



Synthesis and properties of a mixed thiophene-octahomotetraoxacalixarene

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ABSTRACT

The synthesis of a mixed thiophene unit containing octahomotetraoxa[2]thiophenecalix[2]arene is described. Its single-crystal X-ray structure and a preliminary solution complexation study are reported herein.

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1. Introduction

Due to their potentially useful chemical properties and their applications, heterocyclic-based calixarenes such as **1**,¹ **2**,² **3**,³ **4**⁴ and **5**,⁵ have gained considerable attention recently from many research groups. These heterocycle-based calixarenes (Fig. 1), respectively, incorporate pyridine, furan, thiophene, indole or pyrrole units instead of the conventional phenolic units in the construction of the macrocyclic compound.

In some cases, more than one type of heterocyclic unit have been used, as in calix[2]bipyrrole[2]furan (**6**) and calix[2]bipyrrole[2]thiophene (**7**) (Fig. 2). Sessler et al.⁶ have shown that the mixed heterocycle-containing compounds, **6** and **7**, for example, selectively bind with specific anions, such as acetate and benzoate, with high binding constant values. Among other mixed heterocalixarenes some containing imidazolium units within the frameworks of the calixarene (not shown) have also been synthesized and these compounds were found also to be good anion receptors.⁷

As part of our on-going studies concerned with the supramolecular binding abilities of diverse bowl-shaped compounds with neutral guest molecules, in particular, fullerenes⁸ or with other guest species,⁹ we anticipated that the replacement of a single, or of two of the benzene rings in octahomotetraoxacalix[4]arene with thiophene rings, to form new derivatives such as **8** (Scheme 1)

could produce a potential new host for C₆₀- or C₇₀-fullerene (Fig. 3). Although such a molecule would have a large degree of rotational flexibility due to the presence of four (–CH₂–O–CH₂–) ether units linking the phenyl and thiophenyl units together, molecular modelling studies indicated that this compound could have a well-defined cavity which could embrace these fullerenes. Indeed, based on some of our previous experiences,^{8b,c} it was hypothesized that the presence of the four ether oxygen atoms and the two sulfur atoms within the cavity could play an important role and could potentially enhance its complexation ability towards C₆₀ and/or C₇₀ or other guests. Furthermore, molecular mechanics modelling¹⁰ suggested that there could be additional favourable π -CH₃ interactions resulting from the embracing *tert*-butyl groups^{8b} on the phenyl units.

In this Letter, the synthesis of the mixed thiophene unit containing 'octahomotetraoxa[2]thiophenecalix[2]arene' (**8**) is described. As well, its single-crystal X-ray structure and a preliminary solution complexation study are reported.

2. Results and discussion

The synthesis of macrocycle **8**, was achieved¹¹ in 21% overall yield by base-mediated condensation of **9** with 2,6-bis(bromomethyl)-4-*tert*-butylanisole (**10**) as outlined in Scheme 1. The reaction was conducted by slowly adding an equimolar solution of **9** and **10** in THF to a mixture of NaH in THF at reflux temperature. The precursor compound, 2,5-bis(hydroxymethyl)thiophene (**9**)¹² was easily derived via LiAlH₄ reduction of dimethyl thiophene-2,5-dicarboxylate (**11**) which in turn, was readily obtained by esterification of commercially available 2,5-thiophenedicarboxylic

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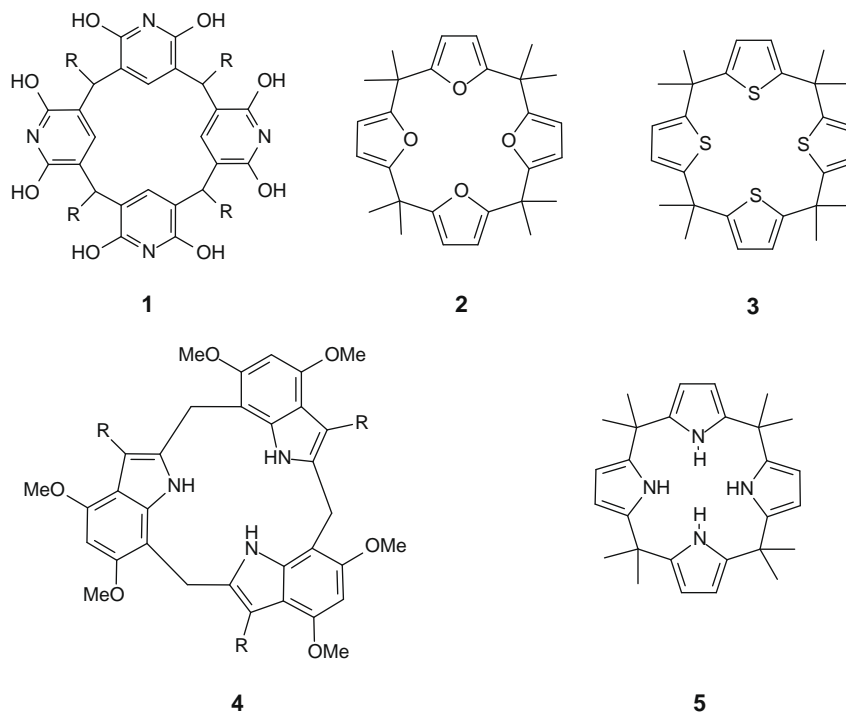


Figure 1.

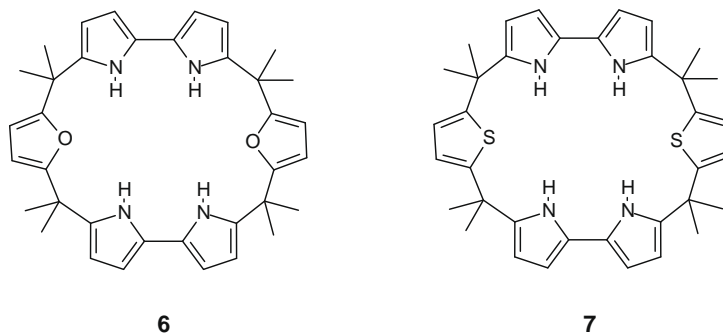
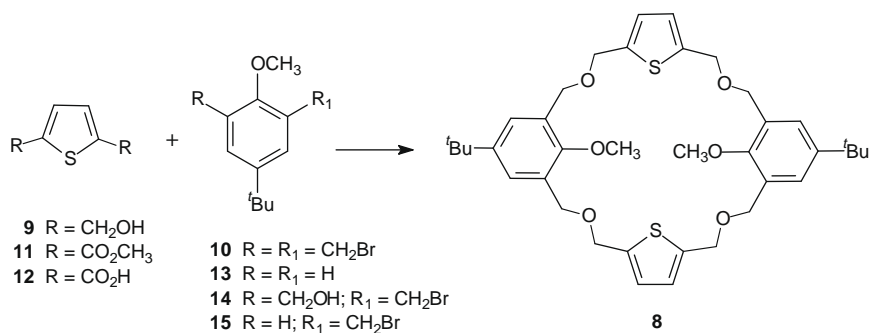


Figure 2.



Scheme 1.

acid (**12**). The other precursor, **10**, was synthesized¹³ in 68% yield, by bis-bromomethylation of *p*-*tert*-butylanisole (**13**) which also afforded the undesired side-products **14** and **15**, in ~10% and 20% yields, respectively.

2.1. NMR spectroscopy

The ¹H and ¹³C NMR spectra of **8** were in agreement with the expected product and its simplicity indicated that this compound

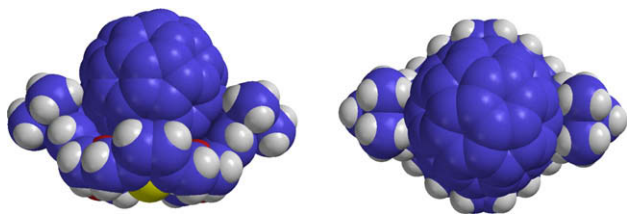


Figure 3. Side- and top views of computer-generated space-filling models of a hypothetical 1:1 supramolecular complex of C_{60} with **8**.

is highly symmetrical. The 1H NMR spectrum shows two signals at low field, one corresponding to the protons of the aryl units and the other for the protons of the thiophenyl units. The bridging methylene protons appeared as two sharp singlet signals, one at $\delta \sim 4.51$ and one at ~ 4.75 ppm in the 1H NMR spectrum, showing that this compound is highly flexible at the ambient temperature. This confirms the hypothesis stated earlier, that a factor contributing to this flexibility is likely due to the presence of four ether bridges which link the aryl and thiophenyls.

The ^{13}C NMR spectrum was also consistent with the structure of **8**, showing only six carbon signals at the low field region corresponding to the aryl and thiophenyl carbons and five signals at higher field for the remaining carbon atoms in the molecule.

2.2. X-ray crystallography

Colourless crystals of **8** which were suitable for single-crystal X-ray diffraction analysis were obtained from a methanol/dichloromethane solution. The single-crystal X-ray structure (Fig. 4)¹⁴ revealed that there are two molecules in the asymmetric unit. A similar supramolecular solid state 'dimer', not commonly found in calixarenes in general, was previously observed by us in a calix[4]naphthalene.¹⁵

In the present case, the two molecules are packed in such a way that one of the phenyl units is situated within the hydrophobic cavity of the second molecule. One of the *tert*-butyl groups of each molecule is situated above a phenyl ring of the second molecule with the aromatic carbon to hydrogen of the *tert*-butyl group having a contact van der Waals distance of 2.73 Å, thus indicating significant π - CH_3 interactions being present. Short $H \cdots O$ contacts of 2.438 and 2.62 Å can also be seen between protons in each of the nested phenyl groups and oxygen atoms of the bridging $-CH_2OCH_2-$ group. These interactions lead to the formation of helical chains that run parallel to the *a*-axis (Fig. 5). Figure 6 shows the conformations of each molecule present in the asymmetric unit. Figure 6a reveals a nearly-'partial cone' conformation in which the two thiophene units and one of the phenolic units are all *syn*, while Figure 6b reveals a nearly-'1,2-alternate' conformation in which the two thiophene units are *anti*.

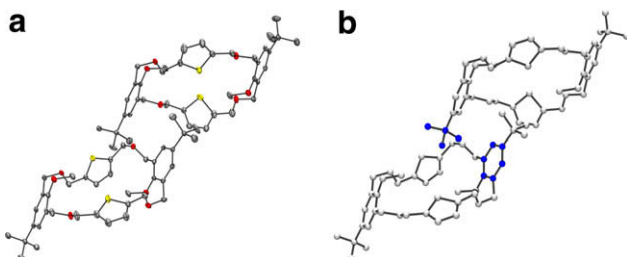


Figure 4. POV-ray rendered asymmetric unit of **8** in which hydrogen atoms have been omitted for clarity, showing: (a: left) 30% probability ellipsoids; and (b: right) showing (blue-coloured atoms) the proximity of a *tert*-butyl group of one molecule with the phenyl ring of its dimer mate.

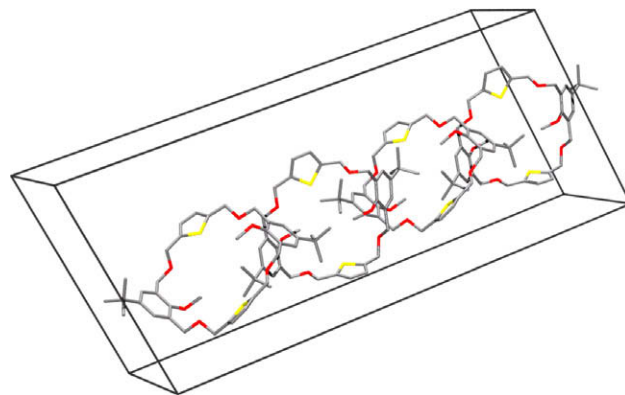


Figure 5. POV-ray rendering of **8** (hydrogen atoms omitted for clarity) showing one chain of macrocycles.

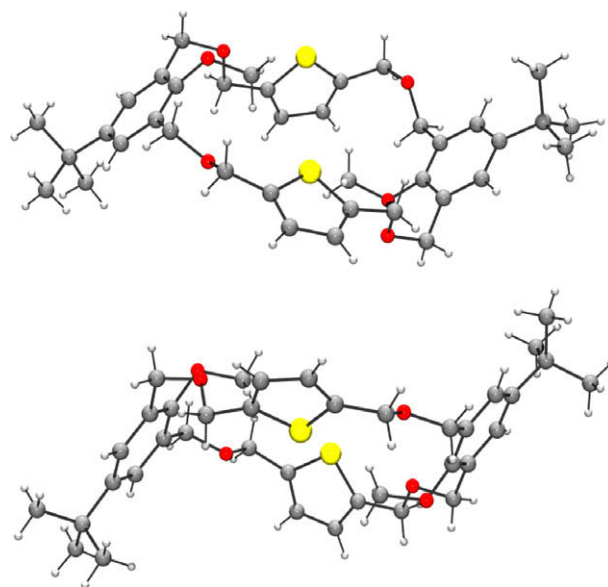


Figure 6. POV-ray rendered structures of the two individual molecules present in the asymmetric unit of the X-ray structure of **8**. The top structure shows the 'partial cone' conformation in which the two thiophene units and one of the phenolic units are *syn* while the bottom structure shows the '1,2-alternate' conformation in which the two thiophene units are *anti*.

2.3. Complexation studies

Solutions of **8** in either toluene- d_8 , benzene- d_6 or CS_2 , solvents which are usually employed for NMR titration complexation studies with fullerenes were treated with C_{60} or C_{70} . In all of the cases examined however, no colour changes which are normally associated with these complex-formation experiments were observed, nor were there any complexation-induced chemical shift changes in the 1H NMR spectra.

In summary, the synthesis of the mixed thiophene-based calix[4]arene **8**, using a [2+2] fragment condensation reaction is described. A single-crystal X-ray structure revealed that this compound forms a 'dimer' in the solid state. Titration experiments with several guest including C_{60} , C_{70} however failed to reveal any evidence of complex formation.

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- Molecular modelling was conducted using SPARTAN'08 (Windows version) Molecular Modelling Software. Molecular mechanics (MMFF94) calculations were conducted on the optimized geometry of the host and/or complexes.
- Octahomotetraoxacalix[2]arene[2]thiophene (**8**): To a mixture of NaH (51.4 mg, 2.14 mmol) in anhydrous THF (30 mL) at reflux was added a solution of 2,5-bis(hydroxymethyl) thiophene (**9**) (100 mg, 0.69 mmol) and 2,6-bis(bromomethyl)-4-*tert*-butylanisole (**11**) (241 mg, 0.69 mmol) in anhydrous THF (50 mL) by syringe-pump over 3 h. The reaction mixture was stirred at reflux temperature for an additional 24 h. The reaction mixture was then cooled to room temperature and washed with water (2 × 25 mL). The organic layers were combined, dried over MgSO₄ and filtered. The solvent was evaporated on a rotary evaporator and the residue was purified by PLC (1:4 ethyl acetate/hexanes) to give **8** (92 mg, 21%) as a colourless solid: mp 253–255 °C; ¹H NMR δ 1.35 (s, 18H), 3.66 (s, 6H), 4.51 (s, 8H), 4.75 (s, 8H), 6.90 (s, 4H), 7.36 (s, 4H); ¹³C NMR δ 31.7, 34.5, 63.8, 67.4, 68.1, 126.3, 128.7, 130.5, 141.9, 146.7, 156.2. MS (APCI+) *m/z* calcd for C₃₈H₄₈NaO₆S₂ 687.3, found 687.2 (M⁺Na)⁺.
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- X-ray crystallography and crystal data for **8**. Monoclinic, *Cc* (no. 9), *a* = 41.256(3), *b* = 10.1714(5), *c* = 17.4177(10) Å, β = 105.5160(10)°, *V* = 7042.7(7) Å³, *Z* = 8, ρ_{calcd} = 1.254 g cm⁻³, μ = 1.96 cm⁻¹, final *R*₁ = 0.0375 for *I* > 2σ(*I*), *wR*₂ = 0.1011 for all data. The intensity data were recorded on a Rigaku AFC8-Saturn 70 system with MoKα radiation (λ = 0.71070 Å) at 173(2) K. The structure was solved by direct methods and refined by full-matrix least-squares analysis on *F*² by using SHELXL. Collection, solution and refinement proceeded normally. Hydrogen atoms were introduced in calculated positions with isotropic thermal parameters set twenty percent greater than those of their bonding partners. All hydrogen atoms were refined on the riding model. All other atoms were refined anisotropically. CCDC 730543 contains the supplementary crystallographic data for this Letter. These can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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