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Synthesis and structural analysis of isomeric pyridinophanes and thiacyclophanes

Perumal Rajakumar,[a,*] Manickam Dhanasekaran,[a] Sivashanmugam Selvanayagam,[b] Venkatachalam Rajakannan,[b] Devadasan Velmurugan[b] and Krishnan Ravikumar[c]

[a]*Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, India*
[b]*Department of Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai 600 025, India*
[c]*Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad 500 007, India*

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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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* Corresponding author. Tel.: +91 44 22351269213; fax: +91 44 22352494; e-mail: perumalrajakumar@hotmail.com

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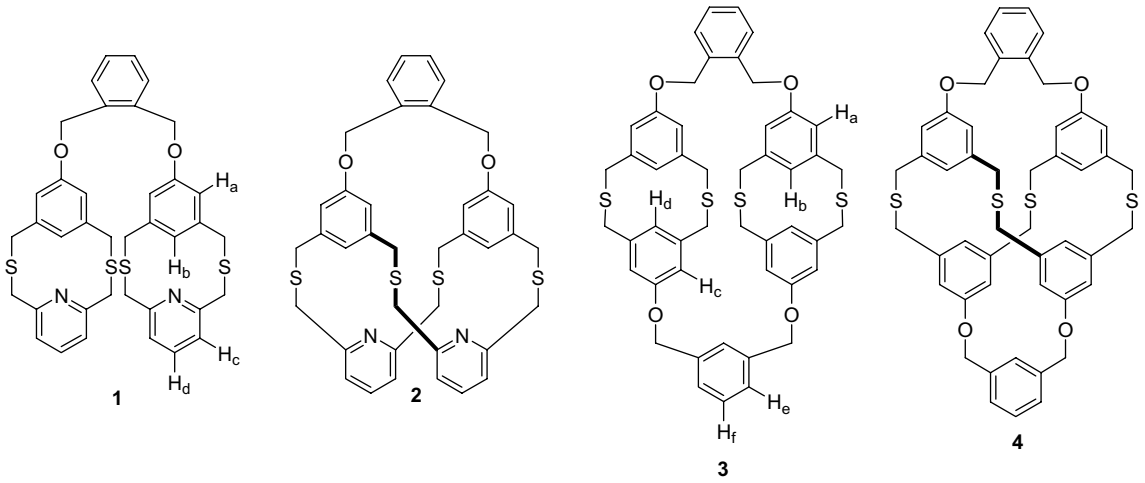
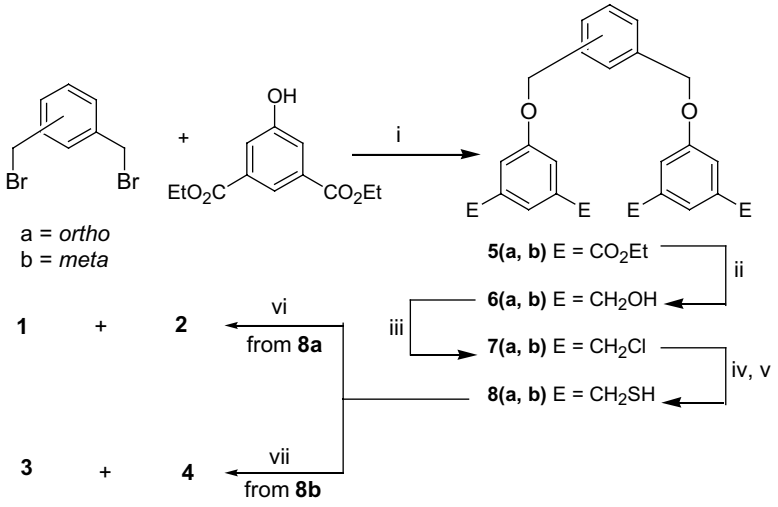


Figure 1. The structures of the isomeric cyclophanes.



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.

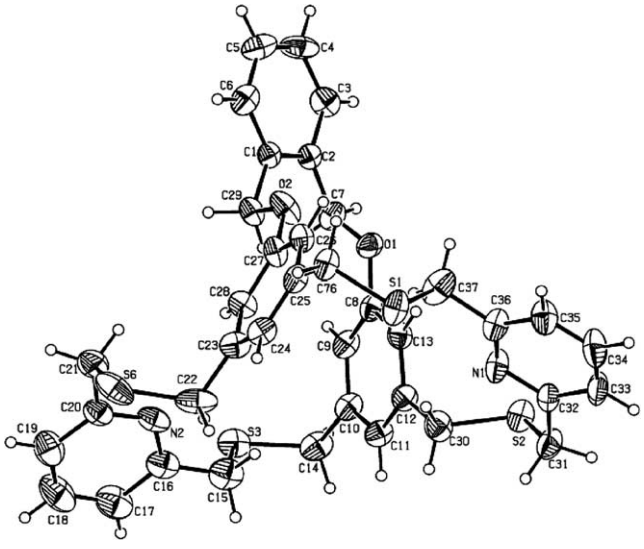


Figure 2. ORTEP diagram of bicyclic pyridinophane **2**.