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New chiral macrocyclic ligands. Design and synthesis of (*R*)-cysteine-containing calix[4]arenes

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Abstract

Four cysteine-containing calix[4]arenes, including three bis-cysteine bridged and one non-bridged, were synthesized by the reaction of calix[4]arene diacid dichloride with the corresponding *S*-alkylated cysteine esters.

1. Introduction

The preparation and properties of chiral macrocyclic ligands have attracted considerable attention from a wide range of chemists especially in the fields of organic, biological, and medicinal chemistry. Recently, applications of this kind of molecule have been further widened to include some currently most-focused areas such as chiral recognition and chiral catalysis.[1,2] One of the main principles in designing asymmetric reagents and catalysts is to allow the reaction center to be surrounded by a recognition site and a chiral moiety, as the former governs the substance selectivity and the latter the stereoselectivity.[3] In this respect, amino acids or peptides may be employed as chiral sources in building the desired molecules because of their accessibility[4] and biological relevance.

Calixarenes, especially calix[4]arenes, are versatile platforms in constructing supramolecular receptors for selective recognition of ions and neutral molecules.[5] Therefore, it would be interesting to incorporate the above-mentioned amino acid or peptide moieties into calixarenes in order to achieve the chirally modified macrocyclic ligands. Indeed, a few such examples have been recently reported.[6] Despite these elegant works, the profound potential of this type of chiral compound in both chemistry and life sciences is still far from cultivated. In particular, only very few multi-cyclic receptor systems combining both cyclopeptide and calix[4]arene have been synthesized.[6e,f] In the present work, we wish to report the

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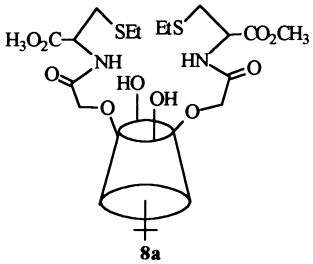
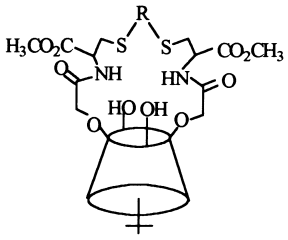
first syntheses and characterizations of the cysteine-bearing calix[4]arenes **8a**–**8d**. We believe that these chiral macrocyclic ligands may serve as good candidates in future studies of chiral recognition and chiral catalysis.



8a

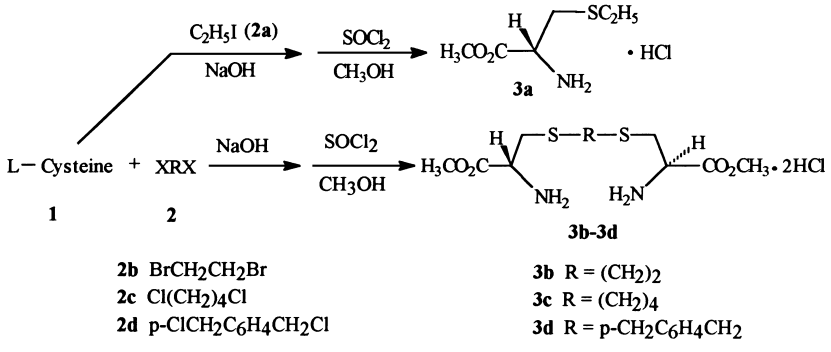


8b-8d

2. Results and discussion

Because both cysteine-based ligands and calix[4]arene thioethers have been shown to be highly effective in inducing regioselectivity[7] and enantioselectivity[8] in catalyzing some reactions, three cyclic **8b**–**8d** and one open-chained **8a** cysteine-containing calixarenes were designed and synthesized in the present work.

One of the starting reagents, *S*-alkylated cysteine **3**, was prepared from (*R*)-cysteine **1** according to a modified literature procedure (Scheme 1).[8d,9] The cysteine **1** was reacted with iodoethane **2a**, 1,2-dibromoethane **2b**, 1,4-dichlorobutane **2c**, and *p*-di(chloromethyl)benzene **2d**, respectively, followed by esterification with thionyl chloride in methanol to give *S*-ethyl cysteine methyl ester hydrochloride **3a** and three bridged bis-cysteine methyl ester hydrochlorides **3b**–**3d** in 65–86% overall yields.

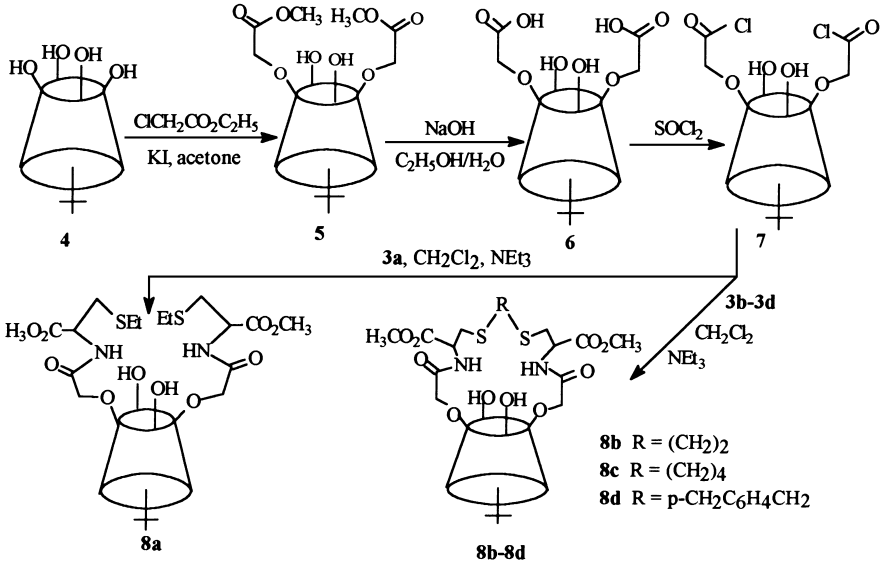


Scheme 1.

The other starting reagent, calix[4]arene diacid dichloride **7**,[10] was prepared by a three-step procedure from *p-tert*-butylcalix[4]arene **4** as demonstrated in Scheme 2. Ethyl chloroacetate was used here as the alkylating reagent instead of ethyl bromoacetate in the literature case because the former is less toxic and less expensive. The 81% product yield indicates that the modified procedure is at least as efficient as that in the normal case.[10]

As depicted in Scheme 2, coupling of **7** with **3a**–**3d** in dichloromethane in the presence of excess triethylamine under high dilution conditions gave the corresponding cysteine-containing calix[4]arenes **8a**–**8d** (in 11–52% yields). The conversion of acid **6** into acyl chloride **7** for the mentioned coordination reactions was mainly to avoid the use of the more expensive coupling reagents (e.g., DCC–HOBt or TBPU[11]). The structures of **8a**–**8d** were identified by ^{1}H NMR (including H, H-COSY, HD), FD-MS,

and elemental analysis. The mass spectra indicated that the bridged calix[4]arenes **8b**–**8d** were '1+1' cyclization products. The NMR data showed that the bridged methylene protons ($ArCH_2Ar$) appeared in two sets of doublets covering a range of δ 3.3–4.8 ppm (J 12.8–13.6 Hz). This demonstrated that all these compounds are in a cone conformation. The splitting pattern may reflect the presence of the chiral moieties in the molecules because it is similar to what were observed in other chiral calix[4]arenes.[6e] Splittings of this type were generally observed for other protons as well (i.e., ArH, OCH_2, and CH_2S) possibly due to the same cause. For examples, the bridged methylene protons in compound **8b** appear in four doublets at δ 4.47, 3.46, 4.23 and 3.29 (J 13.6 Hz); the aromatic protons are also in four doublets at δ 7.09, 7.05, 6.77 and 6.73 (J 1.8 Hz); whereas the methylene protons in $CHCH_2S$ show a multiple pattern.



Scheme 2.

To summarize, we have designed and synthesized four new calix[4]arenes (**8a**–**8d**) bearing a cysteine unit at the lower rim as the chiral modifier. Their chiral recognition and asymmetric induction properties are under current investigation in our laboratory.

3. Experimental

Melting points were taken on a Yanaco melting-point apparatus and are uncorrected. ^1H NMR spectra were registered on a Bruker AC-P200 spectrometer using TMS as the internal standard, chemical shifts are reported in δ values and the coupling constants (J) in hertz. Mass spectra were obtained on Finnigan MAT 90 and AEI MS-50/PS 30 instrument. Elemental analyses were performed on a Perkin–Elmer 240 analytical instrument. Optical rotations were measured on a Perkin–Elmer automatic polarimeter. Thin layer chromatography was carried out on silica gel (60 GF_{254}) and spots located with UV light or iodine vapor.

Dichloromethane was refluxed with calcium hydride for 5 h and distilled before use. Triethylamine was dried over potassium hydroxide pellets overnight, distilled and stored over KOH pellets. *S*-Alkylated cysteine ester hydrochloride **3a**–**3d**[8d,9] and calixarene diacid dichloride **7**[10] were prepared by literature methods.

3.1. Bis-cysteine methyl ester hydrochloride **3d**

This compound was prepared from L-cysteine and 1,4-dichloromethylbenzene (Scheme 1). M.p: 195–196°C; ^{1}H NMR (200 MHz, D_2O): δ 7.31 (s, 4H, PhH), 4.70 (s, 6H, OCH_3), 4.16 (m, 2H, CH), 3.73 (s, 4H, SCH_2Ph), 2.98 (dd, J 4.2, 4.2 Hz, 2H, $CHCH_2S$), 2.90 (dd, J 8.5, 8.5 Hz, 2H, $CHCH_2S$).

3.2. A general procedure for the preparation of cysteine-containing calix[4]arenes **8**

A solution of calix[4]arene diacid dichloride **7** (2.0 mmol) in dry dichloromethane (80 ml) was added dropwise to a well-stirred and ice-cooled solution of *S*-alkylated cysteine ester hydrochloride **3** (4.0 mmol for **3a**, 2.0 mmol for **3b**–**3d**) and triethylamine (9.0 mmol) in dry dichloromethane (400 ml) over 3 h. The mixture was stirred overnight at ambient temperature followed by washing sequentially with dilute hydrochloride in water, water, dilute sodium hydrogencarbonate in water and brine, and finally dried over anhydrous magnesium sulfate. After filtration, the filtrate was evaporated and purified by chromatography using a solvent mixture of dichloromethane and ethyl acetate as eluent on silica gel (200–300 mesh).

Compound **8a**: yield, 52.2%; m.p.: 155–157°C; $[\alpha]_D^{17}$=+33.0 (c 0.013, CH_2Cl_2); FD-MS: 1054 (M^+); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.67 (d, J 8.4, 2H, NH), 7.93 (s, 2H, ArOH), 7.04 (d, J 1.8, 2H, ArH), 7.02 (d, J 1.8, 2H, ArH), 6.93 (d, J 1.8, 2H, ArH), 6.89 (d, J 1.8, 2H, ArH), 4.99 (d, J 15.0, 2H, $ArOCH_2$), 4.93 (m, 2H, CH), 4.36 (d, J 12.8, 2H, $ArCH_2Ar$), 4.30 (d, J 15.0, 2H, $ArOCH_2$), 4.19 (d, J 13.7, 2H, $ArCH_2Ar$), 3.71 (s, 6H, OCH_3), 3.46 (d, J 13.7, 2H, $ArCH_2Ar$), 3.29 (d, J 12.8, 2H, $ArCH_2Ar$), 2.86, 2.76 (dd, J 6.1, 6.8; each 2H, $CHCH_2S$), 2.46 (q, J 7.4, 4H, SCH_2CH_3), 1.24 (s, 18H, Bu^t), 1.08 (t, J 7.4, 6H, CH_3), 1.03 (s, 18H, Bu^t). Anal. calcd for $C_{60}H_{82}N_2O_{10}S_2 \cdot CH_2Cl_2$: C 64.27, H 7.37; found: C 63.84, H 7.74.

Compound **8b**: yield, 12.2%; m.p.: 225–227°C; $[\alpha]_D^{17}$=+10.5 (c 0.018, CH_2Cl_2); FD-MS: 1024 (M^+); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.06 (d, J 6.0, 2H, NH), 7.09 (d, J 1.8, 2H, ArH), 7.05 (d, J 1.8, 2H, ArH), 6.77 (d, J 1.8, 2H, ArH), 6.73 (d, J 1.8, 2H, ArH), 6.72 (s, 2H, ArOH), 5.00 (d, J 15.5, 2H, $ArOCH_2$), 4.70 (m, 2H, CH), 4.47 (d, J 13.5, 2H, $ArCH_2Ar$), 4.23 (d, J 15.5, 2H, $ArOCH_2$), 4.10 (d, J 13.6, 2H, $ArCH_2Ar$), 3.59 (s, 6H, OCH_3), 3.46 (d, J 13.6, 2H, $ArCH_2Ar$), 3.29 (d, J 13.6, 2H, $ArCH_2Ar$), 3.06 (m, 4H, $CHCH_2S$), 2.84 (br s, 4H, SCH_2CH_3), 1.28 (s, 18H, Bu^t), 0.90 (s, 18H, Bu^t). Anal. calcd for $C_{58}H_{76}N_2O_{10}S_2$: C 67.97, H 7.42; found: C 67.58, H 7.76.

Compound **8c**: yield, 15.3%; m.p.: 138–140°C; $[\alpha]_D^{17}$=+26.3 (c 0.019, CH_2Cl_2); FD-MS: 1052 (M^+); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.11 (d, J 7.3, 2H, NH), 7.09 (s, 2H, ArOH), 7.07 (d, J 1.8, 2H, ArH), 7.04 (d, J 1.8, 2H, ArH), 6.84 (d, J 1.8, 2H, ArH), 6.80 (d, J 1.8, 2H, ArH), 5.02 (d, J 15.6, 2H, $ArOCH_2$), 4.82 (m, 2H, CH), 4.50 (d, J 13.5, 2H, $ArCH_2Ar$), 4.28 (d, J 15.6, 2H, $ArOCH_2$), 4.10 (d, J 13.6, 2H, $ArCH_2Ar$), 3.59 (s, 6H, OCH_3), 3.49 (d, J 13.6, 2H, $ArCH_2Ar$), 3.31 (d, J 13.6, 2H, $ArCH_2Ar$), 3.08 (m, 4H, $CHCH_2S$), 2.65 (m, 4H, SCH_2CH_2), 1.77 (m, 4H, SCH_2CH_2), 1.26 (s, 18H, Bu^t), 0.96 (s, 18H, Bu^t). Anal. calcd for $C_{60}H_{80}N_2O_{10}S_2$: C 68.44, H 7.60; found: C 68.11, H 7.98.

Compound **8d**: yield, 11.8%; m.p.: 176–178°C; $[\alpha]_D^{17}$=+254.0 (c 0.008, CH_2Cl_2); FD-MS: 1100 (M^+); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.15 (d, J 7.6, 2H, NH), 7.45 (s, 4H, C_6H_4), 7.33 (s, 2H, ArOH), 7.05 (d, J 1.8, 2H, ArH), 7.02 (d, J 1.8, 2H, ArH), 6.87 (d, J 1.8, 2H, ArH), 6.83 (d, J 1.8, 2H, ArH), 4.83 (d, J 15.6, 2H, $ArOCH_2$), 4.63 (m, 2H, CH), 4.24 (d, J 12.8, 2H, $ArCH_2Ar$), 4.19 (d, J 15.4, 2H, $ArOCH_2$), 3.94 (d, J 13.6, 2H, $ArCH_2Ar$), 3.93, 3.79 (d, J 13.6, each 2H, SCH_2Ph), 3.48 (d, J 13.6, 2H, $ArCH_2Ar$), 3.45 (s, 6H, OCH_3), 3.26 (d, J 13.6, 2H, $ArCH_2Ar$), 2.61 (dd, J 12.4, 11.4, 2H, $CHCH_2S$), 2.07 (dd, J 5.2, 6.2, 2H, $CHCH_2S$), 1.23 (s, 18H, Bu^t), 0.99 (s, 18H, Bu^t). Anal. calcd for $C_{64}H_{80}N_2O_{10}S_2$: C 69.97, H 7.27; found: C 69.64, H 7.65.

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