Pergamon

Tetrahedron Letters 39 (1998) 3873–3876

TETRAHEDRON
LETTERS

Bis-Amidinium Calixarenes: Templates for Self-Assembled Receptors

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Received 10 March 1998; accepted 24 March 1998

Abstract

The synthesis of two bis-amidinium calixarenes **3** and **4** has been achieved. Compounds **3** and **4** self-assemble with carboxylate salts *via* amidinium-carboxylate salt bridges producing ditopic receptor species.

Keywords: amidines; calixarenes; molecular recognition; complexation.

Introduction

The self-assembly of complex, rationally designed molecular architectures is an area of supramolecular chemistry that has attracted much attention [1]. Less attention has been paid to producing self-assembled 'supermolecules' capable of performing a function such as binding a 'third-party' guest species. Recently, very elegant examples of self-assembled receptors capable of binding anions have been reported by Lehn and co-workers [2] and Stoddart et al. [3].

The amidinium ion forms strong ion pairs in aprotic solvents with oxo-anions [4] and, like guanidinium, is a model system for the arginine-aspartate salt bridge found in zinc finger/DNA complexes, [5, 6] RNA stem loops [7] and the active site of dihydrofolate reductase [8]. Amidinium-carboxylate salt bridges have been employed in self-replicating systems [9] and in porphyrin containing molecular arrays designed for the study of electron transfer processes through salt bridges [10]. As part of a new research programme aimed at producing self-assembled receptors for 'third-party' guest species, two new bis-amidinium calixarenes have been synthesised [11]. These species form salt bridges with added carboxylate salts producing supermolecules containing binding sites for other guest species.

Synthesis

p-tert-Butylcalix[4]arene bis methylene nitrile **1** was synthesised according to literature procedures [12]. *para-tert*-Butylcalix[4]arene bis-*m*-tolunitrile **2** was synthesised by stirring a slurry of *p-tert*-butylcalix[4]arene with 2.2 equiv. of α-bromo-*m*-tolunitrile and potassium carbonate in dry acetone for three days affording the desired bis-substituted calixarene as a white powder in 88% yield. Garigipati's method of amidine synthesis [10, 13], i.e. using alkylchloroaluminium amides (obtained *in situ* from Me_3Al and NH_4Cl) to convert nitriles to amidinium moieties, was used to produce the new bis-amidinium chloride species **3** and **4** (Scheme 1). The bis-nitrile calixarenes were dissolved in a 0.67 M solution of methylchloroaluminium amide solution in toluene.

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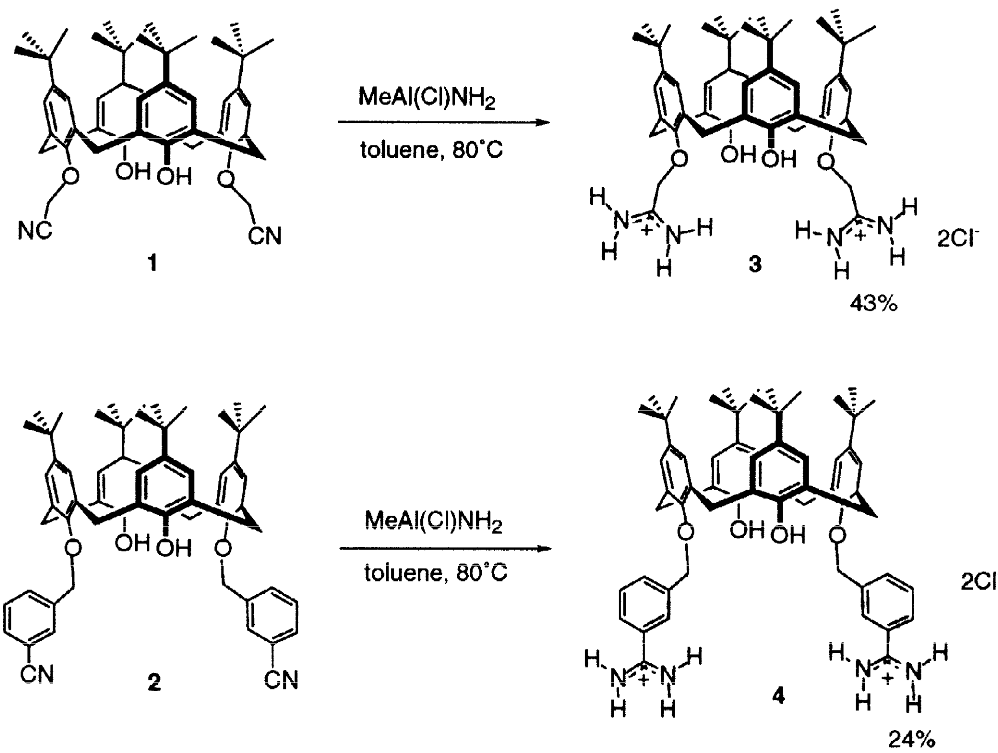
PII: S0040-4039(98)00650-9

The reaction mixture was heated at 80°C for 48 hours and then allowed to cool to room temperature and poured into a slurry of silica in chloroform. The slurry was stirred for 5 minutes and the silica then removed by filtration. The silica plug was washed with dichloromethane and then the combined organic layers reduced *in vacuo* and purified by column chromatography (silica gel CH_2Cl_2/MeOH 8:2) affording the bis-amidinium species **3**[1] and **4**[2] in 43 and 24% respective yields.



Scheme 1

Spectroscopic Studies: Supermolecule Formation

The assembly properties of calixarenes **3** and **4** with carboxylate salts have been studied using UV/vis spectroscopic techniques. In a typical experiment, a solution of calixarene (6.5 x 10^{-5}M) was added to a cuvette and the UV/vis spectrum recorded. A solution of a carboxylate salt (2 x 10^{-3}M) in DMSO was then titrated into the cuvette in sub-stoichiometric amounts and the spectrum recorded after each addition. The UV/vis spectra were then processed by the SPECFIT computer program [14]. This allows the number of UV absorbing species in solution and also the stability constants of supermolecules formed to be determined. As expected, in all cases a 2:1 carboxylate : calixarene complex formed in solution. The stability constants for the formation of the assemblies are shown in Table 1 for a variety of carboxylate salts. All the log β_2 values lie within the range 10.3 - 11.9.

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[1] Characterization data for **3**: δ^1H NMR (CD_3OD, 300MHz) 7.25 (s, 4H, ArH), 7.19 (s, 4H, ArH), 5.07 (s, 4H, OCH_2), 4.66 (br., m, 8H, NH), 4.15 (d, J=13.5 Hz, 4H, $ArCH_2Ar$), 3.59 (d, J=13.5 Hz, 4H, $ArCH_2Ar$), 3.36, (s, 2H, OH), 1.27 (s, 18H, $(CH_3)_3C$), 1.11 (s, 18H, $(CH_3)_3C$). δ^{13}C NMR (CD_2Cl_2/CD_3OD, 125MHz): 167.3, 150.5, 149.3, 148.0, 144.6, 132.8, 127.3, 126.9, 126.7, 70.8, 34.7, 34.2, 32.2, 31.5, 31.1. High resolution FABMS calc for $C_{48}H_{65}N_4O_4^+$ (761.5006). Found 761.5007.

[2] Characterization data for **4**: δ^1H NMR (CD_2Cl_2, 300MHz) 9.19 (s, 4H, NH), 9.00 (s, 4H, NH), 8.63 (s, 2H, tolH), 8.56 (s, 2H, OH), 8.21 (m, 2H, tolH), 8.13 (m, 2H, tolH), 7.29 (m, 2H, tolH) 7.13 (s, 4H, ArH), 7.11 (s, 4H, ArH), 5.23 (s, 4H, OCH_2), 4.35 (d, J=13.0Hz, 4H, CH_2), 3.48 (d, J=13.0Hz, 4H, CH_2), 1.22 (s, 18H, $(CH_3)_3C$), 1.17 (s, 18H, $(CH_3)_3C$). δ^{13}C NMR (CD_2Cl_2, 125MHz) 165.5, 150.0, 149.5, 148.9, 143.6, 139.0, 133.1, 131.9, 130.0, 128.6, 127.7, 127.4, 126.8, 126.2, 125.9, 77.3, 34.6, 34.1, 32.5, 31.7, 31.3. High resolution FABMS calc for $C_{60}H_{73}N_4O_4^+$ (913.5632). Found: 913.5636.

Tetrabutylammonium salt	**Compound 3 (log β_2)**	**Compound 4 (log β_2)**
4-nitrobenzoic acid	10.9	10.5
4-carboxybenzo-15-crown-5	11.9	11.0
meso-octamethylcalix[4]pyrrole-β-mono acid [15]	10.5	10.3

Table 1

Stability constants of carboxylates with compounds **3** and **4** in DMSO (errors are estimated to be ± 15%).

This method also allows the concentration of each species in solution to be determined throughout the titration. This is shown in Figure 1 for compound **3** and tetrabutylammonium 4-carboxybenzo-15-crown-5.

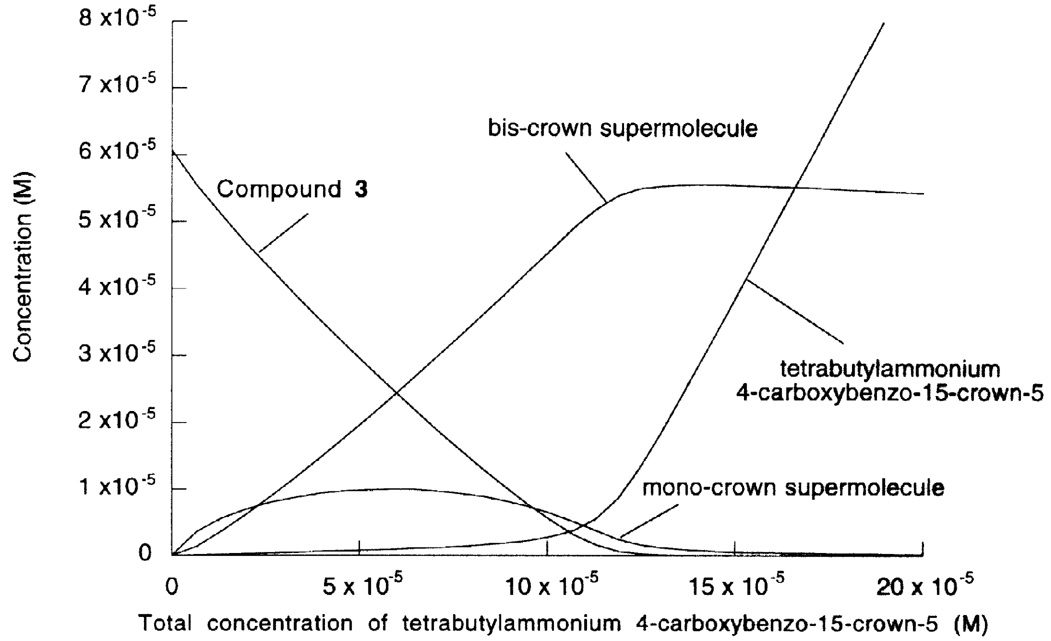
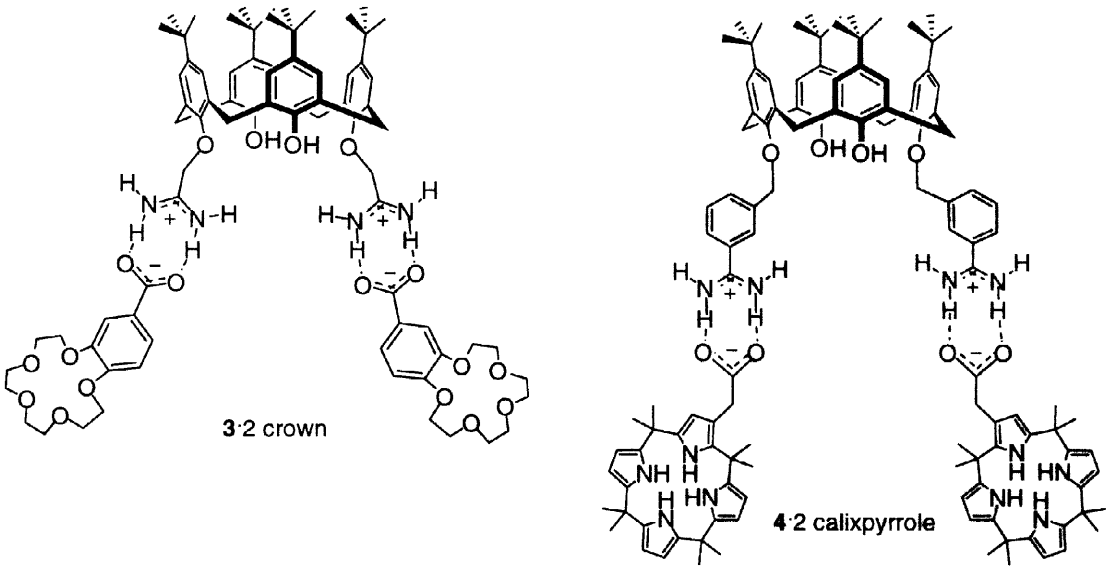


Figure 1

Thus compounds **3** and **4** can be used to assemble ditopic receptor species by mixing with an appropriately functionalised carboxylate (examples are shown in Figure 2).



3·2 crown

4·2 calixpyrrole

Figure 2

Examples of ditopic supermolecules

Conclusions

The bis-amidine calixarenes **3** and **4** provide access to a wide range of self-assembled structures simply by mixing the calixarene with an appropriate carboxylate. In the case of the examples shown in Figure 2, ditopic cation binding bis-crown ether and anion binding bis-calixpyrrole assemblies have been formed. The coordination chemistry of these non-covalently linked molecular arrays is currently under investigation in the author's laboratory and will be reported in due course.

Acknowledgments

I would like to thank the Royal Society for the award of a University Research Fellowship.

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