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Novel molecular receptors based on a thiacalix[4]arene platform. Preparations of the di- and tetracarboxylic acid derivatives and their binding properties towards transition metal ions

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Abstract

Novel molecular receptors, cone- and 1,3-alternate-tetracarboxylic acid (**3**) and *syn*-A,C-dicarboxylic acid (**5**), were prepared by hydrolysis of the ester moiety of the tetra- (**2**) and di-ethers (**4**), which had been synthesized by regio- and conformation-selective *O*-alkylation of the phenolic oxygens of thiacalix[4]arene (**1**) with ethyl bromoacetate. The binding ability of cone- and 1,3-alternate-**3**, *syn*-**5**, as well as cone-shaped, methylene-bridged tetracarboxylic acid (**9**) toward transition metal ions was investigated by solvent extraction to show that the selectivity for the ions depends upon the bridging sulfur, carboxylate group, and the conformation.

Keywords: calixarenes; alkylation; sulfides; complexation.

Since we reported the facile synthesis of *p-tert*-butylthiacalix[4]arene (**1**),[1] in which all four methylene bridges of the parent calix[4]arene (**7**) are replaced by epithio groups, we have developed its novel functions as a molecular receptor which could not be realized by conventional calixarenes (e.g. **7**). For instance, **1** per se exhibited high binding ability toward transition metal ions via coordination of the epithio group in addition to the phenoxy oxygens.[2,3] Conformation selective introduction of four ester groups via tetra-*O*-alkylation of **1** allowed selective recognition of alkali metal ions, which was not achieved by parent **1**.[4] Chemical modification of **1** by sulfonation[5] or amidation[6] could successfully be carried out to enhance the characteristic functions of **1**, showing that thiacalix[4]arene should provide a potential platform for high-performance molecular receptors. Along this line, we report herein the preparation and functions of new molecular receptors (**3** and **5**) from **1** by position and conformation selective introduction of carboxylic acid groups which should provide useful sites for binding metal ions and further modifications (to, for example, **6**[7]).

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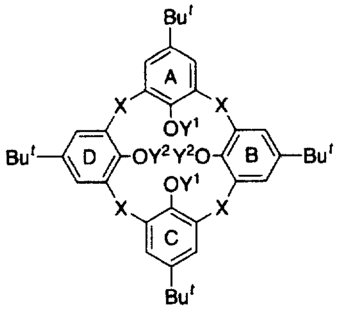
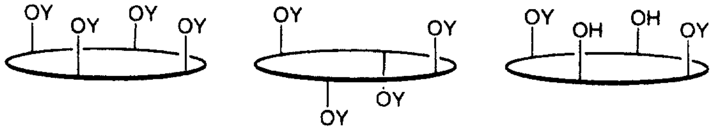


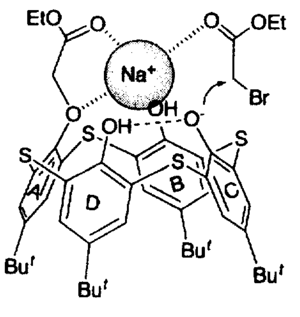
Calix[4]arenes	X	Y^1	Y^2
1	S	H	H
2	S	CH_2CO_2Et	CH_2CO_2Et
3	S	CH_2CO_2H	CH_2CO_2H
4	S	CH_2CO_2Et	H
5	S	CH_2CO_2H	H
6	S	$CH_2CONHCHMePh$	CH_2CO_2Et
7	CH_2	H	H
8	CH_2	CH_2CO_2Et	H
9	CH_2	CH_2CO_2H	CH_2CO_2H

Previously, we reported conformation selective tetra-*O*-alkylation of **1** to give either cone- or 1,3-alternate-**2** by use of a large excess of $BrCH_2CO_2Et$ and Na_2CO_3 or Cs_2CO_3 in acetone (Scheme 1).[4,8] It has now been found that under similar conditions, but by using 2-fold excess of $BrCH_2CO_2Et$ and slight excess of Na_2CO_3, **1** was mainly di-*O*-alkylated to give **4** as the major product (47% yield).[9] The structure of **4** should be *syn*-A,C-diether having C_{2v} symmetry, in which a pair of distal phenyl rings bearing (ethoxycarbonyl)methoxy groups orients to the same direction (Scheme 1), because further modification of **4** via hydrolysis followed by amidation of the ester moiety, and then etherification of the remaining B,D-phenols with $BrCH_2CO_2Et$, yielded *syn*-**6**.[7,10] It should be noted that conformational and/or positional isomers of possible diethers other than *syn*-**4** were not obtained in appreciable amounts. Ogata et al. have reported that similar etherification of methylene-bridged analog **7** also affords the corresponding *syn*-conformer **8**.[11,12] Therefore, it seems that the entity of the bridging group (S or CH_2) does not significantly affect the conformational outcome of the dietherification of calixarenes **1** and **7**. The selective formation of *syn*-**4** may be explained by assuming that, in the initial monoether product, coordination of the phenol and phenoxide oxygens to Na^+ ion highly retards the 'oxygen-through-the-annulus rotation[13]' of the phenyl rings to restrict its conformational freedom (Scheme 2). Furthermore, the weak base (i.e. Na_2CO_3) might be able to deprotonate only the phenolic proton of the C-ring to form the sterically and electronically most stable anion with the aid of hydrogen bondings with the adjacent two OH groups, resulting in the second etherification at the C-ring.



cone-**2** 1,3-alternate-**2** *syn*-**4**

Scheme 1. The conformational isomers of **2** and **4**.[10] Ellipses denote thiacalix[4]arene rings. $Y=CH_2CO_2Et$



Scheme 2. A possible reaction intermediate for dietherification

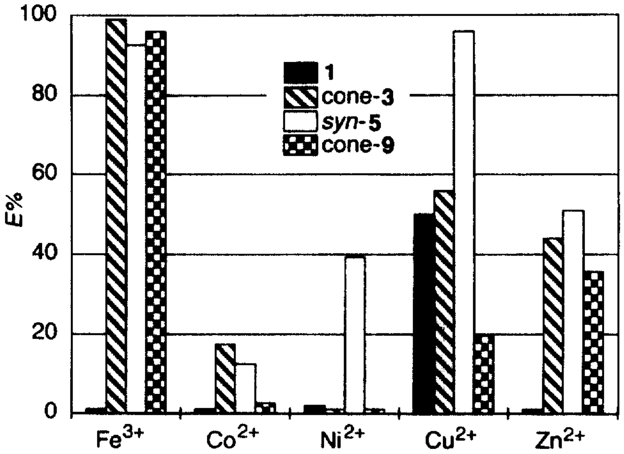
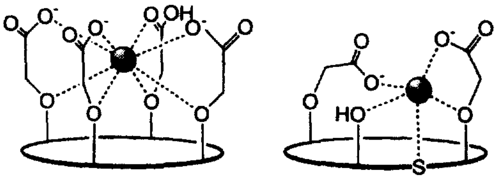


Figure 1. The *E*% of transition metal ions by calix[4]arenes at pH 5.5

Hydrolysis of the ester moiety of **2** and **4** was quite easy by use of a suitable base in an aqueous–organic mixed solvent.[14] The NMR spectra explicitly showed that cone-**3**, 1,3-alternate-**3** and *syn*-**5** retained the stereochemistry of the parent esters, suggesting that the -CH_2COOH group is large enough to prevent the rotation of phenyl rings through thiacalix[4]arene ring. Oxidation of the sulfide and phenol moieties was not observed.

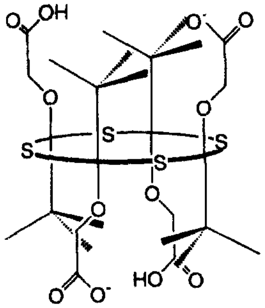
With these novel receptor compounds in hand, we then assessed their ability to bind metal ions by extractability, *E*%.[15] For the sake of comparison, methylene-bridged tetracarboxylic acid cone-**9** was prepared according to the literature procedure.[16] The *E*% of several transition metal ions at pH 5.5 (Fig. 1) indicates some interesting features characteristic of the calixarenes used. First, the parent compound **1** exhibited very low *E*% at this pH except for Cu^{2+} ion,[17] although **1** could extract these metal ions quantitatively from weakly basic solutions (pH 8.0).[2] This may be explained by assuming that a slight change in pH significantly affects the deprotonation and thus the binding ability of **1** to metal ions, since **1** generally requires coordination of two phenolic O^- in addition to one S to bind to metal ions as exemplified by X-ray analysis of a Zn^{2+} complex.[3] Second, cone-**3** and *syn*-**5** could extract metal ions at the weakly acidic region by virtue of the -CH_2COOH groups having higher acidity. It can be seen that the extractability of cone-**3** and *syn*-**5** toward Fe^{3+} ion was very high. It seems that coordination of more than two -OCH_2COO^- groups substantially facilitated complexation with the highly charged ion (Fe^{3+}) in the fashion of either Scheme 3a or b, the former seemingly being slightly preferred over the latter considering the high extraction ability of methylene-bridged cone-**9**. On the other hand, *syn*-**5** showed higher extractability to Cu^{2+}, and especially to the Ni^{2+}, ion than cone-**3** did; the role of the sulfide may become more important to bind to these soft metal ions. Third, by comparing cone-**3** with cone-**9**, the former usually had higher extraction ability than the latter, as was most distinctive in the case of the Co^{2+} and Cu^{2+} ions. This suggests that not only the -COO^- groups but also the S-atom could take some part in the ligation to the metal ions. It is interesting to note that 1,3-alternate-**3** could not extract metal ions under the same conditions (data not shown in Fig. 1),[18] suggesting three possible reasons (Scheme 4): (1) the *p-tert*-butylphenyl groups may sterically hinder the -COO^- groups to bind to metal ions; (2) the conformation lacking coordinating groups in the 1,2-relationship may be insufficient to form stable metal complexes; and (3) partition of the complex from the aqueous solution to an organic phase may be inhibited due to the anchoring effect of free -COO^- groups on the opposite side.

Note added in proof. The conformation of *syn*-**6** was later confirmed to be cone. For details, see Narumi et al.[7]



(a) cone-3 (b) *syn*-5

Scheme 3. Proposed coordination manners of: (a) cone-**3**; and (b) *syn*-**5**. A hydroxy group in (b) behind the metal complex moiety is not drawn for clarity



Scheme 4. A possible explanation of the poor extractability of 1,3-alternate-**3**

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8. Recently, the same results were reported by another group. See: Akdas, H.; Mislin, G.; Graf, E.; Hosseini, M. W.; Cian, A. D.; Fischer, J. *Tetrahedron Lett.* **1999**, *40*, 2113–2116.
9. In a typical run, a mixture of **1** (2.0 g, 2.7 mmol), Na_2CO_3 (0.3 g, 2.7 mmol), and ethyl bromoacetate (0.6 ml, 5.5 mmol) in acetone (20 ml) was heated at reflux for 48 h under nitrogen, to which was added 2 M HCl to terminate the reaction, followed by extraction with chloroform (40 ml×3). After washing with distilled water (15 ml×2), the chloroform layer was dried over magnesium sulfate and evaporated to dryness to obtain a crude product, which was subjected to column chromatography (150 g silica gel, 5:1 ethyl acetate:hexane) followed by recrystallization from ethanol to give a pure sample of *syn*-**4** (1.16 g, 46.8%). The reaction in THF gave a slightly improved yield of *syn*-**4** (51%). Compound *syn*-**4**: mp 268.8°C; FAB MS *m/z* 892 (M^+); IR (KBr) 3396 (OH), 2962 (CH), 1740 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (18H, s, $C(CH_3)_3$), 1.36 (18H, s, $C(CH_3)_3$), 1.37 (6H, t, J=7.1 Hz, $-CH_2CH_3$), 4.40 (4H, q, J=7.1 Hz, $-CH_2CH_3$), 5.29 (4H, s, $-CH_2-$), 6.91 (4H, s, Ar-H), 7.66 (4H, s, Ar-H), 8.02 (2H, s, OH); ^{13}C NMR ($CDCl_3$) δ 14.4 ($-CH_2\mathit{C}H_3$), 30.8, 31.5 ($C(\mathit{C}H_3)_3$), 34.1, 34.2 ($\mathit{C}(CH_3)_3$), 61.4 ($-\mathit{C}H_2CH_3$), 70.3 ($-O\mathit{C}H_2CO_2-$), 169.1 ($-OCH_2\mathit{C}O_2-$), 129.1, 134.8, 148.6, 155.0 ($C_{Ar,A}$), 122.0, 132.6, 142.8, and 155.7 ($C_{Ar,B}$). Calcd for $C_{48}H_{60}O_8S_4$: C, 64.56; H, 6.77; S, 14.36. Found: C, 64.62; H, 6.90; S, 14.05.
10. Although *syn*-**6** may have cone or 1,3-alternate conformation, the conformation of *syn*-**4** could not be assigned to a particular one because of the 'oxygen-through-the-annulus rotation'.
11. Ogata, M.; Fujimoto, K.; Shinkai, S. *J. Am. Chem. Soc.* **1994**, *116*, 4505–4506.
12. See also: Iwamoto, K.; Yanagi, A.; Araki, K.; Shinkai, S. *Chem. Lett.* **1991**, 473–476.
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14. For the hydrolysis of cone-**2** to the corresponding conformer of **3**, see Ref. 6. By the same fashion, 1,3-alternate-**2** was hydrolyzed to give 1,3-alternate-**3**. In a typical run for hydrolysis of *syn*-**4**, a mixture of *syn*-**4** (1.79 g, 2.00 mmol) and potassium hydroxide (1.16 g, 20.7 mmol) in ethanol:water (2:1, 90 ml) was heated at 100°C for 3 h, and then to the cooled

mixture was added 2 M HCl (60 ml) in an ice-water bath. Precipitate was collected by filtration and washed with water, then recrystallized from water–acetone to obtain a pure sample of *syn*-**5** (1.55 g, 92.5%). Properties: 1,3-alternate-**3**: mp 325–327°C (decomp.); FAB MS *m/z* 952 (M^+); IR (KBr) 3448 (OH), 2964 (CH), 1751 (CO) cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 1.25 (36H, s, $\mathrm{C(CH_3)_3}$), 4.55 (8H, s, $\mathrm{-CH_2CO-}$), 7.38 (8H, s, Ar-H); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 30.9 ($\mathrm{C}(\mathit{C}\mathrm{H_3})_3$), 34.6 ($\mathit{C}\mathrm{(CH_3)_3}$) and 127.8, 129.2, 150.0 153.1 ($\mathrm{C_{Ar}}$) 167.7 ($\mathrm{-}\mathit{C}\mathrm{O_2H}$). Calcd for $\mathrm{C_{48}H_{56}O_{12}S_4}$: C, 60.48; H, 5.92; S, 13.46. Found: C, 60.13; H, 5.61; S, 13.42. *syn*-**5**: mp 310°C (decomp.); FAB MS *m/z* 836 (M^+); IR (KBr) 3389 (OH), 2964 (CH), 1732 (CO) cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$: DMSO=1: 1) δ 0.78 (18H, s, $\mathrm{C(CH_3)_3}$), 1.35 (18H, s, $\mathrm{C(CH_3)_3}$), 5.08 (4H, s, $\mathrm{-CH_2-}$), 6.92 (4H, s, Ar-H), 7.67 (4H, s, Ar-H), 8.02 (2H, s, OH). ^{13}C NMR ($\mathrm{CDCl_3}$: DMSO=1: 1) δ 30.4, 31.2 ($\mathrm{C}(\mathit{C}\mathrm{H_3})_3$), 33.7, 33.9 ($\mathit{C}\mathrm{(CH_3)_3}$), 69.6 ($\mathrm{-O}\mathit{C}\mathrm{H_2CO_2H}$), 170.4 ($\mathrm{-}\mathit{C}\mathrm{O_2H}$), 128.6, 134.7, 148.0, 154.5 ($\mathrm{C_{Ar,A}}$), 121.5, 132.2, 142.4, and 155.4 ($\mathrm{C_{Ar,B}}$). Calcd for $\mathrm{C_{44}H_{52}O_8S_4}$: C, 63.13; H, 6.26; S, 15.32. Found: C, 63.02; H, 6.00; S, 15.33.

15. To a 30 ml vial tube was pipetted a solution of a calixarene (5×10^{-4} M **1**, cone-**3**, 1,3-alternate-**3**, *syn*-**5**, or cone-**9**) in chloroform (10 ml) and an aqueous solution (10 ml) containing a metal ion (1×10^{-4} M), pH buffer (5×10^{-2} M $\mathrm{HNO_3}$-$\mathrm{NH_3}$ at pH 2.5, $\mathrm{CH_3COOH}$-$\mathrm{NH_3}$ at pH 5.5, or Tris–HCl at pH 7.5), and tetrabutylammonium chloride (TBACl, 0.01 M for cone-**3**, 1,3-alternate-**3**, and cone-**9**, none for **1**, 1,3-alternate-**3**, and *syn*-**5**). The mixture was shaken at 300 strokes/min for 24 h. The total concentration of the metal species remaining in the aqueous phase, $[\mathrm{Metal}]_{\mathrm{aq}}$, was measured by atomic absorption spectrometer. The concentration of the metal ion extracted into the organic phase, $[\mathrm{Metal}]_{\mathrm{org}}$, as the complex was estimated by $[\mathrm{Metal}]_{\mathrm{org}}=[\mathrm{Metal}]_{\mathrm{aq,init}}-[\mathrm{Metal}]_{\mathrm{aq}}$, where $[\mathrm{Metal}]_{\mathrm{aq,init}}$ is the initial concentration of the metal ion in the aqueous phase. The values of *E%* were calculated by $E\%=[\mathrm{Metal}]_{\mathrm{org}}/[\mathrm{Metal}]_{\mathrm{aq,init}}\times100\%$.
16. The cone conformer of **9** was prepared by the same fashion as in Ref. 14.
17. The specific binding of **1** to $\mathrm{Cu^{2+}}$ ion has been reported previously.[2]
18. The *E%* values for 1,3-alternate-**3** with or without (in parentheses) use of 0.01 M TBACl; $\mathrm{Co^{2+}}$: 1.50 (2.97), $\mathrm{Ni^{2+}}$: 0 (0), $\mathrm{Cu^{2+}}$: 11.08 (13.97), $\mathrm{Zn^{2+}}$: 0% (0%). For $\mathrm{Fe^{3+}}$, *E%* values could not be obtained due to the formation of precipitation.