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Design, Syntheses and Extraction Properties of Novel *Bis*-calix[4]arene and *Tris*-calix[4]arene Containing Two Kinds of Calix[4]arene Derivative Units

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By condensation of calix[4]arene 1,3-bis-hydrazide derivative 5 and calix[4]arene *mono*-benzaldehyde derivative 2, and then intramolecular bridging with triethylene glycol ditosylates, two novel *tris*-calix[4]arenes 6 and 7 containing two kinds of calix[4]arene derivative units were prepared in reasonable yield. When reacting compound 5 with calix[4]arene 1,3-*bis*-benzaldehyde derivative 3, novel *bis*-calix[4]arene 8 containing two different calix[4]arene derivative units was obtained in high yield. The extraction experiments showed that the new hosts 6, 7 and 8 possessed excellent complexation abilities towards metal cations and α-amino acids. T*ris*-calix[4]arene 7 showed good complexation selectivity towards Ag^+ and basic α-amino acid.

Keywords: *Bis*-calix[4]arene; *Tris*-calix[4]arene; Synthesis; Complexation; Cations; Amino acid

INTRODUCTION

Calixarenes and their derivatives are macrocyclic molecules possessing excellent abilities to form host–guest complexes with various small molecules. Many researches were involved in design and syntheses of different kinds of receptor molecules with defined cavities by using calix[4]arenes as a key structural motif [1,2]. Some double (or multiple) calix[4]arenes were prepared as examples of higher order molecular architectures in the recent past [3–5]. For example, Gutsche reported a *tris*-calixarene which could recognize tris(aminoethyl)amine effectively [6]. Double (or multiple) calix[4]arenes were usually synthesized by reacting double (or multiple) functional reagents with calixarenes (or their derivatives) directly. As a result, the structures of their calixarene derivative units were identical and might be unfavorable for binding complicated guests with various functional groups, for example amino acid. On the other hand, some double (or multiple) calix[4]arenes containing different calixarene derivative units were synthesized by indirect method and exhibited excellent complexation properties, although the synthetic procedures were more difficult and the yields were lower in most cases [7–9]. In this paper, we wish to report an indirect method to prepare novel *bis*-calix[4]arene and *tri*-calix[4]arene containing two kinds of different calixarene derivative units in reasonable yields. Their extraction experiments showed that they were excellent receptors for metal cations and α-amino acids.

RESULTS AND DISCUSSION

Syntheses, Structures and Conformations

The synthetic route is showed in Scheme 1. *P*-tosyloxyethoxyl-benzaldehyde, compounds **1** and **4** were prepared according to the published procedures [10]. By refluxing *p-tert*-butylcalix[4]arene **1** with *p*-tosyloxyethoxyl-benzaldehyde (molar ratio = 1:1) in K_2CO_3 / MeCN for 48 h, *mono*-substituted calix[4]arene derivative **2** and 1,3-*bis*-substituted calix[4]arene derivative **3** were obtained in yield of 35% and 15% after column chromatography. When the molar ratio of *p-tert*-butylcalix[4]arene **1** and *p*-tosyloxyethoxyl-benzaldehyde was 1:2, only 1,3-bis-substituted calix[4]arene derivative **3** were obtained in yield of 78% by recrystallization from $CHCl_3$-MeOH. By refluxing 1,3-*bis*-sustituted calix[4]arene ethyl acetate derivative **4** with an excess

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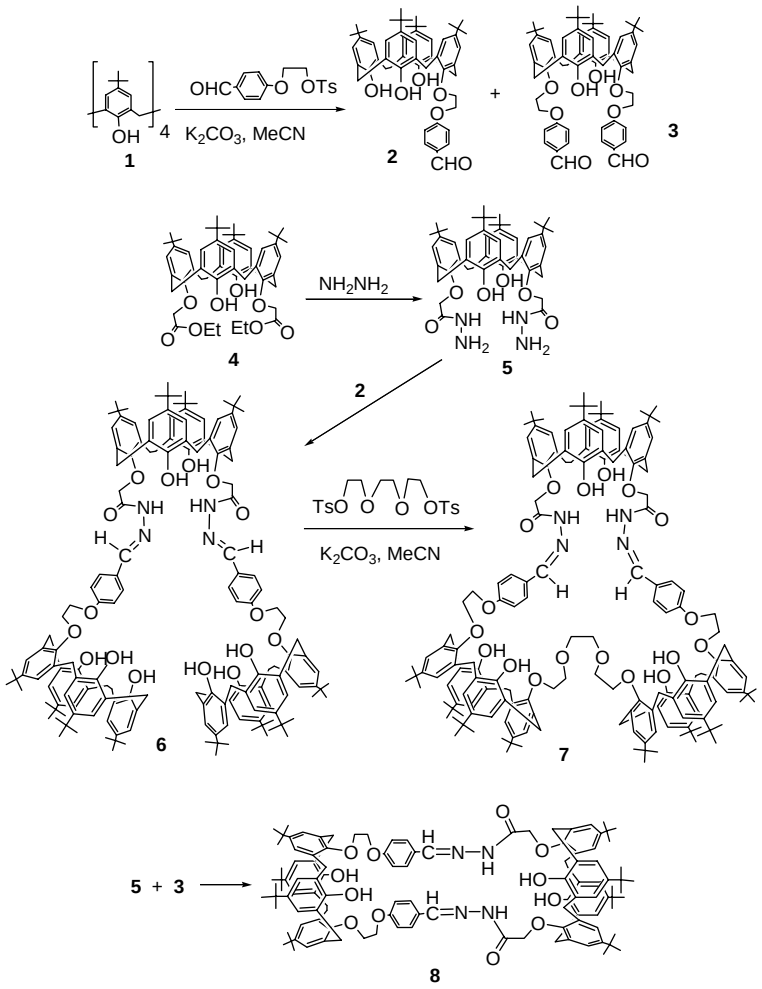


SCHEME 1

$N_2H_4{\cdot}H_2O$ (concentration 80%) in methanol solution for 5 h, 1,3-*bis*-substituted calix[4]arene hydrazide derivative **5** was prepared in almost quantitative yield. By condensation of compound **2** and compound **5** (molar ratio = 2:1) in MeOH-$CHCl_3$ (1:1) solution, two Schiff-base bonds were formed and *tri*-calix[4]arene derivative **6** was obtained in 80% yield. Since calix[4]arenes prefer 1,3-substituted pattern in weak base reaction system, by refluxing compound **6** with triethylene glycol ditosylates in K_2CO_3 / MeCN for three days under diluted condition, novel *tri*-calix[4]arene **7** was obtained via intramolecular bridging by "1 + 1" condensation mode in 45% yield after column chromatography. On the other hand, by condensation of compound **5** and compound **3** (molar ratio = 1:1) in MeOH-$CHCl_3$ (1:1) solution for two days under diluted condition, a novel *bis*-calix[4]arene **8** was obtained in 85% yield.

All new compounds were characterized by elemental analyses, ESI-MS spectra and ^{1}H NMR spectra. The ESI-MS spectra of compounds **2**, **3**, **5**, **6**, **7** and **8** showed clearly M^+ or $(MNa)^+$ peak at 796.6, 967.3, 793.2, 2371.2, 2485.8 and 1724.8, respectively. In the ^{1}H NMR spectra, compound **2** showed three singlets (2:1:1) for the *tert*-butyl groups, two pairs of doublets (1:1) for the methylene bridges of the calix[4]arene skeleton. Compounds **3** and **5** showed two singlets (1:1) for the *tert*-butyl groups, one pair of doublets (1:1) for the methylene bridges of the calix[4]arene skeleton. *Tris*-calix[4]arene **6** and **7** showed five singlets for the *tert*-butyl groups (2:1:1:1:1), two pairs of doublets (2:1, two doublets of compound **7** were overlapped with ethylene signals) for the methylene bridges of the calix[4]arene skeleton. *Bis*-calix[4]arene **8** showed four singlets for the *tert*-butyl groups, two pairs of doublets (1:1) for the methylene bridges of the calix[4]arene skeleton. All the spectral data were in accordance with the assigned structures and certainly indicated that the calix[4]arene units adopt the *cone* conformation as showed in Scheme 1.

Extraction Studies for Cations and Amino Acids

Examination of the CPK molecular models revealed that novel *bis*- and *tris*-calix[4]arene were highly preorganized for binding guests. It can be seen that the novel *bis*- and *tris*-calix[4]arene possessed two

TABLE I Extraction percentage (%E) of picrate salts from water into $CHCl_3$ at room temperature.[†]

host	E%							
	Na^+	K^+	Cs^+	Cu^{2+}	Co^{2+}	Ni^{2+}	Ag^+	Hg^{2+}
6	86.9	89.6	85.5	36.6	28.8	29.3	38.6	25.9
7	90.5	88.4	91.3	35.3	22.5	20.6	86.5	22.6
8	71.3	78.7	60.5	39.9	35.8	32.1	26.3	28.8

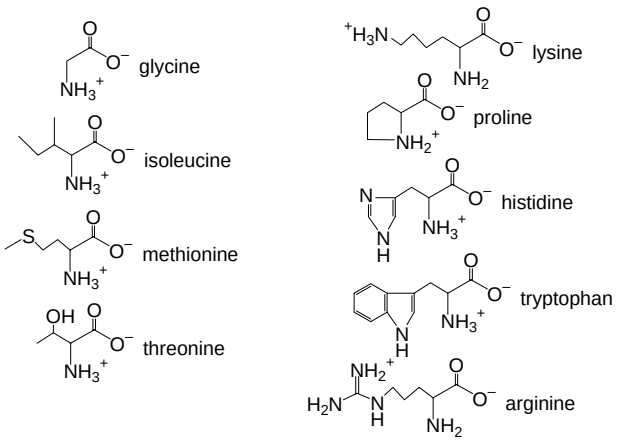
[†] According the published method [11], 1.00 ml of 0.005 M receptor solution in $CHCl_3$ was shaken (20 min) with 1.00 ml of 0.005 M picrate salt solution in triple distilled H_2O and the percentage extraction was measured from the resulting absorbance at 380 nm in $CHCl_3$. Control experiments showed that no picrate extraction occurred in the absence of the calixarene derivatives.

kinds of calix[4]arene derivative units. One calix[4]arene derivative unit was similar to normal calix[4]crown composed by calix[4]arene unit and full-oxygen crown ether chain, which could bind cations, especially, hard metal cations and ammonium ion effectively. Another binding site was similar to calix[4]-*azo*-crown composed by calix[4]arene unit, amido groups and Schiff-base groups, which could bind soft metal cations or recognize anions by hydrogen bond, such as carboxylate. Thus, the complexation abilities of compounds **6**, **7** and **8** towards a series of metal cations and α-amino acids were studied by extraction experiments.

The extraction percentages of series of cations with hosts **6, 7** and **8** from water into $CHCl_3$ at room temperature were summarized in Table I.

From Table I, it can be seen that compounds **6**, **7** and **8** showed excellent complexation abilities towards both soft metal cations and hard metal cations. *Tris*-calix[4]arene **6** and **7** exhibited higher extraction percentage for hard metal cations than that of *bis*-calix[4]arene **8**. On the other hand, *tris*-calix[4]arene **7** exhibited high Ag^+ complexation selectivity among the tested soft metal cations, but compound **6** did not so. From the difference of structures of compound **6** and **7**, it might be deduced that the rigid structure of compound **7** was favorable for complexation selectivity.

The extraction percentages of series of α-amino acid from water into $CHCl_3$ were summarized in Table II. As expected, hosts **6, 7** and **8** exhibited good extraction abilities towards tested α-amino acids, which can be attributed to the cooperative complexation of two kinds of calix[4]arene derivative units of them. *Tris*-calix[4]arene **7** exhibited high extraction percentage for basic α-amino acid (lysine, histidine, tryptophan and arginine) than that of host **6**, which also might indicate that the rigid structure of compound **7** was favorable for complexation selectivity. *Tris*-calix[4]arene **7** was a good example of neutral receptor for effective binding series of α-amino acid in calixarene chemistry, although some calixarene derivatives containing carboxylic acid [12,13], phosphonates [14] or sulphonate [15] were reported to bind amino acids or their esters. Scheme 2



SCHEME 2 List of zwitterionic amino acids

EXPERIMENTAL

Melting points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker-ARX 500 instrument, using TMS as reference. ESI-MS spectra were obtained from DECAX-30000 LCQ Deca XP mass spectrometer. Elemental analyses were performed at Vario EL III Elemental Analyzer. All solvents were purified by standard procedures. *p*-tosyloxyethoxyl-benzaldehyde, compounds **1** and **4** were prepared according to the published procedures [10].

Syntheses of p-Tert-butylcalix[4]arene Derivatives 2 and 3

A mixture of *p-tert*-butylcalix[4]arene (2 mmol, 1.48 g), *p*-tosyloxyethoxyl-benzaldehyde (2 mmol,

TABLE II Extraction percentages (%E) of α-amino acids from water into $CHCl_3$.[‡]

host	E%								
	Gly	Iso	Met	Thr	Lys	Pro	His	Try	Arg
6	32.5	40.3	38.3	47.2	28.9	36.7	31.6	42.5	50.6
7	73.6	80.9	89.2	88.3	84.1	69.8	82.6	86.3	81.8
8	82.8	76.7	48.8	71.9	31.2	49.0	39.9	30.2	30.9

[‡] The extraction experiment was performed by the same method as for metal cations in Table I. The concentration of both hosts and guests were 5×10^{-4} M. The concentrations of amino acids after extraction were assessed by classical ninhydrin test [16]. Control experiments showed that the extraction percentage for amino acids was less than 0.3% in the absence of the calixarene derivatives.

0.64 g) and K_2CO_3 (2 mmol, 0.28 g) was stirred in refluxing acetonitrile (100 mL) for two days under N_2 atmosphere. After distilling off the solvent under reduced pressure, the residue was treated with 30 mL HCl (10%) and extracted with 40 mL $CHCl_3$. The organic layer was separated, dried over anhydrous $MgSO_4$, and then filtered, concentrated. By the purification of column chromatography on silica gel (100–200 mesh) using petroleum ether (60–90°C) / CH_2Cl_2 (1:1) as an eluent, compound **2** was obtained as white powder in yield of 35% and compound **3** was obtained as by-product in yield 15%. When *p*-tosyloxyethoxyl-benzaldehyde was in quantity of 4 mmol (1.28 g) and K_2CO_3 was 10 mmol (1.40 g) in above reaction, only compound **3** was obtained in the yield of 78% by recrystallization from $CHCl_3$ / MeOH. Compound **2**: m.p. 186–188°C; ^{1}H NMR (500 MHz, $CDCl_3$): 1.04 [s, 9H, $C(CH_3)_3$], 1.10 [s, 18H, $C(CH_2)_3$], 1.20 (s, 9H, $C(CH_2)_3$), 3.37 (d, $J = 13.0$ Hz, 2H, $ArCH_2Ar$), 3.42 (d, $J = 13.0$ Hz, 2H, $ArCH_2Ar$), 4.27–4.30 (m, 6H, OCH_2 and $ArCH_2Ar$), 4.33 (d, $J = 13.0$ Hz, 2H, $ArCH_2Ar$), 6.86–7.34 (m, 12H, ArH), 7.33 (s, 1H, ArCHO); 9.42 (s, 2H, OH), 9.64 (s, 1H, OH); MS *m/z* (%): 796.6 (M^+, 70). Anal. calcd for $C_{53}H_{64}O_6$: C 79.86, H 8.09; found C 79.80, H 8.14. Compound **3**: m.p. 199–202°C; ^{1}H NMR (500 MHz, $CDCl_3$): 1.00 [s, 18H, $C(CH_3)_3$], 1.27 [s, 18H, $C(CH_2)_3$], 3.31 (d, $J = 13.0$ Hz, 4H, $ArCH_2$-Ar), 4.32–4.36 (m, 12H, OCH_2 and $ArCH_2Ar$), 6.84(s, 4H, ArH), 7.02 (d, $J = 8.5$ Hz, 4H, ArH), 7.26(s, 4H, ArH), 7.32 (s, 2H, ArCHO), 7.82 (d, $J = 8.5$ Hz, 4H, ArH), 9.89 (s, 2H, OH); MS *m/z* (%): 967.3 (MNa^+, 100). Anal. calcd for $C_{62}H_{72}O_8$: C 78.78, H 7.68; found C 78.72, H 7.71.

Synthesis of p-Tert-butylcalix[4]arene Hydrazine Derivative 5

A mixture of compound **4** (0.82 g, 1 mmol) and 80% hydrazine hydrate solution (1 mL) was refluxed in toluene-methanol (1:1) mixture (60 ml) for 10 h. The solvent was removed under reduced pressure and the residue was treated with water to give crude products, following by crystallizing from MeOH/H_2O, compound **5** was obtained as white powder in yield of 96%. Compound **5** m.p. 173–175°C; ^{1}H NMR (500 MHz, $CDCl_3$): 0.95 (bs, 4H, NH_2), 1.04 [s, 18H, $C(CH_3)_3$], 1.27 [s, 18H, $C(CH_2)_3$], 3.43 (d, $J = 15.0$ Hz, 4H, $ArCH_2Ar$), 4.10 (d, $J = 15.0$ Hz, 4H, $ArCH_2Ar$), 4.64 (s, 4H, $ArOCH_2$), 6.92 (s, 4H, ArH), 7.04 (s, 4H, ArH), 7.76 (bs, 2H, NH), 9.67 (s, 2H, OH), MS *m/z* (%): 793.2 (M^+, 100). Anal. calcd for $C_{48}H_{64}N_4O_6$: C 72.70, H 8.14, N 7.06; found C 72.61, H 8.17, N 7.13.

Synthesis of *Tris*-calix[4]arene Derivative 6

A mixture of compound **5** (0.20 g, 0.25 mmol) and compound **2** (0.40 g, 0.5 mmol) was refluxed in MeOH-$CHCl_3$ (1:1, 100 ml) till starting materials disappeared by the detection of TLC (approximately two days). The solvent was removed under reduced pressure and the residue was treated with MeOH to give compound **6** as white powder in yield of 78%. Compound **6**: m.p. 230–233°C; ^{1}H NMR (500 MHz, $CDCl_3$): 1.03 [s, 18H, $C(CH_3)_3$], 1.20 [s, 36H, $C(CH_3)_3$], 1.26 [s, 18H, $C(CH_2)_3$], 1.29 [s, 18H, $C(CH_3)_3$], 1.29 [s, 18H, $C(CH_3)_3$], 3.42 (d, $J = 13.0$ Hz, 8H, $ArCH_2Ar$), 3.52 (d, $J = 12.0$ Hz, 4H, $ArCH_2Ar$), 4.21(bs, 8H, OCH_2), 4.48 (d, $J = 12.0$ Hz, 4H, $ArCH_2Ar$), 4.55 (d, $J = 13.0$ Hz, 8H, $ArCH_2Ar$), 4.64–4.73 (m, 4H, OCH_2), 6.94–7.14 (m, 24H, ArH), 7.64 (m, 8H, ArH), 7.76 (s, 2H, NH), 8.25 (s, 2H, -CH = N), 9.37 (s, 4H, OH), 10.17 (s, 2H, OH), 11.29 (s, 2H, OH), MS *m/z* (%): 2371.2 (MNa^+, 70). Anal. calcd for $C_{154}H_{188}N_4O_{16}$: C 78.67, H 8.06, N 2.38; found C 78.59, H 8.15, N 2.27.

Synthesis of *Tris*-calix[4]arene Derivative 7

A mixture of compound **6** (0.4 g, 0.17 mmol), triethylene glycol ditosylates (0.1 g, 0.21 mmol,) and K_2CO_3 (0.2 g, 1.4 mmol) was stirred in refluxing acetonitrile (200 mL) till starting materials disappeared by the detection of TLC (approximately three days) in N_2 atmosphere. After distilling off the solvent under reduced pressure, the residue was treated with 20 mL HCl (10%) and extracted with 30 mL $CHCl_3$. The organic layer was separated, dried over anhydrous $MgSO_4$, and then filtered, concentrated. By the purification of column chromatography on silica gel (100–200 mesh) using petroleum ether (60–90°C) / CH_2Cl_2 / diethyl ether (2:2:1) as an eluent, compound **7** was obtained as white powder in yield of 45%. Compound **7**: m.p. 202–205°C; ^{1}H NMR (500 MHz, $CDCl_3$): 0.88 [s, 18H, $C(CH_3)_3$], 1.08 [s, 18H, $C(CH_3)_3$], 1.20 [s, 36H, $C(CH_2)_3$], 1.24 [s, 18H, $C(CH_3)_3$], 1.25 [s, 18H, $C(CH_3)_3$], 3.39 (d, $J = 13.5$ Hz, 8H, $ArCH_2Ar$), 3.44–3.73 (m, 12H, $ArCH_2Ar$ and OCH_2), 4.20 (d, $J = 13.0$ Hz, 4H, $ArCH_2Ar$), 4.31–4.73 (m, 24H, $ArCH_2Ar$ and OCH_2), 6.81–7.10 (m, 24H, ArH), 7.65 (m, 8H, ArH), 7.88 (s, 2H, NH), 7.96 (s, 2H, -CH = N), 9.37 (s, 4H, OH), 10.13 (s, 2H, OH), MS *m/z* (%): 2485.8 (MNa^+, 100). Anal. calcd for $C_{160}H_{198}N_4O_{18}$: C 77.99, H 8.08, N 2.27; found C 77.89, H 8.14, N 2.15.

Synthesis of *Bis*-calix[4]arene Derivative 8

A mixture of compound **5** (0.20 g, 0.25 mmol) and compound **2** (0.24 g, 0.25 mmol) was refluxed in MeOH-$CHCl_3$ (1:1, 100 ml) till starting materials were disappeared by the detection of TLC (approximately 36 h). The solvent was removed under reduced pressure and the residue was treated with MeOH to give compound **8** as white powder in yield of 85%. Compound **8**: m.p. 242–244°C; ^{1}H NMR

(500 MHz, $CDCl_3$): 0.91 [s, 18H, $C(CH_3)_3$], 1.04 [s, 18H, $C(CH_3)_3$], 1.26 [s, 18H, $C(CH_2)_3$], 1.28 [s, 18H, $C(CH_3)_3$], 3.36 (d, $J = 12.0$ Hz, 4H, $ArCH_2Ar$), 3.45 (d, $J = 13.0$ Hz, 4H, $ArCH_2Ar$), 4.21–4.30 (m, 8H, $ArCH_2Ar$ and OCH_2), 4.35 (d, $J = 13.0$ Hz, 4H, $ArCH_2Ar$), 4.40–4.68 (m, 8H, OCH_2), 6.76–7.48 (m, 24H, ArH), 7.74 (s, 2H, NH), 8.23 (s, 2H, -CH = N), 8.55 (s, 2H, OH), 8.58 (s, 2H, OH), MS m/z (%): 1724.8 (MNa^+, 40). Anal. calcd for $C_{110}H_{132}N_4O_{12}$: C 77.62, H 7.82, N 3.29; found C 77.53, H 7.89, N 3.18.

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