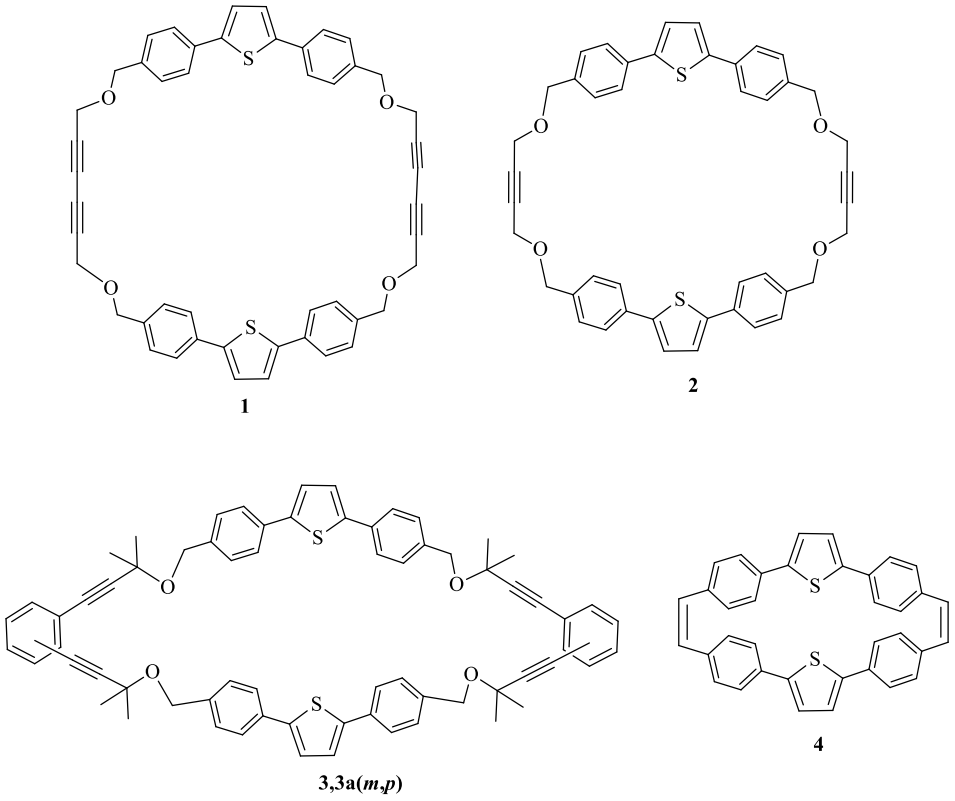
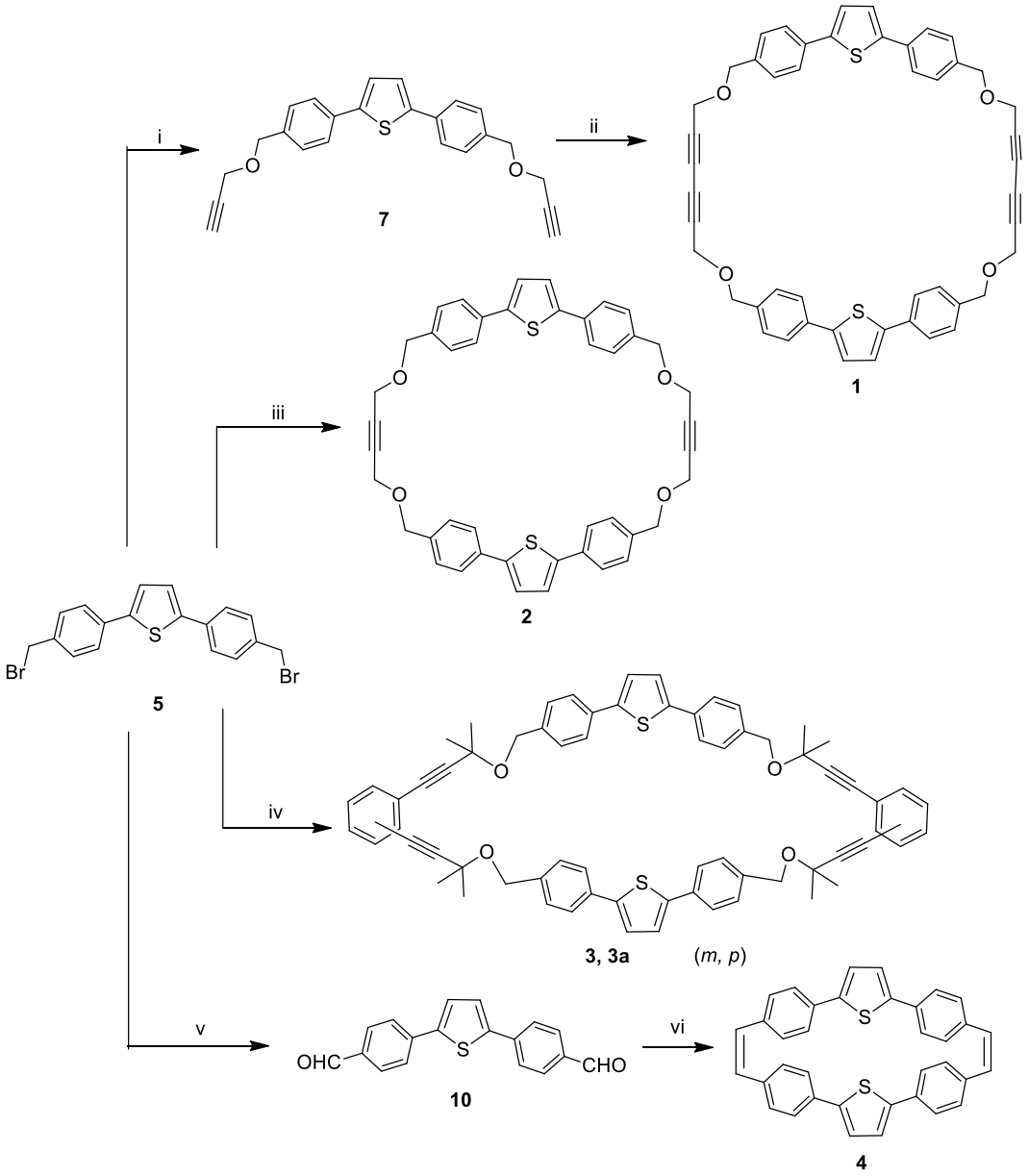


Figure 1. Structures of thiophenophanes **1, 2, 3, 3a** and **4.**

The bispropargylated precyclophane **7** undergoes Glaser-Eglinton coupling in the presence of $Cu(OAc)_2$ in CH_3CN and pyridine at 70 °C for 12 h to give the thiophenophane **1** in 69 % yield. The ^{1}H NMR spectrum of thiophenophane **1** displayed three singlets at δ 4.12, 4.54 and 7.20 for eight, eight and four hydrogens corresponding to the *O*-methylene hydrogens attached to the phenyl unit, *O*-methylene hydrogens attached to the diyne unit and the hydrogen on the

thiophenyl group respectively. The sixteen hydrogens in the benzene ring appeared as an AB quartet at δ 7.29 – 7.53 (J = 8.0 Hz). In the ^{13}C NMR spectrum, thiophenophane **1** showed the *O*-methylene carbon signals at δ 56.0 and 69.7 along with eight signals of carbon in the aromatic region. FAB-MS and elemental analysis are also in accordance with the proposed structure **1**.



Scheme 1. Reagents and conditions: (i) 2.1 equiv. propargyl alcohol **6**, NaH, THF, reflux, 12 h (63%). (ii) $Cu(OAc)_2$, CH_3CN/pyridine (3:1), 80 °C, 12 h (69%). (iii) 1 equiv. but-2-yne-1,4-diol **8**, NaH, THF, reflux, 12 h (57%). (iv) 1 equiv. 1,3-bis- or 1,4-bis-(3-hydroxy-3-methylbut-1-ynyl)benzene **9**/**9a**, NaH, THF, reflux, 12 h (49%, 53%). (v) $NaIO_4$, DMF, reflux, 1 h (69%). (vi) 20 equiv. $TiCl_4$, 40 equiv. Zn, THF, pyridine, reflux, 12 h (68%).

2,5-Bis(4-(bromomethyl)phenyl)thiophene **5** on *O*-alkylation with but-2-yne-1,4-diol **8** in the presence of NaH in refluxing THF afforded the thiophenophane **2** in 57 % yield. The ^{1}H NMR spectrum of thiophenophane **2** displayed three singlets at δ 4.21, 4.50 and 7.40 for eight, eight and four hydrogens corresponding to the *O*-methylene hydrogens attached to the phenyl unit and the acetylene unit and the thiophene ring system respectively. The hydrogens in the benzene ring appeared as two doublets at δ 7.69 – 7.72 (*J* = 8.0 Hz) and 7.81 – 7.83 (*J* = 8.0 Hz) integrating for eight hydrogens each. In the ^{13}C NMR spectrum, thiophenophane **2** showed the *O*-methylene carbon signals at δ 58.6 and 65.7 along with seven signals of carbon in the aromatic region. The structure of the thiophenophane **2** was also confirmed from mass and elemental analysis.

In a similar manner, thiophenophanes **3** and **3a** were synthesized from the corresponding diol **9** and **9a** obtained by the Sonogashira coupling procedure. The structure of the thiophenophanes **3** and **3a** was confirmed from ^{1}H NMR, ^{13}C NMR, FAB-MS and analytical data.

2,5-Bis(4-(bromomethyl)phenyl)thiophene **5** on treatment with sodium periodate in refluxing DMF afforded 2,5-bis[4-(formyl)phenyl]thiophene **10** in 69 % yield. The ^{1}H NMR spectrum of 2,5-bis[4-(formyl)phenyl]thiophene **10** displayed the aldehydic hydrogens at δ 9.99 , the thiophenic hydrogens at δ 7.46, in addition to the other aromatic hydrogens. In the ^{13}C NMR spectrum of 2,5-bis[4-(formyl)phenyl]thiophene **10**, the aldehydic carbon signal appeared at δ 191.4, in addition to the signals of aromatic carbons.

Treatment of one equivalent of the dialdehyde **10** with twenty equivalents of $TiCl_4$ and forty equivalents of Zn in THF under McMurry coupling conditions afforded the thiophenophane **4** in 68 % yield (Scheme 1). In the ^{1}H NMR spectrum, thiophenophane **4** displayed a singlet at δ 7.28 for the four thiophene hydrogens, two doublets at δ 7.18 – 7.21 (*J* = 7.5 Hz) and 7.67 – 7.70 (*J* = 7.2 Hz) for the *cis* olefinic hydrogens integrating for two protons each and two more doublets at δ 7.38 – 7.40 (*J* = 7.2 Hz) and 7.51 – 7.54 (*J* = 7.5 Hz) for the *ortho* substituted hydrogens integrating for eight hydrogens each. The ^{13}C NMR of thiophenophane **4** displayed signals for seven carbons, which further confirmed the structure of thiophenophane **4**. The structure **4** was also confirmed from mass and elemental analysis.

Thiophenophanes with ethyne and ethene spacers have been synthesized in moderately good yield.

Conclusions

In conclusion, we have successfully synthesized electron rich thiophenophanes with ethyne and ethene spacers. The complexation of thiophenophanes with electron deficient guest molecules is under way.

Experimental Section

General. All melting points are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 and 400 MHz spectrometers. The chemical shifts are reported in ppm (δ) with TMS as internal standard and coupling constant (*J*) are expressed in Hz. EI-MS spectra were recorded on JEOL DX-303 mass spectrometer. The FAB-MS spectra were recorded on JEOL SX 102/DA-6000 mass spectrometer using *p*-nitrobenzyl alcohol (NBA) as matrix. Elemental analyses were performed on a Perkin-Elmer 240B elemental analyzer.
Column chromatography was performed on silica gel (ACME, 100 -200 mesh). Routine monitoring of the reaction was made using thin layer chromatography developed on glass plates coated with silica gel-G (ACME) of 25mm thickness and visualized with iodine.

General procedure for *O*-alkylation using sodium hydride
To a solution of sodium hydride (4 mmol) in dry THF (50 mL), alcohol (4 mmol) was added dropwise and stirred for 0.5 h at room temperature. Then the dibromide **5** (1 mmol) was added slowly to the reaction mixture and was refluxed for 12 h. The reaction mixture was allowed to attain room temperature and then methanol (5 mL) was added to the reaction mixture to quench the excess sodium hydride and the reaction mixture was evaporated to dryness. The residue obtained was extracted with CH_2Cl_2 (2×100 mL), washed with water (2×100 mL), brine (100 mL) and dried over anhydrous Na_2SO_4. Evaporation of the organic layer gave a residue, which was purified by column chromatography using suitable eluent as mentioned for each compound to give the corresponding *O*-alkylated product.
2,5-Bis[4-((prop-2-ynyloxy)methyl)phenyl]thiophene (7). Following the general procedure for *O*-alkylation using sodium hydride, 2,5-bis[4-((prop-2-ynyloxy)methyl)phenyl]thiophene **7** was obtained as a yellow solid from 2,5-bis[4-(bromomethyl)phenyl]thiophene **5** (0.42 g, 1 mmol), propargyl alcohol **6** (0.24 g, 4 mmol) and sodium hydride (0.10 g, 4 mmol)**.** The product was purified by column chromatography using hexane/$CHCl_3$ (3:2) as eluent. Yield 63%, mp 189 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.40 (s, 2H), 4.13 (s, 4H), 4.58 (s, 4H), 7.29 (s, 2H), 7.41 – 7.61 (AB q, 8H, J = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 56.2, 70.1, 73.7, 78.5, 123.1, 124.6, 129.4, 132.8, 135.7, 142.2. MS, (EI, 70eV) m/z 372.2 (M^+, 100%), 373.2 (M+1, 31.0%), 374.2 (M+2, 12.6%), 317.1 (22.4%), 262.0 (10.1%) ; Anal. Calcd for $C_{24}H_{20}O_2S$: C, 77.39; H, 5.41%. Found: C, 77.28; H, 5.50%.
2(1,4),13(1,4),15(1,4),26(1,4)-Tetrabenzena-7,14,29,36-tetraoxa-1(2,5),14(2,5)-dithiophena cyclohexacosanaphane-6,8,19,21-tetrayne (1). A solution of bispropargylated precyclophane **7** (0.20 g, 1 mmol) and $Cu(OAc)_2.H_2O$ (0.50 g, 2.5 mmol) in a mixture of CH_3CN (12 mL) and pyridine (3 mL) was stirred at 70 °C for 12 h. The reaction mixture was poured into dilute HCl (250 mL, 5% HCl), extracted with $CHCl_3$ (250 mL), washed with water (200 mL), brine (100 mL) and dried over anhydrous Na_2SO_4. The crude product obtained after the evaporation of the organic layer gave a residue, which was purified by column chromatography over SiO_2 using hexane/$CHCl_3$ (3:2) as an eluent to give the thiophenophane **1** as a yellow solid. Yield 69%, mp

300 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 4.12 (s, 8H), 4.54 (s, 8H), 7.20 (s, 4H), 7.29 – 7.53 (AB q, 16H, *J* = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 56.0, 69.7, 70.9, 76.5, 123.5, 125.6, 129.7, 135.2, 137.4, 143.3. MS, (FAB-MS) m/z 740 (M^+); Anal. Calcd for $C_{48}H_{36}O_4S_2$: C, 77.81; H, 4.90%. Found: C, 77.92; H, 4.81%.

2(1,4),11(1,4),13(1,4),22(1,4)-Tetrabenzena-7,12,27,32-tetraoxa-1(2,5),12(2,5)-dithiophena cycloeicosanaphane-6,17-diyne (2). Following the general procedure for *O*-alkylation using sodium hydride, thiophenophane **2** was obtained as a yellow solid from 2,5-bis[4-(bromomethyl)phenyl]thiophene **5** (0.42 g, 1 mmol), but-2-yne-1,4-diol **8** (0.09 g, 1 mmol) and sodium hydride (0.10 g, 4 mmol). The product was purified by column chromatography using hexane/$CHCl_3$ (2:3) as eluent. Yield 57%, mp 300 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 4.21 (s, 8H), 4.50 (s, 8H), 7.40 (s, 4H), 7.69 – 7.72 (d, 8H, *J* = 8.0 Hz), 7.81 – 7.83 (d, 8H, *J* = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 58.6, 65.7, 76.0, 121.2, 123.4, 124.1, 125.2, 128.9, 136.9. MS, (EI, 70eV) m/z 692 (M^+, 10.8%), 428.1 (54.4%), 260.2 (25.1%); Anal. Calcd for $C_{44}H_{36}O_4S_2$: C, 76.27; H, 5.24%. Found: C, 76.36; H, 5.13%.

2(1,4), 8(1,3),14(1,4),16(1,4), 22(1,3),28(1,4)-Hexabenzena-5,5,11,11,19,19,25,25-octamethyl-7,19,34,46-tetraoxa-1(2,5),15(2,5)-dithiophenacyclooctacosanaphane-6,9,20,23-tetrayne (3). Following the general procedure for *O*-alkylation using sodium hydride, thiophenophane **3** was obtained as a yellow solid from 2,5-bis[4-(bromomethyl)phenyl]thiophene **5** (0.50 g, 1.2 mmol), 1,3-bis(3-hydroxy-3-methylbut-1-ynyl)benzene **9** (0.29 g, 1.2 mmol) and sodium hydride (0.12 g, 4.7 mmol). The product was purified by column chromatography using hexane/$CHCl_3$ (2:3) as eluent. Yield 49%, mp 300 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.91 (s, 24H), 5.32 (s, 8H), 7.19 (s, 4H), 7.26 – 7.42 (m, 8H), 7.71 – 7.86 (AB_q, 16H, *J* = 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 31.6, 63.7, 65.3, 77.3, 98.7, 121.1, 122.3, 123.1, 124.5, 124.8, 127.7, 129.4, 132.5, 135.6, 142.3. MS, (FAB-MS) m/z 1004 (M^+); Anal. Calcd for $C_{68}H_{60}O_4S_2$: C, 81.24; H, 6.02%. Found: C, 81.15; H, 5.91%.

2(1,4), 8(1,4),14(1,4),16(1,4), 22(1,4),28(1,4)-Hexabenzena-5,5,11,11,19,19,25,25-octamethyl-7,18,33,44-tetraoxa-1(2,5),15(2,5)-dithiophenacyclooctacosanaphane-6,9,20,23-tetrayne (3a). Following the general procedure for *O*-alkylation using sodium hydride, thiophenophane **3a** was obtained as a yellow solid from 2,5-bis[4-(bromomethyl)phenyl]thiophene **5** (0.50 g, 1.2 mmol), 1,4-bis(3-hydroxy-3-methylbut-1-ynyl) benzene **9a** (0.29 g, 1.2 mmol) and sodium hydride (0.12 g, 4.7 mmol). The product was purified by column chromatography using hexane/$CHCl_3$ (2:3) as eluent. Yield 53%, mp > 300 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.89 (s, 24H), 5.29 (s, 8H), 7.12 (s, 4H), 7.23 – 7.39 (m, 8H), 7.68 – 7.84 (AB_q, 16H, *J* = 8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 31.2, 63.3, 64.9, 77.1, 98.1, 120.6, 121.7, 122.9, 123.1, 124.2, 127.3, 129.0, 132.1, 135.5, 142.2. MS, (FAB-MS) m/z 1004 (M^+); Anal. Calcd for $C_{68}H_{60}O_4S_2$: C, 81.24; H, 6.02%. Found: C, 81.33; H, 6.13%.

2,5-Bis[4-(formyl)phenyl]thiophene (10). A single-necked round bottom flask charged with 2,5-bis[4-(bromomethyl)phenyl]thiophene **5** (0.43 g, 1 mmol), $NaIO_4$ (0.43 g, 2 mmol) and DMF (40 mL) was kept at reflux for 1 h. After the completion of the reaction (monitored by TLC), the reaction mixture was extracted with CH_2Cl_2 (2 ×100 mL), washed with water (3 ×100 mL), brine

(100 mL) and dried over anhydrous Na_2SO_4. Evaporation of the organic layer gave a residue, which was purified by column chromatography using hexane/$CHCl_3$ (9:1) as an eluent to give the corresponding 2,5-bis[4-(formyl)phenyl]thiophene **12** as a yellow solid. Yield 69%, mp > 260 °C; IR (KBr, ν_{max}, cm^{-1}) 1693.6 (C=O). ^1H NMR (500 MHz, $CDCl_3$): δ_H 9.99. (s, 2H), 7.46 (s, 2H), 7.76 – 7.77 (d, 4H, *J* = 8.0 Hz), 7.88 – 7.90 (d, 4H, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 125.9, 126.4, 130.6, 135.4, 139.5, 143.9, 191.4. MS, (EI, 70eV) m/z 292.2 (M^+, 30.2%), 235.0 (12.0%), 57.1.0 (100%); Anal. Calcd for $C_{18}H_{12}O_2S$: C, 73.95; H, 4.14%. Found: C, 74.11; H, 4.03%.

2(1,4),5(1,4),7(1,4),10(1,4)-Tetrabenzena-1(2,5),6(2,5)-dithiophenacyclodecaphane-3,8-diene (4). A solution of zero valent titanium prepared from $TiCl_4$ (2.73 g, 14 mmol) with zinc (1.88 g, 28 mmol) and a few drops of pyridine (0.5 mL) in dry THF (50 mL) under nitrogen atmosphere at 0 °C was allowed to attain room temperature after 0.5 h and was then refluxed for 1 h. Dialdehyde **10** (0.21 g, 0.9 mmol) was added in one portion to the freshly prepared low valent titanium. After the addition, the reaction mixture was refluxed for 12 h. The reaction mixture was cooled and then quenched with K_2CO_3 solution (20 mL of 40% v/v). The precipitated inorganic material was removed by filtration. The precipitate was thoroughly washed thrice with THF (3 × 100 mL) and the combined THF extract was evaporated under reduced pressure. The residue was then dissolved in water and extracted with $CHCl_3$ (200 mL), washed with water (2 × 200 mL) brine (100 mL) and dried over Na_2SO_4. Crude product obtained after evaporation of $CHCl_3$, was purified by column chromatography using hexane/$CHCl_3$ (4:1) as an eluent to give the corresponding thiophenophane **4**. Yield 68%, mp 134 – 136 °C; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.19– 7.21 (d, 2H, *J* = 7.5 Hz), 7.28 (s, 4H), 7.38– 7.40 (d, 8H, *J* = 7.2 Hz), 7.51– 7.54 (d, 8H, *J* = 7.5 Hz), 7.67– 7.70 (d, 2H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 124.7, 125.7, 126.4, 127.6, 129.7, 131.4, 141.6. MS, (EI, 70eV) m/z 520.0 (M^+, 90.3%), 521.1 (M+1, 29.0%), 522.1 (M+2, 9.6%), 288.1 (22.4%), 236.0 (95.1%); Anal. Calcd for $C_{36}H_{24}S_2$: C, 83.04; H, 4.65%. Found: C, 82.97; H, 4.74%.

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