Recueil des Travaux Chimiques des Pays-Bas, 111/12, December 1992

Recl. Trav. Chim. Pays-Bas **111**, 511-516 (1992) 0165-0513/92/51112-06$2.00

Synthesis and cation complexation selectivity of bis(syn-proximally) functionalized calix[4]arenes

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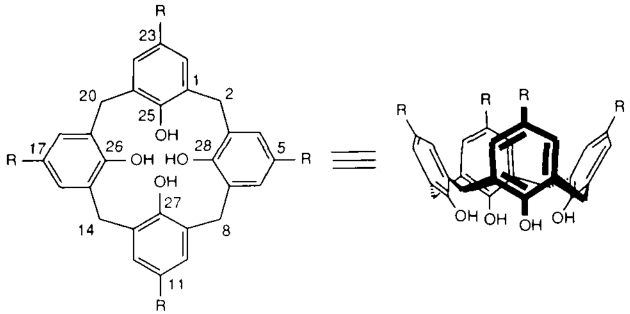
(Received July 22nd, 1992)

Abstract. A general method has been developed for the preparation of bis(syn-proximally) functionalized calix[4]arenes (**6**, **8–10**). Starting from *p-tert*-butylcalix[4]arene **1a** and calix[4]arene **1b** syn-proximally *dialkylated* calix[4]arenes **2a** and **2b**, **4**, and **5**, respectively, were obtained by treatment with 4.2 equiv of NaH and 2.2 equiv of alkylating reagent in DMF. The syn-proximal substitution pattern was unequivocally proven by an X-ray structural determination of **2b**. Furthermore the influence of different bases on the functionalization of the free hydroxyl groups of **2b** with chloroacetone was studied. Cs_2CO_3 as the base gave the bis(syn-proximally) functionalized calix[4]arene **6** in the highest yield (82%). Cation complexation studies, with the picrate extraction method, showed that subtle changes in regioselective functionalization influences the selectivity for Na^+ considerably.

Introduction

Calixarenes have received considerable attention in the past decade in host–guest or supramolecular chemistry[1]. The parent calix[4]arene **1** (Chart 1) can be regarded as a molecular building block that can be functionalized at the phenolic oxygens at the lower rim to give a cavity with cation-complexing properties. The efficiency and selectivity of cation complexing are influenced by the nature and the number of substituents, the substitution pattern, and the conformational mobility of the calix[4]arene[1a].



1a R = Bu^t

1b R = H

Chart 1

Previously, it has been shown that the cone conformer of calix[4]arene derivatives (**1a** and **1b**) with four equivalent ester[2,3,4], keto[4,5], or amide[6] coordinating groups, or calix[4]arenes having two pairs of functional groups with a distal (1,3) regiochemistry[7,8] have a good selectivity for sodium. Calix[4]arenes with a proximal (1,2) regiochemistry have received only little attention. The first syn-proximally substituted calix[4]arenes were obtained by *Pappalardo* et al.[9], by reaction of calix[4]arenes **1a** and **1b** with 2-(chloromethyl)pyridine in *N,N*-dimethylformamide (DMF). The 1,2-dimethyl ether of **1a** has been synthesized by an indirect method, *viz.* the selective removal of two methyl groups from the tetramethyl ether by reaction with two equiv of $TiBr_4$[10]. We have described a syn-proximally *acylated* calix[4]arene by the direct reaction of *p-tert*-butylcalix[4]arene **1a** with *o*-phthaloyl dichloride in the presence of two equiv of KOtBu in THF at room temperature[11]. The same reaction with four equiv of CsF in refluxing acetonitrile yielded a bis(syn-proximally) substituted calix[4]arene derivative. Recently, we have found that syn-proximally *dialkylated* derivatives of calix[4]arene **1a** or **1b** can be obtained by reaction with 2.2 equiv of alkylating agent in the presence of an excess of sodium hydride (NaH)[12]. *Gutsche* and co-workers have reported, very recently, 1,2-bis(3,5-dinitrobenzoate) derivatives of calix[4]arene **1a** both in the anti-proximal and the syn-proximal conformation[13]. Our interest in calix[4]arene derivatives with a high Na^+ selectivity is related to Na^+-selective CHEMFETs*. Recently, we have reported on a Na^+-selective CHEMFET based on symmetrically functionalized calix[4]arene ketones[14]. The tetraphenyl ketone of *p-tert*-butylcalix[4]arene, showed

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* CHEMFET = Chemicaly Modified Field Effect Transistor.

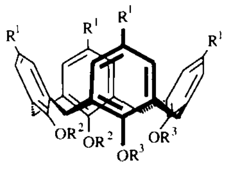
a moderate selectivity of Na^+ towards K^+ ($\log K^{pot}(Na^+,K^+) = -1.9$). Because K^+-selective CHEMFETs[15,16], based on dimethyl calix[4]arene crown-5, show excellent K^+-selectivity relative to Na^+ ($\log K^{pot}(K^+,Na^+) = -2.8$), we are currently trying to improve the Na^+ selectivity of CHEMFETs by variation of the substitution pattern of tetraalkylated calix[4]arenes.

In this paper we describe the synthesis and the complexation properties of novel calix[4]arenes that are bis(syn-proximally) functionalized.

Results and discussion

Synthesis

During our systematic alkylation studies of calix[4]arene we found that the reaction of *p*-*tert*-butylcalix[4]arene **1a** with a large excess of ethyl bromoacetate (NaH/DMF), in addition to the tetraalkylated product **3a** (53%) gave also the syn-proximally functionalized diethyl ester of *p*-*tert*-butylcalix[4]arene acetate **2a** in a yield of 7%. The ^1H NMR spectrum of **2a** shows one signal at δ 8.61 for two OH protons, and two singlets for the protons of the *para*-positioned *tert*-butyl groups at δ 1.21 and 1.18 (each 18 H). The AX signals of the methylene bridge protons at δ 4.47, 4.30, 4.26 (2 : 1 : 1 H_{ax}), and δ 3.31, 3.30, 3.29 (2 : 1 : 1 H_{eq}), confirm that calix[4]arene **2a** is in the cone conformation and syn-proximally substituted with ester groups.



2a $R^1 = Bu^t, R^2 = H, R^3 = CH_2C(O)OCH_2CH_3$

2b $R^1 = R^2 = H, R^3 = CH_2C(O)OCH_2CH_3$

3a $R^1 = Bu^t, R^2 = R^3 = CH_2C(O)OCH_2CH_3$

3b $R^1 = H, R^2 = R^3 = CH_2C(O)OCH_2CH_3$

4 $R^1 = R^2 = H, R^3 = CH_2C(O)OBu^t$

5 $R^1 = R^2 = H, R^3 = CH_2C(O)N(CH_3)_2$

Chart 2

When the same reaction was performed with the de-*tert*-butylated calix[4]arene **1b** the syn-proximally functionalized calix[4]arene **2b** was formed in 15% yield, together with the tetraalkylated calixarene **3b** in 10% yield. When this reaction was carried out in the presence of 4.2 equiv of NaH and 2.2 equiv of ethyl bromoacetate at 60°C[17], the yield of **2b** was enhanced to 39%. The ^1H NMR spectrum of **2b** shows one signal at δ 8.78 for the two OH protons. The AX signals for the methylene bridge hydrogen atoms are difficult to distinguish. For the axial hydrogens, two AX systems appear at δ 4.91 and 4.49 (1 : 2 H), while the AX signal for the remaining axial hydrogen coincides with the quartet of the methylene protons in the ethyl groups. The AX signals of the equatorial protons give a multiplet at δ 3.48–3.33. In the ^{13}C NMR spectrum three signals for the methylene bridge carbons at δ 31.7, 31.6, and 31.2 are present, pointing to syn-proximal substitution pattern when we extrapolate the ^{13}C NMR data for calix[4]arenes recently reported by *de Mendoza* et al.[18]. Single-crystal X-ray analysis of **2b** unambiguously proved that the product is indeed the syn-proximally functionalized diethyl ester. The crystal structure of **2b** is given in Figure 1, which clearly shows the syn-proximal positions of the side groups and the calix[4]arene in the cone conformation. The angles between the best planes fitted to the carbon atoms are 69.2°, 56.5°, 63.9°, and 45.7°, respectively.

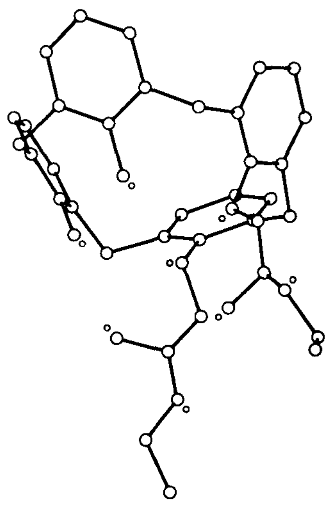


Figure 1. Crystal Structure of **2b**.

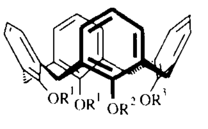
Under the same reaction conditions, the reaction of calix[4]arene **1b** with *tert*-butyl bromoacetate afforded the syn-proximally functionalized calix[4]arene **4** in 58% yield. The corresponding reaction with *N*,*N*-dimethyl-2-chloroacetamide gave **5** in only 17% yield, in addition to some syn-trisubstituted product, and starting material **1b** (28%). The characteristic ^{13}C NMR signals of the methylene bridge carbon atoms prove that **4** and **5** are syn-proximally functionalized, three signals at δ 31.8 (double intensity), 31.6, and 31.5 for **4** and two signals at δ 31.8 (double intensity) and 31.7 for **5**.

For the synthesis of bis(syn-proximally) functionalized calix[4]arenes we focussed on diester **2b** as the starting material, because of the possible higher selectivity for Na^+ of de-*tert*-butylated calix[4]arene esters and ketones compared with the *p*-*tert*-butylcalix[4]arene derivatives and the reported good Na^+ selectivity of the tetraethyl ester of calix[4]arene[4]. First, the influence of different bases on the functionalization of the remaining two hydroxyl groups of **2b** with chloroacetone was studied (Table I). The desired product **6** was obtained in the highest yield (82%) with Cs_2CO_3 as the base (Table I, entry 4). In the reactions with weaker bases (Li_2CO_3 or CsF), only the syn-trisubstituted calixarene **7** was isolated, even after a reaction time of 72 h (Table I, entries 1 and 5).

Table I Results of the base-effect study on the reaction of **1b** *with chloroacetone.*

Entries	Base	Reaction time (h)[a]	Yield (%)	Conformation[b]
1	Li_2CO_3	72	–[c]	–
2	Na_2CO_3	24	52	cone
3	K_2CO_3	27	49	cone
4	Cs_2CO_3	48	82	cone
5	CsF	72	–[d]	–

[a] Reaction time needed for total conversion, or when no further changes occurred in the reaction mixture according to thin-layer chromatography. [b] Confirmed by ^1H NMR and ^{13}C NMR spectroscopy. [c] Recovered calix[4]arene **1b** 80% and isolated trisubstituted product **7** 11% yield. [d] Recovered calix[4]arene **1b** 3% and isolated trisubstituted product **7** 55% yield.



6 $R^1 = CH_2C(O)OCH_2CH_3$, $R^2 = R^3 = CH_2C(O)CH_3$

7 $R^1 = CH_2C(O)OCH_2CH_3$, $R^2 = CH_2C(O)CH_3$, $R^3 = H$

Chart 3

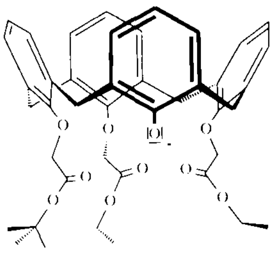


Chart 5

The reaction of **2b** with *tert*-butyl bromoacetate gave a mixture of two compounds, *viz.* cone (**8a**) and the partial-cone (**8b**) (Chart 4) conformer of the bis(syn-proximally) substituted calix[4]arene in yields of 19% and 26%, respectively. However, when the reaction of **2b** with *tert*-butyl bromoacetate was performed in refluxing acetonitrile with Na_2CO_3 as the base, the cone conformer **8a** could be isolated as the only product in 78% yield. The cone and partial-cone conformation of **8** were determined by ^1H NMR and ^{13}C NMR spectroscopy. The ^1H NMR spectrum of cone conformer **8a** shows a singlet at δ 1.39 and a triplet at δ 1.21 for the *tert*-butyl groups and methyl groups of the ester functions, respectively. The partial-cone conformer **8b** exhibits two singlets at δ 1.60 and 1.55 for the *tert*-butyl groups and two triplets at δ 1.35 and 1.22 for the methyl groups of the ester functions. Furthermore, in ^{13}C NMR spectroscopy **8a** gives only one signal at δ 31.5 for the methylene bridge carbons, whereas the partial-cone conformer **8b** gives two signals at δ 31.8 and 34.5; the latter points to a partial-cone conformation[18]. The formation of the two conformers led us to investigate the reaction of **2b** with ethyl bromoacetate under the influence of Cs_2CO_3. We isolated exclusively the cone conformer of the tetraalkylated calix[4]arene **9** (Chart 4) in 95% yield. Reaction of **2b** with *N,N*-dimethyl-2-chloroacetamide gave the bis(syn-proximally) substituted calix[4]arene **10** (Chart 4) in 95% yield. Two factors are probably responsible for the different conformational outcome of the reaction of calix[4]arene **2b** with *tert*-butyl bromoacetate, with either Cs_2CO_3 or Na_2CO_3, *viz.* the steric effect of the ester group and the cation of the base. It is likely that the interaction between the Na^+ cation and the calix[4]arene oxyanion (Chart 5) makes the calix[4]arene moiety in the cone conformation rigid and the only possibility is bis(syn-proximal) functionalization. For the Cs^+ cation, the interaction with the calix[4]arene oxyanion is much weaker, resulting in a more flexible calix[4]arene moiety; rotation of the phenyl oxyanion gives a partial-cone conformer which reacts with *tert*-butyl bromoacetate.

Evidence for different flexibilities of ion pairs of the calix[4]arene oxyanion with different alkali cations has been reported by *Gutsche* et al.[19]. The coalescence temperature of the methylene bridge hydrogen atom signals in ^1H NMR spectroscopy are 140°C (Li^+), 80°C (Na^+), and 20°C (K^+), respectively. Extrapolation of these values for Cs^+ suggests that the calix[4]arene oxyanion will be flexible at reaction temperature. Recently, *Pappalardo* et al.[20] and *Shinkai* et al.[21,22] have also suggested this. Functionalization of the phenolic groups of the syn-proximally substituted [(2-pyridylmethyl)oxy]calix[4]arene, with *tert*-butyl bromoacetate and Cs_2CO_3 as the base gave exclusively the partial-cone[20]. *Shinkai* et al.[22] also showed that the functionalizations can be directed by appropriate choice of the base.

Extraction measurements

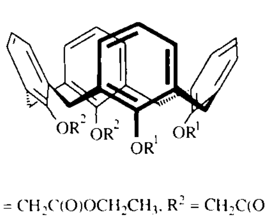
We used the picrate extraction method introduced by *Pedersen* and *Frensdorff* as a convenient, semiquantitative assessment of ion-transport ability from an aqueous into a nonpolar organic solvent[23,24]. Instead of the usual alkali hydroxides, alkali chlorides were used, because of the purity that can be purchased commercially. Tetraethyl ester **9** was included, to control the validity of the alterations by comparing the extraction percentages with the values reported by *Arnaud-Neu* et al.[4].

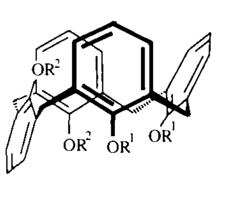
Table II Percentage extraction of alkali metal picrates into CH_2Cl_2 at 20°C[a,b]

Studied ion		Li^+	Na^+	K^+	Rb^+	Cs^+
Entries	Ionophore					
1	**9**	2.3 (1.8)	50.0 (60.4)	1.8 (12.9)	0.2 (4.1)	0 (10.8)[c]
2	**6**	1.8	56.3	3.9	1.8	1.3
3	**8a**	4.4	71.1	8.7	3.1	3.0
4	**8b**	0	1.8	2.3	0.6	0
5	**10**	21.0	93.4	31.7	12.4	10.0

[a] For details see the Experimental Section. [b] Standard deviation is 2%. [c] Between brackets the values of percentage extraction published by *Arnaud-Neu* et al.[4], the standard deviation of these values is 5%.

As can be concluded from the extraction results (Table II, entry 1) the values are more or less in agreement, regardless





8a $R^1 = CH_2C(O)OCH_2CH_3$, $R^2 = CH_2C(O)OBu^t$

9 $R^1 = R^2 = CH_2C(O)OCH_2CH_3$

10 $R^1 = CH_2C(O)OCH_2CH_3$, $R^2 = CH_2C(O)N(CH_3)_2$

8b $R^1 = CH_2C(O)OCH_2CH_3$, $R^2 = CH_2C(O)OBu^t$

Chart 4

of whether the hydroxide salt or the chloride salt is used for the aqueous phase. As expected, the partial-cone conformer **8b** (Table II, entry 4) does not show any extraction ability. For the remaining calix[4]arene derivatives it can be concluded that they have a preference for Na^+ extraction. Noteworthy is the effect of the *tert*-butyl group in the bis(syn-proximally) substituted calix[4]arene **8a** (Table II, entry 3) in comparison with tetraethyl ester **9** (Table II, entry 1). Although the extraction efficiency of **8a** relative to **9** is increased, the extraction selectivity is decreased. This may be caused by the steric effect induced by the bulky *tert*-butyl groups, which lead to an enlarged cavity resulting in a decreased extraction selectivity. The mixed amide-ester calix[4]arene **10** (Table II, entry 5) shows the broadest extraction ability, although the Na^+ selectivity is substantially lower than that of the other calix[4]arene derivatives.

This study clearly shows that subtle changes in regioselective functionalization of calix[4]arenes considerably influence the selectivity for Na^+.

The complexation behaviour of bis(syn-proximally) functionalized calix[4]arenes, *i.e.* determination of the association constants and the practical application of these compounds in membrane transport and CHEMFETs is under current investigation.

Experimental

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AC 250 spectrometer in $CDCl_3$ with Me_4Si as internal standard. Positive-ion FAB mass spectra were obtained using a Finnigan MAT 90 spectrometer with use of *m*-nitrobenzyl alcohol as a matrix. Absorbance readings in the UV-VIS region, for the determination of the cation-complexing properties of an ionophore by means of the picrate extraction method were taken on a Hewlett Packard 8452A spectrophotometer.

Compounds **1a**[25] and **1b**[26] were prepared according to procedures described in the literature. CH_3CN and DMF stored over molecular sieves (3 and 4 Å, respectively) were used. Silica gel 60 (particle size 0.040–0.063 mm, 230–400 mesh) was purchased from Merck. All commercially available chemicals were of reagent-grade quality and obtained either from Janssen or from Aldrich, and were used without further purification. The carbonate bases used in this study were of "reinst" quality and the caesium fluoride and chloride salts were of *pro analysis* quality, except for NaCl (Suprapur) and were obtained from Merck. All reactions were carried out under an argon atmosphere. The presence of solvent in the analytical samples was confirmed by ^{1}H NMR spectra of the samples in $CDCl_3$.

Picrate extraction measurements

Metal picrates ($2.5 \cdot 10\ ^{4}$M) and alkali chlorides (0.1M) were dissolved in doubly distilled and deionized water. Solutions ($2.5 \cdot 10^{-4}$M) of the calix[4]arene derivatives were prepared in dichloromethane. Equal volumes (5 ml) of the two solutions were stirred vigorously in a stoppered glass tube immersed in a thermostated water bath at 20 ± 0.1°C. To make sure that the extraction equilibrium was reached, the glass tubes were also vigorously shaken by hand before and after the magnetic stirring. The two phases were separated with the help of a centrifuge. The percentage extraction was determined by measuring the absorbance of the aqueous phases at the absorption maximum of the picrate anion, *i.e.* 356 nm. The absorbance A, *i.e.* of an experiment containing a calix[4]arene derivative in the dichloromethane, and the absorbance A_0, *i.e.* of a blank experiment without a calix[4]arene derivative in the dichloromethane, were determined spectrophotometrically. The percentage cation extracted was calculated as the ratio $100 \cdot (A_0 - A)/A_0$.

25,26-Bis[(ethoxycarbonyl)methoxy]-27,28-dihydroxycalix[4]arene (**2b**)[27]

A suspension of calix[4]arene **1b** (2.5 g, 5.89 mmol) and NaH (80% in oil, 0.75 g, 25.00 mmol) in DMF (125 ml) was stirred at room temperature for 1 h. Ethyl bromoacetate (2.16 g, 12.93 mmol) was added, the temperature was raised to 60°C and the reaction mixture was stirred for 16–24 h. The progress of the reaction was followed by thin-layer chromatography (TLC: SiO_2, CH_2Cl_2/EtOAc 98/2) and after completion the reaction was quenched with a saturated NH_4Cl solution (10 ml). The residue that remained after removal of most DMF under reduced pressure was taken up in CH_2Cl_2 (25 ml) and washed with saturated NH_4Cl solution (2 × 20 ml) and distilled water (2 × 20 ml). The crude product was purified either by flash chromatography (SiO_2, CH_2Cl_2/EtOAc 98/2) or by trituration with MeOH, to give pure **2b** as a white powder in 39%, for both purification techniques; m.p. 198–200°C (MeOH). MS (FAB) *m/z* 597.3 ($[M + H]^+$, calcd. 597.2). ^{1}H NMR ($CDCl_3$): δ 8.78 (s, 2H, ArOH), 6.95 (d, 8H, *J* 7.6 Hz, *m*-ArH), 6.77, 6.61 (t, 2H, *J* 7.6 Hz, *p*-ArH), 5.08 and 4.70 [AX q, 4H, *J* 16.1 Hz, $CH_2C(O)$], 4.91 (part of AX q, 1H, *J* 13.1 Hz, $ArCH_2Ar$ H_{ax}), 4.49 (part of AX q, 2H, *J* 13.2 Hz, $ArCH_2Ar$ H_{ax}), 4.32 (q, 5H, *J* 7.2 Hz, $OC\underline{H}_2CH_3$ + $ArCH_2Ar$ H_{ax}), 3.48–3.33 (m, 4H, $ArCH_2Ar$ H_{eq}), 1.36 (t, 6H, *J* 7.2 Hz, $OCH_2C\underline{H}_3$). ^{13}C NMR ($CDCl_3$): δ 170.7 [s, C(O)], 72.3 [t, $\underline{C}H_2C(O)$], 61.4 (t, $O\underline{C}H_2CH_3$), 31.7, 31.6, 31.2 (t, $ArCH_2Ar$), 14.2 (q, $OCH_2\underline{C}H_3$). Anal. $C_{36}H_{36}O_8$ calcd.: C 72.47, H 6.08; found: C 72.34, H 6.09%.

Syn-proximally substituted calix[4]arenes **4** and **5** were synthesized in a similar way to compound **2b**.

*25,26-Bis[(*tert*-butoxycarbonyl)methoxy]-27,28-dihydroxycalix[4]arene* (**4**)

Calix[4]arene **4** was obtained as a white powder in 58% yield, after a flash chromatographic purification (SiO_2, CH_2Cl_2/THF 95/5) of the crude product; m.p. 195–197°C (MeOH/CH_2Cl_2). MS (FAB) *m/z* 652.2 ($[M + H]^+$, calcd. 652.3). ^{1}H NMR ($CDCl_3$): δ 8.89 (s, 2H, ArOH), 6.97–6.92 (m, 8H, *m*-ArH), 6.75, 6.60 (t, 2H, *J* 7.5 Hz, *p*-ArH), 5.04 and 4.56 [AB q, 4H, *J* 16.0 Hz, $CH_2C(O)$], 4.89 (part of AX q, 1H, *J* 13.2 Hz, $ArCH_2Ar$ H_{ax}), 4.55 (part of AX q, 2H, *J* 13.2 Hz, $ArCH_2Ar$ H_{ax}), 4.33 (part of AX q, 1H, *J* 13.8 Hz, $ArCH_2Ar$ H_{ax}), 3.44–3.33 (m, 4H, $ArCH_2Ar$ H_{eq}), 1.56 [s, 18H, $OC(CH_3)_3$]. ^{13}C NMR ($CDCl_3$): δ 170.1 [s, C(O)], 82.5 [s, $OC(CH_3)_3$], 73.2 [t, $\underline{C}H_2C(O)$], 31.9, 31.7, 31.6 (t, $ArCH_2Ar$), 28.3 [q, $C(\underline{C}H_3)_3$]. Anal. $C_{40}H_{44}O_8$ calcd.: C 73.60, H 6.79; found: C 73.38, H 7.05%.

25,26-Bis[(dimethylcarbamoyl)methoxy]-27,28-dihydroxycalix[4]arene (**5**)

After flash chromatography (SiO_2, CH_2Cl_2/THF 95/5) diamide **5** was obtained in 17% yield, as a yellowish powder; m.p. 168–170°C (MeOH/CH_2Cl_2). MS (FAB) *m/z* 595.3 ($[M + H]^+$, calcd. 595.3). ^{1}H NMR ($CDCl_3$): δ 9.74 (s, 2H, ArOH), 6.94–6.88 (m, 8H, *m*-ArH), 6.73, 6.57 (t, 2H, *J* 7.5 Hz, *p*-ArH), 5.27 and 4.68 [AB q, 4H, *J* 14.5 Hz, $CH_2C(O)$], 4.88 (part of AX q, 1H, *J* 13.3 Hz, $ArCH_2Ar$ H_{ax}), 4.65 (part of AX q, 2H, *J* 13.0 Hz, $ArCH_2Ar$ H_{ax}), 4.38 (part of AX q, 1H, *J* 13.9 Hz, $ArCH_2Ar$, H_{ax}), 3.41 (part of AX q, 1H, *J* 13.3 Hz, $ArCH_2Ar$ H_{eq}), 3.32 (part of AX q, 3H, *J* 13.4 Hz, $ArCH_2Ar$ H_{eq}), 3.09, 3.04 [s, 6H, $N(CH_3)_2$]. ^{13}C NMR ($CDCl_3$): δ 170.0 [s, C(O)], 73.5 [t, $\underline{C}H_2C(O)$], 35.9, 35.6 [q, $N(CH_3)_2$], 31.8, 31.7 (t, $ArCH_2Ar$). Anal. $C_{36}H_{38}N_2O_6 \cdot CH_3OH$ calcd.: C 70.91, H 6.75, N 4.46; found: C 70.59, H 6.70, N 4.44%.

General procedure for the reaction of calix[4]arene (**2b**) *with chloroacetone under the influence of different bases*

Base (4 equiv), chloroacetone (0.32 g, 3.32 mmol) and a small amount of NaI were added to a suspension of calix[4]arene **2b** (0.50 g, 0.838 mmol) in CH_3CN (40 ml). The temperature was raised to 60°C and the conversion of the reaction was followed with TLC (SiO_2, CH_2Cl_2/EtOAc 94/6). When complete conversion was observed or when no more changes occurred in the reaction mixture as evidenced by TLC, the reaction was stopped. Most of the CH_3CN was removed under reduced pressure. The remaining residue was taken up in CH_2Cl_2 (25 ml) and washed with a saturated NH_4Cl solution (2 × 20 ml), a 0.1M sodium thiosulfate solution (2 × 20 ml), and subsequently with distilled water (2 × 20 ml). After removal of the solvent under reduced pressure the residue was purified by trituration with *n*-hexane, if necessary, followed by a trituration with MeOH. Reaction time, yields, and specific details are summarized in Table I.

25,26-Bis(acetonyloxy)-27,28-bis[(ethoxycarbonyl)methoxy)]-calix[4]arene (**6**)[29]

MS (FAB) *m/z* 731.5 ([M + Na]$^+$, calcd. for $C_{42}H_{44}O_{10}Na^+$ 731.8). ^{1}H NMR ($CDCl_3$): δ 6.60–6.52 (m, 12H, ArH), 4.77 [s, 4H, $CH_2C(O)$], 4.76 (part of AX q, 4H, *J* 13.4 Hz, ArCH$_2$Ar H$_{ax}$), 4.62 [s, 4H, $CH_2C(O)$], 4.13 (q, 4H, *J* 7.1 Hz, $OC\underline{H}_2CH_3$), 3.16 (part of AX q, 3H, *J* 13.7 Hz, ArCH$_2$Ar H$_{eq}$), 3.15 (part of AX q, 1H, *J* 13.5 Hz, ArCH$_2$Ar H$_{eq}$), 2.15 [s, 6H, $C(O)CH_3$], 1.21 (t, 6H, *J* 7.1 Hz, $OCH_2C\underline{H}_3$). ^{13}C NMR ($CDCl_3$): δ 205.0 [s, $\underline{C}(O)CH_3$], 170.2 (s, $\underline{C}(O)OEt$], 79.0 [t, $\underline{C}H_2C(O)CH_3$], 71.2 [t, $\underline{C}H_2C(O)OEt$], 60.6 (t, $O\underline{C}H_2CH_3$), 31.4, 31.3, 31.2 (t, ArCH$_2$Ar), 26.3 [q, $C(O)\underline{C}H_3$], 14.3 (q, $OCH_2\underline{C}H_3$).

25,26-Bis(acetonyloxy)-27-[(ethoxycarbonyl)methoxy]-28-hydroxy-calix[4]arene (**7**)[29]

MS (FAB) *m/z* 653.2 ([M + H]$^+$, calcd. for $C_{39}H_{41}O_9^+$ 653.3). ^{1}H NMR ($CDCl_3$): δ 7.11, 7.05 (d, 2H, *J* 7.4 Hz, ArH), 6.93, 6.72 (t, 1H, *J* 7.5 Hz, *p*-ArH), 6.55–6.48 (m, 6H, ArH), 6.02 (bs, 1H, ArOH), 5.13 and 5.04 [AB q, 2H, *J* 16.9 Hz, $CH_2C(O)$], 4.90 (part of AX q, 2H, *J* 13.3 Hz, ArCH$_2$Ar H$_{ax}$), 4.61 [part of AB q, 1H, *J* 16.7 Hz, $CH_2C(O)$], 4.58 and 4.51 [AB q, 2H, *J* 15.6 Hz, $CH_2C(O)$], 4.38–4.24 [m, 5H, ArCH$_2$Ar H$_{ax}$ + $OCH_2C\underline{H}_3$ + $CH\underline{H}C(O)$], 4.11 (q, 2H, *J* 7.2 Hz, $OC\underline{H}_2CH_3$), 3.37 (m, 4H, ArCH$_2$Ar H$_{eq}$), 2.40 [s, 3H, $C(O)CH_3$], 1.33,η 1.25 (t, 3H, *J* 7.2 Hz, $OCH_2C\underline{H}_3$). ^{13}C NMR ($CDCl_3$): δ 204.7 [s, $\underline{C}(O)CH_3$], 170.7, 169.1 [s, $\underline{C}(O)OEt$], 79.7 [t, $\underline{C}H_2C(O)CH_3$], 72.0, 70.3 [t, $\underline{C}H_2C(O)OEt$], 61.1, 60.4 (t, $O\underline{C}H_2CH_3$), 31.7, 31.5, 30.7 (t, ArCH$_2$Ar), 26.6 [q, $C(O)\underline{C}H_3$], 14.2 (q, $OCH_2\underline{C}H_3$).

General procedure for the reaction of calix[4]arene (**2b**) *with different alkylating reagents*

To a suspension of calix[4]arene **2b** (0.50 g, 0.838 mmol) in CH_3CN (40 ml) were added 4 equiv of Cs_2CO_3 (1.09 g, 3.35 mmol), and 4 equiv of alkylating reagent: *tert*-butyl bromoacetate, ethyl bromoacetate, or *N,N*-dimethyl-2-chloroacetamide. In the case of *N,N*-dimethyl-2-chloroacetamide a small amount of NaI was also added. The temperature was raised to 60°C and the reaction was followed using TLC (SiO_2, CH_2Cl_2/EtOAc 98/2). When complete conversion had occurred according to TLC the reaction was stopped. Most of the CH_3CN was removed under reduced pressure. The remaining residue was taken up in CH_2Cl_2 (25 ml) and washed with a saturated NH_4Cl solution (2 × 20 ml) and subsequently with distilled water (2 × 20 ml). When NaI was used the residue solution in CH_2Cl_2 was also washed with a 0.1M sodium thiosulfate solution (2 × 20 ml).

*25,26-Bis[(ethoxycarbonyl)methoxy]-27,28-bis[(*tert*-butoxycarbonyl)-methoxy]calix[4]arene* (**8**)

The crude reaction mixture was triturated with MeOH. The resulting product was separated with flash chromatography (SiO_2, CH_2Cl_2/EtOAc 98/2) to give cone conformer **8a** and partial-cone conformer **8b** in yields of 19% and 26%, respectively.
Cone Conformer (**8a**). M.p. 168–171°C (MeOH). MS (FAB) *m/z* 847.5 ([M + Na]$^+$, calcd. 847.4). ^{1}H NMR ($CDCl_3$): δ 6.56–6.50 (m, 12H, ArH), 4.83 and 3.15 (AX q, 8H, *J* 13.6 Hz, ArCH$_2$Ar), 4.70 and 4.64 [AB q, 4H, *J* 10.8 Hz, $CH_2C(O)$], 4.57 and 4.52 [AB q, 4H, *J* 9.8 Hz, $CH_2C(O)$], 4.13 (q, 4H, *J* 7.1 Hz, $OC\underline{H}_2CH_3$), 1.39 [s, 18H, $C(CH_3)_3$], 1.21 (t, 6H, *J* 7.1 Hz, $OCH_2C\underline{H}_3$). ^{13}C NMR ($CDCl_3$): δ 170.3 [s, $\underline{C}(O)OEt$], 169.3 [s, $\underline{C}(O)OBu^t$], 81.0 [s, $O\underline{C}(CH_3)_3$, 72.0, 71.2 (t, $\underline{C}H_2C(O)$], 60.5 (t, $O\underline{C}H_2CH_3$), 31.5 (t, ArCH$_2$Ar), 28.1 [q, $C(\underline{C}H_3)_3$], 14.3 (q, $OCH_2\underline{C}H_3$). Anal. $C_{48}H_{56}O_{12}$ calcd.: C 69.89, H 6.84; found: C 69.59, H 6.85%.
Partial-Cone (**8b**). M.p. 128–130°C (MeOH). MS (FAB) *m/z* 847.3 ([M + Na]$^+$, calcd. 847.4). ^{1}H NMR ($CDCl_3$): δ 7.51, 7.49 (d, 1H, *J* 7.6 Hz, ArH), 7.12–6.85 (m, 6H, ArH), 6.49, 6.47 (t, 1H, *J* 7.5 Hz, *p*-ArH), 6.21 (t, 2H, *J* 8.2 Hz, *p*-ArH), 4.53–3.71 [m, 18H, ArCH$_2$Ar H$_{ax}$ + $CH_2C(O)$ + $OC\underline{H}_2CH_3$ + ArCH$_2$Ar H$_{eq}$], 3.18 (part of AX q, 1H, *J* 14.2 Hz, ArCH$_2$Ar H$_{eq}$), 3.16 (part of AX q, 1H, *J* 13.9 Hz, ArCH$_2$Ar H$_{eq}$), 1.60, 1.55 [s, 9H, $C(CH_3)_3$], 1.35, 1.22 (t, 3H, $OCH_2C\underline{H}_3$). ^{13}C NMR ($CDCl_3$): δ 170.7, 169.4, 168.6, 168.4 [s, C(O)], 81.9, 81.7 [s, $O\underline{C}(CH_3)_3$], 72.3, 71.5, 71.3 [t, $\underline{C}H_2C(O)$], 67.8 [t, $\underline{C}H_2C(O)OBu^t$], 60.9, 59.9 (t, $O\underline{C}H_2CH_3$), 34.5, 31.8 (t, ArCH$_2$Ar), 28.2, 28.1 [q, $C(\underline{C}H_3)_3$], 14.3, 14.2 (q, $OCH_2\underline{C}H_3$). Anal. $C_{48}H_{56}O_{12}$ calcd.: C 69.89, H 6.84; found: C 69.92, H 6.84%.

25,26,27,28-Tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene (**9**)

Recrystallization from ethanol gave glassy crystals in >95% yield; m.p. 105–106°C (EtOH) (lit.[4] 108–109°C).

25,26-Bis[(dimethylcarbamoyl)methoxy]-27,28-bis[(ethoxycarbonyl)methoxy]calix[4]arene (**10**)

Trituration with *n*-hexane gave a yellowish precipitate in >95% yield; m.p. 136–137°C (MeOH/CH_2Cl_2). MS (FAB) *m/z* 789.6 ([M + Na]$^+$, calcd. 789.4). ^{1}H NMR ($CDCl_3$): δ 7.16–7.12 (m, 8H, *m*-ArH), 6.88, 6.87 (t, 2H, *J* 7.6 Hz, *p*-ArH), 4.87 and 4.38 [AX q, 4H, *J* 14.3 Hz, $CH_2C(O)$], 4.67 and 4.41 [AX q, 4H, *J* 15.7 Hz, $CH_2C(O)$], 4.54 (part of AX q, 1H, *J* 12.8 Hz, ArCH$_2$Ar H$_{ax}$), 4.43 (part of AX q, 3H, *J* 12.4 Hz, ArCH$_2$Ar H$_{ax}$), 4.33 (q, 4H, *J* 7.2 Hz, $OC\underline{H}_2CH_3$), 3.51 (part of AX q, 1H, *J* 12.5 Hz, ArCH$_2$Ar H$_{eq}$), 3.40 (part of AX q, 3H, *J* 12.2 Hz, ArCH$_2$Ar H$_{eq}$), 3.07 and 3.01 [s, 6H, $N(CH_3)_2$], 1.38 (t, 6H, *J* 7.1 Hz, $OCH_2C\underline{H}_3$). ^{13}C NMR ($CDCl_3$): δ 170.6 [s, C(O)O], 168.6 [s, C(O)N], 74.5, 73.3 [t, $\underline{C}H_2C(O)$], 61.6 (t, $O\underline{C}H_2CH_3$), 36.6, 35.6 [q, $N(CH_3)_2$], 29.7 (t, ArCH$_2$Ar), 14.2 (q, $OCH_2\underline{C}H_3$). Anal. $C_{44}H_{50}N_2O_{10}$ calcd.: C 68.91, H 6.57, N 3.26; found: C 68.51, H 6.67, N 3.66%.

X-ray crystallography

The crystal structure of compound **2b** was determined by X-ray diffraction. Crystal data: $C_{36}H_{36}O_8$, monoclinic, space group $P2_1/c$; $a = 10.318(4)$ Å, $b = 15.462(5)$ Å, $c = 19.612(6)$ Å, $\beta = 97.83(3)°$; $V = 3099(9)$ Å^3; $Z = 4$; $d_{calc} = 1.28\ g \cdot cm^{-3}$, $\mu = 0.84\ cm^{-1}$. Reflections were measured at 273(2)K in the $\omega/2\vartheta$ scan mode [$3.0° < \omega < 25°$; scan width (ω) 0.90 + 0.35 tan ϑ], using graphite monochromated Mo Kα radiation (λ 0.7107 Å). The number of independent reflections measured was 5431. The structure was solved by direct methods[30] and refined with full-matrix least-squares methods. A total of 2408 reflections with $F_o^2 > 3\sigma(F_o^2)$ was used in the refinement. One of the side chains was found to be disordered. No suitable disorder model could be fitted to all peaks in the difference Fourier. Therefore all peaks in the disordered area were treated as carbon atoms (occupancy 0.5) and refined with isotropic thermal parameters. Figure 1 was made using the positions of those disordered atoms similar to the ones in the non-disordered side chain. Hydrogen atoms for which the positions could be calculated were put on calculated positions and treated as riding atoms. The number of parameters refined was 398 [scale factor, positional parameters and (an)isotropic thermal parameters for the non-hydrogen atoms]. The final *R* factors were $R = 10.0\%$, $R_w = 8.5\%$. All calculations were done with SDP[31,32].

Acknowledgements

We gratefully acknowledge financial support obtained from the Technology Foundation (STW), Technical Science Organization of Advanced and Pure Research (NWO). We thank *A. M. Montanaro-Christenhusz* for performing the elemental analyses, and *T. W. Stevens* for recording the FAB-MS spectra.

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