SYNTHESES OF CHIRAL TETRAHOMODIAZACALIX[4]ARENES INCORPORATING AMINO ACID RESIDUES: CHIRAL INDUCTION OF THE CYCLOPHANE MOIETY BY THE CHIRALITY OF THE AMINO ACID RESIDUES

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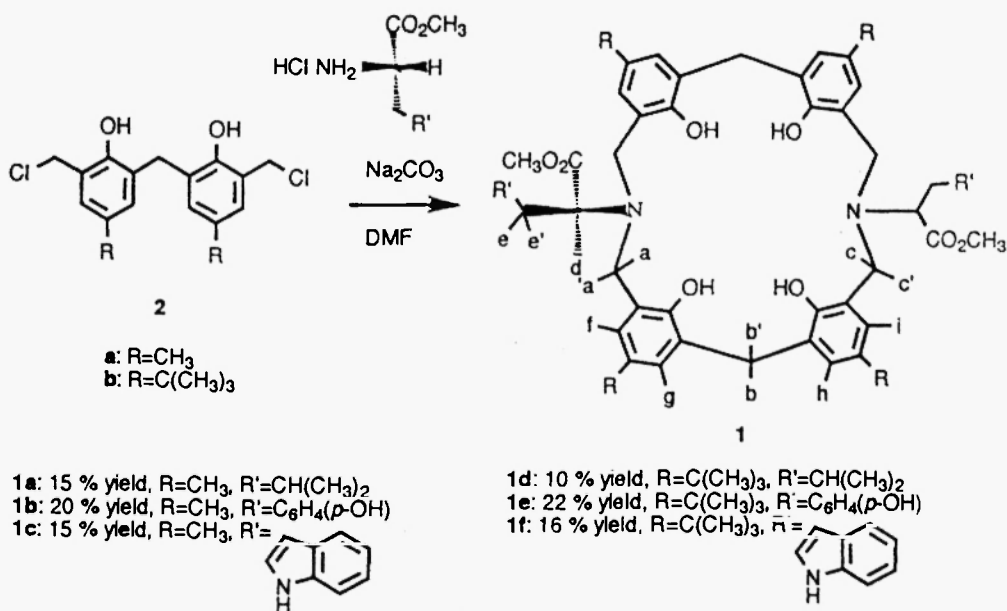
Abstract: Chiral tetrahomodiazacalix[4]arenes containing amino acid residues were prepared. ^1H and ^{13}C NMR spectra indicated that macrocycles are preferable to adopt a cone conformation, and suggested that the cyclophane moiety is a chiral twisted form. CD spectra supported the existence of the chirality of the cyclophane unit, and showed that the intramolecular hydrogen bonding plays an important role in the transmission of the chirality from the amino acid residues to the cyclophane moiety.

Calixarenes and its analogs are considerable interest in the field of molecular recognition chemistry as an useful building block to make artificial hosts (1). Currently calixarene chemists focus their interest on the syntheses of the chiral analogs, which are expected to act as artificial enzymes. Their syntheses have so far been carried out the simply attaching chiral residues at the large (upper) or small (lower) rim of their phenol units and the using of the inherent chirality of their skeleton (2). In contrast, other potential site, methylene moiety, has not been exploited to any great extend owing to the relatively inert reactivity on this site (3). This situation inspired us to synthesize the chiral calixarene analogs incorporating chiral unit into the macrocyclic ring.
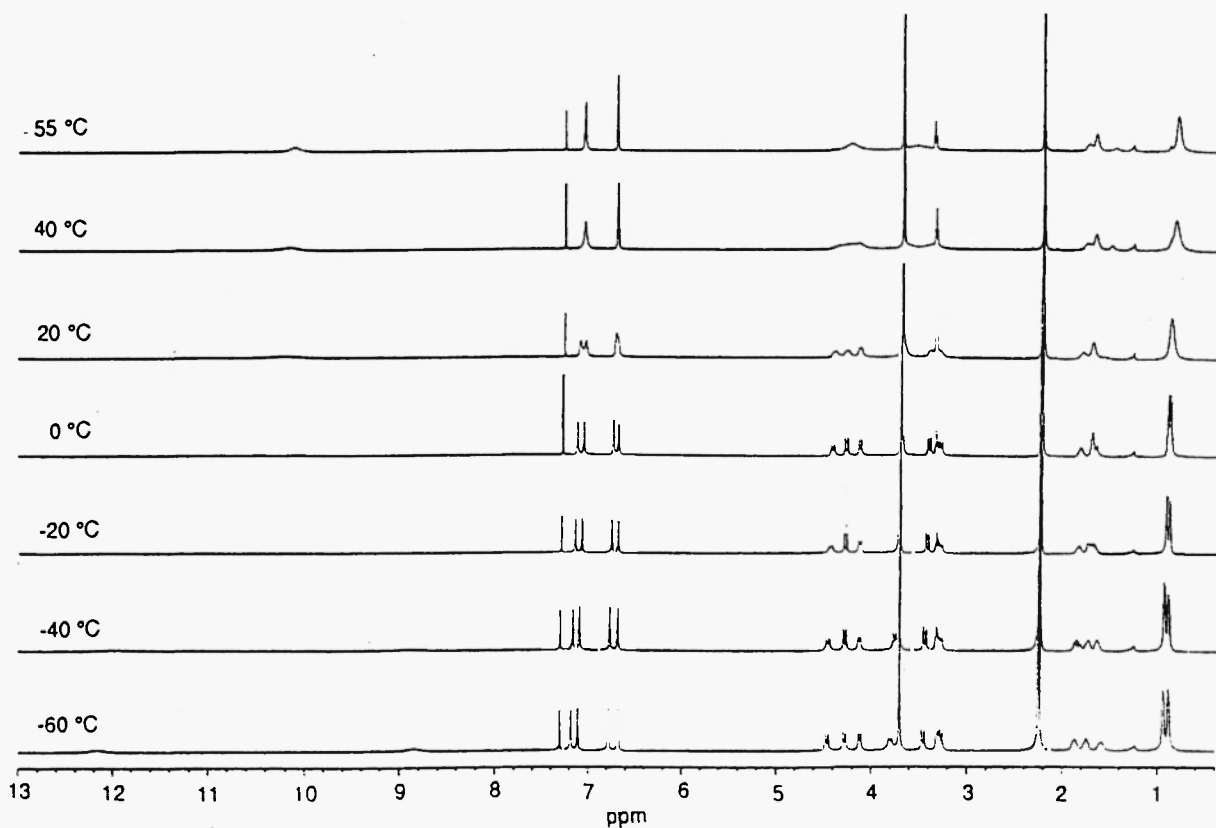
In this paper, we describe the synthesis of chiral calixarene analogs constructed from *L*-amino acid residue and phenol-formaldehyde dimer units, and discuss their chirality by using NMR and CD spectroscopies.

Macrocycles **1** were prepared by the cyclization reaction of bis(chloromethyl) phenol-formaldehyde dimer with *L*-amino acid methylester hydrochloride in dry dimethyl formamide at 30 °C under nitrogen atmosphere in 10-22% yields.

The structures of **1** were identified by the spectroscopies especially NMR. The phenolic OH protons in ^1H NMR spectra were observed at 10.1-10.2 ppm as broad singlets. Upon cooling of the temperature the peak gradually broadened and finally split into two peaks with equal intensities. Taking into account that nitrogen atom is good proton acceptor, the OH peaks observed at lower magnetic field are assigned to the OH proton formed the hydrogen bonding not only with hydroxyl group but also with the adjacent nitrogen atom. In the IR spectra of **1** in chloroform, the OH stretching vibration appeared in the region of 3269-3290 cm^{-1} as broad bands. From these spectral data the intramolecular hydrogen bonding of **1** is somewhat weaker than that of calix[4]arene (ν_{OH} 3138 cm^{-1} in CCl_4, δ_{OH} 10.2 ppm in $CDCl_3$) (1a).

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Syntheses of chiral tetrahomodiazacalix[4]arenes incorporating amino acid residues.
Chiral induction of cyclophane moiety by the chirality of amino acid residues

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a: R=CH$_3$
b: R=C(CH$_3$)$_3$

1a: 15 % yield, R=CH$_3$, R'=CH(CH$_3$)$_2$
1b: 20 % yield, R=CH$_3$, R'=C$_6$H$_4$(p-OH)
1c: 15 % yield, R=CH$_3$, R'=

1d: 10 % yield, R=C(CH$_3$)$_3$, R'=CH(CH$_3$)$_2$
1e: 22 % yield, R=C(CH$_3$)$_3$, R'=C$_6$H$_4$(p-OH)
1f: 16 % yield, R=C(CH$_3$)$_3$, R' =

Scheme 1.

Figure 1. Variable temperature ^{1}H NMR spectra of chiral homoazacalixarene (1a) in CDCl$_3$ at 500 MHz.

The IR spectra also showed that methyl ester (v_{CO} 1726-1732 cm^{-1}) and R groups such as phenol (v_{OH} 3599 cm^{-1}) and indole rings (v_{NH} 3479 cm^{-1}) of the amino acid residues in the molecules did not participate in the intramolecular hydrogen bonding (Table 1).

Conformational analysis of 1 was carried out by using NMR spectroscopy. The ambient temperature ^{1}H NMR spectra of 1 showed broad, semiresolved sets of resonances arising from $ArCH_2Ar$ and $ArCH_2N$ methylene protons that did not coalesce to the singlets even at 55 °C in $CDCl_3$. The low temperature ^{1}H NMR spectra of 1 have three sets of doublets from the methylene protons. The differences in chemical shifts ($\Delta\delta$) of doublets arising from the $ArCH_2Ar$ methylene protons were 0.72-1.36 ppm, indicating that the adjacent aryl rings are preferable to adopt a *syn*-orientation (4). This is further supported by the chemical shifts (δ 30.5-31.3 ppm) of $ArCH_2Ar$ methylene carbons in the ^{13}C NMR spectra (5). A NOESY experiment showed NOE correlation between H_a and H_i protons as well as between $H_{a'}$ and H_i protons. This result is only compatible with a cone conformation. On the basis of these observations a cone conformer is chosen as a preferred conformation in this system (6).

Table 1: Melting points, specific rotations, chemical shifts of hydroxy protons, IR absorptions of OH, NH, and CO groups.

Macrocycle	mp	$[\alpha]^{20}_D$ [a]	v_{OH} [b]	v_{OH} [c]	v_{NH} [c]	v_{CO} [c]
1a	181-187	+19	10.1 (8.85, 12.18) [d]	3284	-	1726
1b	157-166	+12	10.2 (8.30, 10.40) [d]	3290, 3599	-	1732
1c	164-175	+34	10.2 (9.25, 12.10) [d]	3280	3479	1730
1d	213-221	+22	10.1 (9.01, 12.28) [d]	3277	-	1730
1e	166-168	+18	10.2 (8.28, 10.37) [d]	3290, 3599	-	1732
1f	168-175	+31	10.2 (9.30, 12.55) [d]	3269	3479	1728

a) In $CHCl_3$ at 20 °C, c = 0.1. b) In $CDCl_3$ at 20 °C at 500 MHz, c) In $CHCl_3$ at 20 °C, d) In $CDCl_3$ at -60 °C at 500Mz.

Table 2: Elemental analysis and FAB mass spectral data of macrocycles 1.

Macrocycle	Molecular Formula	Elemental Analysis (%) Calculated [Found] C	H	N	FAB mass [a] m/z (M+H)$^+$
1a	$C_{48}H_{62}N_2O_8$	72.52 [72.46]	7.86 [8.03]	3.52 [3.48]	795
1b	$C_{54}H_{58}N_2O_{10}$	72.46 [72.24]	6.53 [6.90]	3.13 [2.96]	895
1c	$C_{58}H_{60}N_4O_8$	74.02 [73.94]	6.43 [6.86]	5.95 [5.71]	941
1d	$C_{60}H_{86}N_2O_8$	74.81 [74.44]	9.00 [9.19]	2.91 [2.81]	964
1e	$C_{66}H_{82}N_2O_{10}$	74.55 [74.67]	7.77 [8.08]	2.63 [2.55]	1064
1f	$C_{70}H_{84}N_4O_8$	75.78 [75.82]	7.63 [7.85]	5.05 [4.66]	1110

a) Used *m*-nitrobenzyl alcohol as a matrix.

Table 3: Chemical shifts of methylene protons (at 500 MHz for ^{1}H) and carbons (at 125 MHz for ^{13}C) in $CDCl_3$.

Macro-cycle	$ArHaHa'N$ [a] (J, Hz; $\Delta\delta$, ppm)	$ArHbHb'Ar$ [a] (J, Hz; $\Delta\delta$, ppm)	$ArHcHc'N$ [a] (J, Hz; $\Delta\delta$, ppm)	$\delta ArCH_2N$ [b]	$\delta ArCH_2Ar$ [b]
1a	3.26, 4.11 (11.5, 0.85)	3.45, 4.28 (13.5, 0.83)	3.80, 4.46 (13.5, 0.66)	53.6, 55.4	30.5
1b	3.18, 3.91 (10.5, 0.73)	3.29, 4.04 (13.0, 0.75)	3.71, 4.37 (12.5, 0.66)	53.3, 54.0	30.5
1c	3.25, 4.21 (12.0, 0.96)	3.26, 4.62 (13.5, 1.36)	3.62, 4.49 (12.5, 0.87)	54.0, 55.8	30.7
1d	3.39, 4.16 (11.0, 0.77)	3.51, 4.32 (14.0, 0.81)	4.05, 4.54 (13.0, 0.49)	54.1, 56.0	31.2
1e	3.30, 4.00 (11.5, 0.70)	3.38, 4.10 (13.0, 0.72)	3.97, 4.43 (12.5, 0.46)	53.5, 55.4	31.0
1f	3.35, 4.28 (12.5, 0.93)	3.52, 4.72 (13.5, 1.20)	3.57, 4.41 (12.5, 0.84)	54.4, 56.5	31.3

a) At -60 °C. b) At 20 °C.

The NOESY experiment of 1 also showed NOE cross peaks between the methylene protons of the cyclophane moiety and RCH_2 group of the amino acid residue. No NOE between the cyclophane moiety and the methyl ester was observed. These observations indicate that the preferred conformation of the amino acid residue in the molecules is as shown in Figure 2. This result suggests that the cyclophane moiety is effected by the chirality of the amino acid residue. Actually, ^1H and ^{13}C NMR spectra of 1 gave C_2 symmetry signal pattern at low or ambient temperature, indicating that the cyclophane moiety could be chiral (7). The different $\Delta\delta$ values of the $ArCH_2N$ methylene protons ($\Delta\delta H_{a\,a'}$ and $\Delta\delta H_{c\,c'}$) imply that the cyclophane moiety is a twisted form, because the $\Delta\delta$ values of the methylene protons of the cyclophane moiety are expected to be sensitive to the dihedral angle between the methylene protons and the plane of the adjacent aromatic rings (1a). Since the smaller $\Delta\delta$ value is ascribed to the $H_{c\,c'}$ methylene protons, it is reasonable to assume that the phenol rings adjacent to the $H_{c\,c'}$ protons somewhat flatten. CPK model consideration also supports that the phenol rings somewhat flatten owing to the steric repulsion between the phenol unit and RCH_2 moiety of the amino acid residue as shown in Figure 3.
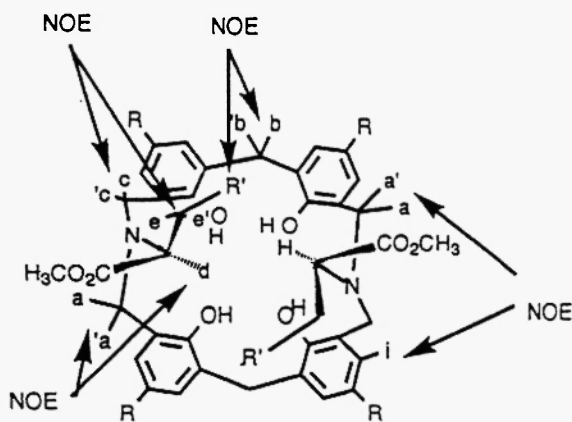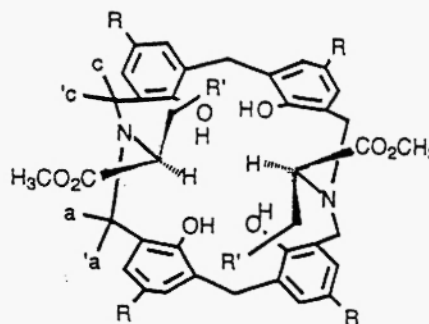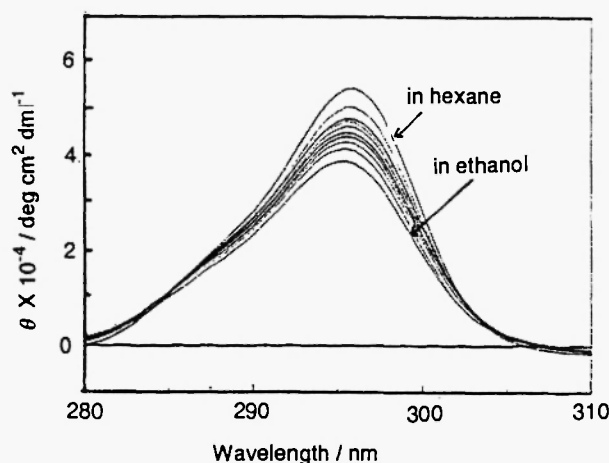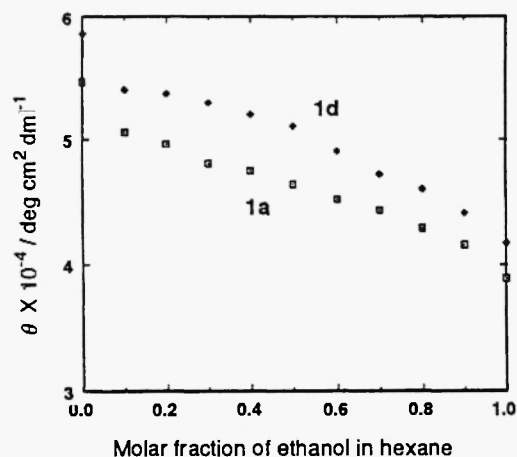

Figure 2. NOE correlation.

Figure 3.

To prove the existence of its chirality, CD measurement was employed. The CD spectral absorption pattern is quite similar to that of known chiral calixarene (2a), therefore the assumption was supported. Interestingly the CD spectra in ethanol drastically decreased the absorption intensity as shown in Figure 4. The θ-values of 1a at 296 nm in mixture of hexane and ethanol, as shown in Figure 5, display a dependence on the mole fraction of ethanol. Even the addition of 10% v/v of ethanol in hexane caused drastically decrease of the spectral intensiy. Similar tendency was also observed in 1d. In contrast, the UV spectra of 1 in both hexane and ethanol gave similar spectral intensities. We postulate that the major effect of ethanol is to disrupt the intramolecular hydrogen bonding, which is the primary force responsible for the preference of the calixarene to adopt the cone conformation. Therefore, these results can be rationalized by assuming that the intramolecular hydrogen bonding could play an important role in the chiral induction of the cyclophane unit from the amino acid residue.

Table 4: CD and UV spectra of 1 in hexane and in ethanol at 20 °C.

Macrocycle	solvent	λ_{ext} [nm] (θ [deg cm^2 dmol^{-1}])		λ_{max} [nm] (ε [cm^{-1} mol dml^{-3}])
1a	in hexane	296 (54600)		290 (12500)
	in ethanol	296 (39000)		289 (12300)
1b	in hexane [a]	-		-
	in ethanol	282 (-7000)	296 (9000)	284 (15500)
1c	in hexane [a]	-		-
	in ethanol	296 (20000)		282 (24100)
1d	in hexane	293 (58600)		290 (12600)
	in ethanol	294 (41700)		289 (10600)
1e	in hexane	277 (-18400)	295 (53000)	283 (12900)
	in ethanol	277 (-5600)	293 (7900)	284 (13800)
1f	in hexane	293 (41400)		282 (19100)
	in ethanol	294 (25900)		283 (19700)

a) Macrocycles (**1b** and **1c**) were not dissolved in hexane

Figure 4. Change in CD spectrum of **1a** at 20 °C in hexane on increase of the molar fraction of ethanol.

Figure 5. Change of θ-value at 296 nm as a function of the composition of hexane-ethanol solvent mixture

In conclusion , we prepared chiral tetrahomodiazacalix[4]arenes by the cyclization reactions of L-amino acid methyl esters and bis(chloromethyl) phenol-formaldehyde dimer. NMR and CD spectra showed that the cyclophane moiety is a chiral twisted form, which is inducted by the chirality of the amino acid residue. In this case, the intramolecular hydrogen bonding plays an important role in the chiral transmission and in making the chiral cavity. The study of the molecular recognition using **1** is now in progress.

Acknowledgment

References and Notes

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(4) According to Gutsche (1a), $\Delta\delta$ value between H_{exo} and H_{endo} is generally *ca.* 0.9 ± 0.2 ppm for *syn*-orientation of phenol ring and zero for *anti*-orientation.

(5) The $ArCH_2Ar$ 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*. C. Jaime, J. de Mendoza, P. Prados, P. M. Nieto, and S. Sanchez, *J. Org. Chem.*, **56**, 3372 (1991).

(6) CPK model consideration suggested that the intramolecular hydrogen bonded array should make the cone form be more stable than the 1,2-alternate form.

(7) For examples, four aromatic protons and twelve aromatic carbons ascribing to the phenol-formaldehyde dimer unit and two kinds of doublet protons and two carbons arising from $ArCH_2N$ methylene units were observed.

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