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

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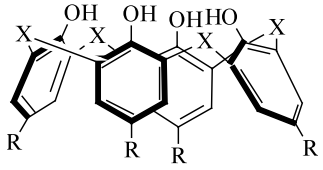
Abstract—The first representatives of 1,3-alt-thiacalix[4]arene bis(crown-5 and -6) ethers were synthesized by the cyclocondensation of thiacalix[4]arenes with tetraethylene glycol ditosylate and 1,14-diiodo-3,6,9,12-tetraoxatetradecane, respectively. The complexing abilities of ligands were determined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

Since 1997, when the first practical synthesis of *p*-*tert*-butylthiacalix[4]arene **1a** was reported by Kumagay et al.,[1] about three dozen papers have appeared on the chemical transformations and complexing properties of thiacalixarenes **1**. The chemical research in this field has been mainly focused on alkylation reactions,[2–7] partial or complete oxidations[8–12] of the sulfur atoms to sulfoxides **1c**,**d** and sulfones **1e**,**f** and on the conformational analysis of products. The relatively low number of publications when compared to calixarenes even in its early period may be due to the so far undiscovered regio- and stereoselective transformations which make calixarenes especially attractive targets for supramolecular chemists. Only a few reactions on the phenolic OH groups of **1a**,**b** and none on the aromatic nuclei were found to be selective. This can be attributed to the larger cavity with weaker internal hydrogen bonds between the OH groups resulting in an increased conformational mobility as compared to calix[4]arenes **2**.

On the contrary, compounds **1** proved to be more effective complexing agents for a great variety of cations, including hard and soft metals, than the parent calixarenes **2**, due to the contribution of the sulfide (sulfoxide or sulfone) bridge to the binding process.[12–15] The selectivity of complexation was more or less controlled by the oxidation state of the bridging sulfur moiety.[12] Several reports have also been published on the cation extracting abilities of thiacalixarenes supplied with ester-,[3] acyl-[6,16] and carbamoyl[16] ligating functions. To the best of our knowledge thiacalix-mono or bis(crown) ethers have not been synthesized yet, although the respective crown bridged calixarenes belong to the most studied supramolecular receptors. Therefore, we aimed to synthesize thiacalixcrowns to investigate how their ion extraction properties are altered compared to calixcrowns.



Bu^t	S	**1a**
H	S	**1b**
Bu^t	SO	**1c**
H	SO	**1d**
Bu^t	SO_2	**1e**
H	SO_2	**1f**
Bu^t	CH_2	**2a**
H	CH_2	**2b**

First, the alkylation of compounds **1** with tetraethylene glycol ditosylate **3** was attempted under conditions described for the synthesis of calixmonocrowns (MeCN solvent, K_2CO_3 base, 48 h reflux) (Scheme 1). Applying a molar ratio of **1a**/**3**/K_2CO_3 = 1:1.1:1, the progress of the reaction was monitored by TLC. In an inefficient process two products (TLC) were formed and, after column chromatography monocrown **5a**, contaminated with about 10% **1a** was obtained in low yield. Na_2CO_3

Keywords: thiacalix[4]arenes; crown ether bridge; complexation; alkali cations.

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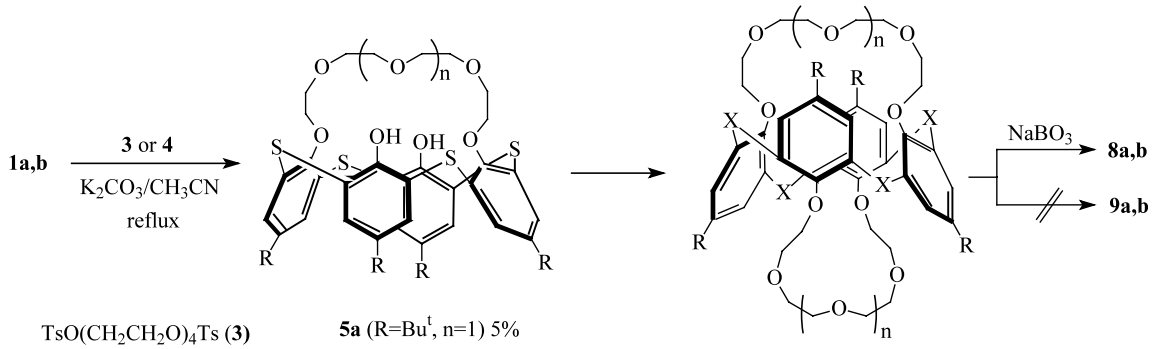

$TsO(CH_2CH_2O)_4Ts$ (**3**)
$I(CH_2CH_2O)_4CH_2CH_2I$ (**4**)

5a (R=Bu^t, n=1) 5%

R	x	n		Yield %
Bu^t	S	1	**6a**	45
H	S	1	**6b**	68
H	CH_2	1	**6c**	
Bu^t	S	2	**7a**	44
H	S	2	**7b**	39
Bu^t	SO_2	1	**8a**	57
H	SO_2	1	**8b**	53
Bu^t	SO	1	**9a**	
H	SO	1	**9b**	

Scheme 1. Synthesis of thiacalix(crown) ethers.

was also used in an attempt to increase the formation of **5a**, but the reaction proceeded much slower with a lack of selectivity. The ^{1}H NMR spectrum of **5a** clearly supports the stable conic structure of C_{2v} symmetry, where the conformational motion of the phenyl rings is blocked by the crown bridge and by the strong hydrogen bonds between the OH groups and the phenol ether oxygens. The chemical shifts of Bu^t (0.78s and 1.34s, both 18H), ArH (6.94s and 7.67s, both 4H) and the downfield shift of OH (8.04s, 2H) are in accordance with those of other *syn*-1,3-dialkylated-thiacalixarenes.[6,7] The proton signals of the crown ring methylenes appearing at 4.76t (4H, $J=5.5$ Hz), 4.15t (4H, $J=5.5$ Hz), 3.90bt (4H) and 3.81bt (4H), respectively, are well separated and fairly well resolved.

In light of previous alkylation studies, the failure to prepare exclusively monocrowns is not surprising, since the selective 1,3-dialkylation of **1** described until now in two instances with methyl iodide[7] and ethyl bromoacetate,[6] respectively, required a large excess of alkylating reagents and an equimolar quantity of K_2CO_3 (Na_2CO_3) and long reaction times. The less reactive **3** or **4**, under these conditions, could not differentiate between the OH groups of thiacalixarenes.

On increasing the molar ratio of **3** to 2.2 and using twofold excess of K_2CO_3, the spots of the monocrowns disappeared after 48 h reflux and biscrowns **6a**,**b** were obtained in 45 and 68% yields,[17] respectively. The ring closure of **1b** with 1,14-diiodo-3,6,9,12-tetraoxatetradecane **4** (the respective ditosylate may also have been used but the diiodide was available) under the above conditions proceeded similarly affording biscrown **7b** in comparable yield. In the case of **1a**, Cs_2CO_3 could be used to effect double cyclization resulting in **7a** in an acceptable yield (44%).[17]

The extremely simple ^{1}H NMR spectra of biscrowns **6a**,**b** and **7a**,**b** show the presence of one conformer. For instance, the one singlet observed for the aromatic and Bu^t protons in the spectra of **6a** (7.27, 1.29) and **7a** (7.35, 1.34) together with the partially resolved signals for the crown CH_2O indicate the highly symmetric 1,3-*alt* conformation similar to that of tetraalkylated derivatives.[2]

General procedure for the cyclization of ***1***: A mixture of compound **1a** or **1b** (1 mmol), ditosylate **3** (1.1 g, 2.2 mmol) or diodide **4** (1.01 g, 2.2 mmol), K_2CO_3 (0.28 g, 2 mmol) in 35 ml MeCN was refluxed with stirring for 48 h. After evaporating the solvent, the residue was extracted with CH_2Cl_2, washed with dilute aqueous HCl and dried furnishing **6a** (45%), **6b** (68%) purified by recrystallization from *n*-BuOH, **7a** (44%), **7b** (39%) purified by chromatography on silica (hexane–EtOAc= 1:1) and recrystallization from *i*-PrOH. All compounds were characterized by ^{1}H, ^{13}C NMR ($CDCl_3$), FAB-MS and elemental analysis.

We have attempted to effect the oxidation of compounds **6a**,**b** to the sulfinyl and sulfonyl counterparts according to literature analogy.[8] We succeeded in preparing sulfones **8a**,**b** (50–55%),[17] but unlike the parent **1a**, twice as many equivalents of $NaBO_3$ and a longer reaction time (48 h) were required to complete the oxidation in $CHCl_3$–AcOH mixture at 50°C. The ^{1}H NMR spectrum of **8a** is quite similar to that of **6a** but the Bu^t and Ar signals are shifted downfield by 0.2 and 1.2 ppm, respectively.

The above procedure using an equimolar amount of $NaBO_3$, could not therefore be applied for partial oxidation[8] to obtain sulfoxides **9a**,**b**. Instead, treatment of **6a**,**b** with *m*-chloroperbenzoic acid[9] in methylene

chloride was attempted but at 25–40°C using a slight excess of *m*-CPBA, a four component mixture of different partially oxidized products was obtained which could not be separated and analyzed. However, when a twofold excess of *m*-CPBA was used with heating at reflux, only sulfones **8a**,**b** were isolated in essentially pure form. This method was found to be more advantageous (shorter reaction, better yields) than the perborate oxidation for the preparation of sulfones.

To overcome the difficulties arising during the partial oxidations of the epithio groups in thiacalixcrowns, the direct ring closure of sulfoxides **1c**,**d**[8] with **3** or **4** could be another obvious approach although until now any alkylations of either sulfoxide **1c**,**d** or sulfone **1e**,**f** have not been described. Our attempt to obtain **9a** under the conditions described for the cyclizations of thiacalixarenes **1a**,**d** was unsuccessful; after 48 h only the unreacted starting materials could be recovered.

With the novel receptor compounds in hand, we then assessed their metal ion binding ability by solvent extraction experiments.[18] For the sake of comparison, calix[4]bis (crown-5) **6c** was prepared as described in the literature.[19] The chloroform solution of ligands (1×10^{-2} M) was equilibrated with aqueous Na^+, K^+, Rb^+ and Cs^+ picrate solutions (5×10^{-3} M) and from the picrate concentration of the latter determined by UV spectrophotometry, the ion extractabilities (E%) were calculated (Fig. 1).

The experimental results clearly show that none of the ligands can extract Na^+ although the respective 15-crown-5 and 18-crown-6 ethers can complex sodium ions. In our receptors, the necessary number of donor oxygen atoms are available but the crown rings attached to the calixarene are too large with somewhat restricted conformational motion and so they cannot provide an appropriate binding site for the relatively small Na^+ ion. As expected, the best extractant was the calix[4]biscrown-5 **6c**, but without selectivity, whereas the respective sulfur analogue **6b** is slightly weaker showing at the same time some discrimination between K^+ (Rb^+) and Cs^+. Due to the steric hindrance of the bulky *tert*-butyl groups, it is not surprising that receptors **6a** and **7a** are poorer extractants than **6b** and **7b**, but **7a** exhibits a remarkable Cs^+ selectivity that may be utilized in developing a potentiometric Cs^+ sensor. This

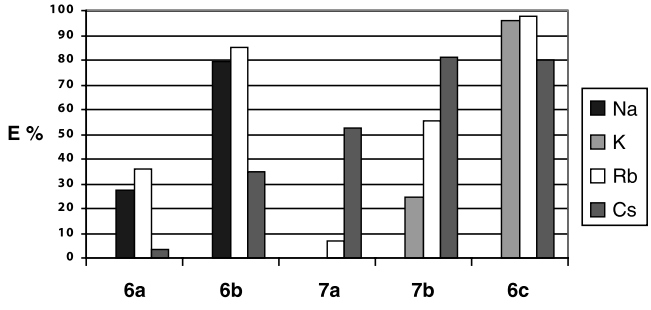

Figure 1. Extractabilities (E%) of alkali cations by thiacalix-(crowns) **6a**,**b**, **7a**,**b** and calixcrown **6c**.

work is in progress in our laboratory. Perhaps the most surprising result is that sulfones **8a** and **8b** virtually do not extract any of the cations investigated (only 1–2% Rb^+ and Cs^+). The inferior extractabilities may be attributed to the strong electron withdrawing effect of the sulfone groups thus preventing the participation of the phenol ether oxygens in coordination and in addition the sulfone oxygen atom cannot provide additional binding sites to compensate their negative effect.

In conclusion, we have synthesized and characterized several thiacalixbis(crowns) for the first time, thus opening the accessibility to a novel class of receptors in the family of thiacalixarenes. The alkali cation extractabilities were determined and some interesting features in the selectivities were discovered. The rational synthesis of monocrowns and further complexation studies are in progress.

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17. Compound **6a**. Mp: 345–346°C (BuOH), ^{1}H NMR $\delta=$ 7.34 (s, 8H, Ar*H*), 3.89 (t, 8H, $J=7.95$ Hz, OCH_2), 3.59 (t, 8H, $J=3.35$ Hz, OCH_2), 3.37 (t, 8H, $J=3.25$ Hz, OCH_2), 2.93 (t, 8H, $J=8$ Hz, OCH_2), 1.36 (s, 36H, Bu^t), ^{13}C NMR $\delta=156.1$, 146.5, 127.9, 126.4 (Ar); 73.8, 71.6, 70.3, 65.4 (O*C*H$_2$), 34.6 (*C*(CH$_3$)$_3$), 31.7 (C(*C*H$_3$)$_3$). FAB MS; m/z: 1059.8 [M+Na]$^+$ (calcd 1059.4) anal. calcd for $C_{56}H_{76}O_{10}S_4$ (1037.47): C, 64.83; H, 7.38, found: C, 64.14; H, 7.29%.
Compound **6b**. Mp: 276–278°C (BuOH), ^{1}H NMR $\delta=$ 7.43 (d, 8H, $J=7.7$ Hz, Ar*H*), 6.93 (t, 4H, $J=7.7$ Hz, Ar*H*), 4.29 (t, 8H, $J=6.3$ Hz, OCH_2), 3.50 (bs, 16H, OCH_2), 3.19 (t, 8H, $J=6.25$ Hz, OCH_2), ^{13}C NMR $\delta=159.3$, 131.7, 129.0, 123.8 (Ar), 72.4, 71.2, 69.9, 67.7 (O*C*H$_2$), FAB-MS; m/z: 835.2 [M+Na]$^+$ (calcd 835.2) anal. calcd for $C_{40}H_{44}O_{10}S_4$ (813.04): C, 59.09; H, 5.45, found: C, 58.44; H, 5.25%.
Compound **7a**. Mp: 238°C, ^{1}H NMR $\delta=7.38$ (s, 8H, Ar*H*), 3.91 (t, 8H, $J=7.45$ Hz, OCH_2), 3.55 (bs, 8H, OCH_2), 3.48 (t, 8H, $J=4.65$ Hz, OCH_2), 3.44 (t, 8H, $J=4.95$ Hz, OCH_2), 1.34 (s, 36H, Bu^t), 2.94 (t, 8H, $J=7.5$ Hz, OCH_2), ^{13}C NMR $\delta=156.5$, 146.7, 136.6, 128.1, 127.2 (Ar), 71.7, 71.4, 70.6, 69.4, 67.0 (O*C*H$_2$), 34.6 (*C*(CH$_3$)$_3$), 31.6 (C(*C*H$_3$)$_3$), FAB MS; m/z: 1125.3 [M+H]$^+$ (calcd 1125.5) anal. calcd for $C_{60}H_{84}O_{12}S_4$ (1125.58): C, 64.03; H, 7.52, found: C, 63.54; H, 7.42.
Compound **7b**. Mp: 163–164°C, ^{1}H NMR $\delta=7.47$ (d, 8H, $J=7.7$ Hz, Ar*H*), 6.93 (t, 4H, $J=7.7$ Hz, Ar*H*), 4.09 (t, 8H, $J=6.1$ Hz, OCH_2), 3.69 (bs, 8H, OCH_2), 3.61 (t, 8H, $J=4.6$ Hz, OCH_2), 3.43 (t, 8H, $J=6.05$ Hz, OCH_2), 3.40 (t, 8H, $J=3.4$ Hz, OCH_2), ^{13}C NMR $\delta=160.4$, 133.2, 129.4, 124.0 (Ar), 71.5, 71.3, 70.0, 69.7 (O*C*H$_2$), anal. calcd for $C_{44}H_{52}O_{12}S_4$ (901.15): C, 58.65; H, 5.82, found: C, 58.22; H, 5.61%. FAB-MS; m/z: 923.3 [M+Na]$^+$ (calcd 923.2).
Compound **8a**. Mp: >370°C, ^{1}H NMR $\delta=8.47$ (s, 8H, Ar*H*), 4.16 (t, 8H, $J=7.7$ Hz, OCH_2), 3.56 (t, 8H, OCH_2), 3.37 (t, 8H, OCH_2), 2.78 (t, 8H, $J=7.85$ Hz, OCH_2), 1.49 (s, 36H, Bu^t), ^{13}C NMR $\delta=151.0$, 148.9, 137.2, 130.5 (Ar); 73.6, 73.4, 71.9, 70.0 (O*C*H$_2$), 35.8 (*C*(CH$_3$)$_3$), 31.5 (C(*C*H$_3$)$_3$), anal. calcd for $C_{56}H_{76}O_{18}S_4$ (1165.47): C, 57.71; H, 6.57, found: C, 57.12; H, 6.39.
Compound **8b**. Mp: >370°C (NMR spectrum could not be recorded due to poor solubility) anal. calcd for $C_{40}H_{44}O_{18}S_4$ (941.04): C, 51.05; H, 4.71, found: C, 51.62; H, 4.50.
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