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Studies on Calix(aza)crowns, II.[1] Synthesis of Novel Proximal Doubly Bridged Calix[4]arenes by Intramolecular Ring Closure of *syn* 1,3-and 1,2- ω- Chloroalkylamides

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Abstract: Inherently chiral calix[4]arenes (**9,10**) with carboxamide bridges spanning the proximal positions on the lower rim and **18** achiral counterparts have been synthesized by double intramolecular cyclization of **7b,8b** 1,3-and **17** 1,2-bis-chloroalkylamides. The conformational analysis of the 1,3- and 1,2-disubstituted calixarene intermediates **5-8** and **15-17** proved an equilibrium of two distorted cone conformations. The success of ring closure was strictly dependent on the chain length of the open chain precursors. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Recently efforts have been made to include crown rings on the calixarene skeleton in order to combine the unique properties of both species in one molecule. Calixcrowns with a linkage in 1,3-and 1,2- position,[2,3,4,5] calixspherands[6] double or triple calixarenes with various connecting chains[7,8,9,10,11,12] have been reported. Some of them were tested as metal ion extractants and applied as selective ligands in ion selective electrodes.[13,14,15] All of these macrocycles were obtained by the ring closure of calix[4]arene tetrols with activated bifunctional reagents. In this approach mostly the distal(1,3) phenolic OH groups were linked affording mono[2,3,6,15]-and 1,3-alternate bis-calixcrowns.[4] There are examples, however, for the cyclization of the proximal (1,2) OH groups giving rise to the formation of calixbiscrowns of cone conformation.[2,5,16,17]

An alternative strategy has been developed for the synthesis of calix(aza)crowns in which the distal positions on the lower rim of calix were linked with 1,3-diamide bridges. The easily accessible *syn* 1,3-diesters **1** or the respective acid chloride were condensed with di- and polyamines to obtain **2** singly capped calix[4]arenes.[1,18,19] In our previous paper some regio-and conformation selective alkylations of **2** leading to **3** macrocycles were reported[1] and an easy access to the 1,3-alternate doubly capped derivatives **4** was also developed.[20] Untiil now, however, calixcrowns or calix(aza)crowns (capped calixarenes) have been synthesized only by intermolecular ring closure. To our knowledge direct intramolecular approaches to obtain bridged calixarenes have not yet

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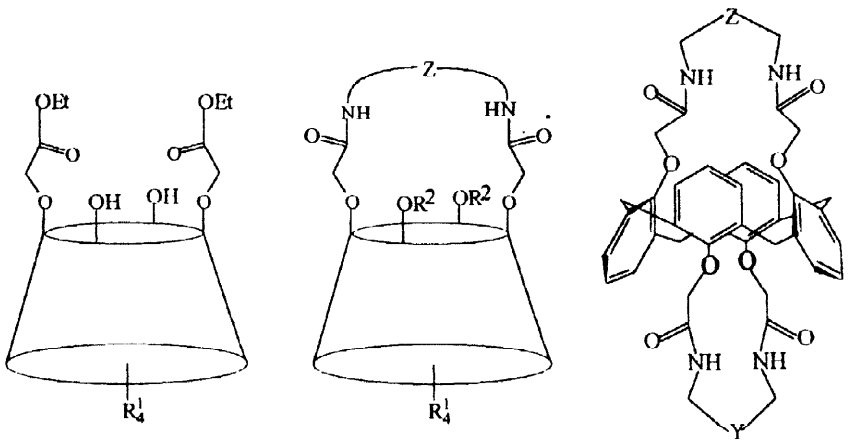
been described. Now we wish to report the utilization of chloroalkylamide precursors preformed prior to cyclization in the preparation of novel **9,10,18** calix[4]arenes with double proximal-carboxamide bridges.



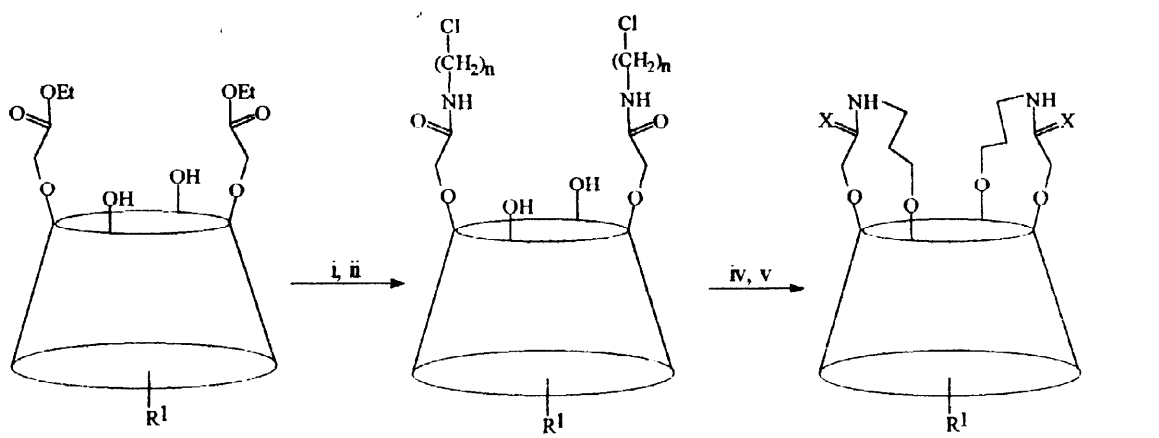
1 **2,3** **4**

R^1= H, Bu^t; R^2= H (**2**); alkyl, CH_2COOEt (**3**); Y,Z= various links

RESULTS AND DISCUSSION

Synthesis of 9 and 10 proximal doubly bridged calix[4]arenes. Regioisomer A

The synthetic approach was based on a multi-step reaction depicted in Scheme 1. The clean amidation of **1a,b** with various alkanolamines in toluene-methanol solvent mixture followed by chlorination of the terminal OH groups in **5a,b,c,d** and **6b** with $SOCl_2$ afforded **7a,b,c,d** and **8b** in good yields. These chloroalkylamides were used to alkylate the neighbouring free OH groups by applying the cone selective PTC alkylation method developed in our laboratory[21] to construct two carboxamide bridges.



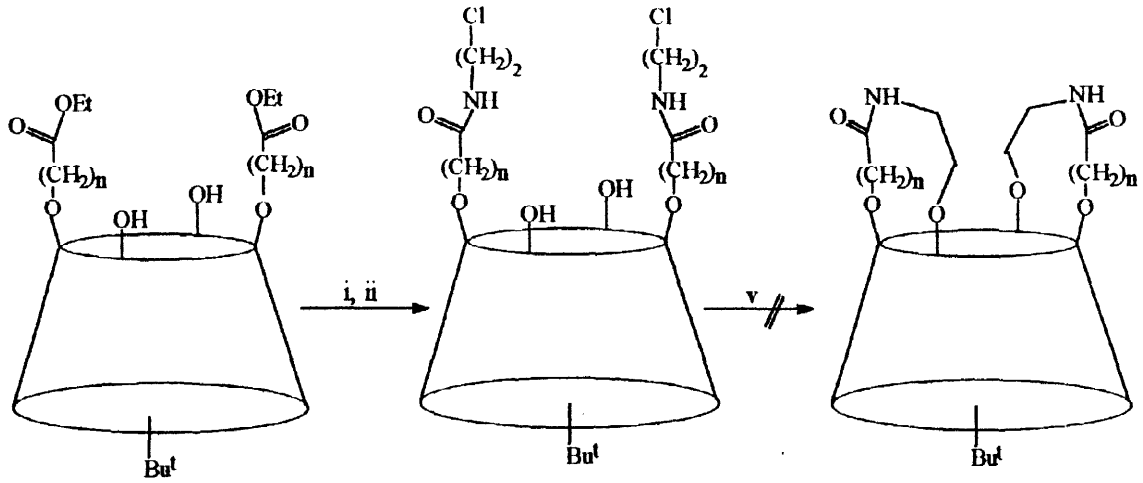
1a (R^1= Bu^t), **b** (R^1=H) **7a,b,c,d** (R^1= Bu^t),**8b** (R^1=H) **9a,b** (R^1= Bu^t), **10a,b** (R=H)

Scheme 1.Reagents i: $H_2N(CH_2)_nOH$/toluene-methanol, Δ, n=2,3,4,5; **5a,b,c,d**(R^1= Bu^t), **6b**(R^1=H); ii: $SOCl_2/CHCl_3$, Δ; iv: aq.NaOH/toluene,PTC,Δ (**9a,10a**, X=O); v: Lawesson reagent/toluene,Δ(**9b,10b**, X=S)

As was previously reported in the case of 1,2-calix(bis)crowns[17] the intramolecular contact between the proximal OH groups could succesfully be accomplished by 5-, 8- and 11- membered flexible chains, as well. Although the chain lengths in the precursors **7a,b,c,d** and **8b** were varied in a similar range (5-8), only **7b** and **8b** (n=3) gave the desired **9a, 10a** cyclized compounds, in the other cases hydrolysis products (**5a,c,d** and dicarboxylic acid) could only be identified. The cone conformation of compounds **9a, 10a** was unambiguously proved by characteristic ^{1}H NMR data.

The partial failure of cyclization can be due to the weak (if any) metal ion template (NaOH base gave the best result) and to some extent, the rigid chain attributed to the planar carboxamide function. Taking into account the high yield of **9a, 10a** and the former considerations, the optimal intramolecular distance of the electrophilic terminus seems to be an important governing factor in the success of this reaction.

We were interested to further investigate the scope and limit of the cyclization, therefore keeping the chain length in the range of 6-8, the position of the carboxamide group was displaced as outlined in Scheme 2.



11b,c **13b,c** **14b,c**

Scheme 2. Reagents i: NaOH/EtOH, $SOCl_2$, ethanolamine(**12b,c**); ii: $SOCl_2/CHCl_3$; v: aq.NaOH/toluene, PTC

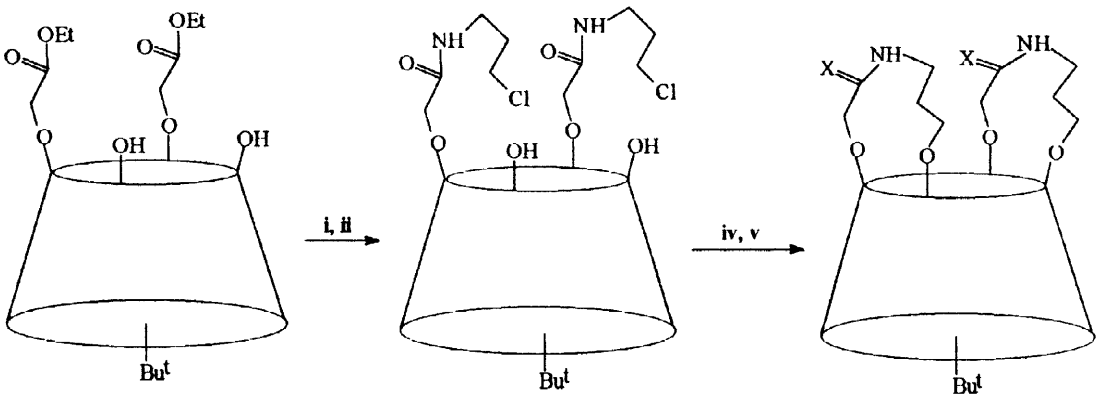
1,3-Dialkylation of p-tert-butylcalix[4]arene with $Br(CH_2)_nCOOEt$ (n=2,3,4) (K_2CO_3, MeCN) furnished **11b** (n=3),**c** (n=4) in fair yields. Diester **11a** (n=2) could not be prepared, instead HBr elimination took place to give ethylacrylate. To our surprise **11b,c** failed to react with ethanolamine even upon prolonged heating, the required **12b,c** were obtained via the acid chloride route. When **13b,c** intermediates were subjected to cyclization an unseparable mixture of compounds was formed which might have contained **14** bicyclic molecules but we failed to isolate them. This negative result supported again our earlier speculation: the success of this kind of ring closure is strictly dependent on the chain length that should be 7σ bonds, not more or less.

The proximal doubly bridged calixarenes **9a, 10a** represent unique macrocycles of characteristic rigid structure possessing inherent chirality. In order to get more information on the structural features, **9b, 10b** thio

analogues were also prepared. Moreover, it seemed to be desirable to synthesize also the other regioisomers **18** also which have a plane of symmetry and are, therefore, achiral.

Synthesis of 18 proximal doubly bridged calix[4]arenes. Regioisomer B

The same series of reactions were planned as previously shown but starting from the syn 1,2- diester **15**. This compound has already been described[22] as a side product obtained in very low yield during the NaH mediated alkylation of p-tert-butylcalix[4]arene with $BrCH_2COOEt$. Therefore we developed a new approach applying protection-deprotection method. Thus **15** was prepared from 5,11,17,23-tetra-tert-butyl-25-benzyloxy-26,27,28-trihydroxycalix[4]arene[23] via cone selective dialkylation with $BrCH_2COOEt$ (BaO, DMF, rt) followed by debenzylation (Me_3SiBr, $CHCl_3$, rfl.). Subsequently the same protocol was followed as described for regioisomer **A** (Scheme 3.)



15 **17** **18a** (X=O), **18b** (X=S)

Scheme 3. Reagents, i: ethanolamine (**16**), ii: $SOCl_2$, iv: NaOH/toluene, PTC, v: Lawesson reagent

STRUCTURE ELUCIDATION AND CONFORMATIONAL ANALYSIS

1,3-Disubstituted calix[4]arene intermediates 5-8

Seemingly, the structure determination of the intermediates **5-8** can be made without any problem. The simple distal (1,3) dialkylated calix[4]arenes are generally agreed and well documented to possess cone conformation based on the AB splitting pattern of the bridging methylene protons in ^1H NMR. Larger substituents, however, can cause conformational distorsion which can be studied if the the ^1H and ^{13}C NMR signals of the two different aromatic nuclei are unambiguously distinguished.

We have recently reported, that the chemical shifts of the CMe_3 and those of the aromatic protons can be utilized for monitoring the extent of the conformational distortion of 1,3-diamide-bridged calixcrowns.[20] This observation can also be applied to the investigation of 1,3- and 1,2-disubstituted calix[4]arenes as well. In the case of an almost symmetrical cone conformation the ^1H chemical shifts of the neighbouring aromatic rings and the attached CMe_3 groups, respectively, are expected to be similar pairwise. With a distorted cone conform-

ation the planes of two oppositely arranged aryl groups are becoming flattened and at the same time the other pair of the aryl groups are getting near to each other and become parallel. This latter arrangement is connected with a characteristic shielding of protons of these moieties caused by the well known diamagnetic anisotropy of aryl rings. It is the reason for the appearance of characteristic $\Delta\delta$ chemical shift differences observed for calixarenes with distorted cone conformation.

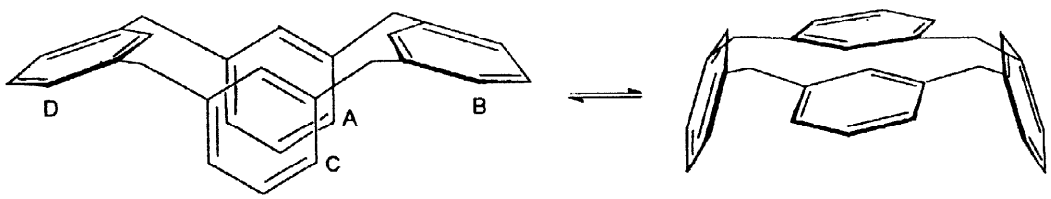
Considering the rather different ^1H chemical shifts observed for the neighbouring aromatic groups we can conclude that compounds **5-8** should appear in the form of a rapidly interconverting equilibrium of two distorted cone conformations $(A/C)_{in},(B/D)_{out} \rightleftharpoons (A/C)_{out},(B/D)_{in}$ as depicted in Fig. 1a. Due to the different steric requirements of OH and OR groups this equilibrium should be shifted. To establish the preferred conformation we should differentiate the Ar-H and CMe_3 signals of A/C and B/D rings, respectively. To achieve this the ^{13}C spectrum of compound **5d** was taken in addition to gs-HMQC,[25] gs-HMBC[26] and semiselective INEPT experiments.[27] A clear entry to the sequential signal assignment is provided by the INEPT experiment (optimized for $J(C,H) = 7$ Hz long-range coupling) where the OCH_2CON proton signal at 4.61 (2H) (see Fig. 1b.) correlates with the carbonyl at 169.3 and marks out over three bonds the quaternary carbon atom at 148.8 ppm. The same signal was also achieved by irradiating at 6.97, so this proton is located on the same aromatic ring. Otherwise, polarization transfer was observed from this proton to the quaternary signal of the CMe_3 group (34.1), which correlates with the proton signal at 1.07. Comparing the chemical shifts 6.97 and 1.07 with the corresponding values of the neighbouring aromatic ring (7.10 and 1.27) we can conclude that for compounds **5-8** the $(A/C)_{in},(B/D)_{out}$ conformation is the energetically preferred.

1,2-Disubstituted calix[4]arene imtermediate 15-17

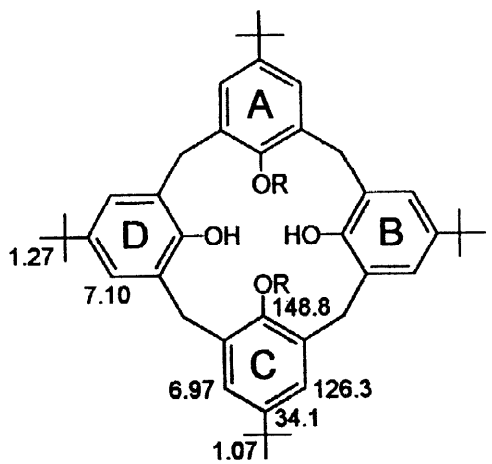
Due to their poor availability proximal calixarene derivatives are rarely found in the literature[28] and nothing has been mentioned on their conformational behaviour.

For compounds **15-17** the two conformers discussed above are energetically identical exhibiting the same population. A characteristic feature of the ^1H spectra of these compounds is the diastereotopic appearance of methylene protons in the chain. It can be observed even with the CH_2OH group of **16** (see Fig 1c.), where under decoupling at 1.88 the methylene protons exhibit an AB doublet pair ($J_{AB} = 11.3$ Hz). This phenomenon proves the chiral character of these compounds and rules out the possibility of a symmetrical cone conform-ation. The sequential signal assignment was performed in a similar way to that discussed above, but in this case gs-HMBC measurement was applied for the detection of long-range $J(C,H)$ responses. The characteristic chemical shifts for compound **16** depicted in Fig. 1b prove that both conformers of the 1,2-disubstituted derivatives are chiral, so despite the rapid conformational interconversion (the chemical shifts of the Ar-H and CMe_3 protons are averaged) the diastereotopic character of methylene protons is preserved.

a.

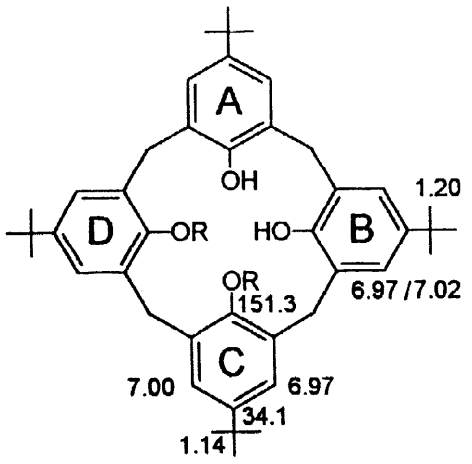


b.



169.3
R = $CH_2CONHCH_2CH_2CH_2OH$
4.61s 3.58q 3.68t

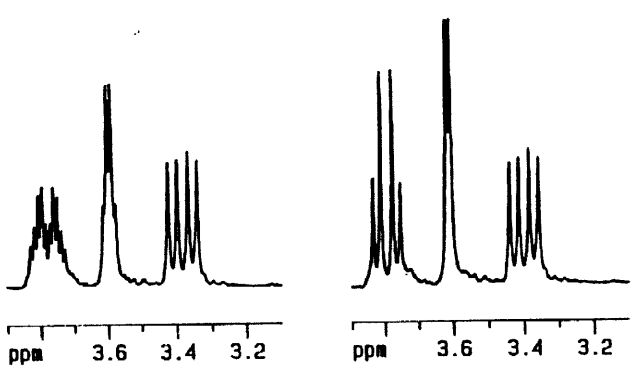
5d



170.3 1.88quint.
R = $CH_2CONHCH_2CH_2CH_2OH$
4.21d 3.58q 3.75m
4.86d 3.60q 3.80m

16

c.



decoupled at 1.88.

Figure 1.

a. Conformational equilibrium of compounds **5-8** and **15-17**.

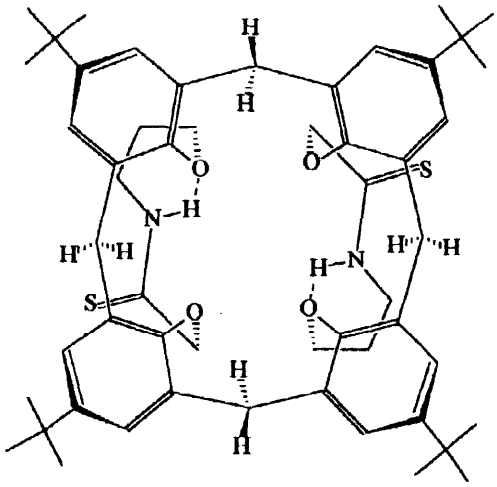
b. Selected ^1H and ^{13}C chemical shifts of compounds **5d** and **16**.

c. Sections of ^1H spectra of **16**.

Doubly bridged calix[4]arenes 9,10 (regioisomer A) and 18 (regioisomer B)

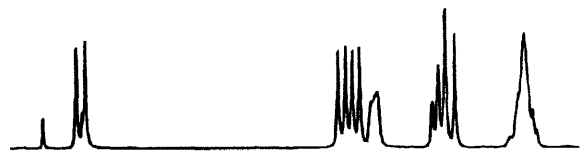
A complete ^{1}H and ^{13}C NMR signal assignment of compounds **9**, **10** and **18** was achieved utilizing different 2D measurements.[29] The comprehensive NMR investigation revealed that the amide groups appear in Z configuration and the bridging chains adopt a preferred conformation, where the N–H bonds are oriented toward the cavity and fixed by hydrogen bonds with the etheric oxigen atoms. On the bases of the NMR data the interatomic proton-proton distances in the bridge could be calculated and thus a stereo model for **9b** was constructed (Scheme 4a.). The short hydrogen-oxygen distance (≈1.8A) measured on the model is in accordance with the high chemical shift of the NH signal (11.52), proving the existence of a strong hydrogen bridge.

a.

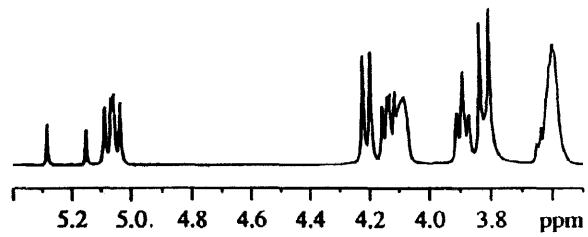


9b

b.



c.



Scheme 4.

a. Stereo picture of **9b**

b. Section of ^{1}H NMR spectrum of **9b**

c. Section of ^{1}H NMR spectrum of **9b** in the presence of Pirkle's reagent

To corroborate that compounds **9,10** are enantiomeric mixtures we measured the ^{1}H NMR spectra in the presence of Pirkle's reagent (R(-)-(9-anthryl)-2,2,2-trifluoroethanol) and splitting of the OCH_2 and $ArCH_2Ar$ methylene protons were detected (for **9b** see Scheme 4b and c). Untill now only a few successful examples have been reported for the optical resolution of inherently chiral calix[4]arenes by HPLC with a chiral-packed column.[30] Our attempts to separate the enantiomers of **9a,b** in this way failed but experiments are in progress with the other racemic molecules.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ at 500 MHz on a Bruker Avance DRX-500 spectrometer. Chemical shifts are given on the δ scale. Mass spectra were taken on a Finnigan MAT 8430 spectrometer (EI: electron energy: 70 eV, ion source temperature: 250°C; FAB: matrix: m-nitrobenzyl alcohol, gas: xenon, accelerating voltage 9kV). Precoated silica gel plates (Merck 60 F_{254}) were used for analytical TLC. All chemicals were reagent grade and used without further purifications. Compounds **1a,b** were prepared as described,[24] $H_2N(CH_2)_nOH$ (n=2,3,4,5) used are commercially available (Fluka). The analytical samples were dried at 110°C in 10^{-1} Torr.

*General procedure for the preparation of **5a,b,c,d** and **6b** hydroxyalkylamides*

Diesters **1a,b**[24] (**1a**: 0.82g, **1b**: 0.6g, 1mmol,) and alkanolamines (5mmol) were refluxed in 1:1 toluene-methanol mixture (40ml) for 6h. The solvent was then removed under reduced pressure and the residue was triturated with water or methanol (**5c**) to give **5a,b,c,d** and **6b** as white solids.

5a: yield: 94%, mp: 243-246°C (toluene) ^{1}H NMR δ: 9.15 (t, 2H, NH), 7.63 (s, 2H, OH), 7.09 (s, 4H, ArH), 6.89 (s, 4H, ArH), 4.58 (s, 4H, OCH_2), 4.18 and 3.42 (d, J=13.3, 8H, $ArCH_2Ar$), 3.71 (t, 4H, CH_2OH), 3.57 (q, 4H, NCH_2), 1.28 and 1.01 (s, 18H each, Bu^t)

5b: yield: 94%, mp: 262-265°C (toluene) ^{1}H NMR δ: 9.06 (t, 2H, NH), 7.84 (s, 2H, OH), 7.09 (s, 4H, ArH), 6.95 (s, 4H, ArH), 4.60 (s, 4H, OCH_2), 4.13 and 3.45 (d, J=13.3, 8H, $ArCH_2Ar$), 3.67 (t, 4H, CH_2OH), 3.56 (q, 4H, NCH_2), 1.84 (m, 4H, CH_2), 1.26 and 1.06 (s, 18H each ,Bu^t)

5c: yield: 95%, mp: 183-185°C ^{1}H NMR δ: 9.18 (t, 2H, NH), 8.02 (s, 2H, OH), 7.09 (s, 4H, ArH), 6.97 (s, 4H, ArH), 4.61 (s, 4H, OCH_2), 4.15 and 3.46 (d, J=13.3, 8H, $ArCH_2Ar$), 3.63 (t, 4H, CH_2OH), 3.44 (q, 4H, NCH_2), 1.71 (quintet, 4H, CH_2), 1.61 (quintet, 4H, CH_2), 1.27 and 1.08 (s, 18H each, Bu^t)

5d: yield: 92%, mp: 136-139°C ^{1}H NMR δ: 8.96 (t, 2H, NH), 7.85 (s, 2H, OH), 7.26 (s, 4H, ArH), 6.94 (s, 4H, ArH), 4.58 (s, 4H, OCH_2), 4.12 and 3.45 (d, J=13.3, 8H, $ArCH_2Ar$), 3.51 (t, 4H, CH_2OH), 3.41 (q, 4H, NCH_2), 1.66 (m, 4H, CH_2), 1.55 (m, 4H, CH_2), 1.43 (m, 4H, CH_2), 1.27 and 1.05 (s, 18H each, Bu^t)

6b: yield: 80%, mp: 230-232°C ^{1}H NMR δ: 8 97 (t, 2H, NH), 8.10 (s, 2H, OH), 7.11 (d, 4H, ArH), 6 96 (d, 4H, ArH), 6.81 (t, 2H, ArH), 6.75 (t, 2H, ArH), 4.62 (s, 4H, OCH_2), 4.17 and 3.51 (d, J=13.4, 8H, $ArCH_2Ar$), 3.67 (t, 4H, CH_2OH), 3.58 (q, 4H, NCH_2), 1.82 (quintet, 4H, CH_2)

*General procedure for the preparation of **7a,b,c,d** and **8b** chloroalkylamides*

Compounds **5a,b,c,d** and **6b** (1mmol) dissolved in $CHCl_3$ (20ml) were allowed to react with $SOCl_2$ (0.5ml, 6.9 mmol) (**5d**: 1.5ml $SOCl_2$ and a drop of pyridine) at room temperature then refuxed for 2h. After evaporating the solvent and the excess of $SOCl_2$ under reduced pressure, the crude products were purified by trituration with methanol (**5d** with water) to yield **7a,b,c,d** and **8b** as white powders.

7a: yield: 92%, mp: 226-229°C (EtOH) ^{1}H NMR δ: 9.24 (t, 2H, NH), 7.77 (s, 2H, OH), 7.09 (s, 4H, ArH), 6.94 (s, 4H, ArH), 4.61 (s, 4H, OCH_2), 4.17 and 3.45 (d, J=11.3, 8H, $ArCH_2Ar$), 3.77 (q,4H, NCH_2), 3.71 (t, 4H, CH_2Cl), 1.28 and 1.05 (s, 18H each, Bu^t)

7b: yield: 90%, mp: 224-226°C (EtOH) ^{1}H NMR δ: 9.01 (t,2H, NH), 7.91 (s, 2H,OH), 7.09 (s, 4H, ArH), 6.95 (s, 4H, ArH), 4.60 (s, 4H, OCH_2), 4.15 and 3.45 (d, J=13.3, 8H, $ArCH_2Ar$), 3.64 (q, 4H, NCH_2), 3.62 (t, 4H, CH_2Cl), 2.08 (quintet, 4H, CH_2), 1.28 and 1.06 (s, 18H each, Bu^t)

7c: yield: 76%, mp: 206-208°C (BuOH) ^{1}H NMR δ: 9.01 (t, 2H, NH), 7.91 (s, 2H, OH), 7.10 (s, 4H, ArH), 6.96 (s, 4H, ArH), 4.60 (s, 4H, OCH_2), 4.15 and 3.46 (d, J=13.3, 8H, $ArCH_2Ar$), 3.55 (t, 4H, CH_2Cl), 3.44 (q, 4H, NCH_2), 1.83 (m, 8H, CH_2), 1.28 and 1.07 (s, 18H each, Bu^t)

7d: yield: 100%, mp: 195-197°C (hexane) ^{1}H NMR δ: 8.95 (t, 2H, NH), 7.89 (s, 2H, OH), 7.10 (s, 4H, ArH), 6.95 (s, 4H, ArH), 4.58 (s, 4H, OCH_2), 4.12 and 3.46 (d, J=13.4, 8H, $ArCH_2Ar$), 3.41 (q, 4H, NCH_2), 3.29 (t, 4H, CH_2Cl), 1.71 (quintet, 4H, CH_2), 1.65 (quintet, 4H, CH_2), 1.47 (quintet, 4H, CH_2), 1.28 and 1.06 (s,1 8H each, Bu^t)

8b: yield: 83%, mp: 206-209°C (BuOH) ^{1}H NMR δ: 8.91 (t, 2H, NH), 8.20 (s, 2H, OH), 7.13 (d, 4H, ArH), 6.94 (d, 4H, ArH),), 6.77 (t, 4H, ArH), 4.63 (s, 4H ,OCH_2), 4.18 and 3.52 (d, J=12.9, 8H, $ArCH_2Ar$), 3.66 (t, 4H, CH_2Cl), 3.58 (q, 4H, NCH_2) 2.07 (m, 4H, CH_2)

*Synthesis of **9a,10a** and **9b,10b** doubly capped calixarenes (regioisomer A)*

The intramolecular alkylation of **7a,b,c,d** and **8b** chloroalkylamides was effected according to our method reported previously[21] (**7a,c,d** gave unsatisfactory results). To a solution of **7b** or **8b** (1mmol) in toluene (40ml) 50% aqueous NaOH (2ml) and tetrabutylammonium bromide (0.05g, 0.115mmol) were added and vigorously stirred at 100°C for 6 h. After cooling, water (10ml) was added and the layers were separated. The organic phase was washed with dilute aq. HCl (10ml) and water (10ml) subsequently. The toluene solution was dried (Na_2SO_4) then evaporated to dryness. The crude product was triturated with water to give **9a** or **10a** as white powders which were purified by recrystallization. The **9b, 10b** thioamides were prepared from **9a, 10a** with Lawesson reagent (toluene, 110°C, 5h) according to ref..[20]

9a: yield: 88%, mp: 333-335°C (BuOH). Anal. calcd. for: $C_{54}H_{70}N_2O_6$ (843.16): C 76.92, H 8.37, N 3.32, Found: C 77.11 H 8.33 N 3.34. EI MS *m/z* 842 (99%) $[M]^{+\bullet}$ Positive FAB MS *m/z* 843 (100%) $[M+H]^+$ Negative FAB MS *m/z* 841 (100%) $[M-H]^-$ ^1H NMR δ: 9.75 (t, 2H, NH), 7.14 (s, 2H, ArH), 7.13 (s, 2H, ArH), 6.82 (s, 2H, ArH), 6.78 (s, 2H, ArH), 4.24 and 3.32 (d, J=12.0, 4H, $ArCH_2Ar$), 4.28 and 3.30 (d, J=12.5, 4H, $ArCH_2Ar$), 5.16 (d, 2H, OCH_2), 3.92 (d, 2H, OCH_2), 3.70 (m, 2H, NCH_2), 3.68 (t, 2H, NCH_2), 2.33 (q, 2H, CH_2), 2.09 (d, 2H, CH_2), 4.16 (m, 4H, OCH_2), 3.96 (m, 4H, OCH_2), 1.28 and 0.94 (s, 18H each, Bu^t)

9b: yield: 91%, mp: 285-287°C (BuOH). Anal. calcd. for: $C_{54}H_{70}N_2O_4S_2$ (875.29): C 74.10, H 8.06, N 3.20, Found: C 74.32 H 8.11 N 3.15. EI MS *m/z* 874 (100%) $[M]^{+\bullet}$ Positive FAB MS *m/z* 875 (98%) $[M+H]^+$ ^1H NMR δ: 11.52 (t, 2H, NH), 7.14 (s, 4H, ArH), 6.81 (s, 2H, ArH), 6.79 (s, 2H, ArH), 4.24 and 3.36 (d, J=12.5, 4H, $ArCH_2Ar$), 4.07 and 3.29 (d, J=12.8, 4H, $ArCH_2Ar$), 5.53 (d, 2H, OCH_2), 4.37 (d, 2H, OCH_2), 3.99 (t, 2H, NCH_2), 3.90 (t, 2H, NCH_2), 2.47 (q, 2H, CH_2), 2.19 (d, 2H, CH_2), 4.20 (m, 4H, OCH_2), 3.99 (m, 4H, OCH_2), 1.28 and 0.93 (s,18H each, Bu^t)

10a: yield: 73%, mp: >400°C (BuOH). Anal. calcd. for: $C_{38}H_{38}N_2O_6$ (618.73): C 73.77, H 6.19, N 4.53, Found: C 73.46 H 6.23 N 4.45 ^1H NMR δ: 9.65 (t, 2H, NH), 7.17 (d, 2H, ArH), 7.09 (d, 2H, ArH), 7.07 (d, 2H, ArH), 7.03 (d, 2H, ArH), 6.86 (t, 2H, ArH), 6.78 (t, 2H, ArH), 4.25 and 3.42 (d, J=12.6, 4H, $ArCH_2Ar$), 4.29 and 3.40 (d, J=12.3, 4H, $ArCH_2Ar$), 4.95 (s, 2H, OCH_2), 3.96 (s, 2H, OCH_2), 3.80 (t, 2H, NCH_2), 3.56 (t, 2H, NCH_2), 2.40 (q, 2H, CH_2), 2.19 (q, 2H, CH_2), 3.96 (m, 4H, OCH_2), 4.05 (m, 4H, OCH_2)

10b: yield: 95%, mp: 306-308°C Anal. calcd. for: $C_{38}H_{38}N_2O_4S_2$ (650.86): C 70.13, H 5.88, N 4.30, Found: C 70.36 H 5.79 N 4.36 ^1H NMR δ: 11.48 (t, 2H, NH), 7.16 (d, 2H, ArH), 7.10 (d, 2H, ArH), 7.04 (d, 2H, ArH), 7.01 (d, 2H, ArH), 6.87 (t, 2H, ArH), 6.78 (t, 2H, ArH), 4.31 and 3.44 (d, J=12.4, 4H, $ArCH_2Ar$), 4.10 and 3.39 (d, J=12.7, 4H, $ArCH_2Ar$), 5.40 (s, 2H, OCH_2), 4.36 (s, 2H, OCH_2), 3.96 (t, 2H, NCH_2), 3.85 (t, 2H, NCH_2), 2.48 (q, 2H, CH_2), 2.20 (q, 2H, CH_2), 4.08 (m, 4H, OCH_2), 3.97 (m, 4H, OCH_2)

5,11,17,23-Tetra-tert-butyl-25,27-bis(ethoxycarbonylpropoxy)-26,28-dihydroxycalix[4]arene (11b) and 5,11,17,23-Tetra-tert-butyl-25,27-bis(ethoxycarbonylbutoxy)-26,28-dihydroxycalix[4]arene (11c)

To a suspension of p-tert-butylcalix[4]arene (6.48g, 10mmol) in DMF (100ml) $Br(CH_2)_3COOEt$ or $Br(CH_2)_4COOEt$ (20mmol) and K_2CO_3 (3.6g, 26mmol) were added and stirred at 70°C for 24 h. After cooling the solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (100ml), washed with dilute HCl and water, subsequently. The organic phase was dried (Na_2SO_4) then evaporated to dryness to give crude products purified by trituration with MeOH.

(d, J=11.5, 2H, OCH_2Ph), 4.89 (d, J=13.5, 1H, $ArCH_2Ar$), 4.79 (d, J=13.0, 1H, $ArCH_2Ar$), 4.61 and 4.48 (d, J=15.6, 2H, OCH_2CO), 4.32 (d, J=13.1, 1H, $ArCH_2Ar$), 4.31 (d, J=13.2, 1H, $ArCH_2Ar$), 4.27 (q, 1H, CH_2O), 4.26 (q, 1H, CH_2O), 3.98 (q, 1H, CH_2O), 3.92 (q, 1H, CH_2O), 3.27 (d, J=13.5, 1H, $ArCH_2Ar$), 3.24 (d, J=13.2, 1H, $ArCH_2Ar$), 3.22 (d, J=13.1, 2H, $ArCH_2Ar$), 1.32 (m, 3+18H, CH_3, Bu^t), 1.17 (t, 3H, CH_3), 0.88 and 0.84 (s, 9H each, Bu^t)

Debenzylation of the above compound (2.0g, 2.2mmol) was carried out in dry $CHCl_3$ (60ml) with Me_3SiBr (0.3ml, 2.2mmol) at reflux temperature (3h) and the reaction mixture was washed with dilute aq. HCl (20ml) and water (20ml), subsequently. The solution was dried (Na_2SO_4) then evaporated to dryness. The crude product was triturated with methanol and 1.7g (94%) **15** was obtained, mp: 183-185°C (BuOH), ^1H NMR δ: 8.56 (s, 2H, OH), 6.96 (d, J=2.0, 2H, ArH), 6.93 (d, J=2.0, 2H, ArH), 6.86 (d, J=2.0, 4H, ArH), 5.10 and 4.67 (d, J=16.9, 4H, OCH_2), 4.80 (d, J=13.0, 1H, $ArCH_2Ar$), 4.49 (d, J=13.2, 2H, $ArCH_2Ar$), 4.32 (m, 4H, OCH_2), 4.33 (d, J=13.0, 1H, $ArCH_2Ar$), 3.37 (d, J=13.0, 1H, $ArCH_2Ar$), 3.34 (d, J=13.2, 2H, $ArCH_2Ar$), 3.30 (d, J=13.0, 1H, $ArCH_2Ar$), 1.36 (t, 6H, CH_3), 1.20 and 1.06 (s, 18H each, Bu^t)

*Synthesis of **18a,b** doubly capped calixarenes (regioisomer B)*

The amidation of **15** with ethanolamine to afford **16** followed by the chlorination to **17**, intramolecular cyclization to **18a** and sulfur exchange to **18b** were carried out exactly in the same way as described for the regioisomer **A.**

16: yield: 93% mp: 229-232°C, ^1H NMR δ: 9.41 (br., 2H, OH), 8.38 (t, 2H, NH), 7.02 (d, J=2.0, 2H, ArH), 7.00 (d, J=2.0, 2H, ArH), 6.97 (d, J=2.0, 4H, ArH), 4.86 and 4.21 (d, J=14.5, 4H, OCH_2), 4.37 and 3.32 (d, J=13.1, 4H, $ArCH_2Ar$), 4.30 and 3.38 (d, J=13.6, 2H, $ArCH_2Ar$), 4.24 and 3.38 (d, J=13.0, 2H, $ArCH_2Ar$), 3.75 and 3.80 (m, J_{gem}=11.3, 4H, CH_2OH), 3.58 and 3.60 (q, 4H, NCH_2), 1.88 (quintet, 4H, CH_2), 1.20 and 1.14 (s, 18H each, Bu^t)

17: yield: 69% mp: 234-236°C (EtOH), ^1H NMR δ: 9.62 (s, 2H, OH), 8.13 (t, 2H, NH), 7.05 (d, J=2.0, 2H, ArH), 7.03 (d, J=2.0, 2H, ArH), 7.00 (d, J=2.0, 4H, ArH), 4.89 and 4.26 (d, J=14.5, 4H, OCH_2), 4.40 and 3.37 (d, J=13.1, 4H, $ArCH_2Ar$), 4.35 and 3.41 (d, J=13.7, 2H, $ArCH_2Ar$), 4.26 and 3.38 (d, J=13.0, 2H, $ArCH_2Ar$), 3.68 and 3.66 (m, J=11.2, 4H, CH_2Cl), 3.62 (m, 4H, NCH_2), 2.16 (quintet, 4H, CH_2), 1.23 and 1.17 (s, 18H each, Bu^t)

18a yield: 71% mp:345-347°C (EtOH) Anal. calcd. for: $C_{54}H_{70}N_2O_6$ (843.16): C 76.92, H 8.37, N 3.32, Found: C 77.15 H 8.32 N 3.36. EI MS *m/z* 842 (100%) $[M]^{+\bullet}$ ^1H NMR δ: 9.47 (t, 2H, NH), 7.00 (s, 2H, ArH), 6.98 (s,

2H, ArH), 6.96 (s, 2H, ArH), 6.90 (s, 2H, ArH), 4.40 and 3.32 (d, J=12.3, 2H, $ArCH_2Ar$), 4.22 and 3.29 (d, J=12.7, 4H, $ArCH_2Ar$), 4.20 and 3.29 (d, J=12.5, 2H, $ArCH_2Ar$), 4.92 (d, 2H, OCH_2), 3.97 (d, 2H, OCH_2), 3.84 (m, 2H, NCH_2), 3.59 (d, 2H, NCH_2), 2.46 (q, 2H, CH_2), 2.11 (d, 2H, CH_2), 4.34 (d, 4H, OCH_2), 3.91 (t, 4H, OCH_2), 1.11 and 1.09 (s, 18H each, Bu^t)

18b yield: 68% mp:315-316°C, Anal. calcd. for: $C_{54}H_{70}N_2O_4S_2$ (875.29): C 74.10, H 8.06, N 3.20, Found: C 74.34 H 8.01 N 3.22. Positive FAB MS *m/z* 875 (85%) $[M+H]^+$ ^1H NMR δ: 11.19 (t, 2H, NH), 6.99 (s, 2H, ArH), 6.97 (s, 2H, ArH), 6.94 (s, 2H, ArH), 6.90 (s, 2H, ArH), 4.40 and 3.34 (d, J=12.0, 2H, $ArCH_2Ar$), 3.99 and 3.28 (d, J=13.2, 4H, $ArCH_2Ar$), 4.22 and 3.31 (d, J=12.8, 2H, $ArCH_2Ar$), 5.22 (d, 2H, OCH_2), 4.40 (d, 2H, OCH_2), 4.04 (t, 2H, NCH_2), 3.99 (t, 2H, NCH_2), 2.61 (q, 2H, CH_2), 2.23 (d, 2H, CH_2), 4.32 (m, 2H, OCH_2), 3.88 (t, 2H, OCH_2), 1.10 and 1.09 (s, 18H each, Bu^t)

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11b: 47%, mp: 178-180°C (BuOH) ^{1}H NMR δ: 7.63 (s, 2H, OH), 7.06 (s,4H, ArH), 6.85 (s, 4H, ArH), 4.26 and 3.33 (d, J=12.9, 8H, $ArCH_2Ar$), 4.17 (q, 4H, OCH_2), 4.06 (t, 4H, OCH_2), 2.87 (t, 4H, CH_2), 2.34 (m, 4H, CH_2), 1.30 (s, 18H, Bu^t), 1.27 (t, 3H, CH_3), 1.24 (t, 3H, CH_3), 1.01 (s, 18H, Bu^t)

11c: 53%, mp: 170-172°C (EtOH) ^{1}H NMR δ: 7.53 (s, 2H, OH), 7.06 (s,4H, ArH), 6.83 (s, 4H, ArH), 4.28 and 3.33 (d, J=13, 8H, $ArCH_2Ar$), 4.15 (q, 4H, OCH_2), 4.01 (t, 4H, OCH_2), 2.50 (t, 4H, CH_2), 2.05 (m, 8H, CH_2), 1.31 and 0.99 (s, 18H each, Bu^t), 1.25 (t, 3H, CH_3), 1.24 (t, 3H, CH_3)

5,11,17,23-Tetra-tert-butyl-25,27-bis[(N-2-hydroxyethylcarbamoyl)propoxy]-26,28-dihydroxycalix[4]arene (12b) and 5,11,17,23-tetra-tert-butyl-25,27-bis[(N-2-chloroethylcarbamoyl)propoxy]-26,28-dihydroxycalix-[4]arene (13b)

To a suspension of **11b** (4.15g, 4.75mmol) in EtOH (70ml) 20g 50% aq. KOH solution was added and refluxed for 2h. After evaporating the solvent under reduced pressure the residue was mixed with water (80ml). and acidified with dilute HCl. White crystals were precipitated which were filtered off, washed with water and EtOH, subsequently, and dried to give the respective diacid (3.9g, 100%). The crude diacid (1.03g, 1.25mmol) was chlorinated with $SOCl_2$ (3ml, 40mmol) in benzene (35ml) under reflux (2 h) to yield diacid chloride which was isolated and condensed with ethanolamine (2.54g, 41mmol) in CH_2Cl_2 (30ml) at 0°C (2h). After standard workup **12b** (1.05g, 93%, mp: 168-170°C) was obtained which was chlorinated analogously as described for compounds **7** resulting in the formation of **13b** (0.35g, 34%, mp: 176-178°C) as a white powder.
Compounds **12c** (90%, mp: 160-161°C) and **13c** (87%, mp: 98-102°C) were prepared in similar manner. The ^{1}H NMR data of **12b,c** and **13b,c** are in accordance with the 1,3-disubstituted cone structure: 6.8-7.1 (2xs, ArH), 3.2-4.3 (AB d, J=13, $ArCH_2Ar$). Attempts to cyclize **13b,c** to **14b,c** were unsuccessful.

5,11,17,23-Tetra-tert-butyl-25,26-bis(ethoxycarbonylmethoxy)-27,28-dihydroxycalix[4]arene (15)

5,11,17,23-Tetra-tert-butyl-25-benzyloxy-26,27,28-trihydroxycalix[4]arene[23] (5g, 6.77mmol), $BrCH_2$-COOEt (15.1g, 90mmol) and BaO (14g, 91.3mmol) were stirred in DMF (100ml) at room temperature for 24h. Subsequently water (150ml) was added and extracted with $CHCl_3$ (2x150ml). The layers were separeted and the organic layer was washed with water several times. After drying (Na_2SO_4) the solvent was evaporated under reduced pressure and the crude product was purified by trituration with MeOH to give 5,11,17,23-tetra-tert-butyl-25-benzyloxy-26,27-bis(ethoxycarbonylmethoxy)-28-hydroxycalix[4]arene as a white powder (4.1g, 67%): mp: 172-173°C (EtOH) ^{1}H NMR δ: 7.55 (d, 2H, ArH), 7.39 (t, 2H, ArH), 7.33 (t, 1H, ArH), 7.11 (d, J=2.0, 1H, ArH), 7.09 (d, J=2.0, 1H, ArH), 7.05 (d, J=2.0, 1H, ArH), 7.04 (d, J=2.0, 1H, ArH), 6.60 (s, 2H, ArH), 6.54 (s, 1H, ArH), 6.53 (s, 1H, ArH), 6.46 (s, 1H, OH), 5.01 and 4.85 (d, J=17.1, 2H, OCH_2CO), 4.97 and 4.88