Selective synthesis of three conformational isomers of tetrakis[(ethoxycarbonyl)methoxy]thiacalix[4]arene and their complexation properties towards alkali metal ions †

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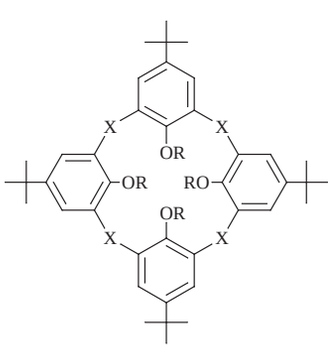
5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-25,26,27,28-tetrol (TCA) underwent facile tetra-*O*-alkylation by treatment with ethyl bromoacetate in the presence of an alkali carbonate as base catalyst in DMF or acetone to provide a mixture of conformational isomers (cone, partial cone, and 1,3-alternate) of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene (**1**), the stereochemistries of which were unambiguously assigned by ^{1}H NMR and X-ray analysis. The isomer distribution depended significantly on the base used, thus providing a facile route for the preparation of a particular conformer; Na_2CO_3, K_2CO_3, and Cs_2CO_3 gave cone- (77% yield), partial-cone- (58% yield), and 1,3-alternate-**1** (78% yield) in acetone, respectively. Cone- and partial-cone-**1**, in turn, showed preference for Na^+ and K^+, respectively, in an ion-pair extraction study, while 1,3-alternate-**1** preferred most Rb^+ ion, followed by K^+ and then Cs^+. These results imply that the size of the cavities provided by the (ethoxycarbonyl)methoxy groups arranged on the periphery of the thiacalix[4]arene skeleton is in the order cone- < partial-cone- < 1,3-alternate-**1**. The ion selectivity of cone-**1** was rather better than that of the methylene-bridged counterpart, 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene (**2**). The stoichiometry of the complex of cone-**1** with Na^+ ion was determined to be 1 : 1 with the stability constant of $10^{2.85}$ mol^{-1} dm^3 in 50 (v/v)% $CDCl_3$–CD_3OD.

Introduction

In the last decade, calixarenes have been drawing much attention as key compounds in molecular recognition chemistry and supramolecular chemistry.[1] Almost all the calixarenes have the metacyclophane skeleton bridged by methylene groups due to their ease of synthesis *via* condensation of *p*-alkylphenols and formaldehyde under alkaline conditions. The general strategy used to develop the important abilities of these molecules such as sensing[2] and separation[3] of metal ions and organic molecules has relied on the modification of the upper[4] and/or lower[5] rims of the parent calixarenes. For example, Shinkai *et al.* reported the introduction of (ethoxycarbonyl)methyl groups into 5,11,17,23-tetra-*tert*-butylcalix[4]arene-25,26,27,28-tetrol (CA) by direct *O*-alkylation. They obtained the conformational isomers of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene (**2**) which were found to be able to recognize particular alkali metal ions selectively.[6] Also Reinhoudt *et al.* studied the effect of solvent, temperature, and base catalysts on the conformational distribution in the formation of ethers in calix[4]arenes.[7]



Compd.	X	R
CA	CH_2	H
TCA	S	H
1	S	CH_2COOEt
2	CH_2	CH_2COOEt

By contrast, development of new functions *via* replacement of the bridge methylene groups by hetero atoms remains to be exploited. Sone *et al.* first reported the synthesis of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-25,26,27,28-tetrol (TCA) by acid catalysed cyclization of an acyclic tetramer.[8] Although the synthesis allowed them to carry out ^{1}H NMR studies of TCA,[9] little is known about the other properties and applications of this cyclic entity because of the difficulty in obtaining it in substantial quantities. Recently, we reported a convenient and facile synthesis of TCA in a satisfactory yield by simply heating *p-tert*-butylphenol with elemental sulfur in the presence of a base.[10] It has been found that TCA has a very high ability to bind transition metal ions,[11] which had been quite unexpected from the poor binding ability of CA. However, neither TCA or CA could form complexes with alkali metal ions in solvent extraction. As a part of our efforts to develop the potential of TCA, herein we report the stereoselective etherification of TCA to give the conformational isomers of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene (**1**). Also reported are the results of selective alkali metal ion extraction with the conformational isomers of **1**.

Results and discussion

Conformation selective etherification of TCA

It is known that TCA exists in a cone conformation but the energy barrier of the ring inversion is somewhat lower than that

† Supplementary data (SUPPL. NO. 57448, pp. 6) is available from the British Library. For details of the Supplementary Publications Scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 2*, available *via* the RSC Web page (http://www.rsc.org/authors). The supplementary data is also available on the RSC's web server (http://www.rsc.org/suppdata/perkin2/1998/2745/).

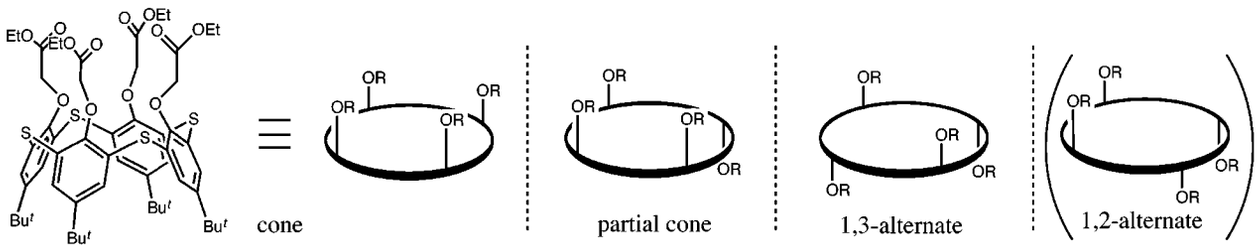


Fig. 1 Schematic representation of four possible conformers of **1**.

Table 1 Conformer distribution for the reaction of TCA with ethyl bromoacetate

						Conformer distribution (%)		
Run	Base	Solvent	Temp/°C	Time/h	Yield (%)	Cone	Partial cone	1,3-Alternate
1[a]	Li_2CO_3	DMF	60	34	0	0	0	0
2	Na_2CO_3	DMF	60	16	81	26	65	9
3	K_2CO_3	DMF	60	6	95	13	63	24
4	Cs_2CO_3	DMF	60	2	85	6	34	60
5[a]	Li_2CO_3	Acetone	Reflux	46	0	0	0	0
6	Na_2CO_3	Acetone	Reflux	36	85	91	9	0
7	K_2CO_3	Acetone	Reflux	28	95	24	61	15
8	Cs_2CO_3	Acetone	Reflux	4	96	3	16	81

[a] A mixture of di- and tri-*O*-substituted TCA was obtained (*ca.* 20% yield each).

of CA due to the weaker intramolecular hydrogen bonding with the ring size slightly enlarged by replacing the methylene linkage with a sulfide bond.[10] As molecular models suggest, however, the (ethoxycarbonyl)methoxy group seems large enough to prevent the so-called oxygen through the annulus rotation[12] even in the case of TCA. Therefore, complete *O*-alkylation of the OH groups of TCA may produce all the four possible isomers at most, each of which should be conformationally stable in the cone, 1,2-alternate, partial cone, and 1,3-alternate conformations (Fig. 1). Thus, TCA was treated with ethyl bromoacetate in the presence of an alkali carbonate in dimethylformamide (DMF) or acetone according to Shinkai's procedure[6] used for the etherification of CA (Table 1). It was found that direct alkylation of TCA affords three conformational isomers out of the possible four, *i.e.* cone-, partial-cone-, and 1,3-alternate-**1**, as unambiguously assigned by ^{1}H NMR and X-ray structure analysis (*vide infra*). Available evidence, including detailed TLC and ^{1}H NMR scrutiny, did not indicate the formation of 1,2-alternate-**1**.

Table 1 lists the combined yields of isolated **1** and the isomer distributions. It is interesting to note that the alkali metal carbonates showed a distinct influence on the distribution of conformers, suggesting that the template effect may be the main controlling factor as in the case of tetra-*O*-alkylation of CA to 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene (**2**) performed by Shinkai *et al.*[6] In DMF, base catalysts Na_2CO_3 and K_2CO_3 gave the partial cone quite selectively whereas Cs_2CO_3 gave the 1,3-alternate. The selectivity was rather conspicuous in acetone; Na_2CO_3, K_2CO_3, and Cs_2CO_3 produced the cone, partial cone, and 1,3-alternate in the isolated yields of 77, 58, and 78%, respectively. One possible explanation for the enhanced template effect in acetone might be that the precursor phenolate intermediates coordinate more tightly to the template metal ions (Fig. 2). On the other hand, Li_2CO_3 gave no **1**, giving a mixture of di- and tri-*O*-alkylated TCA only in a poor yield (*ca.* 20% each) as evidenced by TLC and ^{1}H NMR. The distribution of the conformers in Table 1 suggests that the size of the cavity consisting of the phenyl and ester groups in each conformer is in the order of cone < partial cone < 1,3-alternate which may explain the results of a solvent extraction study (*vide infra*).

Shinkai's results of the direct tetra-etherification show that Na_2CO_3 and K_2CO_3 gave cone-**2** selectivity in either DMF or acetone but Cs_2CO_3 gave partial-cone-**2**.[6] They needed the protect–deprotection technique, using a benzyl group, to obtain 1,3-alternate-**2**. By contrast, TCA could conveniently be derivatized directly into 1,3-alternate-**1** in the presence of Cs_2CO_3. This might be attributed to the intermediate being large enough to accommodate the Cs^+ ion since the TCA skeleton is so much larger than the CA skeleton as discussed below.

Structure analysis by ^{1}H NMR and X-ray

The conformations of usual calix[4]arene derivatives can conveniently be assigned by use of the ^{1}H NMR resonance pattern of the methylene groups linking the phenol nuclei.[13] However, this tactic cannot be applied to **1** because of the bridging epithio groups. So we relied on the chemical shifts and resonance patterns of the other protons. Theoretically, only partial-cone-**1** among the possible four conformers has three non-equivalent *p*-*tert*-butylphenol units, which will give a 2:1:1 resonance pattern in the NMR spectrum. Therefore, the isomer which exhibited Bu^t peaks at 1.05 (18H, s), 1.31 (9H, s), and 1.43 (9H, s) was safely assigned as partial cone. On the other hand, in cone- and 1,3-alternate-**1**, all the phenyl units are equivalent so that both of the conformers should give the same resonance pattern for the Bu^t protons (36H, s), -OCH_2CO- (8H, s), and Ar-H (8H, s) (see the Experimental section). However, it was possible to distinguish between these two isomers by considering their chemical shifts. In 1,3-alternate-**1**, the Bu^t and aromatic protons are in the deshielding zone of not only the attaching phenyl ring but also the two adjacent phenyl units, while those of cone-**1** are in the shielding zone of the adjacent phenyl nuclei. Therefore, it is expected that the Bu^t and aromatic protons of the 1,3-alternate should give resonances at lower field than those of the cone conformer. Furthermore, the -OCH_2CO- moiety of 1,3-alternate-**1** is shielded by the adjacent phenyl rings so that its methylene protons should resonate at higher field than those of the cone conformer. Thus, the isomer which exhibited Bu^t and CH_2 protons at δ 1.09 and 5.18 ppm, respectively, was assigned to cone-**1**, while that which exhibited protons at δ 1.25 and 4.60 ppm was assigned to 1,3-alternate-**1**.

The ^{1}H NMR assignments were eventually confirmed by X-ray structure analysis of the conformation of cone-**1**. The

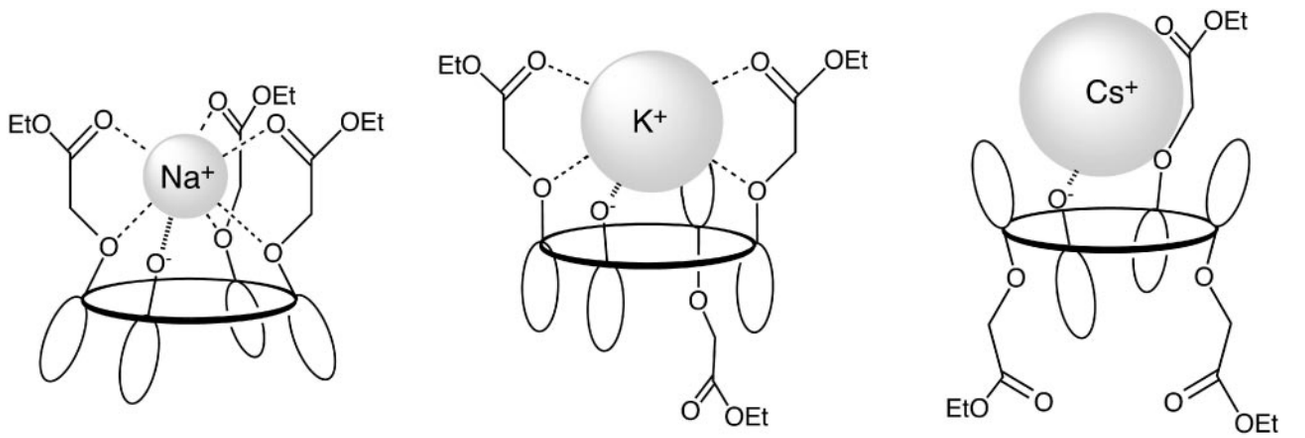


Fig. 2 Possible tri-*O*-alkylated intermediates coordinating to the template metal ions to yield cone-, partial-cone-, and 1,3-alternate-**1**. Small ellipses denote 4-*tert*-butylphenyl moiety.

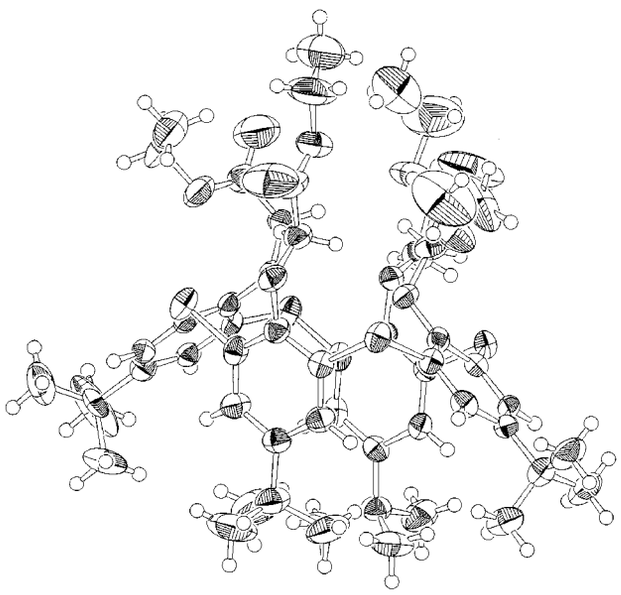


Fig. 3 X-Ray structure of cone-**1**. Cell constants; monoclinic cell with $a = 16.390$ Å, $b = 21.518$ Å, $c = 16.778$ Å, $\beta = 93.92°$, $V = 5903$ Å^3. For $Z = 4$ and FW = 1065.42, the calculated density is 1.2 g cm^{-3}. Space group: $P2_1/n$. $R = 0.052$, $R_w = 0.065$.

ORTEP diagram (Fig. 3) of cone-**1** clearly indicates a typical flattened cone structure, which is frequently observed in tetra-*O*-alkylated calix[4]arenes with cone conformations in the solid state.[14] The (ethoxycarbonyl)methoxy groups seemed to be rather randomly arranged in a unit cell. Its terminal Me group showed a large anisotropic displacement, which implies large thermal motion and/or disorder. Table 2 summarizes the average bond lengths of interest for cone-**1** as well as the reported values for cone-**2**.[15] Only Ar–X, the bond length between the benzene ring and the bridging group, in cone-**1** showed a 15% larger value than Ar–X in cone-**2**. Consequently, it is expected that **1** has a somewhat larger cavity than **2** so that it can accommodate the larger metal ions. This may explain, at least in part, why TCA can undergo direct *O*-alkylation to the 1,3-alternate using Cs_2CO_3 as the template.

Solvent extraction study

In order to evaluate the ability of the three conformers of **1** to recognize alkali metal ions, ion-pair extraction was carried out. The extraction reaction is given by eqn. (1), where M^+, L, Pic^-,

$$M^+ + L_{org} + Pic^- \rightleftharpoons ML^+Pic^-_{org} \qquad (1)$$

ML^+, and ML^+Pic^- denote the metal ion, ligand (here, **1** or **2**), picrate anion, metal complex, and ion-pair. Subscript org means that the species exists in the organic phase. As shown, the formed metal complexes ML^+ are extracted as an ion-pair with the picrate anion into the organic phase. The concentration ‡ of ML^+Pic^- in the organic phase is given by eqn. (2), where

$$[ML^+Pic^-]_{org} = [Pic]_{aq,init} - [Pic]_{aq} \qquad (2)$$

$[Pic]_{aq,init}$ and $[Pic]_{aq}$ are the initial and final concentrations of the picrate ion in the aqueous phase. The percent extraction, E%, was calculated by eqn. (3).

$$E\% = [ML^+Pic^-]_{org}/[Pic]_{aq,init} \times 100\% \qquad (3)$$

Fig. 4 shows the E% of the conformers *versus* alkali metal ions. Cone-**1** showed the highest E% for the Na^+ ion compared to other metal ions using CH_2Cl_2 as the organic phase. By

Table 2 The mean bond lengths of interest for cone-**1** and -**2**[a]

Bond	Cone-**1** (X = S)	Cone-**2** (X = CH_2)[b]
Ar(C–C)	1.39(1)	1.39(1)
Ar–X	1.79(1)	1.55(1)
Bu^t(C–C)	1.52(1)	1.52(1)
CH_2–CO	1.48(1)	1.49(1)
Ar–O	1.39(1)	1.41(1)
CH_2–O	1.42(1)	1.46(1)
C=O	1.19(1)	1.19(1)
O–CO	1.29(1)	1.31(1)

[a] Bond lengths are in Å (1 Å = 0.1 nm). [b] See reference 15.

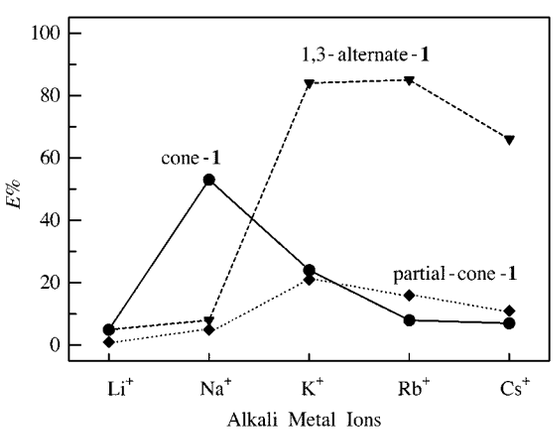


Fig. 4 The percent extraction (E%) by three conformers of **1**. Organic phase: [L (=**1**)]$_{org,init} = 2.5 \times 10^{-3}$ M in CH_2Cl_2. Aqueous phase: $[MOH]_{aq,init} = 0.1$ M, $[HPic]_{aq,init} = 2.5 \times 10^{-4}$ M.

‡ Hereafter, 1 M≡1 mol dm^{-3}.

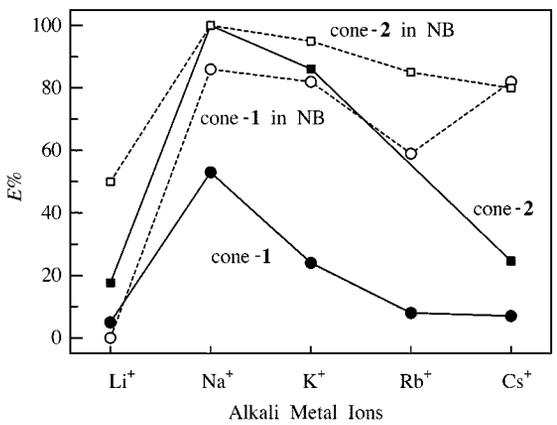


Fig. 5 The percent extraction (E%) by cone conformers of **1** and **2**. Organic phase: $[L\ (=\mathbf{1}\text{ or }\mathbf{2})]_{org,init} = 2.5 \times 10^{-3}$ M in CH_2Cl_2 or in nitrobenzene (NB). Aqueous phase: $[MOH]_{aq,init} = 0.1$ M, $[HPic]_{aq,init} = 2.5 \times 10^{-4}$ M. Data for cone-**2** in CH_2Cl_2 are cited from ref. 6. Circle: cone-**1**, square: cone-**2**, closed symbol: in CH_2Cl_2, open symbol: in nitrobenzene.

contrast, 1,3-alternate-**1** extracted larger metal ions such as K^+ and Rb^+ better than the Na^+ ion. Partial-cone-**1** showed a small E% for all metal ions, among which it showed a preference for the K^+ ion. Although the aquation–deaquation energy of these metal ions must be taken into account, the metal ion selectivity seems to indicate that the cavity size provided by the ligating groups of the conformational isomers of **1** is in the sequence cone < partial cone < 1,3-alternate. This sequence may be said to correspond to the conformational selectivity observed in *O*-alkylation by these metal ions.

Considering the results reported by Shinkai *et al.*, conformers of **2** generally exhibited better E% for alkali metal ions than those of **1** under the same extraction conditions.[6] Among these conformers of **1** and **2**, however, cone-**1** exhibited the highest Na^+ ion selectivity in CH_2Cl_2, which may make it a candidate for the ionophore in an ion-selective electrode.

It has been known that the extractability in ion-pair extraction strongly depends on the relative permittivity of the organic phase.[16] Thus, solvents with high relative permittivity should enhance ion-pair migration from the aqueous to the organic phase. Therefore, nitrobenzene was used as the solvent instead of CH_2Cl_2 for alkali metal ion extraction by cone-**1** and -**2**. In fact, the E% values for cone-**1** and -**2** in nitrobenzene generally exceeded those in dichloromethane as indicated by the broken lines in Fig. 5. However, the extractability of cone-**1** did not equal that of cone-**2** except in the case of Cs^+. The ion-pair extraction given by eqn. (1) is composed of reactions (4)–(7).

$$L_{org} \rightleftharpoons L \quad (4)$$

$$M^+ + L \rightleftharpoons ML^+ \quad (5)$$

$$ML^+ + Pic^- \rightleftharpoons [ML^+Pic^-] \quad (6)$$

$$[ML^+Pic^-] \rightleftharpoons [ML^+Pic^-]_{org} \quad (7)$$

Due to the similarity in the molecular size and shape between cone-**1** and -**2**, it is assumed that free energies for the partition of the ligand [eqn. (4)], ion-pairing of the complex [eqn. (6)], and the partition [eqn. (7)] are similar in the cases of L = cone-**1** and cone-**2**. Consequently, it may be concluded that the smaller extractability of cone-**1** is due to its complexing ability [eqn. (5)].

Stability constants of Na^+ complexes of cone-1 and cone-2

The results of the above solvent extraction suggested that the lower E% of cone-**1** as compared to that of cone-**2** seemingly originated from the difference in the metal–ligand complexation ability [*i.e.* eqn. (5)], which tempted us to study the thermodynamic stability of the metal complexes of **1** and **2**. However, the poor solubility of the complexes in the usual NMR solvents, in addition to the subtle changes in ^1H NMR signals upon complexation with metal ions, restricted the measurements to those of Na^+ complexes with cone-**1** and -**2** in 50 (v/v)% $CDCl_3$–CD_3OD.

The stoichiometry of the cone-**1** complex with Na^+ in the mixed solvent was determined to be 1 : 1 by the continuous variation method, while that of cone-**2** was also known to be 1 : 1.[6] Therefore the reaction to be considered is the same as eqn. (5). In this case, M^+ is Na^+, L is cone-**1** or cone-**2**, and ML^+ is cone-Na**1**$^+$ or cone-Na**2**$^+$. The equilibrium constant, K, is then defined by eqn. (8). In the case of L = cone-**1**, since the

$$K = \frac{[ML^+]}{[M^+][L]} \quad (8)$$

intermolecular exchange of L between free L and ML^+ in eqn. (5) was fast on the ^1H NMR timescale, the chemical shift change of L upon titration by Na^+ ion was analysed as usual. By contrast in the case of L = cone-**2**, two distinct signals for free L and ML^+ were observed, suggesting the inertness of cone-Na**2**$^+$. Then each peak area was used to evaluate the K (for detail, see the Experimental section). As a result, the K values for cone-Na**1**$^+$ and cone-Na**2**$^+$ at 25 °C were estimated to be log (K/M^{-1}) = 2.8_5 and 4.0_3, respectively.

Why is the stability of cone-Na**1**$^+$ lower than that of cone-Na**2**$^+$? One possible explanation may be the fluxional property of the intrinsic framework of the thiacalix[4]arene in **1**, as deduced from the longitudinal relaxation time, T_1, of the parent TCA.[9] Thus, the basic framework as well as the (ethoxycarbonyl)methoxy groups of cone-**1** may show faster thermal motion than cone-**2**, resulting in the looser fixation of the Na^+ ion by cone-**1**. We believe this is not a serious drawback of **1**, because the absolute value of log K is not as important as the selectivity, namely the difference in log K among metal ions, when one intends to use **1** as an ionophore in ion selective sensors.

Conclusion

In this study, we have reported that the conformational stereoselectivity of the tetra-*O*-alkylation of TCA was readily controlled by choosing a suitable alkali carbonate as base catalyst. Although the ability of **1** for alkali metal extraction is lower than that of **2**, the higher ion selectivity of **1** over **2** is an attractive feature of **1** as an ionophore in sensory systems[2] such as ion-selective electrodes and chemically modified field effect transistors.

Experimental

General remarks

Mps were taken using a Yamato MP-21 apparatus and are corrected. Microanalyses were carried out in the Institute of Chemical Reaction Science, Tohoku University. Merck silica gel $60GF_{254}$ was used for TLC. Silica gel columns were prepared by the use of Merck silica gel 60 (63–200 μm). ^1H NMR was measured on a Bruker DPX-400 spectrometer operated at 400 MHz. The δ values are given in ppm and J values in Hz. UV-VIS and IR spectra were obtained with a Shimadzu UV-160 and IR-460, respectively. RP-HPLC, consisting of a Shimadzu LC-10AD pump unit, a SPD-6A UV-VIS detector, and a LiChrosphere RP-18 column (125 mm × 5 mm, 5 μm, MERCK), was used to determine $[Pic]_{aq}$ in the aqueous–nitrobenzene two-phase extraction system.

Materials

Samples of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-25,26,27,28-tetrol (TCA) were generously supplied

by Cosmo Research Institute or synthesised as described before.[10] The cone conformer of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene (**2**) was synthesised as described by Shinkai *et al.*[6] Standard solutions (0.1 M) of alkali metal ions (Li^+, Na^+, K^+, Rb^+, and Cs^+) were prepared by dissolving the hydroxides in distilled water. The accurate concentrations were determined by the usual acid–base titration method. Picric acid was stocked as 0.01 M aqueous solution. All the reagents purchased were of guaranteed reagent grade and used as purchased unless otherwise noted. Acetone and DMF were distilled from CaH_2 before use.

General procedure for the preparation of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene (1)

TCA was suspended in dry acetone or DMF (*ca*. 50 mM solution) containing a 6-fold excess of an anhydrous alkali carbonate and an 8-fold excess of ethyl bromoacetate. The mixture was heated under nitrogen for 4–46 h (see Table 1). The reaction was monitored by TLC. After cooling, the solid residue was removed by filtration. The solution was evaporated to dryness and maintained at 1 mmHg and 60 °C for several hours to ensure the removal of unchanged ethyl bromoacetate. The mixture of conformational isomers was separated by column chromatography using silica gel. The eluents used were *n*-hexane–benzene and *n*-hexane–ethyl acetate mixed solvents. The cone-**1** and partial-cone-**1** were recrystallized from ethanolic solution whereas 1,3-alternate-**1** was recrystallized from benzene solution. The yields for different base/solvent systems are listed in Table 1.

Cone-1. Mp 180.0–180.6 °C (Found: C, 63.18; H, 6.62; S, 12.22. $C_{56}H_{72}O_{12}S_4$ requires C, 63.13; H, 6.81; S, 12.04%); ν_{max}/cm^{-1} 2965 (CH), 1757 and 1732 (CO); δ (400 MHz, $CDCl_3$) 1.09 (36H, s, Bu^t), 1.28 (12H, t, *J* 7.2, CH_3), 4.21 (8H, q, *J* 7.2, $COOCH_2$), 5.18 (8H, s, OCH_2CO), 7.29 (8H, s, ArH).

Partial-cone-1. Mp 212.0–212.8 °C (Found: C, 63.00; H, 6.66; S, 12.21. $C_{56}H_{72}O_{12}S_4$ requires C, 63.13; H, 6.81; S, 12.04%); ν_{max}/cm^{-1} 2960 (CH), 1761 and 1735 (CO); δ (400 MHz, $CDCl_3$) 1.05 (18H, s, Bu^t), 1.31 (9H, s, Bu^t), 1.43 (9H, s, Bu^t), 1.13 (3H, t, *J* 7.2, CH_3), 1.27 (6H, t, *J* 7.2, CH_3), 1.32 (3H, t, *J* 7.2, CH_3), 3.98 (2H, q, *J* 7.2, $COOCH_2$), 4.14–4.29 (6H, m, $COOCH_2$), 4.65 (2H, s, OCH_2CO), 4.71 (2H, d, *J* 15.2, OCH_2CO), 4.74 (2H, s, OCH_2CO), 4.78 (2H, d, *J* 15.2, OCH_2CO), 7.01 (2H, d, *J* 2.5, ArH), 7.52 (2H, d, *J* 2.5, ArH), 7.54 (2H, s, ArH), 7.86 (2H, s, ArH).

1,3-Alternate-1. Mp 329.5–331.0 °C (decomp.) (Found: C, 63.12; H, 6.72; S, 12.11. $C_{56}H_{72}O_{12}S_4$ requires C, 63.13; H, 6.81; S, 12.04%); ν_{max}/cm^{-1} 2960 (CH), 1764 and 1736 (CO); δ (400 MHz, $CDCl_3$) 1.25 (36H, s, Bu^t), 1.28 (12H, t, *J* 7.2, CH_3), 4.22 (8H, q, *J* 7.2, $COOCH_2$), 4.60 (8H, s, OCH_2CO), 7.51 (8H, s, ArH).

X-Ray structure analysis

Single crystals of cone-**1**§ were prepared by recrystallization from ethanol–CH_2Cl_2 solution and sealed in capillaries.

Crystal data. $C_{56}H_{72}O_{12}S_4$, M = 1065.42. Monoclinic, *a* = 16.390(5) Å, *b* = 21.518(4) Å, *c* = 16.778(6) Å, β = 93.92(3)°, *V* = 5903(2) Å^3 (obtained from a least squares refinement using the setting angles of 20 carefully centered reflections in the range 27.88° < 2θ < 29.81°, graphite monochromatized Mo-Kα radiation, λ = 0.71069 Å), space group $P2_1/n$ (No. 14), *Z* = 4, D_{calc} = 1.199 g cm^{-3}. Colourless, prismatic shape. Crystal dimensions 0.40 × 0.30 × 0.20 mm, μ(Mo-Kα) = 2.17 cm^{-1}.

Data collection and processing. Rigaku AFC7R diffractometer, $\omega/2\theta$ mode with ω scan width = (1.26 + 0.30tanθ)°, ω scan speed 16.0° min^{-1}; 14 396 reflections measured, 13 921 unique, giving 3294 with $I > 3\sigma(I)$. An empirical absorption correction based on azimuthal scans of several reflections (transmission factors 0.9334–1.0000).

Structure analysis and refinement. The structure was solved by heavy-atom Patterson methods (PATTY)[17] and expanded using Fourier techniques (DIRDIF94).[18] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was implemented by minimizing $\Sigma w(|F_o| - |F_c|)^2$ for 3294 observed reflections [$I > 3.00\sigma(I)$] and 650 variable parameters and converged (largest parameter shift was 0.09 times its esd) with unweighted and weighted agreement factors of $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.052$ and $R_w = \{\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_c^2\}^{0.5} = 0.065$, where $w = 1/\sigma^2(F_o) = \{\sigma_c^2(F_o) + p^2F_o^2/4\}^{-1}$, $\sigma_c^2(F_o)$ = esd based on counting statistics, and *p* = *p*-factor. The standard deviation of an observation of unit weight given by $\{\Sigma w(|F_o| - |F_c|)^2/(N_o - N_v)\}^{0.5}$ was 1.14, where N_o and N_v are the number of observations and variables, respectively. The weighting scheme was based on counting statistics and included a factor (*p* = 0.075) to downweight the intense reflections. Plots of $\Sigma w(|F_o| - |F_c|)^2$ *versus* $|F_o|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.25 and −0.21 e$^-$ Å^{-3}, respectively. Neutral atom scattering factors were taken from Cromer and Waber.[19] Anomalous dispersion effects were included in F_{calc};[20] the values for $\delta f'$ and $\delta f''$ were those of Creagh and McAuley.[21] The values for the mass attenuation coefficients are those of Creagh and Hubbell.[22] All calculations were performed using the teXsan[23] crystallographic software package of the Molecular Structure Corporation.

Solvent extraction

A typical procedure for the extraction study is as follows. To a 30 cm^3 vial tube were pipetted 5 cm^3 of 0.1 M alkali metal hydroxide solution, 0.125 cm^3 of 0.01 M picric acid and 5 cm^3 of **1** or **2** solution (2.5×10^{-3} M) in CH_2Cl_2 or nitrobenzene, and the mixture was then shaken at 300 strokes per min for 30 min. The concentration of picrate ion remaining in the aqueous phase, $[Pic]_{aq}$, was determined by measuring the absorbance at 360 nm or HPLC analysis [eluent: 40 (v/v)% CH_3OH in water containing 0.01 M tetrabutylammonium bromide, flow rate: 1.0 cm^3 min^{-1}, detection wavelength: 254 nm].

Determination of stoichiometry of cone-$Na1^+$ complex

The stoichiometry was determined by the continuous variation method.[24] The ligand cone-**1** and $NaClO_4$ were first dissolved in 50 (v/v)% $CDCl_3$–CD_3OD solution separately at appropriate concentrations, which were then mixed and made up with the solvent to control the concentrations. The sum of the total concentration of the ligand {$[L]_T$, eqn. (9)} and the metal ion {$[M]_T$, eqn. (10)}, namely $[L]_T + [M]_T$, was maintained to be 4.0

$$[L]_T = [L] + [ML^+] \quad (9)$$

$$[M]_T = [M^+] + [ML^+] \quad (10)$$

§ Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 188/143.

mM in 50 (v/v)% $CDCl_3$–CD_3OD. At the same time, the ratio $[L]_T/[M]_T$ was varied from 3:1 to 2:1, 1:1, 1:2, and 1:3. After measuring the chemical shift, δ, of the -OCH_2CO- protons, it was then converted to the chemical shift change, Δ by eqn. (11),

$$\Delta = \delta_L - \delta \quad (11)$$

where δ_L is the chemical shift value when the Na^+ ion is absent. Finally ΔL_T was plotted against $[L]_T/([L]_T + [M]_T)$. The maximum was observed at $[L]_T/([L]_T + [M]_T) = 0.5$ which implied the stoichiometry is 1:1.¶

Determination of stability constants of cone-Na1$^+$ and cone-Na2$^+$ complexes

The solutions of appropriate concentration were prepared as above. For the cone-Na**1**$^+$ complex, $[L]_T$ was maintained as 1.0 mM for all conditions, whereas $[M]_T$ was varied to be 0, 0.5, 1.0, 2.0, 3.0, 5.0, 8.0, and 12.0 mM. The chemical shift change, Δ [eqn. (11)], for the -OCH_2CO- protons was recorded. Finally a set of $[M]_T$ *versus* Δ data was applied to Lang's routine[25] to obtain K and Δ_c, which is the Δ value at $[M]_T \rightarrow \infty$.‖

For the cone-Na**2**$^+$ complex, the sample of $[L]_T = 1.0$ mM and $[M]_T = 0.5$ mM was prepared. Since the cone-Na**2**$^+$ complex and the free cone-**2** gave discrete ^1H NMR signals, $[ML^+]/[L]$ was directly calculated (to be 0.76) from the peak area of Bu^t protons of each species. Then [L] and $[ML^+]$ were calculated from eqns. (12) and (9). Finally $[M^+]$ was obtained

$$[L] = \frac{[L]_T}{1 + \dfrac{[ML^+]}{[L]}} \quad (12)$$

from eqn. (10) and was introduced into eqn. (8) to obtain K ($=1.0_8 \times 10^4\ M^{-1}$). All measurements were done at 25 °C.

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¶ For raw data and plotting, refer to supplementary data.
‖ For detailed procedure, see reference 25. For the raw data and the Lang's plot, refer to the supplementary material.

References

1 V. Böhmer, *Angew. Chem., Int. Ed. Engl.,* 1995, **34**, 713; M. A. McKervey and V. Böhmer, *Chem. Br.,* 1992, 724; C. D. Gutsche, *Calixarenes, monographs in supramolecular chemistry*, ed. J. F. Stoddard, The Royal Society of Chemistry, Cambridge, 1989.
2 D. Diamond and M. A. McKervey, *Chem. Soc. Rev.*, 1996, 15.
3 K. Ohto, M. Yano, K. Inoue, T. Yamamoto, M. Goto, F. Nakashio, S. Shinkai and T. Nagasaki, *Anal. Sci.*, 1995, **11**, 893; J. M. Harrowfield, M. Mocerino, B. J. Peachey, B. W. Skelton and A. H. White, *J. Chem. Soc.*, *Dalton Trans.*, 1996, 1687.
4 See *e.g.*, C. D. Gutsche and K. C. Nam, *J. Am. Chem. Soc.*, 1988, **110**, 6153; Y. K. Agrawal and M. Sanyal, *Analyst*, 1995, **120**, 2759; F. Arnaud-Neu, V. Böhmer, J.-F. Dozol, C. Grüttner, R. A. Jakobi, D. Kraft, O. Mauprivez, H. Rouquette, M.-J. Schwing-Weill, N. Simon and W. Vogt, *J. Chem. Soc.*, *Perkin Trans. 2*, 1997, 575.
5 See *e.g.*, F. Arnaud-Neu, E. M. Collins, M. Deasy, G. Ferguson, S. J. Harris, B. Kaitner, A. J. Lough, M. A. McKervey, E. Marques, B. L. Ruhl, M. J. Schwing-Weill and E. M. Seward, *J. Am. Chem. Soc.*, 1989, **111**, 8681; A. Arduini, A. Casnati, L. Dodi, A. Pochini and R. Ungaro, *J. Chem. Soc.*, *Chem. Commun.*, 1990, 1597; T. Nagasaki and S. Shinkai, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 471; M. Ogata, K. Fujimoto and S. Shinkai, *J. Am. Chem. Soc.*, 1994, **116**, 4505; J. M. Harrowfield, M. Mocerino, B. J. Peachey, B. W. Skelton and A. H. White, *J. Chem. Soc.*, *Dalton Trans.*, 1996, 1687; F. Arnaud-Neu, G. Barrett, D. Corry, S. Cremin, G. Ferguson, J. F. Gallagher, S. J. Harris, M. A. KcKervey and M.-J. Schwing-Weill, *J. Chem. Soc.*, *Perkin Trans. 2*, 1997, 575.
6 K. Iwamoto and S. Shinkai, *J. Org. Chem.*, 1992, **57**, 7066.
7 See *e.g.*, L. C. Groenen, B. H. M. Ruël, A. Casnati, P. Timmerman, W. Verboom, S. Harkema, A. Pochini, R. Ungaro and D. N. Reinhoudt, *Tetrahedron Lett.*, 1991, **32**, 2675; W. Verboom, S. Datta, Z. Asfari, S. Harkema and D. N. Reinhoudt, *J. Org. Chem.*, 1992, **57**, 5394.
8 T. Sone, Y. Ohba, K. Moriya and H. Kumada, Book of Abstracts for Workshop on Calixarenes and Related Compounds, p. PS/B-36, 2–4 June, 1993, Fukuoka, Japan.
9 T. Sone, Y. Ohba, K. Moriya, H. Kumada and K. Ito, *Tetrahedron*, 1997, **53**, 10 689.
10 H. Kumagai, M. Hasegawa, S. Miyanari, Y. Sugawa, Y. Sato, T. Hori, S. Ueda, H. Kamiyama and S. Miyano, *Tetrahedron Lett.*, 1997, **38**, 3971.
11 N. Iki, N. Morohashi, F. Narumi and S. Miyano, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 1597.
12 K. Araki, K. Iwamoto, S. Shinkai and T. Matsuda, *Chem. Lett.*, 1989, 1747.
13 C. D. Gutsche, B. Dhawan, J. A. Levine, K. H. No and L. J. Bauer, *Tetrahedron*, 1983, **39**, 409.
14 A. Arduini, W. M. McGregor, D. Paganuzzi, A. Pochini, A. Secchi, F. Ugozzoli and R. Ungaro, *J. Chem. Soc.*, *Perkin Trans 2*, 1996, 839.
15 F. Arnaud-Neu, E. M. Collins, M. Deasy, G. Ferguson, S. J. Harris, B. Kaitner, A. J. Lough, M. A. McKervey, E. Marques, B. L. Ruhl, M. J. Schwing-Weill and E. M. Seward, *J. Am. Chem. Soc.*, 1989, **111**, 8681.
16 See *e.g.*, Y. Takeda, H. Sato and S. Sato, *J. Solution Chem.*, 1992, **21**, 1069; M. Billah, T. Honjo and K. Terada, *Fresenius' J. Anal. Chem.*, 1993, **347**, 107; Y. Yamamoto, *Bunseki Kagaku*, 1972, **21**, 418.
17 P. T. Beurskens, G. Admiraal, G. Beurskens, W. P. Bosman, S. Garcia-Granada, R. O. Gould, J. M. M. Smits and C. Smykalla, The DIRDIF program system, Technical Report of the Crystallographic Laboratory, University of Nijmegen, The Netherlands, 1992.
18 P. T. Beurskens, G. Admiraal, G. Beurskens, W. P. Bosman, R. de Gelder, R. Israel and J. M. M. Smits, The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands, 1994.
19 D. T. Cromer and J. T. Waber, *International Tables for X-ray Crystallography*, vol. 4, The Kynoch Press, Birmingham, England, Table 2.2 A, 1974.
20 J. A. Ibers and W. C. Hamilton, *Acta Crystallogr.*, 1964, **17**, 781.
21 D. C. Creagh and W. J. McAuley, *International Tables for Crystallography*, vol. C, ed. A. J. C. Wilson, Kluwer Academic Publishers, Boston, Table 4.2.6.8, pp. 219–222, 1992.
22 D. C. Creagh and J. H. Hubbell, *International Tables for Crystallography*, vol. C, ed. A. J. C. Wilson, Kluwer Academic Publishers, Boston, Table 4.2.4.3, pp. 200–206, 1992.
23 Crystal Structure Analysis Package, Molecular Structure Corporation, 1985 and 1992.
24 K. A. Connors, *Binding Constants. The Measurement of Molecular Complex Stability*, John Wiley & Sons, New York, 1987.
25 R. P. Lang, *J. Am. Chem. Soc.*, 1962, **84**, 1185.

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