Molecular design and synthesis of a calix[6]crown-based lithium-selective ionophore

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Abstract

Several 1,4-bridged calix[6]arene tetraesters were prepared from 1,4-*p*-*tert*-calix[6]crown-4's by etherifying with ethyl bromoacetate. It was found that the 1,4-*p*-*tert*-calix[6]crown-4 tetraethylester (**3a**) and the 1,4-*p*-*tert*-calix[6]benzocrown-4 tetramethylester (**4b**) exhibit very high selectivity toward lithium and sodium ions, respectively. The ion selectivity is very sensitive to the structure of polyoxyethylene spacer and the *R* in the ester moiety. © 2000 Elsevier Science Ltd. All rights reserved.
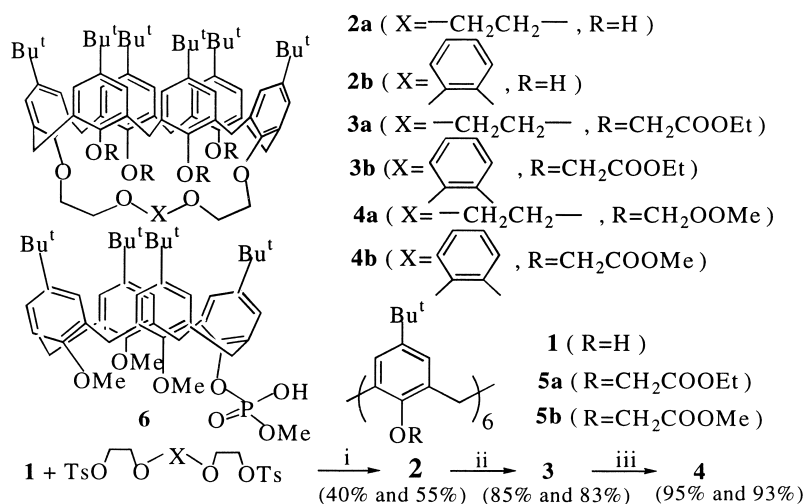
Calixarenes are cyclic oligomers prepared via cyclic condensation of *p*-substituted phenols with formaldehyde under alkaline conditions. They have been used as versatile building blocks for artificial receptors in supramolecular chemistry enabling the design and construction of more elaborated molecules and assemblies.[1–4] In order to preorganize the host it is usually desirable to prepare the calixarenes with well-defined structural features suitable for complexation. It is well known that in calix[4]arenes the ring conversion is inhibited simply through the introduction of substituents bulkier than an ethyl group onto the lower rim and the calix[4]arene conformation can thus be immobilized. Also, the ion selectivity is dependent on cooperation of the conformation and substituents. It was reported that OCH_2COOR, $OCOCH_2NR_2$ etc. are favorable groups for the coordination of alkali metal ions. By skillful combination of conformation and the length and properties of the polyoxyethylene spacer and substituents, a series of excellent ionophores for Na^+, K^+ and Cs^+ ions have been synthesized but not for the lithium ion.[1–4] As the studies of these ionophores of calix[4]arenes approaches maturity, increasing attention is being devoted to some of the larger members of the family which possess a larger π-basic cavities and hydroxyl arrays, such as calix[6]arenes. However, the conformational freedom of these larger molecules limits their application to serve as receptors, and the large cavity is unfavorable for complexation of a small cation. As a result, the studies of recognition behavior of calix[6]arenes are very scarce,[5,6] especially on how to recognize lithium ion selectively.

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As early as 1989,[7] it was reported that *p-tert*-butylcalix[6]arene hexaacetates exhibit high affinity towards alkali metal cations with increasing of ionic radius but had little selectivity due to their flexible conformation. Recently, we have found that *p-tert*-butylcalix[6]-1,3-crown-3 show some lithium ion selectivity.[5] It is known that the binding sites exist deep in the cavity of the calix crown and the intramolecular bridges at the lower or upper rim can reduce the conformational flexibility; in addition, the coordination of alkali metal ions is promoted by OCH_2COOR residues, so it is of interest to observe what happens when both polyoxyethylene spacer and ester groups are incorporated into one caliz[6]arene. In this paper we wish to report our investigation on the synthesis of *p-tert*-calix[6]-1,4-crown-4's and their tetraesters as well as the complexation ability of the tetraesters towards alkali metal ions. As expected, the complexation ability varies remarkably according to the different structure of polyoxyethylene spacer and the different ester groups. Moreover, it was found that one of the tetraesters, *p-tert*-butylcalix[6]benzocrown-4 tetramethylesters **4b**, exhibits outstanding lithium ion selectivity which has not been observed in calixarene chemistry, and another one, the *p-tert*-butylcalix[6]crown-4 tetraethylester **3a** shows outstanding sodium ion selectivity.

The synthetic route is depicted in Scheme 1. Reacting *p-tert*-butylcalix[6]arene **1** with triethylene glycol ditosylates or 1,2-bis(tosyloxyethoxy)benzene in K_2CO_3/toluene afforded calix[6]-1,4-crown-4 **2a** and **2b** in yields of 40 and 55%, respectively. By using toluene as the solvent instead of MeCN, the yields were almost double and the work up was simplified in comparison with that described in the previous method.[5] Further treatment of **2** with ethyl bromoacetate in the presence of NaH (caution!) as a base in dioxane gave **3a** and **3b** in high yields of 85, and 83%, respectively. Compounds **4a** and **4b** were obtained by ester exchange reactions of **3** in near quantitative yields. The structures and conformations of **2**, **3** and **4** as shown in Scheme 1 were confirmed by ^{1}H NMR, FAB-MS and elemental analysis.[9] The ^{1}H NMR spectra of these compounds show two singlets in a ratio of 1:2 for the *tert*-butyl groups, which indicates that they are 1,4-bridged calix[6]arene tetrasubstituted products. Two pairs of doublets (ratio 1:2) with an AB pattern for the methylene protons of the calix[6]arene skeleton and an AB system for the protons of the OCH_2CO, reveals that the calixarene adopts a cone conformation.[5,6]

2a (X=—CH_2CH_2— , R=H)

2b (X= , R=H)

3a (X= —CH_2CH_2— , R=CH_2COOEt)

3b (X= , R=CH_2COOEt)

4a (X= —CH_2CH_2— , R=CH_2OOMe)

4b (X= , R=CH_2COOMe)

1 (R=H)
5a (R=CH_2COOEt)
5b (R=CH_2COOMe)

$1 + TsO$ X OTs →(i) **2** →(ii) **3** →(iii) **4**
(40% and 55%) (85% and 83%) (95% and 93%)

Scheme 1. Reagents and conditions: (i) K_2CO_3/toluene; (ii) NaH/dioxane, $BrCH_2COOEt$; (iii) methanol/toluene

Examination of the CPK molecular models revealed that these compounds were highly pre-organized for binding cations. The percentage extraction of hosts **2**, **3** and **4** as well as *p-tert*-butylcalix[6]arene hexacetates[7] **5** and 25-diethylphosphoryl-26,27,28-trimethoxy-*p-tert*-butylcalix[4]arene[8] **6** (the most effective ionophore towards Li^+ in previous literature) towards Li^+, Na^+, K^+ etc. from water into $CHCl_3$ at 20°C are summarized in Table 1. It can be seen that **3b**, **4a** and **6** show high affinities for lithium ion but no selectivity. The ionophore **5a** and **5b** exhibit high extraction capabilities for alkali metal cations with increasing ion radius, but low extraction capabilities for lithium ion, and **2a**, **2b** show lower complexation ability towards alkali metal cations. However, this is not the case for **3a** and **4b** which show outstanding selectivity towards Na^+ and Li^+, respectively. To the best of our knowledge, **4b** is the first example with high lithium ion selectivity, and also, **3a** is an outstanding selective ionophore for the sodium ion, especially, in calix[6]arene chemistry. The increase of complexation ability towards alkali metal cations could be attributed to the combination of the triethylene glycol spacer reducing the flexibility of conformation, the newly created small cavity in the calix[6]crown-4's and the favorable influence of esters groups on the complexation of alkali metal cations. The high selectivity may be due to the cooperation of the appropriate structure of the polyoxyethylene spacer and the appropriate alkyl chain in the ester moiety that can create an appropriate size of cavity and thus improve complexation selectivity.

Table 1
Percentage extraction (%E) of picrate salts from water into $CHCl_3$ at 20°C. [a]Arithmetic mean of several experiments — standard deviation on the mean: $\sigma_{N-1} \leqslant 1$

| host | %E | | | | | | | | |
	3a	**3b**	**4a**	**4b**	[b]**2a**	[b]**2b**	[c]**5a**	[c]**5b**	[d]**6**
Li^+	1.4	44.7	53.1	34.5	2.6	1.2	11.4	1.7	63
Na^+	35.9	32.4	46.0	1.3	6.5	3.9	50.1	10.3	66
K^+	<1	14.6	27.4	<1	4.5	4.1	85.9	29.1	67
Cs^+	<1	8.6	12.3	<1	/	/	100.0	54.8	/

In conclusion, this paper describes not only the synthesis and the outstanding complexation behavior towards alkali metal cations of 1,4-bridged calix[6]crown tetreacetates, but also demonstrates how to design highly selective ionophores for small alkali ions, especially the lithium ion. This may be helpful in designing and synthesizing other selective ionophores and in promoting studies on recognition properties of calix[6]arene derivatives.

Acknowledgements

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9. The characteristics of **2** were in accordance with Ref. 5. ^{1}H NMR (300 MHz, CDCl$_3$). Compound **3a**: 1.13 (s, 36H, ArC(CH$_3$)$_3$); 1.30 (t, 12H, $J = 7.8$ Hz, CH$_3$); 1.35 (s, 18H, ArC(CH$_3$)$_3$); 2.79 (bs, 4H, OCH$_2$); 3.01 (bs, 4H, OCH$_2$); 3.37 (d, 2H, $J = 15.0$ Hz, ArCH$_2$Ar); 3.95 (s, 4H, OCH$_2$); 4.25–4.37 (m, 16H, COOCH$_2$ and OCH$_2$CO); 4.37 (d, 4H, $J = 15.3$ Hz, ArCH$_2$Ar); 4.43 (d, 4H, $J = 15.3$ Hz, ArCH$_2$Ar); 4.59 (d, 2H, $J = 15.0$ Hz, ArCH$_2$Ar); 6.98, 7.24, 7.65 (s each, 4H each, ArH). MS (FAB): m/z = 1431 (MH$^+$). Anal. calcd for C$_{88}$H$_{118}$O$_{16}$: C, 73.82; H, 8.31. Found: C, 73.80; H, 8.35. Compound **3b**: 0.90 (s, 36H, ArC(CH$_3$)$_3$); 1.10 (t, 12H, $J = 7.5$ Hz, CH$_3$); 1.37 (s, 18H, ArC(CH$_3$)$_3$); 3.15 (bs, 4H, OCH$_2$); 3.33 (d, 2H, $J = 15.3$ Hz, ArCH$_2$Ar); 3.56 (m, 4H, OCH$_2$); 4.08 (bs, 8H, OCOCH$_2$); 4.42 (d, 4H, $J = 13.3$ Hz, OCH$_2$CO); 4.49 (d, 4H, $J = 13.3$ Hz, OCH$_2$CO); 4.52 (d, 4H, $J = 15.6$ Hz, ArCH$_2$Ar); 4.71 (d, 4H, $J = 15.6$ Hz, ArCH$_2$Ar); 4.78 (d, 2H, $J = 15.3$ Hz, ArCH$_2$Ar); 6.61 (s, 4H, ArH); 6.88 (s, 8H, ArH); 7.30 (s, 4H, ArH). MS (FAB) m/z = 1480 (M+2H$^+$). Anal. calcd for C$_{92}$H$_{118}$O$_{16}$: C, 74.67; H, 8.04. Found: C, 74.72; H, 7.95. Compound **4a**: 0.85 (s, 36H, ArC(CH$_3$)$_3$); 1.38 (s, 18H, ArC(CH$_3$)$_3$); 2.92 (bs, 4H, OCH$_2$); 3.18 (bs, 4H, OCH$_2$); 3.34 (d, 2H, $J = 15.0$ Hz, ArCH$_2$Ar); 3.43 (d, 4H, $J = 15.6$ Hz, ArCH$_2$Ar); 3.67 (bs, 4H, OCH$_2$); 3.79 (s, 12H, OCH$_3$); 4.51 (d, 4H, $J = 15.6$ Hz, ArCH$_2$Ar); 4.62 (d, 4H, $J = 13.6$ Hz, OCH$_2$CO); 4.72 (d, 4H, $J = 13.6$ Hz, OCH$_2$CO); 4.84 (d, 2H, $J = 15.0$ Hz, ArCH$_2$Ar); 6.63, 6.95, 7.27 (s each, 4H each, ArH). MS (FAB) m/z = 1375 (MH$^+$). Anal. calcd for C$_{84}$H$_{110}$O$_{16}$: C, 73.33; H, 8.06. Found: C, 73.40; H, 8.01. Compound **4b**: 0.86 (s, 36H, ArC(CH$_3$)$_3$); 1.38 (s, 18H, ArC(CH$_3$)$_3$); 3.17 (bs, 4H, OCH$_2$); 3.32 (d, 2H, $J = 15.3$ Hz, ArCH$_2$Ar); 3.51 (bs, 12H, OCH$_3$); 3.56 (s, 4H, OCH$_2$); 4.44–4.54 (m, 12H, OCH$_2$CO and ArCH$_2$Ar); 4.67 (d, 4H, $J = 15.0$ Hz, ArCH$_2$Ar); 4.72 (d, 2H, $J = 15.3$ Hz, ArCH$_2$Ar); 6.62 (s, 4H, ArH); 6.94 (s, 8H, ArH); 7.30 (s, 4H, ArH). MS (FAB) m/z = 1423 (MH$^+$). Anal. calcd for C$_{88}$H$_{110}$O$_{16}$: C, 74.23; H, 7.79. Found: C, 73.27; H, 7.72.