display and plot the conformations. Conformational searching was performed by systematically varying the torsional angles around all macrocycle bonds with energy minimization at each step.

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Supplementary Material Available: Experimental details for the X-ray structural studies, tables of X-ray structural data, and ^{1}H NMR spectra for compounds 12–18 and 20–25 (33 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Tetra-O-alkylated Calix[4]arenes in the 1,3-Alternate Conformation

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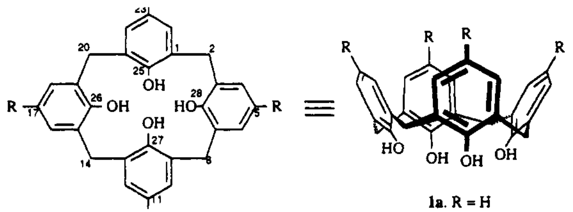
A general method has been developed for the preparation of tetra-*O*-alkylated calix[4]arenes in the 1,3-alternate conformation (**3a,c–e**) starting from *p*-*tert*-butylcalix[4]arenes **1a,b** using Cs_2CO_3 in DMF. The 1,3-alternate conformation was unequivocally proved by an X-ray structure determination of **3a**. The scope of the reaction was investigated starting from a series of diametrically di-*O*-alkylated calix[4]arenes **4a–e** having different substituents R_2 (*t*-Bu, CHO, NO_2, Br, CN) at the para positions of the phenolic rings. The reactions of **4a–d** (R_2 = *t*-Bu, CHO, NO_2, Br) yielded the corresponding tetra-*O*-alkylated calix[4]arenes in the 1,3-alternate conformation **5a–d** (51–73%). However, the dicyanocalix[4]arene **4e** gave the partial cone conformer **6** as the major reaction product.

Introduction

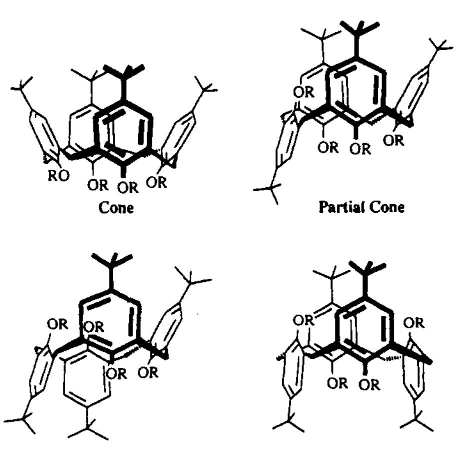
Calixarenes, which are phenol–formaldehyde cyclic oligomers, are receiving increasing attention in the field of supramolecular chemistry.[1,2] Calix[4]arenes (Chart I) can easily be (selectively)[3] functionalized both at the phenolic OH groups (lower rim) and, after removal of the *tert*-butyl groups, at the para positions of the phenol rings (upper rim).[4] Consequently they are now useful building blocks for molecules with different properties.[1,2] These properties are strongly influenced by the conformation of the calix[4]arene which is fixed after substitution with four bulky substituents (R > ethyl) at the phenolic oxygen atoms.[5] Therefore, control of the conformation during the alkylation is highly desirable. The calix[4]arene moiety can exist in four extreme conformations (Chart II) viz. the cone, the partial cone (paco), the 1,2-alternate, and the 1,3-alternate (1,3-alt) conformation. Methods have been developed to selectively prepare *O-alkylated* calix[4]arenes both in the cone and paco conformation.[6,7] The conformation in which a calix[4]arene is fixed upon derivatization depends on the temperature, the solvent, the base, the para substituents of the calixarene, and the reactivity of the electrophile. Recently we have reported an indirect way for the preparation of tetraethoxycalix[4]arene in the 1,2-alternate conformation.[8] The 1,3-alt conformers have been obtained only by *acylation*[9-11] or *aroylation*[10,12] of calix[4]arenes.

Chart I



1a. R = H
1b. R = *t*-Bu

Chart II



Cone

Partial Cone

1,2-Alternate

1,3-Alternate

To the best of our knowledge only a few individual examples, including two metal complexes,[13,14] are known of isolated tetra-*O-alkylated* calix[4]arenes in the 1,3-alt conformation.[7,15-17] Recently, we[3a] and others[3c,6,7] found that in some cases the 1,3-alt could be detected in the reaction mixture of the tetraalkylation of calix[4]arenes. In this paper we describe the first preparative method for

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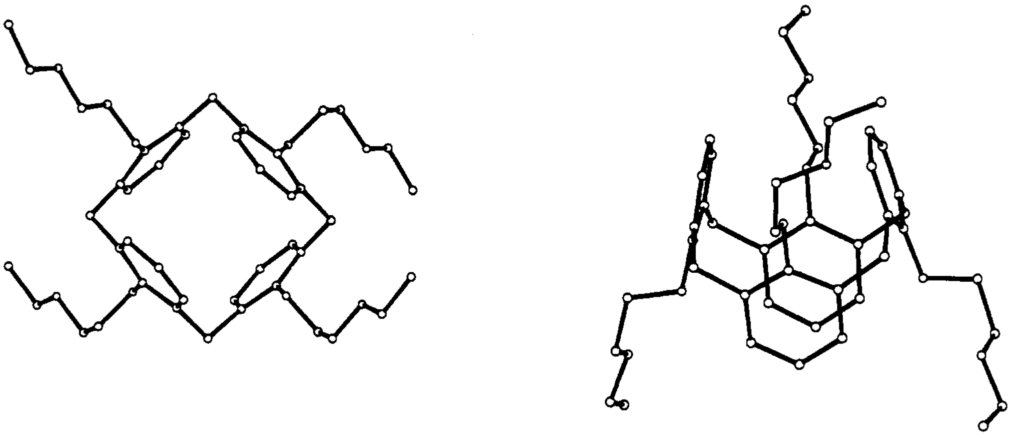

Figure 1. Top and side view of the crystal structure of **3a**.

Table I. Alkylation of Calix[4]arenes 1a,b, 2c–e, and 4a–e[a]

entry	starting compd	electrophile[b] ROTos	reaction temp (°C)	reaction time (h)	relative conformer distribution crude reaction mixture[c] 1,3-alt (%)	paco (%)	isolated compd	isolated yield (%) pure 1,3-alt
1	**1a**	$MeOCH_2CH_2$	80	5	100	–	**3c**	76
2	**1b**	$MeOCH_2CH_2$	80	5	76[d]	16	**3d**	45
3	**2c**	$MeOCH_2CH_2$	80	5	100	–	**3c**	77
4	**2d**	$MeOCH_2CH_2$	80	5	76[d]	16	**3d**	45
5[e]	**1a**	*n*-Pr	80	7	90	10	**3e**	45
6	**2e**	*n*-Pr	80	5	80	20	**3e**	42
7	**2e**	*n*-Pr[f]	80	5	60	40	**3e**	*g*
8	**4a**	$MeOCH_2CH_2$	80	5	90	10	**5b**	53
9	**4b**	$MeOCH_2CH_2$	80	5	90	10	**5c**	50
10	**4c**	$MeOCH_2CH_2$	120	20	75	25	**5d**	51
11	**4d**	$MeOCH_2CH_2$	90	7	92	8	**5e**	73
12	**4e**	$MeOCH_2CH_2$	110	8	30	70	**6**	20 (paco)

[a] Reactions performed in DMF in the presence of 7.5 equiv of Cs_2CO_3 per OH. [b] In all cases 7.5 equiv of electrophile per OH were used. [c] Reported percentages are based on the integration of aromatic signals in a 250-MHz ^1H NMR spectrum of the crude reaction mixture; 1,3-alt = 1,3-alternate, paco = partial cone. [d] Also 8% of the 1,2-alternate is present. [e] Shinkai et al. reported the reaction of **1b** with *n*-propyl bromide in the presence of 10 equiv of Cs_2CO_3 in DMF at 70 °C to afford according to HPLC analysis 24% paco, 9% 1,2-alt, and 67% 1,3-alt; after preparative TLC the 1,3-alt was isolated in 49% yield. [f] In this case *n*-propyl bromide was used. [g] Upon repeated crystallization no pure compound could be isolated.

the synthesis of tetra-*O-alkylated* calix[4]arenes in the 1,3-alt conformation.

Results and Discussion

In the context of another study we needed the diametrically dialkylated calix[4]arene **2a**. Therefore, *p*-H-calix[4]arene **1a** was reacted with 3 equiv of 2-ethoxyethyl tosylate in the presence of 2 equiv of K_2CO_3 as a base in refluxing acetonitrile for 7 d. Crystallization of the crude reaction mixture from hexane/ethyl acetate did not afford the expected **2a** but surprisingly the tetraalkylated calix[4]arene **3a** in the 1,3-alt conformation as a white solid in a yield of 48%.[18] The ^1H NMR spectrum shows the characteristic singlet at δ 3.60 for the methylene bridge protons.[1] In the ^{13}C NMR spectrum the corresponding carbon absorption is present at δ 35.0 which slightly deviates from that of about 37.0 mentioned by De Mendoza et al.[11] for calix[4]arenes in the 1,3-alt conformation. However, a single-crystal X-ray analysis of **3a** unambiguously proved its structure (Figure 1). The phenyl rings and substituents are related by an approximate 4-fold

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(3) A few recent publications on selective functionalization of the lower rim are as follows: (a) Groenen, L. C.; Ruël, B. H. M.; Casnati, A.; Timmerman, P.; Verboom, W.; Harkema, S.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron Lett.* **1991**, *32*, 2675. (b) Groenen, L. C.; Ruël, B. H. M.; Casnati, A.; Verboom, W.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron* **1991**, *47*, 8379. (c) Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* **1991**, *47*, 4325. (d) Shinkai, S.; Fujimoto, K.; Otsuka, T.; Ammon, H. L. *J. Org. Chem.* **1992**, *57*, 1516.

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Table II. Melting Points and Characteristic Spectral Data of Compounds 3a,c–e and 5a–d[a]

		^{1}H NMR ($CDCl_3$) (δ)				^{13}C NMR ($CDCl_3$) (δ)		
compd	mp (°C)	ArH[b]	$ArCH_2Ar$ (s, 8 H)	$ArOCH_2$	OMe (s)	$ArOCH_2$ (t)	$ArCH_2Ar$ (t)	FAB-MS m/e (M^+) (calcd)
3a	182–183	7.09 (d, 8 H) 6.65 (t, 4 H)	3.60	3.85 (t, 8 H, J = 5.7 Hz)		71.3	35.0	712.4 (712.4)
3c	198–200	7.07 (d, 8 H) 6.71 (t, 4 H)	3.65	3.8–3.75 (m, 8 H)	3.38 (12 H)	71.5	35.8	656.2 (656.3)
3d	286–289	7.03 (s, 8 H)	3.75	3.6–3.55 (m, 8 H)	3.27 (12 H)	70.8	33.9	880.6 (880.6)
3e	249–251	7.00 (d, 8 H) 6.66 (t, 4 H)	3.61	3.53 (t, 8 H, J = 7.3 Hz)		73.6	36.3	592.4 (592.4)
5a[d]	136–138	7.69 (s, 4 H) 7.05 (d, 4 H) 6.60 (t, 2 H)	3.61	3.98–3.93 (m, 8 H)	3.50 (12 H)	72.2 72.0	34.0	713.4[e] (713.3)
5b[d]	193–195	7.53 (s, 4 H) 7.05 (d, 4 H) 6.68 (t, 2 H)	3.63	3.9–3.85 (m, 4 H) 3.70 (t, 4 H, J = 7.3 Hz)	3.44 (6 H)	74.4 71.8	34.9	681.3[e] (681.3)
5c	230–232	7.93 (s, 4 H) 7.06 (d, 4 H) 6.71 (t, 2 H)	3.65	3.9–3.85 (m, 4 H) 3.75–3.6 (m, 8 H)[f]	3.43 (6 H)	74.4 72.0	35.3	715.3[e] (715.5)
5d	179–181	7.32 (s, 4 H) 7.04 (d, 4 H) 6.68 (t, 2 H)	3.58	3.86–3.79 (m, 8 H)	3.41 (12 H)	71.8 71.6	34.9	814.2 (814.2)

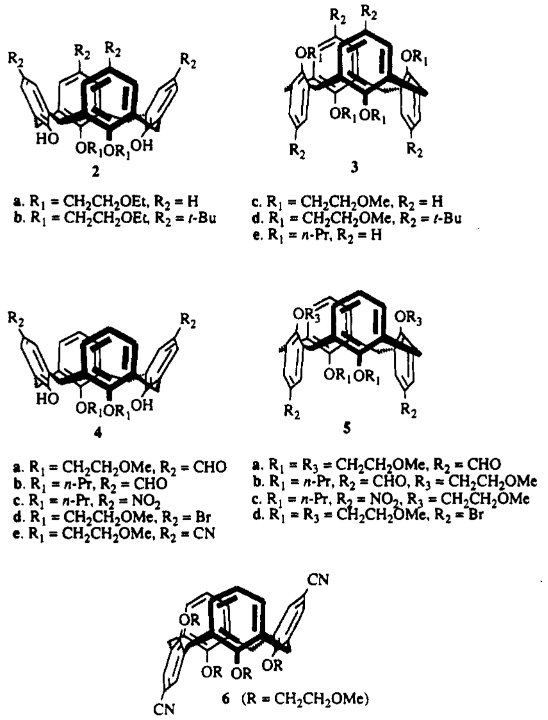
[a] All compounds gave satisfactory elemental analyses. [b] Doublets and triplets have J of 7.5–7.6 Hz. [c] ^{1}H NMR δ 1.30 (s, 36 H, t-Bu). [d] ^{1}H NMR δ 9.70 (s, 2 H, CHO). [e] $[M + H]^+$. [f] Together with $-CH_2OCH_3$ signals.

inversion axis. The angles between the best plane through the bridging methylene carbon atoms and the phenyl rings are 104.4, 76.3, 102.2, and 75.7°, respectively. All phenyl rings have a small, but well-defined, deviation from planarity in a boatlike fashion, the C atoms connected to O having the largest distance to the mean plane of the ring.

This reaction was also performed under the same conditions starting from *tert*-butylcalix[4]arene **1b** which gave the diametrically dialkylated calix[4]arene **2b** in 82% yield; no trace of a tetraalkylated product in the 1,3-alt conformation could be detected. These results indicate the large influence of *tert*-butyl groups in the para position on the outcome of the alkylation of calix[4]arenes.

The surprising formation of **3a** led us to investigate the possibility of developing a general method for tetra-*O*-alkylated calix[4]arenes in the 1,3-alt conformation. The different conformations of calix[4]arenes (Chart II) are not interconvertable when the phenolic oxygens are alkylated by groups larger than ethyl. Consequently propyl- and 2-methoxyethyl tosylate were selected as the electrophiles. Since we (vide supra) and others[20] had found that tetraalkylation of *p-tert*-butylcalix[4]arenes cannot be achieved using K_2CO_3, we have used Cs_2CO_3 in DMF as a stronger base. The optimal amount of base for 1,3-alt formation appeared to be 7.5 equiv of Cs_2CO_3 per OH group. The results of the different alkylation reactions are summarized in Table I. The ^{1}H NMR spectra of the crude reaction mixtures showed that in nearly all cases the 1,3-alt conformer is the major or in some cases even the exclusive reaction product. The compounds were isolated by direct crystallization from the crude reaction mixtures.[21]

Chart III



First we studied the tetraalkylation of the *p*-H-calix[4]arene (**1a**) and *p-tert*-butylcalix[4]arene (**1b**) which gave the corresponding *O*-alkylated compounds **3c–e** in reasonable to good yields (entries 1, 2, and 5). Starting from the diametrically *dialkylated* calix[4]arenes **2c–e** the relative conformer distribution and the yields are hardly influenced, compared with tetraalkylation, indicating that the tetraalkylation of **1a,b** probably proceeds via their diametrically dialkylated species. The influence of the leaving group of the electrophile is illustrated for the propylation of **2e** (entries 6 and 7), a tosylate giving more 1,3-alt than a bromide. The 1,3-alt conformation of **3c–e** clearly followed from the characteristic NMR data[1] (vide supra) summarized in Table II.

To study the scope of the 1,3-alt formation a series of diametrically *O*-dialkylated calix[4]arenes **4** was prepared having different substituents R_2 at the para positions of the remaining phenolic groups. Reaction of **2c,e** with 1,1-dichlorodimethyl ether in CH_2Cl_2 in the presence of the Lewis acid $TiCl_4$ gave after chromatography the selectively diformylated calix[4]arenes **4a,b** in yields of 58% and 55%, respectively. Nitration of **2e** with 65% HNO_3 in CH_2Cl_2 afforded the 11,23-dinitrocalix[4]arene **4c** in 61% yield. The corresponding 11,23-dibromo compound

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[21] Preparative thin layer chromatography may give rise to slightly higher yields.

4d could be obtained in 73% yield by bromination of **2c** with *N*-bromosuccinimide in 2-butanone. In all these reactions we take advantage of the fact that electrophilic aromatic substitutions are much faster on phenols than on alkylated phenols (compare ref 4). A Rosenmund–von Braun[22] reaction of **4d** with CuCN in refluxing 1-methyl-2-pyrrolidinone afforded the dicyanocalix[4]arene **4e** in 63% yield. Reaction of **4a–d** with 2-methoxyethyl tosylate under standard conditions yielded a mixture of 1,3-alt and paco conformers of which the major 1,3-alt conformer could be isolated in reasonable yields. (Table I, entries 8–11). However, in the case of **4c** a significantly higher reaction temperature and a longer reaction time were needed to complete the reaction, probably due to the presence of the electron-withdrawing nitro groups (R_2). Surprisingly, reaction of dicyanocalix[4]arene **4e** with 2-methoxyethyl tosylate gave a mixture of 1,3-alt and paco conformers in a ratio of 3:7 of which the latter (compound **6**) could be isolated in 20% yield upon repeated crystallization. The ^{1}H NMR spectrum of **6** shows one AB quartet at δ 4.19 and 3.11 (J = 13.5 Hz) and one singlet at δ 3.75 for the methylene bridge protons. The ^{13}C NMR spectrum exhibits values of δ 34.1 and 30.3 for the corresponding carbon atoms, all indicating that **6** is present in the paco conformation.[1,11] The deviating behavior of **4e** cannot easily be explained by steric or electronic effects when compared with the outcome of the reactions of, e.g., **2c** and **4c**, respectively. This result emphasizes that a subtle change can have a considerable effect on the product formation.

As mentioned in the Introduction the conformational outcome of functionalization of calix[4]arenes depends on a number of parameters. Despite different speculations in the literature[3a,c,6,7,9] no real "overall" explanation is available yet. Also from the results presented in this paper it is premature to draw definite conclusions. Detailed mechanistic studies will be needed in order to obtain a quantitative picture of the mechanism of tetraalkylation. Nevertheless, we feel that from the synthetic point of view this method for tetra-*O*-alkylation of calix[4]arenes in the 1,3-alt conformation is a valuable addition to the existing procedures for the synthesis of calix[4]arenes in the fixed cone,[6,7] partial cone,[6,7] and 1,2-alternate conformation.[8]

Experimental Section

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with Me_4Si as internal standard. Positive fast atom bombardment (FAB) mass spectra were obtained with *m*-nitrobenzyl alcohol as a matrix. CH_2Cl_2 was distilled from CaH_2 and stored over molecular sieves. Calix[4]arenes **1a**,[10] **1b**,[23] and **2e**,[3c] 2-(m)ethoxyethyl tosylate,[24] and propyl tosylate[25] were prepared according literature procedures. All reactions were carried out under an argon atmosphere.

In the workup procedures the combined organic layers were dried with $MgSO_4$ whereupon the solvent was removed under reduced pressure. The presence of solvent in the analytical samples was confirmed by ^{1}H NMR spectroscopy.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-26,28-bis(ethoxyethoxy)-25,27-dihydroxycalix[4]arene (2b).[26] A suspension of calix[4]arene **1b** (13.0 g, 20 mmol), anhydrous K_2CO_3 (5.6 g, 40 mmol), and 2-ethoxyethyl tosylate (11.0 g, 45 mmol) in CH_3CN (500 mL) was refluxed for 7 d. After evaporation of the solvent, the mixture was taken up in CH_2Cl_2 (500 mL) and washed with 1 N HCl (2 × 100 mL) and brine (2 × 100 mL). The crude reaction mixture was recrystallized from CH_2Cl_2/MeOH to afford pure **2b** as a white solid: yield 82%; mp 158–159 °C; ^{1}H NMR δ 7.45 (br s, 2 H, OH), 7.08 (s, 4 H, ArH), 6.87 (s, 4 H, ArH), 4.46 and 3.28 (AB q, 8 H, J = 14.0 Hz, $ArCH_2Ar$), 4.19–4.15 (m, 4 H, $ArOCH_2$), 3.98–3.93 (m, 4 H, CH_2O), 3.71 (q, 4 H, J = 7.0 Hz, OCH_2CH_3), 1.28, 0.99 (s, 2 × 18 H, $C(CH_3)_3$); ^{13}C NMR δ 75.2 (t, $ArOCH_2$), 33.8 (s, $C(CH_3)_3$), 31.7, 31.0 (q, $C(CH_3)_3$), 31.5 (t, $ArCH_2Ar$); FAB/MS m/e 792.7 (M^+, calcd 792.5). Anal. Calcd for $C_{52}H_{72}O_6$: C, 78.75; H, 9.14. Found: C, 78.98; H, 9.03.

25,27-Dihydroxy-26,28-bis(methoxyethoxy)calix[4]arene (2c) was prepared in a similar way as **2b** starting from calix[4]arene **1a** and 2-methoxyethyl tosylate: reaction time 20 h; yield 43%; mp 212–213 °C; ^{1}H NMR δ 7.84 (s, 2 H, OH), 7.03 (d, 4 H, J = 7.45 Hz, ArH), 6.90 (d, 4 H, J = 7.45 Hz, ArH), 7.8–7.6 (m, 4 H, ArH), 4.45 and 3.35 (AB q, 8 H, J = 13.1 Hz, $ArCH_2Ar$), 4.2–4.15 (m, 4 H, $ArOCH_2$), 3.58 (s, 6 H, OCH_3); ^{13}C NMR δ 75.5 (t, $ArOCH_2$), 59.3 (q, OCH_3), 31.2 (t, $ArCH_2Ar$); FAB/MS m/e 540.3 (M^+, calcd 540.3). Anal. Calcd for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found: C, 75.47; H, 6.76.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,27-dihydroxy-26,28-bis(methoxyethoxy)calix[4]arene (2d) was prepared in a similar way as **2b** starting from calix[4]arene **1b** and 2-methoxyethyl tosylate: reaction time 7 d; yield 78%; mp 228–230 °C; ^{1}H NMR δ 7.32 (s, 2 H, OH), 7.04 (s, 4 H, ArH), 6.79 (s, 4 H, ArH), 4.36 and 3.29 (AB q, 8 H, J = 13.0 Hz, $ArCH_2Ar$), 4.17–4.13 (m, 4 H, $ArOCH_2$), 3.54 (s, 6 H, OCH_3), 1.28, 0.96 (s, 2 × 18 H, $C(CH_3)_3$); ^{13}C NMR δ 75.2 (t, $ArOCH_2$), 59.2 (q, OCH_3), 33.9, 33.8 (s, $C(CH_3)_3$), 31.6, 31.0 (q, $C(CH_3)_3$), 31.5 (t, $ArCH_2Ar$); FAB/MS m/e 764.4 (M^+, calcd 764.5). Anal. Calcd for $C_{50}H_{68}O_6$: C, 78.49; H, 8.96. Found: C, 78.28; H, 9.12.

25,26,27,28-Tetrakis(ethoxyethoxy)calix[4]arene (3a; 1,3-alt). A suspension of calix[4]arene **1a** (8.5 g, 20 mmol), anhydrous K_2CO_3 (5.6 g, 40 mmol), and 2-ethoxyethyl tosylate (14.6 g, 60 mmol) in CH_3CN (1000 mL) was refluxed for 7 d. After evaporation of the solvent, the residue was taken up in CH_2Cl_2 (500 mL) and washed with 1 N HCl (2 × 100 mL) and brine (1 × 100 mL). The crude reaction mixture was recrystallized from hexane/EtOAc (85:15) to give pure **3a** in a yield of 48%. The melting point and characteristic spectral data are summarized in Table II.

25,27-Dihydroxy-26,28-bis(methoxyethoxy)calix[4]arene-11,23-dicarboxaldehyde (4a). To a solution of $TiCl_4$ (1.1 mL, 5.74 mmol) and 1,1-dichlorodimethyl ether (0.9 mL, 7.92 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of **2c** (0.54 g, 0.99 mmol) in CH_2Cl_2 (5 mL) at −10 °C. After the mixture was stirred for 20 min 1 N HCl (25 mL) was added whereupon the reaction mixture was stirred for an additional hour. After separation of the layers, the organic layer was washed with 1 N HCl (3 × 10 mL) and water (2 × 25 mL). The crude reaction mixture was purified by flash chromatography (SiO_2, EtOAc–petroleum ether (bp 60–80 °C), 1:1) to give pure **4a**: yield 58%; mp >300 °C (CH_2Cl_2/MeOH); ^{1}H NMR δ 9.78 (s, 2 H, CHO), 8.89 (s, 2 H, OH), 7.63 (s, 4 H, ArH), 6.96 (d, 4 H, J = 7.5 Hz, ArH), 6.80 (t, 2 H, J = 7.6 Hz, ArH), 4.42 and 3.45 (AB q, 8 H, J = 13.2 Hz, $ArCH_2Ar$), 4.21–4.17 (m, 4 H, $ArOCH_2$), 3.94–3.90 (m, 4 H, OCH_2), 3.57 (s, 6 H, OCH_3); ^{13}C NMR δ 190.9 (d, CHO), 75.6 (t, $ArOCH_2$), 59.3 (q, OCH_3), 31.0 (t, $ArCH_2Ar$); IR (KBr) 1683 (CHO) cm^{-1}; FAB/MS m/e 596.2 (M^+, calcd 596.1). Anal. Calcd for $C_{36}H_{36}O_8 \cdot 0.5$ MeOH: C, 70.57; H, 5.92. Found: C, 70.55; H, 5.82.

25,27-Dihydroxy-26,28-dipropoxycalix[4]arene-11,23-dicarboxaldehyde (4b)[28] was prepared in a similar way as **4a** starting from **2e** (0.34 g, 0.67 mmol): yield 55%; mp >320 °C dec (CH_2Cl_2/MeOH); ^{1}H NMR δ 9.79 (s, 2 H, CHO), 9.27 (s, 2 H, OH), 7.64 (s, 4 H, ArH), 6.96 (d, 4 H, J = 7.5 Hz, ArH), 6.82–6.76 (m, 2 H, ArH), 4.30 and 3.50 (AB q, 8 H, J = 13.1 Hz, $ArCH_2Ar$), 4.04 (t, 4 H, J = 7.3 Hz, $ArOCH_2$), 2.12–2.00 (m, 4 H, $ArOCH_2CH_2$), 1.35 (t, 6 H, J = 7.3 Hz, CH_3); ^{13}C NMR δ 190.9 (d, CHO), 78.6

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(26) For reasons of simplicity and to reduce space in this paper the Gutsche convention[27] is followed using 25,26,27,28-tetrahydroxycalix[4]arene instead of the official Chemical Abstracts pentacyclo[$19.3.1.1^{3,7}.1^{9,13}.1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,26,27,28-tetrol.

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(t, $ArOCH_2$), 31.3 (t, $ArCH_2Ar$); FAB/MS *m/e* 564.3 (M^+, calcd for $C_{36}H_{36}O_6$ 564.3).

25,27-Dihydroxy-11,23-dinitro-26,28-dipropoxycalix[4]arene (4c). To a solution of **2e** (7.6 g, 15 mmol) in CH_2Cl_2 (25 mL) was added 65% HNO_3 (10 mL, 150 mmol) dropwise. After being stirred for 15 min at rt the reaction mixture was poured into water (200 mL). The water layer was extracted with CH_2Cl_2 (3 × 50 mL), whereupon the combined organic layers were washed with water (2 × 50 mL). Recrystallization of the crude reaction product from CH_2Cl_2/MeOH afforded **4c** as a yellow solid: yield 61%; mp >300 °C; ^{1}H NMR δ 9.46 (s, 2 H, OH), 8.04 (s, 4 H, ArH), 7.04 (d, 4 H, J = 7.5 Hz, ArH), 6.88–6.82 (m, 2 H, ArH), 4.29 and 3.51 (AB q, 8 H, J = 13.0 Hz, $ArCH_2Ar$), 4.05–4.0 (m, 4 H, $ArOCH_2$), 2.1–2.05 (m, 4 H, $ArOCH_2CH_2$), 1.35–1.3 (m, 6 H, CH_3); ^{13}C NMR δ 78.6 (t, $ArOCH_2$), 31.1 (t, $ArCH_2Ar$); MS (EI) *m/e* 598.234 (M^+, calcd 598.231). Anal. Calcd for $C_{34}H_{34}N_2O_8$: C, 68.22; H, 5.72; N, 4.68. Found: C, 67.80; H, 5.88; N, 4.50.

11,23-Dibromo-25,27-dihydroxy-26,28-bis(methoxyethoxy)calix[4]arene (4d). To a solution of **2c** (1.0 g, 1.85 mmol) in 2-butanone (20 mL) was added *N*-bromosuccinimide (0.69 g, 3.89 mmol). After the solution was stirred for 3 h at rt 10% aqueous $NaHSO_3$ (20 mL) was added to the yellow solution, whereupon the reaction mixture was stirred for an additional 45 min. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (1 × 25 mL) and water (1 × 25 mL). Recrystallization of the crude reaction mixture from CH_2Cl_2/MeOH gave **4d** as white crystals: yield 73%; mp >300 °C; ^{1}H NMR δ 7.94 (s, 2 H, OH), 7.16 (s, 4 H, ArH), 6.91 (d, 4 H, J = 7.3 Hz, ArH), 6.82–6.76 (m, 2 H, ArH), 4.36 and 3.31 (AB q, 8 H, J = 13.0 Hz, $ArCH_2Ar$), 4.18–4.12 (m, 4 H, $ArOCH_2$), 3.9–3.85 (m, 4 H, $ArOCH_2CH_2$), 3.54 (s, 6 H, OCH_3); ^{13}C NMR δ 75.5 (t, $ArOCH_2$), 59.3 (q, OCH_3), 30.9 (t, $ArCH_2Ar$); FAB/MS *m/e* 698.1 (M^+, calcd 698.1). Anal. Calcd for $C_{34}H_{34}Br_2O_6$: C, 58.47; H, 4.91. Found: C, 58.11; N, 4.78.

25,27-Dihydroxy-26,28-bis(methoxyethoxy)calix[4]arene-11,23-dicarbonitrile (4e). A mixture of **4d** (1.5 g, 2.15 mmol) and CuCN (0.75 g, 8.4 mmol) in 1-methyl-2-pyrrolidinone (30 mL) was refluxed for 3 h. The black solution was cooled to 100 °C, and a solution of $FeCl_3.6H_2O$ (2.5 g, 9.2 mmol) in 1 N HCl (150 mL) was added. After being stirred at 100–110 °C for 1 h the precipitate was filtered off and washed with water (1 × 25 mL). The solid material was recrystallized from CH_2Cl_2/MeOH to give pure **4f**: yield 63%; mp >300 °C; ^{1}H NMR δ 8.79 (s, 2 H, OH), 7.38 (s, 4 H, ArH), 6.95–6.9 (m, 4 H, ArH), 6.85–6.8 (m, 2 H, ArH), 4.38 and 3.39 (AB q, 8 H, J = 13.0 Hz, $ArCH_2Ar$), 4.2–4.15 (m, 4 H, $ArOCH_2$), 3.9–3.85 (m, 4 H, $ArOCH_2CH_2$), 3.55 (s, 6 H, OCH_3); ^{13}C NMR δ 75.7 (t, $ArOCH_2$), 59.3 (q, OCH_3), 30.7 (t, $ArCH_2Ar$); IR (KBr) 2215 (CN) cm^{-1}; FAB/MS *m/e* 591.3 ($[M + H]^+$, calcd 591.3). Anal. Calcd for $C_{36}H_{34}N_2O_6$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.25; H, 6.14; N, 4.49.

General Procedure for the Alkylation of 1a,b, 2c–e, and 4a–e. Formation of 3c–e, 5a–d, and 6. A mixture of calix[4]arenes **1a,b,2c–e**, and **4a–e** (0.50 g) and Cs_2CO_3 (7.5 equiv per calix[4]arene OH) in DMF (20 mL) was heated at 80 °C for 30 min. Subsequently, propyl or 2-methoxymethyl tosylate (7.5 equiv per calix[4]arene OH) was added and the reaction mixture heated (for reaction temperatures and times see Table I). Upon cooling, the reaction mixture was poured into water (200 mL). After extraction with CH_2Cl_2 (3 × 50 mL) the combined organic layers were washed with 1 N HCl (1 × 50 mL) and brine (3 × 50 mL). To remove the excess alkyl tosylate a mixture of the resulting residue, KI (about 1 g), and Et_3N (1 mL) in CH_3CN (30 mL) was refluxed for 1 h. After removal of the solvent, CH_2Cl_2 (50 mL) was added to the residue whereupon the organic layer was washed with 1 N HCl (1 × 50 mL) and water (2 × 50 mL). Trituration of the residue with cold MeOH afforded the tetraalkylated calix[4]arenes mostly as a mixture of conformers. Recrystallization of the triturated products from CH_2Cl_2/MeOH gave the pure compounds **3c–e, 5a–d**, and **6**. The relative conformer distribution after trituration and the yields of the isolated compounds are summarized in Table I. The melting points and characteristic spectral data of **3c–e** and **5a–d** are given in Table II.

25,26,27,28-Tetrakis(methoxyethoxy)calix[4]arene-11,23-dicarbonitrile (6; partial cone): mp 176–177 °C; ^{1}H NMR δ 7.86, 7.40 (s, 4 H, ArH), 7.01 (d, 2 H, J = 7.5 Hz, ArH), 6.49 (t, 2 H, J = 7.5 Hz, ArH), 6.20 (d, 2 H, J = 7.5 Hz, ArH), 4.19 and 3.11 (AB q, 4 H, J = 13.5 Hz, $ArCH_2Ar$), 3.75 (s, 4 H, $ArCH_2Ar$), 3.56 (s, 6 H, OCH_3), 3.50, 3.33 (s, 2 × 3 H, OCH_3); ^{13}C NMR δ 73.5, 72.5 (t, $ArOCH_2$), 34.1, 30.3 (t, $ArCH_2Ar$); IR (KBr) 2220 (CN) cm^{-1}; FAB/MS *m/e* 707.3 ($[M + H]^+$, calcd 707.3). Anal. Calcd for $C_{42}H_{46}N_2O_8$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.49; H, 6.70; N, 3.85.

X-ray Crystallography of Compound 3a. The crystal structure of **3a** was determined by X-ray diffraction. Crystal data: $C_{44}H_{56}O_8$, monoclinic, space group $P2_1/n$; a = 15.525 (2) Å, b = 15.756 (2) Å, c = 17.279 (2) Å, β = 109.75 (2)°; V = 3978 (2) Å^3; Z = 4; d_{calc} = 1.19 g cm^{-3}, μ = 0.75 cm^{-1}. Reflections were measured at 273 (2) K in the $\omega/2\vartheta$ scan mode [3.0° < ω < 25.0°; scan width (ω) 0.90 + 0.34 tan ϑ], using graphite-monochromated Mo Kα radiation (λ = 0.7107 Å). The structure was solved by direct methods[29] and refined with full-matrix least-squares methods. A total of 3651 reflections with $F_o^2 > 2\sigma(F_o^2)$ was used in the refinement. The number of parameters refined was 470 [scale factor, positional parameters and anisotropic thermal parameters for the non-hydrogen atoms]. Hydrogen atoms were put in calculated positions and were treated as riding atoms in the refinements with fixed thermal parameters. The final R factors were R = 6.5%, R_w = 6.1%. All calculations were done with SDP.[30]

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Supplementary Material Available: Tables of positional parameters and bond distances and angles and the ^{1}H NMR spectrum of **4b** (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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