chemistry proceedings

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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† Presented at the 27th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-27), 15–30 November 2023; Available online: https://ecsoc-27.sciforum.net/.

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 bonds has been developed. A clip **1** based on diaza-18-crown-6 demonstrates exceptional selectivity toward barium in the alkaline earth metal series and forms the complexes 2:1 (L:M) with copper and iron cations. With sodium and magnesium cations clip **2** based on diamido-dibenzo-18-crown-6 forms complexes 1:2 (L:M). The same compound interacts with cations of copper, iron and cadmium to form 1:1 complexes with low values of stability constants.

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

Citation: Kulygina, E.; Alekseeva, E.; Rakipov, I.; Kirichenko, T. 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. *Chem. Proc* **2023**, *14*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Name

Published: 15 November 2023

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 cation carriers into phospholipid membranes. In terms of the design of such structures, so-called "hydrophiles" can be said to embody the concept of three macrocycles, where 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 [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 difunctionalized crown ether as the central moiety. It should be noted that to date, one example of such compounds formed from calixarenes attached to central diaza-18-crown-6 ether moiety has been described [3]. Not only diazacrown ethers, but also diaminodibenzocrown ethers can be used as such central fragments.

2. Materials and Methods

2.1. Chemistry

The ^{1}H and ^{13}C NMR spectra were recorded from 10% solutions in chloroform-d on a Bruker Advance DRX 500 spectrometer using tetramethylsilane as internal reference. The mass spectra were recorded on an Agilent 6530 Accurate Mass Q-TOF spectrometer with LC/MS System. Absorption spectra in the UV region were recorded using a spectrophotometer SPECORD 250 Plus. 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 THF (in case of diaza-18-crown-6) or CH_3CN (in case of diamino-dibenzo-18-crown-6) at −5 °C a 0.875 mmol (167.7 mg) EDC was added with stirring. The reaction mixture was left at room temperature for 3–5 h. The solvent was evaporated in vacuo and 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 crude product was purified by 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]diaza-18-crown-6 (Clip 1). White solid; yield 50%. ^{1}H 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, CH_2CO), 4.58 (d, *J* = 12.20 Hz, 2H, $ArCH_2Ar$), 4.56 (d, *J* = 12.20 Hz, 2H, $ArCH_2Ar$), 4.34 (d, *J* = 13.14 Hz, 2H, $ArCH_2Ar$), 4.32 (d, *J* = 13.14 Hz, 2H, $ArCH_2Ar$), 3.61–3.82 (m, 24H, -CH_2CH_2-N, O-CH_2CH_2-O), 3.40 (d, *J* = 13.45 Hz, 4H, $ArCH_2Ar$), 3.38 (d, *J* = 13.45 Hz, 4H, $ArCH_2Ar$), 1.26 (s, 18H, $(CH_3)_3C$), 1.25 (s, 18H, $(CH_3)_3C$), 1.22 (s, 36H, $(CH_3)_3C$). ^{13}C 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,к][1,4,7,10,13,16]hexaoxacyclo octadecin-2,14-diamine (Clip 2). Beige solid; yield 75%. ^{1}H 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, CH_2CO), 4.71 (s, 2H, CH_2CO), 4.40 (d, *J* = 11.26 Hz, 2H, $ArCH_2Ar$), 4.36 (d, *J* = 11.26 Hz, 2H, $ArCH_2Ar$), 4.23 (d, *J* = 12.51 Hz, 2H, $ArCH_2Ar$), 4.14–4.05 (m, 12H, $ArCH_2Ar$, O-CH_2CH_2-O), 3.98 (d, *J* = 12.83 Hz, 2H, $ArCH_2Ar$), 3.87–3.85 (m, 8H, O-CH_2CH_2-O), 3.36 (d, *J* = 12.20 Hz, 4H, $ArCH_2Ar$), 1.18 (s, 36H, $(CH_3)_3C$), 1.17 (s, 18H, $(CH_3)_3C$), 1.15 (s, 36H, $(CH_3)_3C$). ^{13}C 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

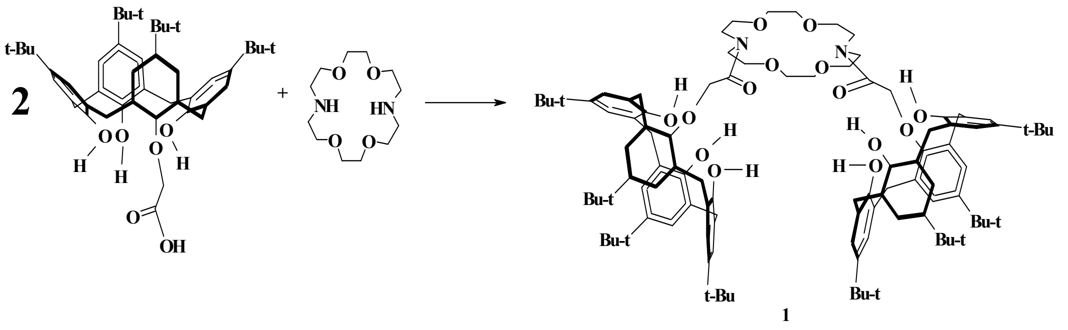
UV–vis titration experiments. A solution of calixarenes **1**–**2** (concentration about $2 \cdot 10^{-5}$–$3.5 \cdot 10^{-5}$ M) in methanol was treated with increasing amounts of metal chloride solution (concentration about 1–$4 \cdot 10^{-4}$ M) containing proper ligand of the same concentration at 20 °C. The host concentration was maintained constant and the molar ratio of guest increased with respect to the host over the range 0.1:1 to 10(20):1 during the titration. The 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 with the 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.

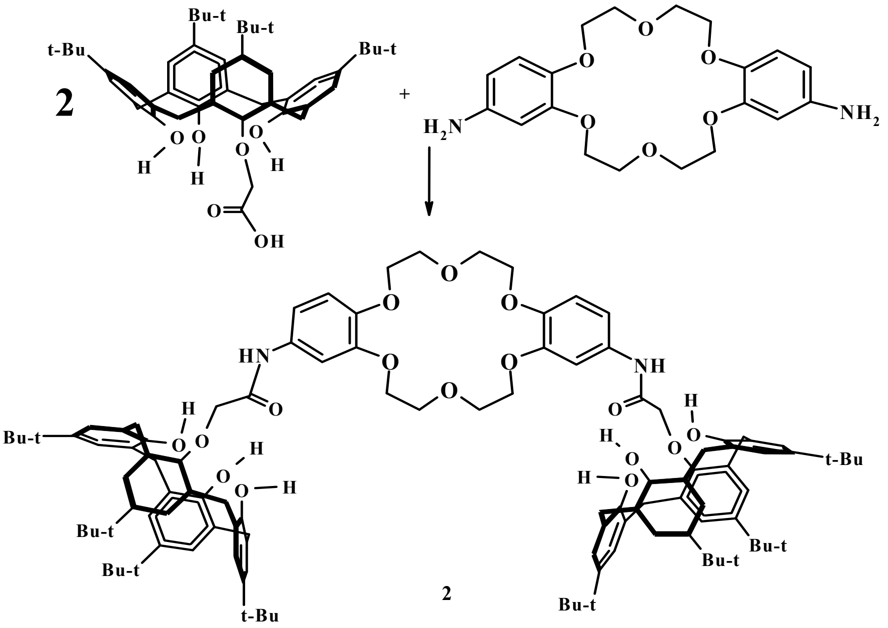
3. Results and Discussion

There are few examples of the synthesis and study of the properties of polycalixarenes or calixarene-dendrimers, 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 by 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, CH_3CN, r.t., 3 h, yield-75%.

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

We examined the ability of clip **1** to interact with transition metal cations using the four cations-iron (III), copper, cobalt, cadmium and also a lead cations were added to this series. With cobalt, cadmium and lead cations, N,N′-bis(calixarene)dicarbonyl-diazacrown ether forms complexes of 1:1 composition. Note that the stability constants of complexes with "large" cadmium and lead cations are relatively high and vary within log$K$ 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 lgK_{21} ≈ 7 (Table 2).

Table 1. Stability constants (lgK_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	lgK_{11}	3.9	3.66	2.74	- *	-	-	4.16
2	lgK_{11}	2.0	5.07	7.1	1.75	3.88	4.25	4.94
	lgK_{12}	7.47			5.75			

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

Clips **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 the 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 a monoligand binuclear complexes with logK_{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).

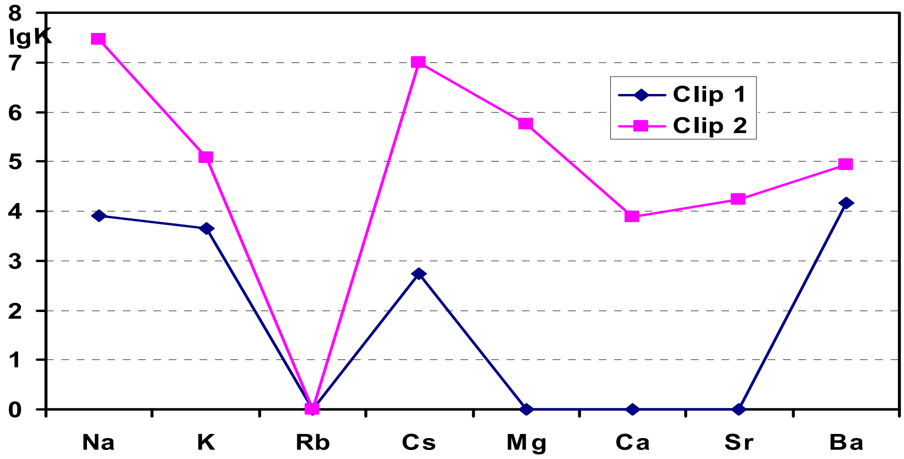


Figure 1. Dependence of the stability of the complexes and the selectivity of the ligands on the nature of the cation of the s-element. In case of clip **2**, data lgK_{12} for complexes with Na^+ and Mg^{2+} are given.

In contrast to the compound based on diazacrown ether, the clip **2** containing diamido-dibenzo-crown ether as a central fragment does not demonstrate 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 changes in spectrum with cations of cobalt and lead were too small and it was impossible to calculate the binding constants (Table 2).

Table 2. Stability constants (lgK_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	lgK_{11}	1.57	2.4	0.41	4.40	5.23
	lgK_{21}	7.33		7.03		
2	lgK_{11}	1.98	- *	2.20	3.12	-

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

4. Conclusions

Thus, we have 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(calixarenecarbonyl)diaza-18-crown-6 towards barium cations in the series of alkaline earth metals and the possibility to forming binuclear monoligand complexes with sodium and magnesium cations with the participation of N,N′-bis(calixarene)diamido-dibenzo-18-crown-6 have been demonstrated.

Author Contributions: Conceptualization, E.A., E.K.; methodology, E.K., E.A.; investigation, E.K., E.A., I.R.; writing—original draft, E.K., E.A.; writing—review and editing, T.K.; project administration, T.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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