Facile Formation of Chiral Calixarene Analogs Incorporating Cystine Peptide into the Macrocyclic Ring

Kazuaki Ito,* Takafumi Tamura, Kazuhito Watanabe, and Yoshihiro Ohba

Department of Chemistry and Chemical Engineering, Faculty of Engineering, Yamagata University, Yonezawa 992–8510, Japan. Received November 5, 2001; accepted December 17, 2001

Chiral calixarene analogs incorporating cystine peptide into their macrocyclic ring were easily prepared by the cyclization reactions of bis(chloromethyl)phenol-formaldehyde oligomers with cystine peptides in moderate yields. Circular dichroism (CD) spectra indicated the existence of the transmission of the chirality from peptide unit to phenol-formaldehyde oligomer moiety.

Key words chiral calixarene analog; cystine; pseudo cyclic peptide; planar chirality

Calixarenes and their derivatives are one of the most important host molecules in molecular recognition field. The chemistry of calixarenes has been extensively studied with respective to the modification of the frameworks at the lower (small) and upper (large) rims of the calixarene skeleton from the viewpoint of additional functionality.[1,2] Despite such progress, the modification on the methylene backbone 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 calixarene analogs, which were constructed by changing from the methylene moiety to other units. Therefore, we synthesized the calixarene analogs incorporating cystine peptide as a building block in the macrocyclic ring.[4] It is known that cystine unit is an important structure element of peptide and protein structure, because the disulfide unit in proteins plays an important functional role in redox processes and in restricting their conformation.[5—7] In this paper we describe the synthesis of the chiral calixarene analogs incorporating cystine peptide and their structural analysis.

Calixarene analog (**1a**) was prepared from the cyclization reaction of 1,5-bis(chloromethyl)-*p*-cresol (**4a**)[8] and an equimolar amount of cystine peptide (NH=Pro–Cys(OMe)–SS–Cys(OMe)–Pro=NH) (**3a**)[9] in chloroform in the presence of triethylamine (NEt_3) at 30 °C for 12 h in 45% yield. Analogously, the reactions using phenol-formaldehyde oligomers (**4b**—**e**)[10,11] instead of **2a** under the same reaction condition gave the corresponding macrocycles (**1b**—**e**) in 36, 35, 32, and 30% yields, respectively. Similarly, the reactions of **4a**—**d** with cystine peptide (NH=Pro–Phe–Cys(OMe)–SS–Cys(OMe)–Phe–Pro=NH) (**3b**)[12] also gave the corresponding macrocycles (**2a**—**d**) in 32, 31, 26, and 8% yields, respectively. But the reaction of **3b** with **4e** did not give any macrocyclic compound except polymeric materials.

The structure of macrocycles (**1**, **2**) was elucidated by using their elemental analyses and spectral data. In the IR spectra the absorption of the hydroxyl groups of phenol unit were observed at the range of 3273—3298 cm^{-1}, indicating the formation of the intramolecular hydrogen bonding.[13] The ^1H- and ^{13}C-NMR spectra of macrocycles (**1**, **2**) gave C_2 symmetry signal pattern. The $ArCH_2Ar$ methylene protons observed as a pair of doublet and/or singlet. According to Gutsche,[14,15] the $\Delta\delta$ values between H_{exo} and H_{endo} of the $ArCH_2Ar$ methylene protons in calixarenes is generally *ca.* 0.9 ± 0.2 ppm for *syn* orientation of aryl rings and zero for *anti*. Considering that the small $\Delta\delta$ values [0.56 ppm (**1c**),

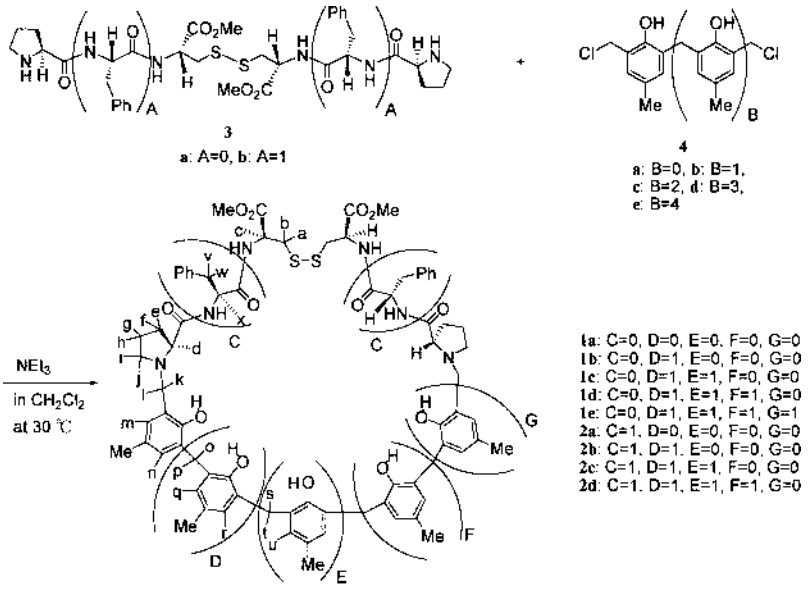

Chart 1

* To whom correspondence should be addressed. e-mail: tm382@dipfr.dip.yz.yamagata-u.ac.jp

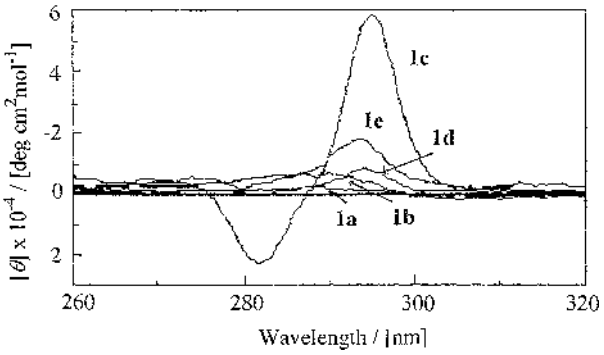

Fig. 1. CD Spectra of Macrocycles (**1**) in $CHCl_3$ at 25 °C

0.08 ppm (**1d**), 0.28, 0.26 ppm (**1e**), 0.61 ppm (**2c**), 0.07 ppm (**2d**)] were observed in the macrocycles (**1**, **2**), the phenol-formaldehyde oligomer moieties may adopt a twisting form. In this case, it is possible that the twisting direction of phenol-formaldehyde oligomer moieties is effected by the chirality of the cystine peptide. Therefore, we carried out the circular dichroism (CD) spectral measurement of **1** in chloroform as shown in Fig. 1. CD spectra of **1** showed the absorption of the phenol chromophore around 290 nm [**1a**: λ_{ext}=289 nm (θ 2400), **1b**: λ_{ext}=290 nm (θ 6600), **1c**: λ_{ext}=294 nm (θ 58600), **1d**: λ_{ext}=293 nm (θ 8000), and **1e**: λ_{ext}=294 nm (θ 17700)], supporting the assumption that the phenol-formaldehyde oligomer moiety is chiral.[16] The discrepancy of the CD signal intensities of **1** may relate to the restriction of the molecular mobility and the degree of the twisting of the phenol-formaldehyde oligomer moiety.

In conclusion, we prepared chiral calixarene analogs containing cystine peptide moiety into their macrocyclic ring in moderate yields. CD spectra of the macrocycles suggested the existence of the chiral transmission from the peptide unit to the phenol-formaldehyde oigomer moiety.

Experimental

Melting points were measured by Yanagimoto micro melting point apparatus and were uncorrected. ^{1}H- and ^{13}C-NMR spectra were measured with a Varian Mercury 200 and a Varian INOVA 500 spectrophotometers, using tetramethylsilane as an internal standard reference. IR spectra were taken on a Horiba FT-200 spectrophotometer. FAB-mass spectra were recorded on a JEOL JMS AX-505HA spectrometer, using *m*-nitrobenzyl alcohol as a matrix. CD spectra were obtained on a Jasco J-720WI spectrophotometer. Column chromatography was performed using silica gel (Kieselgel 60, 63—200 mm, 70—230 mesh, Merck). All amino acids were used in the L-form. Cystine peptides (**3**) and bis(chloromethyl)phenol-formaldehyde oligomers (**4**) were prepared according to the methods reported in literature.[6—10]

General Procedure for the Preparation of the Macrocycles To 50 ml of dichloromethane was added a solution of triethylamine (216 mg, 2.14 mmol) and peptide **3** (0.36 mmol) in 10 ml of dichloromethane and a solution of bis(chloromethyl)phenol-formaldehyde oligomer **4** (0.36 mmol) in 10 ml of dichloromethane at 30 °C over 2 h, simultaneously. After the addition was complete, the mixture was allowed to stir at 30 °C for 20 h. Removal of dichloromethane gave yellow oily residue, which was subjected to column chromatography on silica gel using hexane : ethyl acetate 3 : 1 as an eluent to give **1** or **2** as colorless crystals.

1a: The yield was 45% as crystals, mp 198—199 °C. IR ($CHCl_3$): 3415 (ν_{NH}), 3273 (ν_{OH}), 1745 (ν_{CO}), 1666 (amide I), 1512 (amide II) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.84 (m 4H, H_g, H_h), 2.04 (m, 2H, H_e), 2.24 (s, 3H, Me), 2.32 (m, 4H, H_f, H_i), 3.00 (m, 2H, H_j), 3.19 (dd, 2H, J=5.0, 14.5 Hz, H_a), 3.23 (dd, 2H, J=6.5, 9.5 Hz, H_d), 3.27 (d, 2H, J=13.0 Hz, H_l), 3.34 (dd, 2H, J=8.0, 14.5 Hz, H_b), 3.64 (s, 6H, CO_2Me), 4.34 (d, 2H, 13.0 Hz, H_k), 4.96 (ddd, 2H, J=5.0, 8.0, 8.5 Hz, H_c), 6.81 (s, 2H, H_m), 8.27 (d, 2H, J=8.5 Hz, NH), 10.80 (bs, 1H, OH). ^{13}C-NMR ($CDCl_3$) δ: 20.4, 23.3, 29.9, 43.2, 52.1, 52.5, 53.7, 57.4, 68.1, 123.4, 128.3, 129.5, 153.3, 170.8, 174.1. MS (FAB, *m*/*z*) 595 (M+H)$^+$. *Anal.* Calcd for $C_{27}H_{38}N_4O_7S_2$: C, 54.53; H, 6.44; N, 9.42. Found: C, 54.43; H, 6.33; N, 9.45.

1b: The yield was 36% as crystals, mp 197—198 °C. IR ($CHCl_3$): 3410 (ν_{NH}), 3298 (ν_{OH}), 1743 (ν_{CO}), 1666 (amide I), 1512 (amide II) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.79 (m, 4H, H_g, H_h), 1.98 (m, 2H, H_e), 2.21 (m, 2H, H_f), 2.22 (s, 6H, Me), 2.30 (m, 2H, H_i), 2.93 (m, 2H, H_j), 3.16 (dd, 2H, J=7.0, 9.0 Hz, H_d), 3.22 (d, 2H, J=12.5 Hz, H_l), 3.27 (dd, 2H, J=6.5, 14.0 Hz, H_a), 3.35 (dd, 2H, J=5.5, 14.0 Hz, H_b), 3.73 (s, 6H, CO_2Me), 3.87 (s, 2H, H_o), 4.27 (d, 2H, J=12.5 Hz, H_k), 4.87 (ddd, 2H, J=5.5, 6.5, 8.0 Hz, H_c), 6.73 (d, 2H, J=2.0 Hz, H_m), 7.06 (d, 2H, J=2.0 Hz, H_n), 8.00 (d, 2H, J=8.0 Hz, NH). ^{13}C-NMR ($CDCl_3$) δ: 20.5, 23.1, 29.9, 30.9, 40.7, 52.1, 52.6, 53.5, 57.4, 67.9, 123.9, 127.6, 128.9, 129.3, 130.5, 150.6, 171.0, 173.9. MS (FAB, *m*/*z*) 715 (M+H)$^+$. *Anal.* Calcd for $C_{35}H_{46}N_8O_8S_2\cdot 2.5(H_2O)$: C, 55.32; H, 6.76; N, 7.37. Found: C, 55.11; H, 6.26; N, 7.11.

1c: The yield was 35% as crystals, mp 222—223 °C. IR ($CHCl_3$): 3415 (ν_{NH}), 3275 (ν_{OH}), 1741 (ν_{CO}), 1666 (amide I), 1512 (amide II) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.82 (m, 4H, H_g, H_h), 2.03 (m, 2H, H_e), 2.22 (s, 6H, Me), 2.30 (m, 4H, H_f, H_i), 3.00 (m, 2H, H_j), 3.17 (d, 2H, J=13.0 Hz, H_l), 3.18 (dd, 2H, J=7.0, 9.5 Hz, H_d), 3.31 (dd, 2H, J=4.0, 13.5 Hz, H_a), 3.37 (dd, 2H, J=7.0, 13.5 Hz, H_b), 3.58 (d, 2H, J=14.0 Hz, H_p), 3.68 (s, 6H, CO_2Me), 4.14 (d, 2H, J=14.0 Hz, H_o), 4.32 (d, 2H, J=13.0 Hz, H_k), 5.05 (ddd, 2H, J=4.0, 7.0, 8.0 Hz, H_c), 6.72 (d, 2H, J=2.0 Hz, H_m), 6.95 (s, 2H, H_q), 7.02 (d, 2H, J=2.0 Hz, H_n), 8.23 (d, 2H, J=8.0 Hz, NH). ^{13}C-NMR ($CDCl_3$) δ: 20.4, 20.5, 23.3, 30.1, 31.4, 40.9, 52.1, 52.7, 53.5, 57.5, 68.2, 123.7, 127.5, 128.2, 129.3, 129.4, 130.4, 130.7, 147.5, 150.4, 170.8, 173.7. MS (FAB, *m*/*z*) 835 (M+H)$^+$. *Anal.* Calcd for $C_{43}H_{54}N_4O_9S_2\cdot 0.5(H_2O)$: C, 61.19; H, 6.57; N, 6.64. Found: C, 61.35; H, 6.58; N, 6.46.

1d: The yield was 32% as crystals, mp 178—188 °C. IR ($CHCl_3$): 3413 (ν_{NH}), 3286 (ν_{OH}), 1743 (ν_{CO}), 1666 (amide I), 1512 (amide II) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.91 (m, 4H, H_g, H_h), 2.01 (m, 2H, H_e), 2.16 (m, 2H, H_f), 2.22 (s, 6H, Me), 2.36 (m, 2H, H_i), 3.03 (m, 2H, H_j), 3.20 (dd, 2H, J=7.0, 14.5 Hz, H_a), 3.22 (dd, 2H, J=6.5, 9.0 Hz, H_d), 3.28 (d, 2H, J=12.5 Hz, H_l), 3.38 (dd, 2H, J=5.0, 14.5 Hz, H_b), 3.58 (d, 2H, J=14.0 Hz, H_p), 3.74 (s, 6H, CO_2Me), 3.85 (s, 2H, H_s), 3.87 (d, 2H, J=14.0 Hz, H_o), 4.19 (d, 2H, J=12.5 Hz, H_k), 4.93 (dd, 2H, J=5.0, 7.0 Hz, H_c), 6.72 (s, 2H, H_m), 6.92 (s, 4H, H_q, H_r), 7.01 (s, 2H, H_n), 8.03 (bs, 2H, NH). ^{13}C-NMR ($CDCl_3$) δ: 20.4, 20.5, 23.3, 30.0, 31.3, 31.6, 40.5, 51.7, 52.7, 53.7, 57.3, 67.7, 123.6, 127.6, 128.2, 128.9, 129.3, 129.4, 129.5, 130.4, 130.7, 147.3, 150.5, 171.2, 174.1. MS (FAB, *m*/*z*) 955 (M+H)$^+$. *Anal.* Calcd for $C_{51}H_{62}N_4O_{10}S_2$: C, 64.13; H, 6.54; N, 5.87. Found: C, 64.01; H, 6.78; N, 5.91.

1e: The yield was 30% as crystals, mp 165—167 °C. IR ($CHCl_3$): 3410 (ν_{NH}), 3290 (ν_{CO}), 1745 (ν_{CO}), 1670 (amide I), 1508 (amide II) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (m, 4H, H_g, H_h), 2.05 (m, 2H, H_e), 2.16 (m, 2H, H_f), 2.19 (s, 3H, Me), 2.20 (s, 6H, Me), 2.22 (s, 6H, Me), 2.34 (m, 2H, H_i), 3.02 (m, 2H, H_j), 3.23 (dd, 2H, J=7.0, 14.0 Hz, H_a), 3.24 (dd, 2H, J=6.5, 9.0 Hz, H_d), 3.31 (d, 2H, J=13.0 Hz, H_l), 3.36 (dd, 2H, J=5.0, 14.0 Hz, H_b), 3.68 (d, 2H, J=14.0 Hz, H_s), 3.69 (d, 2H, J=14.0 Hz, H_p), 3.70 (s, 6H, CO_2Me), 3.94 (d, 2H, J=14.0 Hz, H_t), 3.97 (d, 2H, J=14.0 Hz, H_o), 4.20 (d, 2H, J=13.0 Hz, H_k), 4.85 (bs, 2H, H_c), 6.71 (bs, 2H, H_m), 6.88 (bs, 4H, H_q, H_u), 6.89 (bs, 2H, H_r), 6.99 (bs, 2H, H_n), 7.85 (bs, 2H, NH). ^{13}C-NMR ($CDCl_3$) δ: 20.4, 20.5, 23.4, 29.9, 31.1, 31.5, 40.2, 51.7, 52.7, 53.5, 57.2, 67.4, 123.2, 127.4, 127.6, 127.7, 127.9, 128.0, 128.5, 129.1, 129.2, 129.3, 130.3, 130.4, 147.5, 147.7, 150.5, 171.0, 173.9. MS (FAB *m*/*z*) 1075 (M+H)$^+$. *Anal.* Calcd for $C_{59}H_{70}N_4O_{11}S_2$: C, 65.90; H, 6.56; N, 5.21. Found: C, 65.88; H, 6.68; N, 5.41.

2a: The yield was 32% as crystals, mp 130—133 °C. IR ($CHCl_3$): 3411 (ν_{NH}), 3261 (ν_{OH}), 1743 (ν_{CO}), 1662 (amide I), 1508 (amide II) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (m, 2H, H_j), 1.60 (m, 4H, H_f, H_h), 2.08 (m, 2H, H_e), 2.22 (m, 2H, H_i), 2.24 (s, 3H, Me), 2.75 (m, 2H, H_j), 2.92 (dd, 2H, J=6.0, 14.0 Hz, H_a), 3.07 (dd, 2H, J=10.5, 14.0 Hz, H_w), 3.13 (d, 2H, J=12.0 Hz, H_l), 3.16 (dd, 2H, J=6.0, 10.5 Hz, H_d), 3.29 (dd, 2H, J=6.0, 14.0 Hz, H_b), 3.41 (dd, 2H, J=5.0, 14.0 Hz, H_v), 3.73 (s, 6H, CO_2Me), 4.19 (d, 2H, J=12.0 Hz, H_k), 4.84 (m, 2H, H_c), 4.99 (ddd, J=5.0, 10.5, 14.0 Hz, H_x), 6.82 (s, 2H, H_m), 7.12 (m, 10H, Ph), 7.62 (bs, 2H, NH), 7.88 (d, 2H, J=7.0 Hz, NH), 10.39 (bs, 1H, OH). ^{13}C-NMR ($CDCl_3$) δ: 20.4, 22.9, 30.1, 37.8, 42.4, 52.4, 52.7, 53.5, 54.1, 56.7, 65.4, 124.9, 126.4, 128.2, 128.7, 129.2, 130.1, 137.2, 153.1, 170.1, 171.9, 175.0. MS (FAB *m*/*z*) 899 (M+H)$^+$. *Anal.* Cacld for $C_{45}H_{56}N_6O_9S_2$: C, 60.79; H, 6.35; N, 9.45. Found: C, 60.90; H, 6.55; N, 9.61.

2b: The yield was 31% as crystals 142—144 °C. IR ($CHCl_3$): 3410 (ν_{NH}), 3297 (ν_{OH}), 1745 (ν_{CO}), 1668 (amide I), 1506 (amide II) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (m, 2H, H_g), 1.44 (m, 2H, H_f), 1.56 (m, 2H, H_h), 2.04 (m, 2H, H_e), 2.15 (m, 2H, H_i), 2.26 (s, 6H, Me), 2.71 (dd, 2H, J=7.0, 7.5 Hz,

H_j), 2.88 (dd, 2H, J=12.0, 14.5 Hz, H_w), 2.98 (d, 2H, J=11.5 Hz, H_l), 3.03 (m, 2H, H_d), 3.07 (dd, 2H, J=7.5, 14.0 Hz, H_a), 3.20 (dd, 2H, J=5.5, 14.5 Hz, H_v), 3.63 (dd, 2H, J=7.0, 14.0 Hz, H_b), 3.65 (s, 6H, CO_2Me), 3.87 (s, 2H, H_o), 3.90 (d, 2H, J=11.5 Hz, H_b), 4.94 (ddd, 2H, J=7.0, 7.5, 14.0 Hz, H_c), 5.04 (bs, 2H, H_x), 6.71 (d, 2H, J=1.5 Hz, H_m), 7.07 (d, 2H, J=1.5 Hz, H_n), 7.12 (m, 10H, Ph), 7.66 (bs, 2H, NH), 8.20 (bs, 2H, NH). ^{13}C-NMR ($CDCl_3$) δ: 20.4, 22.9, 30.1, 31.1, 38.1, 42.4, 52.1, 52.5, 52.7, 54.1, 55.8, 65.7, 124.5, 126.6, 126.8, 128.3, 128.8, 129.0, 129.3, 130.6, 136.6, 150.1, 170.0, 172.4, 174.6. MS (FAB m/z) 1010 $(M+H)^+$. *Anal.* Calcd for $C_{53}H_{64}N_6O_{10}S_2$: C, 63.07; H, 6.39; N, 8.33. Found: C, 63.01; H, 6.18; N, 8.41.

2c: The yield was 26% as crystals, mp 145—150 °C. IR ($CHCl_3$): 3419 (ν_{NH}), 3297 (ν_{OH}), 1747 (ν_{CO}), 1668 (amide I), 1506 (amide II) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (m, 2H, H_g), 1.42 (m, 2H, H_f), 1.53 (m, 2H, H_h), 1.98 (m, 2H, H_e), 2.06 (m, 2H, H_i), 2.14 (s, 6H, Me), 2.18 (s, 3H, Me), 2.69 (dd, 2H, 2H, J=7.5, 9.0 Hz, H_j), 2.89—2.96 (m, 6H, H_w, H_d, H_l), 2.99 (dd, 2H, J=7.0, 14.0 Hz, H_a), 3.33 (dd, 2H, J=5.0, 14.0 Hz, H_b), 3.39—3.46 (m, 4H, H_v, H_p), 3.52 (s, 6H, CO_2Me), 3.80 (d, 2H, J=12.5 Hz, H_k), 4.03 (d, 2H, J=14.0 Hz, H_o), 4.83 (ddd, 2H, J=5.0, 7.0, 14.0 Hz, H_c), 5.03 (bs, 2H, H_x), 6.62 (d, 2H, J=1.5 Hz, H_m), 6.91 (s, 2H, H_q), 6.94 (d, 2H, J=1.5 Hz, H_n), 7.02 (t, 2H, J=7.5 Hz, Ph), 7.09 (dd, 4H, J=7.0, 7.5 Hz, Ph), 7.19 (d, 4H, J=7.0 Hz, Ph), 7.42 (bs, 2H, NH), 8.33 (d, 2H, J=6.5 Hz, NH). ^{13}C-NMR ($CDCl_3$) δ: 20.4, 20.5, 23.4, 30.3, 31.7, 38.5, 41.8, 52.4, 52.7, 52.9, 54.3, 56.2, 66.5, 124.2, 126.6, 127.4, 128.3, 128.5, 129.0, 129.1, 129.2, 129.4, 130.4, 130.8, 137.0, 147.4, 150.2, 169.9, 172.6, 174.1. MS (FAB m/z) 1130 $(M+H)^+$. *Anal.* Calcd for $C_{61}H_{72}N_6O_{11}S_2$: C, 64.87; H, 6.43; N, 7.44. Found: C, 64.78; H, 6.58; N, 7.31.

2d: The yield was 8% as crystals, mp 143—145 °C. IR ($CDCl_3$) 3410 (ν_{NH}), 3285 (ν_{OH}), 1749 (ν_{CO}), 1670 (amide I), 1508 (amide II) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (m, 2H, H_g), 1.63 (m, 2H, H_h), 1.68 (m, 2H, H_f), 2.08 (m, 2H, H_e), 2.20 (s, 6H, Me), 2.22 (s, 6H, Me), 2.24 (m, 2H, H_i), 2.81 (m, 2H, H_j), 3.00 (dd, 2H, J=10.0, 14.0 Hz, H_w), 3.10 (m, 4H, H_a, H_b), 3.13 (d, 2H, J=12.5 Hz, H_j), 3.15 (dd, 2H, J=5.0, 8.5 Hz, H_d), 3.36 (dd, 2H, J=5.0, 14.0 Hz, H_v), 3.66 (s, 6H, CO_2Me), 3.73 (s, 2H, H_s), 3.78 (d, 2H, J=14.5 Hz, H_p), 3.85 (d, 2H, J=14.5 Hz, H_o), 4.00 (d, 2H, J=12.5 Hz, H_k), 4.89 (m, 2H, H_c), 4.98 (bs, 2H, H_x), 6.68 (s, 2H, H_m), 6.85 (s, 2H, s, 2H, H_r), 6.90 (s, 2H, H_q), 6.96 (s, 2H, H_n), 7.11 (m, 10H, Ph), 7.74 (bs, 2H, NH), 7.94 (d, 2H, J=8.0 Hz, NH). ^{13}C-NMR ($CDCl_3$) δ: 20.4, 20.5, 23.5, 29.7, 30.1, 31.2, 37.5, 40.5, 52.4, 52.7, 53.0, 54.3, 56.4, 66.7, 124.1, 126.5, 127.4, 127.5, 127.8, 128.3, 128.8, 129.0, 129.2, 129.3, 129.4, 130.2, 130.3, 136.9, 148.0, 150.6, 170.5, 171.9, 174.6. MS (FAB m/z) 1249 $(M+H)^+$. *Anal.* Calcd for $C_{69}H_{80}N_6O_{12}S_2$: C, 66.32; H, 6.45; N, 6.73. Found: C, 66.44; H, 6.58; N, 6.91.

References and Notes

1) Gutsche C. D., "Calixarene," Royal Society of Chemistry, London, 1989.
2) Gutsche C. D., "Calixarene Revisited," Royal Society of Chemistry, London, 1998.
3) Ibach S., Prautzsch V., Vogtle F., Chartrouv C., Gloe J., *Acc. Chem. Res*., **32**, 729—745 (1999).
4) Ito K., Ohba Y., Tamura T., Ogata T., Watanabe H., Suzuki Y., Hara T., Morisawa Y., Sone T., *J. Heterocycl. Chem*., **38**, 293—298 (2001).
5) Branden C., Tooze J., "Introduction to Protein Structure," Garland Publishing, Inc., New York, 1991.
6) Amide bonds of cystine peptides are known to bind to ionic species such as carboxylic acids and metal ions through the hydrogen bonding and/or static interactions.[7,12)] Therefore, the macrocycles (**1**, **2**) are also expected to serve as host molecules toward such guests.
7) Ranganathan D., Haridas V., Kurur S., Nagaraj R., Bikshapathy E., Kunwar A. C., Sarma A. V. S., Vairamani M., *J. Org. Chem*., **65**, 365—374 (2000).
8) Ito K., Ohba Y., Sone T., *Heterocycles*, **51**, 2203—2212 (1999).
9) Huang H., Mu L.-J., Cheng J.-P., Lu J.-M., Hu X.-B., *Synth. Commun*., **28**, 4639—4647 (1998).
10) Ito K., Kida A., Ohba Y., Sone T., *Chem. Lett*., **1998**, 1221—1222.
11) Ito K., Yamamori Y., Ohta T., Ohba Y., *J. Org. Chem*., **65**, 8361—8366 (2000).
12) Ranganathn D., Haridas V., Karle I. L., *J. Am. Chem. Soc*., **120**, 2695—2702 (1998).
13) The phenolic OH protons in the ^{1}H-NMR spectra are too broad to observe the signal.
14) Ref. 1 page 110.
15) Gutsche C. D., Bauer L., *J. Am. Chem. Soc*., **107**, 6052—6059 (1985).
16) Ito K., Ohta T., Ohba, Y., Sone T., *J. Heterocycl. Chem*., **37**, 79—85 (2000).