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Notes

Synthesis and Structure of Calix[n]bifurano[n]thiophene (*n* = 2-5) Hybrid Macrocycles†

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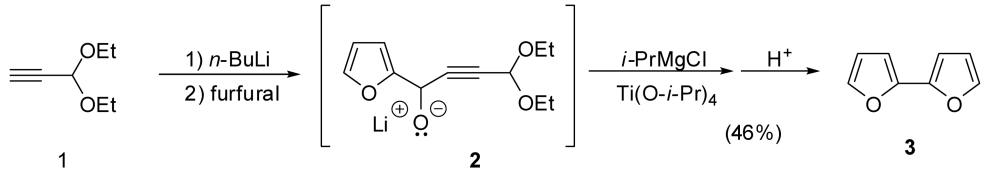
Anion or neutral molecule recognition have been one of the important areas in the molecular recognition due to their potential applications in biology and environmental science.[1-6] Design and synthesis of receptors possessing high affinity and selectivity still remains a challenging task due to rather complex nature of anionic species compared with those of cations. A number of newer and specifically functionalized receptors that bind selectively with anionic or neutral substrates have been reported as a result of these efforts. Among the reported receptors, calix[4]pyrroles and their modified congeners have been verified as one of the selective anion binding motifs. A variety of modification in calix[4]pyrroles including β-pyrrole substitution, *meso*-alterations[7-9] or attachment of fluorescent chromophores at the periphery[10] showed similar binding properties as unmodified receptors. We have been interested in developing new pseudo-calixpyrroles possessing improved stability and solubility in either organic or inorganic solvents by controlling binding characteristics. Incorporation of cation-binding site as well as anion binding site in a single macrocycle will be one of these approaches. With these regards, we here report the synthesis of a new class of hybrid macrocycles containing bifuran and thiophenes.

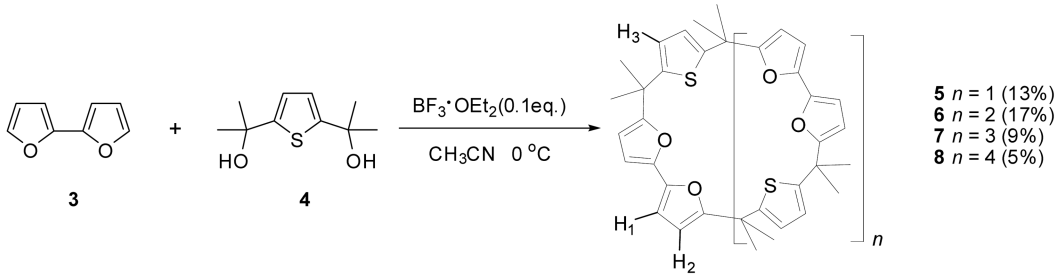
Results and Discussions

The various H-bonding donor group and acceptor group would be good models for studying amphiphilic binding properties. The key precursor 2,2'-bifuran **3** was synthesized from propargyl aldehyde diethyl acetal **1** and furfural.[11] The reaction proceeded *via* intermediate **2** followed by cyclization as shown in Scheme 1. The desired 2,2'-bifuran **3** was obtained in moderate yield.

The macrocyclic compounds **5-8** shown in the Scheme 2, were synthesized by typical acid-catalyzed condensation of 2,2'-bifuran **3** with thiophene diol **4** in acetonitrile. 2,2'-Bifuran **3** was rather unstable and should be used immediately after synthesis. The reaction afforded '3+3' conden-



Scheme 1



Scheme 2

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.

Table 1. ^{1}H NMR chemical shifts of furan and thiophene protons for compounds **5-8** recorded in $CDCl_3$

Compound	H_1 (ppm)	H_2 (ppm)	H_3 (ppm)
5	6.11	6.30	6.66
6	6.03	6.34	6.59
7	6.04	6.34	6.60
8	6.04	6.34	6.59

sation product **6** as major product in TLC along with other macrocycles (**5**, **7** and **8**). Interestingly, the compound **5** was not soluble in THF while others were freely soluble. So, compound **5** was easily isolated by recrystallization in THF (13%). The filtrate was then chromatographed on silica column and the remaining expanded macrocycles **6**, **7** and **8** were isolated in 17%, 9% and 5%, respectively. Since the R_f values of these macrocycles have sufficiently enough difference in TLC, a single and careful chromatographic separation was sufficient to isolate them in pure form.

The ^{1}H NMR spectra of the larger macrocycles **6-8** were almost identical indicating the structural similarity in solution but compound **5** displayed slightly different signals. The signals of the furan-Hs appeared at 6.04 and 6.34 ppm and those of thiophene appeared at 6.59 ppm in the macrocycles **6-8**, whereas in the case of **5**, furan-Hs appeared at 6.11 and 6.30 and 6.66 ppm for thiophene-Hs (Table 1).

Additionally, the structure of macrocycle **5** was characterized by single crystal X-ray diffraction analysis. The crystal was obtained from the slow evaporation of hexane/methylene chloride solution of **5**. The structure revealed that the compound **5** adopts complete 1,3-alternate conformation (Figure 1) and the bifuran units are spatially arranged in *syn*-parallel fashion with each other. The difference in the chemical shift of **5** compared with other larger macrocycles must be related with the relative conformational rigidity of the smaller macrocycle. The 3D packing structure of **5** is shown in Figure 2.

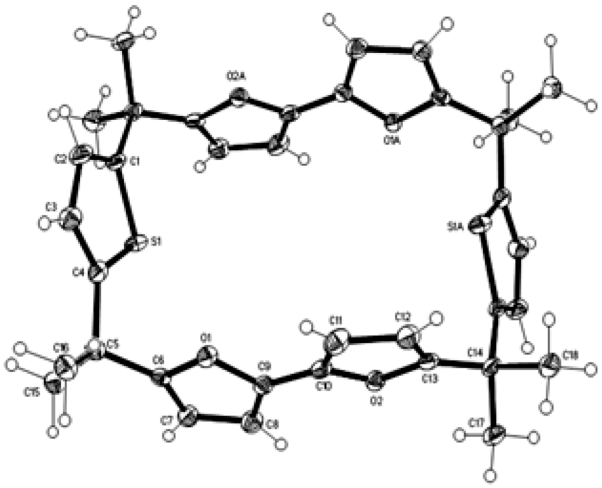


Figure 1. Single crystal X-ray structure of compound **5**. Disordered THF molecule was omitted for clarity. Note that the compound adopts 1,3-alternate conformation. Thermal ellipsoids are 50% probability level.

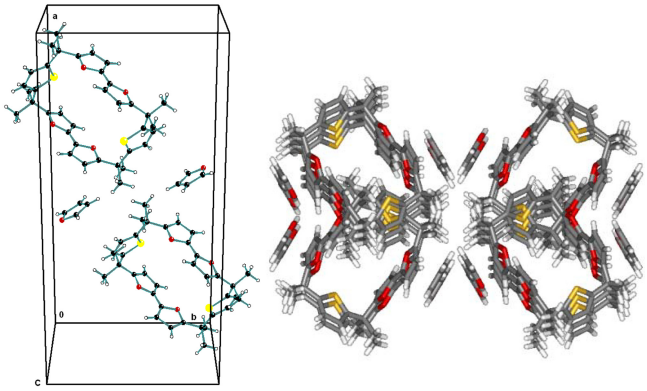


Figure 2. 3D-Packing structure of the macrocycle **5**.

The structure of these thiophene-bifuran hybrid macrocycles was significantly different from those of bithiophene-pyrrole containing macrocycles.[12] Ability of the synthesized hosts as possible metal ion receptors was tested by addition of perchlorate salts of transition metal ions and following the changes in their ^{1}H NMR spectra. Unfortunately, none of the macrocycles showed appreciable changes in their spectra. In summary, we have demonstrated that various size of non-aromatic heterocycles can be synthesized in single batch of reaction. The synthesized macrocycles did not show any particular cation binding affinity.

Experimental

Melting points were measured on Thomas Hoover Melting point apparatus and are uncorrected. ^{1}H and carbon NMR spectra (400 MHz, Bruker DPS-400) were recorded in $CDCl_3$ with TMS as the internal standard. High-resolution FAB mass spectra were obtained on AUTO SPEC M-363 high-resolution mass spectrometer. Column chromatography was performed on silica (Merck, 230-400 mesh). All reagents were obtained from Aldrich or TCI and used as received. Thiophene-2,5-dimethanol was synthesized according to the literature procedure.[12] The compounds **3** was synthesized by previously reported procedure with slight modification.[11]

2,2'-Bifuran (3). A diethylether solution of propagyl aldehyde diethylacetal (2.2 mL, 15 mmol) and *n*-butyl lithium (9.4 mL, 1.0 molar solution in *n*-hexane) was stirred for 1.5 hr at room temperature in argon atmosphere. Then furfural (1.0 mL, 12 mmol) was added and stirred for an additional 1 hr. The temperature was then cooled to −60 °C and then *iso*-propyl magnesiumchloride (34 mL, 45 mmol) followed by $Ti(O\text{-isoprop})_4$ (6.0 mL, 21 mmol) were added and the whole mixture was stirred for 1 hr at −35 °C. Dilute HCl (0.1 N, 50 mL) was added to quench the reaction and extracted with diethyl ether (50 mL × 3). The organic layer was washed with saturated $NaHCO_3$ solution and dried ($MgSO_4$). Solvent was removed in vacuo and the remaining solid was purified by column chromatography on silica (hexanes). Yield 740 mg (46%); ^{1}H NMR ($CDCl_3$) δ 7.41 (d, 2H, furan-H), 6.55 (d, 2H, furan-H), 6.46-6.44 (dd, 2H, furan-

H); ^{13}C NMR ($CDCl_3$) δ 105.49, 111.77, 142.16, 147.04.

Macrocycles (5-8). Bifuran (270 mg, 2 mmol) was dissolved in CH_3CN and $BF_3{\cdot}OEt_2$ (25.3 μL, 0.2 mmol) was added with stirring. Then 2,5-bis[(α-hydroxy-α,α-dimethyl)-methyl]thiophene (400 mg, 2 mmol) dissolved in CH_3CN, was added dropwise and the mixture was stirred for 1 hr at 0 °C. The mixture was combined with aqueous NaOH (0.1 N, 50 mL) and extracted with CH_2Cl_2 (50 mL × 3). TLC analysis showed that the R_f values of the macrocycles are in the following order: **6** > **7** > **8** > **5** (from top to bottom). Solvent was removed in vacuo and compound **5** was selectively crystallized in THF and the remaining dissolved compounds were purified by column chromatography on silica (CH_2Cl_2/hexane = 1/4).

Compound 5: Yield 80 mg (13%); ^{1}H NMR ($CDCl_3$) δ 6.67 (s, 4H, thiophene-H), 6.26-6.27 (d, 4H, furan-H), 6.11-6.12 (d, 4H, furan-H), 1.69 (s, 24H, CH_3); ^{13}C NMR ($CDCl_3$) δ 28.89, 38.57, 105.13, 105.28, 120.67, 145.45, 152.02, 160.21; FAB MS Calcd. for $C_{36}H_{36}O_4S_2$ 596.21, obsd. 596.26.

Compound 6: Yield 99 mg (16%); ^{1}H NMR ($CDCl_3$) δ 6.59 (s, 6H, thiophene-H), 6.33-6.34 (d, 6H, furan-H), 6.02-6.03 (d, 6H, furan-H), 1.71 (s, 36H, CH_3); ^{13}C NMR ($CDCl_3$) δ 30.03, 39.23, 105.35, 106.14, 122.80, 145.87, 150.917, 160.88; FAB MS calcd for $C_{54}H_{54}O_6S_3$ 894.31, obsd. 895.0.

Compound 7 (*n* = 3): Yield 53 mg (9%); ^{1}H NMR ($CDCl_3$) δ 6.60 (s, 8H, thiophene-H), 6.33-6.34 (d, 8H, furan-H), 6.03-6.04 (d, 8H, furan-H), 1.70 (s, 48H CH_3); ^{13}C NMR ($CDCl_3$) δ 29.61, 38.80, 105.01, 105.66, 122.21, 145.46, 150.61, 160.51; FAB MS calcd for $C_{72}H_{72}O_8S_4$, 1192.41, obsd. 1193.0.

Compound 8: Yield 31 mg (5%); ^{1}H NMR ($CDCl_3$) δ 6.59 (s, 10H, thiophene-H), 6.34-6.35 (d, 10H, furan-H), 6.04-6.05 (d, 10H, furan-H), 1.69 (s, 60H, CH_3); ^{13}C NMR ($CDCl_3$) δ 28.89, 38.57, 105.13, 105.28, 120.68, 145.45, 152.02, 160.22; FAB MS calcd for $C_{90}H_{90}O_{10}S_5$ 1490.51, found 1477.0 (M^+-CH_3).

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