SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 19, pp. 3615–3621, 2004

Design and Synthesis of Novel Amino Acid-Bearing Macrocyclic Calix[4]Arenes

GuoZhu Zhang,[1] ZuCheng Li,[1] Min Wang,[1] JiaQi He,[1] and JinPei Cheng[1,2,*]

[1]Department of Chemistry, and [2]State Key Laboratory of Element-Organic Chemistry, Nankai University, Tianjin 300071, China

ABSTRACT

A new family of macrocyclic calix[4]arenes (4a–d) potentially capable of chiral recognition were synthesized by incorporating the chirality inducing moieties, bis α-amino acylated polyethylene glycols, or tripeptide bis-Phe Cystine$(OMe)_2$ to the lower rim.

Key Words: Calix[4]arenes; Chiral recognition; Macrocyclic molecules.

Intensive research activities have been devoted to the design and synthesis of macrocyclic molecules that bear good ability for chiral recognition.[1,2]

*Correspondence: JinPei Cheng, Department of Chemistry, Nankai University, Tianjin 300071, China; E-mail: jpcheng@nankai.edu.cn or chengjp@mail.most.gov.cn.

DOI: 10.1081/SCC-200031049 0039-7911 (Print); 1532-2432 (Online)

The main synthetic strategy for realizing this property is to immerse the active sites in chiral surroundings derived from chiral moiety[3] In this respect, amino acids and peptides should be good candidates for this purpose because of their chiral inherence and biorelevance[4] On the other hand, calixarenes, the third generation of the host cyclic molecules following crown ether and cyclodextrin, can serve as a versatile "platform" that can be modified by various selective receptors for ionic and small molecule recognition.[5–7] Several reports on modifying calixarenes with chiral units have already appeared in the literature and showed promising potential of this category of compounds in molecular recognition, separation, and optical analysis.[8–12] Aiming at searching for better chiral host molecules to mimic biological environment, we also conducted a work on the synthesis and recognition study of certain chiral residue modified calix[4]arenes.[6,9b,13a]

In the present communication, we wish to report the synthesis of a new family of cyclic calix[4]arenes modified at the lower rim by L-amino acid or peptides (4a–4d, Fig. 1). These chiral poly macrocycles may serve as good candidates for chiral recognition and chiral catalysis.

EXPERIMENTAL

Melting points were taken on a Yanaco melting-point apparatus and were uncorrected. ^{1}H NMR spectra were registered on a Bruker AC-P300

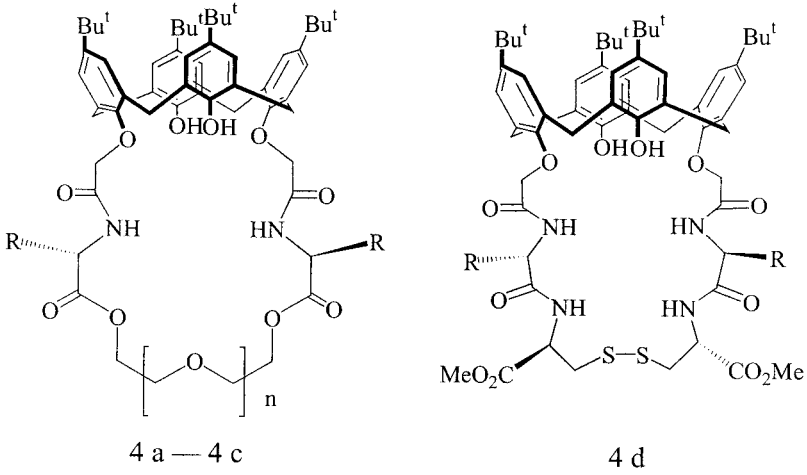
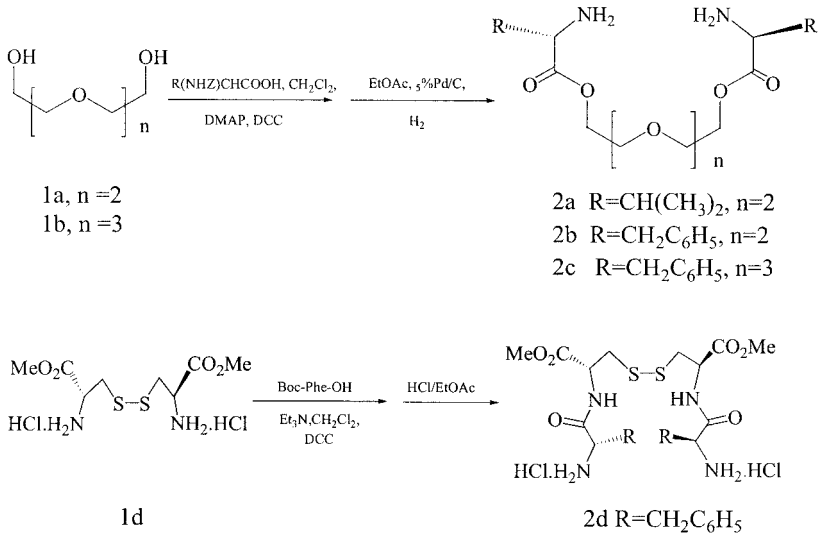


Figure 1. Structures of hosts 4a–4d.

spectrometer using TMS as the internal standard; chemical shifts are reported in δ values and the coupling constants (J) in hertz. Mass spectra were recorded on a Finnigan Mat 90 and AEI MS-50/PS 30 instrument. Elemental analyses were performed on a Perkin-Elmer 240 analytical instrument. Optical activities were measured on a WZZ-1 automatic polarimeter. Thin layer chromatography (TLC) was carried out on silica gel (60 GF_{254}) and spots located with ultraviolet (UV) light or iodine vapor. Dichloromethane was refluxed with calcium hydride for 5 h and distilled. Triethylamine was dried over metal sodium, refluxed, and then distilled.

The synthesis of 4a–4d was achieved through a one-step straightforward procedure by reacting 2a–2d with 3. The synthesis of 2a–2d is shown in Sch. 1. For preparation of 2a–2c, appropriate oligomers of ethylene glycols were first reacted with N^{α}Z-protected amino acid in the presence of equal molar DCC and DMAP to give their bis N^{α}Z-protected amino acid ester derivatives. These intermediates were then N-deprotected by 5% Pd/C with H_2 in dry ethyl acetate to give 2a–2c in satisfactory overall yields. The crude products were used in subsequent preparations without purification.

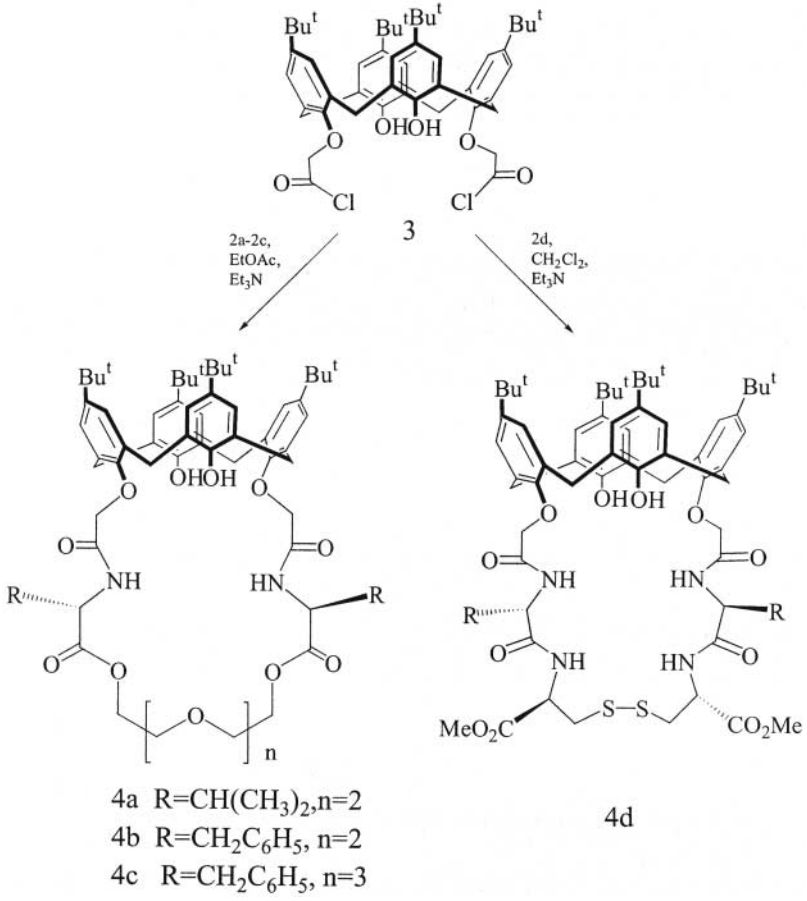
Tripeptide bis-Phe Cystine$(OMe)_2 \cdot 2HCl$, 2d, was prepared using a convergent strategy and standard peptide coupling methods. The L-Cystine dimethyl ester dihydrochloride was treated with two equimolar N^{α}Boc-protected phenylalanine in the presence of two equimolar DCC and triethyl



Scheme 1. The synthesis of 2a–2d.

amine, then it was N-deprotected with HCl/EtOAc to afford the desired 2d (70%).

The other condensation reagent, calix[4]arene diacid dichloride 3, was prepared according to the literature procedure;[14] the yield was 70% As shown in Sch. 2, reaction of **3** with 2a–2d in dichloromethane in the presence of equal mole triethylamine in highly diluted solution at below 0°C provided the corresponding lower-rim-bridged calix[4]arenes 4a–4d in moderate yields. A representative procedure for preparation of 4b is described as follows: A solution of calix[4]arene diacid dichloride 3 (1.5 mmol) in dry dichloromethane (35 mL) was added dropwise to a well-stirred and



Scheme 2. The synthesis of 4a–4d.

ice-cooled solution of 2b (1.5 mmol) and triethylamine (3 mmol) in dry ethyl acetate (100 mL) over 1 h. The mixture was stirred overnight at ambient temperature, then concentrated under the reduced pressure, the residue was dissolved in 100 mL chloroform, loaded with 0.5 g silica gel, and purified by chromatography using a solvent mixture of dichloromethane, ethyl acetate, and methyl alcohol as eluent on silica gel (200–300 mesh).

The structures of 4a–4d were confirmed by ^{1}H NMR, FAB-MS, and elemental analysis. The mass spectra indicated that the bridged calix[4]arenes were "1 + 1" cyclization products. Compounds 4a–4d were found to be chiral as resulted from the chiral sub-ring on the lower rim of calix[4]arenas; such chiral subunits made the two methylenes connected to the same phenol ring nonequivalent.[15] The NMR data showed that the bridged methylene protons ($ArCH_2Ar$) appeared in two sets of doublets covering a range of δ 2.8–4.8 ppm. The NMR signals of the t-butyl at the upper rim of calix[4]arene appeared as two equal singlets at around 1 ppm. These indicated that the compounds all took the cone conformation, which is consistent with that found in previous studies.[6,13,15]

It is reported that chiral crown ethers can serve as good catalysts for stereoselective induction in some C-C bond formation reactions[16] and as selective host molecules for recognizing enantiomers.[17] In this work, the L-amino acids were introduced to the crown ether system as the chiral modifier. The S-S unit of cystine residue in 4d may serve as an active site in relevant enantioselective reactions according to the literature.[18] The rigid calix[4]arene skeleton should provide not only strong topological constraint but also additional binding sites. The straightforward synthesis of these cyclic ligands is also one advantage for their application.

To summarize, we have designed and synthesized four new calix[4]arene derivatives 4a–4d, which have two L-amino acid units as the chiral modifiers at the lower rim of calix[4]arene moiety. The research of their chiral recognition and catalysis properties is underway in our laboratory.

EXPERIMENTAL

Compound 4a: yield, 15%; Melting point (mp) 125–127°C; $[\alpha]_D^{20} = +21$ (c 0.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.62 (d, J = 8.4, 2 H, NH), 8.14 (s, 2 H, OH), 7.03 (d, J = 8.4, 4 H, ArH), 6.96 (d, J = 9, 4 H, ArH), 5.24 (d, J = 15, 2 H, $ArOCH_2$), 4.49 (d, J = 15, 2 H, $ArOCH_2$), 4.82 (m, 2 H, OCHN), 4.71 (m, 2 H, OCH_2CH_2O), 4.12 (m, 2 H, OCH_2CH_2O), 3.85 (m, 4 H, OCH_2CH_2O), 3.73 (m, 4 H, OCH_2CH_2O), 4.20 (d, J = 9, 8 H, $ArCH_2Ar$), 4.11 (d, J = 9, 8 H, $ArCH_2Ar$), 3.51 (d, J = 9, 8 H, $ArCH_2Ar$), 3.73 (d, J = 9, 8 H, $ArCH_2Ar$), 2.11 (m, 2 H, $CHMe_2$), 1.25 (s, 18 H, Bu^t),

1.09 (s, 18 H, Bu^t), 0.92 (d, J = 6.9, 6 H, CH_3), 0.82 (d, J = 6.9, 6 H, CH_3); FAB-Ms: 1077 $(M+1)^+$; Anal. Calcd for: $C_{64}H_{88}O_{12}N_2$: C, 71.35; H, 8.23; N, 2.6; found: C, 71.37; H, 8.29; N, 2.56.

Compound 4b: yield, 12%; mp: 115–117°C; $[\alpha]_D^{20} = +25.0$ (c 0.3, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.64 (d, J = 9, 2 H, NH),7.89 (s, 2 H, OH), 7.02 (s, 14 H, ArH), 6.88 (d, J = 3, 4 H, ArH), 5.31 (m, 2 H, CH), 5.12 (d, J = 14, 2 H, $ArOCH_2$), 2.93–4.65 (m, total 26 H; 12 H, OCH_2CH_2O; 4 H, $CH_2C_6H_5$; 2 H, $ArOCH_2$; 8 H, $ArCH_2Ar$), 1.28 (s, 18 H, Bu^t), 1.04 (s, 18 H, Bu^t); FAB-Ms: 1173 (M^+); Anal. calcd for: $C_{72}H_{88}O_{12}N_2$: C, 73.69; H, 7.56; N, 2.39; found: C, 73.65; H, 7.54; N, 2.15.

Compound 4c: yield, 17%; mp: 110–112°C; $[\alpha]_D^{17} = +17.6$ (c 0.34, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.59 (d, J = 8.1, 2 H, NH), 7.84 (s, 2 H, OH), 7.02 (s, 14 H, ArH), 6.86 (d, J = 9.3, 4 H, ArH), 5.19 (m, 2 H, CH), 5.06 (d, J = 15, 2 H, $ArOCH_2$), 3.08–4.45 (m, total 30 H; 16 H, OCH_2CH_2O; 4 H, $ArCH_2$; 2 H, $ArOCH_2$; 8 H, $CH_2C_6H_5$; 8 H, $ArCH_2Ar$), 1.28 (s, 18 H, Bu^t), 1.03 (s, 18 H, Bu^t); FAB-Ms: 1217 (M^+); Anal. calcd for: $C_{74}H_{92}O_{13}N_2$: C, 73.00; H, 7.62; N 2.30; found: C, 72.95; H, 7.60; N, 2.30.

Compound 4d: yield, 25%; mp: 151–153°C; $[\alpha]_D^{20} = -37.5$ (c 0.4, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.34 (d, J = 9, 2 H, NH-Phe),7.92 (s, 2 H, OH), 7.17 (m, 10 H, ArH), 7.03 (d, J = 13.5, 4 H, ArH), 6.85 (s, 4 H, ArH), 6.24 (d, J = 7.8, 2 H, NH-Cys), 5.18 (t, 2 H, CH-Benzyl), 5.02 (d, J = 15, 2 H, $ArOCH_2$), 4.78 (t, 2 H, $CHCO_2Me$), 4.15 (d, J = 13, 2 H, $ArOCH_2$), 4.06 (d, J = 12.4, 2 H, $ArCH_2Ar$), 3.71 (d, J = 12.9, 2 H, $ArCH_2Ar$), 3.27 (d, J = 13.5, 2 H, $ArCH_2Ar$), 2.95 (d, J = 13.2, 2 H, $ArCH_2Ar$), 3.71 (s, 6 H, CH_3), 3.21 (m, 4 H, $CH_2C_6H_5$; 2 H, SCH_2), 3.02 (m, 2 H, SCH_2), 1.28 (s, 18 H, Bu^t), 1.02 (s, 18 H, Bu^t); FAB-Ms: 1292 $(M+1)^+$; Anal. calcd for: $C_{74}H_{90}O_{12}N_4S_2$: C, 68.81; H, 7.02; N, 4.34; found: C, 68.88; H, 7.05; N, 4.20.

ACKNOWLEDGMENTS

The financial support from the Major State Basic Research Development Program of China (Grant No. G2000078100) and the Natural Science Foundation of China (NSFC No. 20072020) is gratefully acknowledged.

REFERENCES

1. Lehn, J.M. *Superamolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, 1995.
2. (a) Webb, T.H.; Wilcox, C.S. Chem. Soc. Rev. **1993**, *22*, 383; (b) Tejeda, A.; Moran, J.R. Tetrahedron Lett. **2000**, *41*, 4563; (c) Zhao, H.W.; Hua, W.T.J. Org. Chem. **2000**, *65*, 2933.

3. Trost, B.M. Acc. Chem. Res. **1996**, *29*, 355.
4. Voyer, N.; Lamothe, J. Tetrahedron **1995**, *51*, 9241.
5. (a) Gutsche, C.D. Calixarenes; Monographs. In *The Supramolecular Chemistry*; Stoddard, J.F., Ed.; The Royal Society of Chemistry: Cambridge, 1989; (b) Vicens, J.; Böhmer, V. Eds.; *Calixarene, A Versatile Class of Macrocyclic Compounds*; Klumer: Dordrecht, 1991; (c) Böhmer, V. Angew Chem., Int. Ed. Engl. **1995**, *35*, 713.
6. Hu, X.B.; Chan, A.S.C.; Han, X.X.; He, J.Q.; Cheng, J.P. Tetrahedron Lett. **1999**, *40*, 7115.
7. Ikeda, A.; Shinkai, S. Chem. Rev. **1997**, *97*, 1713.
8. Wolff, A.; Bohmer, V.; Vogt, W.; Vgozzoli, F.; Andreetti, G.D. J. Org Chem. **1990**, *55*, 5665.
9. (a) Park, B.S.; Knobler, C.B.; Eid, C.N., Jr.; Warmuth, R.; Cram, D. J. Chem. Commun. **1998**, 55; (b) Guo, W.; Wang, J.; Wang, C.; He, J.Q.; He, X.W.; Cheng, J.P. Tetrahedron Lett. **2002**, *43*, 5665.
10. Pena, M.S.; Zhang, Y.; Warner, I.M. Anal. Chem. **1997**, *69*, 3239.
11. Grady, T.; Harris, S.J.; Smyth, M.R.; Diamond, D.; Hailey, P. Anal. Chem. **1996**, *68*, 3775.
12. He, Y.B.; Xiao, Y.J.; Meng, L.Z.; Zeng, Z.Y.; Wu, X.J.; Wu, C.T. Tetrahedron Lett. **2002**, *43*, 6249.
13. (a) Hu, X.B.; He, J.Q.; Chan, A.S.C.; Han, X.X.; Cheng, J.P. Tetrahedron: Asymmetry **1999**, *10*, 2685; (b) Sansone, F.; Barboso, S.; Casnati, A.; Fabbi, M.; Pochini, A.; Ugozzoli, F.; Ungaro, R. Eur. J. Org. Chem. **1998**, 897.
14. Collins, E.M.; Mckervey, M.A. J. Chem. Soc. Perkin Trans. **1991**, *1*, 3137.
15. Yuan, H.S.; Huang, Z.T. Tetrahedron: Asymmetry **1999**, *10*, 429.
16. (a) Cram, D.J.; Sogah, G.D.Y. J. Chem. Soc., Chem. Commun. **1981**, 625; (b) Alonso-López, M.; Martín-Lomas, M.; Penadés, S. Trtrahedron Lett. **1986**, *27*, 3551; (c) Tõke, L.; Bakó, P.; Keserü, G.M.; Albert, M.; Fenichel, L. Tetrahedron Lett. **1998**, *54*, 213.
17. (a) Wenzel, T.J.; Thurston, J.E. J. Org. Chem. **2000**, *65*, 1243; (b) Wenzel, T.; Thurston, J.E. Tetrahedron Lett. **2000**, *41*, 3769.
18. (a) Kossenjans, M.; Martens, J. Tetrahedron: Asymmetry **1998**, *9*, 1409; (b) Kossenjans, M.; Pennemann, H.; Juanes, O.; Rodriguez-Ubis, J.C.; Brunet, E. Tetrahedron: Asymmetry **1998**, *9*, 4123.

Received in the UK July 3, 2003