

Proceeding Paper

Synthesis and Complexing Ability of a New Type of Molecular Clips Based on Diaza-18-crown-6 or Diamino-Dibenzo-18-crown-6 with Pendant *p*-tert-butylcalix[4]arenes[†]

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Abstract: A convenient method for obtaining a new type of molecular clips based on diazacrown or diamino-dibenzocrown ethers with two calixarene molecules attached to a central fragment using an amide bond was developed. Clip **1**, based on diaza-18-crown-6, demonstrates exceptional selectivity toward barium in the alkaline earth metal series and forms 2:1 (L:M) complexes with copper and iron cations. With sodium and magnesium cations, clip **2**, based on diamido-dibenzo-18-crown-6, forms 1:2 (L:M) complexes. The same compound interacts with cations of copper, iron, and cadmium to form 1:1 complexes with low stability constant values.

Keywords: supramolecular chemistry; calixarenes; molecular clips; complexing properties



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1. Introduction

A distinctive feature of a synthetic membrane ion channel is the presence of ion binding sites at both headgroups of the channel. It was demonstrated [1,2] that molecules of this type act as carriers of cations into phospholipid membranes. In terms of the design of such structures, so-called “hydrophiles” can be said to embody the concept of three macrocycles in which the central macrocyclic ligand serves to pass the cation from one macrocyclic “portal” to another. The hydrophobic sidearms connecting the macrocycles are modified to regulate the length of the channel depending on the nature of the membrane. An idealized representation of the tunnel form of tris(macrocycle) based on the linking of three molecules of diaza-18-crown-6 was produced [1].

The design of molecular clips using a similar principle opens up wide possibilities for creating sensors, molecular switches, and synthetic receptors. The idea that inspired our research into creating molecular clips based on calixarenes and crown ethers is to have the calixarenes act as twin-headed amphiphiles with a difunctionalized crown ether as the central moiety. It should be noted that to date, one example of such a compound formed from calixarenes attached to a central diaza-18-crown-6 ether moiety has been described [3]. Both diazacrown ethers and diaminodibenzocrown ethers can be used as central fragments.

2. Materials and Methods

2.1. Chemistry

¹H and ¹³C NMR spectra were recorded from 10% solutions in chloroform-*d* on a Bruker Avance DRX 500 spectrometer, using tetramethylsilane as an internal reference. The mass spectra were recorded on an Agilent 6530 Accurate Mass Q-TOF spectrometer with

an LC/MS system. Absorption spectra in the UV region were recorded using a SPECORD 250 Plus spectrophotometer. All of the metal chlorides were of analytical grade.

Synthesis of clips: To a solution of 0.7 mmol (0.5 g) of mono(carboxymethoxy)-trihydroxy-*p*-tert-butylcalix[4]arene [4] and 0.3 mmol crown ether in 15 mL of THF (in the case of diaza-18-crown-6) or CH₃CN (in the case of diamino-dibenzo-18-crown-6) at −5 °C, 0.875 mmol (167.7 mg) of EDC was added with stirring. The reaction mixture was left at room temperature for 3–5 h. The solvent was evaporated in vacuo, the dry residue was dissolved in 50 mL of chloroform, and the solution was washed in succession with water, 10% aqueous HCl, and water again. The solvent was distilled off under reduced pressure, and the crude product was purified via recrystallization from heptane (clip 1) or methanol-water (10:1) (clip 2).

N,N'-bis[5,11,17,23-tetra-tert-butyl-25-mono(carbonylmethoxy)-26,27,28-trihydroxycalix[4]aren]diaz-18-crown-6 (Clip 1). White solid; yield 50%. ¹H NMR: δ 9.35 (brs, 2H, OH), 7.10 (d, 4H, arom.), 7.12–7.08 (m, 4H, arom.), 7.06–7.00 (m, 8H, arom., OH), 6.97 (s, 4H, arom.), 5.08 (s, 4H, CH₂CO), 4.58 (d, *J* = 12.20 Hz, 2H, ArCH₂Ar), 4.56 (d, *J* = 12.20 Hz, 2H, ArCH₂Ar), 4.34 (d, *J* = 13.14 Hz, 2H, ArCH₂Ar), 4.32 (d, *J* = 13.14 Hz, 2H, ArCH₂Ar), 3.61–3.82 (m, 24H, -CH₂CH₂-N, O-CH₂CH₂-O), 3.40 (d, *J* = 13.45 Hz, 4H, ArCH₂Ar), 3.38 (d, *J* = 13.45 Hz, 4H, ArCH₂Ar), 1.26 (s, 18H, (CH₃)₃C), 1.25 (s, 18H, (CH₃)₃C), 1.22 (s, 36H, (CH₃)₃C). ¹³C NMR: δ 169.89, 169.73, 151.70, 151.64, 148.51, 148.48, 148.21, 148.18, 147.84, 147.76, 143.11, 142.88, 142.84, 133.86, 133.83, 128.27, 128.00, 127.93, 127.80, 126.32, 126.29, 125.84, 125.82, 125.57, 72.51, 72.40, 71.14, 71.12, 70.90, 70.88, 70.69, 70.01, 69.84, 69.81, 69.42, 48.31, 48.12, 47.93, 47.63, 34.19, 33.95, 33.91, 33.08, 32.83, 32.76, 31.58, 31.47, 31.29, 29.72. MS ESI(+): *m/z* 1641.2598 [M + 1]⁺, 1663.3287 [M + Na]⁺.

N,N'-bis[5,11,17,23-tetra-tert-butyl-25-mono(carbonylmethoxy)-26,27,28-trihydroxycalix[4]arene]-6,7,9,10,17,18,20,21-octahydrodibenzo[b,k][1,4,7,10,13,16]hexaoxacyclooctadecin-2,14-diamine (Clip 2). Beige solid; yield 75%. ¹H NMR: δ 10.38 (brs, 2H, OH), 9.31 (s, 4H, OH), 7.42–7.37 (m, 2H, arom. crown), 7.25–7.20 (m, 4H, arom. crown), 7.15 (s, 4H, arom.), 7.08 (s, 4H, arom.), 7.05–6.99 (m, 8H, arom.), 4.78 (s, 2H, CH₂CO), 4.71 (s, 2H, CH₂CO), 4.40 (d, *J* = 11.26 Hz, 2H, ArCH₂Ar), 4.36 (d, *J* = 11.26 Hz, 2H, ArCH₂Ar), 4.23 (d, *J* = 12.51 Hz, 2H, ArCH₂Ar), 4.14–4.05 (m, 12H, ArCH₂Ar, O-CH₂CH₂-O), 3.98 (d, *J* = 12.83 Hz, 2H, ArCH₂Ar), 3.87–3.85 (m, 8H, O-CH₂CH₂-O), 3.36 (d, *J* = 12.20 Hz, 4H, ArCH₂Ar), 1.18 (s, 36H, (CH₃)₃C), 1.17 (s, 18H, (CH₃)₃C), 1.15 (s, 36H, (CH₃)₃C). ¹³C NMR: δ 169.97, 167.47, 166.51, 157.09, 152.13, 151.81, 150.74, 149.75, 148.46, 148.26, 148.12, 147.92, 144.89, 143.43, 142.18, 134.05, 133.79, 133.43, 132.12, 130.50, 129.02, 128.62, 128.24, 128.00, 127.25, 1126.63, 126.46, 126.09, 125.62, 123.88, 119.05, 69.41, 69.29, 68.27, 68.09, 50.11, 47.47, 34.53, 34.18, 33.80, 31.76, 31.67, 31.36. MS ESI(+): *m/z* 1769.3081 [M + 1]⁺.

2.2. Stability Constant Determination

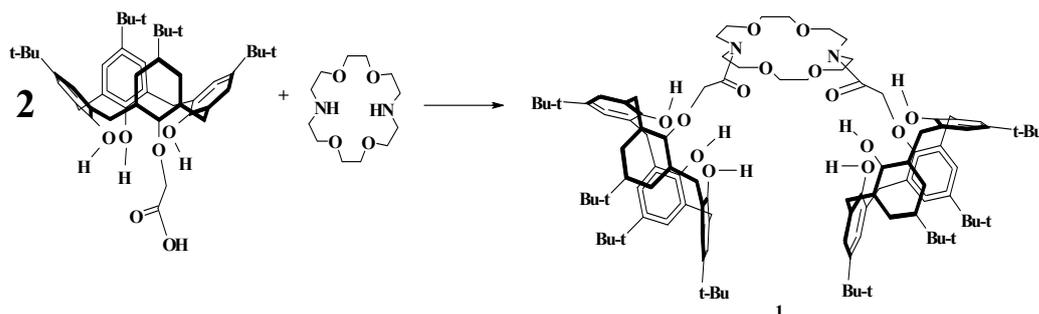
UV-vis titration experiments. A solution of calixarenes **1–2** (a concentration of about 2×10^{-5} – 3.5×10^{-5} M) in methanol was treated with increasing amounts of metal chloride solution (at a concentration of about 1 – 4×10^{-4} M) containing the proper ligand of the same concentration at 20 °C. The host concentration was kept constant, and the molar ratio of the guest increased with respect to the host over a range from 0.1:1 to 10(20):1 during titration. Absorbance measurements were carried out at six–ten wavelengths at which spectral changes were the most notable (220–320 nm) simultaneously, and sets of the obtained experimental values (4×21 points) were used for joint computer processing [5,6]. The data were processed using nonlinear least squares fitting SIRKO software [7].

In the case of studies involving transition metal and lead salts, a solution of a ligand of a certain concentration was prepared with the addition of 0.01 M tris(hydroxymethyl)aminomethane (TRIS) in methanol.

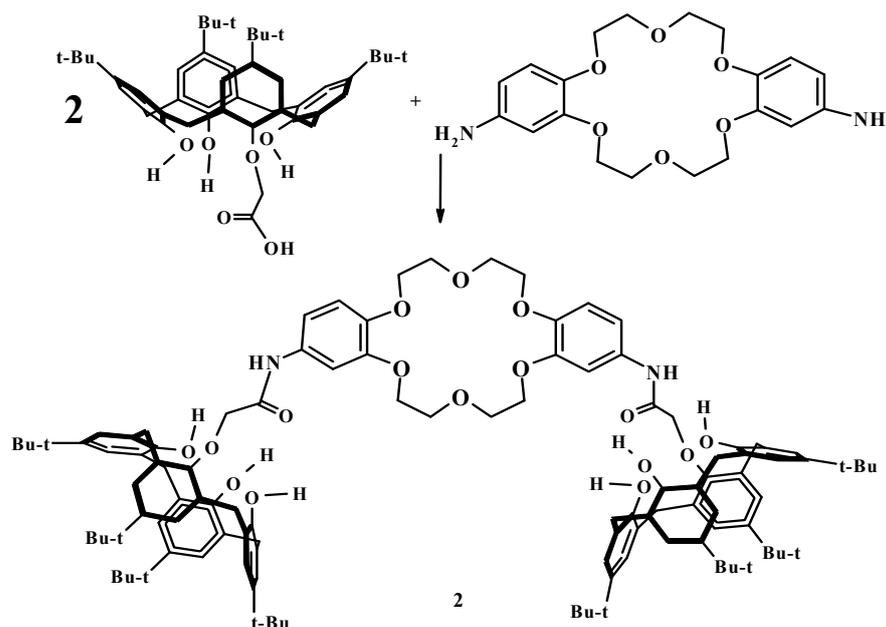
3. Results and Discussion

There are few examples of the synthesis and study of the properties of polycalixarenes or calixarenedendrimers which are connected to each other using various conformationally flexible spacer groups containing amide fragments [8–10].

Taking into account the simplicity of the acylation reaction involving carboxy-substituted calixarenes, the possibility to obtaining of bis(calixarene)diaza(or diaminodibenzo)crown ether via the acylation of diaza-18-crown-6 and diamino-dibenzo-18-crown-6 with the corresponding mono(carboxymethoxy)-substituted p-tert-butylcalix[4]arene was considered (Schemes 1 and 2).



Scheme 1. Synthesis of clip 1: EDC, THF, r.t., 5 h, yield—50%.



Scheme 2. Synthesis of clip 2: EDC, CH₃CN, r.t., 3 h, yield—75%.

The complexing abilities of clips 1 and 2 were studied using the spectrophotometric titration method. Clip 1 forms 1:1 complexes with sodium, potassium, and cesium cations in the series of alkali metals. The stability constants of the complexes with sodium and potassium cations are close and vary within $\lg K$ 3.6–4. The complex with cesium cations is characterized by a relatively low stability, $\lg K$ 2.74. In the series of alkaline earth metals, clip 1 demonstrates exceptional selectivity toward barium cations, with $\lg K$ 4.16 (Table 1).

Table 1. Stability constants ($\lg K_n$) of the complexes of clips **1** and **2** with alkali and alkaline earth metal cations in MeOH.

Comp.		Cation						
		Na ⁺	K ⁺	Cs ⁺	Mg ²⁺	Ca ²⁺	Sr ²⁺	Ba ²⁺
1	$\lg K_{11}$	3.9	3.66	2.74	- *	-	-	4.16
	$\lg K_{12}$	2.0	5.07	7.1	1.75	3.88	4.25	4.94
2	$\lg K_{12}$	7.47			5.75			

* The changes in the spectrum were too small and it was impossible to calculate the binding constant.

We examined the ability of clip **1** to interact with transition metal cations using the four cations iron (III), copper, cobalt, and cadmium, and lead cations were also added to this series. With the cobalt, cadmium, and lead cations, N,N'-bis(calixarene)dicarbonyl-diazacrown ether forms complexes of a 1:1 composition. Note that the stability constants of complexes with "large" cadmium and lead cations are relatively high and vary within $\lg K$ 4.4–5.23. Somewhat unexpected for us were the results of studying the complex formation of the same compound with iron and copper cations. With these cations, clip **1** can form not only 1:1 but also 2:1 (L:M) complexes with $\lg K_{21} \approx 7$ (Table 2).

Table 2. Stability constants ($\lg K_n$) of the complexes of clips **1** and **2** with cations of d- and p-elements in MeOH.

Comp.		Cation				
		Fe ³⁺	Co ²⁺	Cu ²⁺	Cd ²⁺	Pb ²⁺
1	$\lg K_{11}$	1.57	2.4	0.41	4.40	5.23
	$\lg K_{21}$	7.33		7.03		
2	$\lg K_{11}$	1.98	- *	2.20	3.12	-

* The changes in the spectrum were too small, and it was impossible to calculate the binding constant.

Clip **2**, based on diamidodibenzo-18-crown-6 ether, exhibits a different behavior in the processes of complexation with both s-element cations and transition metal cations. In the series of alkali metals, clip **2** forms binuclear complexes with sodium cations. Also, the stability of the complexes with potassium and cesium cations are significantly higher compared to the results obtained for clip **1** (Table 1). However, both compounds do not demonstrate an affinity for rubidium cations. When clip **2** interacts with cations of alkaline earth metals, the formation of stable complexes with cations of all representatives of this series is observed. But if clip **2** forms 1:1 complexes with calcium, strontium, and barium cations, then when interacting with magnesium cations, the formation of monoligand binuclear complexes with $\lg K_{12}$ 5.75 is observed. Figure 1 shows a graph of the dependence of the stability of the complexes and the selectivity of the ligands on the nature of the cation of the s-elements (Figure 1).

In contrast to the compound based on diazacrown ether, clip **2** containing diamidodibenzo-crown ether as a central fragment does not demonstrate a high affinity for transition metal cations. When studying the complexing ability of this compound, we observed the formation of exclusively mononuclear complexes with copper, iron, and cadmium cations with a minimum $\lg K$ value for complexes with iron cations of 1.98 and a maximum $\lg K$ value of 3.12 for complexes with cadmium cations. The spectral changes with cations of cobalt and lead were too small, and it was impossible to calculate the binding constants (Table 2).

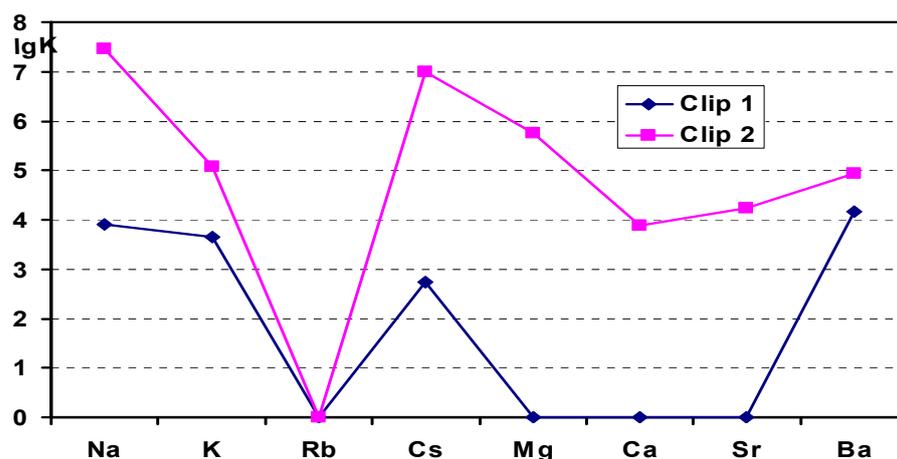


Figure 1. Dependence of the stability of the complexes and the selectivity of the ligands on the nature of the cation of the s-element. In case of clip 2, data $\lg K_{12}$ for complexes with Na^+ and Mg^{2+} are given.

4. Conclusions

Thus, we obtained new examples of molecular clips based on crown ethers difunctionalized at nitrogen atoms in which calixarene molecules act as pendant headgroups. We compared the complexing abilities of the novel members of these series based on diaza-18-crown-6 ether and diamido-dibenzo-18-crown ether. The exceptional selectivity of *N,N'*-bis(calixarene-carbonyl)diaza-18-crown-6 toward barium cations in the series of alkaline earth metals and the possibility of forming binuclear monoligand complexes with sodium and magnesium cations with the participation of *N,N'*-bis(calixarene)diamido-dibenzo-18-crown-6 were demonstrated.

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