Syntheses of Chiral Calixarene Analog Incorporating Amino Acid Residues: Molecular Recognition for a Racemic Ammonium Ion by the Macrocycles

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Chiral calixarene analog incorporating amino acid residues into macrocyclic rings was prepared. The macrocycles form a chiral concave, which is induced by the chiral transmission from the amino acid to the phenol-formaldehyde tetramer unit through the hydrogen bonds. Molecular recognition for a chiral ammonium ion by the macrocycles was investigated.

Modifying calixarenes to provide various properties into the molecules is a field that has great promise. Many studies of the modification of calixarenes have so far been made at the small (lower) and large (upper) rims of the calixarene skeleton.[1] Although some groups have made calixarene analog,[2] we noticed that the modification of the methylene backbone has not been exploited to any great extent. It occurred to us to make the chiral calixarene analog, which was constructed by changing from the methylene moiety to the chiral unit. Introduction of a chiral unit into the macrocyclic ring is expected to transfer the chirality from the chiral unit to the entire molecule.[3] In this case, a hydrogen bonded array could play an important role in making the chiral cavity because it is relatively strong and is a directed non-covalent bond.[4]

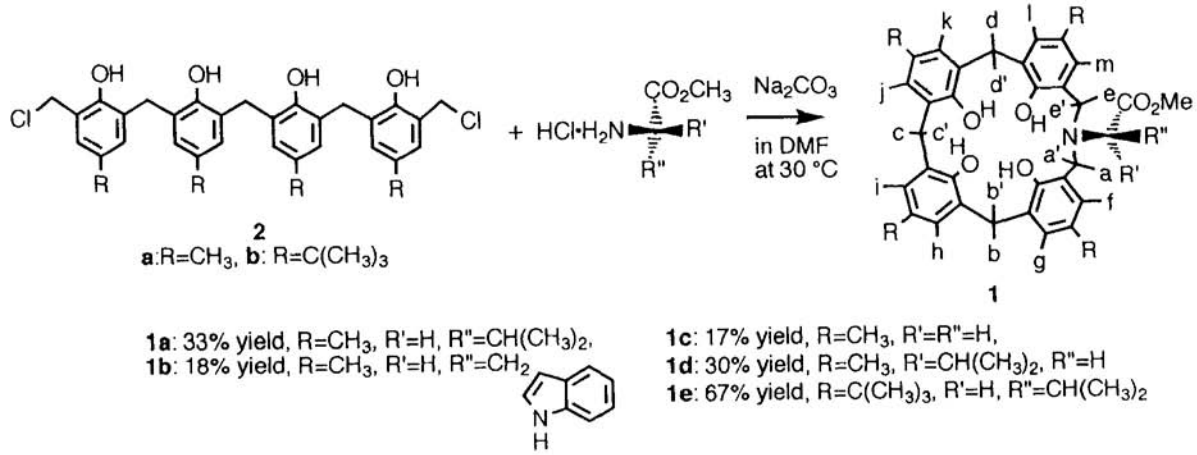
In this paper, we describe the preparation of chiral calixarene analog incorporating amino acid residues into their macrocyclic rings and the molecular recognition for a chiral ammonium ion by the macrocycles.

Macrocycles **1** were prepared by the cyclization reaction of the bis(chloromethyl) phenol-formaldehyde tetramer **2**[5] with amino acid methyl ester in dry DMF at 30 °C under a nitrogen atmosphere in 17-67% yields. They were identified on the basis of IR, mass, and 1D and 2D NMR spectral data and elemental analysis.[6] Achiral homoazacalixarenes have already been synthesized by Takemura *et al.*[2b]

The conformations of the macrocycles were determined using NMR spectroscopy. The $ArCH_2Ar$ methylene protons of **1** appeared as pairs of doublets due to the geminal coupling between H_{exo} and H_{endo} even at 20 °C and did not coalesce in $CDCl_3$ up to 55 °C. The differences between the chemical shifts of the doublets ($\Delta\delta$) of **1** are in the range of 0.67-0.76 ppm, indicating that the adjacent aryl rings adopt a *syn*-orientation.[1a,7] The chemical shifts of the $ArCH_2Ar$ carbon atoms of **1** (31.6-32.7 ppm) provided further support for the all *syn*-orientation.[8] These observations indicate that these calixarene analogs adopt a cone form as the preferred conformation in a solution.

The small $\Delta\delta$ values between H_{exo} and H_{endo} (0.67-0.76 ppm) of **1** compared with that (0.9 ppm) of the typical cone-type calixarenes[1a] imply that the aryl rings in the molecule are twisted. The different $\Delta\delta$ values[7] in the macrocycle suggest that the cavity of **1** is chiral. In order to elucidate the existence of the chiral phenol-formaldehyde tetramer unit, we measured the CD spectrum of **1a** in hexane at 20 °C. The CD spectral absorption pattern of **1a** is quite similar to that of the known chiral calixarenes,[9] supporting the assumption that the phenol-formaldehyde tetramer unit is chiral. The corresponding enantiomer **1d** showed the completely opposite CD spectrum. The CD spectrum of **1a** in methanol drastically decreased the signal intensities compared with that in hexane.[10] It implies that the hydrogen bonded array plays an important role in the transmission of chirality from the amino acid to the phenol-formaldehyde tetramer unit.

It is known that calixarenes bind quaternary ammonium ions.[11] We investigated the complexation ability of **1** using the α-methylbenzyl trimethyl ammonium iodide **3** in $CDCl_3$ by ^{1}H-NMR spectroscopy. In the presence of **1a**, all protons of the ammonium salt moved to a high field due to the ring current effect of the π-cavity of **1a** during the formation of the complex ([**1a**] = [**3**] = 10 mM, $\Delta\delta = \delta_{obs} - \delta_{free}$, $\Delta\delta_{N\text{-}CH3}$ = -0.137 and -0.153 ppm, $\Delta\delta_{CH}$ = -0.084 ppm, $\Delta\delta_{CH3}$ = -0.023 ppm). The higher chemical shifts of the N-CH_3 protons suggests that the N-CH_3 group is included in the cavity of **1a**.



2
a:R=CH_3, **b**: R=$C(CH_3)_3$

1

1a: 33% yield, R=CH_3, R'=H, R"=$CH(CH_3)_2$,
1b: 18% yield, R=CH_3, R'=H, R"=CH_2

1c: 17% yield, R=CH_3, R'=R"=H,
1d: 30% yield, R=CH_3, R'=$CH(CH_3)_2$, R"=H
1e: 67% yield, R=$C(CH_3)_3$, R'=H, R"=$CH(CH_3)_2$

Scheme 1.

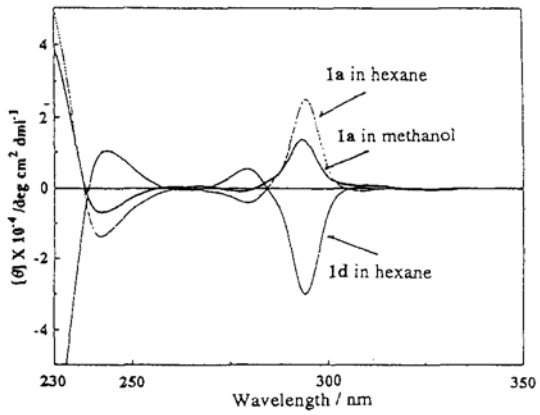


Figure 1. CD spectra of **1a** and **1d**.

Figure 2 shows the trimethyl signal ($\delta_{N\text{-}CH_3}$ 3.393 ppm) of the racemic **3** in the ^{1}H-NMR spectra. In the presence of **1a**, the trimethyl signal of the racemic ammoniun ion was split into two peaks ($\delta_{N\text{-}CH_3}$ 3.240 and 3.256 ppm) with a 1:1 intensity ratio. The ^{1}H-NMR spectrum of **1a** with the *R*- or *S*-ammoniun ion showed a single peak ($\delta_{N\text{-}CH_3}$ 3.240 ppm for the *R*-form, $\delta_{N\text{-}CH_3}$ 3.256 ppm for the *S*-form). The same phenomenon was also observed in the complex of the racemic **3** with **1b** ($\delta_{N\text{-}CH_3}$ 3.219 ppm for the *R*-form, $\delta_{N\text{-}CH_3}$ 3.234 ppm for the *S*-form). Contrary to this, the methyl signal of the racemic **3** in the presence of the achiral macrocycle **1c** shifted to high field ($\delta_{N\text{-}CH_3}$ 3.310 ppm) but did not split. In the same experiment using **1e**, which has *t*-butyl groups at the *p*-position of the phenol ring, the chemical shift of the methyl group ($\delta_{N\text{-}CH_3}$ 3.385 ppm) of **3** scarcely changed due to the steric repulsion of the *t*-butyl group during the formation of the complex. The 1:1 stoichiometry of the complexes (**1**-**3**) was confirmed using Job's method. The association constants (K_a) of **1** to **3** were determined by a nonlinear least-squares fitting method of a binding curve obtained from the ^{1}H NMR titrations ($\log K_a$= 1.17±0.04 for **1a**-(*R*)-**3** complex, $\log K_a$=1.08±0.04 for **1a**-(*S*)-**3** complex, $\log K_a$=1.09±0.04 for **1b**-(*R*)-**3** complex, $\log K_a$=1.01±0.04 for **1b**-(*S*)-**3** complex). These results indicate that **1a** and **1b** form the diastereomeric complexes with the racemic ammonium ion through the cation-π interaction[12].

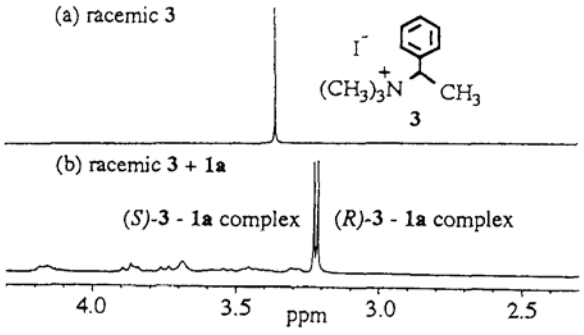


Figure 2. Partial ^{1}H NMR spectra of racemic ammonium iodide (**3**) in $CDCl_3$. (a) [**3**] = 1.0 X 10^{-2} M. (b) [**3**] = [**1a**] = 1.0 X 10^{-2} M.

In conclusion, we synthesized the chiral calixarene analog incorporating amino acid residue into their macrocyclic ring. The ^{1}H-NMR and CD spectroscopies imply that the macrocycles form the chiral cavity and the hydrogen bonded array plays an important role in the transmission of the chirality from the amino acid to the cavity. The macrocycles have the cavity π-basic enough to include the ammonium ion due to the cation-π interaction and can serve as a shift reagent for the racemic ammonium ion during a ^{1}H NMR analysis.

References and Notes

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5 Compounds (**2**) were prepared from the reaction of the correspondi ng bis(hydroxymethyl)phenol-formaldehyde tetramer with thionyl chloride in dry benzene at rt for 5 h in 80~90% yields.

6 The assignment of the protons was confirmed by H-H COSY and NOESY experiments. Spectral data of macrocycles (**1**) are as follows. **1a**: mp 183-186 °C. $[\alpha]^{20}_D$ = +58 ° ($CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 0.88 (d, CH_3, J=6.5Hz), 1.35 (br s, CH_3), 2.17 (s, $ArCH_3$), 2.18 (s, $ArCH_3$ X 3), 2.41 (m, C*H*$(CH_3)_2$), 3.03 (d, H_a), 3.07 (d, NC*H*RCO_2CH_3, J=10.5Hz), 3.39 (d, H_b), 3.42 (d, H_d), 3.43 (d, H_c), 3.44 (d, H_e), 3.75 (s, CO_2CH_3), 3.97 (d, $H_{a'}$), 4.06 (d, $H_{b'}$), 4.17 (d, $H_{d'}$), 4.18 (d, $H_{c'}$), 4.39 (d, $H_{e'}$), 6.52 (d, H_f), 6.72 (d, H_m), 6.85 (d, H_h), 6.91 (d, H_j), 6.94 (d, H_i), 6.96 (d, H_g), 6.97 (d, H_k), 7.02 (d, H_l), 10.32 (br s, OH X 4). Coupling constants in Hz; $J_{aa'}$ = 14.5, $J_{bb'}$ = $J_{cc'}$ =$J_{dd'}$ = 13.5, $J_{ee'}$ = 12.2, J_{fg} = J_{hi} =J_{jk} = J_{lm} = 2.0. **1b**: mp 216-220 °C. $[\alpha]^{20}_D$ = +60 ° ($CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 2.14 (s, $ArCH_3$), 2.19 (s, $ArCH_3$), 2.21 (s, $ArCH_3$), 2.22 (s, $ArCH_3$), 3.31 (d, H_b and H_e), 3.44 (d, H_d), 3.46 (d, H_c), 3.47 (dd, C*H*H-indole, J=5.2, 12.5 Hz), 3.54 (d, H_a), 3.61 (dd, CH*H*-indole, J=8.1, 12.5 Hz), 3.70 (s, CO_2CH_3), 3.77 (d, $H_{b'}$), 3.87 (dd, NC*H*RCO_2CH_3, J=5.2, 8.1 Hz), 3.90 (d, $H_{a'}$), 4.18 (d, H_c and $H_{d'}$), 4.52 (d, $H_{e'}$), 6.55 (d, H_f), 6.75 (H_m), 6.85 (d, H_h), 6.89 (d, H_g), 6.94 (d, H_j), 6.96 (d, H_i), 6.98 (d, H_k), 7.02 (dd, indole ring proton, J=7.0, 8.0Hz), 7.04 (d, H_l), 7.15 (br s, indole ring proton), 7.16 (dd, indole ring proton, J=7.0, 8.0 Hz), 7.36 (d, indole ring proton, J=8.0Hz), 7.45 (d, indole ring proton, J=8.0 Hz), 8.00 (br s, NH), 10.27 (br s, OH X 4). Coupling constants in Hz; $J_{aa'}$ = 14.0, $J_{bb'}$ = $J_{cc'}$ = $J_{dd'}$ = 13.5, $J_{ee'}$ = 11.5, J_{fg} = J_{hi} =J_{jk} = J_{lm} = 2.0. **1c**: mp 237-241 °C. ^{1}H-NMR ($CDCl_3$) δ 2.19 (s, $ArCH_3$ X 4), 3.10-4.10 (m, H_a, $H_{a'}$, H_b, $H_{b'}$, H_c, $H_{c'}$, H_d, $H_{d'}$, H_e, $H_{e'}$, $NCH_2CO_2CH_3$), 6.66 (d, H_f and H_m), 6.90 (d, H_h and H_k), 6.93 (d, H_i and H_j), 7.00 (d, H_g and H_l), 10.28 (br s, OH X 4). Coupling constants in Hz; J_{fg} = J_{hi} =J_{jk} = J_{lm} = 2.0. **1d**: mp 176-180 °C . $[\alpha]^{20}_D$ = -60 ° ($CHCl_3$). **1e**: mp 232-235 °C. $[\alpha]^{20}_D$ = +57 ° ($CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 0.90 (d, C*H*CH_3, J=5.5 Hz), 1.23 (s, C(CH_3)$_3$ X 3), 1.24 (s, C(CH_3)$_3$), 1.40 (d, CHCH_3, J=5.5 Hz), 2.43 (m, C*H*$(CH_3)_2$), 3.03 (d, H_a), 3.11 (d, NC*H*RCO_2CH_3, J=10.5 Hz), 3.44 (d, H_b and H_d), 3.47 (d, H_c), 3.50 (d, H_e), 3.72 (s, CO_2CH_3), 4.00 (d, $H_{a'}$), 4.14 (d, $H_{b'}$), 4.19 (d, $H_{c'}$), 4.21 (d, $H_{d'}$), 4.42 (d, $H_{e'}$), 6.65 (d, H_f), 6.83 (d, H_m), 7.00 (d, H_h), 7.01 (d, H_j), 7.11 (d, H_i), 7.13 (d, H_g), 7.14 (d, H_k), 7.16 (d, H_l), 10.33 (bs, OH X 4). Coupling constants in Hz; $J_{aa'}$ = 14.5, $J_{bb'}$ = $J_{cc'}$ = $J_{dd'}$ = 13.6, $J_{ee'}$ = 12.2, J_{fg} = J_{hi} =J_{jk} = J_{lm} = 2.0.

7 The Δδ values between H_{exo} and H_{endo} protons of $ArCH_2Ar$ are as follows. **1a**: $\Delta\delta_{bb'}$=0.67, $\Delta\delta_{cc'}$=0.75, $\Delta\delta_{dd'}$=0.75 ppm, **1b**, 0.46, 0.72, 0.74 ppm, **1e**: 0.69, 0.72, 0.76 ppm. The small $\Delta\delta_{bb'}$ (0.46 ppm) in **1b** having tryptophane residue was observed. NOESY experiments showed that $H_{b'}$ proton is located close to indole ring of tryptophane residue. Therefore, the small $\Delta\delta_{bb'}$ value results from the ring current effect of indole ring ($\delta_{Hb'}$ ppm, 3.77 (**1b**), 4.06 (**1a**), 4.14 (**1e**)).

8 The chemical shifts of the $ArCH_2Ar$ methylene carbon atoms of **1** are as follows. **1a**: 31.6, 31.6, 32.1 ppm, **1b**: 31.3, 31.6, 32.1 ppm, **1c**: 31.6, 32.1 ppm, **1e**: 31.9, 32.1, 32.7 ppm. C. Jaime, J. de Mendoza, P. Prados, P. M. Nieto, and C. Sanchez, *J. Org. Chem.* **56**, 3372 (1991).

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