Communication

Enantioselective Recognition of Calix[4]arene Derivative Bearing Bicyclic Guanidinium for *D/L* Amino Acid Zwitterions

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The *p*-tetra-*tert*-butyl calix[4]arene derivatives (3 and 4) with (*S*, *S*) chiral bicyclic guanidinium, as the receptors of amino acid zwitterions, have been synthesized *via* a *O*-alkylation reaction of *p*-tetra-*tert*-butyl calix [4] arene with chloromethyl chiral bicyclic guanidinium 2 in the presence of anhydrous K_2CO_3 in acetonitrile. The results obtained from liquid-liquid competitive extraction experiments indicate that the two receptors may selectively recognize *L*-aromatic amino acids, and that the enantioselective recognizability of the receptor 4 with two chiral bicyclic guanidinium units reachs up to about 90% for *L*-Phe.

Keywords Functionalized calix[4]arene, bicyclic guanidinium, molecular recognition, amino acid

Calixarenes which are selectively functionlized at the upper or the lower rim can become good receptors in the process of molecular recognition due to their special cleft structures.[1-3] Guanidinium group possessing much high *p*K value (13.5) remains protonated form over a much wider range of pH than the ammonium group. Therefore, guanidinium derivatives have been successfully employed for the molecular recognition of the anions, such as carboxylate (amino acids),[4-6] phosphate (nucleotides)[7-8] *via* hydrogen bonding and electrostatic interactions. However, calix[4]arenes with incorporated guanidinium functionality have not been reported so far. We report here, for the first time, the *p*-tetra-*tert*-butyl calix[4]arene derivatives (**3**, **4**) bearing mono- and dichiral bicyclic guanidinium units in the lower rim were prepared by selective *O*-alkylation of *p*-tetra-*tert*-butyl calix[4]arene with chloromethyl chiral bicyclic guanidinium **2** in the presence of anhydrous K_2CO_3 in acetonitrile. The synthesis of compound **2** was achieved from **1** which was available from *L*-asparaginate through 9 step reactions,[5,9] respectively (Scheme 1).

Generally, 25, 27-*O*-dialkylated calix [4] arene derivatives can be prepared by refluxing *p*-tetra-*tert*-butyl calix[4]arene with etherifying reagent in the presence of anhydrous K_2CO_3 in acetone, acetonitrile or DMF.[10,11] In the present case, the similar procedure was used to give the 25-*O*-monoalkylated calix [4] arene derivatives **3** in much higher yield than 25,27-*O*-dialkylated derivatives **4**. The molar conversion for **3** is ~75%, while for **4** is only ~10%. The steric congestion in the low rim area of calix[4]arene and the bulk bicyclic guanidinium units may be the main reason.

The compounds **3** and **4** were characterized by ^1H NMR (2D H-H Cosy spectra), ^{13}C NMR, MS (ES-IMS), IR and elemental analysis.[12] In the ^1H NMR and ^{13}C NMR spectra, the peaks of $ArCH_2Ar$ protons and ^{13}C of **3**, **4** appeared as doublet at δ_H 3.35—3.46 (H_{exo}), δ_H 4.14—4.21 (H_{endo}) and about δ_C 31.5. Obviously they are consistent with the cone conformation.[11,13,14]

Despite the ionic structure of the receptors, they are scarcely soluble in water, but freely soluble in common organic solvents such as dichloromethane. The affinity of **3** or **4** for amino acid zwitterions was therefore investigated by liquid - liquid competitive extraction

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Scheme 1

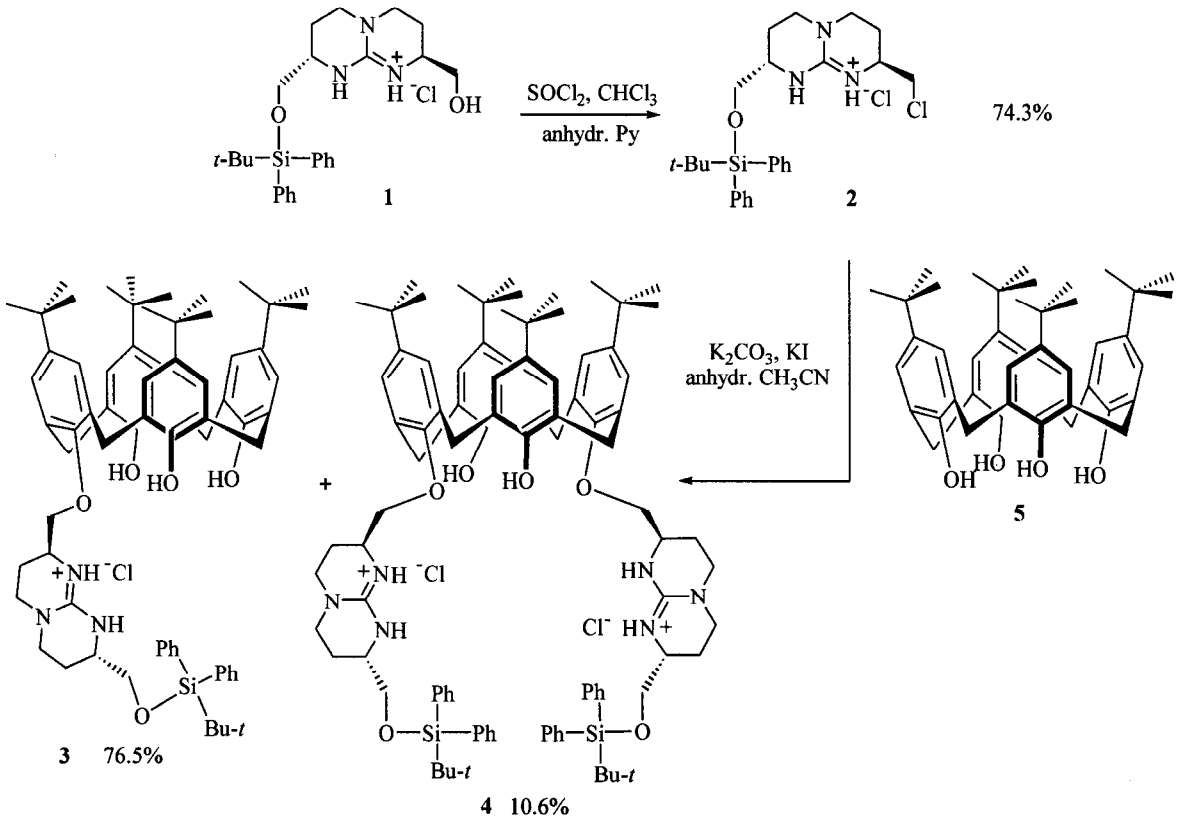

Table 1 Results of competitive extraction of *L* or *D*-amino acids (25℃)[a]

Amino acid	3		4	
	Extractive amont (μmol)	Percentage (%)	Extractive amont (μmol)	Percentage (%)
L-Phe	0.618	12.4	2.359	47.2
L-Trp	0.428	8.6	0.794	15.9
L-Tyr	0.436	8.7	0.640	12.8
L-Leu	0.352	7.0	0.490	9.8
L-Ile	0.174	3.5	0.199	4.0
Gly	0.348	6.9	0.058	1.5
L-His	0.340	6.8	0.054	1.1
L-Arg	0.286	5.7	0.026	0.5
D-Phe	0.194	3.9	0.263	5.3
D-Trp	0.156	3.1	0.240	4.8
D-Val	0.176	3.5	0.242	4.9
D-Leu	0.174	3.4	0.206	4.1
D-Asp	0.046	0.9	0.082	1.6

[a]In the blank extractions without adding the receptor, the extractive amounts for *L*-amino acids are: *L*-Phe, 0.035; *L*-Trp, 0.033; *L*-Tyr, 0.041; *L*-Leu, 0.045; *L*-Ile, 0.038; Gly, 0.071; *L*-His, *L*-Arg, no found.

experiments. The experiments were performed according to the procedure given in references.[4,5] 2 mL of mixed *L*- or *D*-amino acids aqueous solution (5.0×10^{-2} mol/L for each) and 2 mL of CH_2Cl_2 solution of the receptor **3** or **4** (5.0×10^{-3} mol/L) were mixed in centrifuge tube, shaken mechanically for 30 min at 25℃, centrifuged for 10 min. Then, the separated organic phase was dried with Na_2SO_4, extracted with water (3 × 2 mL). The combined aqueous phase was evaporated to dryness *in vacuo*. The residue was dissolved in buffer solution and the content of each amino acid was determined by amino acid analyzer (HITACHI-835-50). The

results of competitive extraction of receptors **3** and **4** for *L*- or *D*-amino acids are listed in Table 1.

As shown in Table 1, the extractive amounts of the receptor **4** or **3** with (*S*, *S*) chiral configuration for *L*-amino acids are much larger than for *D*-amino acids. This can be explained by the matching of (*S*, *S*) chiral configuration of the receptors with *L*-configuration of amino acids. No similar CPK model can be assembled for the *D*-amino acids. Compared with receptor **3** (with a chiral bicyclic guanidinium unit), receptor **4** (with two chiral bicyclic guanidinium units) increases its extractive efficiency pronouncedly. Moreover, the extractive amount of **4** for *L*-Phe is as about 9 times as that for *D*-Phe. Obviously, the **4** has high degree of chiral recognition ability. The cooperative effect of two guanidinium units and the matching of V-shape cleft of **4** with *L*-Phe may be the main reasons.

References and notes

1 Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, 97, 1713.

2 Molenveld, P.; Engbersen, J. F. J.; Reinhoudt, D. N. *Chem. Soc. Rev.* **2000**, *29*, 75.

3 Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609.

4 Galan, A.; Andreu, D.; Echavarren, A. M.; Prados, P.; Mendoza, J. D. *J. Am. Chem. Soc.* **1992**, *114*, 1511.

5 Lu, G. Y.; Liu, F.; He, W. J.; Wang, Z. L.; Hu, H. W.; Prados, P.; Mendoza, J. D. *Chin. J. Chem.* **1999**, *17*, 508.

6 Metzger, A.; Gloe, K.; Stephan, H.; Schmidtchen, F. P. *J. Org. Chem.* **1996**, *61*, 2051.

7 Andreu, C.; Galán, A.; Kobiro, K.; Mendoza, J. De.; Park, T. K.; Rebek, J. Jr.; Salmerón, A.; Usman, N. *J. Am. Chem. Soc.* **1994**, *116*, 5501.

8 Berger, M.; Schmidtchen, F. P. *J. Am. Chem. Soc.* **1999**, *121*, 9986.

9 Kurzmeièr, H.; Schmidtchen, F. P. *J. Org. Chem.* **1990**, *55*, 3749.

10 Dijikstra, P. J.; Brunink, J. A.; Bugge, K. E.; Reinhoudt, D. N.; Herkema, S.; Ungaro, R.; Ugozzoli, F.; Ghidini, E. *J. Am. Chem. Soc.* **1989**, *111*, 7567.

11 Lu, G. Y.; Li, Q.; Liu, F.; Wen, X. B. *Chin. J. Chem.* **2000**, *18*, 207.

12 5,11,17,23-tetra-*tert*-butyl-25-[(2*S*,8*S*)-8-[[(*tert*-butyldiphenylsilyl) oxy] methyl]-3, 4, 6, 7, 8, 9-hexahydro-2*H*-pyrimido[1,2-a]-pyrimido-2-methoxy]-26,27,28-trihydroxy calix[4]arene hydrochloride (**3**): m.p. 154—156℃, R_f = 0.64 ($CHCl_3$: CH_3OH = 8 : 1), $[\alpha]_D^{25}$ + 37.5 (*c* 0.25, $CHCl_3$); ^1H NMR (500 MHz, 2D H-H Cosy, $CDCl_3$) δ: 10.09 (s, 1H, OH), 9.40 (s, 2H, 2 × OH), 9.18 (s, 1H, NH), 8.22 (s, 1H, NH), 7.63—7.64 (m, 4H, Si—ArH), 7.36—7.44 (m, 6H, Si—ArH), 7.08—6.97 (m, 8H, ArH), 4.28—4.30 (m, 1H, 1/2 × OCH_2), 4.21 (d, *J* = 13.5 Hz, 4H, 4 × *endo*-ArCHAr), 4.12—4.15 (m, 1H, 1/2 × OCH_2), 3.80—3.82 (m, 1H, 1/2OCH_2), 3.64—3.66 (m, 4H, 2 × NCH_2), 3.53—3.55 (m, 1H, NCH), 3.46 (d, *J* = 13.5 Hz, 4H, 4 × *exo*-ArCHAr), 3.38—3.41 (m, 1H, 1/2OCH_2), 3.35—3.37 (m, 1H, NCH), 2.56—2.59 (m, 2H, CH_2), 2.11—2.15 (m, 1H, 1/2 × CH_2), 1.98—2.01 (m, 1H, 1/2 × CH_2), 1.19—1.24 (m, 27H, 3 × $C(CH_3)_3$), 1.18 (s, 9H, $C(CH_3)_3$), 1.06 (s, 9H, Si—$C(CH_3)_3$); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 151.4 (C═N), 148.7, 148.0, 142.8, 135.5, 134.8, 133.5, 132.6, 130.0, 128.7, 128.2, 128.0, 127.7, 126.5, 126.1, 125.8, 125.6 (aromatic C), 77.3, 65.6 (OCH_2), 49.6, 48.4 (NCH), 45.9, 45.0 (NCH_2), 34.2, 33.9, 33.6 ($C(CH_3)_3$), 32.1 ($ArCH_2Ar$), 31.8, 31.5, 31.2 (CH_3), 26.7 (CH_3), 23.4, 23.1 (CH_2), 19.2 (Si—C); IR (KBr) ν: 3276.8 (br, NH_2, OH), 3047.4 (Ar—H), 1628.5 (C═N); MS (ESIMS) *m/z*: 1068.9 ([M − Cl]$^+$, calc. 1068.7); Anal. calcd for $C_{69}H_{90}N_3O_5SiCl$: C 75.00, H 8.21, N 3.80; found: C 75.28, H 8.04, N 3.57.

5,11,17,23-tetra-*tert*-butyl-25,27-bis[(2*S*,8*S*)-8-[[(*tert*-butyldiphenylsilyl) oxy] methyl]-3, 4, 6, 7, 8, 9-hexahydro-2*H*-pyrimido[1,2-a]-pyrimido-2-methoxy]-26,28-dihydroxy calix[4]arene hydrochloride (**4**): m.p. 145—147℃, R_f = 0.55 ($CHCl_3$: CH_3OH = 8 : 1), $[\alpha]_D^{25}$ + 62.5 (*c* 0.10, $CHCl_3$); ^1H NMR (500 MHz, 2D H-H Cosy, $CDCl_3$) δ: 9.36 (s, 2H, 2 × NH), 8.57 (s, 2H, 2 × NH), 7.70—7.72 (m, 8H, Si—ArH), 7.61—7.64 (m, 12H, Si—ArH), 7.05, 6.74 (2 × s, 8H, ArH), 4.29—4.32 (m, 2H, 2 × 1/2OCH_2), 4.14 (d, *J* = 12.8 Hz, 4H, 4 × *endo*-ArCHAr), 4.07—4.098 (m, 2H, 2 × 1/2OCH_2), 3.97—4.02 (m, 2H, 2 × 1/2OCH_2), 3.80—3.84 (m, 4H, 2 × NCH_2), 3.61—3.65 (m, 4H, 2 × NCH_2), 3.54—3.58 (m, 2H, 2 × NCH), 3.35 (d, *J* = 13.5 Hz, 4H, 4 × *exo*-ArCHAr), 3.27—3.32 (m, 4H, 2 × NCH, 2 × 1/2OCH_2), 2.50—2.54 (m, 2H, 2 × 1/2CH_2), 2.22—2.34 (m, 2H, 2 × 1/2CH_2), 2.01—2.07 (m, 2H, 2 × 1/2CH_2), 1.94—1.97 (m, 2H, 2 × 1/2CH_2), 1.26 (s, 18H, 2 × $C(CH_3)_3$), 1.06 (s, 18H, 2 × $C(CH_3)_3$), 0.93 (s, 18H, 2 × Si—$C(CH_3)_3$); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 151.4 (C═N), 148.0, 142.3, 135.6, 135.5, 134.8, 132.7, 131.9, 130.0, 127.9, 127.6, 125.9, 125.3 (aromatic C), 76.4, 65.2 (OCH_2), 49.4, 47.4 (NCH_2), 45.0, 44.6 (NCH), 31.7, 31.5 ($C(CH_3)_3$), 31.0 ($ArCH_2Ar$), 29.7, 29.4 (CH_3), 26.9

(CH_3), 22.9, 22.6 (CH_2), 19.2 (s, Si—C); IR (KBr) ν: 3396.8 (br, NH_2, OH), 3070.2 (Ar—H), 1624.6 (C=N); MS (ESIMS) *m/z*: 1524.6 ($[M - Cl]^+$, calcd 1524.8), 1488.9 ($[M - 2Cl - H]^+$, calcd 1488.9), 745.1 ($[M - 2Cl]^{2+}$, calcd 745.0); Anal. calcd for $C_{94}H_{124}N_6O_6Si_2Cl_2$: C 72.32, H 8.01, N 5.38; found: C 72.14, H 7.65, N 5.69.

13 Wamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* **1991**, *47*, 4325.

14 Jaime, C.; Mendoza, J.D.; Prados, P.; Nieto, P.M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372.

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