Syntheses of Chiral Bishomodiazacalix[4]arenes Incorporating Amino Acid Residues: Molecular Recognition for Racemic Ammonium Ions by the Macrocycles Possessing Tyrosine Residues

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Chiral bishomodiazacalix[4]arenes containing amino acid residues were prepared. The ^1H and ^{13}C nmr spectra indicated that the macrocycles preferably adopted a cone conformation, which suggested that the cyclophane moiety was in a chiral twisted form. Circular dichroism spectra supported the existence of the chirality of the cyclophane unit, and showed that intramolecular hydrogen bonding plays an important role in the transmission of the chirality from the amino acid residues to the cyclophane moiety. Macrocycles bearing a tyrosine residue have a π-base cavity large enough to include the ammonium ion, and can serve as a shift reagent for the racemic ammonium ions upon complexation during a ^1H nmr analysis.

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Introduction.

Calixarenes and their analogs are of considerable interest in the field of molecular recognition chemistry as useful building blocks to make artificial hosts [1]. Currently, calixarene chemists focus their interest on the syntheses of chiral analogs, which are expected to act as synthetic enzymes. Their syntheses have so far been carried out by simply attaching chiral residues to the large (upper) or small (lower) rim of the calixarene skeleton and using the inherent chirality of their structures [2]. In contrast, other potential sites, such as the methylene moiety, have not been exploited to any great extend due to the relatively inert reactivity of this site [3]. This situation inspired us to synthesize chiral calixarene analogs incorporating a chiral unit into the macrocyclic ring. Therefore, we designed a chiral bishomodiazacalix[4]arene constructed from the phenol-formaldehyde dimer and *L*-amino acid residue as another type of chiral calixarene analog. Introduction of the chiral unit into the macrocyclic ring could be expected to efficiently induce chirality to the cyclophane moiety by the *L*-amino acid residues. In this case, hydrogen bonding in the macrocycle could play an important role in making the cavity chiral, because it is relatively strong and is a directed non-covalent bond [4].

In this paper, we describe the synthesis of the chiral calixarene analogs constructed from *L*-amino acid residue and phenol-formaldehyde dimer units, and discuss their chirality using nmr and circular dichroism spectroscopies. We also report complexation behavior of the macrocycles for racemic ammonium ions using ^1H nmr spectroscopy.

Results and Discussion.

Macrocycles **1** were prepared by the cyclization reactions of bis(chloromethyl)phenol-formaldehyde dimer **2** with various *L*-amino acid methylesters in the presence of sodium carbonate in dry dimethylformamide at 30° under a nitrogen atmosphere in 10-22% yields.

The structures of **1** were identified based on their spectral data especially nmr. The phenolic OH protons in ^1H nmr spectra were observed at 10.1-10.2 ppm as broad singlets. Upon cooling, the peak gradually broadened and finally split into two peaks with equal intensities (Figure 1). Considering that a nitrogen atom is a good proton acceptor, the OH peaks observed at lower magnetic field are assigned to the OH proton formed by hydrogen bonding not only with a hydroxy group but also with the adjacent nitrogen atom. In the ir spectra of **1** in chloroform, the OH stretching vibrations appeared in the region of 3269-3290 cm^{-1} as broad bands. These data are summarized in Table 1. Based on these spectral data, the intramolecular hydrogen bonding of **1** is somewhat weaker than that of calix[4]arene (ν_{OH} 3138 cm^{-1} in carbon tetrachloride, δ_{OH} 10.2 ppm in deuteriochloroform) [1a].

Conformational analysis of **1** was carried out by using nmr spectroscopy. The ambient temperature ^1H nmr spectra of **1** showed broad, semiresolved sets of resonances arising from the $ArCH_2Ar$ and $ArCH_2N$ methylene protons that did not coalesce to singlets even at 55° in deuteriochloroform. The low temperature ^1H nmr spectra of **1** have three sets of doublets from the methylene protons as shown in Figure 1. The differences in the chemical shifts ($\Delta\delta$) of the doublets arising from the $ArCH_2Ar$ methylene

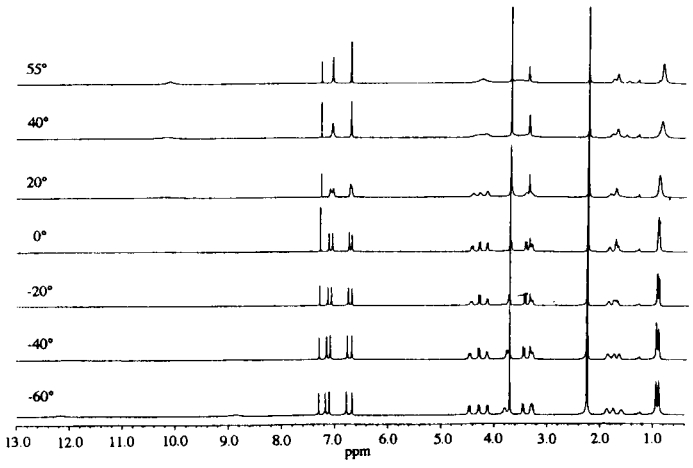
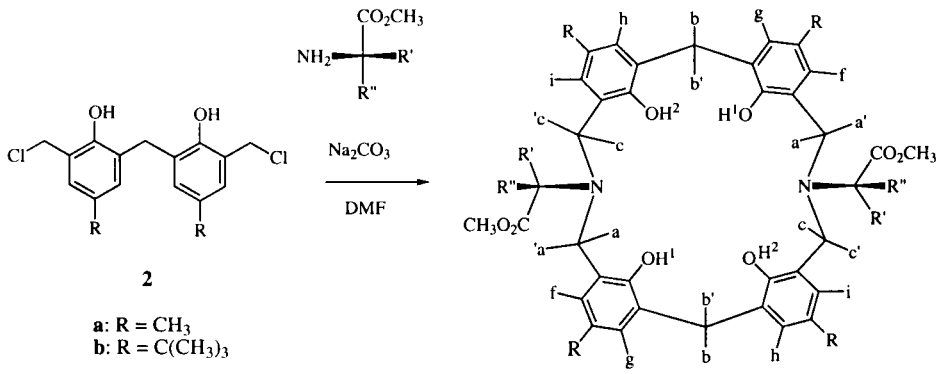


Figure 1. Variable temperature ^1H nmr spectra of chiral dihomoazacalixarene **1b** in deuteriochloroform at 500 MHz.

Scheme 1



2

a: R = CH_3
b: R = $C(CH_3)_3$

1

1a: R = CH_3, R' = H, R" = $CH(CH_3)_2$
1b: R = CH_3, R' = H, R" = $CH_2CH(CH_3)_2$
1c: R = CH_3, R' = H, R" = $CH_2C_6H_5$
1d: R = CH_3, R' = H, R" = $CH_2C_6H_4$(*p*-OH)
1e: R = CH_3, R' = H, R" = CH_2

1f: R = $C(CH_3)_3$, R' = H, R" = $CH_2CH(CH_3)_2$
1g: R = $C(CH_3)_3$, R' = H, R" = $CH_2C_6H_4$(*p*-OH)
1h: R = $C(CH_3)_3$, R' = H, R" = CH_2

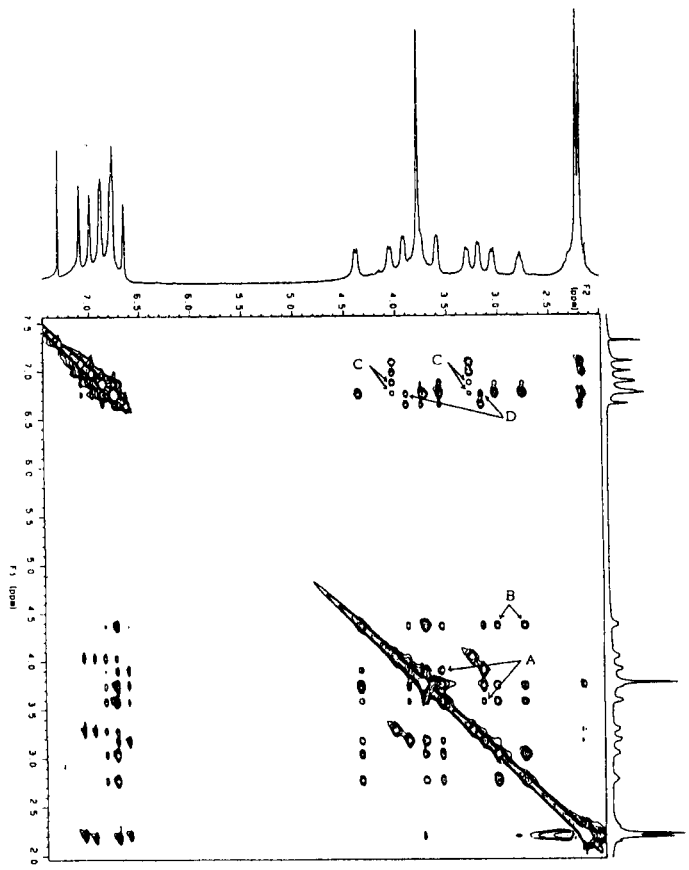


Figure 2. ^{1}H NOESY spectrum (300 ms mixing time, 500 MHz) of **1d** in deuteriochloroform at -60°.

protons were observed in the range of 0.72-1.36 ppm, indicating that the adjacent aryl rings preferably adopted a *syn*-orientation [5]. This is further supported by the chemical shifts (δ 30.5-31.3 ppm) of the $ArCH_2Ar$ methylene carbons in the ^{13}C nmr spectra [6]. These data are summarized in Table 2. NOESY experiments of **1d** and **1g**, which bear tyrosine residues, showed an nOe correlation between the H_a and H_i protons as well as between the $H_{a'}$ and H_i protons (nOe correlation (D) in Figure 2 and 3). These results are only compatible with a cone conformation. Therefore, the preferred conformation of **1d** and **1g** will be a cone form [7]. On the other hand, other macrocycles did not show the corresponding nOe responses, indicating that other macrocycles exist as somewhat flattened structures.

The NOESY experiment of **1** also showed nOe cross peaks between the methylene protons of the cyclophane moiety and the amino acid residue (nOe correlation (A), (B),

Table 1

Chemical Shifts of Hydroxy Protons in the ^{1}H NMR Spectra and IR Spectral Absorptions of OH, NH, and CO Groups.

Macrocycle	δ_{OH}[a]	ν_{OH}[b]	ν_{NH}[b]	ν_{CO}[b]
1a	10.1 (8.75, 11.50)	3290	-	1726
1b	10.1 (8.85, 12.18)	3284	-	1726
1c	10.1 (8.68, 11.99)	3290	-	1731
1d	10.2 (8.30, 10.40)[c]	3290, 3599	-	1732
1e	10.2 (9.25, 12.10)	3280	3479	1730
1f	10.1 (9.01, 12.28)	3277	-	1730
1g	10.2 (8.28, 10.37)[c]	3290, 3599	-	1732
1h	10.2 (9.30, 12.55)	3269	3479	1728

[a] In deuteriochloroform at 20° (at -60°) at 500 MHz. [b] In chloroform at 20°. [c] Hydroxy protons of tyrosine residues were also observed at 8.20 (**1d**) and 8.16 (**1g**) at -60°.

Table 2

Chemical Shifts of Methylene Protons (at 500 MHz for ^1H at -60°) and Carbons (at 125 MHz for ^{13}C at 20°) in Deuteriochloroform

Macrocycle	$ArH_aH_{a'}N$ (J, Hz; $\Delta\delta$, ppm)	$ArH_bH_{b'}Ar$ (J, Hz; $\Delta\delta$, ppm)	$ArH_cH_{c'}N$ (J, Hz; $\Delta\delta$, ppm)	$\delta ArCH_2N$	$\delta ArCH_2Ar$
1a	2.97, 4.08 (13.5, 1.11)	3.44, 4.20 (14.0, 0.76)	3.61, 4.44 (13.5, 0.83)	53.6, 55.4	30.9
1b	3.26, 4.11 (11.5, 0.82)	3.45, 4.28 (13.5, 0.83)	3.80, 4.46 (13.5, 0.66)	53.6, 55.4	30.5
1c	3.26, 4.08 (11.5, 0.82)	3.33, 4.48 (14.0, 1.15)	3.47, 4.27 (13.5, 0.80)	51.4, 53.4	30.9
1d	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, 55.1	30.5
1e	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
1f	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
1g	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
1h	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

and (C) in Figures 2 and 3). Also, nOe between the cyclophane moiety and the methyl ester was not observed. Based on these observations, the preferred conformation of the amino acid residue in the molecules is as shown in Figure 3.

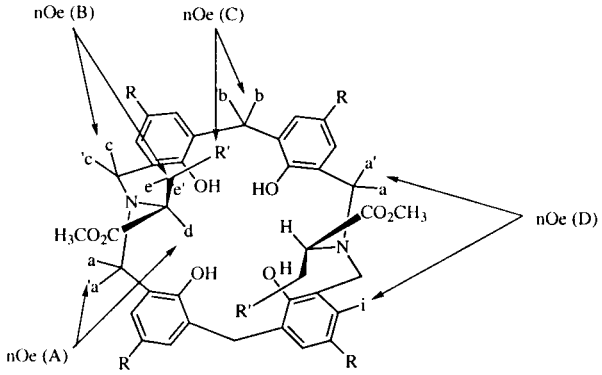


Figure 3. NOe correlation.

These results suggests that the cyclophane moiety is affected by the chirality of the amino acid residue. Actually, the ^1H and ^{13}C nmr spectra of **1** gave a C_2 symmetry signal pattern at low or ambient temperature, indicating that the cyclophane moiety could be chiral. 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 as shown in Figure 4. 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 are somewhat flattened like conformation A in Figure 4. Considering the flattened phenol unit makes it possible to form a strong intramolecular hydrogen bond between the hydroxy proton and the adjacent nitrogen atom, the observation of the hydroxy proton (OH_2) of the flattened phenol at lower magnetic field further supports this speculation. From these observations, it can be assumed that the cyclophane moiety of the macocycles adopt a chiral twisted form as shown in Figure 5.

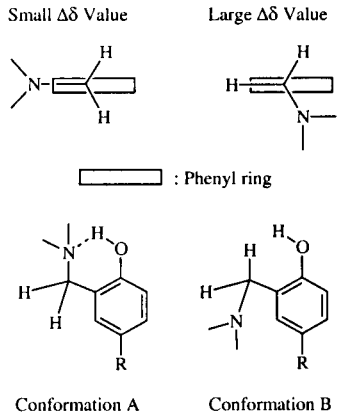


Figure 4

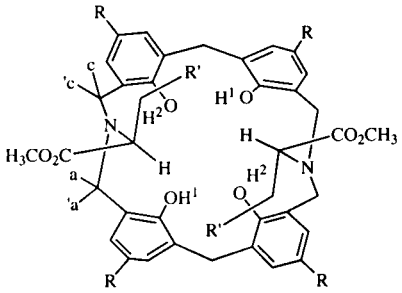


Figure 5

To prove the existence of its chirality, a circular dichroism measurement was employed. The circular dichroism spectral absorption pattern is quite similar to that of a known chiral calixarene [2a], therefore, the assumption was supported. Interestingly, the circular dichroism spectra in ethanol drastically decreased the absorption intensity as summarized in Table 3. The θ-values of **1b** at 296 nm in a mixture of hexane and ethanol, as shown in Figures 6 and 7, display a dependence on the mole fraction of ethanol. Even the addition of 10% v/v ethanol in hexane caused a gradual decrease in the spectral intensity. A similar tendency was also observed in other macrocycles. In contrast,

Table 3
Circular Dichroism and Uv Secptra of **1** in Hexane and Ethanol at 20°.

Macrocycle	solvent	λext [nm] (θ [deg cm^2 dmol^{-1}])		λmax [nm] (ε [cm^{-1} mol dml^{-3}])
1a	in hexane	295 (41600)		294 (11600)
	in ethanol	295 (32100)		284 (13900)
1b	in henxane	296 (54600)		290 (12500)
	in ethanol	296 (42000)		289 (12300)
1c	in hexane	296 (28100)		289 (12400)
	in ethanol	296 (7700)		284 (16600)
1d	in hexane[a]	-		-
	in ethanol	282 (-7000)	296 (9000)	284 (15500)
1e	in hexane[a]	-		-
	in ethnaol	296 (20000)		282 (24100)
1f	in hexane	293 (58600)		290 (12600)
	in ethnaol	294 (41700)		289 (10600)
1g	in hexane	277 (-18400)	295 (53000)	283 (12900)
	in ethnaol	277 (-5600)	293 (7900)	284 (13800)
1h	in hexane	293 (41400)		282 (19100)
	in ethnaol	294 (25900)		283 (19700)

[a] Macrocycles **1d** and **1e** were not dissolved in hexane.

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. Therefore, these results can be rationalized by assuming that the intramolecular hydrogen bonding plays an important role in the chiral induction of the cyclophane unit from the chirality of the amino acid residue.

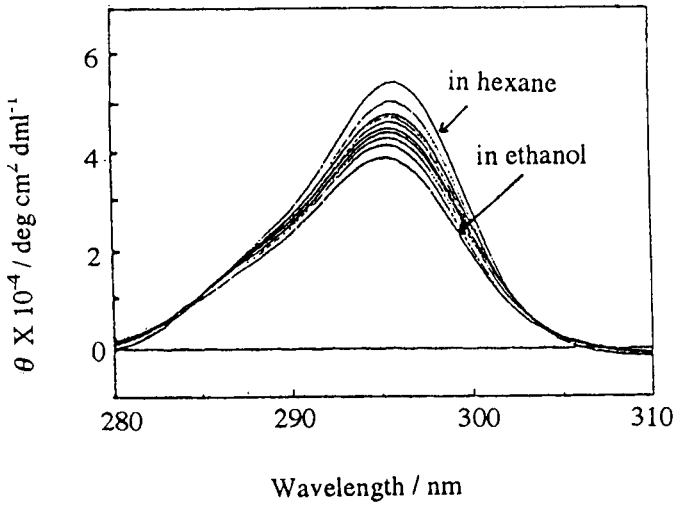


Figure 6. Change in circular dichroism spectrum of **1b** at 20° in hexane on increase of the molar fraction of ethanol.

It is known that cyclophanes form complexes with ammonium ions [8]. We examined the complexation ability of these macrocycles with racemic ammonium ions using ^{1}H nmr spectroscopy. Figure 8 shows the ^{1}H nmr spectra for α-methylbenzyl trimethylammonium iodide **3** as a racemic mixture in the absence (a) and presence (d) of **1g**. All proton resonances of **3** undergo complexation induced upfield shifts. The higher induced shifts of the methyl protons of $N^+(CH_3)_3$ and the methine protons suggest that the cation moiety is included in the aromatic π-cavity of **1g**. In the presence of **1g** (d), the methyl protons of $N^+(CH_3)_3$ ($\Delta\delta = \delta_{obs} - \delta_{free}$: $\Delta\delta$ = -0.063, -0.069 ppm) and the methine protons ($\Delta\delta$ = -0.098, -0.110 ppm) appear as a pair of signals with equal intensities, corresponding to the respective enantiomers. In the presence of **1d**, the methine proton of **3** is split ($\Delta\delta$ = -0.083, -0.089 ppm), however, the methyl protons of $N^+(CH_3)_3$ is observed as a single peak. On the other hand, the proton signals of the racemic ammonium ion **3** in the presence of other macrocycles **1b, 1c, 1e, 1f,** and **1h** shifted to a higher field but did not split. These results are summaried in Table 4. Considering the macrocycles **1d** and **1g** bearing tyrosine residues adopt the cone structure and others exist as flattened structures, the results indicate that the cation is favorably included in the cone cavity.

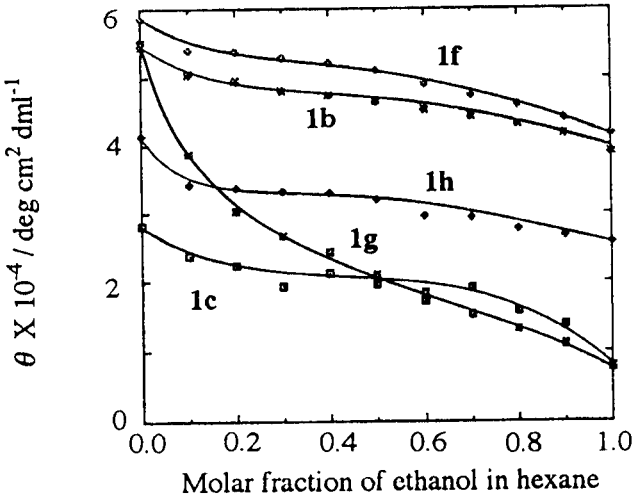


Figure 7. Change of θ-value at 296 nm of **1** as a function of the composition of hexane-ethanol solvent mixture at 20°.

In conclusion, we prepared chiral bishomodiazacalix[4]arenes by the cyclization reactions of various *L*-amino acid methyl esters and the bis(chloromethyl)phenol-formaldehyde dimer. The nmr and circular dichroism spectra showed that the cyclophane moiety adopts a chiral twisted form, which is induced by the chirality of the amino acid residue. In this case, the intramolecular hydrogen bonding plays an important role in the chiral transmission from the amino acid residues to the cyclophane moiety and in making the cavity chiral.

Macrocycles **1d** and **1g** bearing tyrosine residues have cavity π-base large enough to include ammonium ions, and can serve as a shift reagent for a racemic ammonium ion upon complexation during a ^{1}H nmr analysis.

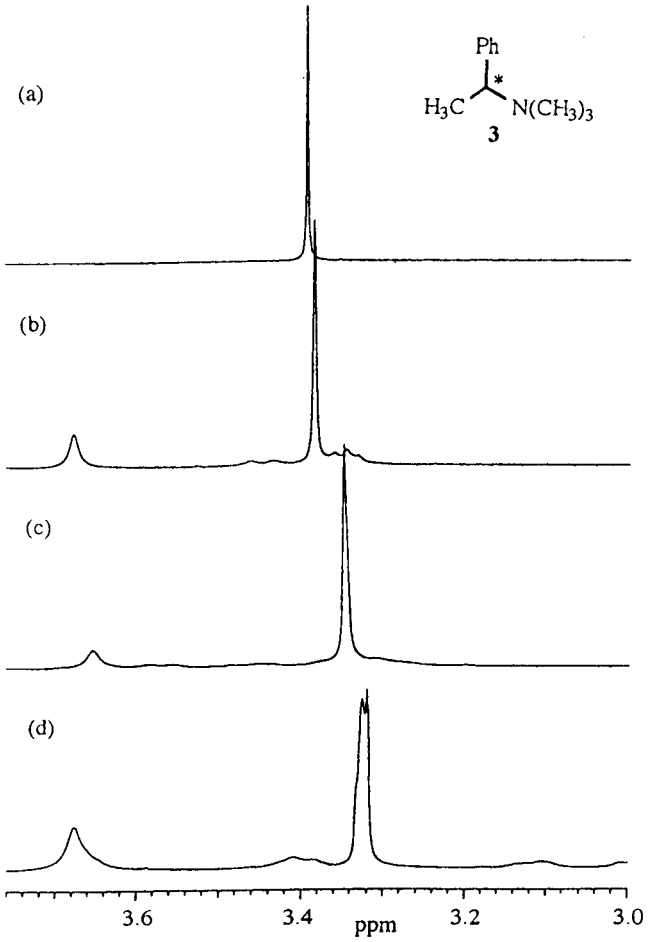


Figure 8. Partial ^1H nmr spectra of racemic ammonium iodide (**3**) in deuteriochloroform at 20°. [**3**] = 10 mM. (b) [**3**] = [**1b**] = 10 mM. (c) [**3**] = [**1e**] = 10 mM. (d) [**3**] = [**1g**] = 10 mM.

ence. Ir and uv spectra were taken on Horiba FT-200 and Hitachi 228A spectrophotometers, respectively. Circular dichroism spectra were obtained on a Jasco J-720WI spectrophotometer. Fab-mass spectra were recorded on a JEOL JMS AX-505HA spectrometer, using *m*-nitrobenzyl alcohol as a matrix. Optical rotations were measured on a Atago AA-5 digital polarimeter. Column chromatography was performed using silica gel (Kieselgel 60, 63-200 mm, 70-230 mesh, Merck). All chemicals were reagent grade and were used without further purification. 2-(3-Hydroxymethyl-2-hydroxy-5-methylbenzyl)-6-hydroxymethyl-4-methylphenol [9a] and 2-(3-hydroxymethyl-2-hydroxy-5-*tert*-butylbenzyl)-6-hydroxymethyl-4-*tert*-butylphenol [9b] were prepared according to the reported methods.

Synthesis of Bis(chloromethyl)phenol-formaldehyde Dimer (**2**).

To a solution of 2-(3-hydroxymethyl-2-hydroxy-5-methylbenzyl)-6-hydroxymethyl-4-methylphenol or 2-(3-hydroxymethyl-2-hydroxy-5-*tert*-butylbenzyl)-6-hydroxymethyl-4-*tert*-butylphenol (10 mmoles) in 50 ml of dry benzene was added a solution of thionyl chloride (40 mmoles) in 20 ml of dry benzene over 30 minutes. After the addition was completed, the mixture was allowed to stir at room temperature for 5 hours. Removal of benzene and excess thionyl chloride *in vacuo* gave colorless crystals, which were recrystallized from benzene-hexane to give **2** as colorless crystals.

2-(3-Chloromethyl-2-hydroxy-5-methylbenzyl)-6-chloromethyl-4-methylphenol (**2a**).

The yield of **2a** was 80% as colorless crystals, mp 131-135° (lit 135° [10]); ^1H nmr (deuteriochloroform): δ 2.25 (6H, s, CH_3), 3.88 (2H, s, $ArCH_2Ar$), 4.63 (4H, s, CH_2Cl), 6.95 (2H, d, aromatic protons, J = 1.4 Hz), 7.07 (2H, d, aromatic protons, J = 1.4 Hz); ^{13}C nmr (deuteriochloroform): δ 20.4, 30.7, 43.1, 123.9, 127.5, 129.3, 130.7, 132.1, 149.4; fab-ms: m/z 325 $(M+H)^+$.

2-(3-Chloromethyl-2-hydroxy-5-*tert*-butylbenzyl)-6-chloromethyl-4-*tert*-butylphenol (**2b**).

The yield of **2b** was 92% as colorless crystals, mp 134-136°; ^1H nmr (deuteriochloroform): δ 1.28 (18H, s, $C(CH_3)_3$), 3.95 (2H, s, $ArCH_2Ar$), 4.66 (4H, s, CH_2Cl), 7.16 (2H, d, aromatic protons,

Table 4

^1H-Nmr Data for the Complexation of α-Phenethyl Trimethylammonium Iodide **3** with Macrocycle **1** in Deuteriochloroform at 500 MHz at 20.41 ([**1**]=[**3**]=10 mM).

Macrocycle	CH_3 δ, ppm (Δδ, ppm)	$N^+(CH_3)_3$ δ, ppm (Δδ, ppm)	CH δ, ppm (Δδ, ppm)	Ph δ, ppm (Δδ, ppm)
none	1.857	3.388	5.430	7.630
1b	1.848 (-0.009)	3.374 (-0.014)	5.420 (-0.010)	7.629 (-0.001)
1c	1.848 (-0.009)	3.376 (-0.012)	5.430 (0.000)	7.627 (-0.003)
1d	1.820 (-0.037)	3.330 (-0.058)	5.341 (-0.089)	7.592 (-0.038)
			5.347 (-0.083)	
1e	1.841 (-0.016)	3.362 (-0.026)	5.406 (-0.024)	7.619 (-0.011)
1f	1.853 (-0.004)	3.382 (-0.006)	5.424 (-0.006)	7.630 (0.000)
1g	1.816 (-0.041)	3.319 (-0.069)	5.320 (-0.110)	7.585 (-0.045)
		3.325 (-0.063)	5.332 (-0.098)	
1h	1.830 (-0.027)	3.345 (-0.043)	5.385 (-0.045)	7.607 (-0.023)

EXPERIMENTAL

All melting points are uncorrected. ^1H and ^{13}C nmr spectra were measured with Varian Mercury 200 and Varian 500 INOVA spectrophotometers, using tetramethylsilane as an internal standard reference.

J = 1.4 Hz), 7.30 (2H, d, aromatic protons, J = 1.4 Hz); ^{13}C nmr (deuteriochloroform): 31.2, 31.4, 34.1, 43.6, 123.4, 125.6, 127.4, 128.5, 144.2, 149.3; ei-ms (70 eV): m/z 408 (M^+, 23%).

Anal. Calcd. for $C_{23}H_{30}O_2Cl_2$: C, 67.48; H, 7.39. Found: C, 67.74; H, 7.55.

General Procedure of the Preparation of Bishomodiazacalix-[4]arenes (**1**).

To a suspension of sodium carbonate in dry dimethylformamide (30 ml) was simultaniously added a soution of bis-(chloromethyl)-*p*-substitued phenol-formaldehyde dimer **2** (0.73 g, 1.0 mmole) in dry dimethylformamide (30 ml) and a solution of amino acid methylester monohydrochloride (1.0 mmole) in dry dimethylformamide (30 ml) over 2 hours. After the addition was completed, the mixture was allowed to react at 30° for 4 hours. Removal of dimethylformamide under reduced pressure gave a yellow oily residue, which was subjected to column chromatography on silica gel using hexane:ethyl acetate, 2:1 as an eluent to give **1** as crystals.

3,17-Bis[(1*S*)-1-(methoxycarbonyl)-2-methylpropyl]-7,13,21,27-tetramethyl-29,30,31,32-tetrahydroxy-2,3,16,17-tetrahomo-3,17-diazapentacyclo[23.3.1.$1^{5,9}$.$1^{11,15}$.$1^{19,23}$]dotriaconta-1(28),5,7,9(29),11,13,15(30),19,21,23(31),25,27-dodecaene (**1a**).

The yield of **1a** was 10% as colorless crystals, mp 132-139°, $[\alpha]_D^{20}$ = -30° (c 0.1, chloroform); ir (chloroform): 3290 (ν_{OH}), 1726 (ν_{CO}) cm^{-1}; ^1H nmr (deuteriochloroform, at -60°): δ 0.84 (6H, d, CHC*H*$_3$, J = 7.0 Hz), 0.89 (6H, d, CHC*H*$_3$, J = 7.0 Hz), 1.28 (2H, m, C*H*CH$_3$), 2.23 (6H, s, ArCH$_3$), 2.25 (6H, s, ArCH$_3$), 2.89 (2H, d, NCH, J = 11.0 Hz), 2.97 (2H, d, H_a, J = 13.5 Hz), 3.44 (2H, d, H_b, J = 14.0 Hz), 3.61 (2H, d, H_c, J = 13.5 Hz), 3.72 (6H, s, CO_2CH_3), 4.08 (2H, d, H_a, J = 13.5 Hz), 4.20 (2H, d, $H_{b'}$, J = 14.0 Hz), 4.44 (2H, d, $H_{c'}$, J = 13.5 Hz), 6.61 (2H, bs, H_f), 6.79 (2H, bs, H_i), 7.11 (2H, s, H_h), 7.16 (2H, s, H_g), 8.75 (2H, bs, OH), 11.60 (2H, bs, OH); ^{13}C nmr (deuteriochloroform): δ 20.0, 20.4, 27.5, 30.9, 50.6, 53.0, 55.5, 68.1, 122.1, 127.4, 129.5, 130.4, 150.7, 171.8; fab-ms: m/z 767 $(M+H)^+$.

Anal. Calcd. for $C_{46}H_{58}N_2O_8$ 1/2(H_2O): C, 71.20; H, 7.66; N, 3.61. Found: C, 70.98; H, 8.05; N, 3.51.

3,17-Bis[(1*S*)-1-(methoxycarbonyl)-3-methylbutyl]-7,13,21,27-tetramethyl-29,30,31,32-tetrahydroxy-2,3,16,17-tetrahomo-3,17-diazapentacyclo[23.3.1.$1^{5,9}$.$1^{11,15}$.$1^{19,23}$]dotriaconta-1(28),5,7,9(29),11,13,15(30),19,21,23(31),25,27-dodecaene (**1b**).

The yield of **1b** was 15% as pale yellow crystals, mp 181-187°, $[\alpha]_D^{20}$ = +19° (c 0.1, chloroform); ir (chloroform) 3284 (ν_{OH}), 1726 (ν_{CO}) cm^{-1}; ^1H nmr (deuteriochloroform, at -60°): δ 0.88 (6H, d, CHC*H*$_3$, J = 5.0 Hz), 0.94 (6H, d, CHC*H*$_3$, J = 5.0 Hz), 1.60 (2H, bs, C*H*(CH$_3$)$_2$), 1.75 (2H, bs, NCHC*H*), 1.87 (2H, bs, NCHC*H*), 2.23 (6H, s, ArCH$_3$), 2.24 (6H, s, ArCH$_3$), 3.26 (2H, d, H_a, J = 11.5 Hz), 3.30 (2H, dd, NCH, J = 5.5, 13.0 Hz), 3.45 (2H, d, H_b, J = 13.5 Hz), 3.70 (6H, s, CO_2CH_3), 3.80 (2H, d, H_c, J = 13.5Hz), 4.11 (2H, d, $H_{a'}$, J = 11.5Hz), 4.28 (2H, d, $H_{b'}$, J = 13.5 Hz), 4.46 (2H, d, $H_{c'}$, J = 13.5 Hz), 6.67 (2H, bs, H_f), 6.78 (2H, bs, H_i), 7.10 (2H, bs, H_h), 7.17 (2H, bs, H_g), 8.85 (2H, bs, OH), 12.18 (2H, bs, OH); ^{13}C nmr (deuteriochloroform): δ 20.4, 21.8, 22.7, 24.8, 30.5, 39.1, 51.0, 53.6, 55.4, 58.2, 121.3, 122.5, 127.0, 127.7, 128.1, 128.2, 129.2, 129.8, 130.9, 131.3, 150.7, 151.4, 172.9; fab-ms: m/z 795 $(M+H)^+$.

Anal. Calcd. for $C_{48}H_{62}N_2O_8$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.46; H, 8.03; N, 3.48.

3,17-Bis[(1*S*)-1-(methoxycarbonyl)-2-phenylethyl]-7,13,21,27-tetramethyl-29,30,31,32-tetrahydroxy-2,3,16,17-tetrahomo-3,17-diazapentacyclo[23.3.1.$1^{5,9}$.$1^{11,15}$.$1^{19,23}$]dotriaconta-1(28),5,7,9(29),11,13,15(30),19,21,23(31),25,27-dodecaene (**1c**).

The yield of **1c** was 19% as colorless crystals, mp 193-198°, $[a]_D^{20}$ = -27° (c 0.1, chloroform); ir (chloroform): 3290 (ν_{OH}), 1732 (ν_{CO}) cm^{-1}; ^1H nmr (deuteriochloroform, at -60°): δ 2.19 (6H, s, ArCH$_3$), 2.22 (6H, s, ArCH$_3$), 3.26 (2H, d, H_a, J = 11.5 Hz), 3.33 (2H, d, H_b, J = 14.0 Hz), 3.47 (2H, d, H_c, J = 13.5), 3.68 (6H, s, CO_2CH_3), 4.08 (2H, d, $H_{a'}$, J = 11.5 Hz), 4.27 (2H, d, $H_{c'}$, J = 13.5 Hz), 4.48 (2H, d, $H_{b'}$, J = 14.0 Hz), 6.67 (2H, bs, H_f), 6.76 (2H, bs, H_i), 7.11 (4H, H_g and H_h), 7.20 (10H, m, aromatic protons), 8.68 (2H, bs, OH), 12.0 (2H, bs, OH); ^{13}C nmr (deuteriochloroform): δ 20.3, 30.9, 36.1, 51.4, 51.5, 53.4, 63.4, 121.5, 123.0, 127.6, 128.3, 129.0, 129.5, 131.3, 131.9, 149.5, 151.0, 170.7; fab-ms: m/z 863 $(M+H)^+$.

Anal. Calcd. for $C_{54}H_{58}N_2O_8$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.22; H, 7.01; N, 3.09.

3,17-Bis[(1*S*)-2-(4-hydroxyphenyl)-1-(methoxycarbonyl)ethyl]-7,13,21,27-tetramethyl-29,30,31,32-tetrahydroxy-2,3,16,17-tetrahomo-3,17-diazapenta-cyclo[23.3.1.$1^{5,9}$.$1^{11,15}$.$1^{19,23}$]dotriaconta-1(28),5,7,9(29),11,13,15(30),19,21,23(31),25,27-dodecaene (**1d**).

The yield of **1d** was 20% as pale yellow crystals, mp 157-166°, $[\alpha]_D^{20}$ = +12° (c 0.1, chloroform); ir (chloroform) 3599 (ν_{OH}), 3290 (ν_{OH}), 1732 (ν_{CO}) cm^{-1}; ^1H nmr (deuteriochloroform, at -60°): δ 2.18 (6H, s, ArCH$_3$), 2.21 (6H, s, ArCH$_3$), 2.77 (2H, bs, NCHC*H*), 3.04 (2H, bs, NCHC*H*), 3.18 (2H, d, H_a, J = 10.5 Hz), 3.29 (2H, d, H_b, J = 13.0 Hz), 3.58 (2H, bs, NCH), 3.71 (2H, d, H_c, J = 12.5 Hz), 3.76 (6H, s, CO_2CH_3), 3.91 (2H, d, $H_{a'}$, J = 10.5 Hz), 4.04 (2H, d, $H_{b'}$, J = 13.0 Hz), 4.37 (2H, d, $H_{c'}$, J = 12.5 Hz), 6.64 (2H, bs, H_f), 6.74 (2H, bs, H_i), 6.77 (4H, bs, aromatic protons), 6.87 (4H, bs, aromatic protons), 6.98 (2H, s, H_h), 7.08 (2H, s, H_g), 8.20 (2H, bs, OH), 8.30 (2H, bs, OH), 10.40 (2H, bs, OH); ^{13}C nmr (deuteriochloroform): δ 20.4, 30.5, 34.3, 51.2, 53.3, 55.1, 61.8, 115.2, 121.2, 122.2, 127.4, 128.8, 129.4, 130.1, 130.7, 151.1, 154.0, 172.4; fab-ms: m/z 895 $(M+H)^+$.

Anal. Calcd. for $C_{54}H_{58}N_2O_{10}$: C, 72.46; H, 6.53; N, 3.13. Found: C, 72.24; H, 6.90; N, 2.96.

3,17-Bis[(1*S*)-2-indol-3-yl-1-(methoxycarbonyl)ethyl]-7,13,21,27-tetramethyl-29,30,31,32-tetrahydroxy-2,3,16,17-tetrahomo-3,17-diazapentacyclo[23.3.1.$1^{5,9}$.$1^{11,15}$.$1^{19,23}$]dotriaconta-1(28),5,7,9(29),11,13,15(30),19,21,23(31),25,27-dodecaene (**1e**).

The yield of **1e** was 15% as pale yellow crystals, mp 164-175°, $[\alpha]_D^{20}$ = +34° (c 0.1, chloroform); ir (chloroform) 3479 (ν_{NH}), 3280 (ν_{OH}), 1730 (ν_{CO}) cm^{-1}; ^1H nmr (deuteriochloroform, at -60°): δ 2.18 (6H, s, ArCH$_3$), 2.30 (6H, s, ArCH$_3$), 3.25 (2H, d, H_a, J = 12.0 Hz), 3.26 (2H, d, H_b, J = 13.5 Hz), 3.27 (2H, bs, NCHC*H*), 3.62 (2H, d, H_c, J = 12.5 Hz), 3.64 (2H, bs, NCHC*H*), 3.68 (6H, s, CO_2CH_3), 3.76 (2H, bs, NCH), 4.21 (2H, d, $H_{a'}$, J = 12.0 Hz), 4.49 (2H, d, $H_{c'}$, J = 12.5 Hz), 4.62 (2H, d, $H_{b'}$, J = 13.5 Hz), 6.69 (2H, s, H_f), 6.81 (2H, s, H_i), 7.09 (2H, dd, indole ring protons, J = 7.4, 7.6 Hz), 7.11 (2H, dd, indole ring protons, J = 7.6, 8.9 Hz), 7.12 (2H, s, H_g), 7.18 (2H, s, H_h), 7.37 (2H, d, indole ring protons, J = 8.9 Hz), 7.51 (2H, d, indole ring protons, J = 7.4 Hz), 8.14 (2H, s, indole ring protons), 9.25 (2H, bs, OH), 12.10 (2H, bs, OH); ^{13}C nmr (deuteriochloroform): δ 20.4, 26.4, 30.7, 51.0, 54.0, 55.8, 60.7, 110.9, 111.6, 118.7, 119.0, 121.7, 122.3, 123.3, 127.3, 128.6, 130.2, 130.9, 136.1, 151.1, 171.7; fab-ms: m/z 941 $(M+H)^+$.

Anal. Calcd. for $C_{58}H_{60}N_4O_8$: C, 74.02; H, 6.43; N, 5.95 . Found: C, 73.94; H, 6.86; N, 5.71.

3,17-Bis[(1*S*)-1-(methoxycarbonyl)-2-methylbutyl]-7,13,21,27-tetra-*tert*-butyl-29,30,31,32-tetrahydroxy-2,3,16,17-tetrahomo-3,17-diazapentacyclo[23.3.1.$1^{5,9}$.$1^{11,15}$.$1^{19,23}$]dotriaconta-1(28),5,7,9(29),11,13,15(30),19,21,23(31),25,27-dodecaene (**1f**).

The yield of **1f** was 10% as pale yellow crystals, mp 213-221°, $[\alpha]_D^{20}$ = +22° (c 0.1, chloroform); ir (chloroform) 3277 (ν_{OH}), 1730 (ν_{CO}) cm^{-1}; ^1H nmr (deuteriochloroform, at -60°): δ 0.88

(6H, d, $CHCH_3$, J = 5 Hz), 0.98 (6H, d, $CHCH_3$, J = 5 Hz), 1.27 (36H, s, *t*-Bu), 1.48 (2H, bs, $CH(CH_3)_2$), 1.80 (2H, bs, NCHC*H*), 1.98 (2H, bs, NCHC*H*), 3.37 (2H, bs, NC*H*), 3.39 (2H, d, H_a, J = 11.0 Hz), 3.51 (2H, d, H_b, J = 14.0 Hz), 3.67 (6H, s, CO_2CH_3), 4.05 (2H, d, H_c, J = 13.0 Hz), 4.16 (2H, d, $H_{a'}$, J = 11.0 Hz), 4.32 (2H, d, $H_{b'}$, J = 14.0 Hz), 4.54 (2H, d, $H_{c'}$, J = 13.0 Hz), 6.86 (2H, bs, H_f), 6.97 (2H, bs, H_i), 7.27 (2H, bs, H_h), 7.35 (2H, bs, H_g), 9.01 (2H, bs, OH), 12.28 (2H, bs, OH); ^{13}C nmr (deuteriochloroform): δ 21.6, 22.9, 24.7, 31.2, 31.5, 33.8, 33.9, 39.3, 51.1, 54.1, 56.0, 58.1, 120.6, 122.0, 124.2, 125.9, 126.8, 127.3, 127.5, 127.8, 141.7, 142.5, 150.7, 151.3, 173.3; fab-ms: m/z 964 $(M+H)^+$.

Anal. Calcd. for $C_{60}H_{86}N_2O_8$: C, 74.81; H, 9.00; N, 2.91. Found: C, 74.44; H, 9.19; N, 2.81.

3,17-Bis[(1*S*)-2-(4-hydroxyphenyl)-1-(methoxycarbonyl)ethyl]-7,13,21,27-tetra-*tert*-butyl-29,30,31,32-tetrahydroxy-2,3,16,17-tetrahomo-3,17-diazapentacyclo[23.3.1.$1^{5,9}$.$1^{11,15}$.$1^{19,23}$]dotriaconta-1(28),5,7,9(29),11,13,15(30),19,21,23(31),25,27-dodecaene (**1g**).

The yield of **1g** was 22% as pale yellow crystals, mp 166-168°, $[a]_D^{20}$ = +18° (c 0.1, chloroform); ir (chloroform) 3599 (ν_{OH}), 3290 (ν_{OH}), 1732 (ν_{CO}) cm^{-1}; ^1H nmr (deuteriochloroform, -60°): δ 1.23 (36H, s, *t*-Bu), 2.86 (2H, bs, NCHC*H*), 3.07 (2H, d, NCHC*H*), 3.30 (2H, d, H_a, J = 11.5 Hz), 3.38 (2H, d, H_b, J = 13.0 Hz), 3.64 (2H, bs, NC*H*), 3.77 (6H, s, CO_2CH_3), 3.97 (2H, d, H_c, J = 12.5 Hz), 4.00 (2H, d, $H_{a'}$, J = 11.5 Hz), 4.10 (2H, d, $H_{b'}$, J = 13.0 Hz), 4.43 (2H, d, $H_{c'}$, J = 12.5 Hz), 6.83 (2H, s, H_f), 6.89 (4H, bs, aromatic protons), 6.91 (2H, bs, H_i), 7.16 (2H, bs, H_h), 7.29 (2H, bs, H_g), 8.16 (2H, bs, OH), 8.28 (2H, bs, OH), 10.37 (2H, bs, OH); ^{13}C nmr (deuteriochloroform): δ 31.0, 31.5, 33.8, 51.3, 53.5, 55.4, 61.0, 115.2, 120.4, 121.7, 124.6, 126.1, 126.7, 127.2, 127.5, 129.1, 130.1, 141.8, 142.4, 150.4, 151.1, 153.9, 172.8; fab-ms: m/z 1064 $(M+H)^+$.

Anal. Calcd. for $C_{66}H_{82}N_2O_{10}$: C, 74.55; H, 7.77; N, 2.63. Found: C, 74.67; H, 8.08; N, 2.55.

3,17-Bis[(1*S*)-2-indol-3-yl-1-(methoxycarbonyl)ethyl]-7,13,21,27-tetra-*tert*-butyl-29,30,31,32-tetrahydroxy-2,3,16,17-tetrahomo-3,17-diazapentacyclo[23.3.1.$1^{5,9}$.$1^{11,15}$.$1^{19,23}$]-dotriaconta-1(28),5,7,9(29),11,13,15(30),19,21,23(31),25,27-dodecaene (**1h**).

The yield of **1h** was 16% as pale yellow crystals, mp 168-175°, $[a]_D^{20}$ = +31° (c 0.1, chloroform); ir (chloroform) 3479 (ν_{NH}), 3269 (ν_{OH}), 1728 (ν_{CO}) cm^{-1}; ^1H nmr (deuteriochloroform, -60°): δ 1.22 (18H, s, *t*-Bu), 1.29 (18H, s, *t*-Bu), 3.34 (2H, bs, NCHC*H*), 3.35 (2H, d, H_a, J = 12.5 Hz), 3.52 (4H, m, H_b and NCHC*H*), 3.57 (2H, d, H_c, J = 12.5 Hz), 3.67 (6H, s, CO_2CH_3), 3.83 (2H, dd, NC*H*, J = Hz), 4.28 (2H, d, $H_{a'}$, J = 12.5 Hz), 4.41 (2H, d, $H_{c'}$, J = 12.5 Hz), 4.72 (2H, d, $H_{b'}$, J = 13.5 Hz), 6.91 (2H, bs, H_f), 6.98 (2H, bs, H_i), 7.11 (2H, dd, indole ring protons, J = 6.5, 8.0 Hz), 7.19 (2H, dm, indole ring protons, J = 6.5 Hz), 7.27 (2H, bs, H_g), 7.33 (2H, bs, H_h), 7.37 (2H, d, indole ring protons, J = 8.0 Hz), 7.58 (2H, bs, indole ring protons), 8.19 (2H, s, indole ring protons), 9.30 (2H, s, OH), 12.55 (2H, s, OH); ^{13}C nmr (deuteriochloroform): δ 26.8, 31.3, 31.5, 33.7, 51.0, 54.4, 56.5, 60.4, 110.9, 111.7, 118.8, 119.2, 120.8, 121.8, 123.3, 124.3, 126.2, 126.9, 127.4, 136.2, 141.8, 142.6, 150.8, 151.1, 172.0; fab-ms: m/z 1110 $(M+H)^+$.

Anal. Calcd. for $C_{70}H_{84}N_4O_8$: C, 75.78; H, 7.63; N, 5.05. Found: C, 75.82; H, 7.85; N, 4.66.

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[5] According to Gutsche [1a], Δδ value between H_{exo} and H_{endo} is generally approximately 0.9±0.2 ppm for *syn*-orientation of phenol ring and zero for *anti*-orientation.

[6] The $ArCH_2Ar$ methylene carbon resonances for calixarenes appear at approximately δ 30-33 ppm when the adjacent aryl rings are *syn* and at approximately 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).

[7] Considering that the hydroxy protons of the tyrosine residues of **1d** and **1g** were observed at 8.20 ppm for **1d** and 8.16 ppm for **1g** and the hydroxy protons of the phenol-formaldehyde dimer units were observed at a lower magnetic field compared with those of other macrocycles, it suggests that the hydroxy protons of the tyrosine residues perturb the intramolecular hydrogen bonded array in the macrocycles.

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