Research Article

C-Silylated Calix[4]Arene as a New Receptor for Aspartate in Polar Solvents

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The recognition of aspartic acid derivatives such as N-benzyloxycarbonyl-D-aspartate (NZDA) with the calix[4]arene derivatives with multiple silicon groups at the upper rim in polar solvents is investigated.

1. Introduction

The development of synthetic receptors for a chosen substrate (host-guest chemistry) is a well-established area of research, and selective receptors have now been described for a whole range of substrates, from simple metal cations to polyfunctional molecules such as peptides, proteins, and carbohydrates [1, 2]. Carboxylic acids (or carboxylates) are a particularly common functional group in biological and synthetic organic molecules and have inspired the elaboration of a number of different approaches for their recognition. Binding sites have been developed both for simple carboxylic acids and for incorporation into sophisticated receptors for more complex carboxylic acid derivatives, both in polar and nonpolar solvents [3].

The development of synthetic receptors for enantioselective binding of L-glutamate and L-aspartate derivatives has been of particular interest because of the critical role of these amino acids in the central nervous system as excitatory transmitters. Several groups have successfully developed receptors to be able to bind a range of dicarboxylates [4–6].

Calixarenes have been widely studied as hosts and potential hosts for molecular recognition [7]. For example, the binding affinities between *p*-tert-butylcalix[4]arene-based dipodal and some aliphatic diacetates such as malonate, succinate, glutarate, adipate, pimelate, and suberate in CH₃CN were studied by Singh et al. [8]. We have recently introduced a different type of substituted calix[4]arene derivatives,

which have a multiple functional groups at the upper rim. These receptors can bind selective amino acids such as arginine and lysine in polar solvents [9]. The recognition of aspartic acid derivatives such as N-benzyloxycarbonyl-D-aspartate (NZDA) with the calix[4]arene derivatives with multiple silicon groups at the upper rim is investigated.

2. Results and Discussion

2.1. Synthesis. Disilylated calixarene, **6** and **7** were synthesized according to the following procedure (Figure 1).

The main synthetic route starts from *n*-butyl-protected free calix[4]arene **1** [10, 11] which is butylated in one pot to give **2** [12]. Partial butylation of **1** afforded **3** in good yield [13].

The tetrabromo derivative **4** and dibromo derivative **5** can be prepared with the NBS bromination and subsequently butylation [14]. After bromine-lithium exchange on **4** and **5** with Li powder proceeds smoothly, the phenyllithium intermediate is then efficiently trapped by trimethylsilyl chloride (TMSCl) that give the disilylated derivatives **6** and **7** [15, 16].

3. Binding Experiments

The compounds **6** and **7** were selected for preliminary study of host-guest properties in chloroform and methanol (1:1) at 25°C. To evaluate the binding ability of calix[4]arene

TABLE 1: Association constants between various receptors and NZDA **8** and aspartic acid **9**.

Entry	Receptor	Guest	K_a (M^{-1}) ⁴	Stoich.
1	4	NZDA 8	1000 ($\pm 4\%$)	1 : 1
2	6	NZDA 8	5000 ($\pm 6\%$)	1 : 1
3	7	NZDA 8	6000 ($\pm 10\%$)	1 : 1
4	10	NZDA 8	2000 ($\pm 6\%$)	1 : 1
5	11	NZDA 8	20000 ($\pm 10\%$)	2 : 1
6	4	Aspartic acid 9	700 ($\pm 7\%$)	1 : 1
7	6	Aspartic acid 9	3000 ($\pm 8\%$)	1 : 1
8	7	Aspartic acid 9	900 ($\pm 11\%$)	1 : 1
9	10	Aspartic acid 9	300 ($\pm 8\%$)	1 : 1
10	11	Aspartic acid 9	5000 ($\pm 4\%$)	1 : 1

FIGURE 1: Synthetic route to calix[4]arene receptors **6/7**; (i) BuBr, NaH, dry DMF, (ii) BuBr, K_2CO_3 , (iii) NBS, MEK, (iv) NBS, MEK, K_2CO_3 , (v) and (vi) Li powder, THF, $-78^\circ C$, TMSCL.

receptors **6** and **7** towards different aspartate anions, UV-vis experiments were carried out. The anion recognition via the formation of stable hypercoordinate complexes between the anion and the silylated calixarenes can be easily monitored by anion-complexation induced changes in UV-vis spectra. The stoichiometries of the complexes formed between the anions and the host were determined from Job's plot.

The aspartate derivative, N-benzyloxycarbonyl-D-aspartate (NZDA) **8**, (10^{-4} M) shows an absorption band at 265 nm in the UV spectrum in the absence of receptors. Upon increasing amounts of receptor **6** in the solution of NZDA **8**, a marked increase in UV intensity was observed. This indicates a strong interaction with an association constant $5 \times 10^3 M^{-1}$, and producing a sharply kinked titration curve (Figure 2).

For the determination of complex stoichiometry between receptor **6**/NZDA **8**, we have used the job methods [17]. The resulting plot shows an approximate 1 : 1 stoichiometry (Figure 3).

Table 1 shows the binding constant and stoichiometry between NZDA **8** and aspartic acid **9** and different calix[4]arene receptors.

The results show that receptor **7** has a good affinity to the NZDA **8**. (Table 1 entry 3), in comparison to the latter interaction, the association constant between receptors **6** and **8** decreases because of the steric effect of bromine groups at the upper rim of **6**. The binding affinities of **6** and **7** for NZDA **8** are greater than the affinities of **6** and **7** for aspartic acid (Table 1 entry 2, 3 and 7, 8). The receptors **4** and **10**, which have not silyl group at the upper rim, could bind aspartate and aspartic acid weaker than receptors **6** and **7**. This may be due to the formation of hypercoordinate complexes between the guests and silylated host (**6** and **7**), (Figure 2). In the case of receptor **11**, it is believed that the electrostatic interaction is the main interaction (Figure 4).

4. Experimental Section

4.1. General Remarks. All reagents were purchased at highest commercial grade and used as supplied. All solvents were dried over molecular sieve. Anhydrous solvents were distilled

FIGURE 2: UV enhancing and resulting titration curve for the interaction of **6** with NZDA ($\text{CHCl}_3/\text{MeOH}$ 1 : 1).

FIGURE 3: Job plot between **6** and NZDA ($\text{CHCl}_3/\text{MeOH}$ 1 : 1).

from the following drying agents: acetonitrile (calcium hydride), dichloromethane (calcium hydride), and methanol (magnesium). Reactions were monitored by thin layer chromatography (TLC) with *Merck* silica gel 60 F254 plates. Silica gel 60 for flash chromatography (particle size 230–400 mesh) was supplied by *Merck*. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. Melting points were determined on a Büchi melting point apparatus B545 and are uncorrected. ^1H and ^{13}C spectra were recorded at 300 K on a *Bruker* Avance DMX 300 or DRX 500 spectrometer. Chemical shifts are reported as δ values in ppm and calibrated on the particular solvent signal; multiplicities are indicated by s (singlet), d (doublet), t (triplet), m (multiplet), and br (broad). ^{13}C spectra are broadband decoupled and calibrated on the particular solvent signal. High-resolution electron spray ionisation (ESI) mass spectra were recorded on a MAT 95 S *Finnigan* spectrometer. Samples (20 μL) were introduced as 10^{-7} M solutions in HPLC-grade methanol at flow rates of

20 $\mu\text{L} \cdot \text{min}^{-1}$; heated capillary temperature: 150°C; ion spray potential: 3.5 kV (positive ESI), 3.0 kV (negative ESI). About 20–30 scans were averaged to improve the signal to noise ratio. UV-vis experiments were performed on an Agilent 8453E unit. *Helma* cuvettes with 0.2 mm inner diameter were used for the experiments.

4.2. Synthesis of 5,17-Bis(trimethylsilyl)-11,23-dibromo-25,26,27,28-tetra-butoxy-calix[4]arene 6. The synthesis of the tetrabromocalixarene **4** and dibromocalixarene **5** starts with butylation of the parent calixarene **1**, followed by bromination according to the literature [13–16].

A solution of 5,11,17,23-tetrabromo-25,26,27,28-tetrabutoxy Calix[4]arene(**4**) (0.25 g, 0.26 mmol) in dry THF (5 mL) was stirred under argon and cooled to -78°C . Then butyllithium 1.6 M in hexane (0.033 g, 0.52 mmol) was added dropwise, and the mixture was stirred for 0.5 h at -78°C , and 1.5 h at room temperature. Again the solution cooled to -65°C and to the mixture was added dropwise

FIGURE 4: The complex structure between **6** and **8**. Lewis structure of **8**, **10**, and **11**.

trimethylchlorosilane. The result solution was stirred at room temperature for 12 h, and then the reaction mixture was refluxed for 2 h. The mixture was washed with 10 mL of saturated ammoniumchlorid. The organic layer was separated, dried over sodium sulfate, and the solvent was removed under reduced pressure. The purification of the residue by column chromatography (pet. ether/ethyl acetate, 99 : 1) gave 0.06 g (24%) of **6**.

$^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 0.16(s, 18H, SiMe₃), 0.91(t, 6H, J = 7 Hz), 0.96(t, 6H, J = 7 Hz), 1.86(m, 8H, J = 7 Hz), 2.12(m, 8H, J = 7 Hz), 3.45(d, 4H, J = 13 Hz), 4.09(t, 8H, J = 7 Hz), 4.40(d, 4H, J = 13 Hz), 6.21(s, 4H), 7.21 (s, 4H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ = 1.44, 10.73, 14.42, 19.68, 23.71, 31.16, 31.51, 31.89, 32.49, 115.59, 125.28, 131.43, 134.25, 136.89, 155.98.

TOF-MS (ESI-positive): Calcd for $\text{C}_{50}\text{H}_{70}\text{Br}_2\text{O}_4\text{Si}_2$, m/z = 951.0674 (M^+).found: 951.3159.

4.3. Synthesis of 5,17-Bis(trimethylsilyl)-25,27-dibutoxy-calix[4]arene 7. A stirred activated Li powder (0.01632 g, 2.4 mmol) in dry THF (3 ml) was cooled to -78°C and was stirred vigorously under argon for 30 min in -78°C . Then a solution of 5,17-dibromo-25,27-dibutoxy calix[4]arene **5** (0.38 g, 0.39 mmol) in dry THF(10 mL) was added dropwise, and the mixture was stirred for 0.5 h at -78°C . After warming to room temperature, the mixture was stirred at room temperature for 2 h. Then trimethylchlorosilane (0.8 mL, mmol) was added dropwise to the mixture, and the reaction was continued for 12 h. After this time, the suspense dark precipitate was filtered. Then, the filtrate was heated to reflux for 1.5 h, and after cooling, the mixture was evaporated under reduced pressure. The residue is then dissolved in the minimum amount of CH_2Cl_2 , and, to this solution, MeOH was dropwise added till further addition leads to turbidity and the obtained solution was let in -15°C for overnight. The obtained pure 5,17-bis(trimethylsilyl)-25,27-dibutoxy calix[4]arene(**7**) crystals (0.3 g, 78%) was filtered.

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ = 0.16(s, 18H, SiMe₃), 0.96 (t, 6H, J = 6.3 HZ), 1.86 (m, 4H), 2.12 (m, 4H), 3.45 (d, 4H, J = 12.95 Hz), 4.09 (t, 4H, J = 6.3 HZ), 4.40 (d, 4H, J = 12.95 Hz), 7.00 (m, 10H), 8.31 (s, 2H, OH).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ = 1.45, 14.52, 14.55, 19.84, 23.13, 29.80, 30.14, 31.68, 31.87, 32.37, 32.70, 76.96, 119.31, 119.38, 123.63, 125.68, 128.60, 128.84, 129.33, 130.15, 133.90, 152.42, 153.80.

TOF-MS (ESI-positive): Calcd for $\text{C}_{50}\text{H}_{72}\text{O}_4\text{Si}_2$, m/z = 792.4669 (M^+).found: 792.4344.

5. Conclusions

It is possible to recognize N-benzyloxycarbonyl-D-aspartate (NZDA) **8** with silylated calix[4]arene **6** and **7**, in polar solvent. The investigation shows that the silyl groups at upper calix[4]arene have great effect on binding process. Since NZDA is very similar to NMDA, as a channel blocker, the further studies could lead to introducing these new generation receptors **6** and **7** for clinically favorable NMDA receptor.

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