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Design, synthesis and cation-binding properties of novel adamantane- and 2-oxaadamantane-containing crown ethers

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Abstract—The synthesis of a series of adamantane- and 2-oxaadamantane-functionalized crown ethers **1**–**7** is described. Alkali metal picrate extraction profiles have been determined for these novel ionophores. The ability of crown ethers **1**–**7** to extract the alkali metal picrates was compared with that of benzo-15-crown-5 and 18-crown-6. Also, Na^+- and K^+-transport, the ability of ionophores **l**–**3** to transport Na^+- and K^+ across a bulk liquid membrane was measured. The results of alkali metal cation extraction experiments showed that the complexation properties of crown ethers **1** and **2** are comparable to that of benzo-15-crown-5 and 18-crown-6, respectively. Crown ether **3** showed enhanced extractability for all cations but lower selectivity compared to 18-crown-6. However, adamantano-crown ethers **4**–**7** showed almost negligible extraction capability toward any of the alkali cations. The observed differences among the complexation abilities of the ionophores **1**–**3** and **4**–**7** are rationalized on the basis of the results of a molecular modeling study of their corresponding K^+ complexes.

1. Introduction

Synthetic macrocyclic polyethers that contain intramolecular cavities of the appropriate size and shape are interesting complexing agents from the standpoint of their recognition capabilities.[1,2] Their structural features determine the stability and the properties of their respective complexes with inorganic and organic ions as well as with neutral molecules.[3,4] Although a vast literature has been accumulated during the past thirty years, a relatively small number of papers are concerned with crown ethers that incorporate a polycyclic moiety as part of crown-backbone. The synthesis and complexation properties of some macrocyclic polyethers that contain cubane, pentacycloundecane or adamantane moiety have been reviewed recently.[5] Incorporation of a rigid polycyclic moiety into crown ethers should affect their conformational mobility and also their complexation abilities. The lipophilic polycyclic moiety should increase the solubility of the crown ethers in nonpolar solvent and thereby increase their ability to perform selective ion extraction and ion transport via their complexation with metal ions.

As a part of our extensive program which is involved with the synthesis and complexation properties of adamantane-[6] and 2-oxaadamantane-[7] containing macrocyclic polyethers, we have prepared a series of novel mono- and bis-1,3-bridged adamantane and 2-oxaadamantane crown ethers **1**–**7**[8] and investigated their binding ability and selectivity towards alkali metal compared with that of benzo-15-crown-5 and 18-crown-6. In addition, transport of sodium and potassium picrates across a bulk chloroform membrane containing crown ethers **1**–**3** as carriers was performed. The difference between the complexation abilities of ionophores **1**–**3** and **4**–**7** can be understood on the basis of the results obtained from a molecular modeling study of their corresponding K^+ complexes.

2. Results and discussion

2.1. Synthesis of ionophores 1–7

The 2-oxaadamantane-containing crown ethers **1**, **2** and **3** were prepared from diol **8** by using an approach based upon the Williamson ether synthesis (Scheme 1).

Thus, NaH promoted reaction of diol **8** with 1-tosyloxy-2-benzyloxyethane in DMF afforded **9** in 40% yield. Subsequent hydrogenation of **9** produced the corresponding diol **10** quantitatively. The Na^+-templated reaction of the conjugated base of diol **10** with ethylene glycol ditosylate resulted in the formation of crown ether **1** in 33% yield. By using the same conditions, condensation of diol **8** with tetraethylene glycol ditosylate afforded crown ether **2** in 36% yield.

Diol **10** was converted into the corresponding tosylate, **11**, in 98% yield via a standard procedure that employed TsCl–pyridine. Subsequent Na^+-templated, base promoted

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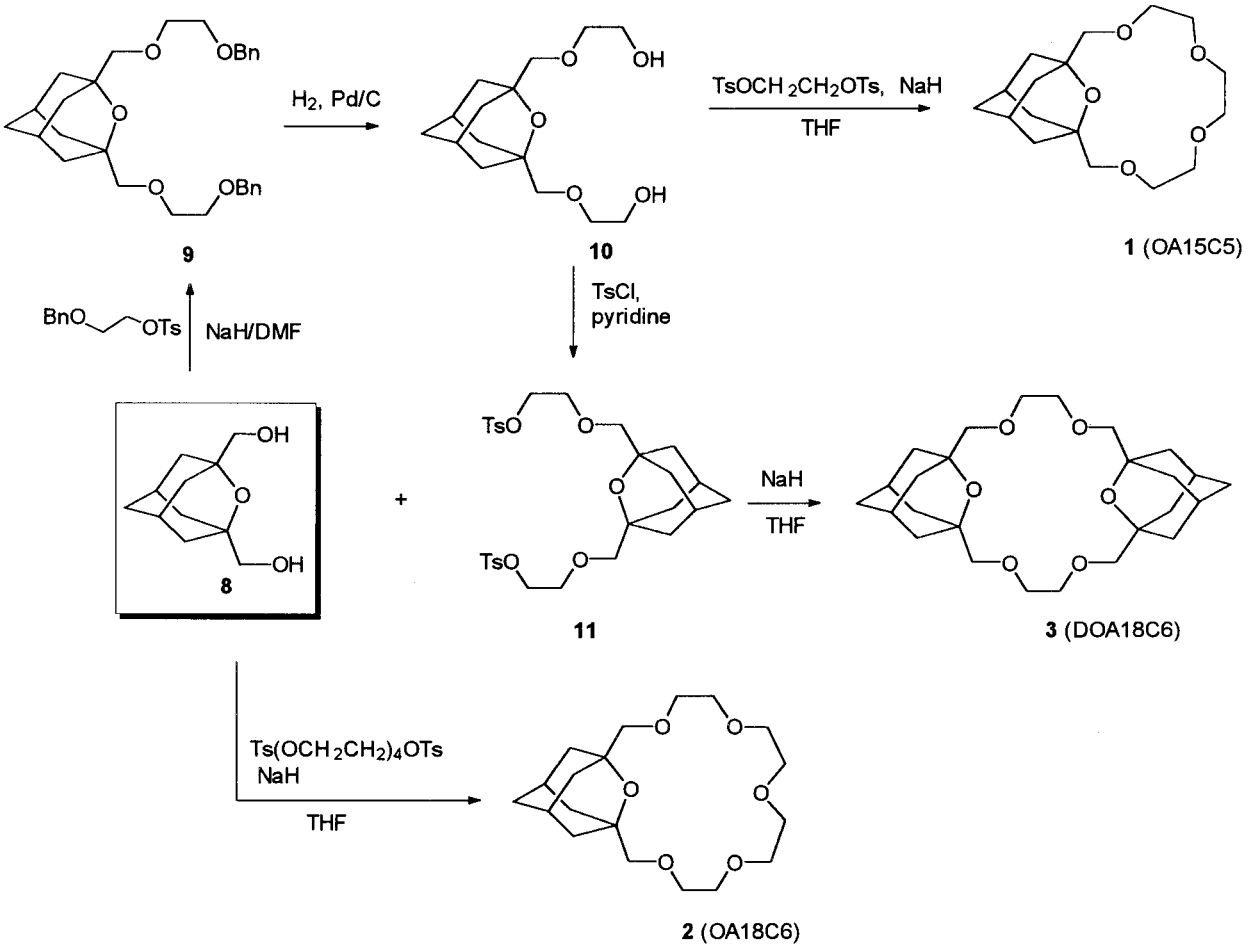


Scheme 1.

reaction of diol **8** with ditosylate **11** gave crown ether **3** in 30% yield.

Novel 1,3-bis(hydroxymethyl)-2-oxaadamantane (**8**) was prepared in 37% overall yield via vinylmagnezium bromide addition to 7-*exo*-epoxymethylenebicyclo[3.3.1]nonan-3-one[9] followed by ozonization and reductive cleavage of the intermediate ozonide by using BH_3–SMe_2 complex.[10]

Similarly, Na^+-templated, base promoted condensation was employed to prepare crown ethers **4**–**7** (Scheme 2). NaH promoted condensation of diols **12**[11] and **13**[6c] with tetraethylene glycol ditosylate afforded crown ethers **4** and **5** in 40 and 25% yield, respectively.

NaH promoted reaction of diol **14** with diethylene glycol ditosylate gave crown ether **6** in 57% yield. Base promoted cyclization between diol **14** and the corresponding ditosylate, **15**, afforded crown ether **7** in 32% yield.

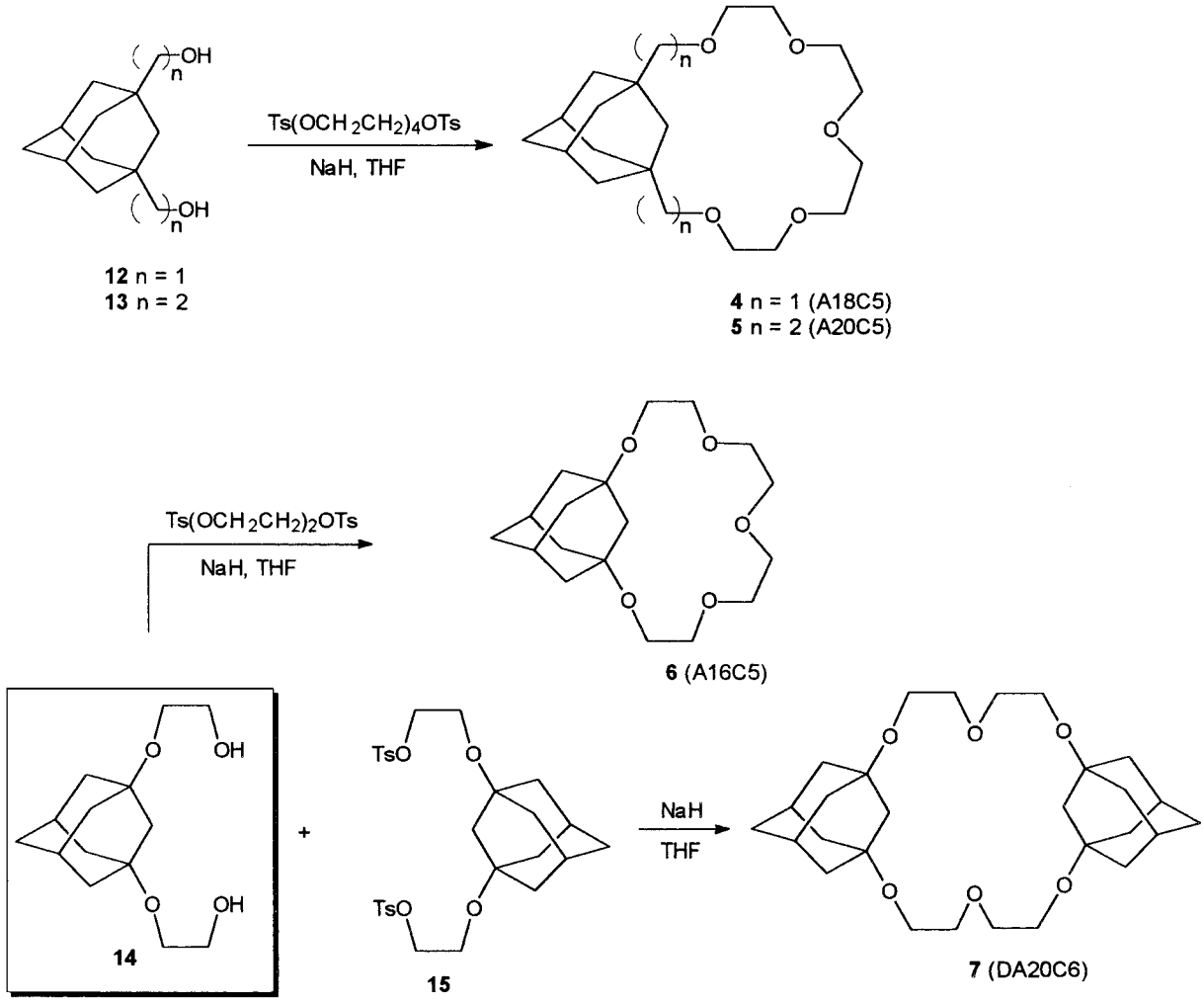
Hitherto unknown diol **14** was prepared in one step by Ag^+-promoted alkylation. Thus, reaction of 1,3-dibromoadamantane with ethylene glycol and two equivalents of $AgNO_3$ afforded the corresponding diol, **14**, in 62% yield.

The structures of new compounds **1**–**7** were established spectroscopically (see Experimental). The structure of **3** was confirmed by X-ray[12] crystallographic analysis.

2.2. Alkali metal ion selectivities of ionophores 1–7

In order to survey cation binding abilities of ionophores **1**–**7**, alkali metal picrate extraction experiments were carried out. Since picrate ion concentration can be easily determined by UV, extractions of aqueous alkali picrates (Li^+, Na^+, K^+, Rb^+ and Cs^+; 5×10^{-3} M) were carried out at 25°C with chloroform solutions of crown ethers **1**–**7** (5×10^{-3} M), and results were compared with those obtained by using commercially available 18-crown-6 and benzo-15-crown-5. In addition 'blank' experiments in which $CHCl_3$ contained no crown ether were carried out for each alkali metal picrate salt. The results are shown in Table 1.

As can be seen from the data in Table 1, the extractabilities of oxaadamantano-crown ethers **1**–**3** toward alkali cations are in good agreement with the generally accepted 'ion-cavity' concept.[1,4] However, adamantano-crown ethers **4**–**7** showed almost negligible extractions toward any of the alkali cations studied. Thus, the alkali metal cation complexation and extraction properties displayed by 2-oxaadamantano-15-crown-5 (**1**) and 2-oxaadamantano-18-crown-6 (**2**) are similar to those shown by benzo-15-crown-5 and 18-crown-6,



Scheme 2.

respectively. However, ionophore **2** showed lower extractability toward K^+ but somewhat increased extractability toward Na^+ and Cs^+ ions compared to that of 18-crown-6.

Symmetrical bis(2-oxaadamantano)-18-crown-6 (**3**) showed high extractability towards all alkali cations, particularly K^+ and Rb^+. Ionophore **3** displayed surprisingly high affinity toward Na^+ or even Li^+ cations when compared to parent 18-crown-6. One might assume that the unusual extraction behavior of ionophore **3** could be attributed to the formation of a relatively stable complex in which the metal cation guest is surrounded additionally with two bulky groups.[12b] It is generally believed that polyethers form a complex with a cation guest by surrounding it with an electronegative environment of oxygen atoms that screen the ion from the surrounding nonpolar solvent.[1] How extensively the cation is complexed, and, hence, how effectively it is transported, depend on how well it fits into the macrocyclic cavity and also the facility with which the cation and anion depart from the host carrier at the membrane interface. In order to obtain

Table 1. Extraction of alkali picrates with $CHCl_3$ containing crown ethers

Ionophore	Extractability (%)[a]				
	Li^+	Na^+	K^+	Rb^+	Cs^+
18-Crown-6	1.5±0.4	4.0±0.6	73.7±0.2	61.3±0.4	34.7±0.5
Benzo-15-crown-5	<1	8.1±0.3	6.4±0.2	1.8±0.3	1.1±0.1
1 (OA15C5)	1.3±0.7	6.8±0.6	8.2±0.8	3.4±0.7	3.1±0.9
2 (OA18C6)	<1	9.8±0.3	64.0±0.7	61.0±0.1	41.9±0.5
3 (DOA18C6)	17.5±0.5	21.7±0.3	88.1±0.2	86.8±0.1	69.4±0.4
4 (A18C5)	<1	1.2±0.2	<1	<1	<1
5 (A20C5)	<1	<1	<1	<1	<1
6 (A16C5)	<1	2.3±0.2	<1	<1	<1
7 (DA20C6)	3.6±0.4	<1	<1	<1	<1

[a] Defined as percent of picrate extracted into organic phase. Each value is the average of three independent experiments.

Table 2. Transport rate of Na^+ and K^+ picrate through chloroform membrane containing crown ethers

Crowns[a]	$(j_c)^b$ mol $h^{-1}\times10^{-7}$		$(n)^c$ mol$\times10^{-6}$ in 24 h	
	Na^+	K^+	Na^+	K^+
1 (OA15C5)	0.18	0.16	0.39	0.36
2 (OA18C6)	0.43	2.48	0.67	3.58
3(DOA18C6)	0.52	1.55	0.87	2.03
18-C-6	0.12	2.04	0.21	3.58

[a] Chloroform membrane contained $7.5\cdot10^{-4}$ mol of corresponding crown ether. The molar ratio of crown ether:M-picrate was 1:10.
[b] Each value is the average of two or three independent measurements with deviation less than ±5%.
[c] Measured value.

convincing evidence regarding this point, we carried out a series of ion transport studies. We studied the transport rates (j_c, in mol h^{-1}) through organic liquid membrane (H_2O–$CHCl_3$–H_2O) for sodium and potassium picrate by crown ether **1**, **2**, **3**, and 18-crown-6. The results are shown in Table 2.

A plot of moles of cation transported into aqueous phase vs time was constructed for each carrier-containing system. Linear increase in concentration in the receiving phase with increasing time was observed through the first 7 h (see Figs. 1 and 2). In each case, the transport rate (j_c) could be obtained from the slope of the line. A similar linear increase in salt concentration in the receiving phase with increasing time was reported earlier.[13]

The transport rates of Na^+ picrate with ionophores **1**–**3** are in accord with their low extractability (Table 1). From the data obtained for transport of K^+ picrate (Table 2, Fig. 1), it can be seen that ionophore **2** transports K^+ picrate ca. 20% faster than does the parent 18-crown-6. However, the transport rate obtained by using crown ether **3** is approximately 25% lower than the corresponding transport rate of 18-crown-6. Since crown ether **3** extracts >88% of K^+ picrate, it appears that the rate of cation-release is responsible for the relatively low transport rate. It has been found that the transport rate depends significantly upon cation-carrier complex stability.[13,14a,b] If the complex is unstable, cations are not extracted from the source phase into the organic phase. On the other hand, if the complex is very stable, cations are not released rapidly from the membrane into the receiving phase.[14c]

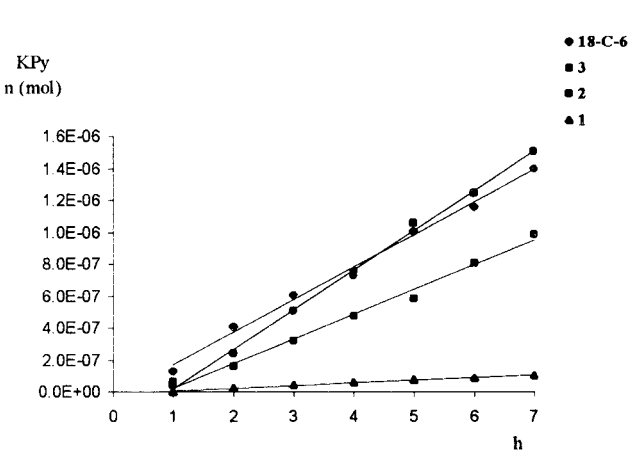


Figure 1. Transport of KPy through $CHCl_3$ membrane containing ionophores **1**, **2**, **3** or 18-crown-6.

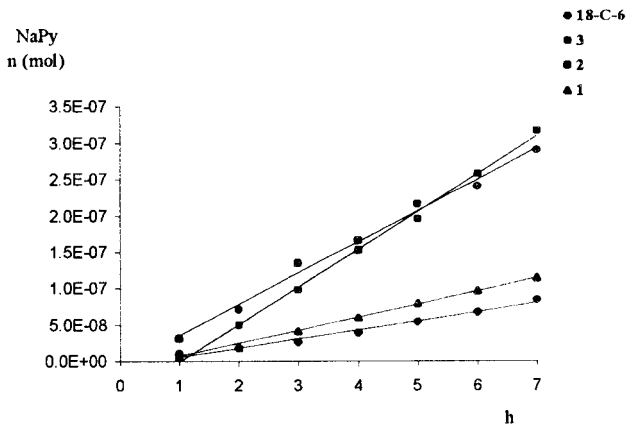


Figure 2. Transport of NaPy through $CHCl_3$ membrane containing ionophores **1**, **2**, **3** or 18-crown-6.

In order to better understand the remarkable difference between the complexation abilities of the 2-oxaadamantane ionophores **1**–**3** and adamantane crowns **4**–**7**, we carried out molecular modeling calculations for the corresponding complexes with potassium ion. According to the results of the molecular mechanics calculations, ionophore **3** possesses the ideal cavity size to complex K^+. In addition, ionophore **3** has reduced conformational mobility and therefore is better preorganized to complex K^+ than is the less symmetrical crown ether **2** or even the corresponding parent 18-crown-6.[15] The complexation of potassium ion with six ether oxygens stabilizes the macrocyclic ring.[12c] One bulky oxaadamantane moiety is situated below and another above the macrocyclic ring, and they provide additional 'steric support' to maintain potassium ion inside the cavity (Fig. 3a).

The macrocyclic ring-cavity in adamantano-18-crown-5 (**4**) can also accommodate K^+. However in the resulting complex, K^+ is expelled from the cavity due its steric interactions with the C–H bonds of adamantane moiety that are directed toward the center of cavity (Fig. 3b). Raevsky et al.[16] have obtained similar results for an unsubstituted 18-crown-6 and 18-crown-5. On the other hand, diminished binding of K^+ can be rationalized on the replacement of favorable O···K^+ interaction by an unfavorable C–H···K^+ interaction.

Adamantano-20-crown-5 (**5**) and bis(adamantano)-20-crown-6 (**7**) showed no ability to complex alkali metal cations (see Table 1). These observations are in agreement with the results obtained by Ouchi et al.,[17] who observed that cation-binding abilities of the ring-extended crown ethers showed a significant shift in cation selectivity, probably due to the enlarged cavity size. They found that the cation-binding abilities of less symmetrical crown ethers generally are lower than those displayed by common symmetrical crown ethers. Contrary to 16-crown-5,[17] adamantano-16-crown-5 (**6**) showed very low extractability toward Na^+ (Table 1). The molecular modeling studies

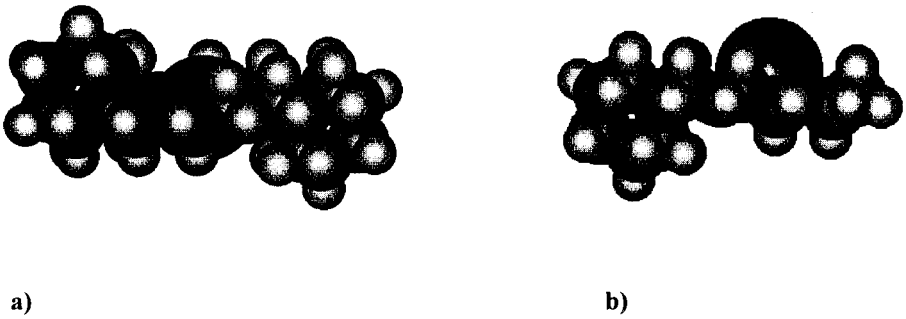


Figure 3. Side view of CPK models (obtained from calculations): (a) K^+ complex of bis(2-oxaadamantano)-18-crown-6 (**3**); (b) K^+ complex of adamantano-18-crown-5 (**4**).

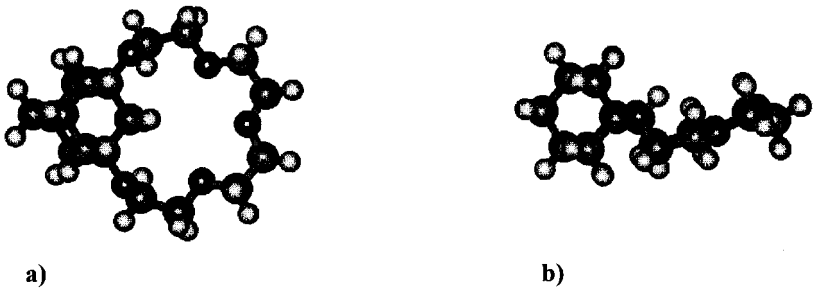


Figure 4. Illustration of the most stable conformation of adamantano-16-crown-5 (**6**): (a) top view; (b) side view.

showed that oxygen-atoms, which are connected to the C1 and C3-atoms of adamantane units, have reduced cation-binding abilities due to the steric effect of the C–H bonds situated at the C2 carbon atom in adamantane (Fig. 4). The adamantane-methylene group reduces the cavity size of crown ether **6** and also makes it less symmetrical, thereby impeding the potential binding interactions of all five oxygen-atoms with cation.

3. Conclusions

A number of new adamantane and 2-oxaadamantane containing crown ethers were synthesized, and their cation-binding abilities were evaluated by using a solvent extraction technique. The results of extraction experiments that involved alkali metal cations indicate that the complexation properties of crown ethers **1** and **2** are comparable to those of benzo-15-crown-6 and 18-crown-6, respectively. By way of comparison, crown ether **3** showed enhanced extractability for all cations, but **3** displayed lower selectivity when compared to 18-crown-6. However, adamantano crown ethers **4**–**7** showed practically no extraction capabilities toward any of the alkali metal cations. The results of molecular modeling studies of the various crown ethers studied and their corresponding K^+ complexes indicate that the observed lower complexation properties of crown ethers **4**–**7** may be due to steric hindrance presented by the methylene group at the adamantane C2 position. Transport of Na^+ and K^+ picrate, through liquid membrane by ionophores **l**–**3** and 18-crown-6 showed a linear increase in ion concentration in the receiving phase with increasing time.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were obtained by using Varian Gemini 300 nuclear magnetic resonance spectrometer. IR spectra were recorded on a Perkin–Elmer M-297 spectrophotometer. UV-spectra were recorded on Philips P 8730 spectrophotometer. The purity of all compounds was determined by GLC and/or via ^{13}C NMR spectral analysis. GLC analyses were carried out on a Varian 3300 gas chromatograph equipped with a DB-210 capillary column. Melting points were determined on Kofler apparatus and are uncorrected. Elemental analyses were performed at Central Analytical Laboratory, IRB, Zagreb. Unless stated otherwise, reagent grade solvents were employed.

4.2. Molecular modeling studies

All molecular modeling studies were carried out with complete geometry optimization by using HyperChem 5.0.[18] To obtain the most stable conformer of the corresponding crown ether the molecular mechanics calculations were performed by using AMBER parameters.[19] The charge distribution was first estimated by using PM3 semiempirical method, then K^+ was introduced into the crown ether-ring, and the geometry of corresponding complex was optimized by using the same AMBER parameters as had been employed for the ligand.

4.3. General procedure for the synthesis of ionophores 1–7

Sodium hydride obtained as a 50% suspension of NaH in

mineral oil (ca. 10 equiv. relative to the diol), was washed with pentane (3×40 mL) under nitrogen to remove the mineral oil. Pentane was decanted after the last washing, and dry THF (250 mL) was added under nitrogen to the residue. The resulting suspension then was heated to reflux, and a solution of corresponding alcohol and ditosylate (1:1 ratio, ca. 1–2 mmol) in dry THF (150 mL) was added dropwise during 16 h. The resulting mixture was refluxed for an additional 5 days, and then was allowed to cool gradually to ambient temperature. Excess of NaH was destroyed via careful addition of water (ca. 1 mL), and the resulting mixture was filtered. The filtrate was concentrated in vacuo, water (500 mL) was added to the residue, and the resulting aqueous suspension was extracted with CH_2Cl_2 (4×150 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue thereby obtained was purified via column chromatography.

4.3.1. 2,15-[(1,3)2-Oxaadamantano]-15-crown-5 (1). By following the general procedure, compound **1** was obtained via reaction of diol **10** (500 mg, 1.76 mmol) with ethylene glycol ditosylate (680 mg, 1.76 mmol). The crude product was purified by column chromatography on silica gel by eluting with 0→2% MeOH in CH_2Cl_2. Pure **1** (180 mg, 33%) was thereby obtained as a colorless oil: IR (KBr/film) 2900, 2850, 1445, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.43 (d, J=9.5 Hz, 4H), 1.75–1.80 (m, 6H), 2.21 (bs, 2H), 3.30 (s, 4H), 3.65–3.75 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.8, 35.4, 36.2, 70.4, 71.3, 72.7, 78.5. Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.30; H, 9.11.

4.3.2. 2,18-[(1,3)2-Oxaadamantano]-18-crown-6 (2). By following the general procedure, compound **2** was obtained via reaction of diol **8** (440 mg, 2.22 mmol) with tetraethylene glycol ditosylate (1.12 g, 2.22 mmol). The crude product was purified via column chromatography on silica gel by eluting with 0→2% MeOH in CH_2Cl_2. Pure **2** (290 mg, 36%) was thereby obtained as a colorless oil: IR (KBr/film) 2900, 2860, 1470, 1450, 1350, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (d, J=12.2 Hz, 4H), 1.77–1.81 (m, 6H), 2.22 (bs, 2H), 3.32 (s, 4H), 3.67–3.72 (m, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.8, 35.4, 36.1, 70.2, 70.6, 71.1, 72.5, 78.4. Anal. Calcd for $C_{19}H_{32}O_6$: C, 64.02; H, 9.05. Found C, 63.91; H, 9.10.

4.3.3. 2,18:9,11-Bis[(1,3)2-oxaadamantano]-18-crown-6 (3). By following the general procedure, compound **3** was obtained via reaction of diol **8** (300 mg, 1.52 mmol) with ditosylate **11** (900 mg, 1.52 mmol). The crude product was purified via column chromatography on silica gel by eluting with 10→20% EtOAc in CH_2Cl_2. Pure **3** (200 mg, 30%) was thereby obtained as a white crystals: mp=210–212°C. IR (KBr) 2920, 2900, 2850, 2815, 1440, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (d, J=12.2 Hz, 8H), 1.78–1.85 (m, 12H), 2.22 (bs, 4H), 3.33 (s, 8H), 3.73 (s, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.9, 35.5, 36.1, 71.3, 72.8, 78.0. Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.62; H, 9.16.

4.3.4. 15,17-(1,3)Adamantano-18-crown-5 (4). By following the general procedure, compound **4** was obtained via reaction of diol **12** (400 mg, 2.02 mmol) with tetraethylene glycol ditosylate (1.01 g, 2.02 mmol). The crude product was purified via column chromatography on silica gel by eluting with 10→20% EtOAc in CH_2Cl_2. Pure **4** (285 mg, 40%) was thereby obtained as a colorless oil: IR (KBr) 2900, 2850, 1450, 1350, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31 (d, J=11.5 Hz, 4H), 1.55–1.65 (m, 8H), 2.03 (bs, 2H), 3.06 (s, 2H), 3.54–3.56 (m, 4H), 3.62–3.64 (m, 4H), 3.70 (s, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.0, 34.2, 37.1, 39.0, 40.9, 69.9, 70.2, 70.6, 70.8, 81.4. Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.8; H, 9.7. Found: C, 67.61; H, 9.63.

4.3.5. 16,18-(1,3)Adamantano-20-crown-5 (5). By following the general procedure, compound **5** was obtained via reaction of diol **15** (225 mg, 1.00 mmol) with tetraethylene glycol ditosylate (505 mg, 1.00 mmol). The crude product was purified via column chromatography on silica gel by eluting with 10→20% EtOAc in CH_2Cl_2. Pure **5** (93 mg, 25%) was thereby obtained as a colorless oil: IR (KBr/film) 2900, 2850, 1450, 1350, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29–1.48 (m, 14H), 1.56 (bs, 2H), 1.95 (bs, 2H), 3.49–3.66 (m, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.8, 32.2, 36.5, 42.4, 43.1, 45.3, 67.1, 70.2, 70.7, 70.8, 70.9. Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.08; H, 10.01. Found: C, 69.17; H, 9.94.

4.3.6. 14,16-(1,3)Adamantano-16-crown-5 (6). By following the general procedure, compound **6** was obtained via reaction of diol **14** (370 mg, 1.46 mmol) with diethylene glycol ditosylate (610 mg, 1.46 mmol). The crude product was purified via column chromatography on silica gel by eluting with 0→2% MeOH in CH_2Cl_2. Pure **6** (185 mg, 57%) was thereby obtained as a white crystals: mp=39–41°C. IR (KBr/film) 2910, 2860, 1450, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.49 (bs, 2H), 1.62–1.75 (m, 8H), 1.79 (bs, 2H), 2.30 (bs, 2H), 3.60 (bs, 8H), 3.67 (bs, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.5, 35.1, 40.3, 44.7, 59.7, 70.3, 70.4, 70.6, 74.2. Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.25; H, 9.25. Found: C, 66.41; H, 8.99.

4.3.7. 8,10:18,20-Bis[(1,3)adamantano]-20-crown-6 (7). By following the general procedure, compound **7** was obtained via reaction of diol **14** (410 mg, 1.61 mmol) with ditosylate **13** (920 mg, 1.61 mmol). The crude product was purified via column chromatography on silica gel by eluting with 0→2% MeOH in CH_2Cl_2. Pure **7** (230 mg, 32%) was thereby obtained as a white crystals: mp=174–176°C; IR (KBr) 2920, 2890, 2860, 1450, 1355, 1115, 1075, 1000 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50 (bs, 4H), 1.61 (d, J= 11.5 Hz, 8H), 1.74 (d, J=11.5 Hz, 8H), 1.86 (bs, 4H), 2.27 (bs, 4H), 3.57–3.63 (m, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.4, 35.1, 40.6, 44.0, 60.3, 70.9, 74.3. Anal. Calcd for $C_{28}H_{44}O_6$: C, 70.56; H, 9.30. Found: C, 70.47; H, 9.21.

4.3.8. 1,3-Bis(hydroxymethyl)-2-oxaadamantane (8). Ozone was bubbled during 6 h through the solution of 1-hydroxymethyl-3-vinyl-2-oxaadamantane[9b] (6.41 g, 33.00 mmol) in CH_2Cl_2 (250 mL) at −75°C. The solution was then allowed to warm up to room temperature, purged with N_2 for 30 min, and BH_3×SMe_2 (3×5 mL) was added in the intervals of 15 min. The reaction mixture was stirred

overnight at room temperature, then 5% HCl (10 mL) was added, and stirring was continued for another 4 h. The resulting suspension was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated. The residue was chromatographed on silica gel with 0→5% MeOH in CH_2Cl_2 as the eluant, to give 4.10 g (63%) of 1,3-bis(hydroxymethyl)-2-oxaadamantane (**8**), mp=131–134°C. IR (KBr): 3360, 3280, 2920, 2840, 1450, 1055, 1045, 1025 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.37 (d, J=12.3 Hz, 4H), 1.65–1.80 (m, 8H), 2.21 (bs, 2H), 3.32 (s, 4H), 3.74 (2×OH); ^{13}C NMR ($CDCl_3$) δ 26.6, 35.4, 35.6, 69.8, 72.9. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.66; H, 9.14.

4.3.9. 1,3-Bis[(2-benzyloxyethyloxy)methyl]-2-oxaadamantane (9). Solution of 1,3-bis(hydroxymethyl)-2-oxaadamantane (**8**, 3.63 g, 18.30 mmol) in dry DMF (25 mL) was added to a stirred, cooled (ice/water) suspension of NaH (3.50, 73.00 mmol; 50% in mineral oil) in dry DMF (50 mL) under N_2. The cooling bath was removed after 30 min, reaction mixture was stirred on room temperature for 3 h and cooled again with ice/water. To a cooled reaction mixture solution of 2-benzyloxy-1-tosyloxyethane[20] (12.30 g, 40.25 mmol) in dry DMF (15 mL) was added. The reaction mixture was stirred for additional 48 h and then water (250 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3×100 mL). Organic extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated and residue was chromatographed on silica gel with 10→25% EtOAc in pentane as the eluant, to give 3.35 g (40%) of 1,3-bis-[(2-benzyloxyethyloxy)methyl]-2-oxaadamantane (**9**) as colorless oil: IR (KBr/film) 3070, 3030, 2910, 2850, 1450, 1270, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.58 (d, J=12.0 Hz, 4H), 1.70–1.77 (m, 6H), 2.23 (bs, 2H), 3.29 (s, 4H), 3.59–3.63 (m, 4H), 3.67–3.71 (m, 4H), 4.57 (s, 4H), 7.25–7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.5, 34.5, 36.3, 68.9, 70.8, 72.0, 72.6, 78.6, 127.0, 127.2, 127.9, 138.0. Anal. Calcd for $C_{29}H_{38}O_5$: C, 74.65; H, 8.21. Found: C, 74.45: H, 8.15.

4.3.10. 1,3-Bis[(2-hydroxyethyloxy)methyl]-2-oxaadamantane (10). Suspension of 1,3-bis[(2-benzyloxyethyloxy)methyl]-2-oxaadamantane (**9**, 3.24 g, 6.95 mmol) and 10% Pd/C (1.20 g) in of dry ethanol (40 mL) was hydrogenated for 48 h. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give 1.94 g (98%) of 1,3-bis[(2-hydroxyethyloxy)methyl]-2-oxaadamantane (**10**) as colorless viscous oil. Analytically pure sample was obtained by chromatography on alumina (act. II/III) with 0→2% MeOH in CH_2Cl_2 as the eluant. IR (KBr/film) 3370, 2910, 2850, 1445, 1120 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (d, J=12.0 Hz, 4H), 1.82–1.88 (m, 6H), 2.25 (bs, 2H), 3.32 (s, 4H), 3.58–3.62 (m, 4H), 3.67–3.71 (m, 4H), 4.09 (bs, 2×OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.5, 35.3, 35.9, 61.1, 73.1, 73.4, 77.8. Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 62.83; H, 9.29.

4.3.11. 1,3-Bis[(2-tosyloxyethyloxy)methyl]-2-oxaadamantane (11). To a stirred, cooled (ice/water) solution of 1,3-bis[(2-hydroxyethyloxy)methyl]-2-oxaadamantane (**10**, 810 mg, 2.84 mmol) in dry pyridine (2.5 mL) tosyl chloride (1.08 g, 5.68 mmol) was added during 3 h. The reaction mixture was stirred overnight at ~5°C, diluted with water (50 mL) and extracted with CH_2Cl_2 (4×40 mL). Organic extracts were washed with 6M HCl (2×50 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give 1.66 g (98%) of 1,3-bis[(2-tosyloxyethyloxy)methyl]-2-oxaadamantane (**11**) as colorless viscous oil: IR (KBr/film) 3070, 3030, 2920, 2850, 1600, 1445, 1360 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.44 (d, J=12.1 Hz, 4H), 1.58 (d, J=12.1 Hz, 4H), 1.72 (bs, 2H), 2.17 (bs, 2H), 2.44 (s, 6H), 3.17 (s, 4H), 3.65–3.69 (m, 4H), 4.11–4.15 (m, 4H), 7.34 (d, J=8.2 Hz, 4H), 7.79 (d, J=8.2 Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 26.7, 34.8, 36.3, 69.0, 69.3, 72.3, 78.8, 127.8, 129.7, 132.9, 144.7. Anal. Calcd for $C_{29}H_{38}O_9S_2$: C, 58.57; H, 6.44. Found: C, 58.49; H, 6.70.

4.3.11. 1,3-Bis(hydroxyethyloxy)adamantane (14). Stirred suspension of 1,3-dibromadamantane (**16**, 1.50 g, 5.00 mmol), dry ethylene glycol (7 mL) and $AgNO_3$, (1.80 g, 10.6 mmol) was warmed up during 15 min to 100°C and stirred for 30 min at that temperature. The reaction mixture was then cooled to room temperature and diluted with CH_2Cl_2 (25 mL). Insoluble part was filtered off and washed with CH_2Cl_2 (100 mL). The filtrate was evaporated under reduced pressure and the residue was diluted with water (250 mL). Water solution was filtered, saturated with NaCl, and extracted with CH_2Cl_2 (6×100 mL). The combined extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated and residue was chromatographed on silica gel with 10% MeOH in CH_2Cl_2 as the eluant, to give 790 mg (62%)[21] of 1,3-bis(2-hydroxyethyloxy)adamantane (**14**): mp=71–75°C; IR (KBr) 3390, 2910, 2860, 1115, 1060, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50 (bs, 2H), 1.65–1.72 (m, 8H), 1.78 (bs, 2H), 2.33 (bs, 2H), 3.53 (t, J=4.6 Hz, 4H), 3.61 (s, 2×OH), 3.69 (t, J=4.6 Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.3, 34.8, 40.1, 45.1, 61.3, 61.7, 74.4. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.40. Found: C, 65.52; H, 9.34.

4.3.12. 1,3-Bis(2-tosyloxyethyloxy)adamantane (15). To a stirred, cooled (ice/water) solution of 1,3-bis(2-hydroxyethyloxy)-adamantane (**14,** 540 mg, 2.13 mmol) in dry pyridine (2.5 mL), tosyl chloride (830 mg, 4.35 mmol) was added during 4 h. The reaction mixture was stirred overnight at ~5°C, diluted with water (50 mL) and extracted with CH_2Cl_2 (4×35 mL). Organic extracts were washed with 6 M HCl (2×50 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give 950 mg (80%) of 1,3-bis(2-tosyloxyethyloxy)adamantane (**15**) as colorless viscous oil: IR (KBr) 3060, 3030, 2910, 2860, 1595, 1450, 1355, 1190, 1170, 1125, 1095, 1010, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (bs, 2H), 1.45–1.65 (m, 10H), 2.26 (bs, 2H), 2.44 (s, 6H), 3.55–3.60 (m, 4H), 4.05–4.15 (m, 4H), 7.34 (d, J=7.95 Hz, 4H), 7.79 (d, J=7.95 Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 30.3, 34.8, 39.9, 44.9, 58.2, 69.7, 74.5, 127.8, 129.7, 133.0, 144.7. Anal. Calcd for $C_{28}H_{36}O_8S_2$: C, 59.55; H, 6.43. Found: C, 59.35; H, 6.35.

4.4. Alkali metal picrate extraction experiments

Alkali metal (Li^+, Na^+, K^+, Rb^+, and Cs^+) picrates were freshly prepared by reacting each of the respective alkali

metal hydroxides, M^+OH^-, with picric acid.[22] Due to its high solubility in water and EtOH, Li^+ picrate was prepared and subsequently used in situ. All other alkali metal picrates were isolated and dried prior to use. An aqueous solution was prepared which was 5.0 mM in the alkali metal picrate. Reagent grade $CHCl_3$ was washed three times with redistilled water and then utilized to prepare 5.0 mM solution of crown ethers **1–7**.

A $CHCl_3$ solution (0.5 mL) of the corresponding crown ether was placed into a 5 mL screw-top vial, and the aqueous solution of the alkali metal picrate (0.5 mL) was added. Another portion of the metal picrate solution (0.5 mL) was added to the second vial to the $CHCl_3$ (0.5 mL), which contained no host (blank probe). The vials were stoppered, shaken on a Termolyne Maxi-Mix III Type 65800 mixer for 4 min, and then allowed to stand at ambient temperature for 1 h. A 0.1 mL aliquot of the aqueous phase was taken with automatic pippete and diluted in volumetric flask via addition of redistilled water to a total volume of 10 mL. UV–Visible spectra were obtained for the two solutions, and the percent of picrate extracted in each case was calculated from the absorbance measured on 355 nm. For each combination of crown ether and alkali metal picrate, the picrate extraction was conducted on three different samples, and the average value of percent picrate extracted was calculated. In the absence of crown ether, no metal picrate extraction was detected.

4.5. Transport of alkali metal picrates across bulk chloroform membranes

The transport studies were conducted at ambient temperature in 'hollow-tube-within-a-vial' cells. A hollow glass tube (20 mm ID) was suspended vertically within a glass vial (40 mm ID) so that the bottom of the glass tube extended below the surface of the $CHCl_3$ membrane which separated the aqueous source phase (7.5 mmol of alkali metal picrate in 3 mL of redistilled water) from aqueous receiving phase (10 mL of redistilled water). The liquid membrane consisted of 0.75 mmol of crown ether in 10 mL of $CHCl_3$. The molar ratio of crown ether to alkali metal picrate was 1:10. The organic phase was stirred at ca. 200 rpm by means of internal small magnetic stirring bar. During first 7 h, aliquot of the aqueous receiving phase (3 mL) was taken at 1 h intervals, and the concentration of alkali metal picrate was determined by recording the UV–visible spectra (percent of picrate transported was calculated from the absorbance measured on 355 nm with ϵ=14400). Aliquot was returned to the receiving phase and transport experiment was continued. Transport rate was calculated as a slope of moles of picrate transported vs time data, fitted to a straight line. After first 7 h transport experiment was continued for another 17 h (total of 24 h), and total amount of picrate transported in 24 h was determined.

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8. (a) According to the crown-ether nomenclature[1] macrocyclic polyethers **1–7** could be named: 2,15-[(1,3)2-oxaadamantano]-15-crown-5 (**1**); 2,18-[(1,3)2-oksaadamantano]-18-crown-6 (**2**); 2,18:9,11-bis [(1,3)2-oksaadamantano]-18-crown-6 (**3**); 15,17-(1,3)adamantano-18-crown-5 (**4**); 16,18-(1,3)adamantano-20-crown-5 (**5**); 14,16-(1,3)adamantano-16-crown-5 (**6**) and 8,10:18,20-bis-[(1,3)adamantano]-20-crown-6 (**7**); (b) According to the IUPAC recommendation, Powell, W. H. Phane nomenclature. *Pure Appl. Chem.* **1998**, *70*, 1513–1545, new crown ethers could be named: 3,6,9,12-tetraoxa-1(1,3)-(2-oxaadamantana)cyclotridecaphane (**1**); 3,6,9,12,15-pentaoxa-1(1,3)-(2-oxaadamantana)cyclohexadecaphane (**2**); 3,6,10,13-tetraoxa-1,8(1,3)-bis(2-oxaadamantana)cyclotridecaphane (**3**); 3,6,9,12,15-pentaoxa-1(1,3)-adamantana-cyclohexa-decaphane (**4**); 4,7,10,13,16-pentaoxa-1(1,3)-adamantanacyclooctadecaphane (**5**); 2,5,8,11,14-pentaoxa-1(1,3)-adamantanacyclotetradecaphane (**6**); 2,5,8,10,13,16-hexaoxa-1,9(1,3)-diadamantanacyclohexadecaphane (**7**).
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