SYNTHESES AND PROPERTIES OF CALIXARENE ANALOGS CONTAINING THIOPHENE RING

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Abstract - Calixarene analogs containing a thiophene unit in the macrocyclic ring were prepared by a stepwise method. The macrocycles adopt a cone-like form as the preferred conformation in solution. The induced chemical shift change, NOE experiment, and relaxation time (T_1) measurement supported the fact that the macrocycle forms a complex with the *N*-methylpyridinium salt.

Calixarenes are macrocycles available in a variety of ring sizes and are of interest both as complexation hosts for ion and molecules and as a skeleton for producing more complex structures.[1] Although the chemistry of calixarenes has been extensively studied with respect to the modification of the frameworks at the lower (small) or upper (large) rims from the viewpoint of additional functionality, there has been relatively little research concerning the modification of the methylene moiety due to the relatively inert reactivity on this site.[2,3]

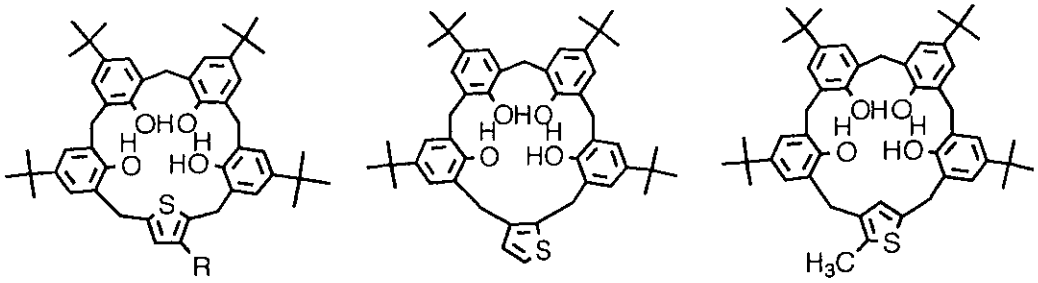


Figure 1.

This situation inspired us to synthesize the calixarene analogs, which were constructed by changing from the methylene moiety to other units as the bridge. Therefore, we synthesized the calixarene analogs containing a thiophene unit in the macrocyclic ring. The use of thiophene as a building block offers the possibility of interesting modifications on the thiophene ring due to the high reactivity. We now describe the syntheses of the calixarene analogs containing the thiophene unit and their complexation behavior with the *N*-methylpyridinium ion.

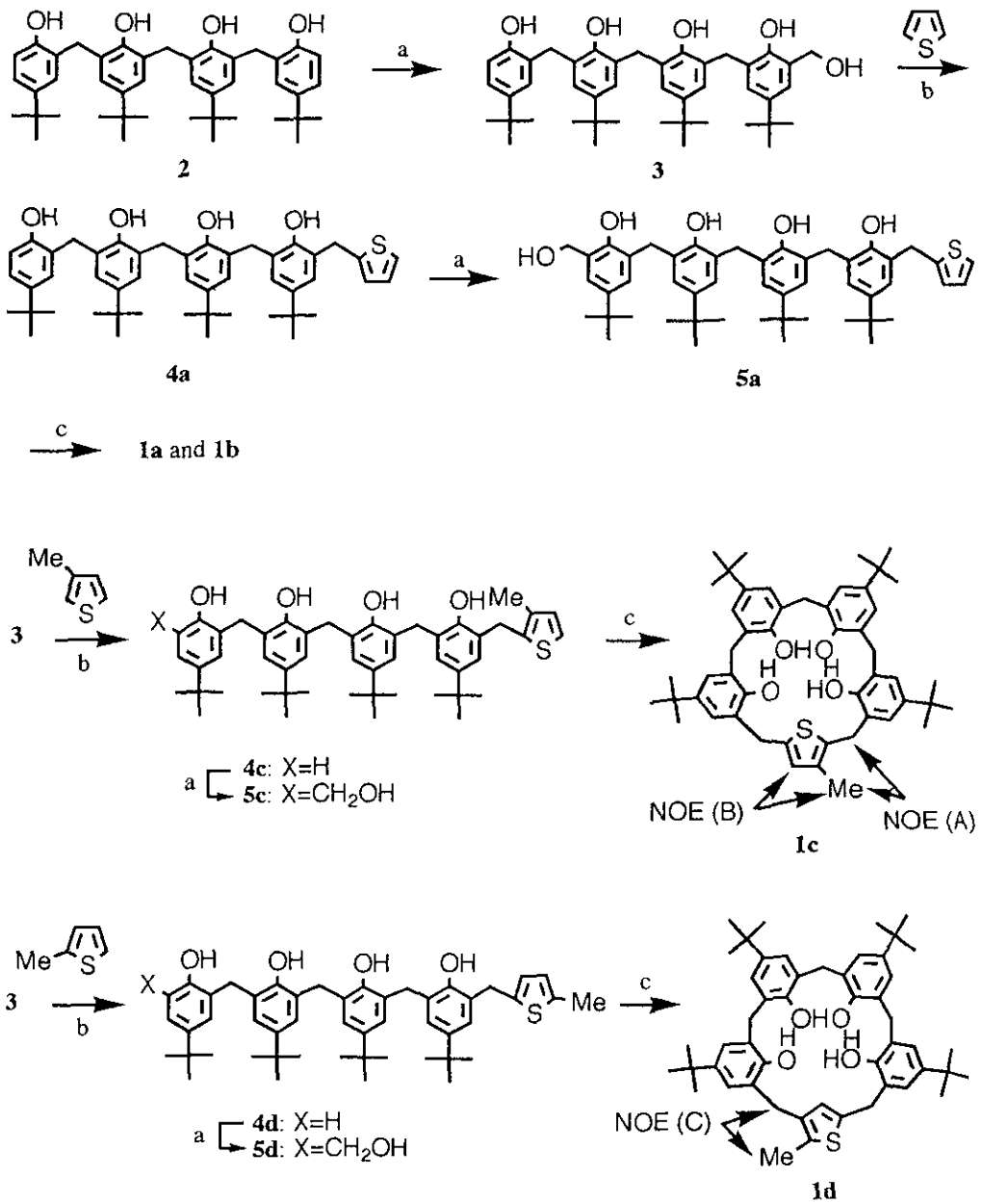
Macrocycles (**1**) were prepared from the corresponding acyclic oligomers in a stepwise method as shown in Scheme 1. Hydroxymethylation of the phenol-formaldehyde tetramer (**2**)[4] with 35 % formalin in the presence of 25% aqueous NaOH solution led to the monohydroxymethyl tetramer (**3**) in 25 % yield. Condensation of **3** with an excess of thiophene in the presence of *p*-toulenesulfonic acid without solvent gave the linear oligomer (**4a**) in 58 % yield. **4a** was hydroxymethylated again, then followed by acid-catalyzed cyclization of the resulting alcohol (**5a**) under high dilution conditions (0.3-1.0 x 10^{-3} M) to yield **1a** and **1b** in 50 and 40 % yields, respectively. Similar reactions using 2- and 3-methylthiophene instead of thiophene gave the corresponding calixarene analogs (**1c** and **1d**) in 29 and 53 % yields, respectively.

The spectroscopic properties such as NMR, IR, and FAB MS spectra of the macrocycles (**1**) were in agreement with the assigned structures.[5] Coupling constant values of the thiophene ring protons of **1a** and **1b** indicated that **1a** (J= 0.0 Hz) is the 2,5-disubstituted thiophene derivative and **1b** (J= 5.3 Hz) is 2,3-disubstituted. NOE experiments in the NMR spectra of **1c** and **1d** supported the structures as shown in Scheme 1. Strong NOEs between the methyl group of the thiophene ring and the adjacent methylene protons (NOE (A) and (C)) were observed in both **1c** and **1d**. The NOE between the methyl group and the aromatic proton of the thiophene ring (NOE (B)) is also observed in **1c**, however, there is no NOE between the methyl group and the aromatic proton of the thiophene ring in **1d**.

In the IR spectra, OH absorptions of **1** were observed in the range of 3357-3401 cm^{-1} as broad bands in chloroform. In the ^{1}H NMR spectra of **1** in $CDCl_3$ at 20 °C, OH proton signals were observed in the range of 6.18-9.11 ppm. Comparing the IR and ^{1}H-NMR spectra of the phenolic OH groups of **1** with those of calix[*n*]arene (ν_{OH}=3138 (*n*=4), 3280 (*n*=5) cm^{-1}, δ_{OH}=10.2 (*n*=4), 8.0 (*n*=5) ppm),[1a] the intramolecular hydrogen bonding in **1** is weaker than that of the calix[*n*]arene due to the introduction of the thiophene ring, which does not contribute to the intramolecular hydrogen bonding.

The methylene protons of **1** in the ^{1}H-NMR spectra appeared as singlets at room temperature. These signals did not split even at -60 °C in $CDCl_3$, indicating that **1** is conformationally flexible. Therefore, the conformation of **1** was evaluated using the ^{13}C NMR chemical shift of the $ArCH_2Ar$ methylene carbon, which is used as a means for assessing calixarene conformations. It is known that the methylene carbon resonances for calixarenes appear at *ca.* δ 30-33 ppm when the adjacent aryl rings are *syn* and at *ca.* δ 36-38 ppm when they are *anti*.[6] Applying this

to **1**, the chemical shifts of the methylene carbon atoms, which were observed in the range of δ 31.1-31.3 ppm, suggested that all phenol units adopt a *syn*-orientation. Thus, a cone-like form is the preferable conformation in this system.



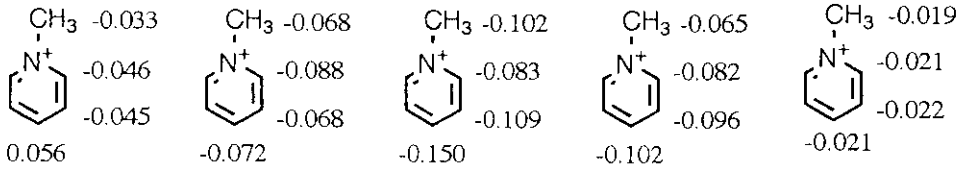
a) 25% NaOHaq., 35% HCHOaq., MeOH/dioxane, 50 °C, 1.5 h. b) *p*-TsOH, reflux, 4 h.
c) *p*-TsOH, benzene, high dilution conditions (0.3-1.0 X 10^{-3} M), reflux, 8 h.

Scheme 1.

It is known that calixarenes bind quaternary ammonium ions in solution.[7] We also investigated the host-guest complexation behavior of **1a** with *N*-methylpyridinium iodide (**Pyr**$^+$). In the presence of **1**, all resonance peaks of the salt moved to a higher magnetic field due to the ring current effect of the cyclophane core. In contrast, the linear tetramer (**2**) could not induce any significant up-field shift. This discrepancy suggests the importance of the ring structure during the inclusion of cationic guest molecules.

Table 1. Chemical shift values of $ArCH_2Ar$ methylene protons, hydroxyl protons and carbons atoms (500 MHz for ^1H and 125 MHz for ^{13}C in $CDCl_3$) at 25 °C, and stretching absorption of hydroxyl group in the IR spectra (in $CHCl_3$) at 20 °C.

	$ArC\underline{H}_2Ar$ [ppm] (intensity)	$ArC\underline{C}H_2Ar$ [ppm]	δ_{OH} [ppm]	ν_{OH} [cm^{-1}]
1a	3.76, 4.06 (3:2)	31.2, 31.3	6.60, 7.43	3357
1b	3.80, 3.87, 4.00 (1:3:1)	31.1, 31.3	6.48, 6.80, 8.99, 9.11	3357
1c	3.75, 3.77, 3.78, 3.96, 4.02 (1:1:1:1:1)	30.9, 31.1	6.70, 6.82, 7.60, 7.63	3401
1d	3.73, 3.78, 3.80, 3.81, 3.98 (1:1:1:1:1)	31.6, 31.8	6.18, 7.10, 8.44, 8.51	3311



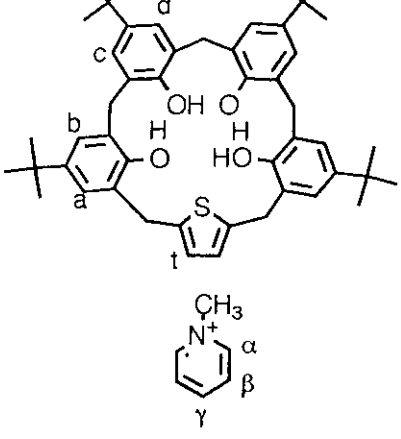
1a + **Pyr**$^+$ **1b** + **Pyr**$^+$ **1c** + **Pyr**$^+$ **1d** + **Pyr**$^+$ **2** + **Pyr**$^+$

Figure 2. Chemical shift changes of the protons in *N*-methylpyridinium iodide (**Pyr**$^+$) induced by added calixarene analogs (**1**) or phenol-formaldehyde tetramer (**2**) as a reference compound at 25 °C, $CDCl_3$:CD_3CN=10:1 (v/v), [**1**]=[**2**]=[**Pyr**$^+$]=1.00X10^{-2}M, - denote the shift to higher magnetic field.

Table 2. NOEs in the complex of **1a** with **Pyr**$^+$ at 25 °C in $CDCl_3$:CD_3CN=10:1 (v/v).

		Observed NOE, % *N*-methylpyridinium iodide (**Pyr**$^+$)			
Irradiated		N-CH_3	H-α	H-β	H-γ
phenol	H-a	5.6	8.7	11.0	9.5
	H-b	6.6	8.9	11.2	9.8
	H-d	6.7	8.5	10.0	10.9
thiophene	H-t	2.6	4.2	5.4	9.4

H-c proton was overlapped with the proton of chloroform.



Further evidence for the inclusion of **Pyr**$^+$ in **1a** was obtained from the NOE experiment.[7b] The NOE peak intensities with respect to the protons of **Pyr**$^+$ are shown in Table 2. The peak intensities are strong enough to support the inclusion of **Pyr**$^+$ into the cavity of **1a**.

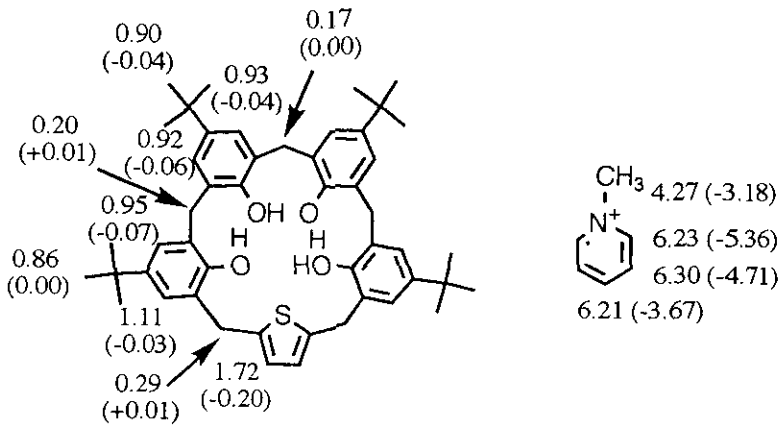


Figure 3. ^{1}H NMR relaxation times (T_1/s) of calixarene analog (**1a**) in the absence of *N*-methylpyridinium iodide (**Pyr**$^+$) at 25 °C in $CDCl_3$:CD_3CN=10:1 (v/v). The figures in the parentheses denote the changes in T_1 in the presence of **Pyr**$^+$.

The ^{1}H-NMR relaxation time (T_1) measurement also supported the fact that **Pyr**$^+$ was included in the core.[8] The T_1 values for all protons of **Pyr**$^+$ drastically decreased when **1a** was complexed with **Pyr**$^+$, indicating that the formation of the complex suppressed the molecular motion of both **Pyr**$^+$ and **1a**. Interestingly, a larger decrease was observed at the β-proton in the thiophene ring of **1a** during the formation of the complex, implying that the

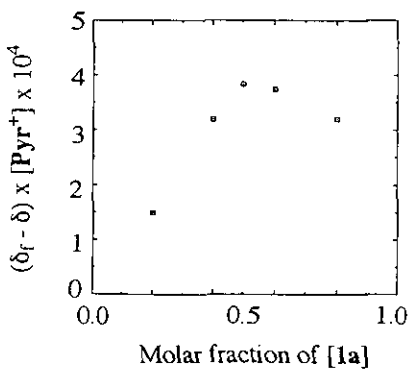


Figure 4. Job's plot. (δ_f - δ) is shift in ppm induced in the NCH_3 proton of **Pyr**$^+$, and the total concentration of **1a** plus **Pyr**$^+$ maintained at 10 mM in $CDCl_3$:CD_3CN=10:1 (v/v) at 20 °C.

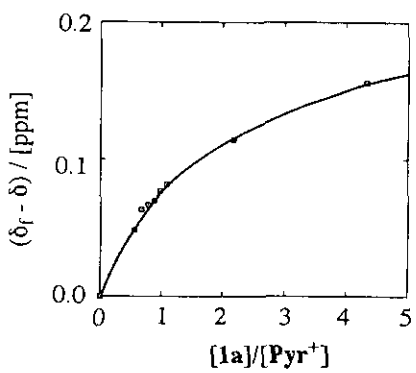


Figure 5. ^{1}H NMR titration of **Pyr**$^+$ with **1a** in $CDCl_3$:CD_3CN=10:1 (v/v) at 20 °C. (δ_f - δ) is change in chemical shift of NCH_3 proton of **Pyr**$^+$ as a result of added **1a**.

thiophene ring also participated in the formation of the complex as a π-base as well as the phenol ring.

We estimated the stoichiometry of the complex using Job's plot method.[9] The 1:1 stoichiometry of the complex was confirmed by the plot that contained a maximun at the mole ratio of 0.5 in this case. The association constants (K_a) of **1a** to **Pyr**$^+$ was determined by a nonlinear least-squares fitting method of a binding curve obtained from the ^{1}H NMR titration (K_a = 104±10 M^{-1}).[10] This value is quite similar to those of calix[*n*]arenes (K_a = 52 M^{-1} (*n*=4), K_a = 190 M^{-1} (*n*=6), K_a = 132 M^{-1} (*n*=8)).[7b]

In conclusion, we prepared the calixarene analogs containing the thiophene ring, which is expected to be a highly potential functionalizable unit. We also elucidated that the macrocycles have a binding ablility for *N*-methylpyridinium iodide. The formation of the complex was supported by the induced chemical shifts, NOE experiment, and T_1 measurement. The functionalization study of the thiophene ring is now in progress.

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5. Selected spectral data are as follows. **1a**: mp 141-144 ℃ (chloroform-hexane). ^{1}H NMR ($CDCl_3$): δ 1.25 (s, 18H, *t*-Bu x 2), 1.28 (s, 18H, *t*-Bu x 2), 3.76 (s, 6H, CH_2 x 3), 4.06 (s, 4H, CH_2 x 2), 6.60 (br s, 2H, OH x 2), 6.75 (s, 2H, thiophene ring proton x 2), 7.00 (d, 2H, Ar-H x 2, *J*=2.5 Hz), 7.19 (d, 2H, Ar-H x 2, *J*=2.5 Hz), 7.21 (d, 2H, Ar-H x 2, *J*=2.5 Hz), 7.24 (d, 2H, Ar-H x 2, *J*=2.5 Hz), 7.43 (br s, 2H, OH x 2). FAB-MS (*m*-nitrobenzyl alcohol): m/z 745 $(M+H)^+$. **1b**: mp 168-173 °C (chloroform-hexane). ^{1}H NMR ($CDCl_3$): δ 1.22 (s, 9H, *t*-Bu), 1.23 (s, 9H, *t*-Bu), 1.25 (s, 9H, *t*-Bu), 1.30 (s, 9H, *t*-Bu), 3.80 (s, 2H, CH_2), 3.87 (s, 6H, CH_2 x 3), 4.00 (s, 2H, CH_2), 6.48 (br s, 1H, OH), 6.70 (d, 1H, thiophene ring proton, *J*=5.3 Hz), 6.80 (s, 1H, OH), 6.99 (d, 1H, thiophene ring proton, *J*=5.3 Hz), 7.07 (d, 1H, Ar-H,

J=2.4 Hz), 7.10 (d, 1H, Ar-H, *J*=2.4 Hz), 7.12 (d, 1H, Ar-H, *J*=2.4 Hz), 7.13 (d, 1H, Ar-H, *J*=2.4 Hz), 7.15 (d, 1H, Ar-H, *J*=2.4 Hz), 7.18 (d, 1H, Ar-H, *J*=2.4 Hz), 7.19 (d, 1H, Ar-H, *J*=2.4 Hz), 7.20 (d, 1H,Ar-H, *J*=2.4 Hz), 8.99 (br s, 1H, OH), 9.11 (br s, 1H, OH). FAB-MS (*m*-nitrobenzyl alcohol) : m/z 745 $(M+H)^+$. **1c**: mp 153-155 ℃ (hexane). ^{1}H NMR ($CDCl_3$): δ 1.24 (s, 18H, *t*-Bu x 2), 1.27 (s, 18H, *t*-Bu x 2), 2.14 (s, 3H, CH_3), 3.75 (s, 2H, CH_2), 3.77 (s, 2H, CH_2), 3.78 (s, 2H, CH_2), 3.96 (s, 2H, CH_2), 4.02 (s, 2H, CH_2), 6.70 (br s, 1H, OH), 6.72 (s, 1H, thiophene ring proton), 6.82 (br s, 1H, OH), 6.98 (d, 1H, Ar-H, *J*=2.4 Hz), 7.00 (d, 1H, Ar-H, *J*=2.4 Hz), 7.15-7.29 (m, 5H, Ar-H x 5), 7.22 (d, 1H, Ar-H, *J*=2.4 Hz), 7.60 (br s, 1H, OH), 7.63 (br s, 1H, OH). FAB-MS (*m*-nitrobenzyl alcohol): m/z 759 $(M+H)^+$. **1d**: mp 110-112 ℃ (hexane). ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 9H, *t*-Bu), 1.27 (s, 9H, *t*-Bu), 1.28 (s, 9H, *t*-Bu), 1.29 (s, 9H, *t*-Bu), 2.28 (s, 3H, CH_3), 3.73 (s, 2H, CH_2), 3.78 (s, 2H, CH_2), 3.80 (s, 2H, CH_2), 3.81 (s, 2H, CH_2), 3.98 (s, 2H, CH_2), 6.18 (br s, 1H, OH), 6.92 (s, 1H, thiophene ring proton), 6.97 (d, 1H, Ar-H, *J*= 2.5 Hz), 7.05 (d, 1H, Ar-H, *J*= 2.5 Hz), 7.10 (br s, 1H, OH), 7.13-7.19 (m, 5H, Ar-H x 5), 7.24 (d, 1H, Ar-H, *J*=2.5 Hz), 8.44 (br s, 1H, OH), 8.51 (br s, 1H, OH). FAB-MS (*m*-nitrobenzyl alcohol): m/z 759 $(M+H)^+$.

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