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Synthesis and Complexation of New Molecular Clips Based on Benzoaza-15-Crown-5 and Diphenylglycoluril with Alkali and Alkaline Earth Metal Cations †

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Abstract: New molecular clips were obtained by reacting benzoaza-15-crown-5 derivatives with diphenylglycoluryl bis-ether in polyphosphoric acid (PPA). The complexing properties of the synthesized compounds depend on the nature of the substituent at the nitrogen atoms of the crown ether fragments have been demonstrated. The unsubstituted clip interacts weakly with alkali cations, but forms very stable 2:1 (L:M) complexes with alkaline earth metal cations. Among the alkali metal cations, the N-Me derivative forms the most stable complexes with K+ and Rb+, and the clip containing an ester group forms the most stable complexes with the sodium cation.

Keywords: supramolecular chemistry; molecular clips; diphenylglycoluril; benzoaza-15-crown-5; complexing properties

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1. Introduction

Glycoluril and its derivatives are among the most commonly used fragments in the construction of synthetic receptors. It should be noted that all glycoluril-based receptors contain methylene (bridging) bonds, due to which they have a U-shape, which provides the formation of a pseudocavity. Nolte in 1991 called such receptors molecular clips [1]. We have previously obtained a series of molecular clips based on diphenylglycoluril and benzo(dibenzo)crown ethers and studied their complexation with alkali metal cations and paraquat [2–6]. Among the obtained crown ethers, benzoazacrown ethers have received relatively little attention. The advantage of these compounds is the possibility of introducing substituents with different nature at the nitrogen atom, which should lead to a change in their complexation properties. To date, no molecular clips with benzoazacrown ether fragments have been demonstrated. Only one bis(benzoaza-15-crown-5) has been described, in which the crown ether rings are connected by a trimethylene linker [7]. The subject of this work was the synthesis of molecular clips based on diphenylglycoluril and benzoaza-15-crown-5 derivatives.

2. Materials and Methods

2.1. Chemistry

The ^1H and ^{13}C NMR spectra were obtained from 10% solutions in chloroform-d on a Bruker Advance DRX 500 spectrometer using tetramethylsilane as internal reference. Fast atom bombardment (FAB) mass spectrometry was performed on a VG 70-70EQ mass spectrometer, equipped with an argon primary atom beam, and an *m*-nitrobenzyl alcohol matrix was utilized. Absorption spectra in the UV region (200–310 nm) were recorded using a spectrophotometer SPECORD 250 Plus. All of the metal chlorides were of analytical grade. Benzo-15-crown-5 **1** was prepared according to the procedure described in [8].

N-(Methoxycarbonylmethyl)benzoaza-15-crown-5 (2). An oily substance; yield 78%. A 0.03 mol (3.2 mL) of bromomethyl acetate was added to a solution of 0.02 mol (5.35 g) of crown ether **1** and 0.04 mol (5.56 mL) of triethylamine in 50 mL of methyl alcohol, and the reaction mixture was boiled for 24 h. The solvent was evaporated under reduced pressure to dryness, the resulting residue was recrystallized from heptane. ^{1}H NMR: δ 6.91–6.86 (m, 4H, ArH), 4.17–4.12 (m, 8H, CH_2-CH_2O), 3.96 (t, 2H, CH_2-CH_2O), 3.87 (t, 2H, CH_2-CH_2O), 3.49 (c, 2H, N-CH_2CO), 2.97 (m, 7H, CH_3, CH_2N). ^{13}C NMR: δ 171.58, 148.82, 121.18, 113.59, 70.94, 70.50, 68.83, 59.16, 58.70, 51.93. FAB-MS (+): *m/z* (%): 354 $[M+H]^+$ (100).

N-Methylbenzoaza-15-crown-5 (3). White solid; yield 72%. A 10.5 mmol (0.483 g) of formic acid (99.5%, d 1.22) and 5.25 mmol (0.1575 g) of a 40% formalin solution were added to 5.0 mmol (1.336 g) of benzoaza-15-crown-5 **1**. The reaction mixture was heated in a water bath for 8 h, cooled, neutralized with a saturated sodium carbonate solution, and the pH was adjusted to 9. The product was extracted with chloroform (3 × 50 mL). The combined chloroform extracts were dried over anhydrous $MgSO_4$. Chloroform was evaporated under reduced pressure, the product was extracted from the obtained residue with boiling hexane with the addition of 10–15% ethyl acetate (3 × 70 mL). After evaporation of the solvents, the product was additionally recrystallized from hexane with the addition of ethyl acetate. ^{1}H NMR: δ 6.61–6.70 (m, 4H, ArH), 4.13 (t, 4H, CH_2O), 3.67 (t, 4H, CH_2O), 3.39 (t, 4H, OCH_2CH_2N), 3.25 (t, 4H, CH_2N), 2.34 (s, 3H, CH_3). ^{13}C NMR: δ 148.80, 121.16, 113.67, 70.94, 70.49, 67.85, 59.15, 45.53. FAB-MS (+): *m/z* (%): 282 $[M+H]^+$ (100).

Synthesis of clips: The mixture of 2.65 mmol (1g) bis(ether) **7** and 5.42 mmol of the corresponding benzoazacrown ether **1–3** in PPA was intensively stirred at 85–90 °C until the reagents were completely dissolved and for another 40 min. The cooled mixture was poured into water (150 mL) and stirred for 2–3 h. The precipitate was filtered, and an aqueous solution of Li_2CO_3 was added. The resulting oily suspension was extracted with chloroform (2 × 50 mL). The combined chloroform solutions were dried over $MgSO_4$, and the chloroform was distilled off under reduced pressure. Further processing was performed as described below.

Clip 4. Yield 27%. Benzene (50 mL) was added to the oily residue with stirring. The crystalline product was filtered off. Mp: 248–249 °C. ^{1}H NMR: δ 7.28–7.14 (m, 10H, Ph), 7.06 (s, 4H, ArH), 5.85 (s, 2H, NH), 4.63 (d, *J* = 16.1 Hz, 4H, N-CH_2), 4.12–3.73 (m, 28H, O-CH_2CH_2-O, N-CH_2), 2.78–2.75 (m, 8H, O-CH_2CH_2-N). ^{13}C NMR: δ 160.05, 1467.84, 137.29, 127.71, 127.69, 126.83, 124.88, 110.37, 86.52, 71.50, 70.98, 70.50, 65.84, 57.61. FAB-MS (+): *m/z* (%): 877 $[M+H]^+$ (100).

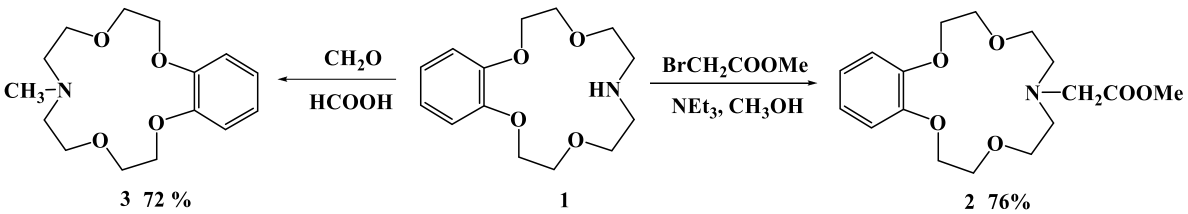
Clips 5 and 6. Beige solid; yield 40% for clip **5**, 42% for clip **6**. The residue was dissolved in benzene, washed with water (2x50 mL), and the benzene was distilled off under reduced pressure. The crystalline residue was dried in a vacuum at 60–70 °C. **Clip 5**: Mp: 172–173 °C. ^{1}H NMR: δ 7.11–7.04 (m, 10H, Ph), 6.76 (s, 4H, ArH), 4.65 (d, *J* = 16.1 Hz, 4H, NCH_2), 4.14–3.70 (m, 28H, O-CH_2CH_2-O, N-CH_2), 2.73–2.70 (m, 8H, O-CH_2CH_2-N), 2.33 (s, 6H, N-CH_3).^{13}C NMR: δ 157.72, 147.51, 133.77, 129.90, 128.58, 128.21, 115.31, 85.35, 69.62, 69.34, 69.13, 56.68, 44.93, 44.13. FAB-MS (+): *m/z* (%): 905 $[M+H]^+$ (100). **Clip 6**: Mp: 121–122 °C. ^{1}H NMR: δ 7.36–7.10 (m, 10H, Ph), 6.78 (s, 4H, ArH), 4.68 (d, *J* = 15.74 Hz, 4H, N-CH_2), 4.13 (d, *J* = 15.74 Hz, 4H, N-CH_2), 4.06–3.93 (m, 24H, 6H, O-CH_2CH_2-N, O-CH_2CH_2-O, N-CH_2), 3.81 (s, 6H, $COOCH_3$), 3.28–3.09 (m, 8H, O-CH_2CH_2-O), 2.79 (br.s, 4H, CH_2-$COOCH_3$). ^{13}C NMR: δ 157.70, 147.34, 133.61, 129.85, 128.69, 128.55, 128.24, 128.15, 115.17, 85.32, 69.25, 69.19, 68.90, 56.63, 56.37, 44.85, 43.82. FAB-MS (+): *m/z* (%): 1021 $[M+H]^+$ (100).

2.2. Stability Constant Determination

UV-vis titration experiments. A solution of molecular clip **4–6** (concentration about 1×10^{-5}–5×10^{-5} M) in methanol was treated with increasing amounts of alkali metal chloride solution (concentration about $2 \cdot 10^{-3}$ M) containing proper molecular clip 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 30:1 during the titration. The obtained solutions were leaving at room temperature for 12–15 h to achieve equilibrium. The absorbance measurements were carried out at four wavelengths, at which spectral changes were the most notable (200–310 nm) simultaneously, and sets of the obtained experimental values (4 × 30 points) were used for joint computer processing. The data were processed with the nonlinear least squares fitting MatLab [9] software.

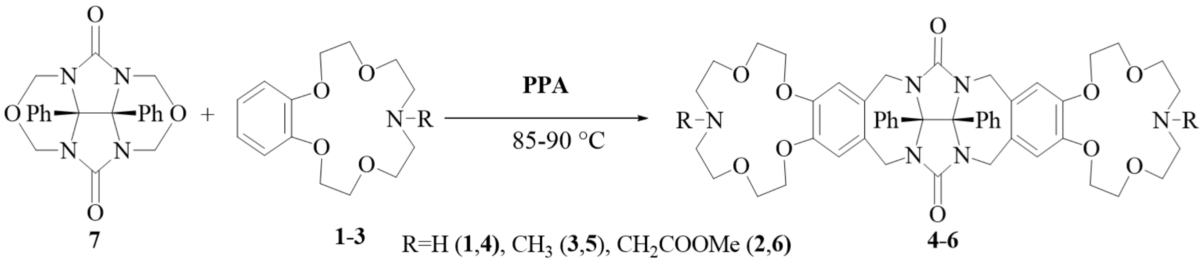
3. Results and Discussion

Alkylation of crown ether **1** with bromomethyl acetate in methanol in the presence of triethylamine gave derivative **2** with a 76% yield. Alkylation of **1** with formalin in 99.5% formic acid gives the N-methylbenzoaza-15-crown-5 **3** with a 72% yield (Scheme 1).



Scheme 1. Synthesis of benzoaza-15-crown-5 derivatives **2** and **3**.

For the synthesis of molecular clips **4–6**, we used the previously developed method for obtaining clips with fragments of benzocrown ethers, based on heating 2.1 equivalents of crown ether with one equivalent of bis-ether **7** in polyphosphoric acid (PPA) [2] (Scheme 2).



Scheme 2. Synthesis of molecular clips **4–6**.

It should be noted that in the case of crown ether **1**, complete conversion of the reagents required the reaction to be carried out at a higher temperature (85–90 °C instead of 80 °C). The total reaction time is 3–4 h, during which the reagents are completely dissolved, plus an additional 40 min of stirring. In the original method [2], the total reaction time is 40 min. The yield of molecular clip **4** was less than expected (27%). The yields of clips **5** and **6** were 40–42%. Clip **6** was isolated from the reaction medium in the form of a sodium complex that is difficult to destroy. Such a strong interaction may indicate the participation of oxygen atoms of the ester group in coordination with the sodium ion. Therefore, we changed the product isolation procedure and used Li_2CO_3 instead of NaOH.

The stability of complexes of molecular clips **4–6** with alkali and alkaline earth metal cations was determined by spectrophotometric titration (Table 1). Data for clip **8** with a fragment of benzo-15-crown-5 are given for comparison [3].

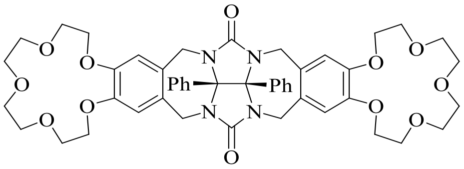


Figure 1. Clip **8**.

Table 1. Stability constants (lg*K*) of the complexes of clips **4**–**6**, **8** with alkali and alkaline earth metal cations in MeOH at 20 °C.

Comp.		**Cation**						
		Na$^+$	**K$^+$**	**Rb$^+$**	**Cs$^+$**	**Ca^{2+}**	**Sr^{2+}**	**Ba^{2+}**
4	lgK_{11}	2.94	**	**	**	2.36	0.86	-
	lgK_{21}	-	-	-	-	-	6.86	>7
5	lgK_{11}	2.87	3.18	3.31	2.79	3.18	3.40	3.23
6	lgK_{11}	3.90	3.51	3.69	2.99	2.88	3.99	5.57
	lgK_{21}	-	-	-	-	-	-	6.33
8 *	lgK_{11}	4.13	6.25	6.34	3.74			

* Studied with alkali metal ions only; ** Too small changes in spectra*.

As follows from the Table 1 data, the complexing properties of molecular clips **4**–**6** strongly depend on the nature of the substituent at the nitrogen atoms. The tendency of selectivity toward to cations of alkaline metals, which is demonstrated by clips **5** and **8** coincides. This suggests the formation of intramolecular sandwich complexes in the case of potassium and rubidium ions. But the observed constants for clip **5** are significantly lower (up to 3 orders of logarithmic units for potassium and rubidium). Molecular clip **4** with unsubstituted nitrogen atoms interacts very weakly with alkali metal cations. It was possible to calculate the stability constant only for the sodium ion. Much stronger interactions with alkaline earth metal cations for clip **4** are observed. With large cations of strontium and barium, very stable complexes of composition 2:1 (L:M) are formed (logK_{21} > 7 for Ba^{2+}). Clip **6** with an ester group at nitrogen atoms, as expected, forms the most stable complexes among alkaline cations with sodium ion. The stability constant value of this complex is an order of magnitude higher than for the other two clips, and is close to the value observed for clip **8**. Among alkaline earth cations, the stability of the complexes increases with increasing cation size. Moreover, the formation of stable complexes of both 1:1 and 2:1 compositions were observed with the barium ion.

4. Conclusions

New molecular clips with fragments of diphenylglycoluril and benzoaza-15-crown-5 have been obtained. It have been demonstrated that their complexation depends on the nature of the substituent at the nitrogen atom. In general, clips with benzoaza-15-crown-5 form less stable complexes with alkali metal cations than their analogue with the benzo-15-crown-5 fragment. With large alkaline earth cations, very stable complexes of composition 2:1 (L:M) are formed.

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