Synthesis of Chiral Calix[4]resorcinarenes *via* Mono-*O*-benzylation. Complexation Behavior with a Chiral Trimethylammonium Compound

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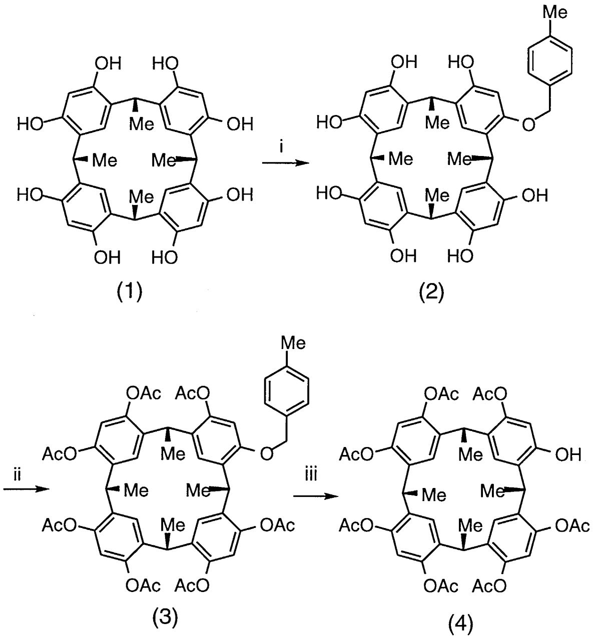
Chiral calix[4]resorcinarenes were prepared *via* mono-*O*-benzylation, and their conformational properties in solution were described. The complexation behavior of the heptahydroxy derivative with a chiral trimethylammonium compound in methanol was investigated by ^{1}H NMR spectroscopy.



Reagents. i. 4-$CH_3C_6H_4CH_2Cl$, $KOBu^t$. ii. Ac_2O. iii. $(CH_3)_3SiBr$

Calix[4]resorcinarenes are [1.1.1.1]metacyclophanes in which four resorcinol units are linked via methylene bridges at the 4,6-positions. These compounds have attracted much interest in the field of supramolecular chemistry as artificial receptors[1-3] and starting materials for the preparation of more sophisticated molecules.[4] In order to synthesize useful building blocks for molecular receptors with chiral recognition ability, we are studying the generation of molecular asymmetry in calix [4]resorcinarenes.[5]

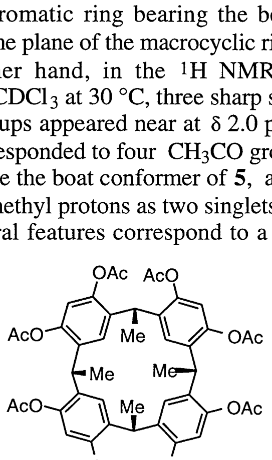
The metacyclophanes are readily available by the acid-catalyzed condensation of resorcinol with aliphatic or aromatic aldehydes in high yield.[6,7] This reaction leads to a mixture of four stereoisomers due to the presence of substituents at the bridge positions. When aliphatic aldehydes were used as condensation reagents, the thermodynamically most stable isomers, in which the relative configuration of the alkyl substituents derived from aldehydes are all-*cis*, can be selectively obtained. Since the all-*cis* isomers possess effective C_{4v} symmetry in solution, mono-functionalization of the hydroxyl groups at the peripheral position results in disappearance of the plane of symmetry in the cyclophanes.[8] For example, mono-*O*-benzylated calix[4]resorcinarenes consist of a pair of enantiomers. We thus studied the partial benzylation of the metacyclophanes. Although the reaction gave a mixture of several products, a mono-*O*-benzyl derivative could be readily isolated. In this communication, we present the preliminary results on the preparation and conformational properties of chiral calix[4]resorcinarenes and complexation behavior with a chiral trimethylammonium ion in solution.

The calix[4]resorcinarene (**1**), obtained from resorcinol and acetaldehyde, was used as a framework molecule in this study. The reaction of **1** with 1.2 molar amount of 4-methylbenzyl chloride was carried out in dry DMF with potassium *tert*-butoxide as a base. The solution was gently refluxed for 24 h under an argon atmosphere. The mono-*O*-benzylated derivative (**2**) was isolated by dry column chromatography (silicagel, acetonitrile /chloroform 3:2) in 32% yield, m.p. 200 °C(dec.). Treatment of **2** with acetic anhydride in the presence of pyridine gave the heptaacetate (**3**) in 64% yield, m.p. 205-208 °C. Debenzylation was conducted by refluxing a solution of **3** and bromotrimethylsilane in chloroform. After TLC separation (silicagel, ethyl acetate/hexane 2:1), the monohydroxy derivative (**4**) was purified by recrystallization from methanol in 23% yield, m.p. 217-220 °C.

The ^{1}H NMR spectrum of **2** in methanol-d_4 at 30 °C showed eight singlets with equal intensities, four of which at lower field were assigned to the intraannular protons of the metacyclophane. Judging from their chemical shifts (Figure 1a. δ 6.720, 6.743, 7.043, 7.099 ppm), a "boat-like" arrangement seems to be the preferred conformation.[6]

Variable-temperature ^{1}H NMR spectra of the heptaacetate **3** in $CDCl_3$ or DMSO-d_6 showed features similar to the octaacetate (**5**); several broad peaks were observed at 30 °C, which narrowed at higher temperatures. At 100 °C in DMSO-d_6, eight singlets for the aromatic protons of the cyclophane core were found. On the other hand, in $CDCl_3$ at -30 °C, the spectrum indicated the presence of two boat conformers in a ratio of 4:1.[9] In the major conformer, the aromatic ring bearing the benzyloxy group is perpendicular to the plane of the macrocyclic ring.

On the other hand, in the ^{1}H NMR spectrum of the heptaacetate **4** in $CDCl_3$ at 30 °C, three sharp singlets assigned to three CH_3CO groups appeared near at δ 2.0 ppm, and a slightly broad singlet corresponded to four CH_3CO groups appeared near at δ 2.3 ppm. Since the boat conformer of **5**, at -30 °C in $CDCl_3$, shows its acetyl methyl protons as two singlets at δ 2.03 and 2.40 ppm, these spectral features correspond to a single structure of



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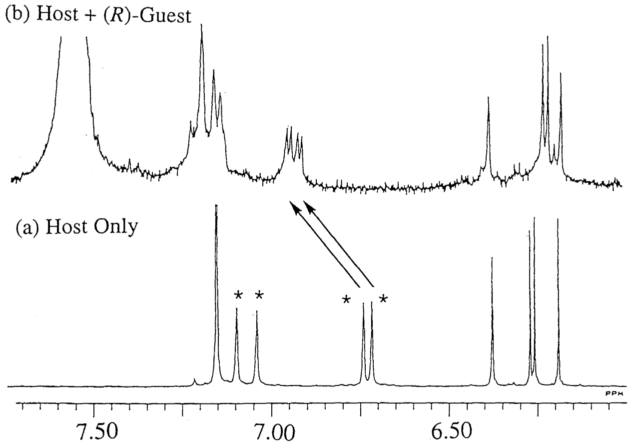
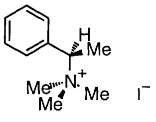


Figure 1. Changes in ^{1}H NMR spectra by the host-guest complexation between the calix[4]resorcinarene mono-*O*-benzyl ether **2** and the trimethylammonium ion (*R*)-**6** in CD_3OD: (a) [**2**]= 3 mM. (b) [**2**]= 3 mM, [(*R*)-**6**] = 10 mM. The asterisks indicate the intraannular aromatic protons of **2**.

the possible two boat conformers. From the comparison of the chemical shifts of **4**[10] with those of **5**, both determined at -30 °C, we concluded that the aromatic ring bearing the hydroxyl group is vertically oriented in the boat conformation.



(6)

Calix[4]resorcinarenes bind quaternary ammonium ions in alkaline[11] and neutral water.[12] We have also found the host-guest type complexation in methanol. Thus, we examined the complexation behavior of **2** with a chiral ammonium salt in this solvent by ^{1}H NMR spectroscopy. In the presence of **2**, all resonance peaks of the ammonium salt **6** (*R* isomer) moved to a higher magnetic field due to the ring current effect of the metacyclophane core. Examination of the chemical shift changes of **6** revealed that the trimethylammonium group is included in the cavity of **2**.

Figure 1 shows the aromatic region of the ^{1}H NMR spectra for **2** in CD_3OD: (a) in the absence of **6**, (b) in the presence of enantiomerically pure **6** (*R*-isomer). The host **2** shows eight singlets for the aromatic protons of the macrocycles. In the presence of the optical active **6** (*R*-isomer), some of the singlets were split into doublets. This indicates the formation of diastereomeric complexes.

With respect to the protons of the host compound, the largest chemical shift changes to lower field were observed for the intraannular protons of the horizontally oriented aromatic rings of the host compound. Their chemical shift changes were indicated by the arrows in Figure 1. On the other hand, the chemical shift changes for the aromatic protons at the extraannular position are negligible. These chemical shift changes are most likely explained by the conformational change due to the complexation; the boat conformation for the free host and the cone conformation for the complexed host.

In conclusion, chiral calix[4]resorcinarenes could be prepared by mono-*O*-functionalization in moderate yields. Facile preparation encourages further design of functional calix[4]resorcinarenes for artificial receptors with chiral recognition ability.

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10 In $CDCl_3$ at -30 °C, the aromatic protons of the macrocycle resonate at δ 5.925, 5.935, 6.407, 6.747, 6.893, 6.937, 7.236, 7.410 ppm.

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