Synthesis of potential receptor molecules by combination of upper-rim-functionalized calix[4]arenes and partly bridged resorcinarenes

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Abstract. Combination of upper-rim-1,3-difunctionalized calix[4]arenes **14**, **16**, and **18** with tri-bridged resorcinarenes **4** and **6** and A,C-di-bridged resorcinarenes **10** and **13** yields both 1/1 calix-resorcinarenes (**22–24**) and 2/1 calix-resorcinarenes (**25**, **26**). 1/1 Calix-resorcinarene **22** mainly exists as one conformer (**a**), but at low temperatures (-60°C) very small amounts ($< 5\%$) of a second conformer (**b**) can be observed. Both conformers equilibrate via rotation about one of the C(arene)–N bonds, with an activation free energy ($\Delta G^{\ddagger}$) of 13 kcal/mol. 2/1 Calix-resorcinarenes **25** and **26** are more flexible and exist as a mixture of conformers. In order to be able to rigidify the structure of 2/1 calix-resorcinarenes via rigid spacers between the calix[4]arene fragments, 1,3-di-aminocalix[4]arene derivatives **31**, **32**, and **34** were synthesized carrying nitro, carboxylic ester, and cyano groups at the unsubstituted aromatic rings. With these calix[4]arene derivatives, three new, functionalized 2/1 calix-resorcinarenes **35–37** have been synthesized.

Introduction

One of the aims of supramolecular chemistry is the mimicry of biological processes with synthetic molecules. Most synthetic receptor molecules are prepared via *de-novo* synthesis using modern synthetic methodologies, which allow almost unlimited variation. The strategy focuses on the complementarity of functional groups between receptor and guest species and aims for minimal reaction steps and molecular weights. Nature constructs biological receptors by combination of a limited number of components. Amino acids are combined to proteins, nucleosides to DNA or RNA, and monosaccharides to carbohydrates. Systematic variation of the monomer sequence gives access to an almost infinite number of different receptors. However, this is achieved at the expense of a high molecular weight.

An alternative strategy for the synthesis of artificial receptor molecules, which is a compromise between the two extremes described above, starts from medium-sized molecules that can be used as platforms to which functional groups for intermolecular interactions can be attached¹. Several components can be covalently connected to build up larger structures. The components must have a well-defined shape, be readily available from cheap starting materials and easy to functionalize. Representatives of such molecular building blocks are calix[4]arenes^{2–4}, cyclodextrins⁵, and resorcinarenes^{6–8}.

Using this modular approach we have synthesized several types of new receptor molecules, each exhibiting specific complexation properties. Calix[4]crown ethers bridged at the lower rim with a polyethylene glycol chain show very high association constants for K^+ ($8.9 \cdot 10^9 \text{ M}^{-1}$ in CDCl_3)^{9–12}. Kinetically stable Rb^+ complexes (half-life time in CDCl_3 of 180 days) have been prepared from calixspherands, calix[4]arenes bridged at the lower rim

with a *m*-terphenyl moiety^{13,14}. We have also combined calix[4]arenes with a uranyl-containing salophen unit¹⁵ for the synthesis of lipophilic carriers for selective transport of urea through supported liquid membranes¹⁶ and a ditopic receptor able to selectively complex NaH_2PO_4 was synthesized by connecting a salophen unit at the upper rim of a calix[4]arene tetraester¹⁷. Recently, we have combined calix[4]arenes with resorcinol-based cavitands in the synthesis of molecules with rigid cavities of nanosize dimensions¹⁸, and for the synthesis of calix[4]arene-based carcerands¹⁹.

In this paper we describe the combination of calix[4]arenes with partly-bridged resorcinarenes. Partly-bridged resorcinarenes were initially isolated by Cram et al. as side-products in the synthesis of resorcinol-based cavitands^{20,21}. As part of a study on the selective functionalization of resorcinarenes²², we have optimized the reaction conditions for the synthesis of both tri-bridged resorcinarene **1**²³ (54%) and A,C-di-bridged resorcinarene **7** (29%)²⁴. These compounds possess free phenolic hydroxyl groups which render them suitable candidates for combination with upper-rim-functionalized calix[4]arenes in order to give molecules with large hydrophobic surfaces. Such molecules might be the starting materials for receptors for hydrophobic organic guest species like steroids.

Results and discussion

Synthesis of calix-resorcinarenes

The easiest way to connect partly bridged resorcinarenes to upper-rim-functionalized calix[4]arenes is to react the phenolic hydroxyl groups of the resorcinarene via a nucleophilic substitution reaction with electrophilic sites at the upper rim of the calix[4]arene. However, the reactivity of

electrophilic groups in electron-rich aromatic rings like those in cavitands and calix[4]arenes is rather low^{25,26}. For this reason we decided to introduce nucleophilic groups at the upper rim of calix[4]arenes, *viz.* hydroxyl or amino groups. In order to connect the two building blocks, we have used a spacer containing two electrophilic end groups. A spacer that meets this requirement is the $-\text{CH}_2\text{C}(\text{O})-$ spacer. It can be easily incorporated using reagents like $\text{BrCH}_2\text{C}(\text{O})\text{OMe}$ or $\text{ClCH}_2\text{C}(\text{O})\text{Cl}$.

First of all, the combination of tri-bridged resorcinarene **1**²⁴ with several 1,3-di-functionalized calix[4]arenes was studied. Subsequently A,C-di-bridged resorcinarenes like **7**²⁴, containing two pairs of phenolic groups, were studied for the combination with 1,3- and 1,2-diaminocalix[4]arenes. Diol **1** was converted to diester **2** by reaction with two equivalents of $\text{BrCH}_2\text{C}(\text{O})\text{OMe}$. Diester **2** was hydrolyzed under basic conditions to give diacid **3** which, upon treatment with oxalyl chloride gave the corresponding diacid dichloride **4**. The overall yield was essentially quantitative. Analogously, tetrol **7** and tetraester **11**²⁴ were converted to the corresponding tetraacid tetrachlorides **10** and **13**, respectively, in high yields.

Upper-rim-1,3-difunctionalized calix[4]arenes **14**²⁷, **16**²⁸,

and **17**²⁹ were prepared according to literature procedures. For the synthesis of 1,2-dinitrocalix[4]arene **19**²⁹ a slightly modified literature procedure was used (see Experimental). Reduction of 1,2-dinitro **19** with hydrazine/Raney Ni gave impure 1,2-diamine **21**, which was purified by flash column chromatography after conversion to the corresponding bis(phthalimide) **20** by refluxing impure **21** with phthalic anhydride in toluene. After removal of the phthalimide groups, pure 1,2-diamine **21** was obtained in 40% yield.

The coupling of diacid dichloride **4** with 1,3-diamine **14** was performed under moderately high-dilution conditions in CH_2Cl_2 using NEt_3 as a base to give 1/1 calix-resorcinarene **22** in 46% yield. The same yield was obtained when diamine **14** was first acylated with $\text{ClCH}_2\text{C}(\text{O})\text{Cl}$ to **15** and subsequent reaction with diol **1**. Reaction of diacid dichloride **4** with 1,3-diol **16** under the same conditions used for the synthesis of **22** gave 1/1 calix-resorcinarene **24** in only 13% yield. Stronger bases like NaH did not improve the yield. This much lower yield is attributed to the enhanced flexibility of diol **16** as a result of the presence of the additional methylene group between the calix fragment and the reactive hydroxyl group. The fact

Chart 1.

that this difference in rigidity decreases the yield to such an extent, emphasizes the fact that compounds **4** and **14** are highly preorganized for the formation of calix-resorcinarene **22**. When NaH in combination with Cs_2CO_3 was used as a base, **24** was obtained in 48% yield. This increased yield is the result of the well known cesium-template effect³⁰. In the same way 2/1 calix-resorcinarenes **25** and **26** were synthesized in 20% and 53% yield, starting from tetraacid tetrachlorides **10** and **13** and diamines **14** and **18**, respectively. All compounds gave satisfactory MS-FAB spectra and elemental analyses.

Conformational properties of calix-resorcinarenes

The ^1H -NMR spectra of the resorcinarene diester **2** and diacid **3** show an AB system for the two methylene protons adjacent to the carbonyl with $\Delta\delta$ 0.4 ppm, which might indicate that rotation about the $\text{ArO}-\text{CH}_2$ bond is restricted in these compounds. CPK models show that the bulky bromo atoms considerably hinder this rotation. Experimental evidence for this was found in the synthesis of diacid **5**, prepared by debromination of tetrabromo diacid **3** with KOH/Raney-Ni in MeOH. In diacid **5** the difference in chemical shift between the two methylene protons is reduced to 0.13 ppm. This residual difference is most

probably caused by the fact that the carboxymethoxy moieties sterically hinder each other in rotation about the $\text{ArO}-\text{CH}_2$ bond.

The presence of the bromo atoms and the hindered rotation about the $\text{ArO}-\text{CH}_2$ bond play an important role in determining the structure of 1/1 calix-resorcinarene **22** (*vide infra*). This compound is not completely rigid. Variable-temperature ^1H -NMR experiments showed that **22** exists as a mixture of two conformers. An activation free energy ($\Delta G^\ddagger$) of 13 kcal/mol at -58°C for interconversion was determined by ^1H -NMR EXSY. At low temperatures ($< -58^\circ\text{C}$), both conformers can be observed separately, but around 0°C , the spectrum coalesces to give an averaged spectrum at room temperature. The two conformers are not present in equal amounts. At -58°C , the minor conformer is only present in very small amounts ($< 5\%$). The spectrum at 60°C strongly resembles that of the major conformer at low temperature, which indicates that at higher temperatures compound **22** is almost exclusively present in this conformation.

The major conformer shows only a single resonance for the amide protons, indicating that, precluding accidental isochrony, both spacers are chemically equivalent. The two singlets at 5.45 and 6.7 ppm correspond to the aromatic protons *ortho* to the NH (denoted as *o*-NHArH).

Figure 1. Structure of conformers *a* and *b* of 1/1 calix-resorcinarene **22** together with part of the 400-MHz ^1H -NMR EXSY spectrum at -58°C revealing the equilibrium between the two conformers.

The large difference in chemical shift between these two signals is the result of hindered rotation about the C(arene)–N bond. As a consequence of this hindered rotation half of the *o*-NHArH protons are located in relatively close proximity to the amide protons, while the other *o*-NHArH protons are close to the carbonyl moiety. Due to the magnetic anisotropy of the carbonyl moiety³¹, the *o*-NHArH protons close to the carbonyl moiety resonate at much lower field (6.7 ppm) compared with the other *o*-NHArH protons (5.45 ppm). The close proximity of the *o*-NHArH protons resonating at 5.45 ppm and the amide protons was proven by NOESY, showing a connectivity between the signal at 5.45 ppm and the amide protons, while an NOE between the signal at 6.7 ppm and the amide protons was not observed. The marked upfield shift of all *o*-NHArH protons is caused by the fact that the calix[4]arene fragment in **22** is completely frozen in a “pinched” cone conformation³². In this conformation the B and D rings are almost co-planar, while the aromatic rings carrying the amide spacers (A and C ring) are almost parallel. As a consequence the *o*-NHArH protons point directly into the electron-rich region of the B and D rings causing an upfield shift. Similar upfield shifts have been reported for calix[4]arene derivatives that are fixed in a pinched cone conformation^{28,33}. The highest upfield shifts were observed for calix[4]arenes bridged at the upper rim with ethylene or ethine spacers³⁴. In these cases, the aromatic protons *ortho* to the bridge resonate at 5.35 ppm.

The only structure that fully explains the ¹H-NMR data is that of conformer **a** (Figure 1). In this structure the methylene groups adjacent to the carbonyl moieties point away from the resorcinarene cavity. The structure in which the methylene groups are positioned in-between the two bromo atoms is impossible for steric reasons. The ¹H-NMR spectrum at –60°C exhibits two singlets for the amide protons (7.6 and 7.8 ppm) and four signals for the *o*-NHArH protons (5.7, 5.8, 6.3, and 6.75 ppm) of the minor conformer, which proves that in this conformer the spacers are chemically non-equivalent. The interconversion between the two conformers was studied by ¹H-NMR EXSY. The spectrum (see Figure 1) reveals that the *o*-NHArH protons of conformer **a** (5.45 ppm), located

close to the amide protons, exchange with the protons of the minor conformer resonating at 5.8 ppm (close to amide protons) and 6.75 ppm (close to carbonyl moiety). Similarly, the *o*-NHArH protons of conformer **a** (6.7 ppm), located close to the carbonyl moiety, exchange with the protons of the minor conformer resonating at 6.3 ppm (close to the carbonyl moiety) and 5.7 ppm (close to the NH). These data strongly suggest that both conformers equilibrate via rotation about one of the C(arene)–N bonds. This leads to the conclusion that conformer **b** (see Figure 1) represents the structure of the minor conformer. Molecular-mechanics calculations have shown that conformers **a** and **b** are the lowest energy structures of a number of possible conformations, with a difference in total energy between conformer **a** and the next lowest energy conformation of approximately 8 kcal/mol.

As was stated before, the bromo substituents play an important role in determining the structure of 1/1 calix-resorcinarene **22**. In order to prove this, 1/1 calix-resorcinarene **23**, in which the four bromo atoms have been substituted for hydrogens, was synthesized in 42% yield starting from diacid dichloride **6** and diamine **14** according to the procedure described for 1/1 calix-resorcinarene **22** (*vide supra*). The ¹H-NMR spectrum of **23** is very complicated and most probably reflects a mixture of many different conformers. Apparently, removal of the bromo atoms destabilizes conformer **a** considerably, leading to many other conformers. A possible explanation for the largely different conformational distribution of 1/1 calix-resorcinarene **23** might be that the bromo atoms in 1/1 calix-resorcinarene **22** participate in hydrogen bonding with the amide protons, something that has been observed before for halogen atoms³⁵, leading to stabilization of conformer **a**.

2/1 Calix-resorcinarenes **25** and **26** exhibit conformational behavior very similar to that of 1/1 calix-resorcinarene **22**. The ¹H-NMR spectrum at room temperature shows two broad singlets at 5.9 and 6.5 ppm for the *o*-NHArH protons. These signals are much less far apart than in the corresponding 1/1 calix-resorcinarene **22**, indicating that conformations in which the spacers are arranged asymmetrically, are much more populated than in case of **22**. This may be explained by an increase in

flexibility due to the additional replacement of a O-CH₂-O bridge for a "calixarene bridge". The ¹H-NMR spectrum at -60°C confirms this observation as it represents a mixture of more than two equally populated conformers. The complexity of the spectrum prevents determination of the appropriate thermodynamic and kinetic parameters for the different interconversion processes.

1/1 Calix-resorcinarene diester **24** is a much more flexible molecule. No hydrogen bonds can be formed in this structure and elongation of the connecting spacers with one atom gives the molecule enhanced rotational freedom. This can be seen from the ¹H-NMR spectrum in which the aromatic protons *ortho* to the CH₂O spacer are almost identical ($\Delta\delta$ 0.02) and the ArCH₂O protons give a singlet above room temperature, indicating that rotation about the ArC-CH₂ and the CH₂-O bonds is fast on the ¹H-NMR chemical-shift timescale at this temperature. This rotation becomes slightly hindered below room temperature as can be seen from the transformation of the singlet for the ArCH₂O protons into an AB quartet. As a result of the flexibility of this compound it was not studied further³⁶.

Synthesis of functionalized calix-resorcinarenes

Subsequently, the introduction of functional groups at the unsubstituted aromatic rings of the two calix[4]arene fragments (see Chart 1) was investigated because functional groups at these positions can be used to introduce a rigid spacer in between the calix[4]arene fragments. In principle, the introduction of a spacer could also be used to shield the cavity of calix-resorcinarene **26** or to introduce catalytically active sites in close proximity to the molecular cavity.

Functionalization of calix-resorcinarenes **22**, **25**, and **26** or 1,3-diamines **14** and **18** at the unsubstituted aromatic rings is confronted with the problem that these molecules preferentially react at the positions *ortho* to the amide or amino groups in electrophilic aromatic substitution reactions, due to the electron-releasing effect of the amido or amino substituents^{37,38}. Therefore, we have developed new procedures for the introduction of amino and carboxylic ester groups at the upper rim of calix[4]arenes in the presence of nitro groups, as described recently⁹. The methodology starts with the iodination of 1,3-dinitro-calix[4]arenes **17**²⁹ and **27**⁴⁰. Treatment of **17** and **27** with 2.5 equivalents of AgCF₃COO/I₂ in CHCl₃ gave 1,3-diiodo-2,4-dinitrocalix[4]arene **28** and **29** in 93% and 99% yield, respectively.

The iodo atoms in **28** were substituted for amino groups using the Gabriel reaction⁴¹. To the best of our knowledge this reaction has hardly been studied for aromatic compounds. When **28** was reacted with 1.5 equivalents of Cu₂O and 3.0 equivalents of phthalimide in refluxing collidine for 24 h, diphthalimide **30** was isolated in 70% yield. Deprotection of the masked amino groups in **30** with hydrazine and HCl in EtOH⁴² gave **31** in quantitative yield. The signal at 6.05 ppm in the ¹H-NMR spectrum of **31** is characteristic of aromatic protons *ortho* to an amino group.

Substitution of the iodo atoms in 1,3-diiodo-2,4-dinitrocalix[4]arene **29** for carboxylic ester groups was performed using the procedure of Heck et al.⁴³ by reaction with CO and MeOH in anisole at 100°C and 10 atm. for 24 h using NEt₃ as a base and Pd(PPh₃)₂Cl₂ as a catalyst³⁹. Subsequent reduction of the nitro groups²⁷ afforded diamine **32** in 74% overall yield.

Substitution of the iodo groups in calix[4]arene **28** for cyano groups was performed using the Rosenmund-von Braun reaction⁴⁴. Reacting **28** with 3.5 equivalents of CuCN in refluxing 1-methyl-2-pyrrolidinone gave dicyanide **33** in quantitative yield. Reduction of the nitro

groups in **33** with hydrazine/Raney Ni²⁷ proceeded smoothly in the presence of the cyano groups to give **34** in 73% yield.

Reaction of tetraacid tetrachloride **13** with difunctionalized 1,3-diamines **31**, **32**, and **34** under the same reaction conditions as used for the synthesis of 1/1 calix-resorcinarene **22**, gave 2/1 calix-resorcinarenes **35–37** in 22%, 25%, and 13% yield, respectively. Although the yields of **35–37** are somewhat lower than that of unsubstituted 2/1 calix-resorcinarene **26** (53%), it can be concluded that the presence of the carboxylic ester, nitro, and cyano groups does not severely hinder the formation of 2/1 calix-resorcinarenes. The ¹H-NMR spectra of **35–37** are very similar to those of **25** and **26**. Apparently, the introduction of functional groups does not alter the structure of these host molecules to a considerable extent.

Conclusions

Combination of upper-rim-functionalized calix[4]arenes with partly bridged resorcinarenes provides the synthetic methodology for a new class of potential receptor molecules with large concave surfaces. Both tri-bridged resorcinarenes **4** and **6** and A,C-di-bridged resorcinarenes **10** and **13**, functionalized with chlorocarbonylmethoxy groups, were coupled with 1,3-diaminocalix[4]arene **14** and **18**. 1/1 Calix-resorcinarene **22** mainly exists as one conformer, but at low temperatures a second conformer can be observed, which is only present in small amounts (<5%). Both conformers equilibrate via rotation about one of the C(arene)-N bonds, with an activation free energy ($\Delta G^\ddagger$) of 13 kcal/mol. 2/1 Calix-resorcinarenes **25** and **26** are present in at least three different conformations of comparable energy. With the ultimate objective to rigidify the structure of 2/1 calix-resorcinarenes, several 1,3-diaminocalix[4]arenes, functionalized at the residual aromatic rings with carboxylic ester, nitro, and cyano substituents, were synthesized. With these calix[4]arene derivatives, three new functionalized 2/1 calix-resorcinarenes **35–37** were synthesized.

Experimental

General

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ¹H-NMR spectra were recorded in CDCl₃ (unless otherwise indicated) with Me₄Si as internal standard on a Bruker AC 250 spectrometer. Fast-atom-bombardment (FAB) mass spectra were recorded with a Finnigan MAT 90 spectrometer using (*m*-NBA) as a matrix. THF was freshly distilled from Na/benzophenone-ketyl and hexane (referring to petroleum ether with b.p. 60–80°C), CH₂Cl₂, and EtOAc from K₂CO₃. CH₃CN was dried over 3 Å molecular sieves for at least 3 days. NaH was a 80% dispersion in mineral oil and was used as such, unless otherwise stated. Other chemicals were of reagent-grade and were used without further purification. Flash column chromatography was performed with silica gel 60 (0.040–0.063 mm, 230–400 mesh) or when necessary silica gel 60H (0.005–0.040 mm) from Merck. All reactions were carried out in an argon atmosphere. Dropwise addition over a period of several hours was always carried out with a perfusor. Partly bridged resorcinarenes **1**²⁴, **7**²⁴, and **11**²⁴ and upper-rim-functionalized calix[4]arenes **14**²⁷, **16**²⁸, **17**²⁹, **27**⁴⁰, **29**³⁹, and **32**³⁹ were prepared according to literature procedures.

4,8,12,16-Tetrabromo-3,17-bis[(methoxycarbonyl)methoxy]-20,22,24,25-tetrakis(2-phenylethyl)-2,18-methano-20H,22H,24H-dibenzo-[d,d']-[1,3]dioxocino[5,4-i:7,8-i']bis[1,3]benzodioxocin (**2**)

To a suspension of diol **1** (1.00 g, 0.80 mmol) and K₂CO₃ (1.1 g, 8.0 mmol) in CH₃CN (25 ml) was added methyl bromoacetate (0.16 ml, 1.7 mmol) and the mixture was refluxed for 2½ h. After evaporation of the solvent, the residue was taken up in CH₂Cl₂ (50 ml), succes-

sively washed with 1N HCl (20 ml), H₂O (3 × 10 ml), and brine (10 ml), and dried over MgSO₄. The solvent was removed in *vacuo* to give diester **2** as a white solid (1.05 g, 94%); m.p. 153–155°C (CH₂Cl₂/MeOH). Anal. calcd. for C₆₉H₆₀Br₄O₁₂·0.3H₂O (1400.81): C 58.93, H 4.34; found: C 58.55, H 4.30%. Karl–Fischer titration calcd. for 0.3 H₂O: 0.38; found: 0.38%. ¹H-NMR: δ 2.3–2.8, m, 16H, CH(CH₂)₂C₆H₅; 3.81, s, 6H, C(O)OCH₃; 4.38, 4.46, 2d, J 7.4 Hz, 3H, inner OCH₂O; 4.53 and 4.76, ABq, J 15.4 Hz, 4H, OCH₂C(O); 4.9–5.1, m, 3H, CH(CH₂)₂C₆H₅; 5.49, t, J 7.7 Hz, 1H, CH(CH₂)₂C₆H₅; 5.99, 6.01, 2d, J 7.4 Hz, 3H, outer OCH₂O; 7.1–7.3, m, 24H, CH(CH₂)₂C₆H₅ + *p*-BrArH. MS (FAB), *m/z* 1400 (M⁺).

4,8,12,16-Tetrabromo-3,17-bis[(hydroxycarbonyl)methoxy]-20,22,24,25-tetrakis(2-phenylethyl)-2,18-methano-20H,22H,24H-dibenzo-[d,d']-[1,3]-dioxocino[5,4-i:7,8-i]bis[1,3]benzodioxocin (3)

A solution of diester **2** (0.72 g, 0.51 mmol) in a 1:1 (v/v) mixture of THF (20 ml) and 2N NaOH (20 ml) was stirred at room temperature for 17 h. The solution was subsequently acidified with 1N HCl (40 ml) and a white precipitate was formed which redissolved upon the addition of CH₂Cl₂ (50 ml). The two resulting layers were separated, the organic layer was successively washed with H₂O (3 × 10 ml) and brine (10 ml), and dried over MgSO₄. Evaporation of the solvent gave diacid **3** (0.70 g, > 99%) as a white solid; m.p. 192–194°C. Anal. calcd. for C₆₇H₅₆Br₄O₁₂ (1372.76): C 58.62, H 4.11; found: C 58.37, H 4.44%. ¹H-NMR: δ 2.3–2.8, m, 16H, CH(CH₂)₂C₆H₅; 4.33, 4.42, 2d, J 7.5 Hz, 3H, inner OCH₂O; 4.43 and 4.80, ABq, J 16.2 Hz, 4H, OCH₂C(O); 4.96, 5.44, 2t, J 7.6 and 7.3 Hz, 4H (3:1), CH(CH₂)₂C₆H₅; 5.98, d, J 7.4 Hz, 3H, outer OCH₂O; 7.0–7.3, m, 24H, CH(CH₂)₂C₆H₅ + *p*-BrArH. MS (FAB), *m/z* 1372 (M⁺).

General procedure for the synthesis of diacid dichlorides **4 and **6** and tetraacid tetrachlorides **10** and **13****

To a solution/suspension of the appropriate diacid or tetraacid in dry CH₂Cl₂ was added oxalyl chloride (20 equivalents) and the reaction mixture was refluxed for 1 h. After evaporation of the solvent and careful drying under vacuum, the corresponding diacid dichloride or tetraacid tetrachloride was isolated in essentially quantitative yield and used without further purification or characterization.

3,17-Bis[(hydroxycarbonyl)methoxy]-20,22,24,25-tetrakis(2-phenylethyl)-2,18-methano-20H,22H,24H-dibenzo-[d,d']-[1,3]-dioxocino[5,4-i:7,8-i]bis[1,3]benzodioxocin (5)

To a suspension of diacid **3** (0.69 g, 0.50 mmol) and KOH (0.34 g, 6.0 mmol) in MeOH (30 ml) was added a catalytic amount of Raney Ni and the mixture was stirred for 24 h at room temperature in a H₂-atmosphere. CH₂Cl₂ was added until the milky solution became clear and the Raney Ni was filtered off using Hyflo. The filtrate was evaporated to dryness and the residue was taken up in CH₂Cl₂ (50 ml). The resulting suspension was shaken with 1 N HCl until the solution became clear, whereupon it was washed with H₂O (3 × 10 ml) and brine (10 ml) and dried over MgSO₄. After evaporation of the solvent diacid **5** was obtained (0.53 g, 78%); the compound decomposes before melting. Anal. calcd. for C₆₇H₆₀O₁₂·1.25H₂O (1057.15): C 74.53, H 5.84; found: C 74.62, H 5.84%. Karl–Fischer titration calcd. for 1.25 H₂O: 2.09; found: 2.17%. ¹H-NMR: δ 2.3–2.7, m, 16H, CH(CH₂)₂C₆H₅; 4.28, 4.37, 2d, J 7.3 Hz, 3H, inner OCH₂O; 4.39 and 4.52, ABq, J 16.5 Hz, 4H, OCH₂C(O); 4.75, 5.02, 2t, J 7.6 and 7.8 Hz, 4H (3:1), CH(CH₂)₂C₆H₅; 6.28, 6.47, 2s, 4H, *o*-OCH₂OArH; 5.67, d, J 7.2 Hz, 3H, outer OCH₂O; 7.0–7.3, m, 24H, CH(CH₂)₂C₆H₅ + *m*-OCH₂OArH. MS (FAB), *m/z* 1057 (M⁺).

5,11,17,23-Tetrabromo-4,12,16,24-tetrakis[(methoxycarbonyl)methoxy]-2,14,27,32-tetrakis-(2-phenylethyl)-7,9,19,21-tetraoxaheptacyclo-[13.9.5.5^{3,13}.0^{6,33}.0^{10,31}.0^{18,28}.0^{22,26}]tetratriaconta-3,5,10,12,15,17,22,24,25,28,30,33-dodecaene (8)

The reaction was carried out following the procedure for diester **2** using tetrol **7** (0.29 g, 0.23 mmol), K₂CO₃ (0.32 g, 2.3 mmol), methyl bromoacetate (0.10 ml, 1.1 mmol), and CH₃CN (15 ml) to give pure tetraester **8** (0.26 g, 73%) as a white solid; m.p. 213–215°C (CH₂Cl₂/EtOH). Anal. calcd. for C₇₄H₆₈Br₄O₁₆ (1532.92): C 57.98, H 4.47; found: C 57.95, H 4.45%. ¹H-NMR: δ 2.2–2.8, m, 16H, CH(CH₂)₂C₆H₅; 3.83, s, 12H, C(O)OCH₃; 4.32 and 4.75, ABq, J 15.1 Hz, 8H, OCH₂C(O); 4.38, d, J 7.5 Hz, 2H, inner OCH₂O; 5.31, 5.49, 2t, J 7.0 Hz, 4H, CH(CH₂)₂C₆H₅; 6.02, d, J 7.4 Hz, 2H, outer OCH₂O; 7.0–7.3, m, 20H, CH(CH₂)₂C₆H₅; 7.51, s, 4H, *p*-BrArH. MS (FAB), *m/z* 1533 [M + H]⁺.

5,11,17,23-Tetrabromo-4,12,16,24-tetrakis[(hydroxycarbonyl)methoxy]-2,14,27,32-tetrakis-(2-phenylethyl)-7,9,19,21-tetraoxaheptacyclo-[13.9.5.5^{3,13}.0^{6,33}.0^{10,31}.0^{18,28}.0^{22,26}]tetratriaconta-3,5,10,12,15,17,22,24,25,28,30,33-dodecaene (9)

A solution of tetraester **8** (0.26 g, 0.17 mmol) in a 1:1 (v/v) mixture of THF (10 ml) and 2N NaOH (10 ml) was stirred for 24 h at room temperature. The cloudy solution was acidified with 1N HCl (25 ml) whereupon the THF was removed under vacuum. The resulting suspension was filtered, the solid was thoroughly washed with H₂O and dried at 100°C under vacuum to give tetraacid **9** (0.22 g, 88%); m.p. > 290°C. Anal. calcd. for C₇₀H₆₀Br₄O₁₆·1.5H₂O (1476.82): C 55.90, H 4.22; found: C 55.81, H 4.09%. Karl–Fischer titration calcd. for 1.5 H₂O: 1.80; found: 1.73%. ¹H-NMR (DMSO-*d*₆): δ 2.4–2.8, m, 16H, CH(CH₂)₂C₆H₅; 4.40 and 4.56, ABq, J 15.4 Hz, 8H, OCH₂C(O); 4.42, d, J 7.6 Hz, 2H, inner OCH₂O; 4.70, 5.45, 2t, J 7.7 Hz, 4H, CH(CH₂)₂C₆H₅; 5.97, d, J 7.6 Hz, 2H, outer OCH₂O; 7.0–7.3, m, 20H, CH(CH₂)₂C₆H₅; 7.79, s, 4H, *p*-BrArH. MS (FAB), *m/z* 1499 [M + Na]⁺.

5,11,17,23-Tetrabromo-4,12,16,24-tetrakis[(hydroxycarbonyl)methoxy]-2,14,27,32-tetramethyl-7,9,19,21-tetraoxaheptacyclo-[13.9.5.5^{3,13}.0^{6,33}.0^{10,31}.0^{18,28}.0^{22,26}]tetratriaconta-3,5,10,12,15,17,22,24,25,28,30,33-dodecaene (12)

The reaction was carried out according to the procedure described for tetraacid **9** using tetraester **11** (1.75 g, 1.49 mmol) in THF (150 ml) and 2 N NaOH (150 ml) to give tetraacid **12** (1.65 g, 99%) as a white solid; m.p. > 300°C. Anal. calcd. for C₄₂H₃₆Br₄O₁₆·3.25H₂O (1116.35): C 42.93, H 3.65; found: C 43.32, H 3.59%. Karl–Fischer titration calcd. for 3.2 H₂O: 4.98; found: 4.94%. ¹H-NMR: δ 1.58, 1.91, 2d, J 7.3 Hz, 12H, CHCH₃; 4.40, d, J 7.5 Hz, 2H, inner OCH₂O; 4.45 and 4.64, ABq, J 16.1 Hz, 8H, OCH₂C(O); 5.1–5.3, m, 4H, CHCH₃; 6.03, d, J 7.5 Hz, 2H, outer OCH₂O; 7.60, s, 4H, *p*-BrArH. MS (FAB), *m/z* 1117 [M + H]⁺.

5,17-Bis(2-chloroacetamido)-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (15)

To a solution of 1,3-diamine **14** (0.3 g, 0.4 mmol) in CH₂Cl₂ (10 ml) was added successively NET₃ (0.17 ml, 1.2 mmol) and ClC(O)CH₂Cl (0.10 ml, 1.2 mmol). After stirring the solution for 5 min at room temperature, H₂O (10 ml) and CH₂Cl₂ (40 ml) were added. The layers were separated and the organic layer was washed with 1 N HCl (10 ml), H₂O (10 ml), 1 N NaOH (10 ml), H₂O (3 × 10 ml), and brine (10 ml). After drying the solution over Na₂SO₄ the solvent was evaporated to give pure **15** (0.35 g, > 99%); m.p. 80–81°C (EtOAc). Anal. calcd. for C₄₈H₆₀Cl₂N₂O₁₀·0.4H₂O (895.88): C 63.83, H 6.70, N 3.10; found: C 63.64, H 6.71, N 3.03%. Karl–Fischer titration calcd. for 0.4 H₂O: 0.79; found: 0.74%. ¹H-NMR: δ 1.20, t, J 7.0 Hz, 12H, OCH₂CH₃; 3.14 and 4.51, ABq, J 13.3 Hz, 8H, ArCH₂Ar; 3.53, q, J 7.0 Hz, 8H, OCH₂CH₃; 3.8–3.9, m, 8H, ArOCH₂CH₂; 4.08, s, 4H, CH₂C(O); 4.1–4.2, m, 8H, ArOCH₂CH₂; 6.82, s, 4H, *o*-NHArH; 7.5–7.7, m, 6H, ArH; 7.95, s, 2H, NH. MS (FAB), *m/z* 894 (M⁺).

5,17-Diamino-25,26,27,28-tetrapropoxycalix[4]arene (18)

A suspension of dinitro **17** (2.00 g, 2.93 mmol), hydrazine monohydrate (4.0 ml), and a catalytic amount of Raney Ni in MeOH (200 ml) was refluxed for 2 h. The reaction mixture was filtered over Celite and the solvent was evaporated. The residue was taken up in CH₂Cl₂ (50 ml), washed with H₂O (3 × 10 ml) and brine (10 ml), and dried over MgSO₄. After filtration, the solvent was evaporated to give pure **18** (1.58 g, 87%); m.p. 243–245°C (CH₂Cl₂). Anal. calcd. for C₄₀H₅₀N₂O₄·0.35H₂O (622.82): C 76.36, H 8.12, N 4.45; found: C 76.34, H 8.09, N 4.32%. Karl–Fischer titration calcd. for 0.35 H₂O: 1.00; found: 1.01%. ¹H-NMR: δ 0.95, 0.98, 2t, J 7.5 and 7.4 Hz, 12H, ArO(CH₂)₂CH₃; 1.8–2.0, m, 8H, ArOCH₂CH₂CH₃; 2.7, bs, 4H, NH₂; 3.03 and 4.38, ABq, J 13.3 Hz, 8H, ArCH₂Ar; 3.73, 3.84, 2t, J 7.4 and 7.6 Hz, 8H, ArOCH₂CH₂CH₃; 5.93, s, 4H, *o*-NH₂ArH; 6.6–6.8, m, 6H, ArH. MS (FAB), *m/z* 622 (M⁺).

5,11-Dinitro-25,26,27,28-tetrapropoxycalix[4]arene (19, modified procedure)

To a solution of tetrapropoxycalix[4]arene (5.0 g, 8.4 mmol) in a mixture of CH₂Cl₂ (500 ml) and glacial acetic acid (80 ml) was added 65% HNO₃ (40 ml) and the reaction mixture was stirred at room temperature. After approximately 30 min the reaction mixture became black (if not, a few drops of 100% HNO₃ should be added). The reaction was quenched with H₂O (500 ml) after mononitrated

calix[4]arene had almost disappeared, but *before* trinitrocalix[4]arene was formed (checked with TLC). The organic layer was washed with H₂O (100 ml) until pH 7 and with brine (100 ml) and finally dried over MgSO₄. Removal of the solvent afforded a crude mixture of 5,17-dinitro **17** and 5,11-dinitro **19**, from which the 5,17-isomer crystallized (2.06 g, 36%) upon dissolution of the crude mixture in a small amount of CH₂Cl₂ (25 ml) and subsequent addition of hexane (250 ml). The filtrate was evaporated to dryness and the residue was purified by flash column chromatography (SiO₂, 60H, CH₂Cl₂/hexane, 50/50) to give reasonably pure 5,11-dinitro **19** (1.83 g, 32%) as a yellow oil. For spectral data see Ref. 29.

5,11-Bis(phthalimido)-25,26,27,28-tetrapropoxycalix[4]arene (**20**)

The reduction of 5,11-dinitro **19** to crude 5,11-diamino **21** was carried out following the procedure for the synthesis of 5,17-diamino **18**, using **19** (1.03 g, 1.51 mmol), hydrazine monohydrate (1.0 ml), and MeOH (125 ml) to afford crude 5,11-diamino **21**. This crude material was dissolved in dry toluene (100 ml), phthalic anhydride (0.44 g, 3.0 mmol) and NEt₃ (4.18 ml, 30 mmol) were added, and the resulting solution was refluxed for 3½ h. After evaporation of the solvent, the residue was taken up in CH₂Cl₂ (100 ml), washed successively with 1N HCl (25 ml), H₂O (3 × 25 ml), and brine (25 ml), and dried over Na₂SO₄. Removal of the solvent afforded crude phthalimide **20**, which was purified by flash column chromatography (SiO₂, 60H, CH₂Cl₂/hexane, 75:25) to give pure phthalimide **20** (0.53 g, 40%); m.p. 122–124°C (hexane). Anal. calcd. for C₅₆H₅₄N₂O₈ (883.01): C 76.17, H 6.16, N 3.17; found: C 76.12, H 6.51, N 3.02%. ¹H-NMR: δ 1.01, t, *J* 7.4 Hz, 12H, ArO(CH₂)₂CH₃; 1.8–2.1, m, 8H, ArOCH₂CH₂CH₃; 3.19, 3.21, 3.25, and 4.48, 4.50, 4.53, 3ABq, *J* 13.3 Hz, 8H, ArCH₂Ar; 3.87, q, *J* 7.8 Hz, 8H, ArOCH₂CH₂CH₃; 6.52, t, *J* 7.4 Hz, 2H, *p*-ORArH; 6.6–6.7, m, 4H, *m*-ORArH; 6.81, s, 4H, *o*-phthalimidoArH; 7.7–7.8, m, 4H, phthalimide ArH; 7.8–7.9, m, 4H, phthalimide ArH. MS (FAB), *m/z* 883 (M⁺).

5,11-Diamino-25,26,27,28-tetrapropoxycalix[4]arene (**21**)

To a solution of 5,11-bis(phthalimide) **20** (0.63 g, 0.71 mmol) in EtOH (25 ml) was added hydrazine monohydrate (0.20 ml, 4.1 mmol) and the solution was refluxed for 2 h, followed by treatment with concentrated HCl (0.69 ml, 8.2 mmol) for 30 min. The reaction mixture was cooled to room temperature and the precipitate formed was filtered off. The filtrate was evaporated to dryness, the residue taken up in CH₂Cl₂ (25 ml), subsequently washed with 2N NaOH (10 ml) and H₂O (10 ml) till neutrality, and brine (10 ml), and dried over Na₂SO₄. The solution was filtered and evaporated to dryness to give pure 5,11-diamino **21** (0.43 g, 97%) as a yellow solid; m.p. 94–96°C (CH₂Cl₂). A satisfactory elemental analysis could not be obtained. ¹H-NMR: δ 0.9–1.0, m, 12H, ArO(CH₂)₂CH₃; 1.8–2.0, m, 8H, ArOCH₂CH₂CH₃; 2.90, 3.03, 3.15, and 4.30, 4.38, 4.46, 3ABq, *J* 13.2, 13.3, and 13.4 Hz, 8H (1:2:1), ArCH₂Ar; 3.1, bs, 4H, NH₂; 3.73, 3.83, 2t, *J* 7.5 Hz, 8H, ArOCH₂CH₂CH₂CH₃; 5.96, 6.00, 2d, *J* 2.8 Hz, 4H, *o*-NH₂ArH; 6.5–6.7, m, 6H, ArH. MS (FAB), *m/z* 622 (M⁺).

7,11,15,50-Tetrabromo-23,33,54,60-tetrakis(2-ethoxyethoxy)-1,43,45,47-tetrakis(2-phenylethyl)-25H,31H,37H-22,34-(methanol[1,3]benzenomethano)-2,42:3,41:20,24:26,30:32,36-pentametheno-1H,17H,43H,45H,47H-[1,3]dioxocino[5'',4'':8',9']-[1,3]benzodioxocino[5',4':8,9]/[1,3]benzodioxocino[5,4-e₁]/[1,25,4,22]benzodioxadiacyclotriaccontine-18,38(19H,39H)-dione (**22**)

To a solution of diacid dichloride **4** (0.36 g, 0.25 mmol) in dry CH₂Cl₂ (10 ml) was added a solution of diamine **14** (0.19 g, 0.25 mmol) and NEt₃ (77 µl, 0.55 mmol) in dry CH₂Cl₂ (10 ml) in 6 h, whereupon the reaction mixture was stirred for an additional 10 h. The solvent was removed under vacuum and the residue was purified by column chromatography (SiO₂, EtOAc/CH₂Cl₂, 5:95) to afford diamide **22** (0.24 g, 46%); m.p. 205–210°C (CHCl₃/EtOH). Anal. calcd. for C₁₁₁H₁₁₀Br₄N₂O₁₈·2.75H₂O (2079.65): C 62.61, H 5.47, N 1.32; found: C 62.31, H 5.34, N 1.22%. Karl–Fischer titration calcd. for 2.75 H₂O: 2.33; found: 2.30%. ¹H-NMR: δ 1.1–1.3, m, 12H, OCH₂CH₃; 2.3–2.7, m, 16H, CH(CH₂)₂C₆H₅; 3.08, 3.20, 2d, *J* 13.8 and 13.7 Hz, 4H, ArCH₂Ar; 3.50, 3.58, 2q, *J* 6.9 and 7.0 Hz, 8H, OCH₂CH₃; 3.7–3.9, m, 14H, OCH₂C(O) + ArO(CH₂)₂; 4.2–4.6, m, 14H, inner OCH₂C(O) + CH(CH₂)₂C₆H₅ + OCH₂C(O) + ArOCH₂CH₂ + ArCH₂Ar; 4.94, 4.97, 2t, *J* 7.7 Hz, 3H, CH(CH₂)₂C₆H₅; 5.62, bs, 2H, *o*-NHArH; 6.00, 6.01, 2d, *J* 7.4 Hz, 3H, outer OCH₂O; 6.78, bs, 2H, *o*-NHArH; 6.86, t, *J* 7.4 Hz, 1H, *p*-OPrArH; 7.0–7.3, m, 29H, CH(CH₂)₂C₆H₅ + *p*-BrArH + *m*-OPrArH + *p*-OPrArH; 7.83, s, 2H, NH. MS (FAB), *m/z* 2079 (M⁺).

23,33,54,60-Tetrakis(2-ethoxyethoxy)-1,43,45,47-tetrakis(2-phenylethyl)-25H,31H,37H-22,34-(methanol[1,3]benzenomethano)-2,42:3,41:20,24:26,30:32,36-pentametheno-1H,17H,43H,45H,47H-[1,3]dioxocino[5'',4'':8',9']-[1,3]benzodioxocino[5',4':8,9]/[1,3]benzodioxocino[5,4-e₁]/[1,25,4,22]benzodioxadiacyclotriaccontine-18,38(19H,39H)-dione (**23**)

The reaction was carried out following the procedure for diamide **22**, using diacid dichloride **6** (0.16 g, 0.15 mmol), diamine **14** (0.11 g, 0.15 mmol), NEt₃ (46 µl, 0.33 mmol), and CH₂Cl₂ (20 ml) to give pure diamide **23** (0.11 g, 42%) after column chromatography (SiO₂, EtOAc/CH₂Cl₂, 20/80); m.p. 231–235°C (CHCl₃/EtOH). Anal. calcd. for C₁₁₁H₁₁₄N₂O₁₈ (1764.04): C 75.57, H 6.51, N 1.59; found: C 75.65, H 6.67, N 1.72%. MS (FAB), *m/z* 1764 (M⁺)⁴⁵.

7,11,15,52-Tetrabromo-24,34,56,62-tetrakis(2-ethoxyethoxy)-1,45,47,49-tetrakis(2-phenylethyl)-26H,32H,38H-23,35-(methanol[1,3]benzenomethano)-2,44:3,43:21,25:27,31:33,37-pentametheno-1H,17H,45H,47H,49H-[1,3]dioxocino[5'',4'':8',9']-[1,3]benzodioxocino[5',4':8,9]/[1,3]benzodioxocino[5,4-e₁]/[1,4,24,27]benzotetraoxacyclodotriacontine-18,40(19H,41H)-dione (**24**)

To a solution of bis(hydroxymethyl)calix[4]arene **16** (0.13 g, 167 µmol) in THF (20 ml) was added excess NaH (30 mg, 1 mmol) and Cs₂CO₃ (120 mg, 0.37 mmol) and the solution was stirred at room temperature for 45 min. A solution of diacid dichloride **4** (0.24 g, 167 µmol) in CH₂Cl₂ (11 ml) was added over a period of 7 h and the mixture was stirred for an additional 12 h. The reaction mixture was evaporated to dryness, the residue was dissolved in EtOAc/CH₂Cl₂ (15/85) and filtered over silica gel. After evaporation of the solvent and trituration of the residual solid with MeOH pure diester **24** (0.17 g, 48%) was obtained; m.p. 110–120°C (CH₂Cl₂/EtOH). Anal. calcd. for C₁₁₃H₁₁₂Br₄O₂₀ (2109.67): C 64.33, H 5.35; found: C 64.40, H 5.43%. ¹H-NMR: δ 1.1–1.3, m, 12H, OCH₂CH₃; 2.3–2.8, m, 16H, CH(CH₂)₂C₆H₅; 3.10, 3.13, 2d, *J* 13.6 Hz, 4H, ArCH₂Ar; 3.47, 3.49, 3.78, 3q, *J* 7.0 Hz, 8H (1:1:2), OCH₂CH₃; 3.7–4.0, m, 12H, ArO(CH₂)₂; 4.2–4.4, m, 7H, inner OCH₂O + OCH₂C(O) + ArOCH₂CH₂; 4.4–4.6, m, 6H, inner OCH₂O + ArCH₂Ar; 4.61 and 4.68, ABq, *J* 13.4 Hz, 4H, ArCH₂OC(O); 4.85, d, *J* 15.0 Hz, 2H, OCH₂C(O); 4.9–5.0, m, 3H, CH(CH₂)₂C₆H₅; 5.32, t, *J* 7.4 Hz, 1H, CH(CH₂)₂C₆H₅; 6.00, 6.02, 2d, *J* 7.3 Hz, 3H, outer OCH₂O; 6.10, 6.12, 2s, 4H, *o*-C(O)OCH₂ArH; 6.58, 6.90, 2t, *J* 7.4 Hz, 2H, *p*-OPrArH; 7.01, d, *J* 7.4 Hz, 2H, *m*-OPrArH; 7.1–7.3, m, 26H, CH(CH₂)₂C₆H₅ + *p*-BrArH + *m*-OPrArH. MS (FAB), *m/z* 2108 [M – H]⁺.

4,30,34,60-Tetrabromo-12,22,42,52,76,83,87,93-octakis(2-ethoxyethoxy)-64,66,68,69-tetrakis(2-phenylethyl)-14H,20H,26H,44H,50H,56H,61-(epoxymethano)-2,62-methano-11,23:41,53-bis(methanol[1,3]benzenomethano)-9,13:15,19:21,25:39,43:45,49:51,55-hexametheno-6H,36H,64H,66H,68H-dibenzo[*z,z'*]/[1,3]dioxocino[5,4-e₁]:7,8-e₁]/bis[1,25,4,22]benzodioxadiacyclotriaccontine-7,27,37,57(8H,28H,38H,58H)-tetrone (**25**)

The reaction was carried out according to the procedure described for diamide **22** using tetraacid tetrachloride **10** (0.20 g, 0.14 mmol), 1,3-diamine **14** (0.25 g, 0.34 mmol), NEt₃ (0.12 ml, 0.81 mmol), and CH₂Cl₂ (2 × 20 ml) to give tetramide **25** (81 mg, 20%) after flash column chromatography (SiO₂, 60H, EtOAc/hexane, 40/60); m.p. 251–255°C (EtOAc/hexane). Anal. calcd. for C₁₅₈H₁₆₈Br₄N₄O₂₈·2.5H₂O (2890.60): C 64.64, H 5.94, N 1.91; found: C 64.40, H 5.90, N 2.30%. Karl–Fischer titration calcd. for 2.5 H₂O: 1.53; found: 1.53%. ¹H-NMR: δ 1.09, 1.18, 2t, *J* 7.0 Hz, 24H, OCH₂CH₃; 2.1–2.7, m, 16H, CH(CH₂)₂C₆H₅; 3.05, 3.17, and 4.46, 2ABq, *J* 13.7 Hz, 16H, ArCH₂Ar; 3.43, 3.52, 2q, *J* 7.0 Hz, 16H, OCH₂CH₃; 3.6–4.1, m, 32H, OCH₂C(O) + ArO(CH₂)₂; 4.2–4.3, m, 10H, inner OCH₂O + ArOCH₂CH₂; 4.58, 4.91, 2q, *J* 7.7 Hz, 4H, CH(CH₂)₂C₆H₅; 5.9, 6.5, 2bs, 8H, *o*-NHArH; 5.94, d, *J* 7.5 Hz, 2H, outer OCH₂O; 6.8–7.2, m, 32H, CH(CH₂)₂C₆H₅ + ArH; 7.34, s, 4H, *p*-BrArH; 7.64, s, 4H, NH. MS (FAB), *m/z* 2891 [M + H]⁺.

4,30,34,60-Tetrabromo-64,66,68,69-tetramethyl-12,22,42,52,76,83,87,93-octapropoxy-14H,20H,26H,44H,50H,56H-3,61-(epoxymethano)-2,62-methano-11,23:41,53-bis(methanol[1,3]benzenomethano)-9,13:15,19:21,25:39,43:45,49:51,55-hexametheno-6H,36H,64H,66H,68H-dibenzo[*z,z'*]/[1,3]dioxocino[5,4-e₁]:7,8-e₁]/bis[1,25,4,22]benzodioxadiacyclotriaccontine-7,27,37,57(8H,28H,38H,58H)-tetrone (**26**)

The reaction was carried out according to the procedure described for diamide **22** using tetraacid tetrachloride **13** (0.59 g, 0.50 mmol), 1,3-diamine **18** (0.62 g, 1.0 mmol), NEt₃ (0.35 ml, 2.5 mmol), and

CH_2Cl_2 (50 ml) to give tetramide **26** (0.61 g, 53%) after flash column chromatography (SiO_2 60H, $\text{EtOAc}/\text{CH}_2\text{Cl}_2$, 5/95); m.p. $> 300^\circ\text{C}$ ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$). Anal. calcd. for $\text{C}_{122}\text{H}_{128}\text{Br}_4\text{N}_4\text{O}_{20} \cdot 1.75\text{H}_2\text{O}$ (2289.92): C 63.10, H 5.71, N 2.41; found: C 63.47, H 5.61, N 2.23%. Karl–Fischer titration calcd. for 1.75 H_2O : 1.38; found: 1.38%. $^1\text{H-NMR}$: δ 0.81, 1.04, 2t, J 7.4 Hz, 24H, $\text{ArO}(\text{CH}_2)_2\text{CH}_3$; 1.55, 1.80, 2d, J 7.4 Hz, 12H, CHCH_3 ; 1.7–1.9, m, 16H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$; 3.06, 3.13, and 4.40, 2ABq, J 13.3 Hz, 16H, ArCH_2Ar ; 3.58, 3.98, 2t, J 4.9 Hz, 16H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$; 3.95 and 4.21, ABq, J 13.6 Hz, 8H, $\text{OCH}_2\text{C}(\text{O})$; 4.30, d, J 7.4 Hz, 2H, inner OCH_2O ; 4.80, 5.04, 2q, J 7.4 Hz, 4H, CHCH_3 ; 5.9, 6.5, 2bs, 8H, $o\text{-NHArH}$; 5.94, d, J 7.4 Hz, 2H, outer OCH_2O ; 6.8–6.9, m, 4H, ArH ; 7.04, 7.13, 2d, J 7.4 Hz, 8H, ArH ; 7.42, s, 4H, $p\text{-BrArH}$; 7.72, s, 4H, NH. MS (FAB), m/z 2290 (M^+).

5,17-Diiodo-11,23-dinitro-25,26,27,28-tetrapropoxycalix[4]arene (**28**)

To a suspension of AgCF_3COO (1.23 g, 5.58 mmol) in refluxing CHCl_3 (100 ml) was added a solution of 1,3-dinitro **17** (1.27 g, 1.86 mmol) in CHCl_3 (25 ml) and the cloudy solution was refluxed for 15 min. Then I_2 (1.4 g, 5.6 mmol) was added in portions until the deep purple color was permanent. During the addition, AgI precipitated from the solution as a yellow powder. The reaction mixture was refluxed for another 15 min, cooled to room temperature, filtered over Celite, and evaporated to dryness. The residue was taken up in EtOAc (50 ml), washed with a 10% $\text{Na}_2\text{S}_2\text{O}_3$ solution (10 ml), H_2O (3×10 ml), and brine (10 ml), and dried over MgSO_4 . The solvent was removed under vacuum to give **28** (1.62 g, 93%); m.p. $269\text{--}270^\circ\text{C}$ (EtOAc). Anal. calcd. for $\text{C}_{40}\text{H}_{44}\text{I}_2\text{N}_2\text{O}_8$ (934.57): C 51.41, H 4.75, N 3.00; found: C 51.48, H 4.81, N 2.93%. $^1\text{H-NMR}$: δ 0.97, 1.00, 2t, J 7.5 Hz, 12H, $\text{ArO}(\text{CH}_2)_2\text{CH}_3$; 1.8–2.0, m, 8H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$; 3.21 and 4.40, ABq, J 13.7 Hz, 8H, ArCH_2Ar ; 3.82, 3.92, 2t, J 7.7 and 7.4 Hz, 8H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$; 7.08, s, 4H, $o\text{-IArH}$; 7.48, s, 4H, $o\text{-NO}_2\text{ArH}$. MS (FAB), m/z 935 ($\text{M} + \text{H}^+$).

5,17-Dinitro-11,23-bis(phthalimido)-25,26,27,28-tetrapropoxycalix[4]arene (**30**)

A mixture of diiodo **28** (2.00 g, 2.14 mmol), phthalimide (0.94 g, 6.4 mmol), and Cu_2O (0.61 g, 4.3 mmol) in collidine (50 ml) was refluxed for 24 h. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (50 ml), washed subsequently with 5% H_2SO_4 (2×25 ml), 2N NaOH (10 ml), H_2O (10 ml) till neutrality, and brine (10 ml), and dried over Na_2SO_4 . After filtration the solution was evaporated to dryness. The crude product was purified by column chromatography (SiO_2 , CH_2Cl_2 /hexane, 95/5) to give pure diphthalimide **30** (1.46 g, 70%); m.p. $> 300^\circ\text{C}$ (CH_2Cl_2 /hexane). Anal. calcd. for $\text{C}_{56}\text{H}_{52}\text{N}_4\text{O}_{12}$ (973.02): C 69.12, H 5.39, N 5.76; found: C 69.24, H 5.51, N 5.85%. $^1\text{H-NMR}$: δ 0.97, 1.09, 2t, J 7.4 Hz, 12H, $\text{ArO}(\text{CH}_2)_2\text{CH}_3$; 1.8–2.1, m, 8H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$; 3.37 and 4.53, ABq, J 13.5 Hz, 8H, ArCH_2Ar ; 3.77, t, J 7.0 Hz, 4H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$; 4.1–4.2, m, 4H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$; 6.53, s, 4H, $o\text{-phthalimido ArH}$; 7.2–7.4, m, 8H, phthalimide ArH ; 7.95, s, 4H, $o\text{-NO}_2\text{ArH}$. MS (FAB), m/z 974 ($\text{M} + \text{H}^+$).

5,17-Diamino-11,23-dinitro-25,26,27,28-tetrapropoxycalix[4]arene (**31**)

The reaction was carried out following the procedure described for diamine **21**, using diphthalimide **30** (0.29 g, 0.30 mmol), hydrazine monohydrate (90 μl , 1.8 mmol), and conc. HCl (0.30 ml, 3.6 mmol) in EtOH (25 ml) to afford **31** (0.17 g, 80%); m.p. $> 290^\circ\text{C}$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$). Anal. calcd. for $\text{C}_{40}\text{H}_{48}\text{N}_4\text{O}_8 \cdot 0.3\text{H}_2\text{O}$ (712.82): C 66.89, H 6.82, N 7.80; found: C 66.96, H 6.89, N 7.62%. Karl–Fischer titration calcd. for 0.3 H_2O : 0.75; found: 0.74%. $^1\text{H-NMR}$: δ 0.9–1.1, m, 12H, $\text{ArO}(\text{CH}_2)_2\text{CH}_3$; 1.8–2.0, m, 8H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$; 3.12 and 4.40, ABq, J 13.6 Hz, 8H, ArCH_2Ar ; 3.3, bs, 4H, NH_2 ; 3.75, 3.90, 2t, J 7.6 and 7.3 Hz, 8H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$; 6.05, s, 4H, $o\text{-NH}_2\text{ArH}$; 7.51, s, 4H, $o\text{-NO}_2\text{ArH}$. MS (FAB), m/z 979 ($\text{M} + 2\text{Cs}^+$).

5,17-Dicyano-11,23-dinitro-25,26,27,28-tetrapropoxycalix[4]arene (**33**)

A solution of 1,3-diiodo **28** (2.00 g, 2.14 mmol), CuCN (0.67 g, 7.5 mmol) in 1-methyl-2-pyrrolidinone (50 ml) was refluxed for 4 h. After cooling the reaction mixture to room temperature, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (1.58 g, 9.74 mmol) and 2N HCl (100 ml) were added and the mixture was stirred at 100°C for 1 h. After cooling the reaction mixture again to room temperature, the formed precipitate was filtered off over Hyflo. The solid was dissolved in CH_2Cl_2 (50 ml), washed with brine (10 ml), and dried over MgSO_4 . After removal of the solvent, the crude product was recrystallized from CH_2Cl_2 /hexane to give pure dicyano **33** (1.54 g, 98%); m.p. $> 300^\circ\text{C}$. Anal. calcd. for

$\text{C}_{42}\text{H}_{44}\text{N}_4\text{O}_8 \cdot 0.1\text{H}_2\text{O}$ (732.81): C 68.67, H 6.06, N 7.63; found: C 68.31, H 6.06, N 7.42%. Karl–Fischer titration calcd. for 0.1 H_2O : 0.25; found: 0.29%. $^1\text{H-NMR}$: δ 0.9–1.1, m, 12H, $\text{ArO}(\text{CH}_2)_2\text{CH}_3$; 1.8–2.0, m, 8H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$; 3.32 and 4.48, ABq, J 13.9 Hz, 8H, ArCH_2Ar ; 3.89, 3.96, 2t, J 7.6 and 7.4 Hz, 8H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$; 6.99, s, 4H, $o\text{-CNArH}$; 7.59, s, 4H, $o\text{-NO}_2\text{ArH}$. MS (FAB), m/z 734 ($\text{M} + \text{H}^+$).

5,17-Diamino-11,23-dicyano-25,26,27,28-tetrapropoxycalix[4]arene (**34**)

The reaction was carried out analogously to the procedure described for diamine **18** using dicyanide **33** (1.15 g, 1.57 mmol), hydrazine monohydrate (2 ml), and a catalytic amount of Raney Ni in MeOH (100 ml) to give pure diamine **34** (0.77 g, 73%); m.p. $278\text{--}281^\circ\text{C}$ (CH_2Cl_2). A satisfactory elemental analysis could not be obtained. $^1\text{H-NMR}$: δ 0.96, 1.03, 2t, J 7.4 Hz, 12H, $\text{ArO}(\text{CH}_2)_2\text{CH}_3$; 1.86, sextet, J 7.3 Hz, 8H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$; 3.04 and 4.35, ABq, J 13.5 Hz, 8H, ArCH_2Ar ; 3.7–3.9, m, 8H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$; 6.10, s, 4H, $o\text{-NH}_2\text{ArH}$; 6.89, s, 4H, $o\text{-CNArH}$. MS (FAB), m/z 806 ($\text{M} + \text{Cs}^+$).

4,30,34,60-Tetrabromo-64,66,68,69-tetramethyl-17,47,80,91-tetranitro-12,22,42,52,76,83,87,93-octapropoxy-14H,20H,26H,44H,50H,56H-3,61-(epoxymethanoxy)-2,62-methano-11,23:41,53-bis(methanol[1,3]-benzenomethano)-9,13:15,19:21,25:39,43:45,49:51,55-hexametheno-6H,36H,64H,66H,68H-dibenzo[z,z'][1,3]dioxocino[5,4- e_1 :7,8- e'_1]-bis[1,25,4,22]benzodioxadiazacyclotriacantine-7,27,37,57(8H,28H,38H,58H)-tetrone (**35**)

The reaction was carried out according to the procedure described for diamide **22**, using tetraacid tetrachloride **13** (0.38 g, 0.32 mmol), diamine **31** (0.45 g, 0.63 mmol), NEt_3 (0.22 ml, 1.6 mmol), and CH_2Cl_2 (100 ml) to give tetramide **35** (0.17 g, 22%) after flash column chromatography (SiO_2 60H, $\text{EtOAc}/\text{CH}_2\text{Cl}_2$, 5:95–10:90); m.p. $> 300^\circ\text{C}$ ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$). Anal. calcd. for $\text{C}_{122}\text{H}_{124}\text{Br}_4\text{N}_8\text{O}_{28} \cdot 2.25\text{H}_2\text{O}$ (2469.93): C 58.35, H 5.16, N 4.46; found: C 58.26, H 5.18, N 4.42%. Karl–Fischer titration calcd. for 2.25 H_2O : 1.61; found: 1.57%. $^1\text{H-NMR}$: δ 0.91, 1.11, 2t, J 7.4 Hz, 24H, $\text{ArO}(\text{CH}_2)_2\text{CH}_3$; 1.60, d, J 7.4 Hz, 6H, CHCH_3 ; 1.8–2.0, m, 22H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3 + \text{CHCH}_3$; 3.30, 3.36, and 4.50, 2ABq, J 13.5 Hz, 16H, ArCH_2Ar ; 3.67, t, J 6.6 Hz, 8H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$; 3.99, d, J 14.2 Hz, 4H, $\text{OCH}_2\text{C}(\text{O})$; 4.1–4.3, m, 12H, $\text{OCH}_2\text{C}(\text{O}) + \text{ArOCH}_2\text{CH}_2\text{CH}_3$; 4.40, d, J 7.5 Hz, 2H, inner OCH_2O ; 4.87, 5.07, 2q, J 7.5 and 7.4 Hz, 4H, CHCH_3 ; 6.00, d, J 7.5 Hz, 2H, outer OCH_2O ; 6.0, 6.6, 2bs, 8H, $o\text{-NHArH}$; 7.47, s, 4H, $p\text{-BrArH}$; 7.87, s, 4H, NH; 8.08, 8.14, 2s, 8H, $o\text{-NO}_2\text{ArH}$. MS (FAB), m/z 2471 (M^+).

4,30,34,60-Tetrabromo-12,22,42,52,76,83,87,93-octakis(2-ethoxyethoxy)-17,47,80,91-tetrakis(methoxycarbonyl)-64,66,68,69-tetramethyl-14H,20H,26H,44H,50H,56H-3,61-(epoxymethanoxy)-2,62-methano-11,23:41,53-bis(methanol[1,3]benzenomethano)-9,13:15,19:21,25:39,43:45,49:51,55-hexametheno-6H,36H,64H,66H,68H-dibenzo[z,z'][1,3]dioxocino[5,4- e_1 :7,8- e'_1]-bis[1,25,4,22]benzodioxadiazacyclotriacantine-7,27,37,57(8H,28H,38H,58H)-tetrone (**36**)

The reaction was carried out according to the procedure described for diamide **22**, using tetraacid tetrachloride **13** (0.27 g, 0.23 mmol), diamine **32** (0.43 g, 0.47 mmol), NEt_3 (0.16 ml, 1.2 mmol), and CH_2Cl_2 (50 ml) to give tetramide **36** (0.16 g, 25%) after flash column chromatography (SiO_2 60H, $\text{EtOAc}/\text{CH}_2\text{Cl}_2$, 15:85–25:75); m.p. $> 300^\circ\text{C}$ ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$). Anal. calcd. for $\text{C}_{138}\text{H}_{152}\text{Br}_4\text{N}_4\text{O}_{36}$ (2762.28): C 60.00, H 5.55, N 2.03; found: C 60.19, H 5.95, N 1.99%. $^1\text{H-NMR}$: δ 1.1–1.3, m, 24H, OCH_2CH_3 ; 1.59, 1.85, 2d, J 7.4 and 7.5 Hz, 12H, CHCH_3 ; 3.19, 3.28, and 4.54, 2ABq, J 13.9 Hz, 16H, ArCH_2Ar ; 3.44, 3.57, 2q, J 7.0 Hz, 16H, OCH_2CH_3 ; 3.7–4.1, m, 40H, $\text{OCH}_2\text{C}(\text{O}) + \text{ArOCH}_2\text{CH}_2 + \text{C}(\text{O})\text{OCH}_3$; 4.24, d, J 14.8 Hz, 4H, $\text{OCH}_2\text{C}(\text{O})$; 4.3–4.4, m, 10H, inner $\text{OCH}_2\text{O} + \text{ArOCH}_2\text{CH}_2$; 4.89, 5.11, 2q, J 7.4 Hz, 4H, CHCH_3 ; 5.99, d, J 7.4 Hz, 2H, outer OCH_2O ; 6.0, 6.5, 2bs, 8H, $o\text{-NHArH}$; 7.49, s, 4H, $p\text{-BrArH}$; 7.81, s, 8H, $o\text{-CH}_3\text{OC}(\text{O})\text{ArH}$; 7.89, s, 4H, NH. MS (FAB), m/z 2761 ($\text{M} - \text{H}^+$).

4,30,34,60-Tetrabromo-17,47,80,91-tetracyano-64,66,68,69-tetramethyl-12,22,42,52,76,83,87,93-octapropoxy-14H,20H,26H,44H,50H,56H-3,61-(epoxymethanoxy)-2,62-methano-11,23:41,53-bis(methanol[1,3]benzenomethano)-9,13:15,19:21,25:39,43:45,49:51,55-hexametheno-6H,36H,64H,66H,68H-dibenzo[z,z'][1,3]dioxocino[5,4- e_1 :7,8- e'_1]-bis[1,25,4,22]benzodioxadiazacyclotriacantine-7,27,37,57(8H,28H,38H,58H)-tetrone (**37**)

The reaction was carried out according to the procedure described for diamide **22**, using tetraacid tetrachloride **13** (0.53 g, 0.45 mmol),

diamine **34** (0.60 g, 0.90 mmol), NEt_3 (0.31 ml, 2.2 mmol), and CH_2Cl_2 (90 ml) to give tetramide **37** (0.14 g, 13%) after flash column chromatography (SiO_2 60H, EtOAc/hexane, 45:55–60:40); m.p. > 300°C ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$). A satisfactory elemental analysis could not be obtained. $^1\text{H-NMR}$: δ 0.89, 1.10, 2t, J 7.4 Hz, 24H, $\text{ArO}(\text{CH}_2)_2\text{CH}_3$; 1.63, d, J 7.3 Hz, 6H, CHCH_3 ; 1.7–2.0, m, 22H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3 + \text{CHCH}_3$; 3.19, 3.26, and 4.44, 2ABq, J 13.6 Hz, 16H, ArCH_2Ar ; 3.64, 4.14, 2t, J 6.6 and 8.1 Hz, 16H, $\text{ArOCH}_2\text{CH}_2\text{CH}_3$; 4.01, 4.30, 2d, J 14.2 and 13.3 Hz, 8H, $\text{OCH}_2\text{C}(\text{O})$; 4.4–4.5, m, 2H, inner OCH_2O ; 4.91, 5.11, 2q, J 7.4 Hz, 4H, CHCH_3 ; 5.9, 6.5, 2bs, 8H, $o\text{-NHArH}$; 6.03, d, J 7.5 Hz, 2H, outer OCH_2O ; 7.4–7.6, m, 12H, $p\text{-BrArH} + o\text{-CNArH}$; 7.89, s, 4H, NH. MS (FAB), m/z 2390 (M^+).

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