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Bithiophene-containing super-expanded calixpyrrole analogues

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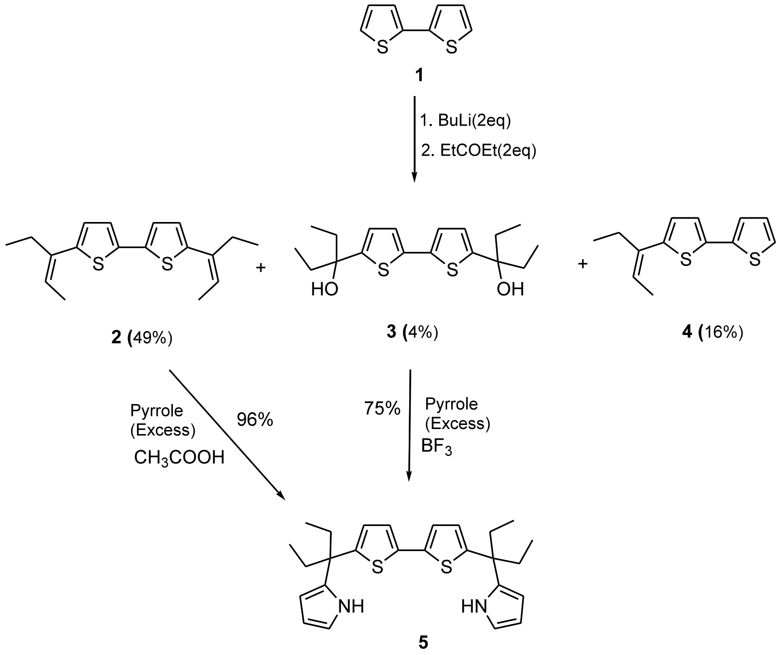
Abstract—Calixpyrrole-like mixed cyclic oligomers containing bithiophenes and pyrroles have been synthesized by condensing hybrid oligopyrrolic precursors. Condensation of 1,7-bis[(α-hydroxy-α,α-diethyl)bithiophene with oligopyrroles afforded a mixture of large cyclic oligomers. © 2002 Elsevier Science Ltd. All rights reserved.

Sensing of anions with reasonable selectivity is one of the leading issues in the field of molecular recognition chemistry[1] and considerable efforts have been devoted to the design and synthesis of neutral anion sensing systems. As a results of those active studies, various anion receptors having different degree of affinity have been designed and synthesized.[2–6] Generally, anion binding is more difficult to achieve than cation binding due to the weak interactions and diverse geometries of anions.[1b]

Since pyrrole-, furan- or thiophene-based macrocycles can manifest recognition and selectivity toward different guest ions, proper design of the host molecules



Scheme 1.

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containing those heterocycles would result in unique binding modes and activities.[7] If the macrocycles possess different cavity sizes, they can recognize guests by size and function as selective hosts. In order to accommodate larger guest molecules or multiple guest molecules by a folding–unfolding mode of action, the host molecules must have multiple binding functionalities, conformational flexibilities and proper geometrical constraints. With these regards, we have been interested in developing receptors based on the combination of five-membered aromatic heterocycles. The synthesis of larger cyclic oligomers containing furan,[8] pyrrole and thiophene has been reported recently.[9]

Herein, we report the synthesis and characterization of expanded hybrid calixpyrroles containing bithiophene and/or pyrrole rings. Our goal is to develop neutral receptors so that cyclic structures possess recognition and binding.

The synthetic route involves the condensation of oligopyrryl subunits with 1,7-bis[(α-hydroxy-α,α-diethyl)methyl]bithiophene in the presence of acid catalyst. α-Hydroxylation of 2,2′-bithiophene was carried out as shown in Scheme 1. Treatment of bithiophene (**1**) with *n*-butyl lithium followed by adding 3-pentanone was expected to afford the corresponding diols **3**. However, the major product was identified as **1**, which was possibly formed by dehydration of **3** during the column chromatographic isolation. The fact that independent treatment of **3** with silica gel in CH_2Cl_2 resulted in quantitative dehydration indicates the easiness of dehydration. The monohydoxylated compound **4** was also isolated in 16% yield. Treatment of **1** with excess pyrrole in the presence of $BF_3{\cdot}OEt_2$ (0.1 mol equiv.) afforded 1,7-bis-(2′-pyrryl)bithiophene (**5**). Dehydrated compound **2** was also quantitatively converted to **5** when **2** was treated with aqueous acetic acid. Oxatripyrromethane (**7**), which had been synthesized as reported previously,[10] was treated with diols **6**[10] in the presence of $BF_3{\cdot}OEt_2$ to afford **8** in 55% yield.

The solid-state structure of **5**, obtained by slow evaporation of dichloromethane/hexane solution, reveals that the two thiophene rings are almost coplanar each other with sulfur pointing opposite direction (Fig. 1). The offset angle of the two thiophene ring is only 7.80° and the compound adapted almost alternating conformation.[11]

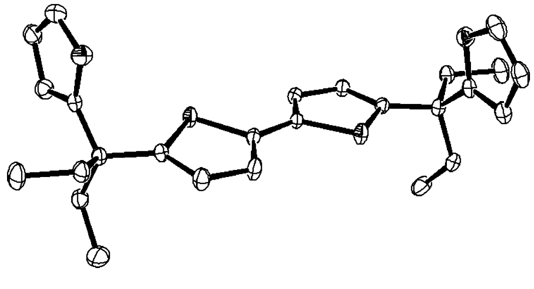
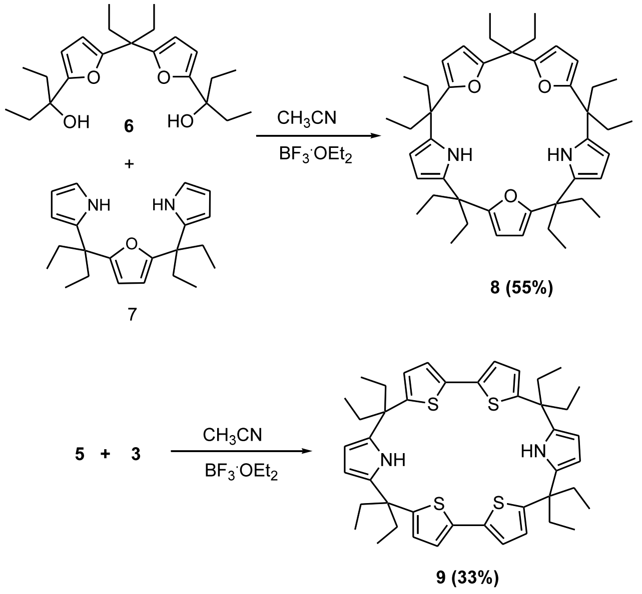


Figure 1. Solid-state structure of compound **5**. The structure clearly shows an almost *anti*-periplanar conformation of the two sulfur atoms.



Scheme 2.

Condensation of **5** with diol **3** (10 mM in acetonitrile, 0°C) in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$ (1 mM) afforded the hybrid hexameric macrocycle **9** in 33% yield (Scheme 2). When **6** was condensed with **7** in the presence of BF_3, the pentameric compound **8** was obtained in 55% yield.[12] The solid-state structure of compound **8**, shown in Fig. 2, shows that the molecule adapts a bowl-shaped conformation and a modified alternating conformation, wherein two adjacent furans are almost coplanar pointing inward. It is also observed that one of the *meso*-ethyl groups is pointing inward. The observed structural characteristics of solid-state **8** indicate that the multi-nuclear receptors based on the super-expanded pyrrolic macrocycles should be designed by carefully manipulating the functional groups and *meso*-substituents.

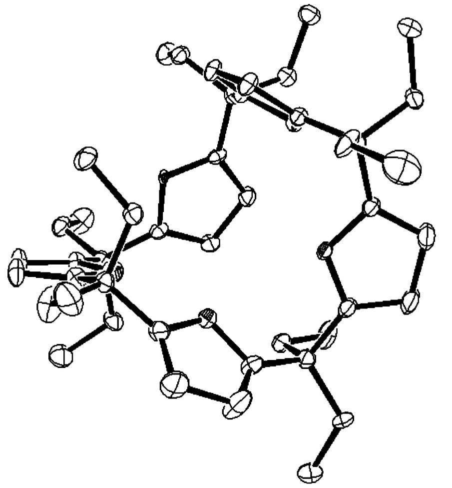
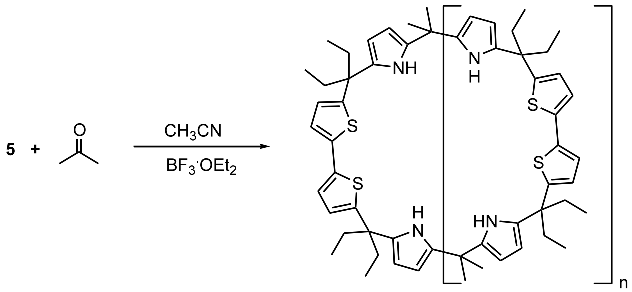


Figure 2. Solid-state structure of compound **8**. The two adjacent furans are pointing inwards.



10 (n = 1) 11%
11 (n = 2) 3%

Scheme 3.

The full characterization of each oligomer was achieved using mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy. Condensation of **5** with acetone carried out in acetone solvent resulted in the formation of cyclic octamer **10** and dodecamer **11** in 11 and 2.5% yields, respectively (Scheme 3).[13] The ^{1}H NMR spectra of the isolated oligomers showed symmetrical pattern and all the pyrrolic and thiophene protons displayed almost identical chemical shifts regardless the size of the macrocycles. However, the pyrrolic N–H of **10** shows a rather sharp singlet at 7.39 ppm, while that of **11** appears at 7.28 ppm. These observation indicate that the octamer **10** may have stronger intramolecular N–H–S hydrogen bonding than that of the dodecamer **11**. Attempts to produce macrocycles that could be formed by condensing with 3-pentanone were unsuccessful under the conditions investigated. The preliminary binding studies for halides anions (as tetrabutylammonium salts) carried out with **9**–**11** in organic solvent (DMSO-d_6) with ^{1}H NMR spectroscopy did not show any indication of appreciable binding.

In conclusion, we were able to synthesize and isolate bithiophene-containing expanded calixpyrrole analogues by condensation of hybrid oligopyrrolic compounds with ketone.

Considering the known applications of calixpyrroles,[12] the facile synthesis of the super-expanded calixpyrrole analogues outlined with this article may be contribute the development of the ion-binding chemistry. Currently, work is in progress to evaluate various cationic binding characteristics of the macrocycles.

Acknowledgements

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12. The formation of larger cyclic oligomers was minimized by adapting higher reaction concentrations.
13. *Typical procedure*: To a solution of **5** (44 mg, 0.10 mmol) and acetone (0.8 mL) was added $BF_3{\cdot}OEt_2$ (15 mg, 0.11 mmol) and the mixture was stirred for 30 min at 0°C. The reaction mixture was combined with aqueous NaOH (2 mL), then extracted with methylene chloride. The solvent was dried over $NaHCO_3$ and removed in vacuo. The remaining solid was separated by repeating column chromatography on silica (CH_2Cl_2/hexanes = 1/1 and CH_2Cl_2/petroleum ether = 1/1). Macrocycle **10**: yield 11%; ^{1}H NMR ($CDCl_3$): δ 0.65 (t, 24H, J = 7.3 Hz), 1.54 (s, 12H, *meso*-CH_3), 1.87 (m, 16H, *meso*-CH_2), 5.91 (t, 4H, pyrrole-H), 5.94 (t, 4H, pyrrole-H), 6.50 (d, 4H, thiophene-H), 6.79 (d, 4H, thiophene-H), 7.39 (bs, 2H, N-H); FAB MS calcd for $C_{58}H_{72}N_4S_4$: 953.48; found: 953.63. Macrocycle **11**: yield 3%; ^{1}H NMR ($CDCl_3$): δ 0.62 (t, 36H, J = 7.25 Hz), 1.50 (s, 18H, *meso*-CH_3), 1.83 (m, 24H, *meso*-CH_2), 5.92 (t, 4H, pyrrole-H), 5.94 (t, 4H, pyrrole-H), 6.52 (d, 4H, thiophene-H), 6.80 (d, 4H, thiophene-H), 7.28 (bs, 2H, N-H); FAB MS calcd for $C_{87}H_{108}N_6S_6$: 1430.22; found: 1430.05.