JOC*Note*

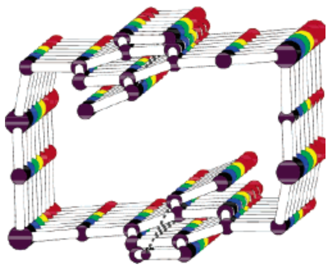
Synthesis and Structural Study of Thiacyclophanes Utilizing Dibromides and Methane Dithiolate

Perumal Rajakumar,*,† Manickam Dhanasekaran,†
Subramaniyan Selvam,†
Paduthapillai Gopal Aravindan,‡ and
Devadasan Velmurugan‡

Department of Organic Chemistry and Department of Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai, India 600 025

perumalrajakumar@hotmail.com

Received November 23, 2004

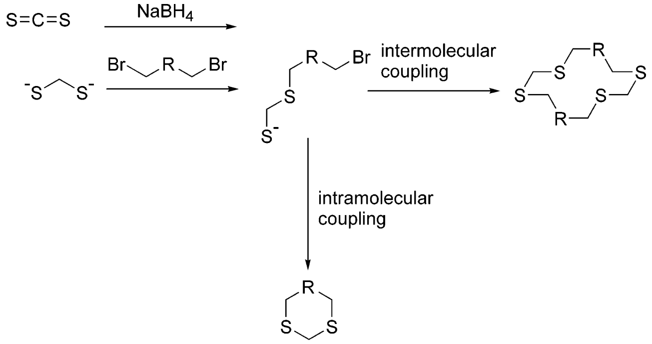


The synthesis of a series of thiacyclophanes and optically active binaphthol-based chiral thiacyclophanes is reported with XRD structure. Two diastereomeric tetrathiacyclophanes are designed and synthesized. The two diastereomers are evidenced by crystal structure; the single- crystal X-ray studies reveal that one of the isomers possesses an inherent property of self-assembling into a vertical stack of tunnel-like structures.

The synthesis of [2.2]paracyclophane by Cram and Steinberg[1] in 1951 was a revolutionary breakthrough in the field of cyclophane chemistry. Since then, many methods have been developed for the synthesis of cyclophanes in which a ring-closing step is very often crucial.[2] The unique chemistry of cyclophane was applied to molecular recognition, catalysis, liquid crystals, and mimicry of natural enzymes.[3]

Thiacyclophanes are important members in the cyclophane family since they can undergo functional group transformations, interesting aromatic ring-tilting, and bridge-flipping processes.[4−6] Macrocyclic crownophanes are important for creating highly organized linear supramolecular assembly[7] and neutral ditopic super structures.[8] Herz has reported a series of diastereomeric paracyclophanes[9] by a coupling reaction of suitable dibromide and dithiol. Only a few synthetic methods[10] are available in the literature for the synthesis of thiacyclophanes. The requirement of high dilution, slow addition conditions, and long reaction time pose some difficulties when using thiols in the synthesis of thiacyclophanes. Moreover, thiols are unstable, difficult to synthesize, highly sensitive, and most of the time used as such with out purification, resulting in poor yield of thiacyclophanes.

SCHEME 1. Generation of Methane Dithiolate



With this in mind we report herein a novel synthesis of thiacyclophanes by a simple one-pot reaction utilizing dibromides and methane dithiolate (Scheme 1).

Methane dithiolate [$^{-}$S-CH$_2$-S^{-}] was generated from double reduction of CS_2 with $NaBH_4$, which displaces the bromides via a two-step (inter- followed by an intramolecular or two successive intermolecular) nucleophilic substitution. However, the mode of cyclization was entirely dependent on the nature of the substrate. Recently, methane dithiolate (generated *in situ*) was used for the synthesis of dithianes and dithiepines.[11]

Synthesis. The *O*-alkylation of 4-hydroxybenzaldehyde with xylenyl and pyridyl dibromides **1a**−**c** furnished the dialdehydes **2a**−**c**. The dialdehyde groups present in

---

† Department of Organic Chemistry.

‡ Department of Crystallography and Biophysics.

(1) Cram, D. J.; Steinberg, H. *J. Am. Chem. Soc.* **1951**, *73*, 5691.

(2) (a) Yamato, T.; Hideshima, C.; Nagano, Y.; Tashiro, M. *J. Chem. Res., Synop*. **1996**, 266. (b) Losensky, H. W.; Selthanan, H.; Ehlen, A.; Vögtle, F.; Bargon, J. *Angew. Chem.* **1988**, *100*, 1225. (c) Larkins, H. L.; Hamilton, A. D. *Tetrahedron Lett.* **1986**, *27*, 2721. (d) Müller, E.; Röscheisen, G. *Chem. Ber*. **1957**, *90*, 543. (e). Elix, J. A.; Sargent, M. V. *J. Am. Chem. Soc.* **1968**, *90*, 1631. (f) Vinod, T. K.; Hart, H. *Tetrahedron. Lett.* **1988**, *29*, 885. (g) Kang, H. C.; Hanson, A. W.; Eaton, B.; Boekelheide, V. *J. Am. Chem. Soc.* **1985**, *107*, 1979. (h) Chastette, M.; Chastrette, F. *Chem. Commun*. **1973**, 534. (i) Vogel, E.; Köcher, S.; Lex, J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 257. (j) Rubin, Y.; Parker, T. C.; Khan, S. I.; Holliman, C. L.; McElvany, W. *J. Am. Chem. Soc.* **1996**, *118*, 5308. (k) Camacho, D. H.; Salo, E. V.; Guan, Z. *Org. Lett.* **2004**, *6*, 865. (l) Smith, B. B.; Hill, D. E.; Cropp, T. A.; Walsh, R. D.; Cartrette, D.; Hipps, S.; Shachter, A. M.; Pennington, W. T.; Kwochka, W. R. *J. Org. Chem.* **2002**, *67*, 5333. (m) Heuft, M.; Collins, S. K.; Fallis, A. G.; *Org. Lett.* **2003**, *11*, 1911. (n) Smith, A. B., III; Adams, C. M.; Kozmin, A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925.

(3) (a) Steed, J. W., Atwood, J. L., Eds.;*Supramolecular Chemistry*; John Wiley & Sons: West Sussex, U.K., 2000. (b) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348. (c) Fulton, D. A.; Stoddart, J. F. *Bioconjugate Chem.* **2001**, *12*, 655. (d) Mizutani, T.; Yagi, S.; Morinaga, Y.; Nomura, T.; Takagishi, T.; Kitagawa, S.; Ogoshi, H. *J. Am. Chem. Soc.* **1999**, *121*, 754. (e) *Cyclophanes*; Keehn, P. M., Rosenfeld, S. M., Eds.; Academic: New York, 1983. (f) Benson, D. R.; Valentekovich, R.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 191.

(4) (a) Boekelheide, V.; Lawson, J. A. *Chem. Commun.* **1970**, 1558. (b) Vinod, T. K.; Hart, H. *J. Org. Chem.* **1990**, *55*, 881.

(5) Anker, W.; Berveridge, K. A.; Bushnell, G. W.; Mitchell, R. H. *Can. J. Chem.* **1984**, *62*, 661.

(6) Mitchell, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 2352.

(7) Xu, J.; Lai, Y. *Org. Lett.* **2002**, *4*, 3211.

(8) Barboiu, M.; Vaugan, G.; Lee, A. V. *Org. Lett.* **2003**, *5*, 3073.

(9) Staab, H. A.; Herz, C. P. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 799.

(10) (a) Vogtle, F. *Top. Curr. Chem.* **1983**, *113*, 3−24. (b) Newkome, G. R.; Roper, J. M.; Robinson, J. M. *J. Org. Chem.* **1980**, *45*, 4380. (c) Reistad, K. R.; Groth, P.; Lie, R.; Undheim, R. *Chem. Commun.* **1972**, 1059.

10.1021/jo047922v CCC: $30.25

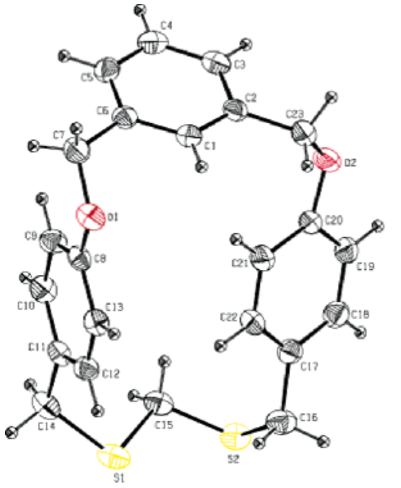
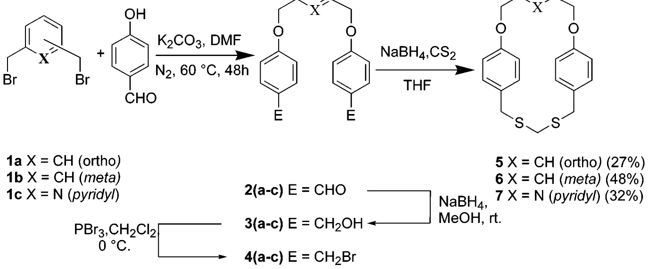


FIGURE 1. ORTEP drawing of cyclophane **6** showing 30% probability level.

SCHEME 2. Synthesis of Dithiacyclophanes



2a−**c** were reduced with $NaBH_4$ to afford the hydroxymethyl compounds **3a**−**c**, which on treatment with PBr_3 gave the dibromides **4a**−**c**.[12] A solution of the dibromides **4a**−**c** (5 mmol) and CS_2 (10 mmol) in THF (75 mL) was added to the slurry of $NaBH_4$ (20 mmol) in THF (25 mL) at room temperature followed by reflux for 6 h to afford the thiacyclophanes **5**−**7** in 27%, 48%, and 32% yields, respectively (Scheme 2). No appreciable change in the yield of the cyclophanes was observed when the same amount of the dibromides and CS_2 in THF (150 mL) was added dropwise for 2−3 h to the slurry of $NaBH_4$ in excess THF (300 mL). The ORTEP[13] drawing of **6** is shown in Figure 1.

The methodology was extended for the synthesis of binaphthol-based chiral thiacyclophanes. The synthetic pathway leading to chiral cyclophanes is outlined in Scheme 3. Optically pure (*S*)-1,1-binaphthol was bisalkylated with *m*/*p*-carbethoxy-substituted benzyl bromide in DMF in the presence of anhydrous K_2CO_3 to give diester **8a/8b**, which was then converted into the corresponding diol **9a/9b** using $LiAlH_4$. The desired dibromide **10a/10b** was obtained by treating the diol **9a/9b** with phosphorus tribromide in dry CH_2Cl_2 at 0 °C. The dibromide **10a/10b** underwent coupling reaction with *in situ* generated methane dithiolate in THF to afford the corresponding chiral thiacyclophanes **11** and **12** in 41% and 55% yield, respectively.

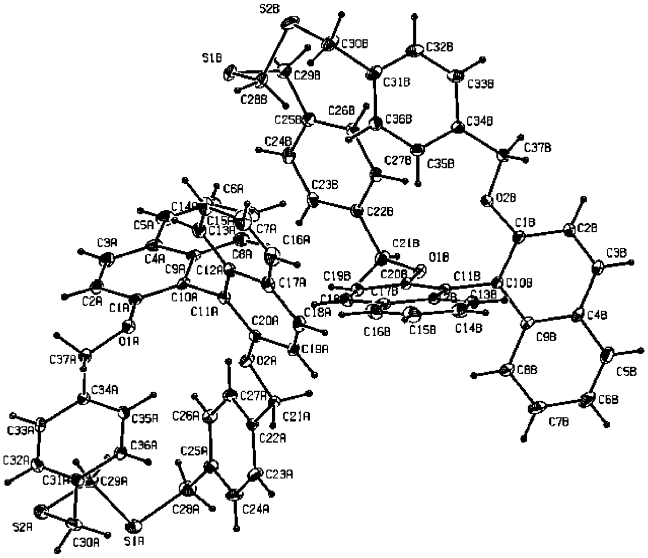
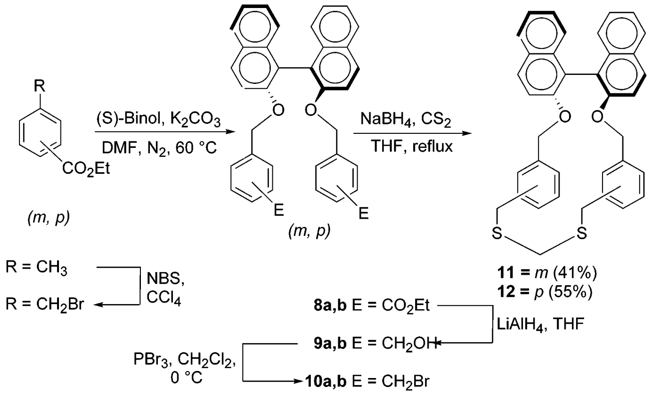


FIGURE 2. ORTEP diagram of cyclophane **12** showing 20% probability level.

SCHEME 3. Synthesis of Chiral Dithiacyclophanes



Suitable crystals of **12** for X-ray[14] diffraction study were obtained by slow evaporation of its ethyl acetate solution. The crystal structure of **12** is shown in Figure 2. The two molecules (A and B) in the asymmetric unit of the chiral binaphthol moiety display a significant twist about the C10−C11 bond by 78.4(1) and 85.1(1)°, respectively. The dihedral angle between two benzene rings is 81.1(2) and 63.3(2)° for molecules A and B, respectively. There is a short contact between H2A and H37A (2.09 Å) resulting in the widening of the bond angle C2A−C1A−O1A = 123.3(2)° from the ideal value. A similar short contact is also observed in molecule B. The confor-

---

[11] Wan, Y.; Kurchan, A. N.; Barnhurst, L. A.; Kutateladze, A. G. *Org. Lett.* **2000**, *2*, 1133.

[12] (a) Rajakumar, P.; Murlai, V. *Tetrahedron* **2004**, *60*, 2351. (b) Rajakumar, P.; Srisailas, M. *Tetrahedron* **2001**, *57*, 9749.

[13] Aravindan, P. G.; Velmurugan, D.; Dhanasekaran, M.; Rajakumar, P. *Acta Crystallogr.* **2003**, *E59,* o1677.

[14] **Crystal data for 12.** X-ray intensity data were collected on a SMART CCD with Mo Kα radiation (λ = 0.71073 Å) using a colorless crystal with dimensions of 0.23 × 0.22 × 0.20 mm^3. Intensity data were reduced with the SAINT program. The crystal structure was solved by direct methods with SHELXS and refined by the full-matrix least-squares method using SHELXL. All of the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were positioned geometrically and were allowed to ride on the atoms to which they are attached: $C_{37}H_{30}O_2S_2$, FW = 570.73 g/mol^3, monoclinic, space group = $P2_1$ (No.4), unit cell dimensions a =15.6234(1) Å, b = 10.6788(9) Å, c = 18.9084(2) Å; β = 97.85 (3)°, V = 3125.1(5) Å^3, Z = 4, D_c =1.213 g/cm^3, $2\theta_{max}$= 52.74°, $R(F)$ = 8.67% for 12107 reflections with $F_o > 4\sigma(F_o)$ and wR(F^2) = 0.228 for all independent reflections with 739 parameters, GOF(F^2) = 1.16, CCDC 254296.

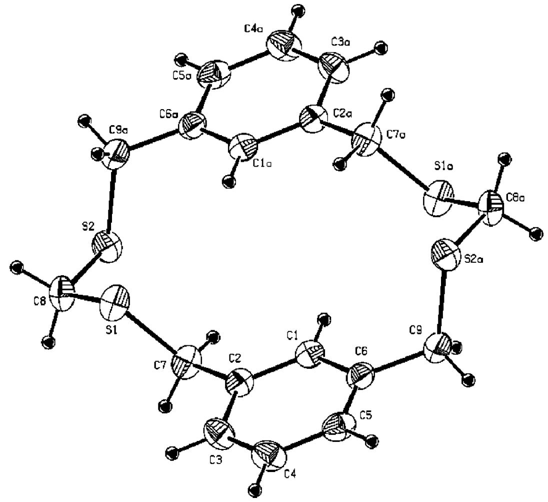
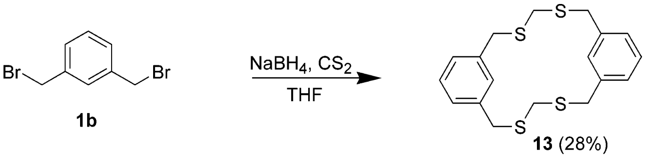


FIGURE 3. ORTEP drawing of cyclophane **13** showing 30% probability level.

SCHEME 4. Synthesis of Tetrathia[5.5]metacyclophane



mation of the two benzene rings is maintained by edge-tilted T-shape C$-$H$\cdots\pi$ interaction between H36A and the centroid of benzene ring (C22A→C26A) with a distance of 2.81 Å. The molecular packing is stabilized by weak C$-$H$\cdots\pi$ and van der Waals forces.

Having succeeded in the process of assembling dithiacyclophanes **5**, **6**, **7**, **11,** and **12**, we then focused our attention on the synthesis of tetrathiacyclophane through two successive intermolecular coupling reactions utilizing methane dithiolate and dibromide. Reaction of *m*-xylenyl dibromide **1b** with CS_2 and $NaBH_4$ in THF afforded the corresponding tetrathia[5.5]metacyclophane **13** in 28% yield (Scheme 4). The ORTEP[15] drawing of **13** is shown in Figure 3.

Similarly two diastereomeric tetrathia[5.5]paracyclophanes **15** and **16** were designed and successfully synthesized in 27% and 18% yields, respectively, from the coupling reaction of 1,4-bis(bromomethyl)-2,5-dimethoxy benzene (**14**) with *in situ* generated methane dithiolate in THF (Scheme 5). The mixture of the two diastereomers can be separated by column chromatography, and the two isomeric cyclophanes **15** and **16** are noninterconvertible.

SCHEME 5. Synthesis of Diastereomeric [5.5]paracyclophanes

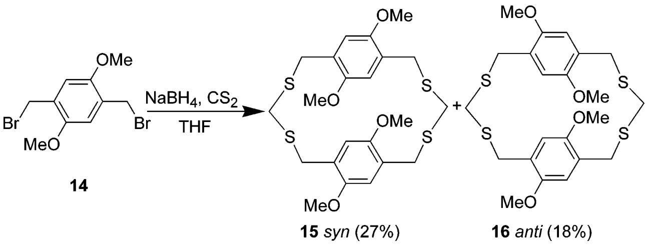


TABLE 1. Comparison of ^{1}H NMR of Diastereomeric [5,5]paracyclophanes

entry	$-S-CH_2-S-$ (δ)	Ar-CH_2-S- (δ)	$-OCH_3$ (δ)	Ar-H (δ)
15	2.98 (d, 2H), 3.27 (d, 2H)	3.35 (d, 4H), 4.15 (d, 4H)	3.71 (s, 12H)	6.67 (s, 4H)
16	3.15 (s, 4H)	3.31 (d, 4H), 4.13 (d, 4H)	3.72 (s, 12H)	6.75 (s, 4H)

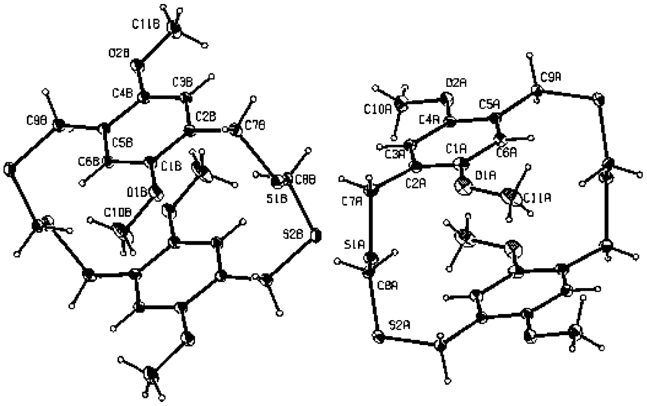


FIGURE 4. ORTEP diagram of cyclophane **15** showing 30% probability level.

The X-ray-quality crystals of the cyclophane **15** and **16** were grown from its ethyl acetate solution and chloroform solution, respectively. The ORTEP drawing of **15** is shown in Figure 4.

The X-ray structure[16] of **15** shows that the asymmetric unit contains two independent half molecules, each in turn symmetrically related with the other half molecule. In both molecules A and B, two benzene rings are separated by 4.622(2) and 4.630(2) Å, respectively. The orientation of the benzene ring can be defined by the torsion angle, such as C2A−C7A−S1A−C8A = −62.7(2)° and C2B−C7B−S1B−C8B = 53.1(2)°. In the molecules A and B increase in bond angle at C5 [C6A−C5A−C9A = 123.6(2); C6B−C5B−C9B = 124.2(2)°] from the ideal value (120°) is due to intramolecular C9−H9A2$\cdots$

---

[15] **Crystal Data for 13.** X-ray intensity data were collected on an Enraf Nonius CAD4 diffractometer with Mo Kα radiation (λ = 0.71073 Å) using a colorless crystal with dimensions 0.25 × 0.20 × 0.22 mm^3. Intensity data were reduced with the XCAD4PC program. The crystal structure was solved by direct methods with SHELXS and refined by the full-matrix least-squares method using SHELXL. All of the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were positioned geometrically and were allowed to ride on the atoms to which they are attached: $C_{18}H_{20}S_4$, FW = 364.58 g/mol^3, monoclinic, space group = $P2_1/n$ (No. 14), unit cell dimensions a = 11.6920(10) Å, b = 5.268(3) Å, c = 15.011(4) Å; β = 108.56(2)°, V = 876.5(6) Å^3, Z = 2, D_c = 1.381 g/cm^3, $2\theta_{max}$ = 54.1°, $R(F)$ = 6.5% for 1848 reflections with $F_o > 4\sigma(F_o)$ and wR(F^2) = 0.168 for all independent reflections with 100 parameters, GOF(F^2) = 0.81 and CCDC 259796.

[16] **Crystal Data for 15.** X-ray intensity data were collected on an Enraf Nonius CAD4 diffractometer with Mo Kα radiation (λ = 0.71073 Å) using a colorless crystal with dimensions 0.25 × 0.20 × 0.20 mm^3. Intensity data were reduced with the XCAD4PC program. The crystal structure was solved by direct methods with SHELXS and refined by the full-matrix least-squares method using SHELXL. All of the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were positioned geometrically and were allowed to ride on the atoms to which they are attached: $C_{22}H_{28}O_4S_4$, FW = 484.68 g/mol, triclinic, space group = $P\bar{1}$ (No.2), unit cell dimensions a = 8.426(1) Å, b = 9.219(3) Å, c = 16.820(4) Å; α= 82.93(3)°, β = 104.02(2)°, γ = 108.97(2)°; V = 1197.4(5) Å^3, Z = 2, D_c = 1.344 g/cm^3, $2\theta_{max}$ = 60.4°, $R(F)$ = 4.95% for 5124 reflections with $F_o > 4\sigma(F_o)$ and wR(F^2) = 0.134 for all independent reflections with 275 parameters, GOF(F^2) = 1.01, CCDC 244414.

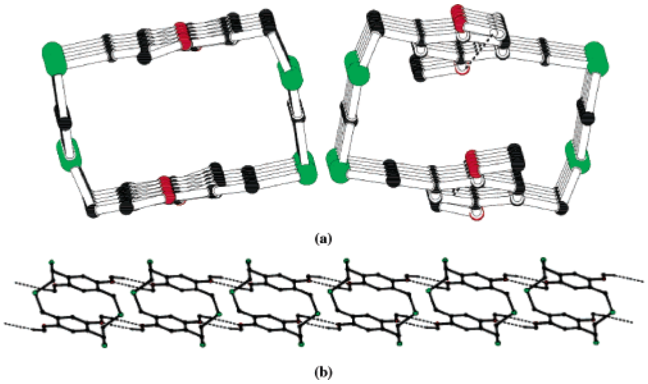


FIGURE 5. View of self-assembly in cyclophane **15**: (a) vertical stack of rectangular tunnel; (b) linear chain forming by C−H···O intermolecular hydrogen bond.

S1A^i [H9A2···S1A^i = 2.85, C9A···S1A^i = 3.326(3) Å and C9−H9A2···S1A^i = 111.3°; i = (2 − x, 1 − y, 1 − z)] hydrogen bond. The area of the molecule is about 36.633 Å^2. The C−H···O hydrogen bond links the two molecules in a tunnel like shape along the b axis (Figure 5). The weak C−H···π interaction exists between the centroid of the ring (C1B → C6B) and hydrogen H9B2 of C9 with a C9···Cg at (−x, 2 − y, −z) [H9B2···Cg = 2.68, C9B··· Cg = 3.503(3) Å; Cg is centroid of the ring (C1B→C6B)] riding along the a axis in the molecule B.[17] The molecular packing is controlled by C−H···O and C−H···π interactions between neighboring molecules in the solid state.

The ORTEP[18] drawing of **16** is shown in Figure 6. The isomer **16** contains one molecule in the asymmetric unit, which differs from **15** in the molecular packing. The intramolecular C−H···S [H6···S1 = 2.76, C6···S1 = 3.181(3) Å and C6−H6···S1 = 108.6°] and C−H···O [H9B···O3 = 2.34, C9···O3 = 2.807(4) Å and C9B−H9B···O3 = 108.2°] hydrogen bonds play a major role in stabilizing the molecule. The maximum distance between sulfur atoms S2 and S4 shows a cavity size of 8.814(2) Å. The substitution of methoxy groups at C1 and C4 causes a slight twist between the two rings [as indicated by dihedral angle of 9.3(1)°] with an interplanar distance of 4.135(3) Å. The intramolecular C−H···S and C−H···O hydrogen bonds make an angular strain [C18−C2−C1, O1−C1−C6, C6−C5−C7, O3−C15−C14, C15−C14−C13, and C14−C13−C16] from the normal value of 120°. The weak C−H···π interactions [H16A···Cg = 2.80 Å and C16···Cg = 3.506(1) Å, C16−H16A···Cg = 130°; Cg is centroid of the ring (C10−C5)][17] and van der Waals forces are involved in the crystal packing.

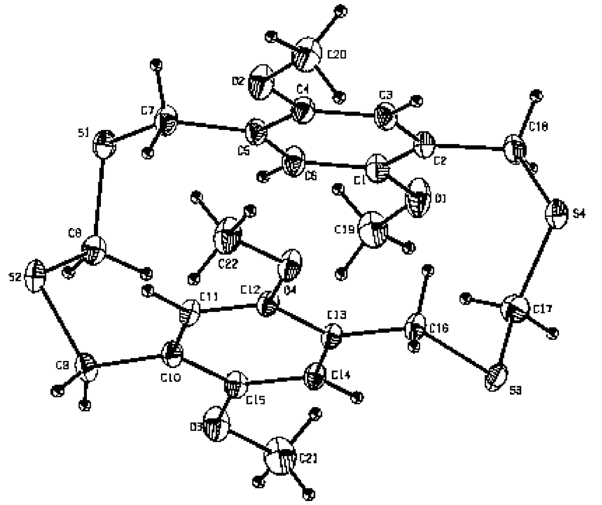


FIGURE 6. ORTEP drawing of cyclophane **16** showing 30% probability.

In summary, we have developed a simple and highly efficient synthetic route to prepare thiacyclophanes via coupling reaction of dibromides and methane dithiolate. Crystal structure analyses of diastereomeric [5.5]paracyclophanes clearly demonstrated that the orientation of the methoxy groups plays a vital role in deciding the self-assembly property. The isomer **15** having syn orientation of methoxy groups is capable of forming C−H···O dimer through intermolecular hydrogen bonds, which leads to tunnel like structure (intermolecular stacking); whereas the other isomer **16** did not show the intermolecular stacking due to anti orientation of methoxy groups. The present work describes a one-pot reaction for the synthesis of thiacyclophanes involving intra and intermolecular coupling with three components. Synthesis and self-assembling properties of other related systems are underway.

Experimental Section

General Experimental Procedure. A mixture of dibromide (5 mmol) and CS_2 (10 mmol) in dry THF (75 mL) was added to a slurry of $NaBH_4$ (20 mmol) in THF (25 mL) at room temperature, and the resulting solution was refluxed for 6 h. The reaction mixture was then quenched with aqueous ammonium chloride, solvent was evaporated under reduced pressure, and the crude product was extracted with $CHCl_3$ (2 × 100 mL) and dried over sodium sulfate. The product was purified by column chromatography (SiO_2) using ethyl acetate/hexane solvent mixture as eluent.

Cyclophanes **7**: 32% yield as a colorless solid; mp 196−198 °C; ^{1}H NMR ($CDCl_3$) δ 3.03 (s, 2H), 3.53 (s, 4H), 5.19 (s, 4H), 6.73 (d, 4H, J = 8.8 Hz), 6.83 (d, 4H, J = 8.8 Hz), 7.30 (d, 2H, J = 7.8 Hz), 7.62 (t, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 156.8, 156.7, 135.7, 129.8, 129.6, 122.3, 114.9, 70.2, 34.9, 29.3; MS (EI) (m/z) 78, 105 (100), 213, 216, 316, 349, 395 (M^+). Anal. Calcd for $C_{22}H_{21}NO_2S_2$: C, 66.80; H, 5.35; N, 3.54. Found: C, 66.98; H, 5.47; N, 3.48.

Acknowledgment. We are grateful to the Council of Scientific and Industrial Research (New Dehli) for financial assistance. M.D. thanks CSIR for SRF and D. Suresh Kumar, IISc, Bangalore, for his help.

Supporting Information Available: General experimental procedure; spectral data for all cyclophanes; X-ray data (CIF) for **12**, **13**, **15**, and **16**; ^{1}H NMR and mass spectra of compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO047922V

---

[17] (a) Suezawa, H.; Yoshida, T.; Umezawa, Y.; Tsuboyama, S.; Nishio, M. *Eur. J. Inorg. Chem.* **2002**, 3148. (b) Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond In Structural Chemistry And Biology*; Oxford University Press: Oxford, 1999; p 122.

[18] **Crystal Data for 16.** X-ray intensity data were collected on an Enraf Nonius CAD4 diffractometer with Mo Kα radiation (λ = 0.71073 Å) using a colorless crystal with dimensions 0.28 × 0.20 × 0.20 mm^3. Intensity data were reduced with the XCAD4PC program. The crystal structure was solved by direct methods with SHELXS and refined by the full-matrix least-squares method using SHELXL. All of the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were positioned geometrically and were allowed to ride on the atoms to which they are attached: $C_{22}H_{28}O_4S_4$, FW = 484.68 g/mol^3, triclinic, space group $P\bar{1}$ (No. 2), unit cell dimensions a = 9.109(2) Å, b = 10.048(6) Å, c = 13.347(5) Å; α = 97.39(4)°, β = 90.96(3)°, γ = 103.47(3)°; V = 1176.8(9) Å^3, Z = 2, D_c = 1.368 g/cm^3, $2\theta_{max}$ = 60.0°, $R(F)$ = 5.51% for 6834 reflections with $F_o > 4\sigma(F_o)$ and wR(F^2) = 0.161 for all independent reflections with 271 parameters, GOF(F^2) = 1.04, CCDC 244415.