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Synthesis and structure of lower rim C-linked tetra-*N*-tosyl peptidocalix[4]arenes

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Abstract—Chiral *p-tert*-butylcalix[4]arenes perfunctionalised at the lower rim with amino acid residues have been prepared. The ^{1}H and ^{13}C NMR spectra indicate that the macrocycles adopt a cone conformation. Calix[4]arenes bearing amino acid moieties **5a** shows strong complexation towards Cl^{-}, Br^{-}, HSO_4^{-}, $H_2PO_4^{-}$ and *N*-tosyl-(L)-alaninate.

Recognition of an anion by neutral receptors continues to be a very attractive and challenging area of research owing to the wide variety of applications in biological and environmental systems.[1,2] Calixarenes are extremely popular building blocks in molecular recognition forming host-guest or supramolecular complexes.[3] The three-dimensional surface and conformationally rigid structure make calixarenes most convenient for synthetic elaboration. It would be interesting to chemically modify the calixarene platform with amino acid or peptide moieties to achieve chirally modified macrocyclic ligands. The chemical modifications can occur either on the upper[2,4,5] or lower[6,7] rim of the calixarene core.

In the course of this study, we have previously reported the synthesis and the complexation behaviour towards anions of 19 novel 1,3-chiral cone *p*-butylcalix[4]arenes functionalised with D or L amino acid units.[6]

The conjugation of α-amino acids or peptides to calixarenes can be performed through the terminal amino or carboxylic groups.[2a] Thus, two possibilities of functionalisation on the upper rim have been explored: N-linked[4] and C-linked[5] peptidocalix[4]arene.

Herein, we describe five new calix[4]arene receptors featuring an anion binding site in the form of four C-linked L-aminoacid moieties at the lower rim of the calix[4]arene scaffold.

The amino acid chloride derivatives **1a**–**e** (Scheme 1) were prepared from the corresponding amino acid in two steps as already described.[6] Tetra(cyanomethoxy)-calix[4]arene **3**[8] was obtained by *O*-substitution of the free hydroxyl groups of the di(cyanomethoxy) derivative **2**.[9] Compound **4** was prepared according to known procedures using BH_3·THF as a reducing agent.[9,10] The amides **5a**–**e**[11–15] were synthesised through the condensation of the amino acid chlorides **1a**–**e** with the tetrakis(aminoethoxy)calix[4]arene derivative **4** in dry CH_2Cl_2 with Et_3N as a catalyst. The calix[4]arene derivatives substituted by chiral amino acids were obtained in moderate yields due to steric bulk effect of the substituent. The product structures were supported by their spectral and analytical data (^{1}H NMR, ^{13}C NMR, ESI data), and confirmed by the amide group absorption in the FT-IR spectra. The cone conformation of all compounds (**3**, **4**, **5**) were reflected in the characteristic AB system for the methylene groups bridging the aromatic rings in the ^{1}H and ^{13}C NMR spectrum.[16] For example, in the case of **5a**, the cone conformation is proved by the presence of two doublets ($\delta = 3.17$ ppm, $J_{AB} = 12.7$ Hz and 4.27 ppm, $J_{AB} = 12.7$ Hz) for $ArCH_2Ar$ groups and one signal ($\delta = 31.32$ ppm) for the corresponding carbon.

As we have previously described,[6] the introduction of hydrogen bonding donor and acceptor groups at the lower rim of calixarenes affects their host–guest properties. We report a preliminary study of the complexation

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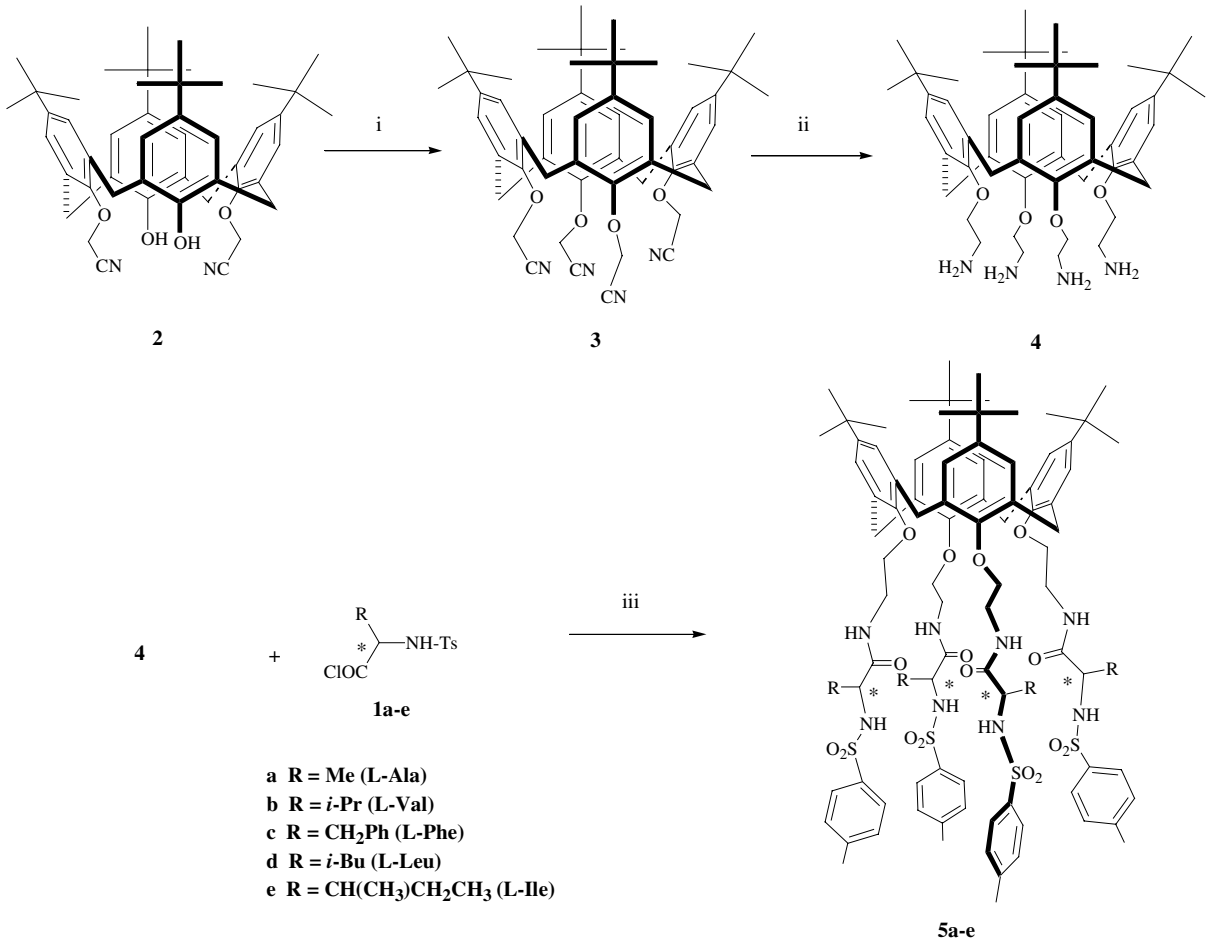

Scheme 1. Synthesis of calixarene derivatives **5**. Reagents and conditions: (i) NaH, $BrCH_2CN$, DMF, 60%; (ii) BH_3·THF, THF, reflux, 93%; (iii) Et_3N, CH_2Cl_2, 0 °C, **5a** 41%, **5b** 37%, **5c** 22%, **5d** 24%, **5e** 16%. Abbreviations: DMF = *N*,*N*′-dimethylformamide, THF = tetrahydrofuran.

properties of various anions such as tetrabutylammonium chloride, bromide, dihydrogen phosphate, hydrogen sulfate and *N*-tosyl-L-alaninate. The recognition properties of compound **5a** were investigated by ^1H NMR experiments in $CDCl_3$. The ^1H NMR titration curves of the complexation are depicted in Figure 1. In all cases the stoichiometry is 1:1 as was confirmed by Job plots (e.g., Fig. 2). The association constants of the anion receptor were determined by the Benesi–Hildebrand method[17] and are summarised in Table 1.

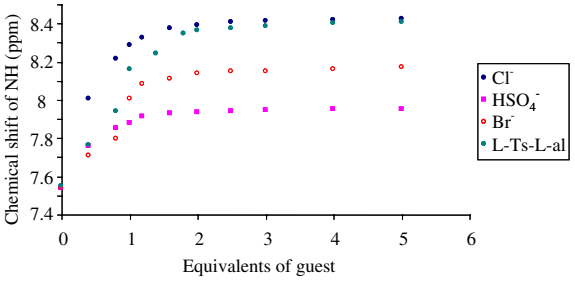

Figure 1. Titration curves of calix[4]arene **5a** with Bu_4NCl, Bu_4NBr, Bu_4NHSO_4, Bu_4N–*N*-Ts-L-alaninate in $CDCl_3$. Concentration of the host is 10^{-2} M.

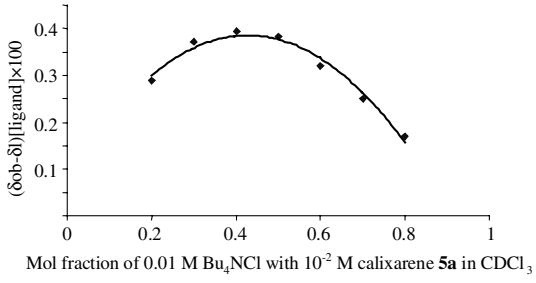

Figure 2. Job plot of the titration of 0.01 M Bu_4NCl with 10^{-2} M calix[4]arene **5a** in $CDCl_3$.

Table 1. K_{ass} values (M^{-1}) of **5a**

Compound	Cl^-	Br^-	HSO_4^-	$H_2PO_4^-$	*N*-Tosyl-(L)-alaninate
5a	4900	3800	3700	2300	6900

Addition of anions to the receptor resulted in significant downfield shifts of the amide protons indicating that the anions are bound by the hydrogen bonding moieties.

Since it is known that Cl^- and Br^- anions are good hydrogen bond acceptors, it was expected that we obtained stronger complexation constants than with HSO_4^- and $H_2PO_4^-$ anions. Our results are in accordance with those previously described.[5,18] Nevertheless, the greatest selectivity is observed for *N*-tosyl-(L)-alaninate. With the di-*N*-tosylpeptidocalix[4]arenes,[6] we showed that the binding constant was dependent of the length of the spacer. In this study, we pointed out the influence of the number of peptide chains. Regarding to the length of the spacer, the tetra-amide receptor in which additional hydrogen bond donor sites are available shows larger association constants ($K_a = 6900\,M^{-1}$ vs $1600\,M^{-1}$ for the di-substituted compound) towards *N*-tosyl-(L)-alaninate. It is known that the presence of intramolecular hydrogen bonding contributes to stabilise the conformation of the calixarene.[5,19] In the case of the tetrasubstituted derivative; we suppose that not all the hydrogen bond donor or acceptor are involved. The free groups could be more available for the complexation and it could explain the enhancement of the association constants. Ungaro and co-workers[2a] reported that aromatic α-amino acids are more strongly bounded than aliphatic ones. H-Bonding interactions between the carboxylate anions and the amide NH groups, together with π–π stacking, are mentioned to explain the selectivity of such anion receptors. In our case, the *N*-tosyl protecting group may play a cooperative role in the binding and could explain the enhancement in the host–guest complexation of alaninate.

In conclusion, new chiral calix[4]arene-amino-acid conjugates have been prepared using the reaction of the *N*-tosylated acid chlorides of five L-amino acids with calix[4]arene derivative. We have verified that these hosts adopt a cone conformation in solution. The *N*-tosylated calix[4]arene derivatives **5a** behaves as a good receptor for anion binding in a 1:1 stoichiometry. The highest selectivity is obtained for *N*-tosyl-(L)-alaninate as expected. This tetra *O*-substituted calix[4]arene derivative seems to be a more efficient receptor than the di-*O*-substituted corresponding compound. This class of receptor enables us to extend study to the recognition of chiral carboxylate derivatives. The pre-organisation of the calix[4]arene platform associated to suitable chemical functionalisations allow this class of macrocycle to be a good template for the design of artificial neutral receptors for anions binding.

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8. Compound **3**: Solid, mp 247–249 °C; ^{1}H NMR δ: 1.01 (s, 36H), 3.20 (AB, J = 13.35, 4H), 4.27 (AB, J = 13.17, 4H), 4.80 (s, 8H), 6.78 (s, 8H); ^{13}C NMR (selected) δ: 31.51, 34.45, 59.71, 126.26, 133.15, 147.3, 152.04, 170.97; IR ν: 2245 cm^{-1}; ES-MS(+): m/z = 828.5 $[M+Na]^+$; 805.5 $[M+H]^+$.
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10. Compound **4**: Solid, mp 147–149 °C; ^{1}H NMR δ: 108 (s, 36H), 3.20–3.27 (s, 16H), 3.99 (br t, 8H), 4.33 (AB, J = 12.7, 4H), 6.86 (s, 8H); ^{13}C NMR (selected) δ: 30.35, 30.97, 34.32, 41.39, 62.94, 125.82, 133.88, 146.08, 150.97, 152.53; IR ν: 3264 cm^{-1}. ES-MS(+): m/z = 843.5 $[M+Na]^+$, 821.5 $[M+H]^+$.
11. Compound **5a**: Solid, mp = 156–158 °C; $[\alpha]_D^{20}$ + 14 (c 0.3, $CHCl_3$); ^{1}H NMR δ: 1.08 (br s, 36H), 1.23 (d, J = 7.14, 6H), 2.39 (s, 12H), 3.17 (AB, J = 12.7, 4H), 3.82–4.03 (m, 18H), 4.27 (AB, J = 12.7, 4H), 6.27 (d, J = 7.71, 4H), 6.79 (br s, 8H), 7.29 (d, J = 9.81, 4H), 7.54 (br s, 4H), 7.82 (d, J = 8.28, 8H); ^{13}C NMR (selected) δ: 19.42, 21.91, 31.32, 31.78, 34.26, 40.73 53.23, 73.28, 125.63, 127.60, 129.84, 130.25, 137.14, 143.84, 144.26, 145.54, 173.20; IR ν: 3264, 1651 cm^{-1}; ES-MS(+): m/z = 1744.9 $[M+Na]^+$ (calcd.1743.76),1722.9; $[M+H]^+$, 883.6 $[M+2Na]^{2+}$.
12. Compound **5b**: Solid, mp = 256–258 °C; $[\alpha]_D^{20}$ + 5.7 (c 0.3, $CHCl_3$); ^{1}H NMR δ: 0.81 (d, J = 7.35, 12H), 1.08 (br s, 36H), 1.62–1.73 (m, 4H), 2.30 (s, 12H), 3.17 (d, J = 12.8, 4H), 3.71–3.94 (m, 16H), 4.26 (d, J = 12.8, 4H), 6.37 (br d, J = 7.53, 4H), 6.80 (br s, 8H), 7.29 (d, J = 6.78, 8H), 7.48 (br s, 4H), 7.82 (d, J = 8.28, 8H); ^{13}C NMR (selected) δ: 17.82, 19.64, 21.91, 31.33, 31.59, 34.27, 40.54, 63.0, 73.44, 125.66, 127.71, 130.04, 133.69, 137.22, 144.06, 145.58, 149.34 172.66; IR ν: 1649, 3269, 3317 cm^{-1}; ES-MS(+): m/z = 1856 $[M+Na]^+$ (calcd 1854.89), 939.7 $[M+2Na]^{2+}$ (calcd 938.94).
13. Compound **5c**: Solid, mp = 136–138 °C; $[\alpha]_D^{20}$ − 76.7 (c 0.3, $CHCl_3$); ^{1}H NMR δ: 1.09 (s, 36H), 2.36 (s, 12H), 2.80–2.88 (dd, J = 13.92, 4H), 3.09–3.20 (m+d, 8H+4H), 3.85–

4.11 (m, 20H), 4.32 (AB, J = 12.60, 4H), 6.14 (d, J = 7.35, 4H) 6.80 (br s, 8H), 6.91–7.08 (m+d, 28H), 7.47 (d, J = 8.28, 8H), 7.58 (br s, 4H); ^{13}C NMR (selected) δ: 21.90, 31.35, 31.79, 39.01, 40.86, 58.93, 73.05, 125.58, 125.72, 127.02, 127.50, 128.85, 129.61, 129.98, 136.17, 136.31, 143.76, 145.50, 172.37; IR v: 1657, 3288 cm^{-1}. ES-MS (+): m/z = 2049 $[M+Na]^+$ (calcd 2047.89), 1036.2 $[M+2Na]^{2+}$ (calcd 1035.44), $[M+H]^+$ 2027 (calcd 2025.91).

14. Compound **5d**: Solid, mp = 136–139 °C; $[\alpha]_D^{20}$ + 9.7 (c 0.3, $CHCl_3$); ^{1}H NMR δ: 0.55 (br s, 12H), 0.76 (br s, 12H), 1.08 (br s, 36H), 1.53 (br m, 12H), 2.37 (s, 12H), 3.14 (AB, J = 12.5, 4H), 3.66–4.02 (m, 20H), 4.27 (AB, J = 12.5, 4H), 6.37 (br s, 4H), 6.78 (br s, 8H), 7.30 (d, J = 8.46, 8H) 7.47 (br s, 4H), 7.83 (d, J = 8.28, 8H); ^{13}C NMR (selected) δ: 21.37, 21.91, 23.37, 24.74, 31.37, 31.76, 34.25, 40.77, 42.59, 56.36, 73.06, 125.44, 125.86, 127.84, 130.09, 133.65, 137.02, 144,18, 145.54, 153.04, 173.80; IR v: 1635, 3281 cm^{-1}. ES-MS: m/z = 1913 $[M+Na]^+$ (calcd 1910.95), 1602.9 $[M+Na-2Ts]^+$ (calcd 1600.56), 968.2 $[M+2Na]^{2+}$ (calcd 966.97).
15. Compound **5e**: Solid, mp = 275–277 °C; $[\alpha]_D^{20}$ − 11.3 (c 0.3, $CHCl_3$); ^{1}H NMR δ: 0.72–0.77 (m, 24H), 1.09 (br s, 36H), 1.27–1.82 (m, 8H), 2.36 (s, 12H), 3.17 (AB, J = 12.7, 4H), 3.73–3.92 (m, 20H), 4.27 (AB, J = 12.7, 4H), 6.24 (d, J = 8.46, 4H), 6.80 (br s, 8H), 7.29 (d, J = 8.10, 8H), 7.50 (br s, 4H), 7.81 (d, J = 8.07, 8H); ^{13}C NMR (selected) δ: 11.61, 15.88, 21.91, 24.66, 31.35, 33.78, 34.27, 37.98, 40.54, 62.29, 73.31, 125.67, 127.74, 130.03, 133.72, 137.23, 144.06, 145.55, 149.40, 172.53; IR v: 1656, 3282 cm^{-1}; ES-MS: m/z = 1913 $[M+Na]^+$ (calcd 1910.95), 1602.7 $[M+Na-2Ts]^+$ (calcd 1600.56), 968.2 $[M+2Na]^{2+}$ (calcd 966.97).
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