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Synthesis and structural analysis of isomeric pyridinophanes and thiacyclophanes

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Abstract—A one-pot synthesis of structurally isomeric tetrathiacyclophanes through four-centre coupling reactions of suitable bromides and thiols is reported. The structures of the isomers were confirmed by spectroscopy and XRD analysis. Single crystal X-ray analysis reveals interestingly shaped molecular structures with large cavities.

Cyclophanes are macrocyclic compounds with bridged aromatic units, which have been investigated since the 1950s because of the unique interactions of the π-electron systems of the benzene rings and for their potential applications as molecular hosts.[1] The synthesis and design of cyclophanes and cage compounds with novel shapes and geometries continues to be of interest.[2] Various cyclophane architectures have been used in molecular recognition, catalysis, liquid crystals and mimicry of natural enzymes.[3] Thiacyclophanes are an important class in the cyclophane family as they can undergo interesting functional group transformations[4] and aromatic ring-tilting and bridge flipping processes.[5] Hart and co-workers reported the synthesis of rigid cavity, non-collapsible pyridinophanes[6] and a one-pot synthesis of a cyclophane with two conformers from a coupling reaction of a tetrathiol and a tetrabromide.[7] Recently, Takemura et al. reported the synthesis of isomeric pyridinophanes and the effect of topology (spatial arrangement) of the isomeric pyridinophanes in complexation behaviour.[8] We wish to report herein the synthesis and structural analysis of structurally isomeric pyridinophanes **1** and **2** and the cyclophanes **3** and **4** from a one-pot reaction involving a four centre, two-fold coupling of a suitable tetrathiol and a dibromide or a four-centre, four-fold coupling of a suitable tetrathiol and a tetrachloride (Fig. 1).

The synthetic pathway leading to the structurally isomeric pyridinophanes **1** and **2** is outlined in Scheme 1. The reaction of *o*-xylenyl dibromide with 2.1 equiv of ethyl 5-hydroxyisophthalate gave the tetra-ester **5a**, which was reduced using LAH in THF to afford the tetra-alcohol **6a**. Treatment of the tetra-alcohol **6a** with $SOCl_2$ and pyridine in CH_2Cl_2 led to the tetrachloride **7a** in excellent yield. The latter was smoothly converted into the corresponding tetrathiol **8a**.[9] The reaction of one equivalent of the tetrathiol **8a** with 2.1 equiv of 2,6-bis(bromomethyl)pyridine (**9**) in the presence of KOH in benzene/ethanol (1:9) led to a mixture of the pyridinophanes **1** and **2**. A careful column chromatographic separation of the mixture on silica gel (ethyl acetate and hexane 1:9) afforded the isomeric pyridinophanes **1**[10] and **2**[11] in 8% and 42% yields, respectively (Scheme 1).

The ^{1}H NMR spectrum (Fig. 4) of pyridinophane **1** showed the *S*-methylene groups as two singlets at δ 3.81 and 3.94 and the *O*-methylene protons as a singlet at δ 4.99. The pyridine protons appeared as a doublet at δ 6.85 for four protons and as a triplet at δ 7.15 for two protons. In the isophthalic moiety, the four protons *ortho* to oxygen appeared as a singlet at δ 6.54 and the two protons *para* to oxygen appeared as a singlet at δ 6.85. The *o*-xylenyl protons appeared as two doublet

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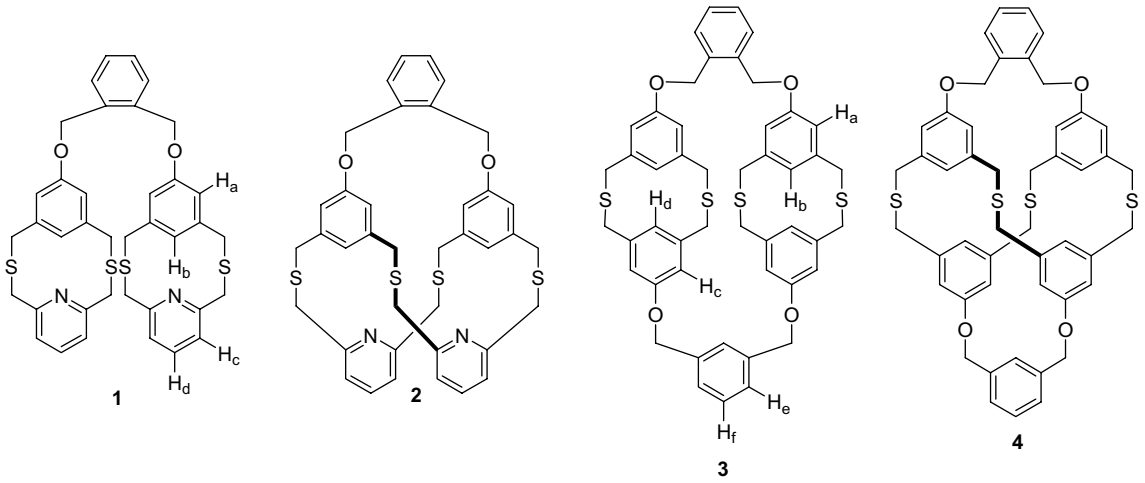
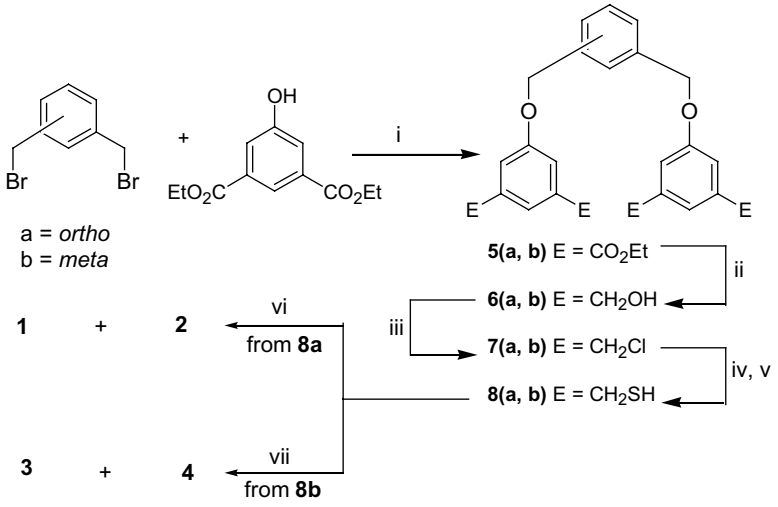


Figure 1. The structures of the isomeric cyclophanes.



Scheme 1. Reagents and conditions: (i) K_2CO_3, DMF, N_2, rt, 80%; (ii) LAH, THF, 60 °C, 78%; (iii) $SOCl_2$, py, CH_2Cl_2, 90%; (iv) H_2NCSNH_2, THF; (v) $H_2N(CH_2)_2NH_2$, dioxane, H_2O, 65%; (vi) 2.1 equiv 2,6-bis(bromomethyl)pyridine (**9**), KOH, EtOH/benzene, 12 h, (vii) 1 equiv **7a**, KOH, EtOH/benzene, 12 h.

of doublets between δ 7.38–7.47. The ^{13}C NMR of **1** showed the *S*-methylene and *O*-methylene carbons at δ 38.5 and 67.9 in addition to the aromatic carbons. The ^{1}H NMR spectrum (Fig. 5) of pyridinophane **2** is different from that of **1**. The two protons of the *S*-methylene groups are not equivalent and are more shielded than the corresponding protons in pyridinophane **1**. The *S*-methylene protons exhibited geminal coupling and appeared as two AB_q's at 3.52 and 3.94 with $J = 13.5$ and 14.2 Hz, respectively. This is due to the anisotropy introduced by the molecular geometry. The *O*-methylene protons are slightly deshielded and appeared as a singlet at δ 5.06. Similarly, deshielding and shielding effects were observed for the protons derived from the isophthalic acid and pyridine moieties (Table 1). The ^{13}C NMR of **2** showed the *S* -methylene and *O*-methylene carbons at δ 35.0, 36.6 and 69.5, in addition to other aromatic carbons. The ORTEP diagram of the bicyclic pyridinophane **2** is shown in Figure 2.

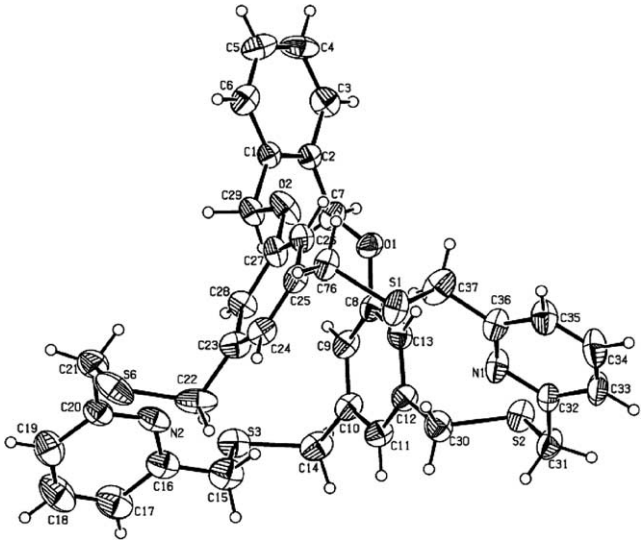


Figure 2. ORTEP diagram of bicyclic pyridinophane **2**.

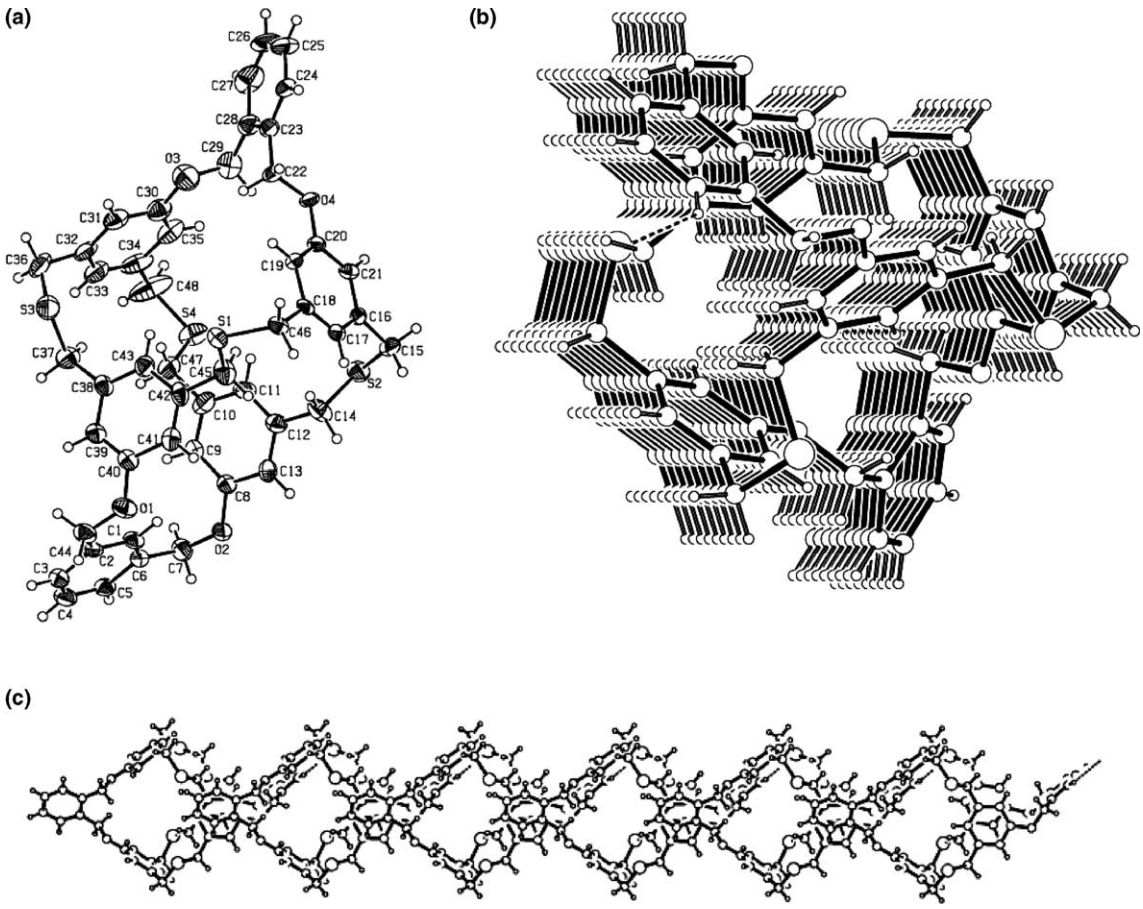


Figure 3. (a) ORTEP diagram of cyclophane **4**: A view of crystal packing in the cyclophane **4**: (b) vertical arrangement (c) linear arrangement by C–H···S intermolecular hydrogen bond.

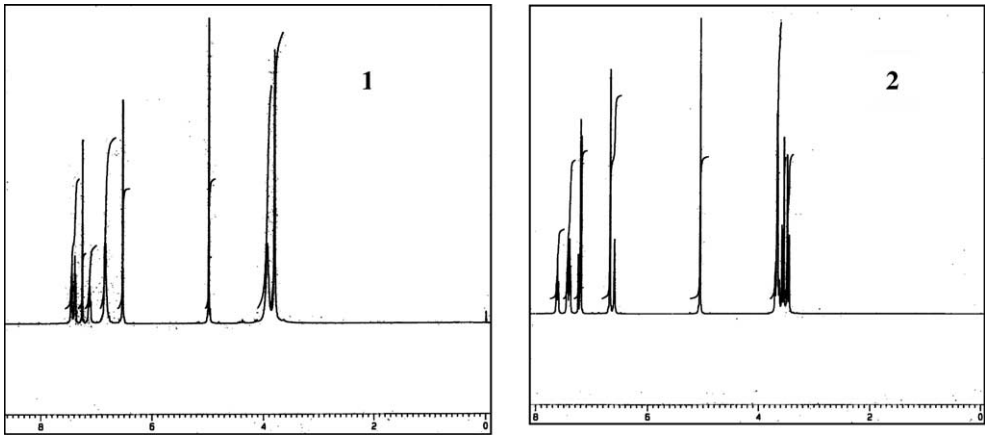


Figure 4. ^{1}H NMR spectra of pyridinophanes **1** and **2**.

The synthesis and NMR spectral features of pyridinophanes **1** and **2** prompted our attention to the synthesis of the structurally isomeric cyclophanes **3** and **4** via a fourfold coupling reaction. The desired tetrathiol **8b** was synthesized by bis-alkylation of *m*-xylenyl dibromide with 2.1 equiv of ethyl 5-hydroxyisophthalate, followed by conventional functional group transformations as depicted in Scheme 1. Reaction of tetrathiol **8b** with tetrachloride **7a** in the presence of KOH in benzene/ethanol (1:9) afforded a mixture of cyclophanes **3**[12] and **4**.[13] The two isomeric cyclophanes **3** and **4** were separated by column chromatography on silica gel (ethyl acetate and hexane 1:9) in 7% and 38% yields (Scheme 1).

The ^{1}H NMR spectrum (Fig. 4) of cyclophane **3** displayed *S*-methylene and *O*-methylene protons as singlets at δ 3.75, 3.78 and at 4.75, 4.84, respectively. The

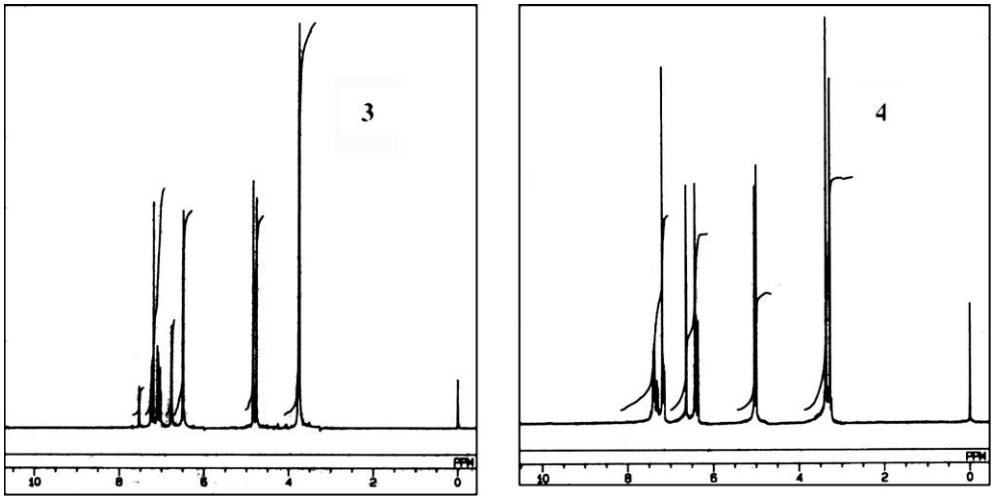


Figure 5. ^{1}H NMR spectra of cyclophanes **3** and **4**.

Table 1. Comparison of the ^{1}H NMR spectra of the isomeric pyridinophanes **1** and **2**

Entry	–*S*–CH_2		–*O*–CH_2	Isophthalic-H		Pyridine-H	
				H_a	H_b	H_c	H_d
1	3.81(s)	3.94(s)	4.99(s)	6.54(s)	7.26(s)	6.85(d)	7.15(t)
2	3.52(AB_q)	3.94(AB_q)	5.06(s)	6.69(s)	6.61(s)	7.21(d)	7.65(t)

Table 2. Comparison of the ^{1}H NMR spectra of isomeric pyridinophanes **3** and **4**

Entry	–*S*–CH_2		–*O*–CH_2		Isophthalic-H		*m*-Xylene-H	
					H_a and H_c	H_b and H_d	H_e	H_f
3	3.75(s)	3.78(s)	4.75(s)	4.84(s)	6.48(s) 6.49(s)	6.76(s) 6.77(s)	7.02(d)	7.13(t)
4	3.27(s)	3.36(s)	4.99(s)	5.03(s)	6.35(s) 6.40(s)	6.42(s) 6.63(s)	7.16(d)	7.31(t)

protons derived from the isophthalic moieties appeared as singlets at δ 6.48, 6.49, 6.76 and 6.77. A two proton doublet and a one proton triplet were observed for the *m*-xylene moiety at δ 7.02 and 7.13, respectively. In the ^{13}C NMR of **3**, the *S*-methylene and *O*-methylene carbons appeared at δ 38.5, 38.6, 67.9 and 69.9. In the ^{1}H NMR spectrum of cyclophane **4** (Fig. 5), the *S*-methylene protons were shielded and appeared as singlets at δ 3.27 and 3.36, in contrast to the ^{1}H NMR spectrum of bicyclic pyridinophane **2**. The anisotropy introduced by the molecular geometry in **4** is lost due to the enlargement of the cavity size and the *S*-methylene protons become indistinguishable. The *O*-methylene protons of **4** are deshielded and appeared as singlets at δ 4.99 and 5.03. However, all the protons of the isophthalic moiety in **4** are shielded compared to those of **3** and appeared as singlets at δ 6.35, 6.40, 6.42 and 6.63. Similar shielding and deshielding effects were observed for the *m*-xylene protons (Table 2). Due to the poor solubility of cyclophane **4** in organic solvents, the ^{13}C NMR could not be recorded. The ORTEP diagram and self-assembling view of tetrathiacyclophane **4** is shown in Figure 3.

In conclusion, we have developed an efficient route to synthesize structurally isomeric cyclophanes by one-pot coupling reactions of appropriate chlorides and thiols. The largest cyclophane system that we prepared also proved to have the most interesting crystal structure, self-assembling through C–H $\cdots$ S hydrogen bonds. The synthesis and structural analysis of other isomeric cyclophanes and self-assembling properties of such cyclophanes are under way.

Crystallographic data for the structures (pyridinophane **2** and cyclophane **4**) in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplemental publications CCDC 258295 and 258296. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 0 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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10. Yield 8%; dec >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 8H), 3.94 (s, 8H), 4.99 (s, 4H), 6.54 (s, 4H), 6.85 (d, 4H, J = 7.6 Hz), 7.15 (t, 2H, J = 7.6 Hz), 7.26 (s, 2H), 7.38–7.47 (m, 4H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 38.58, 67.92, 111.44, 113.70, 125.63, 128.26, 128.90, 135.23, 139.09, 151.03, 158.82; *m/z* (FAB-MS) 680 (M^+). Anal. Calcd for $C_{38}H_{36}N_2O_2S_4$: C, 67.02; H, 5.33; N, 4.11. Found. C, 67.21; H, 5.40; N, 4.20.
11. Yield 42%; dec >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (AB_q, 8H, J = 13.5 Hz), 3.94 (AB_q, 8H, J = 14.2 Hz), 5.06 (s, 4H), 6.61 (s, 2H), 6.69 (s, 4H), 7.21 (d, 4H, J = 7.7 Hz), 7.41–7.46 (m, 4H), 7.65 (t, 2H, J = 7.6 Hz); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 35.09, 36.61, 69.50, 111.45, 113.89, 121.16, 121.76, 128.98, 130.69, 135.98, 139.78, 151.82, 159.02; *m/z* (FAB-MS) 680 (M^+). Anal. Calcd for $C_{38}H_{36}N_2O_2S_4$: C, 67.02; H, 5.33; N, 4.11. Found. C, 67.25; H, 5.50; N, 4.18.
12. Yield 7%; dec >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 8H), 3.78 (s, 8H), 4.75 (s, 4H), 4.84 (s, 4H), 6.48 (s, 4H), 6.49 (s, 4H), 6.76 (s, 2H), 6.77 (s, 2H), 7.02 (d, 2H, J = 7.8 Hz), 7.08–7.25 (m, 4H), 7.13 (t, 1H, J = 7.8 Hz), 7.52 (s, 1H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 38.57, 38.65, 67.98, 69.98, 114.13, 114.28, 124.73, 124.83, 125.45, 125.87, 127.51, 127.59, 128.06, 134.39, 137.39, 138.68, 158.50, 158.83; *m/z* (FAB-MS) 812 (M^+). Anal. Calcd for $C_{48}H_{44}O_4S_4$: C, 70.90; H, 5.45. Found. C, 71.04; H, 5.38.
13. Yield 38%; dec >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.27 (s, 8H), 3.36 (s, 8H), 4.99 (s, 4H), 5.03 (s, 4H), 6.35 (s, 2H), 6.40 (s, 2H), 6.42 (s, 4H), 6.63 (s, 4H), 7.14 (s, 1H), 7.16 (d, 2H, J = 7.8 Hz), 7.31 (t, 1H, J = 7.8 Hz), 7.08–7.25 (m, 6H); *m/z* (FAB-MS) 812 (M^+). Anal. Calcd for $C_{48}H_{44}O_4S_4$: C, 70.90; H, 5.45. Found. C, 71.12; H, 5.55.