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Synthesis, Alkali Metal Cation Binding and Computational Analysis of Adamantane-substituted Hexaaza Crown Ethers

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Abstract: We prepared a so far unknown class of hexaaza crown ethers substituted with six adamantyl side-arms and used them for extraction of alkali metal cations from an aqueous medium. These host molecules were designed to take advantage of intramolecular London dispersion interactions in order to tune the host's structural organization and enhance its binding capability. The studied adamantyl hexaaza crown ethers all showed efficient extraction capabilities for alkali metal cations, unlike the parent hexaaza-18-crown-6. The experimental study was supported by a computational analysis and a global minima structure search afforded geometries that highlighted the importance of non-covalent interactions for complex formation and adoption of specific molecular conformations. In addition, the obtained binding energies for complex formation further supported our experimental findings. This new class of alkali metal cation binding hosts could find future application in bioactivity studies that apply supramolecular recognition processes.

Keywords: hexaaza crown ethers, adamantane, alkali metal cations, extraction experiments, London dispersion, conformer search.

INTRODUCTION

EXPLORATION of innovative host molecule scaffolds remains an ever present pursuit of supramolecular chemistry. Among many attractive classes of hosts, aza crown ethers[1] have a special place due to their ability to bind both cations and anions, depending on the pH value of their solution.[2] Some supramolecular applications of hexaaza crown ethers include their use as complexation agents for transition metals,[3] as receptors with multiple redox-active groups,[4] as components in ultrathin separation membranes,[5] as ionophores in PVC membrane ion-selective electrodes, *etc*.[6] Various hexaaza crown ethers were also studied as monolayer-forming amphiphiles,[7] as complexing agents in ion pairing studies,[8] as cores in dendrimers capable of binding metal nanoparticle,[9] as organocatalysts for polymerizations,[10] and in biological systems as chelating agents applicable in radioimmunotherapy.[11]

Although many different subclasses of aza crown ethers are known,[12] with some novel synthetic methods for their preparation recently developed,[13] in this study we focused our attention on substituted hexaaza crown ethers, macrocycles containing six nitrogen atoms in the crown core (Figure 1), in order to apply them for alkali metal cation extractions. Since these nitrogen centers can be readily functionalized with side-arms, we set out to use the influence of a bulky adamantane group on conformational re-organization of the crown scaffold. Our goal was to encourage the formation of numerous intramolecular close contacts between the introduced hydrocarbon subunits and thereby stabilize the system by taking advantage of London dispersion interactions.[14] Dispersion in general arises from instantaneous induced dipoles and is crucial for molecular aggregation.[15] Its influence thrives in increasingly larger and hence more polarizable structures,[11] and it can therefore be used as "molecular glue" in many otherwise unstable molecules, resulting in many practical applications.[16] Notably, some diamondoid[17] structures containing extremely long C–C bonds can thank their existence to London dispersion

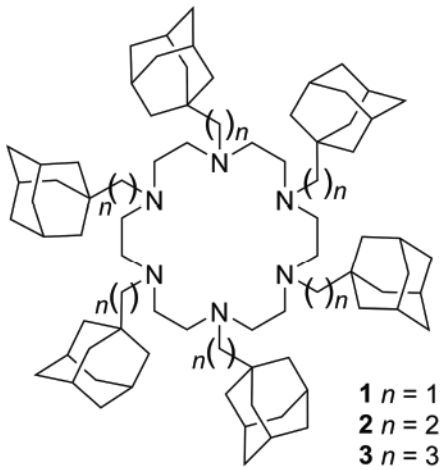


Figure 1. Structures of hexaaza crown ethers **1**–**3** substituted with six adamantyl subunits.

interactions.[18] Bulky, hydrocarbon-based groups are ideal candidates to act as dispersion energy donors (DEDs)[19] and, if designed accordingly, enable the overall prevalence of dispersion contributions in a given system.

Since we have prior experience in preparing similar polycyclic oxa and aza crown ethers[20] and cryptands,[21] we now expanded our study to a sterically demanding hexaaza crown scaffold. Thus, the crown core functionalized with six adamantyl side-arms was designed with an intention to maximize the DED potential of the incorporated adamantane cages. The resulting dense substituent packing in the host structures was envisioned to be beneficial for alkali metal cation binding and to enable the formation of more stable complexes when compared to the parent hexaaza-18-crown-6, in the end resulting in more efficient extraction of cations from the water environment.

EXPERIMENTAL DETAILS

Synthesis. ^{1}H and ^{13}C NMR spectra were recorded with Bruker AV-300 or AV-600 NMR spectrometers and the NMR spectra were measured in $CDCl_3$ and referenced to tetramethylsilane as an internal standard. IR spectra were recorded with a FT-IR ABB Bomem MB 102 spectrophotometer. MALDI-TOF MS spectra were obtained in "reflectron" mode with an Applied Biosystems Voyager DE STR instrument (Foster City, CA). UV-Vis spectra were recorded on a Phillips P 8730 spectrophotometer. All solvents and the parent hexaaza-18-crown-6·3H_2SO_4 were obtained from commercial sources and used without further purification. 1-Adamantanoyl chloride (**8**),[22] 1-(chloroethanoyl)adamantane (**9**),[23] 1-(2-chloropropanoyl)-adamantane (**10**),[19] 1-(2-tosyloxyethyl)adamantane (**11**),[20a] and 1-(3-tosyloxypropyl)adamantane (**12**)[20a] were prepared according to previously published procedures.

Hexaaza-18-crown-6 (7). Hexaaza-18-crown-6·3H_2SO_4 (**3**·3H_2SO_4) (1.0 g, 1.81 mmol) was dissolved in 50 mL of distilled water and aqueous 20 % NaOH was added until pH = 13 was reached. The resulting mixture was continuously extracted in a Soxhlet apparatus (extraction liquid-liquid) using 500 mL of chloroform. The layers were then separated and the organic phase was evaporated yielding 0.41 g (88 %) of hexaaza-18-crown-6 (**7**). ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.38 (br. s, 6H), 2.77 (br. s, 24H). ^{13}C NMR ($CDCl_3$) δ/ppm: 48.8 (t, 12C).

General Procedure for the Preparation of Amido-hexaaza Crown Ethers 4–6

Hexaaza-18-crown-6 (**7**) (0.100 g, 0.39 mmol) and 4-dimethylaminopyridine (DMAP, 0.005 g, 0.039 mmol) were dissolved in 25 mL of dimethylacetamide (DMA) and 50 mL of CH_2Cl_2 under a nitrogen atmosphere and 0.64 ml (6.8 mmol) Et_3N was added. The reaction mixture was cooled to 0 °C and a solution of the corresponding adamantanoyl chloride (4.8 mmol) in 25 mL of CH_2Cl_2 was added dropwise during 60 min. The mixture was then heated to 50 °C and refluxed for 5 days. After cooling to room temperature 50 mL of a saturated aqueous solution of NH_4Cl was added and the layers were separated in a separation funnel. The water phase was washed with chloroform (2 × 50 mL) and the combined organic extracts were washed with 50 mL of a saturated aqueous solution of $NaHCO_3$, with water (2 × 100 mL) and with 50 mL of a saturated aqueous solution of NaCl. The obtained organic extract was dried over Na_2SO_4, filtered off and evaporated, yielding the crude product that was purified by column chromatography (Al_2O_3, activity II/III, 0→10 % MeOH/CH_2Cl_2), yielding a colorless oil. Analytically pure sample of the product was obtained by rechromatography (Al_2O_3, activity II/III, 0→10 % MeOH/CH_2Cl_2).

1,4,7,10,13,16-hexa(1-adamantanoyl)-1,4,7,10,13,16-hexaazacyclooctadecane (4). Hexaaza crown ether **4** (0.240 g, 34 %) was obtained from 0.150 g (0.58 mmol) of crown **7** and 1.100 g (5.60 mmol) of **8**. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.72 (br. s, 36H), 1.95–2.10 (m, 54H), 3.45–3.65 (m, 24H). ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 28.5 (d, 18C), 36.5 (t, 18C), 39.1 (t, 18C), 42.1 (s, 6C), 47.7 (t, 12C), 178.1 (s, 6C). IR (KBr) $\tilde{\nu}_{max}$/cm^{-1}: 2904 (s), 2850 (m), 1630 (s), 1402 (m), 1228 (w), 1173 (m), 1101 (w), 1051 (w), 729 (w), 665 (w). HRMS (MALDI): calcd. for $C_{78}H_{114}N_6O_6$ 1231.8872; found 1231.8842.

1,4,7,10,13,16-hexa[1-oxo-2-(adamantyl)ethyl]-1,4,7,10,13,16-hexaazacyclooctadecane (5). Hexaaza crown ether **5** (0.302 g, 59 %) was obtained from 0.100 g (0.39 mmol) of crown **7** and 0.932 g (4.80 mmol) of **9**. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.50–1.90 (m, 72H), 1.90–2.15 (m, 24H), 2.25–2.50 (m, 6H), 3.30–3.65 (m, 24H). ^{13}C NMR

(75 MHz, $CDCl_3$) δ/ppm: 28.7 (d, 18C), 33.9 (s, 6C), 36.7 (t, 18C), 42.7 (t, 6C), 42.9 (t, 18C), 45.9 (t, 12C), 172.3 (s, 6C). IR (KBr) $\tilde{\nu}_{max}$/cm^{-1}: 2902 (s), 2847 (m), 1640 (m), 1457 (w), 1416 (w), 1196 (w), 1144 (w). HRMS (MALDI): calcd. for $C_{84}H_{126}N_6O_6$ 1137.9631; found 1137.9673.

1,4,7,10,13,16-hexa[1-oxo-3-(adamantyl)propyl]-1,4,7,10,13,16-hexaazacyclooctadecane (6). Hexaaza crown ether **6** (0.231 g, 50 %) was obtained from 0.080 g (0.31 mmol) of crown **7** and 0.700 g (3.10 mmol) of **10**. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.35–1.80 (m, 84H), 1.95 (br. s., 18H), 2.10–2.55 (m, 12H), 3.25–3.70 (m, 24H). ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 26.7 (t, 6C), 28.6 (d, 18C), 32.1 (s, 6C), 37.0 (t, 18C), 39.7 (t, 6C), 42.1 (t, 18C), 47.2 (t, 12C), 175.0 (t, 6C). IR (KBr) $\tilde{\nu}_{max}$/cm^{-1}: 2901 (s), 2845 (m), 1645 (w), 1419 (w), 1191 (w), 1098 (w). HRMS (MALDI): calcd. for $C_{90}H_{138}N_6O_6$ 1137.9631; found 1400.0653.

General Procedure for the Preparation of Amino-hexaaza Crown Ethers 1–3

A solution of amido-hexaaza crown ether (0.10 mmol) in 5 mL of dry ether was added dropwise to a suspension of $LiAlH_4$ (0.78 mmol) in 10 mL of dry ether. The reaction mixture was refluxed for 7 h, cooled to room temperature and the excess of $LiAlH_4$ was decomposed by adding water, accompanied by a formation of a white precipitate. The organic layer was decanted, the precipitate washed with CH_2Cl_2 (3 × 50 ml) and the combined organic phase was washed with a saturated aqueous solution of NaCl and dried over $MgSO_4$. After filtration and evaporation of the solvent the crude oily product was purified by column chromatography (Al_2O_3, activity II/III, 0→10 % MeOH/CH_2Cl_2). Analytically pure sample of the product was obtained by rechromatography (Al_2O_3, activity II/III, 0→10 % MeOH/CH_2Cl_2).

1,4,7,10,13,16-hexa[2-(1-adamantyl)methyl]-1,4,7,10,13,16-hexaazacyclooctadecane (1). Hexaaza crown ether **1** (0.031 g, 15 %) was obtained from 0.219 g (0.18 mmol) of amido-hexaaza crown ether **4**. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.44 (br. s, 36H), 1.58–1.72 (m, 36H), 1.93 (br. s, 18H), 2.01 (br. s, 12H), 2.48 (br. s, 24H). ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 28.6 (d, 18C), 34.9 (s, 6C), 37.3 (t, 18C), 41.4 (t, 18C), 56.8 (t, 12C), 70.1 (s, 6C). IR (KBr) $\tilde{\nu}_{max}$/cm^{-1}: 2901 (s), 2843 (m), 1450 (w), 1093 (m), 611 (w). HRMS (MALDI): calcd. for $C_{78}H_{126}N_6$ 1148.0116; found 1148.0115.

1,4,7,10,13,16-hexa[2-(1-adamantyl)ethy]-1,4,7,10,13,16-hexaazacyclooctadecane (2). Hexaaza crown ether **2** (0.067 g, 36 %) was obtained from 0.200 g (0.152 mmol) of amido-hexaaza crown ether **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.20–1.30 (m, 12H), 1.49 (br. s, 36H), 1.55–1.75 (m, 36H), 1.93 (br. s, 18H), 2.42–2.70 (m, 36H). ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 28.6 (d, 18C), 31.7 (s, 6C), 37.1 (t, 18C), 40.8 (t, 6C), 42.5 (t, 18C), 49.2 (t, 6C), 52.5 (t, 12C). IR (KBr) $\tilde{\nu}_{max}$/cm^{-1}: 3440 (m), 2901 (s), 2845 (s), 1676 (w), 1449 (m), 1344 (w), 1098 (w), 1012 (w), 733 (w). HRMS (MALDI): calcd. for $C_{84}H_{138}N_6$ 1232.1055; found 1232.1097.

1,4,7,10,13,16-hexa[3-(1-adamantyl)propyl]-1,4,7,10,13,16-hexaazacyclooctadecane (3). Hexaaza crown ether **3** (0.035 g, 24 %) was obtained from 0.148 g (0.11 mmol) of amido-hexaaza crown ether **6.** ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.95–1.08 (m, 12H), 1.34–1.55 (m, 48H), 1.55–1.75 (m, 36H), 1.93 (br. s, 18H), 2.35–2.45 (m, 12H), 2.50–2.65 (m, 24H). ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 20.2 (t, 6C), 28.8 (d, 18C), 32.2 (s, 6C), 37.3 (t, 18C), 42.3 (t, 6C), 42.6 (t, 18C), 52.8 (t, 12C), 56.7 (t, 6C). IR (KBr) $\tilde{\nu}_{max}$/cm^{-1}: 3432 (m), 2900 (s), 2845 (s), 1450 (m), 1098 (w), 733 (w). HRMS (MALDI): calcd. for $C_{90}H_{150}N_6$ 1316.1995; found 1316.1997.

Alternative Procedure for the Preparation of Amino-hexaaza Crown Ethers 2 and 3

Adamantane tosylate (1.0 mmol) and hexaaza-18-crown-6 (**7**) (0.10 mmol) were dissolved in dry acetonitrile (50 mL) under a nitrogen atmosphere, Na_2CO_3 (4.00 mmol) was added and the reaction mixture was refluxed for 5 days. The reaction mixture was cooled to the ambient temperature and concentrated in vacuuo. The oily residue was dissolved in CH_2Cl_2 and filtered through a plug of celite. The combined filtrates were concentrated under reduced pressure to afford the crude product which was purified by column chromatography (Al_2O_3, activity II/III, 0→10 % MeOH/CH_2Cl_2).

Hexaaza crown ether **2** (0.065 g, 13 %) was obtained from 1-(2-tosyloxyethyl)adamantane (**11**) (0.777 g, 2.32 mmol) and hexaaza-18-crown-6 (**7**) (0.050 g, 2.0 mmol).

Hexaaza crown ether **3** (0.074 g, 16 %) was obtained from 1-(3-tosyloxypropyl)adamantane (**12**) (0.674 g, 2.0 mmol) and hexaaza-18-crown-6 (**7**) (0.050 g, 2.0 mmol).

Computational methods. Global minima structures for compounds **1**–**3** and their Na^+ complexes were found using the semiempirical GFN2-xTB[24] method through the Global Optimizer Algorithm (GOAT) implemented in the Orca 6.0. program package.[25] The obtained minima geometries were further refined at the r^{2}SCAN-3c level of theory[26] and verification of the minima by frequency computations was done. Non-covalent interactions (NCI) plots were constructed using Multiwfn 3.6[27] and visualized with Visual Molecular Dynamics (VMD) software.[28]

Extraction experiments. Alkali metal picrate salts were used for performing the respective cation extraction from an aqueous environment. Na^+, K^+, Rb^+, and Cs^+ picrates were freshly prepared by reacting each of the respective

alkali metal hydroxide with picric acid, the formed salts were then isolated and dried prior to use. Li^+ picrate was prepared *in situ* due to its high solubility in water and subsequently used as such. **CAUTION:** Alkali metal picrates are highly explosive compounds and should be handled with extreme care! We prepared solutions of alkali metal picrates in redistilled water, $c = 3 \times 10^{-4}$ mol dm^{-3}, and solutions of the studied hexaaza crown ethers in two times distilled CH_2Cl_2, $c = 3 \times 10^{-4}$ mol dm^{-3}. A CH_2Cl_2 solution (0.5 mL) of the corresponding hexaaza crown ether was placed into a 5 mL screw-top vial, and the aqueous solution of alkali metal picrate (0.5 mL) was added. Another portion of alkali metal picrate solution (0.5 mL) was added to the second vial containing only pure CH_2Cl_2 (0.5 mL) with no host compound (blank probe). The vials were stoppered, shaken on a Termolyne Maxy-Mix III Type 65800 mixer for 4 min and then allowed to stand at ambient temperature for 1 h. A 0.3 mL aliquot of the respective aqueous phase was taken with an automatic pipette and diluted in a volumetric flask by adding redistilled water to a total volume of 2 mL. UV-Vis spectra were then obtained for the two solutions and the percentage of the extracted picrate was in each case calculated from the absorbance value measured at 356 nm, using the following formula: % extraction = $[(A_{blank} - A_{sample}) / A_{blank}] \times 100$. All respective extraction measurements were performed five times in order to obtain the average value of the percent picrate extracted (Table 1). Note that in the absence of a hexaaza crown ether, no alkali metal picrate extraction was detected.

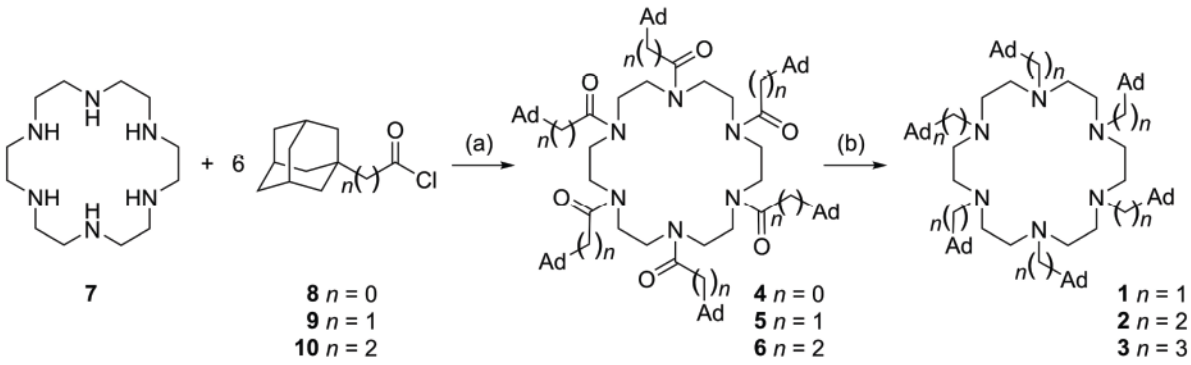
RESULTS AND DISCUSSION

During the design of target hexaaza crown ethers **1**–**3** and their amido-analogues **4**–**6** some concerns were raised whether such derivatives would be feasible for preparation due to their sterically demanding framework. However, preliminary molecular modeling studies revealed that the planned derivatives would possess enough conformational freedom of their side-arm groups to overcome potential steric hindrances. Moreover, the fine balance between repulsion and London dispersion interactions was tilted in favor of the attractive effect in the studied adamantyl hexaaza crown ethers and we were therefore confident to undertake synthetic efforts to obtain such derivatives.

Preparation of hexaadamantyl hexaaza crown ethers **1**–**3** was thus accomplished according to a modified literature procedure.[29] Commercially available hexaaza-18-crown-6·3H_2SO_4 was neutralized[30] to obtain the parent compounds **7** in order to perform a coupling reaction with six equivalents of the corresponding adamantanoyl chlorides **8**–**10** (Scheme 1). The obtained amido-derivatives **4**–**6** were subsequently reduced using $LiAlH_4$, giving the desired adamantyl hexaaza compounds **1**–**3** in acceptable overall yields. Note that we also prepared more flexible hexaaza crown ethers **2** and **3** according to a previously published method using adamantyl tosylates,[20a] but the yields were lower and the purification was much more challenging. This approach included the condensation of the parent crown **7** with 1-(2-tosyloxyethyl)adamantane (**11**) or 1-(3-tosyloxypropyl)adamantane (**12**), respectively (see the Experimental section for more details).

After the successful synthesis of hosts **1**–**3**, we tested their ability to bind alkali metal cations by performing the corresponding picrate salt extraction experiments. Extractions of aqueous alkali metal (Li^+, Na^+, K^+, Rb^+, and Cs^+) picrates were carried out at room temperature with dichloromethane solutions of the hexaaza crown ethers (3×10^{-4} M) and the picrate ion concentrations were determined by UV/Vis spectroscopy. The obtained values of the percent picrate extracted for **1**–**3** were compared with the parent hexaaza crown ether **7** (Table 1).

The measurement results show that host molecules **1**–**3** are indeed capable of extracting alkali metal cations from water into the organic phase. As no extraction was observed when no hexaaza crown ethers were added (blank experiment), it can be concluded that the cation transfer is a consequence of complex formation between the hexaaza crown ether hosts and alkali metal cation



Scheme 1. Preparation of hexaadamantyl hexaaza crown ethers **1**–**3**. (a) DMA, DMAP, Et_3N, CH_2Cl_2, (b) $LiAlH_4$, Et_2O.

Table 1. Extraction of alkali metal picrates with studied hexaaza crown ethers[a].

Host	% of picrate salt extracted[b]				
	Li^+	Na^+	K^+	Rb^+	Cs^+
1	47.7 ± 0.5	43.2 ± 0.8	35.0 ± 0.7	27.8 ± 0.3	35.2 ± 0.5
2	73.3 ± 0.4	83.9 ± 0.6	75.3 ± 0.5	72.3 ± 0.3	55.5 ± 0.3
3	15.2 ± 0.5	68.3 ± 0.7	52.4 ± 0.5	59.9 ± 0.7	48.4 ± 0.5
7	< 2	< 2	7.6 ± 0.5	2.7 ± 0.1	< 2

[a] The extraction experiments were performed using a 3×10^{-4} M CH_2Cl_2 solution of hexaaza crown ethers and a 3×10^{-4} M aqueous solution of alkali metal picrates. The picrate ion concentrations were determined by UV/Vis spectroscopy.

[b] Defined as a percentage of picrate extracted into the organic phase. Each value is the average of five independent extraction experiments.

guests occurring on the water-dichloromethane phase boundary. Even though no marked selectivity for a specific alkali metal was observed, hosts **1**–**3** bind alkali metal cations quite well and are much more efficient when compared to the poorly performing parent hexaaza crown ether **7**. The best extraction percentages were found for smaller cations like Li^+ and Na^+, where smaller host **1** showed a similar preference for both of those cations, while a larger host **3** showed a pronounced preference for Na^+. In general, there is an underlying trend that smaller and more rigid hosts extract better smaller alkali metal cations, while bigger and flexible hosts prefer to incorporate alkali metals of larger radii. Additionally, the highest overall alkali metal cation extraction percentage was achieved with hexaaza crown ether **2** (83.9 % for Na^+), making it the most efficient host in the series. Here it should also be noted that the amido derivatives **4**–**5** bind alkali metal cations very poorly or not at all (< 2 %) in the described experimental conditions. Such behavior of amido macrocyclic receptors of this type is in line with previous observations, both in the literature and in our laboratory.

To gain more insight into the complex structures and stabilities of hexaaza crown ethers **1**–**3**, we performed a computational analysis of both the host molecules and the formed complexes. Since all three hosts extracted Na^+ very well and since compound **2** possessed the best overall extraction capability in the explored series for exactly that alkali metal, we narrowed down our computational study to complexes of **1**–**3** with a sodium cation. Conformational flexibility of the crown host plays an important role in energetic stabilization of the whole scaffold but the question remains how exactly this structural reorganization is driven. We have previously shown that similar crown ethers and cryptands have a wide conformer distribution due to their inherent high flexibility.[20,21] This molecular feature can also be observed from the NMR spectra of pure hexaaza crown ethers prepared in this study (see Figures S1–S12). Namely the peaks in ^{13}C NMR corresponding to the crown core are not symmetry equivalent but are instead distinct. Our hypothesis was that intramolecular dispersion interactions significantly influence the conformer distribution of such hexaaza crown ethers substituted with bulky adamantyl side-arms (and of their complexes), but this needed to be confirmed. We therefore first performed a global minima search for compounds **1**–**3** and for their Na^+ complexes with the Global Optimizer Algorithm (GOAT) that uses a GFN2-xTB method, as implemented in Orca 6.0. After identifying the minima structures, we then further optimized the obtained geometries at the r²SCAN-3c level of theory to get the final structures. Other hexaaza derivatives have been studied previously by computational means and the use of DFT proved to be a valid approach.[31] In case of our somewhat larger molecules, use of the composite electronic-structure method r²SCAN-3c that incorporates adapted D4 (for London dispersion) and geometrical counter-poise (for basis set superposition error) corrections allowed for a reliable analysis of structures where non-covalent interactions are prominent.

Firstly, one immediately notices the stark structural difference between the respective hexaaza crown ether and its sodium cation complex (Figure S13). In principle, the host molecule not engaged in binding exhibits a kind of expansion of its side-arms into the surrounding space; this is especially apparent for the most rigid compound **1**. As the linker size and flexibility increases, so does the tendency of the present bulky substituents to group and engage in intramolecular close contacts. This is effectively a demonstration of London dispersion in action after the conformational energetic penalties originating from the crown core are reduced, since in host **2** four + two adamantane cages are in close contact and in the most flexible host **3** even five of them interact with each other. Going next to the complexes, when comparing the obtained structures of **1**·Na^+, **2**·Na^+, and **3**·Na^+, respectively (Figure 2), we found that all studied hexaaza crown ethers bind Na^+ with the crown core, as is to be expected since this is the primary binding region of the host. However, in all three complexes the adamantane side arms also take part in the binding stabilization (Figure S13, Table S2). One can observe that the hexaaza crown ether **1** additionally binds the cation with three adamantane side arms. As these adamantyl cages are connected to the crown core through

one CH_2 group, the conformational flexibility of the molecule is somewhat reduced and the remaining three side-arms do not appear to engage in complex formation. Apart from the previously mentioned complementarity of the host size with the alkali metal radius, this effect can also contribute to the observed lower extraction capabilities of **1**. On the other hand, in the structure of complex **2**·Na^+ four adamantyl substituents connected with the core through two CH_2 groups are engaged in cation stabilization, with a fifth side-arm providing further dispersion stabilization through close contacts with two of these four cages. Note that only the sixth side-arm is not conformationally grouped around the binding region. Such close packing of the bulky substituent seems to be very beneficial for sodium cation capture and is in line with the experimentally observed 83.9 % of Na^+ extraction (Table 1). Lastly, the structure of the hexaaza crown ether **3** complex with a sodium cation again points to a beneficial effect of the four adamantyl substituents on the binding but since the linker to the crown core is composed of three CH_2 groups, the host possesses more flexibility when compared to **2**. Consequently, the fifth and the sixth side-arm can more easily orient closer to each other and therefore engage in dispersion interactions between themselves (Figure S13 and S14). This added flexibility is also reflected in a slightly reduced Na^+ extraction percentage (68.3 %). Based on these observations we can conclude that for this type of bulky hexaaza crown ethers one needs to hit the sweet spot to achieve the most efficient alkali metal cation extraction: a structure that is too rigid binds poorly but too much flexibility also leads to a reduced performance. It appears that host **2** with a linker two CH_2 groups long is positioned just right on this flexibility scale.

In addition to qualitative comparison of the global minima structures, we also computed binding energies for the complex formation. Thus, for complexes **1**·Na^+, **2**·Na^+, and **3**·Na^+ the binding energies amount to –44.1, –76.9, and –64.1 kcal mol^{-1}, respectively (Table S1). It is gratifying to see that the obtained values closely match both the experimental extraction data and the structural analysis rationale. Namely, host **2** that extracts the sodium cation the best, also has the most favorable binding energy (–76.9 kcal mol^{-1}) and the best 4+1 side-arm stabilization of the binding region. Analogous comparisons can be made for hexaaza crown ethers **1** and **3**.

Lastly, we also constructed non-covalent interactions (NCI) plots for the studied complexes in order to better visualize the regions in the computed structures where the intramolecular attractive contributions are the strongest. The performed r^2SCAN-3c computations provided us with the needed electron density and its derivatives that we then used for the NCI plot generation. The corresponding structures are depicted in Figure S14 and their inspection once more confirms the prevalence and importance of non-covalent stabilizing interactions in the structures of adamantane-substituted hexaaza crown ether complexes.

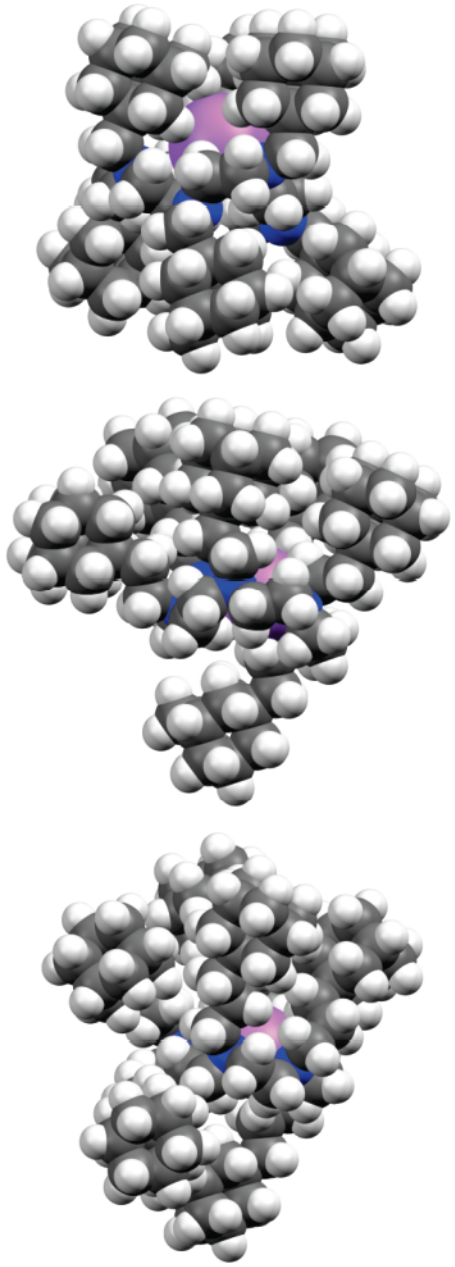


Figure 2. Optimized structures of sodium complexes with hosts **1**–**3**, from top to bottom: **1**·Na^+, **2**·Na^+, and **3**·Na^+.

CONCLUSIONS

We designed and prepared hexaaza crown ethers **1**–**3** substituted with six adamantyl side-arms of different

linker length for application as alkali metal cation binders. These hexaadamantyl hexaaza crown ethers were specifically tailored to take advantage of London dispersion interactions acting inside the molecules and subsequent complexes, in order to surpass the poor binding capabilities of the parent hexaaza-18-crown-6 (**7**), which was successfully accomplished. While the performed extraction experiments did not reveal a marked preference for any single alkali metal cation type, the studied host molecules **1**–**3** all demonstrated efficiency in alkali metal extraction from the aqueous to the organic phase. The best result in the series was achieved for the extraction of Na^+ with host **2**, reaching 83.9 %. The computational analysis that included a global minima search and structure refinement revealed the structural characteristics of the host molecules and the formed complexes with a sodium cation. In addition to identifying numerous close contacts between the adamantyl side-arms in the final geometries and thereby confirming the importance of dispersion interactions for conformer stabilization, the obtained binding energies for complex formation and their match with experimental extraction percentage trends further supported our proposed structural analysis rationale. We next plan to test these new adamantyl hexaaza crown ethers **1**–**3** for their potential biological activity, especially for disrupting the alkali metal cation intake into cells. A possible strategy would be to use the lipophilic adamantyl side-arms as an anchoring unit in various lipid bilayers (liposomes or cell membranes),[32] while the crown core would be partially exposed and could act as an alkali metal cation receptor unit. Such dual supramolecular system would thereby take advantage of its inherent non-covalent interaction capability and its highly flexible and adaptable nature to push the resulting conformational distribution towards a desired mode of action, like supramolecular recognition processes[33] applicable in medicinal chemistry.

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Supplementary Information. Supporting Information contains NMR spectra of the prepared compounds, figures depicting computed structures, computational details and coordinates of the computed structures, and is attached to the electronic version of the article at: https://doi.org/10.5562/cca4146.

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