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Synthesis, crystal structure, and alkali metal picrate extraction capabilities of molecular clips based on diphenylglycoluril and benzocrown ethers

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ABSTRACT

A convenient method for the synthesis of a series of molecular clips based on the diphenylglycoluril framework and benzocrown ether moieties by the reaction of bis(cyclomethoxymethylene)diphenylglycoluril with benzocrown ethers in polyphosphoric acid is proposed. X-ray diffraction analysis of molecular clips with the benzo-12-crown-4 and benzo-15-crown-5 fragments showed that both compounds are chloroform solvates with the stoichiometry clip:chloroform 1:1. By theoretical and experimental methods the existence of obtained clips in an *anti–anti* conformation was proved. The complexation properties of the obtained molecular clips were examined toward alkali metal and ammonium ions by FABMS spectrometry and extraction experiments.

1. Introduction

Creating synthetic receptors that can effectively bind organic and inorganic, neutral and charged substrates requires a fine tuning of their topological and electronic properties.[1] The basis of the receptor/substrate interaction are specific, mostly nonvalent interactions: relatively strong and therefore often dominant hydrogen bonding, ion pair interactions, hydrophobic effect, noncovalent interaction of arenes with other aromatic molecules (π–π and C–H···π interactions) or with positively charged ions (cation–π interactions).[2] Besides commonly used cyclic and therefore well preorganized receptors, such as crown ethers,[3a,b] calixarenes,[3c] cyclophanes,[3d] and compounds of similar type, a promising group in this respect are the non-cyclic receptors having a molecular pseudocavity with geometric parameters, which are easily to change. These receptors can be considered as molecular tweezers or clips that selectively bind electron-deficient neutral aromatic and aliphatic substrates, as well as organic and inorganic cations.[4] Lately, special attention has been drawn to conformationally rigid compounds containing a glycoluril fragment, diphenylglycoluril in particular. Using a variety of synthetic approaches, a large number of tetrakis derivatives of diphenylglycoluril was obtained. They represent U-shaped molecular receptors containing as donor centers aromatic, heterocyclic, and polyoxyethylene fragments, and combinations thereof.[5]

We have previously described the new representatives of bis(-benzocrown ethers),[6] in which two benzocrown ethers are bound by the diphenylglycoluril fragment (first described by Nolte et al.).[7] Bis(crown ethers) are interesting because the interaction of individual crown ether units within their structure can act independently (the statistical complex formation) or with the appearance of both positive and negative cooperative or allosteric effects.[8] Positive effects are usually observed during the formation of sandwich type complexes of bis(crown ethers) with the large metal cations (Fig. 1a), which can't fit into the cavity of the separate

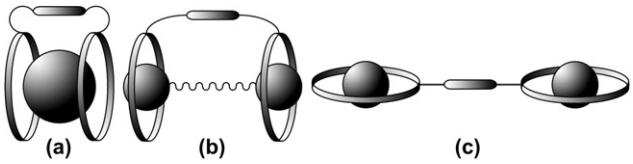

Fig. 1. Schematic representation of cooperative effect: (a, b) positive and (c) negative/independent guest interaction.

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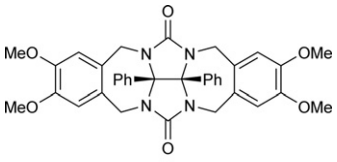
macrocycle, or by interaction of bis(crown ethers) with bifunctional guest molecules, such as diamines or dicarboxylates (Fig. 1b).

We now report the syntheses of a series of molecular clips **1**–**5** based on the diphenylglycoluril framework and benzocrown ether moieties; and preliminary data of the alkali metal binding properties by these host molecules, which have been evaluated via picrate extraction and fast atom bombardment ionization–mass spectrometric (FABMS) methods.

2. Results and discussion

2.1. Synthesis

For the first time, the synthesis of molecular clip **2** based on the diphenylglycoluril and benzocrown ether was described by Nolte et al. with 92% yield (method A).[7] Using a similar reaction with veratrole, the authors[7] obtained product **6** with only 40% yield, although the yield decrease compared to **2** is not explained.



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However, despite the high yield mentioned by the authors of compound **2**, we were able to obtain a molecular clip based on B18C6 **3** only with 50% yield.[6b] In this case, the isolation of the product is considerably complicated by the necessity to remove the intermediate complex **3** from the tin salts. The main disadvantages of the following method are utilizing a relatively hard to get tetrachloride **7**, its hydrolytic instability and complications with isolation of target compounds from the Lewis acid adducts.

Previously we have shown that polyphosphoric acid (PPA) is an excellent catalyst and medium for the synthesis of various amidomethyl derivatives of benzocrown ethers in the Chernyak–Einhorn reaction conditions.[9] Meanwhile, products of 4,5-disubstitution in the benzene ring are obtained with high yields after short (up to 30 min) heating of the mixture of reagents in PPA.

Synthetic precursors of tetrachloride **7**, tetraol **9**, and its bisether **8**, are also widely used reagents for building various molecular clips.[7] On other hand, the presence of the –CO–N(H)–CH_2–O– fragment allows us to consider **8** and **9** to be classic Einhorn reagents. This was a reason for the synthesis based on the above-mentioned conditions of the new type of molecular clips containing fragments of benzocrown ethers, as shown on Scheme 1.

Molecular clips (**1**–**5**) were synthesized by heating at 80 °C the mixture of 1 equiv **8** (method B) or **9** (method C) and 2.1 equiv of corresponding benzocrown ether in PPA for 30 min. Using bisether **8** as starting reagent allows considerably higher yields of target products (>70%) compared to tetraol **9** (~40%).[6a] Possible explanation of this fact is the elimination of formaldehyde in the conditions of reaction with formation of linear polycondensation products, which decreases the yields of target compounds.

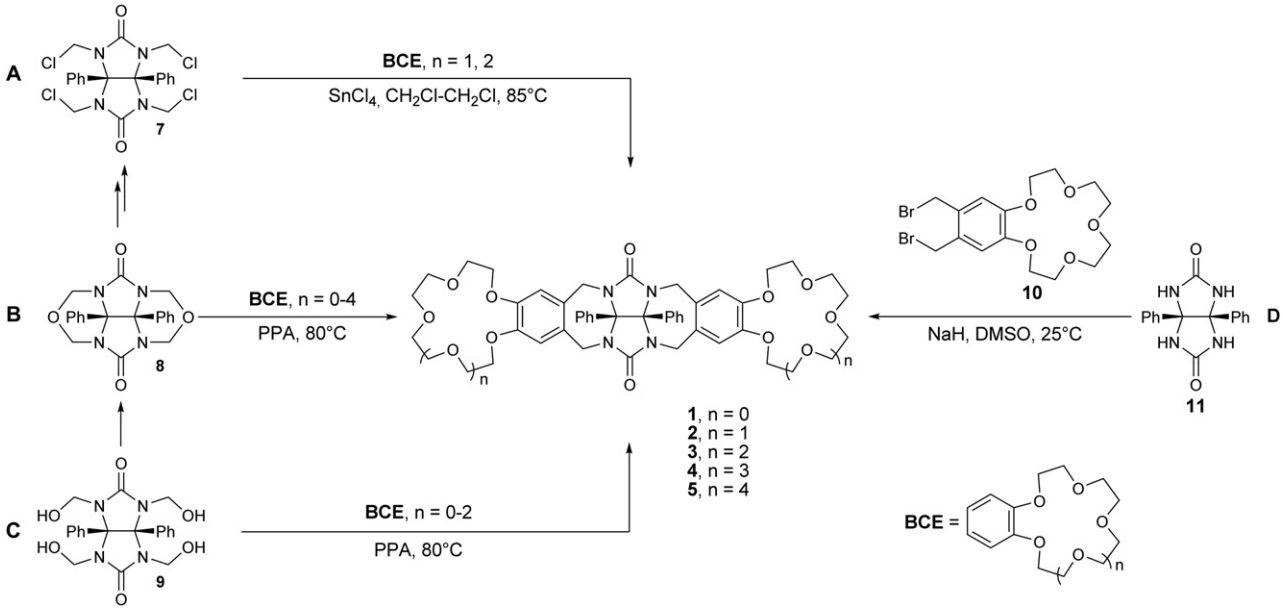
Another synthesis of glycoluril derivatives is alkylation of diphenylglycoluril **11** by reactive halides in the presence of strong bases (method **D**). Many compounds including benzene derivatives were obtained in this way. Utilizing 4′,5′-bis(bromomethyl)benzo-15-crown-5 we have obtained clip **2** with a relatively low yield of 35%. This result clearly justifies the formation of the products of 4,5-disubstitution in the conditions of methods A–C. The disadvantage of the method lies in the necessity of the synthesis of the series of bis(bromomethyl) derivatives of crown ethers while it is much more convenient to modify **11**.

This way, we can make the conclusion that the optimal way of obtaining clips **1**–**5** is method B because it allows obtaining products with high yields from available reagents.

The ^{1}H NMR spectra of **1**–**5** in $CDCl_3$ shows one singlet for the protons of the catechol moieties at δ=6.80 ppm, indicating that there is only one type of aromatic proton; NCH_2 protons gave rise to one characteristic AB pattern (4.1 and 4.7 ppm, J=15.9 Hz). The C_{2v} symmetry for these molecules is also confirmed by single signals for the C=O and NCH_2 groups in the ^{13}C NMR spectra. Protons of the phenyl groups show a multiplet signal at δ=7.00–7.20 ppm that indicates existence of molecular clips in *anti–anti* (***aa***) conformation with adjacent crown ether moieties.[10]

2.2. Computational studies

In order to perform an estimation of the structure of the obtained molecular clips **1**–**5**, we have performed molecular modeling using the method of statistical mechanics, Monte Carlo



Scheme 1. The synthetic approaches to the diphenylglycoluril based molecular clips.

(MMFF force field, Spartan'06 software).[11] The resulting data indicates that stable conformations for **1**–**5** are structures with ***aa*** orientation of crown ether fragments relative to the phenyl groups, which lead to polyether fragments being spatially closely spaced (Fig. 2). This has to facilitate the formation of stable sandwich complexes due to the fixation of the substrate's molecule between sidewalls of the molecular clip containing donor centers.

the relative compounds[12] and approximately obeys the C_m symmetry: the dihedral angle between the diazacyclopentane rings is 69.5° in **1** and 69.2° in **2**. The seven-membered diazacycloheptane fragments fused with the five-membered rings take the chair conformation, the dihedral angle between the planes of the benzene rings of the two fragments of benzocrown ethers is 36.2° in **1** and 36.8° in **2**.

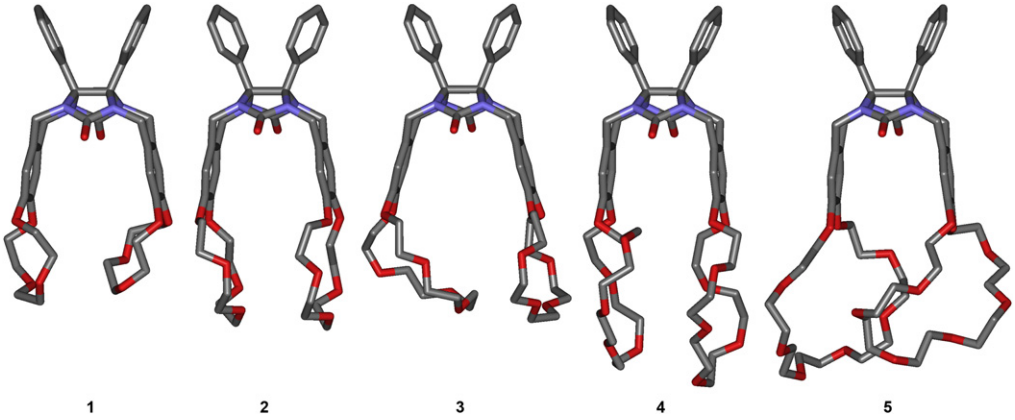


Fig. 2. Energy-minimized structures of molecular clips **1**–**5**. Hydrogen atoms are omitted for clarity.

2.3. X-ray crystallography

The calculated data was confirmed by single crystal X-ray diffraction analysis carried out for molecular clips **1** and **2** (Figs. 3 and 4). Both compounds are chloroform solvates with the stoichiometry clip:chloroform=1:1. Compound **1**·$CHCl_3$ crystallizes in the centrosymmetric monoclinic space group C_2/c while the crown molecule occupies a general position in the unit cell. Two crystallographically different chloroform molecules both reside on the 2-fold axes. Compound **2**·$CHCl_3$ crystallizes in the centrosymmetric monoclinic space group $P2_1/c$ with crown and chloroform molecules residing on general positions. Similar to the previous reported by us on the complex of molecular clip **3** with sodium picrate,[6a] in both macrocyclic molecules two fragments of benzocrown ether are in ***aa*** conformation relative to the phenyl groups of diphenylglycoluril, that determines their U-shapes. The geometry of the diphenylglycoluril fragment does not differ significantly from

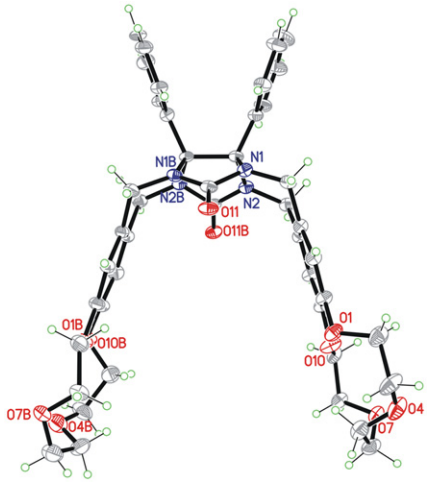


Fig. 3. ORTEP drawing of bis-crown **1** with partial labeling scheme. Thermal ellipsoids are shown with the 50% probability level. The disordered $CHCl_3$ molecules are omitted.

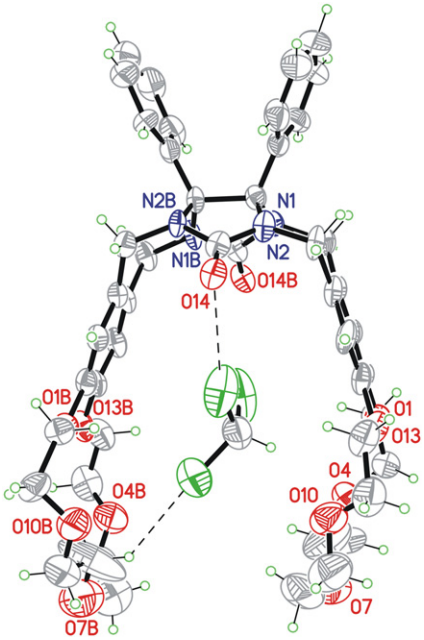


Fig. 4. ORTEP drawing of complex **2**·$CHCl_3$ with partial labeling scheme. Thermal ellipsoids are shown with the 30% probability level.

In the crystal solid, molecules of **1** are coupled into self-included dimers in such a way that one of the crown-moieties of each molecule is located within the clip of another molecule through the intermolecular C–H···O interactions including carbonyl and ether's oxygen atoms, C(8)···O(11)(1−x, y, 0.5−z)=3.306(7) Å [H(8B)···O(11)=2.37 Å], C(9B)···O(7)(1−x, y, 0.5−z)=3.208(7) Å [H(9B)···O(7)=2.53 Å]. This results in a sequence of four 12-membered rings in the form of a channel (Fig. 5). These dimeric associates are further stacked in the columns along the crystallographic *c*-axis with the C–H···O [C(17B)···O(7B)(0.5−x, 0.5−y, 1−z)=3.410, H···O=2.49 Å] interactions between those related by the inversion

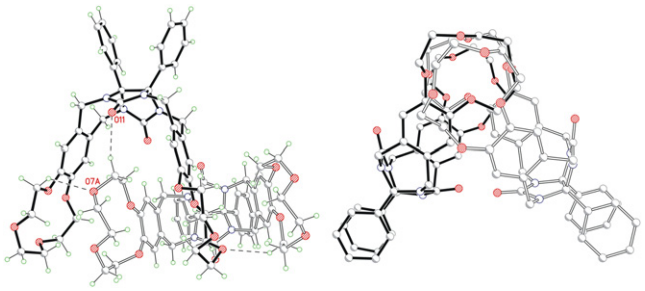


Fig. 5. Side view of self-included dimer **1**. H-bonds are shown by dotted lines; symmetry transformation for O(7A): 1−*x*, *y*, 0.5−*z*. (left) Top view. H-atoms are omitted for clarity. (right).

centers dimers. The chloroform molecules occupy the channels between these columns and are held within these channels via predominantly van der Waals interactions (Fig. 6).

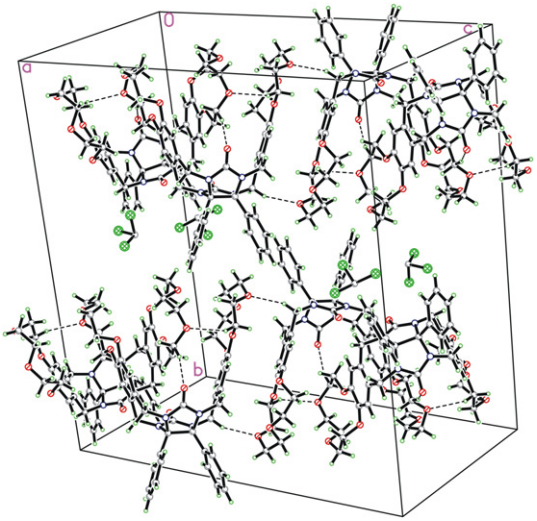


Fig. 6. Crystal packing of **1**·$CHCl_3$. H-atoms in the disordered chloroform molecules were not found.

In the crystal structure of **2**·$CHCl_3$ the chloroform molecule is located deep in the cavity of the molecular clip being held there via intermolecular interactions, Cl(3)···O(14)=3.250(6) Å and C(8B)···Cl(1)=3.44(2) Å [H(8B2)···Cl(1)=2.72 Å]. Only a few examples of the chloroform inclusion in the pseudocavity formed by two crown ether fragments with the formation of crystalline complexes are known so far.[13]

These 1:1 aggregates, related by the glide plane, stack along the crystallographic *c*-axis with significant π−π interactions between adjacent aromatic fragments. It is indicated because the dihedral angle between the nearly parallel aromatic rings is 0.35°, and the distance between the centroids of the aromatic rings being 3.560 Å (Fig. 7).

Thus, the theoretical and experimental data suggest the structural readiness of the molecular clips **1**–**5** to the complex formation with different substrates.

2.4. Complexation studies

FABMS has proven to be a versatile method for the analysis of supramolecular complexes formed in solution and transported into the gas phase for detection.[14] Based upon the intensities of complexes in the resulting mass spectra, it is possible to estimate the

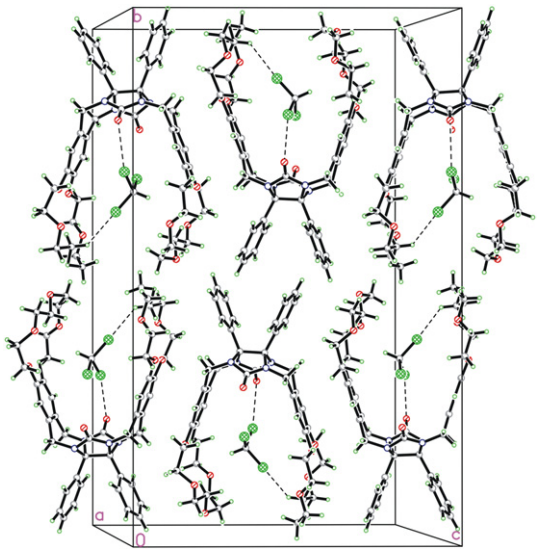


Fig. 7. Crystal packing of **2**·$CHCl_3$.

relative binding selectivity of structurally similar hosts toward different guests. This general method has been used previously to assess the alkali metal binding properties of a wide range of hosts, such as crown ethers,[14d] lariat ethers,[14e] bis(crown ethers),[14f] and it provides the basis for the results reported herein.

The solutions of the mixture of corresponding clips **1**–**5** with metal picrate (1 and 3 equiv) in 3-nitrobenzyl alcohol were analyzed (Table 1).

Even with an excess of metal picrate, in the mass spectra of all cases showed that the most intensive peak is the one corresponding to the single-charged ion of the complex with ratio 1:1. For the compound **1** the peak corresponding to the complex with the structure $[\mathbf{1}+2Na]^+$ is observed with minor intensity only with an excess of sodium picrate. For bis(benzo-15-crown-5) **2**, formation of such complex is observed only with sodium picrate and its relative contribution is increasing with the increase of the concentration of sodium picrate in the mixture. Formation of the complex with a 1:2 ratio is observed in clips **3**–**5** only with an excess of picrate. For **3** and **4**, contribution of such complexes is decreasing with the increase of the cation size, but in the case of **5** there is no such dependence. Since the ratio of peak intensities of ions of structurally similar complex particles is correlated with their stability,[14] we can make the conclusion that in the conditions of the mass-spectral experiment, the most stable complexes are the ones with a 1:1 ratio. Obtained intensity ratios [M]:[M+Me]:[M+2Me] reflect the tendencies of selectivity and bonding ability of clips **1**–**5** toward alkali metal picrates.

The intensity of the complex ions of clips **1**–**5** with the NH_4^+ cation is considerably lower than with cations of alkali metals. Complex with a 1:2 ratio is only observed with an excess of ammonium picrate for the molecular clip **4**. The possible reason is that the main contribution in the complex stabilization is achieved by hydrogen bonds O···H–NH_3^+. Highly polar and solvating 3-nitrobenzyl alcohol results to suppression of these interactions.

Cation extraction as an ion pair is a widely common method in host–guest chemistry of estimating the efficiency of interaction of macrocyclic receptors with a substrate. The most commonly metal picrates are used for these purposes, which allow a fast and easy spectrophotometrical[15] determination of extracted cation quantity. Thereby, estimation of the complex formation ability of molecular clips **1**–**5** was performed on the basis of the extraction results of cations of alkali metals from the aqueous phase into the chloroform ligand solution. For the sake of correct comparison, extractability of

Table 1
Normalized peak intensity for clips **1**–**5** mixtures with alkali metal picrates

Compound	Cation	Clips to metal picrate ratio					
		1:1			1:3		
		$[M+H]^+$	$[M+Me]^+$	$[M+2Me]^+$	$[M+H]^+$	$[M+Me]^+$	$[M+2Me]^+$
1	Na	0	100	0	0	100	Trace
	K	25	75	0	10	90	0
	Rb	42	58	0	16	84	0
	Cs	38	62	0	32	68	0
	NH_4	77	23	0	71	29	0
2	Na	3	86	11	0	76	24
	K	0	100	0	0	100	0
	Rb	0	100	0	0	100	0
	Cs	6	94	0	0	100	0
	NH_4	21	79	0	7	93	0
3	Na	6	94	Trace	0	69	31
	K	7	93	0	0	87	13
	Rb	4	96	0	0	93	7
	Cs	3	97	0	4	96	Trace
	NH_4	31	69	0	30	70	0
4	Na	12	85	3	0	84	16
	K	15	84	1	0	87	13
	Rb	9	90	1	6	81	13
	Cs	7	92	1	3	85	12
	NH_4	35	65	0	23	68	9
5	Na	3	97	Trace	0	86	14
	K	6	94	Trace	0	85	15
	Rb	2	98	Trace	0	92	8
	Cs	10	90	Trace	6	82	12
	NH_4	49	51	0	40	60	0

monobenzocrown ethers B12C4, B15C5, B18C6, B21C7, and B24C8 was determined in identical conditions. Control of the extractability was performed on the basis of spectrophotometrical detection of residual concentration of metal picrates in aqueous solution. Extractability of the investigated compounds was determined as metal/ligand concentration ratios according to the equation:

$$\text{Extractability}\ (\%) = \frac{([C_0\text{MPi}] - [C_x\text{MPi}])_{H_2O}}{[C_0L]_{CHCl_3}} \times 100$$

where $[C_0\text{MPi}]$—initial concentration of metal picrate in the aqueous phase, $[C_x\text{MPi}]$—concentration of metal picrate in the aqueous phase after extraction, $[C_0\text{L}]$—initial concentration of ligand in the organic phase.

Since molecular clips **1**–**5** contain two potential sites for cation binding, their maximal theoretical extractability is 200%, but for benzocrown ethers it is 100%. Obtained results are presented in Table 2 and Fig. 8.

Table 2
Extractability of alkali metal picrates by compounds **1**–**5**, B12C4, B15C5, B18C6, B21C7, B24C8, (%)[a]

Compound	Cation				
	Na^+	K^+	Rb^+	Cs^+	NH_4^+
1	10.6	13.7	4.5	14.5	5.95
2	41.6	91.6	85.4	50.1	28.55
3	44.2	142.5	111.6	107.8	77.85
4	5.8	59.2	112.5	106.75	80.75
5	19.0	22.9	34.7	49.6	15.00
B12C4	17.6	14.5	10.6	19.2	5.15
B15C5	22.0	15.8	12.5	15.2	7.70
B18C6	25.3	88.5	53.8	36.8	37.20
B21C7	3.75	5.6	13.95	8.7	4.25
B24C8	5.25	10.6	20.2	19.9	3.85

[a] Averaged values of three extraction experiments.

Extractability of bis(crown ethers) **2**–**5** is considerably higher than for the corresponding benzocrown ethers. It is probably the result of formation of more stable complexes. Particularly notable changes are observed for bis(benzo-18-crown-6) **3** and bis(benzo-21-crown-7) **4**. Extractability of potassium, rubidium, and cesium picrates for **3**, and rubidium, and cesium for **4** is over 100%, which clearly indicates the formation of complexes with 1:2 ratio along with ligand:cation complexes with 1:1 ratio. Formation of such complexes is described by us in the mass-spectral experiment conditions, and also in the crystalline state for the complex of **3** with sodium picrate.[6a] For bis(crown ethers) **2**–**5** more potent interactions with large cations, such as potassium, rubidium, and cesium are also observed in comparison to the small sodium cation. However, if for compounds **2** and **3** the highest extractability is for ion K^+, in the case of compounds **4** and **5** it increases with the increase of the size of the metal cation and reaches its maximum for ions Rb^+ and Cs^+, respectively. Bis(benzo-12-crown-4) **1** and benzo-12-crown-4, as expected, interact weakly with the metal ions, furthermore, extractability for **1** is even slightly lower. There is almost no dependence on the size of the cation, but the highest extractability in both cases is observed for the Cs^+ ion and the lowest—for Rb^+ ion. Similar decrease of bis(benzocrown ethers) extraction constants in comparison with their monocyclic analogs is described for the complexes of non-sandwich type bis(benzocrown ethers) with cations of alkali metals,[15e] when each crown ether cycle acts as an individual unit, and the slight decrease of extraction constants is explained by repulsion of two cations, bonded by crown ether cycles (anti-cooperative effect). However, formation of such complexes with bis(benzo-12-crown-4) **1** is highly unlikely, which is proved by the mass-spectral experiment, which didn't note formation of a considerable amount of complexes with a structure and ratio of ligand:cation 1:2 for compound **1** even with an excess of metal picrates (Table 2).

3. Conclusions

The current paper describes the facile synthesis of new molecular clips, including benzocrown ether fragments and diphenylglycoluril core. The X-ray structures for compounds **1** and **2**, showing an encapsulated $CHCl_3$ molecule, were determined. Theoretical and experimental studies show the existence of **1**–**5** in conformation, in which benzocrown ether moieties have an *anti*–*anti* orientation. The complexation properties of the obtained molecular clips were examined toward alkali metal and ammonium ions by FABMS spectrometry and extraction experiments. The obtained results by extraction experiments indicate that the extractabilities of **2**–**5** are much greater comparing to benzocrown ethers. Molecular clip **3** shows distinct selectivity to K^+. Our efforts in this direction will be reported in timely manner.

4. Experimental

4.1. General

Solvents were purified using standard procedures before use.[16] Benzocrown ethers,[17] diphenylglicoluril **11**,[18] tetrachloride **7**,[7] tetraol **9**, and bisether **8**,[19] 4′,5′-bis(bromomethyl)benzo-15-crown-5 **10**[20] were prepared according to the literature procedures. Polyphosphoric acid was prepared by dissolving of 150 g P_2O_5 in 75 ml 85-% H_3PO_4. All other materials were reagent grade chemicals used as received.

Silica gel 60 F_{254} (Merck) plates were used for TLC. Silica gel 60 (0.063–0.100 mm, Merck) was used for column chromatography. The plates were inspected by UV light and, if required, developed in I_2 vapor. ^1H and ^{13}C NMR spectra were obtained on a Varian VXR-300 (300 MHz and 75.5 MHz, respectively) spectrometer. All

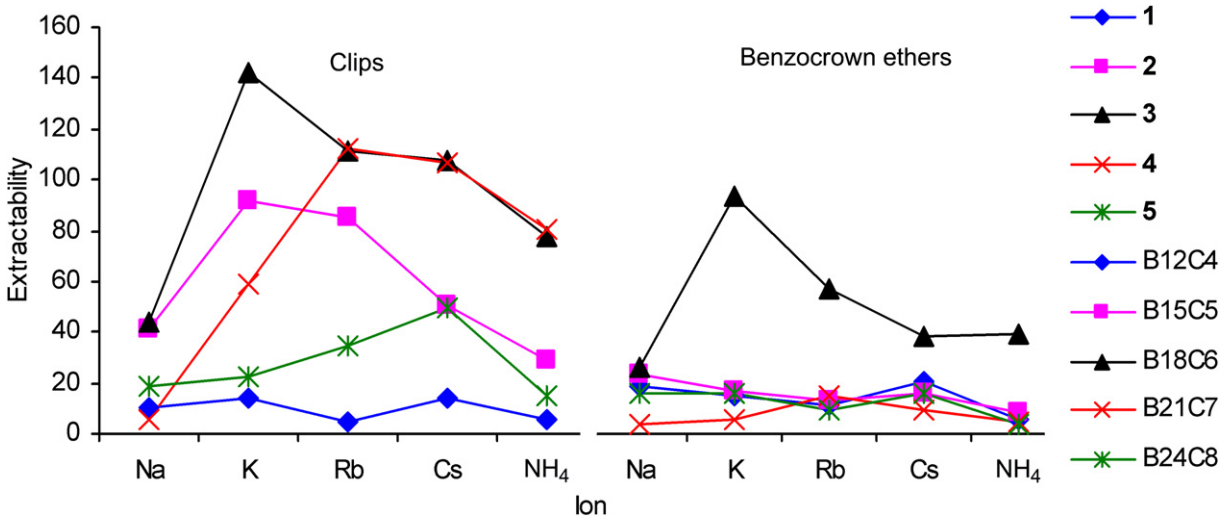


Fig. 8. Dependence between alkali metal picrates extractability and the type of extragent.

chemical shifts are quoted in parts per million on the δ scale with TMS or residual solvent as an internal standard. The coupling constants are expressed in Hertz.The melting points were determined by the open capillary tube method and were uncorrected. Electronic absorption spectra were obtained on a Specord M 40 spectrophotometer in quartz cells. 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. Elemental analysis was carried out on a EuroVector EA3000 CHNS elemental analyzer.

4.2. General procedure for the synthesis of molecular clips 1–5

*4.2.1. Method A. molecular clip **2** was obtained in 50% yield as described.*[6b] Method **B**. A mixture of bisether **8** (1 g, 2.65 mmol) and corresponding benzocrown ether (5.42 mmol) in PPA (30 g) was stirred vigorously at 80–85°C for 30 min. A deep purple color was formed in 5 min. To the cooled reaction mixture was added water (150 mL) and product was extracted with $CHCl_3$ (3×50 mL). The organic layer was washed with water until neutral (~3×50 mL) and subjected to azeotropic drying. The solvent was removed at reduced pressure and the residue was dissolved in a mixture of $CHCl_3$/MeOH (50:1, 100 mL) and filtered through SiO_2 (~30 mL). The solvent was removed at reduced pressure and the crude product was purified as described below.

Method **C**. The procedure is similar to Method **B**, with exception that tetraol **9** (1.1 g, 2.65 mmol) was used instead bisether **8**.

Method **D**. A suspension of NaH (0.288 g, 12 mmol) in DMSO (26 mL) was heated with stirring at 70°C for 30 min. The resulting mixture was cooled to room temperature and a solution of **11** (0.78 g, 2.65 mmol) in DMSO (40 mL) was added. Stirring was continued for 20 min and then solution of **10** (5.92 g, 5.83 mmol) in DMSO (40 mL) was added dropwise over 5 min and the resulting mixture was stirred at room temperature for 24 h. The mixture was poured into ice water (400 mL) and acidified with HCl to pH≈2. The resulting solid was filtered off, washed with water (3×50 mL). The crude product was purified as described below.

*4.2.2. Molecular clip (**1**).* The crude product was recrystallized from MeOH/$CHCl_3$ mixture (30:1) to give **1** as colorless crystals. Yield: 1.57 g, 75% (Method **B**); 0.75 g, 36% (Method **C**). Mp: 315 °C (dec). ^{1}H NMR ($CDCl_3$): δ 3.61–4.26 (m, 24H, CH_2O), 4.13 (d, 4H, J=15.9 Hz, CH_2N), 4.69 (d, 4H, J=15.9 Hz, CH_2N), 6.91 (s, 4H, C_6H_2), 7.03–7.18 (m, 10H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 44.8, 69.5, 70.7, 71.2, 85.3, 119.4, 128.1, 128.6, 128.7, 131.3, 133.6, 149.0, 157.7. MS, *m*/*z* (%): 791 ($[M+H]^+$, 100). Anal. Calcd for $C_{44}H_{46}N_4O_{10}\cdot CHCl_3$: C, 59.38; H, 5.20; N, 6.16. Found: C, 59.48; H, 5.26; N, 6.24.

*4.2.3. Molecular clip (**2**).* The crude product was recrystallized from MeOH/$CHCl_3$ mixture (50:1) to give **2** as colorless crystals. Yield: 1.86 g, 80% (Method **B**); 0.93 g, 40% (Method **C**); 0.77 g, 35% (Method **D**). Mp: 285–288 °C (dec). ^{1}H NMR ($CDCl_3$): δ 3.66–3.78 (m, 16H, CH_2O), 3.80–3.90 (m, 8H, CH_2O), 3.99–4.21 (m, 8H, CH_2O), 4.12 (d, 4H, J=15.6 Hz, CH_2N), 4.67 (d, 4H, J=15.6 Hz, CH_2N), 6.80 (s, 4H, C_6H_2), 7.04–7.17 (m, 10H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 44.9, 68.9, 69.6, 70.5, 71.0, 85.3, 115.6, 128.2, 128.6, 128.7, 129.9, 133.7, 147.6, 157.7. MS, *m*/*z* (%): 879 ($[M+H]^+$, 100). Anal. Calcd for $C_{48}H_{54}N_4O_{12}\cdot CHCl_3$: C, 58.95; H, 5.55; N, 5.61. Found: C, 59.01; H, 5.51; N, 5.73.

*4.2.4. Molecular clip (**3**).* The crude product was recrystallized from MeOH to give **3** as colorless needles. Yield: 50% (Method **A**); 2.00 g, 78% (Method **B**); 0.97 g, 38% (Method **C**). Mp: 231.5–233 °C. ^{1}H NMR ($CDCl_3$): δ 3.55–3.79 (m, 24H, CH_2O), 3.80–3.95 (m, 8H, CH_2O), 3.98–4.27 (m, 8H, CH_2O), 4.13 (d, 4H, J=15.8 Hz, CH_2N), 4.67 (d, 4H, J=15.8 Hz, CH_2N), 6.80 (s, 4H, C_6H_2), 7.00–7.20 (m, 10H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 44.9, 69.1, 69.7, 70.7, 70.8, 70.8, 85.4, 115.8, 128.2, 128.6, 128.7, 130.0, 133.8, 147.6, 157.7. MS, *m*/*z* (%): 967 ($[M+H]^+$, 100) Anal. Calcd for $C_{52}H_{62}N_4O_{14}$: C, 64.58; H, 6.46; N, 5.79. Found: C, 64.35; H, 6.41; N, 5.74.

*4.2.5. Molecular clip (**4**).* The crude product was purified by column chromatography ($CHCl_3$/MeOH, 100:1) and crystallized under hexane layer to give **4** as off white powder. Yield: 1.45 g, 52% (Method **B**). Mp: 83–85 °C. ^{1}H NMR ($CDCl_3$): δ 3.58–3.94 (m, 40H, CH_2O), 4.02–4.23 (m, 8H, CH_2O), 4.13 (d, 4H, J=15.9 Hz, CH_2N), 4.67 (d, 4H, J=15.9 Hz, CH_2N), 6.80 (s, 4H, C_6H_2), 7.02–7.18 (m, 10H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 44.9, 69.1, 69.7, 70.4, 70.8, 71.0, 71.0, 85.2, 115.4, 128.0, 128.4, 128.5, 129.8, 133.4, 147.1, 157.4. MS, *m*/*z* (%): 1055 ($[M+H]^+$, 100). Anal. Calcd for $C_{56}H_{70}N_4O_{16}$: C, 63.74; H, 6.69; N, 5.30. Found: C, 63.86; H, 6.68; N, 5.31.

*4.2.6. Molecular clip (**5**).* The crude product was purified by column chromatography ($CHCl_3$/MeOH, 100:1) to give **5** as light yellow oil, which solidifies on standing. Yield: 1.76 g, 58% (Method **B**). ^{1}H NMR ($CDCl_3$): δ 3.56–3.94 (m, 48H, CH_2O), 4.01–4.23 (m, 8H, CH_2O), 4.13 (d, 4H, J=15.8 Hz, CH_2N), 4.68 (d, 4H, J=15.8 Hz, CH_2N), 6.80 (s, 4H,

C_6H_2), 7.00–7.21 (m, 10H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 44.9, 69.3, 69.8, 70.7, 70.7, 70.7, 70.8, 71.1, 85.3, 115.8, 128.0, 128.4, 128.5, 129.9, 133.5, 147.3, 157.5. MS, *m*/*z* (%): 1143 ([M+H]$^+$, 100). Anal. Calcd for $C_{60}H_{78}N_4O_{18}$: C, 63.03; H, 6.88; N, 4.90. Found: C, 62.96; H, 6.86; N, 4.77.

4.3. X-ray crystal structure

Single crystals suitable for X-ray crystallography were grown by crystallization of **1** and **2** from a MeOH/$CHCl_3$ mixture. The X-ray measurements were made on a Nonius Kappa CCD diffractometer with graphite monochromated MoKα radiation using ω rotation. Both structures were solved by direct methods (SHELXS-97) and refined on F^2 by full-matrix least-squares techniques (SHELXL-97).[21] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions with isotropic temperature factors and refined using a riding model. Chloroform molecules in **1** are disordered around a twofold axis and were refined as partially populated. Their hydrogen atoms are not localized. Main crystallographic data are given in Table 3.

Table 3
Crystal and structure refinement data for **1**·$CHCl_3$ and **2**·$CHCl_3$

Parameter	**1**·$CHCl_3$	**2**·$CHCl_3$
Formula	$C_{45}H_{47}Cl_3N_4O_{10}$	$C_{49}H_{55}Cl_3N_4O_{12}$
fw	910.22	998.32
Cryst system	Monoclinic	Monoclinic
Space group	C_2/c	$P2_1-c$
Z	8	4
a (Å)	13.245(3)	8.2360(2)
b (Å)	27.674(6)	32.1830(8)
c (Å)	25.129(5)	19.6430(5)
β (deg)	97.18(3)	113.3471(9)
V (Å^3)	9139(3)	4780.2(2)
D_c (gcm^{-3})	1.323	1.387
μ (mm^{-1})	0.261	0.259
F(000)	3808	2096
Reflns. collected/unique	7800	31,985/7492
Reflns. with [$I>2\sigma(I)$]	2824	2585
Data/restraints/params	7800/0/577	7492/1/614
GOF on F^2	0.937	0.863
R_1, wR_2 [$I>2\sigma(I)$]	0.0709, 0.1517	0.0871, 0.2191
R_1, wR_2 (all data)	0.2290, 0.2198	0.2490, 0.2716

4.4. Molecular modeling

A search for the optimum structures of molecular clips **1**–**5** was carried out in two steps. First, thermodynamically favorable conformations were found using the Monte Carlo method of statistical mechanics (MMFF94 force field, Spartan'06 program package).[11] Then, out of the resulting 100 structures of each compound in an energy gap of 10 kcal mol^{-1}, the most favorable one to five structures were selected so that their total population exceeded 90%. Each of these conformations was optimized by the semi-empirical PM3 method to find a structure with the minimum energy.

4.5. Alkali metal picrate extraction

$5\cdot10^{-3}$ M aqueous solution of corresponding picrate (2 mL) and $1\cdot10^{-3}$ M solution of molecular clips **1**–**5** in water saturated $CHCl_3$ (2 mL) were stirred vigorously for 20 min and then centrifuged to complete phase separation. An aliquot was removed from the water phase (0.100 mL) and added to distilled water (5.00 mL). Another portion of the metal picrate solution was extracted by $CHCl_3$, which contained no clips and then diluted similarly with water. Optical density for these solutions was measured at λ=354 nm and the extractability in each case was calculated. For each experiment the picrate extraction was performed 5 times on different samples, and the average value was calculated. In the absence of molecular clips no metal ion picrate extraction was detected.

4.6. FABMS evaluation of complexing ability of 1–5

The mixture of molecular clips **1**–**5** ($5\cdot10^{-6}$ mol) and corresponding alkali metal picrate ($5\cdot10^{-6}$ or $1.5\cdot10^{-5}$ mol) was dissolved in the minimal amount of 3-nitrobenzyl alcohol and this solution was subjected to analysis. Spectra were recorded in positive mode, providing a primary argon atom beam at 8 keV. Obtained spectral data is normalized to 100% total intensity for macrocycle containing species ([M+H]$^+$, [M+Me]$^+$, [M+2Me]$^{2+}$ and [M+2Me+Pi]$^+$).

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Supplementary data

X-ray crystal data for molecular clips **1** and **2** (Table 3) is available. Crystallographic data for these structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 850842 and 850843. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [e-mail: deposit@ccdc.cam.ac.uk]. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.04.009.

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