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Synthesis and alkali cation extraction ability of 1,3-alt-thiacalix[4]mono(crown) ethers

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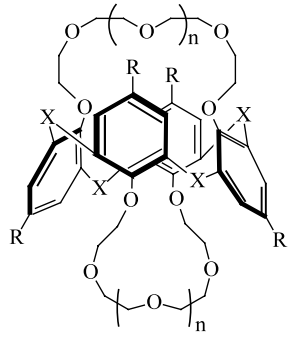
Abstract—The first representatives of 1,3-alt-thiacalix[4]mono(crown-5 and -6) ethers were synthesized by the cyclocondensation of 25,27-dialkoxythiacalix[4]arenes with tetraethylene glycol ditosylate and 1,14-diiodo-3,6,9,12-tetraoxatetradecane, respectively. The complexing abilities of ligands were determined by the alkali (Li^+, Na^+, K^+, Rb^+, Cs^+) picrate extraction method.

Recently, Lamare et al.[1] and subsequently Bitter et al.[2] have reported the synthesis of a number of 1,3-*alt*-thiacalix[4]bis(crown-5 and -6) ethers which are the first representatives of crown bridged compounds in the thiacalixarene series.[1,2] (Fig. 1). The alkali cation (Na^+, K^+, Rb^+, Cs^+) complexing ability of ligands **1**, **2** and **3** have been assessed in neutral medium by liquid–liquid extraction experiments[2] which revealed that none of the ligands extracted Na^+, while sulfones **3a** and **3b** did not extract significantly any of the cations investigated (only 1–2% Rb^+ and Cs^+). The best extractant was **1b** showing at the same time some discrimination between K^+ (Rb^+) and Cs^+. Due to the steric hindrance of the bulky *tert*-butyl groups receptors **1a** and **2a** were poorer extractants than **1b** and **2b**, but **2a** exhibited a remarkable Cs^+ selectivity. So far it has been utilized in developing a potentiometric cesium sensor of excellent electroanalytical characteristics.[3] The selectivity values $\log K_M{}^+ = -3.2$ (K^+), -4.0 (Na^+) are comparable with those of the best Cs-electrodes based on 1,3-*alt*-calix[4](dibenzo-crown-6) ether derivatives ($\log K_M{}^+ = -2.16$ (K^+), -4.88 (Na^+)).[4]



	R	n	X	ref.
1a	Bu^t	1	S	[2]
1b	H	1	S	[1,2]
2a	Bu^t	2	S	[2]
2b	H	2	S	[1,2]
3a	Bu^t	1	SO_2	[2]
3b	H	1	SO_2	[2]

Figure 1. Thiacalix[4]bis(crown-5 and 6) ethers described until now.

During the synthesis of **1** and **2** the cyclization of thiacalixarenes with tetra- and pentaethylene glycol derivatives could not be stopped at an intermediate stage to obtain mono-crowns in an efficient way, although we succeeded in separating and characterizing one mono(crown-5) compound in low yield.[2] Since thiacalix[4]mono-crowns are expected to possess as good complexing properties as bis(crowns) do, moreover they may provide the possibilities of further derivatizations, we aimed to synthesize some of these new receptors. Herein our interest was focused only on the *tert*-butyl series as the presence of this bulky substituent in the 1,3-*alt* conformers significantly enhanced the binding selectivities.[2]

The synthesis required 25,27-dialkoxy-*t*-butylthiacalixarenes as starting materials. Until now only the 25,27-dimethoxy derivative of the parent thiacalix[4]arene has been described which was obtained in a 5 day alkylation reaction of thiacalix[4]arene using a 20-fold excess of MeI and an equimolar quantity of K_2CO_3 in boiling acetone.[5] Under these conditions we prepared compounds **4** (33%) and **5** (70%) then cyclized with tetraethylene glycol ditosylate **6** and with 1,14-diiodo-

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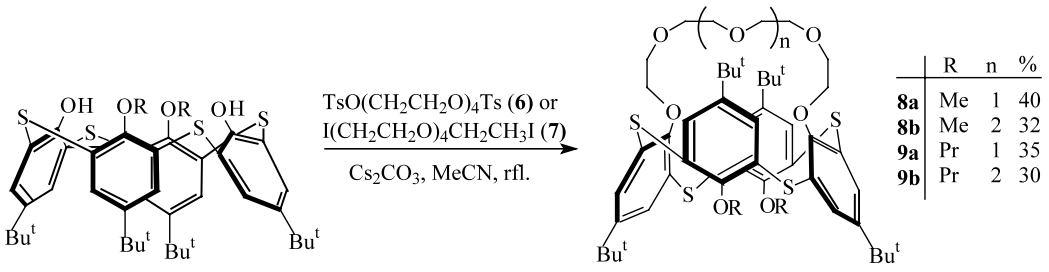

	R	n	%
8a	Me	1	40
8b	Me	2	32
9a	Pr	1	35
9b	Pr	2	30

Scheme 1. Synthesis of thiacalixmono(crown) ethers.

3,6,9,12-tetraoxatetradecane **7** (the respective ditosylate could also have been used but **7** was available) (Scheme 1). The ring closure using K_2CO_3 in boiling MeCN was more sluggish (only partial reaction was observed after 1 week) than the double cyclization affording bis-(crowns) **1** or **2**. However, in the presence of a large excess of Cs_2CO_3 the reaction proceeded faster resulting in the formation of **8a**, **9a** (72 h) and **8b**, **9b** (96 h) in 30–40% yields.

The extremely simple ^1H NMR spectra ($CDCl_3$) of crowns **8a**,**b** and **9a**,**b** show the presence of one conformer. For instance, the two singlets observed for the aromatic and Bu^t protons in the spectra of **8a** (7.51, 7.36; 1.36, 1.27) and **8b** (7.46, 7.42; 1.37, 1.20) together with the partially resolved signals of the crown CH_2O indicate the highly symmetric 1,3-*alt* conformation, similarly to that of bis(crowns).[2]

General procedure for the cyclization: A mixture of compound **4**, **5** (1 mmol), ditosylate **6** (0.75 g, 1.5 mmol) or diodide **7** (0.72 g, 1.5 mmol), Cs_2CO_3 (3.12 g, 10 mmol) in 50 ml MeCN was refluxed with stirring for 72–96 h. After evaporating the solvent, the residue was extracted with $CHCl_3$, washed with dilute aqueous HCl and dried furnishing **8a** (40%), **8b** (32%), **9a** (35%), **9b** (30%) purified by chromatography on silica (hexane–EtOAc = 9:1). All compounds were characterized by ^1H, ^{13}C NMR ($CDCl_3$), FAB-MS and elemental analysis.[6]

Competitive FAB-MS spectra[7] were taken in *m*-NBA matrix in the presence of alkali picrate salts for a fast, qualitative screening of the complexation abilities of ligands **8** and **9**. Since the $[L+M]^+/[L]^+$ ratio could not be determined due to the lack of the $[L]^+$ peaks in the spectra, the intensity ratios of the $[L+M]^+$ peaks were compared. Assuming that all ligands form similar 1:1 complexes, these values were expected to provide a rough estimate for the binding selectivities (Table 1).

The data suggest the relative order of cation complexing abilities for crown-5 **8a**, **b** $K^+ > Rb^+ > Na^+ \gg Cs^+$, for crown-6 derivatives **9a** $Cs^+ > Rb^+ > Na^+ \gg K^+$ and for **9b** $Cs^+ > K^+ > Rb^+ \gg Na^+$, respectively.

To obtain more reliable data, we then assessed the metal ion complexing abilities by solvent extraction experiments.[8] Dichloromethane solutions of ligands (1×10^{-2} M) were equilibrated with aqueous Li^+, Na^+, K^+, Rb^+ and Cs^+ picrate solutions (5×10^{-3} M) and from the picrate concentration of the aqueous phase determined by UV spectrophotometry, the ion extractabilities (E%) were calculated. For the sake of comparison the literature extraction percentages of 25,27-di-*i*-propoxycalix[4]ar-ene-crown-6 (**10**)[9] is also included in Fig. 2.

The experimental results, in accord with those of bis-(crowns) **1** and **2**,[2] revealed that again none of the ligands could extract Na^+, whereas each of them could extract the smaller Li^+ (8–15%). Crown-5 derivatives **8a** and **9a** prefer Rb^+ over K^+ without noticeable selectivities. Crown-6 derivatives, however, show remarkable selectivities: both **8b** and **9b** highly prefer Cs^+ over Rb^+ (**8b**) and K^+ (**9b**), respectively. It is of interest that in FAB MS a reverse order of binding was systematically detected in respect of K^+ and Rb^+ which could be due to the extremely different conditions when compared to liquid–liquid extraction.

It is worth comparing the picrate extraction data of 25,27-di-*i*-propoxycalix[4]arene-crown-6 (**10**) obtained under identical conditions by Casnati et al.[9] with those of **9b** (in parentheses): (E%) Cs^+ 64.5 (69), Rb^+ 43.8 (10.8), K^+ 15.8 (1.3), Na^+ 2.4 (0). These values clearly

Table 1. FAB-MS complexation studies of **8**, **9** with alkali cations

	K^+/Cs^+	K^+/Rb^+	K^+/Na^+
8a	>50	1.73	9.14
9a	>50	2.5	12.5
	Cs^+/K^+	Cs^+/Rb^+	Cs^+/Na^+
8b	22	5.3	13.7.
9b	2.9	7.5	>50

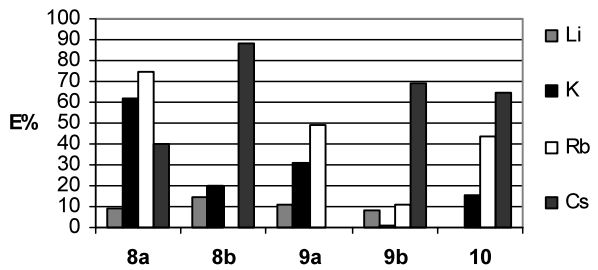

Figure 2. Extractabilities (E%) of alkali cations by thiacalix-(crowns) **8a**,**b**, **9a**,**b** and calixcrown **10**.[9]

show that thiacalix(crown-6) derivatives including bis-crown **2a**[2] are as efficient Cs^+ extractants as the respective calixcrown analogues but with significantly higher selectivities in respect of the other alkali ions. Compounds **8b** and especially **9b**, therefore, are expected to be promising candidates for developing potentiometric cesium sensors, although the extraction characteristics of **9b** are not better than those of bis(crown-6) **2a**.[2] This work and further studies to immobilize thiacalix(crown-6) ethers on polymer matrices are underway in our laboratory.

In conclusion, we have synthesized and characterized several thiacalixmono(crowns) for the first time, thus widening the scope of thiacalixarene chemistry with this remarkable class of receptors. The alkali cation extractabilities were determined and roughly similar trends of selectivities were found as those obtained recently for bis(crowns).

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6. NMR spectra were recorded in $CDCl_3$ at 500/125 MHz on a Bruker-Avance DRX-500 instrument. Compound **4**. Mp: 246–248°C, ^{1}H NMR $\delta=7.73$ (s, 2H, O*H*), 7.63 (s, 4H, Ar*H*), 7.16 (s, 4H, Ar*H*), 4.02 (s, 6H, OCH_3), 1.33 (s, 18H, Bu^t), 0.96 (s, 18H, Bu^t), ^{13}C NMR $\delta=157.4$, 155.8, 148.2, 142.7, 133.5, 132.9, 128.7, 121.5 (Ar), 63.1 (O*C*H$_3$), 34.4 (*C*(CH$_3$)$_3$), 34.3 (*C*(CH$_3$)$_3$), 31.6 (*C*(CH$_3$)$_3$), 31.1 (*C*(CH$_3$)$_3$), FAB-MS; *m*/*z*: 748.7 [M+H]$^+$ (calcd 748.3), anal. calcd for $C_{42}H_{52}O_4S_4$ (749.13): C, 67.34; H, 7.00, found: C, 67.02; H, 6.89%. Compound **5**. Mp: 208–209°C, ^{1}H NMR $\delta=7.99$ (s, 2H, O*H*), 7.68 (s, 4H, Ar*H*), 6.99 (s, 4H, Ar*H*), 4.48 (t, 4H, $J=6.8$ Hz, OCH_2), 2.07 (m, 4H, CH_2), 1.36 (s, 18H, Bu^t), 0.82 (s, 18H, Bu^t), 0.59 (t, 6H, CH_3), ^{13}C NMR $\delta=156.6$, 156.1, 147.9, 142.7, 134.5, 132.9, 129.1, 122.3 (Ar), 77.7 (O*C*H$_2$), 34.3 (*C*(CH$_3$)$_3$), 34.2 (*C*(CH$_3$)$_3$), 31.6 (*C*(CH$_3$)$_3$), 31.0 (*C*(CH3)3), 23.1 (*C*H$_2$), 10.6 (*C*H$_3$), FAB-MS; *m*/*z*: 804.6 [M+H]$^+$ (calcd 804.3), anal. calcd for $C_{46}H_{60}O_4S_4$ (805.24): C, 68.61; H, 7.51, found: C, 67.72; H, 7.34%. Compound **8a**. Mp: 266–268°C, ^{1}H NMR $\delta=7.51$ (s, 4H, Ar*H*), 7.36 (s, 4H, Ar*H*), 3.81 (t, 4H, $J=5.6$ Hz, ArOCH_2), 3.46–3.41 (m, 12H, OCH_2), 3,39 (s, 6H, OCH_3), 1.36 (s, 18H, Bu^t), 1.27 (s, 18H, Bu^t), ^{13}C NMR $\delta=158.2$, 146.6, 145.9, 131.7, 130.1, 127.7, 127.0, (Ar), 71.7, 70.8, 70.7 (O*C*H$_2$), 57.0 (O*C*H$_3$), 34.6 (*C*(CH$_3$)$_3$), 34.3 (*C*(CH$_3$)$_3$), 31.6 (*C*(CH$_3$)$_3$), 31.4 (*C*(CH$_3$)$_3$), FAB-MS; *m*/*z*: 945.8 [M+K]$^+$ (calcd 945.4), anal. calcd for $C_{50}H_{66}O_7S_4$ (907.33): C, 66.19; H, 7.33, found: C, 66.01; H, 7.25%. Compound **8b**. Mp: 272–274°C, ^{1}H NMR $\delta=7.46$ (s, 4H, Ar*H*), 7.42 (s, 4H, Ar*H*), 3.96 (t, 4H, OCH_2), 3.68 (t, 4H, OCH_2), 3,55 (s, 6H, OCH_3), 3.54 (t, 12H, OCH_2), 1.37 (s, 18H, Bu^t), 1.20 (s, 18H, Bu^t), ^{13}C NMR $\delta=158.9$, 146.5, 146.1, 132.9, 130.5, 129.4, 128.2, (Ar), 72.9, 71.6, 71.5, 71.3, 71.1 (O*C*H$_2$), 58.1 (O*C*H$_3$), 34.8 (*C*(CH$_3$)$_3$), 34.4 (*C*(CH$_3$)$_3$), 31.8 (*C*(CH$_3$)$_3$), 31.6 (*C*(CH$_3$)$_3$), FAB-MS; *m*/*z*: 1083.3 [M+Cs]$^+$ (calcd 1083.4), anal. calcd for $C_{52}H_{70}O_8S_4$ (951.38): C, 65.65; H, 7.42, found: C, 65.39; H, 7.38%. Compound **9a**. Mp: 262–264°C, ^{1}H NMR $\delta=7.32$ (s, 4H, Ar*H*), 7.29 (s, 4H, Ar*H*), 3.92 (t, 4H, OCH_2), 3.79 (t, 4H, OCH_2), 3.72 (t, 4H, OCH_2), 3.58 (t, 4H, OCH_2), 3.38 (t, 4H, OCH_2), 3.01 (m, 4H, CH_2CH$_3$), 1.35 (s, 18H, Bu^t), 1.27 (s, 18H, Bu^t), 0.59 (t, 6H, CH_3), ^{13}C NMR $\delta=156.0$, 145.0, 144.4, 128.8, 127.0, 126.7, 126.3, 125.2 (Ar), 72.6, 70.4, 69.4, 69.0 (O*C*H$_2$), 33.4 (*C*(CH$_3$)$_3$), 33.2 (*C*(CH$_3$)$_3$), 30.6 (*C*(CH$_3$)$_3$), 30.3 (*C*(CH$_3$)$_3$), 20.7 (*C*H$_2$), 9.1 (*C*H$_3$), FAB-MS; *m*/*z*: 1001.4 [M+K]$^+$ (calcd 1001.4), anal. calcd for $C_{54}H_{74}O_7S_4$ (963.44): C, 67.32; H, 7.74, found: C, 67.16; H, 7.68%. Compound **9b**. Mp: 280–282°C, ^{1}H NMR $\delta=7.34$ (s, 4H, Ar*H*), 7.32 (s, 4H, Ar*H*), 3.94 (t, 4H, $J=7.0$ Hz, OCH_2), 3.73 (t, 4H, $J=7.5$ Hz, OCH_2), 3,56 (t, 4H, OCH_2), 3.46 (t, 4H, $J=3.6$ Hz, OCH_2), 3.41 (t, 4H, $J=3.9$ Hz, OCH_2), 3.09 (t, 4H, $J=7.1$ Hz, OCH_2), 1.34 (s, 18H, Bu^t), 1.26 (s, 18H, Bu^t), 0.88 (m, 4H, CH_2CH$_3$), 0.60 (t, 6H, $J=7.3$ Hz, CH_3), ^{13}C NMR $\delta=157.2$, 156.6, 146.3, 145.82, 128.5, 128.2, 127.8, 126.9 (Ar), 71.7, 71.5, 70.9, 70.1, 69.7, 67.6 (O*C*H$_2$), 34.6 (*C*(CH$_3$)$_3$), 34.4 (*C*(CH$_3$)$_3$), 31.7 (*C*(CH$_3$)$_3$), 31.4 (*C*(CH$_3$)$_3$), 21.9 (*C*H$_2$), 10.2 (*C*H$_3$), FAB-MS; *m*/*z*: 1139.3 [M+Cs]$^+$ (calcd 1139.4), anal. calcd for $C_{56}H_{78}O_8S_4$ (1007.49): C, 66.76; H, 7.80, found: C, 66.49; H, 7.75%.
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