Abstract
Two procedures for the synthesis of benzo-21-crown-7 have been explored. The [1+1] macrocyclization with KBF$_4$ as the template was found to be more efficient than the intramolecular macrocyclization without template. Pseudorotaxanes form with secondary ammonium ions bearing at least one alkyl chain narrow enough to slip into the crown ether. Substitution on benzo-21-crown-7 or on the secondary ammonium axle alters the binding affinity and binding mode. Compared to dibenzo-24-crown-8, the complexing properties of benzo-21-crown-7 turn out to be more susceptible to modifications at the crown periphery.

Introduction
Mechanically interlocked structures [1-4] are attractive to chemists not only because they are aesthetically appealing but also due to their potential applications in molecular machines and smart materials [5-9]. Although a few covalent templates are known [10-12], their synthesis most often makes use of non-covalent templates [13-16], for which quite a number of different binding motifs are available that make the synthesis of many diverse and complex interlocked structures possible. Among these, the threaded interaction of secondary ammonium ions with larger crown ethers is a prominent example [17-22]. Recently, Huang and co-workers reported that the macrocycle size for forming pseudorotaxane can be reduced to only 21 atoms, namely benzo-21-crown-7 [23] (C$_7$; Scheme 1) and pyrido-21-crown-7 [24], which could still slip over a secondary dialkylammonium ion when one of the alkyl groups is a narrow alkyl chain. By using this binding motif, the so far smallest [2]rotaxane consisting of only 76 atoms and having a molecular weight of not more than 510 Da was synthesized by Chiu and co-workers [25]. More recently, we applied C$_7$ together with dibenzo-24-crown-8 (DB24C8) to the construction of a four-component self-sorting system based on the fact that C$_7$ cannot pass over a phenyl stopper group at the end of a dialkylammonium axle, while DB24C8 can [26]. This system was further extended to construct more complex multiply interlocked struc-
Scheme 1: Two synthetic procedures for the preparation of benzo-21-crown-7 (C7) and its formyl analogue 4: Top: The non-templated macrocyclization of 1 yields a mixture of crown ethers of different sizes. Bottom: With K\(^+\) as the template, benzo-21-crown-7 can be obtained in much better yields.

Modification of crown ethers and their secondary ammonium guests allows variation of their binding properties and enables them to be incorporated into more complex assemblies [28]. In this respect, benzocrown ethers are more preferable than their aliphatic analogs due to the easy-to-achieve substitution on the benzene ring. One prerequisite for the generation of more complex supramolecular architecture based on such ammonium/crown binding motifs is the efficient synthesis of the building blocks. Here we report on attempts to improve the synthesis of C7 and the preparation of substituted derivatives. Two synthetic routes, one which utilizes a templating cation and one which does not involve a template, are compared. Finally, the effects of substituents on the crown ether binding behavior are examined to lay the basis for a more precise control over the assembly of future complex assemblies.

Results and Discussion

Synthesis of C7. Several synthetic procedures for C7 have been explored systematically under phase-transfer conditions by Lukyanenko et al. [28]. Among them, intramolecular macrocyclization via monotosylate 1 generated in situ gives rise to the highest yield (68%). To test the efficiency of intramolecular ring closure in the absence of phase-transfer catalysis, we synthesized the monotosylate 1 which is then used in a separate macrocyclization (Scheme 1). Disappointingly, only 24% yield was achieved for the synthesis of C7 from 1. A second fraction of 31% turned out to be a mixture of C7’s bigger homologues 2-(n) (n = 1–7). There are two reasons responsible for the relatively low yield: (i) the initial concentration (90 mM) of 1 is too high, favoring polycondensation over the intramolecular macrocyclization; (ii) the sodium ion originating from the NaH used as the base is not an appropriate template for C7 [29]. Meanwhile, the low yield and long procedure discourage the application of intramolecular macrocyclization to the synthesis of C7’s derivatives. Therefore, an alternative procedure with improved efficiency was sought.

The synthetic procedure with catechol and hexa(ethylene glycol) ditosylate (3) (Scheme 1) is advantageous since they are commercially available or easily prepared from commercially available materials. However, under phase-transfer conditions, this procedure gives C7 in a relatively low yield (22%), which is not acceptable for synthesizing complex C7 derivatives. Huang et al. [23] modified this procedure by introducing KPF\(_6\) as a template, which increased the yield to 69%. Nevertheless, we found it difficult to cleanly separate the KPF\(_6\) salt from C7 during the reaction workup, since their complex dissolves well in organic solvents (e.g. CDCl\(_3\), ethylacetate). This can be attributed to the quite high hydrophobicity of the PF\(_6^-\) anion. Instead, KBF\(_4\) was found to be a very good template which gives a satisfying yield (70%) and could be completely removed after column chromatography. This was further supported by the application to the synthesis of 4 (yield: 62%).

Characterization of higher crown oligomers 2-(n). The signals in the \(^1\)H NMR spectra of 2-(n) (Figure 1c) appear at almost exactly the same position as those of C7 (Figure 1c). The broadening of the signals is the only indication that the sample contains more than just C7. Consequently, it is difficult
to distinguish the larger oligomers from C7 by simple $^1$H NMR experiments. In the corresponding ESI mass spectra, the ionization efficiency is quite low. Some of the major components can be observed easily, but minor products are hard to detect. Therefore, we added charged guest 5-H•PF$_6$ (Scheme 2) to the mixture to (i) detect signal shifts in the NMR spectra characteristic for the formation of complexes and (ii) to facilitate the ionization of the crown ether oligomers as ammonium complexes. This guest will furthermore provide straightforward evidence for the formation of crown ethers larger than C7, because the phenyl group in 5-H•PF$_6$ is too bulky to thread through the cavity of C7 [23]. Complex formation thus immediately indicates that the crown ether must have a larger cavity than C7. As seen in Figure 1b, the spectra of the equimolar mixture of 5-H•PF$_6$ and C7 is the simple superimposition of their individual spectra (Figure 1a, Figure 1c). However, addition of 5-H•PF$_6$ to the fraction containing the larger oligomers 2-(n) caused shifts of all signals for both of guest and host indicative of complex formation (Figure 1d, Figure 1e). From these experiments, we can conclude that crown ethers larger than C7 have formed, but the composition of the fraction containing 2-(n) is still not yet clear. From the structure of the starting material 1, dibenzo-42-crown-14 (2-(1)) is certainly the most likely candidate, but even larger structures cannot be ruled out yet.

**Scheme 2:** Molecular structures of guests 5-H•PF$_6$, 6-H•PF$_6$, and 7-H•PF$_6$, and their complexes with 2-(n), C7 and 4.
To further elucidate the structure of 2-(n), ESI-MS experiments were performed with the mixture of the second crown ether fraction and 5-H•PF₆. To our surprise, a broad series of several peaks evenly spaced by a distance of Δm = 356 amu was observed in the ESI mass spectrum (Figure 2). Considering that [5-H]⁺ does not simultaneously form complexes with several C₇ crown ethers, this peak distribution can only be assigned to a series of macrocycles with different sizes ranging from dibenzo-42-crown-14 (2-(1)) up to heptabenzo-168-crown-56 (2-(7)). Although the peak intensity does not necessarily reflect the solution composition quantitatively [30], the mass spectra indicate 2-(1) – 2-(4) to be the major components in the mixture, while the larger crown ethers are likely present only in trace amounts. Since we are focusing on C₇, no attempt was made to separate the larger crown ethers by more sophisticated methods such as HPLC.

Characterization of (C₇+KPF₆) formed in the KPF₆-templated synthesis of C₇. The ¹H NMR spectrum (Figure 3c) of the C₇ product obtained from the KPF₆-templated reaction through extraction with dichloromethane (DCM) from water and column chromatography (eluent gradient: ethylacetate:methanol = 50:1 to 20:1) clearly indicates the formation of a potassium complex which even survived the column chromatography. A comparison with the spectrum of pure C₇ (Figure 3a) and a mixture of pure C₇ and KPF₆ (Figure 3b) reveals that the product obtained from the column shows similar signal shifts as compared to those of the KPF₆ complex. This is supported by ESI-MS experiments. In the ESI mass spectrum (Figure S1, Supporting Information) of (C₇+KPF₆) sprayed from DCM, three intense peaks at m/z 379, 395, and 935 are observed, which can be assigned to [C₇+Na]⁺, [C₇+K]⁺ and [C₇₂⁻+K⁺+KPF₆]⁺, respectively. Since no KPF₆ was added to the solution after column chromatography, the presence of the latter two signals indicated survival of the (C₇+KPF₆) complex.

Addition of axle 5-H•PF₆ to (C₇+KPF₆) caused no obvious ¹H NMR signal changes of one of the building blocks, 5-H•PF₆ and (C₇+KPF₆) (Figure 4). Axle 5-H•PF₆ is consequently not able to replace the potassium ion in (C₇+KPF₆) likely because it cannot thread through the cavity.

In marked contrast, the ¹H NMR spectrum (Figure 4) of a mixture of 6-H•PF₆ and (C₇+KPF₆) shows a set of new complexation-induced signals, which appear at the same positions as those of independently generated [6-H@C₇]•PF₆, suggesting that the thinner axle can thread into the crown ether to form the pseudorotaxane even in competition with the potassium ion. This conclusion is further supported by the formation of a white precipitate (KPF₆) after addition of axle 6-H•PF₆ to the

![Figure 2: ESI-FTICR mass spectrum of a mixture of 5-H•PF₆ and 2-(n) in dichloromethane.](image)

![Figure 3: ¹H NMR spectra (500 MHz, 298 K, CDCl₃, 10.0 mM) of (a) C₇, (b) C₇ in the presence of 1 eq. KPF₆, (c) the compound obtained after column chromatography from the KPF₆-templated reaction, and (d) 2-(n).](image)

![Figure 4: ¹H NMR spectra (500 MHz, 298 K, CDCl₃, CD₃CN = 2:1, 10.0 mM) of (a) 6-HoPF₆, (b) mixture of 6-HoPF₆ and (C₇+KPF₆), (c) (C₇+KPF₆), (d) mixture of 5-HoPF₆ and (C₇+KPF₆), (e) 5-HoPF₆. Asterisk = solvent.](image)
According to related crystal structures [23-25], no π-π stacking between and the larger analogue dibenzo-24-crown-8. (i) There are two reasons for this remarkable difference -H•PF$_7$ and -H•PF$_6$. Surprisingly, the binding as compared to -H•PF$_7$. Analogously, stronger binding of C7 would be expected with π-system in -H•PF$_6$.

The effect of substituents on binding affinity and binding mode. The binding of axles 6-H•PF$_6$ and 7-H•PF$_6$ to C7 is a slow process on the NMR time scale. Consequently, the corresponding binding constants of [6-H@C7]+PF$_6$, [6-H@4]+PF$_6$, [7-H@C7]+PF$_6$, and [7-H@4]+PF$_6$ in 2:1 CDCl$_3$/CD$_2$CN solution (Figures S3–S10, Supporting Information) can easily be determined from the total host concentration and the relative integration of the separate signals for free and complexed hosts [31]. They are 17090 (±500) M$^{-1}$, 8000 (±270) M$^{-1}$, 5640 (±190) M$^{-1}$, and 3050 (±60) M$^{-1}$, respectively. The lower binding ability of 4 relative to C7 is certainly due to the electron-withdrawing aldehyde group which decreases the electron-donating and hydrogen-bond accepting ability of the oxygen atoms on the catechol [32]. Consequently, electron-withdrawing substitution on C7 should be avoided when aiming at strong binding between the two building blocks.

Conclusion

In summary, two procedures have been explored for the synthesis of C7. The one with catechol and hex(ethylene glycol) ditosylate as starting materials and KBF$_4$ as template turned out to be quite efficient synthetic pathway allowing easy introduction of a variety of substituents by choosing the appropriate catechol building block. In addition, two guests 5-H•PF$_6$ and
6-H•PF₆ are found to be very useful for the characterization of C7 and its homologues on the basis of the fact that C7 could not pass over phenyl group. Modifications of C7 and secondary dialkylammonium guests significantly alter the binding ability. Replacing a benzyl stopper on the axle by an arachencyl methyl group even changes the binding mode: Formation of C-H•••O hydrogen bonds is hampered for the methylene group between the anthracene and the ammonium. Compared to DB24C8, the complexing property of C7 is more susceptible to modification probably because the smaller macrocycle is more or less rigidified after complexation with secondary dialkylammonium, thus weakening its adjustability. This has to be taken into account if one desires to construct more complex interlocked assemblies by using C7 and secondary dialkylammonium ions as building blocks in the future.

Experimental

General Methods. All reagents were commercially available unless explicitly stated and used without further purification. 1,2-Bis{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}benzene [34], 5-H•PF₆ [35] and 6-H•PF₆ [23] were synthesized according to literature procedures. Solvents were either employed as purchased or dried prior to use by usual laboratory methods. Thin-layer chromatography (TLC) was performed on aluminum sheets coated with silica gel 60F₂₅₄ (Merck KGaA). The plates were inspected by UV light, and if required, developed in I₂ vapor. Column chromatography was performed on silica gel 60 (Merck 40–60 nm, 230–400 mesh). ¹H and ¹³C NMR spectra were recorded on Bruker ECX 400 MHz and Jeol Eclipse 500 MHz. All chemical shifts are reported in ppm with residual protomolecule signals as the internal standards, and the coupling constants (J) are in Hertz. The following abbreviations were used for signal multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet. Electrospray- ionization time-of-flight high-resolution mass spectrometry (ESI-TOF-HRMS) experiments were conducted on an Agilent 6210 ESI-TOF, Agilent Technologies and a Varian/Inotec QFT-7 FTICR (Fourier-transform ion-cyclotron-resonance) mass spectrometer equipped with a superconducting 7 Tesla magnet and a micromass Z-spray Electrospray-ionization (ESI) ion source utilizing a stainless steel capillary with a 0.75 mm inner diameter.

2-[2-[2-[2-(2-Hydroxyethoxy)ethoxy]ethoxy]phenoxo]ethoxy]ethoxy]-4-methylbenzene-sulfonate (1): To a mixture of 1,2-Bis{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}benzene (5.15 g, 13.8 mmol) in THF (60 mL) and sodium hydroxide (2.2 g, 55 mmol) in H₂O (60 mL) in an ice bath was added dropwise tosyl chloride (3.2 g, 16.8 mmol) in THF (150 mL) for 2 h. The mixture was continued to stir overnight in ice bath, THF was evaporated under reduced pressure. The residue was suspended in H₂O (50 mL), extracted with CH₂Cl₂ (100 mL × 3) and then dried over anhydrous Na₂SO₄. After the solvent was removed in vacuo, the crude product was subjected to column chromatography (silica gel, eluent: ethyl acetate:hexane = 2:1) to afford a pale-yellow oil (3.0 g, 41%). ¹H NMR (400 MHz, CDCl₃, 298 K): δ (ppm) = 2.42 (s, 3H), 3.58–3.62 (m, 4H), 3.64–3.75 (m, 10H), 3.80–3.88 (m, 4H), 4.12–4.17 (m, 6H), 6.89–6.91 (m, 4H), 7.31 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃, 298 K): δ (ppm) = 21.7, 61.9, 68.8, 68.91, 68.94, 69.4, 69.89, 69.90, 70.5, 70.8, 70.9, 71.0, 72.6, 115.0, 121.8, 128.0, 129.9, 133.0, 144.9, 149.0; ESI-TOF-HRMS: m/z calcd for [M+Na⁺]⁺ (100%): 551.1921, found: 551.1926; m/z calcd for [M+K]⁺ (20%): 567.1661, found: 567.1664.

Benzo-21-crown-7 (C7) and its homologues (2-(n)): The mixture of 1 (2.37 g, 4.5 mmol) and NaH (0.60 g, 25.0 mmol) in anhydrous THF (50 mL) was refluxed for 3 d. After cooling down to room temperature, water (100 mL) was added to quench the superfluous NaH. THF was removed under reduced pressure, and the residue was extract by CH₂Cl₂ (100 mL × 3). The organic phase was collected, dried over anhydrous Na₂SO₄, and concentrated in vacuo to give the crude product, which was isolated by column chromatography (silica gel, eluent: ethyl acetate/MeOH, 100:1 to 20:1) to afford C7 [23,28] (380 mg, 24%) and 2-(n) (490 mg, 31%) as yellow oil. For C7, ¹H NMR (400 MHz, CDCl₃, 298 K): δ (ppm) = 3.64–3.69 (m, 8H), 3.71–3.75 (m, 4H), 3.77–3.81 (m, 4H), 3.92 (t, J = 4.6 Hz, 4H), 4.16 (t, J = 4.6 Hz, 4H), 6.87–6.91 (m, 4H); ¹³C NMR (100 MHz, CDCl₃, 298 K): δ (ppm) = 69.3, 69.9, 70.6, 71.07, 71.13, 71.16, 114.5, 121.6, 149.0; For 2-(n): ¹H NMR (400 MHz, CDCl₃, 298 K): δ (ppm) = 3.57–3.68 (m, 12(n+1)H), 3.68–3.76 (m, 4(n+1)H), 3.79–3.87 (m, 4(n+1)H), 4.12–4.18 (m, 4(n+1)H), 6.86–6.94 (m, 4(n+1)H); ¹³C NMR (100 MHz, CDCl₃, 298 K): δ (ppm) = 68.9, 69.0, 69.1, 69.8, 69.9, 70.6, 70.66, 70.71, 70.75, 70.87, 70.89, 70.93, 71.08, 71.14, 71.17, 114.8, 115.0, 121.6, 121.7, 149.1.

Hexa(ethylene glycol) ditosylate (3): Hexa(ethylene glycol) (5.0 g, 17.7 mol) in THF (50 mL) and sodium hydroxide (4.8 g, 120 mmol) in H₂O (50 mL) was mixed in 500 mL flask. To the mixture in an ice bath was added dropwise tosyl chloride (12 g, 63 mmol) in THF (100 mL) for 2 h. The reaction mixture was stirred for another 5 h in ice bath, and THF was then concentrated under reduced pressure. The residue was suspended in H₂O (150 mL) and extracted with dichloromethane (100 mL × 3) and then dried over anhydrous Na₂SO₄. The solvent was removed in vacuo to give 3 [23] as a pale-yellow oil (10 g, 96%) which is pure enough for next step. ¹H NMR (400 MHz, CDCl₃, 298 K): δ (ppm) = 2.44 (s, 6H), 3.55–3.64 (m, 16H), 3.67 (t, J = 4.8 Hz, 4H), 4.14 (t, J = 4.8 Hz, 4H), 7.33 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H).
General procedure for synthesis of C7 KPF₆ or KBF₄ as template and 4 with KBF₄ as template: While stirring vigorously under argon atmosphere, a suspension of K₂CO₃ (2.07 g, 15 mmol) and KPF₆ or KBF₄ (7.5 mmol) in anhydrous CH₂Cl₂ (100 mL) was heated to reflux. To the suspension was added dropwise a solution of 3 (2.95 g, 5.0 mmol) and catechol or 3,4-dihydroxyphenylalanine (5.0 mmol) in CH₂Cl₂ (100 mL) during 12 h. The resulting reaction mixture was stirred under reflux for another 3 d. Upon cooling down to ambient temperature, the suspension was filtered and washed with CH₂Cl₂ (100 mL). The filtrate was concentrated under vacum to ambient temperature, the residue was partitioned between CH₂Cl₂ (100 mL) and water (100 mL), and the aqueous phase was extracted twice with CH₂Cl₂ (50 mL) (three times 50 mL). The combined organic phase was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The resulting residue was treated with water and the compound was extracted twice by CH₂Cl₂ (100 mL) and water (100 mL), and partitioned between CH₂Cl₂ and water until the aqueous phase was extracted. The aqueous phase was then evaporated off under reduced pressure. The solvent was removed in vacuo, and water (100 mL) was added to the residue. The resulting mixture was stirred at ambient temperature overnight. The mixture was then filtered, washed with copious amounts of H₂O, and dried to give 7-H•PF₆ as a yellow solid (1.39 g, 92%). 1H NMR (400 MHz, CD₂CN, 298 K): δ (ppm) = 1.36–1.44 (m, 2H), 1.46–1.54 (m, 2H), 1.69–1.78 (m, 2H), 3.25–3.34 (m, 2H), 3.48 (t, J = 6.2 Hz, 2H), 5.23 (t, J = 6.2 Hz, 2H), 7.58–7.64 (m, 2H), 7.70–7.76 (m, 2H), 8.14–8.19 (m, 2H), 8.30–8.34 (m, 2H), 8.74 (m, 1H); 13C NMR (100 MHz, CD₂CN, 298 K): δ (ppm) = 23.4, 26.2, 32.3, 44.9, 49.9, 62.0, 122.0, 124.2, 126.6, 128.6, 130.4, 131.8, 132.3; ESI-TOF-HRMS: m/z calcd for [M-PF₆]⁺ (100%): 294.1852; found: 294.1852.

Supporting Information

Supporting Information File 1
NMR and MS spectra of the corresponding complexes. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-14-S1.pdf]

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (SFB 765) and the Fonds der Chemischen Industrie for financial support.

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