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Synthetic cation transporters incorporating crown ethers and calixarenes as headgroups and central relays: a comparison of sodium and chloride selectivity†

José Carlos Iglesias-Sánchez^a, Wei Wang^e, Riccardo Ferdani^d, Pilar Prados^a, Javier de Mendoza^{a,b}, and George W. Gokel^{c,d}

^a Facultad de Ciencias, Departamento de Química Orgánica (C-I), Universidad Autónoma de Madrid, 28049 Madrid, Spain

^b Institute of Chemical Research of Catalonia (ICIQ), 43007 Tarragona, Spain

^c Departments of Chemistry & Biochemistry and Biology, Center for Nanoscience, University of Missouri – St. Louis, St. Louis, MO 63121, USA

^d Department of Molecular Biology & Pharmacology, Washington University, St. Louis, MO 63130, USA. E-mail: gokelg@umsl.edu; Fax: 314/516-5342; Tel: 314/516-5321

^e Department of Chemistry, Washington University, St. Louis, MO 63130, USA

Abstract

An earlier study showed that a calix[4]arene could function as a central relay unit to form an ion conductance pathway through a phospholipid bilayer membrane. The present study expands the range of compounds from calix[4]arene to calix[6]arene and incorporates them either as central units or as headgroups, substituting one or more diaza-18-crown-6 residues in functioning hydraphiles. Ion release was assayed by detecting either Na⁺ or Cl⁻ release from phospholipid vesicles. The ion transport activity for calix[4]arenes in either position is modest, but is almost non-existent when calix[6] residues were incorporated either as head groups or central relay units. The poor activity of the calix[6]arenes may result from an inability to penetrate to the midplane of the bilayer or pass entirely through it to form a conductance pathway. The transmembrane “flip-flop” may result from high polarity or steric bulk, or both. A hydraphile incorporating a single –NHCOC₆H₄OCH₂CONH– as a central relay proved to be an excellent Na⁺ conductor, but less selective for Cl⁻. The fact that this new hydraphile molecule shows selectivity for Na⁺ over Cl⁻ transport and possesses two secondary amide residues in the central relay suggests a means to control ion selectivity in synthetic ion transporters.

Introduction

Less than a decade ago, no solid state structure had been reported for any protein channel molecule. In the years preceding the appearance of the Nobel prize winning^{1,2} structures,^{3,4} a number of synthetic ion channel mimics were devised in the hope that they could model channel function and reveal mechanistic details of transport. Several different channel designs emerged, some of which were based on the cation complexing and polar properties of crown ethers. The crown compounds served in the earliest model systems as headgroups⁵ and in others^{6,7} as what we have termed a “central relay.” The “central relay” that was

†Dedicated to Professor Jerry Atwood on the occasion of his 65th birthday.

Correspondence to: George W. Gokel.

designed into synthetic channels is equivalent to the “water and ion filled capsule” that was discovered in proteins⁸ when the first solid state structures were reported.

In considering channel design, there are several structural, steric, and polarity issues that must be considered. These include the span of the channel, the polarity of the headgroups, the presence and type of selectivity filter, the presence and type of central relay, and the general question of whether the channel will be flexible or rigid. These issues have been dealt with in a variety of ways by different investigators.⁹ Roks and Nolte,¹⁰ for example, used stacked isocyanocrown ethers as a rigid channel while Meillon and Voyer¹¹ used crown ethers oriented into a pore by an α -helical peptide backbone. The span of synthetic unimolecular ion channels has varied, but has typically been between 35 and 45 Å. Where a distinguishable central relay was present, there was considerable variation as well. Thus Lehn and co-workers used β -cyclodextrin¹² while we^{13,14} and Fyles *et al.*¹⁵ used crown ethers. The crown ethers often comprised both the selectivity filter and the polar head groups. Of course, entirely different, unique, and successful approaches have been reported.^{16–20}

In addition to these important design variants, chemical characterization and documented function are critical. Demonstrating chemical purity is a routine matter for synthetic laboratories, but assaying ion transport is less common. Various methods have been used to detect ion transport. Probably the most informative technique is the use of planar bilayer voltage clamp methods.²¹ Although this method gives comprehensive information about channel behavior, it requires expensive instrumentation, considerable time, and operator expertise. Alternative methods use NMR,²² various fluorescent dyes,²³ and ion selective electrodes (ISEs).²⁴ Not all methods give identical information, but it is critical for claimed ion transport to be documented or a compound designed to be a channel may not be a transporter at all.

In a previous study, we used calixarenes as central units²⁵ in a crown ether headgroup channel. In these studies, we compared synthetic systems in which the calixarenes were more or less sterically encumbered. Transport in these systems was assayed by using planar bilayer methods. In the work presented here, we have prepared ion transporters using calixarene headgroups in concert with our well-studied diaza-18-crown-6 central relay. The efficacy of these compounds as transporters was determined by using ISE methods to detect ion release from phospholipid vesicles.

Results and discussion

To our knowledge, only limited use has been made of the calixarene unit in ion transporters.²⁶ In our previous report on²⁵ calix[4]arenes as central relay units the structures had the form $[\text{PhCH}_2 \langle \text{N18N} \rangle (\text{CH}_2)_{12}]_2 \text{calix}[(\text{CH}_2)_{12} \langle \text{N18N} \rangle \text{CH}_2\text{Ph}]_2$, where $\langle \text{N18N} \rangle$ represents 4,13-diaza-18-crown-6.²⁷ Three derivatives were prepared for the present study. One was a control compound in which the calix[4]arene was in the cone conformation. This means that all four of the $-(\text{CH}_2)_{12} \langle \text{N18N} \rangle \text{CH}_2\text{Ph}$ chains emanating from the calixarene were oriented on the same side of that macrocycle. As such, there was insufficient overall length to span the bilayer, although all of the requisite structural elements were present.

Two 1,3-alternate calixarene derivatives were also prepared. These were intended to probe channel formation *per se* and the ability of a calix[4]arene to pass a cation through the center of the calix. Each arene's *para* position in the calix[4]arene was either hydrogen (calix-H) or *tert*-butyl (calix-Bu). The planar bilayer conductance evidence showed that the calix-H and calix-Bu channels were similar in ion transport behavior. Since the *tert*-butylated calixarene

was too sterically hindered to pass Na^+ through its center, it was concluded that the amphiphiles were forming pores that afforded Na^+ a conductance pathway.²⁵

Design criteria

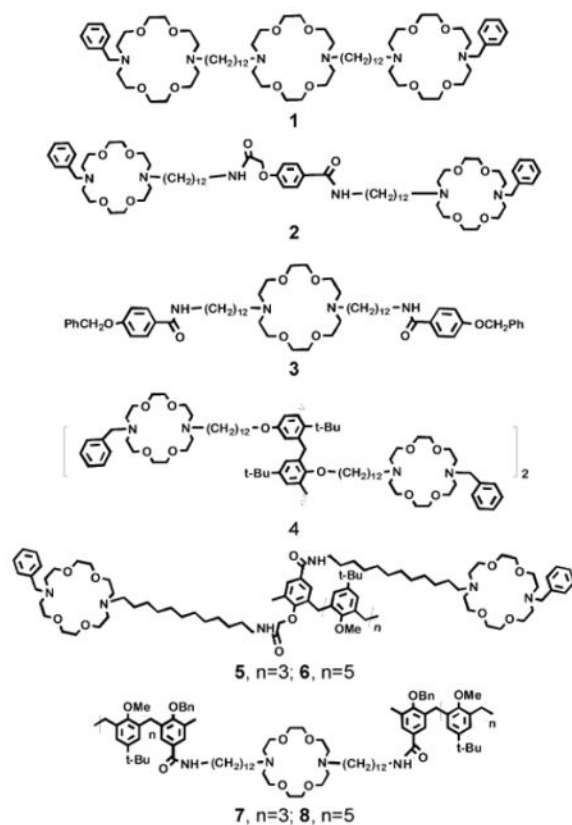
The calixarene-derived channels reported here incorporate both calix[4]- and calix[6]arenes. The passage of Na^+ through the calixarene's interior has been reported.²⁸ To the extent this occurs, passage of Na^+ must be more favorable through a calix[6]arene owing to its larger interior size. It is worth noting that determining a precise size for the hole of calixarenes is difficult owing to the conformational dynamics of these macrocycles. Even so, calix[4]arene and calix[6]arene residues were incorporated into putative channels as either head groups or central relays in the expectation that they might be effective but behave differently as transporters.

The compounds of the present study were designed based on the successful benzyl-terminated hydrophiles that are now well characterized. The best studied of these is $\text{PhCH}_2 \langle \text{N18N} \rangle (\text{CH}_2)_{12} \langle \text{N18N} \rangle (\text{CH}_2)_{12} \langle \text{N18N} \rangle \text{CH}_2\text{Ph}$, **1**. The strategy was to replace either the two distal diaza-18-crown-6 macrocycles with calixarenes or to replace the central (medial) macrocycle of **1** by a single calixarene. By doing so, it would be possible to assess how the calixarenes compared to diazacrown ethers either as head groups or as central relay elements.

Compounds studied

Eight compounds are compared in the present study. Compounds **1** and **4** were prepared previously. Compound **1** is, as noted above, the best studied^{13,14} member of the hydrophile family. It is known to span the bilayer²⁹ and to transport Na^+ in a unimolecular fashion.³⁰ Its transport efficacy constitutes the benchmark for the present study.

Compounds **2** and **3** were prepared to serve as controls. The 4-acetyloxybenzoic acid central relay of **2** is a fragment of the calixarene central units present in **5** and **6**. Similarly, compound **3** is a control for **7** and **8**, which are terminated by calix[4]arene or calix[6]arene head groups, respectively.



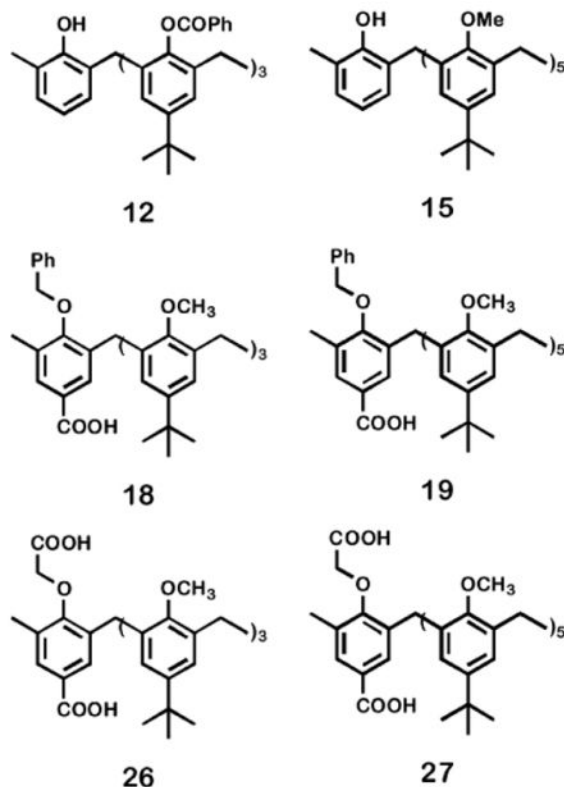
Compounds **5–8** are the major focus of this study. They incorporate calix[4]arene or calix[6]arene residues either as a central relay (**5, 6**) or as the amphiphile's polar head groups (**7, 8**). We anticipated that any free hydroxyl groups present on the calix might make these structures too polar to insert into the bilayer. A particular concern in this connection was that the calixes of **5** and **6** needed to reside at the midplane of the bilayer to serve as the central relay unit. The midplane is the least polar portion of the bilayer and a component of the channel having high polarity might simply disrupt the membrane.

An additional issue is that the formation of a conductance pathway requires, in principle at least, compounds **5–8** to extend through both leaflets of the bilayer membrane. If the calix is too large or too polar, it may be unable to penetrate the hydrocarbon regime of the bilayer and anchor on the opposite membrane surface. It is well known that the polar head groups of phospholipids do not readily pass through (“flip-flop”) the bilayer, even though they have high mobility within a single membrane leaflet.

Synthetic access

Compounds **2** and **3** incorporated a 4-hydroxybenzoic acid unit as a mimic of a calixarene, positioned either to function as the central relay (**2**) or head groups (**3**). Calix[4]- and calix[6]-arenes were incorporated as central units (**5, 6**) and as headgroups (**7, 8**). Compound **2** was prepared in three steps from ethyl 4-hydroxybenzoate. The ester was treated with methyl bromoacetate and K_2CO_3 in acetone followed by KOH hydrolysis to give 4-(carboxymethoxy)benzoic acid, **9**, and coupling with *N*-benzyl-*N'*-12-aminododecyl-4,13-diaza-18-crown-6 (**12BDA**)₁₃ (63% overall yield). The preparation of **3** was also accomplished from ethyl 4-hydroxybenzoate, by *O*-benzylation, hydrolysis of the ethyl ester to give 4-benzyloxybenzoic acid, **10**, and coupling with *N,N'*-bis(12-aminododecyl)-4,13-diaza-18-crown-6 (**12DA12**)₁₃ (64% overall).

The preparation of calix channels **5–8** required the formation of the appropriate calixarene having one (**7, 8**) or two (**5, 6**) connection points on the same arene. Once the appropriately functionalized precursors were in hand, a carboxylic acid on the calixarene was coupled (using benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate PyBOP \cdot PF $_6$, see Experimental section) with the appropriate azacrown **12DA12** and **12BDA**, respectively. The key calixarene structures are shown as **12, 15, 18, 19, 26** and **27**. Compounds **12** and **15** are the starting materials for the calix[4]arene and calix[6]arene channels, respectively. Compounds **18** and **19** are the head groups for channels **7** and **8**. The central units of **5** and **6** were prepared from **26** and **27**, respectively.



As with the control structures **2** and **3**, the preparation of **5–8** required extensive functionalization of the calixarene starting materials (**12, 15**). Coupling of two **12BDA** or one **12DA12** units on calixarenes **26–27** or **18–19**, respectively gave **5–8** with good yields. Details of this effort are presented in the Experimental section. Therein, the conformational status of the calixarene derivatives are addressed. The final coupling step and the key calixarene derivatives are shown in Chart 1.

Ion transport behavior

As noted above, the calixarene transporters were designed to incorporate the successful central relay system of the hydraphiles¹⁴ but bring to the system greater size, polarity and rigidity. The latter term may seem ambiguous considering the conformational flexibility of the calixarenes. The much larger surfaces of the arenes were expected to provide a better defined entry portal or central relay than do the crowns. It was known from previous studies that ion transport mediated by **4** did not permit passage of Na⁺ through the calixarene.²⁵ It was anticipated that this would be the case for calix[4]arene compounds, whether the calix was incorporated as the central relay (**5**) or as headgroups (**7**). The calix[6]arene derivatives

having larger central relay (**6**) or headgroup (**8**) elements were expected to readily pass cations.

The planar bilayer voltage clamp method gives extensive and detailed information concerning ion transport.²¹ Unfortunately, this technique is both tedious and time-consuming. Considering the number of compounds that were required to be assayed, we decided to use ion selective electrode methods to assess ion egress from liposomes.

The liposomes used in the studies reported here were prepared by the method of Szoka and Papahadjopoulos³³ from 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC). In the Na⁺ release experiments, the internal buffer was 750 mM NaCl–15 mM HEPES buffer at pH 7.0. The liposomes were filtered through a 200 nm membrane and passed over a Sephadex G25 column and then equilibrated in sodium-free buffer (750 mM cholineCl–15 mM HEPES, pH 7.0). In the Cl⁻ release experiments, liposomes were prepared similarly, but loaded with 600 mM KCl and 10 mM HEPES (pH = 7.0), then equilibrated with an external buffer (400 mM K₂SO₄–10 mM HEPES, pH = 7.0). The expected vesicle size (~200 nm) was confirmed by light scattering measurements (particle analyzer). Ion efflux was measured by using either a pH/Na⁺ combination microelectrode²⁴ or a chloride selective membrane electrode relative to the final value determined after vesicular lysis.

The results of the Na⁺ release studies for compounds **1–3** and **5–8** are shown in the upper panel of Fig. 1. Hydraphile **1** is equal or superior to all of the other compounds studied. It released ~95% of the available sodium during our customary (arbitrary) 1500 s period of observation. We note that once a conductance pore is formed, ion release occurs nearly instantly. Thus, we presume that the curves shown in Fig. 1 reflect a combination of insertion dynamics and conformational adjustment required to establish an appropriate conductance pathway.

Compound **2** is similar in overall structure to **1**. It incorporates the –NHCOCH₂OC₆H₄CONH– unit, a single element of the calixarene central relay present in compounds **5** and **6**. In previous studies³⁴ we noted that replacement of the diazacrown central relay of **1** by 4,4'-bipiperidyl gave a hydraphile that was 40% as active as **1**. In this case, **2** is about 64% as active as **1** in releasing Na⁺ from liposomes. Compound **3** contains the diazacrown central relay but lacks the crown headgroups. Its distal residues were designed to mimic a single calixarene element of **7** and **8**. The transport activity of **3** is measurable but too small to be of interest. Likewise, **5** and **7** show very low Na⁺ transport although it is above baseline. Only **6** and **8** parallel the baseline for the entire 1500 s observation period.

Benzyl channel **1** is an unusually effective Na⁺ transporter. In previous studies, only hydraphiles having crown or oligo(oxyethylene) central units approached its transport efficacy.¹⁴ Thus, the high release observed for **2** is particularly interesting. The central unit of **2**, *i.e.*, –NHCOCH₂OC₆H₄CONH–, contains two carbonyl groups that can serve as H-bond acceptors from water and two NH residues that can donate hydrogen bonds to water. The carbonyl groups and the amide NH groups are both spaced about 9 Å apart. The carbonyl group spacing is too large for the carbonyl oxygens to directly ligate with a transient cation—an interaction that should dramatically slow transport. The activity of this compound supports our general understanding of the central relay unit, but is a very interesting alternative to crown ether relays.

The O–O or N–N spacing in diaza-18-crown-6 is typically only about 6 Å. In principle, any interaction with a transient cation should be stronger with a crown owing to this shorter distance. The carbonyl groups of **2** are farther apart but also more polar. It is interesting to note that the selectivity filter of the KcsA potassium selective channel uses carbonyl groups

to replace the solvation shell of a transient K^+ cation.¹ In any event, sodium ion transport selectivity is apparent between **1** and **2**.

The Na^+ transport ability of **2** stands in contrast to that of **3**, which contains a diaza-18-crown-6 central relay. In this case, the $PhCH_2OC_6H_4CONH-$ sidechains that replace the distal diaza-18-crown-6 macrocycles of **1** apparently lack sufficient polarity to function as headgroups or sufficient size to serve as cation entry portals. The presence of this molecule in the liposomal bilayer leads to Na^+ release of barely 15% during 1500 s.

Ion transport by calixarene-containing amphiphiles

Compounds **5–8** incorporate calix[4]arenes (**5, 7**) or calix[6]-arenes (**6, 8**) as a central relay (**5, 6**) or as putative headgroups (**7, 8**). Transport of Na^+ by **5** or **7** is modest. The overall transport behavior for **5** and **7** is indistinguishable from that found for **3**, *i.e.*, ~15% at 1500 s. Compounds **6** and **8** show no evidence of Na^+ transport during the 1500 s observation period. Taken together, these observations reveal two facts. First, and perhaps obviously, calix[6]arenes are bulkier and more polar than their calix[4]arene counterparts. Second, for the calix[4]arenes, it does not seem to matter whether a single calix is present as a central relay unit or two are incorporated as headgroups. Transport is poor suggesting that the formation of a stable conductance pathway is problematic.

Perhaps the most interesting observation is the inability of compound **8**, which incorporates two distal calix[6]arene residues, to transport Na^+ or Cl^- , shown in the bottom panel of Fig. 1. In the Cl^- transport case, a more limited sample of compounds was tested, but the results proved to be interesting. As with Na^+ transport, compounds **3** and **6** proved to be only modest transporters, although both ultimately mediated the release of about 25% of the available Cl^- ion.

The low transport activity of calixarenes amphiphiles

In order to evaluate the behavior of compounds **5–8**, it is useful to consider the presumed active conformations. These are shown in Fig. 2. Diaza-18-crown-6 is represented by the ovals and the blocks represent the calixarenes.

In order for any of these molecules to form a conductance pathway, the molecule must insert into the upper leaflet of the bilayer and then unfold into the lower leaflet, ultimately passing half of the structure through the midplane of the bilayer to the opposite surface. Compounds **5–8** present a challenge in this respect because the calixarenes are both large and polar. The ability of the calixarene central units in either **5** or **6** to reside at the midplane of the bilayer is limited by their polarity and their ability to penetrate the upper leaflet's hydrophobic regime. The problem is exacerbated in **7** because one of the calix[4]arene units must pass all the way from the outer leaflet surface to the inner leaflet surface, *i.e.*, transverse relaxation or “flip-flop”, a process that occurs very slowly. The problem is most severe for **8**, in which the calix[6]arene is both large and polar. The data of Fig. 1 show that **8** is essentially inactive as a transporter either of cations or anions. Compound **8** might prove active if it was present and incorporated into the bilayer during liposome formation, but this experiment has not been attempted because insertion is critical for these compounds to be of biological relevance. Fig. 2 shows schematically how **7** or **8** might insert in the upper bilayer but fail to mediate ion transport.

Presumably, the diaza-18-crown-6 residues of **1, 2, 4, 5** and **6** have sufficient polarity to serve as headgroups and entry (or exit) portals, but they can still pass through the bilayer's hydrophobic regime to the opposite surface. This accounts, in part, for their efficacy as transporters, although transport mediated by **5** proved to be marginal.

Ion transport by compounds **1** and **2**

The results obtained for **1** and **2** were especially interesting. Although there is a minor difference in line shape, probably reflecting small differences in insertion or conformational dynamics, both compounds release about 90% of the available Cl^- ion by 1500 s. In previous studies of **1**, we have focused on Na^+ transport and the competition with other cations, such as K^+ and Ag^+ . The fact that Cl^- release is so effective is surprising and will merit additional study, which is beyond the scope of this work. Even so, it is interesting to compare **1**, which effectively releases both Na^+ and Cl^- , with **2**.

The central relay in **2** is $-\text{NHCOCH}_2\text{OC}_6\text{H}_4\text{CONH}-$ rather than 4,13-diaza-18-crown-6. Certainly either of these units can serve to organize water, which would comprise the requisite midplane polarity for transport. Both the amide carbonyl groups of **2** and the ether oxygens of **1** would show an affinity for alkali metal cations but only the amide NH groups of **2** should interact effectively with Cl^- . Thus, it is not surprising that **2** shows a modest 1.5 : 1 transport selectivity for Na^+ over Cl^- (*cf.* upper and lower panels). The transport efficacies of the other compounds in this study are too low to determine selectivity with any confidence.

The results presented here show that replacement of the diazacrown central unit of **1** by a residue containing secondary amides alters the Na^+/Cl^- transport selectivity. In previous studies, we have prepared numerous amides,³⁵ but in all cases prior to this one, they have been tertiary. Presumably the presence of a secondary amide alters the affinity of these molecules for Cl^- compared to Na^+ but this remains to be confirmed generally.

Conclusions

Previous work showed that a calix[4]arene could function effectively as a central unit to induce an ion conductance pathway in a phospholipid bilayer. In this case, each arene was substituted by a dodecylene chain terminated by a benzyldiazacrown residue. Structural modification showed that although a conductance path was formed, ions did not flow through the calix[4]arene. The present study expanded the calixarene size (4 and 6) and placed the calixarenes to function as either headgroups or central units. Only modest ion transport (cation or anion) was realized from compounds in which the calix[4]arene was present in either position. When the calixarene was placed to serve as a headgroup, low activity was observed for the four-arene macrocycle and no transport was apparent when the macrocycle was calix[6]arene. We speculate that the lack of transport activity reflects the inability of the large and polar calixarene to cross the bilayer and establish a conductance pathway. Ultimately, the most interesting and surprising observation relates to **1** and **2**, which were included as control compounds. Compound **1**, which has been extensively studied as a cation transporter, conducts Cl^- as well as it does Na^+ . The fact that **2** favors Na^+ over Cl^- transport and possesses two secondary amide residues in the central relay suggests a strategy to incorporate a selective element in the design of more selective ion transporters.

Experimental

General methods

Unless otherwise indicated, reactions were conducted under dry and deoxygenated argon. Solvents were freshly distilled and dried by standard methods before use. Melting points are uncorrected and were measured in open capillaries on a Gallenkamp melting point apparatus. The NMR experiments (^1H , $^{13}\text{C}\{^1\text{H}\}$), COSY (H,H), HMQC and ROESY) were carried out at 500 MHz (^1H) or 125 MHz (^{13}C) in CDCl_3 at ambient temperature, unless otherwise specified. Chemical shifts (δ , ppm) are externally referenced to solvent residual

signal. Mass spectra were performed on a REFLEX spectrometer (MALDI-TOF) using ditranol (1,8-dihydroxyanthrone) as matrix and NaI as additive. Elemental analyses, performed on a LECO CHN 932 microanalyser and reported as percentage, indicated inclusion of solvent molecules for nearly all calixarene products and were supported by separate ^1H NMR studies. TLC was performed on silica gel Alugram Sil G/UV254 (Macherey–Nagel).

Vesicle preparation and ion transport measurements

Liposomes were formed (20 s sonication) from 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (Avanti Polar Lipids, AL). The buffer captured within the liposomes was 750 mM NaCl–15 mM *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid (HEPES), pH 7.0. The liposomes were filtered (200 nm membrane) and passed over a Sephadex G25 column equilibrated in sodium-free buffer (750 mM cholineCl–15 mM HEPES, pH 7.0). Lipid concentration was measured as previously reported³⁶ and vesicle size was confirmed by light scattering (submicron particle analyzer) to be \sim 200 nm. Sodium efflux was measured by using a pH/Na⁺ combination microelectrode (Thermo-Orion). Aliquots of the amphiphile solution (15 μL , 5 mM in 2-PrOH, except **5**, 5 mM in DMSO) were added into the system after the base line is stable. Final values were determined after vesicular lysis (*n*-octylglucose) and curve calibration.

Determination of chloride release by ISE methods

Liposomes were prepared as above, and loaded with 600 mM KCl and 10 mM (HEPES, pH = 7.0), then equilibrated with an external buffer (400 mM K₂SO₄, 10 mM HEPES, pH = 7.0). The pH of the buffers prepared was adjusted using 10% NaOH. An Accumet Chloride Combination Electrode was equilibrated (5 min) in external buffer (2.0 mL) and the vesicle solution was added. After recording the baseline voltage, aliquots of the amphiphile solution (5 mM in 2-PrOH, except **5**, 5 mM in DMSO) were added. The amount of isopropyl alcohol was limited to 15 μL to avoid alcohol-induced leakage. Vesicles were lysed by addition of aqueous Triton X100 (100 μL , 2%). The lipid concentration used in the studies presented here was 0.40 mM.

Data analysis

The data were acquired in mV units, which were converted to concentration units by using the electrode calibration curve. After conversion from mV to concentration units, the release data were normalized to the total ion concentration, as determined by lysing the vesicles. Data manipulation was done using Origin Pro 7 software.

General procedure for azacrown-carboxylic acid coupling

To a solution of the carboxylic acid (1 mmol) was added benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP⁺PF₆⁻, 2.2 mmol), EtN₃ (2.2 mmol), and the corresponding azacrown (2.2 mmol) in THF (10 mL). The mixture was stirred (under Ar) at rt for 24 h. The solvent was removed *in vacuo* and the residue was partitioned between CH₂Cl₂ and HCl (1 M). The organic soluble residue was purified by flash column chromatography over silica gel (solvent: 4% v/v MeOH in CH₂Cl₂).

***N*-Benzyl diaza-18-crown-6 (BDA, PhCH₂⟨N18N⟩H)** was prepared as previously reported.¹³

***N*-Benzyl-*N'*-12-aminododecyl-4,13-diaza-18-crown-6 (12BDA, PhCH₂⟨N18N⟩(CH₂)₁₂NH₂)** was prepared as previously reported.¹³

***N,N'*-Bis(12-aminodecyl)-4,13-diaza-18-crown-6 (12DA12, H₂N(CH₂)₁₂ <N18N> (CH₂)₁₂NH₂)** was prepared as previously reported.¹³

N,N'*-Bis[12-(*N'*-benzylidiazia-18-crown-6) dodecyl]diazia-18-crown-6, [C₆H₅CH₂ <N18N> (CH₂)₁₂(N18N)(CH₂)₁₂ <N18N> CH₂C₆H₅], **1*, was prepared as previously reported.¹³

C₆H₅CH₂ <N18N> (CH₂)₁₂ NHCOCH₂OC₆H₄CONH (CH₂)₁₂- <N18N> CH₂C₆H₅, **2**—This was prepared by the coupling between **9** (44 mg, 0.22 mmol, general procedure), and **12BDA** (250 mg, 0.54 mmol). Yield: 201 mg, 73%. ¹H NMR: 1.25 [m, 36H, (CH₂)₉], 1.59 (m, 4H, CH₂), 2.18 (m, 16H, CH₂-N-CH₂), 2.82 (m, 4H, CH₂NHCO + CH₂N), 3.67 (m, 32H, CH₂OCH₂CH₂OCH₂), 3.76 (s, 4H, OCH₂Ar), 6.11 (s, 2H, NH), 6.54 (s, 7.02 (d, 4H, *J* = 8.8 Hz, ArH), 7.38 (m, 4H, ArH), 7.46 (m, H, NH), 6.96 (d, 2H, *J* = 8.7, Hz, ArH), 7.25 (m, 4H, ArH), 7.32 (m, 6H, ArH), 7.77 (d, 2H, *J* = 8.7 Hz, ArH); ¹³C NMR: 27.1, 27.5, 28.9, 29.2, 29.3, 29.4 [(CH₂)₁₀], 39.2, 40.2 (CH₂NH), 46.1, 46.3 (CH₂N), 53.9, 54.0 (CH₂NCH₂), 68.0 (OCH₂CO), 69.8, 69.9 (CH₂OCH₂CH₂OCH₂), 70.4 (OCH₂Ar), 114.5, 126.9, 128.2, 128.7, 128.9, 129.0 (ArH), 127.1, 139.5, 159.5 (ArC), 166.6, 167.4 (CO); MALDI-TOF MS *m/z* (Ditranol + NaI), 1231.9 [M + H]⁺. Anal. (%). Calc. for C₇₁H₁₁₈N₆O₁₁: C, 69.23; H, 9.66; N, 6.82. Found: C, 69.55; H, 9.82; N, 6.95.

PhCH₂OC₆H₄CONH(CH₂)₁₂ <N18N> (CH₂)₁₂ NHCOC₆H₄OCH₂Ph, **3**—This was prepared by the general procedure from **10** (100 mg, 0.44 mmol) and **12DA12** (207 mg, 0.51 mmol). Yield: 376 mg, 82%, mp 217 °C. ¹H NMR: 1.30 [m, 36H, (CH₂)₉], 1.64 (q, 4H, *J* = 7.1 Hz, CH₂), 2.72 (m, 8H, CH₂-N-CH₂), 3.05 (br s, 4H, CH₂NHCO), 3.45 (c, 4H, *J* = 7.1 Hz, CH₂NHCO), 3.65 (m, 16H, CH₂OCH₂CH₂OCH₂), 5.02 (s, 4H, OCH₂Ar), 6.20 (s, 2H, NH), 7.02 (d, 4H, *J* = 8.8 Hz, ArH), 7.38 (m, 4H, ArH), 7.46 (m, 6H, ArH), 7.77 (d, 4H, *J* = 8.8 Hz, ArH); ¹³C NMR: 27.0, 29.3, 29.5, 29.7 [(CH₂)₁₀], 40.1 (CH₂NH), 50.4 (CH₂NCH₂), 69.7, 69.9 (CH₂OCH₂CH₂OCH₂), 70.1 (OCH₂Ar), 114.6, 127.5, 128.2, 128.7 (ArH), 126.5, 136.5, 162.4 (ArC), 167.5 (CO); MALDI-TOF MS *m/z* (Ditranol + NaI), 1049.4 [M + H]⁺, 1072.4 [M + Na]⁺. Anal. (%). Calc. for C₆₄H₉₆N₄O₈: C, 73.25; H, 9.22; N, 5.34. Found: C, 73.30; H, 9.25; N, 5.41.

Calix[4]arene channel 4—This has been previously reported.²⁵

Calix[4]arene channel 5—This was prepared from **26** (50 mg, 0.068 mmol) by coupling (general procedure) with **12BDA** (91 mg, 0.17 mmol). Yield: 82 mg, 69%. *Asymmetric partial cone*: ¹H NMR: 0.84 [s, 9H, C(CH₃)₃], 1.12 [s, 9H, C(CH₃)₃], 1.25 [s, 9H, C(CH₃)₃], 1.32 [m, 36H, (CH₂)₉], 2.69 (m, 4H, CH₂-N-CH₂), 2.75 (s, 3H, OCH₃), 3.02 (br s, 4H, CH₂NHCO), 3.15–3.25 (m, 2H, ArCH₂Ar), 3.62 (s, 3H, OCH₃), 3.68 (m, 8H, CH₂OCH₂CH₂OCH₂), 3.74 (s, 3H, OCH₃), 3.70–3.80 (m, 4H, ArCH₂Ar), 4.17 (m, 1H, ArCH₂Ar), 4.23 (m, 1H, ArCH₂Ar), 4.35 (s, 2H, OCH₂CO), 5.70 (1H, NH), 5.75 (br s, 1H, NH), 6.34 (d, 1H, *J* = 2.0 Hz, ArH), 6.92 (d, 1H, *J* = 2.0 Hz, ArH), 7.13 (2H, ArH), 7.18 (s, 1H, *J* = 1.9 Hz, ArH), 7.34 (2H, ArH), 7.68 (d, 1H, *J* = 1.9 Hz, ArH); ¹³C NMR: 27.0, 29.3, 29.5, 29.7 [(CH₂)₁₀], 30.8, 31.6, 31.7 [C(CH₃)₃], 30.9, 31.2, 37.7, 38.4 (ArCH₂Ar), 33.4, 33.8, 34.2 [C(CH₃)₃], 40.1 (CH₂NH), 50.4 (CH₂NCH₂), 58.4, 59.8, 60.6 (OCH₃), 69.7, 69.9 (CH₂OCH₂CH₂OCH₂), 70.4 (OCH₂CO), 124.9, 126.2, 126.4, 127.3, 128.2, 128.3, 128.6, 130.4, 131.8 (ArH), 132.0, 132.7, 132.8, 134.6, 134.8, 135.8, 136.4, 137.3, 143.5, 144.2, 145.4, 151.6, 154.8, 155.3, 155.7 (Ar), 169.0, 170.5 (CO). *Cone*: ¹H NMR: 0.72 [s, 9H, C(CH₃)₃], 1.32 [m, 36H, (CH₂)₉], 1.35 [s, 18H, C(CH₃)₃], 2.69 (m, 4H, CH₂-N-CH₂), 3.02 (br s, 4H, CH₂NHCO), 3.27 (m, 2H, ArCH₂Ar), 3.29 (m, 2H, ArCH₂Ar), 3.61 (s, 3H, OCH₃), 3.68 (m, 8H, CH₂OCH₂CH₂OCH₂), 3.73 (s, 6H, OCH₃), 4.40 (d, 2H, *J* = 9.8 Hz, ArCH₂Ar), 4.42 (d, 2H, *J* = 10.0 Hz, ArCH₂Ar), 4.62 (s, 2H, OCH₂CO), 5.70 (br s, 1H, NH), 5.75 (br s, 1H, NH), 6.26 (s, 2H, ArH), 7.02 (s, 2H, ArH), 7.14 (s, 2H, ArH), 7.24 (s,

2H, ArH); ^{13}C NMR: 30.7, 31.4 [$\text{C}(\text{CH}_3)_3$], 30.9, 31.1 (ArCH_2Ar), 33.8, 34.2 [$\text{C}(\text{CH}_3)_3$], 51.4, 51.9 (CO_2CH_3), 58.3, 60.5 (OCH_3), 71.2 (OCH_2CO), 169.0, 170.5 (CO); MALDI-TOF MS m/z (Ditranol + NaI), 1722.5 [M] $^+$, 1795.5 [$\text{M} + \text{Na}$] $^+$. Anal. (%): Calc. for $\text{C}_{108}\text{H}_{166}\text{N}_6\text{O}_{14}$: C, 73.18; H, 9.44; N, 4.74. Found: C, 73.41; H, 9.57; N, 4.87.

Calix[6]arene channel, 6—This was prepared by general procedure, from **27** (30 mg, 0.028 mmol) and (**12BDA**, 37 mg, 0.07 mmol). Yield: 36 mg, 60%. ^1H NMR ($\text{C}_2\text{D}_2\text{Cl}_4$, 388 K (115 °C): 0.95 [s, 9H, $\text{C}(\text{CH}_3)_3$], 1.00 [s, 18H, $\text{C}(\text{CH}_3)_3$], 1.22 [s, 18H, $\text{C}(\text{CH}_3)_3$], 1.32 [m, 36H, $(\text{CH}_2)_9$], 1.61 (m, 4H, CH_2), 2.69 (m, 4H, $\text{CH}_2\text{-N-CH}_2$), 3.02 (br s, 4H, CH_2NHCO), 3.16 (s, 2H, OCH_2CO_2), 3.26 (s, 6H, OCH_3), 3.41 (s, 6H, OCH_3), 3.46 (s, 3H, OCH_3), 3.68 (m, 8H, $\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2$), 3.92 (s, 8H, ArCH_2Ar), 3.98 (s, 4H, ArCH_2Ar), 5.02 (s, 4H, OCH_2Ar), 5.70 (br s, 1H, NH), 5.75 (1H, NH), 6.71 (s, 2H, ArH), 6.73 (s, 2H, ArH), 6.85 (s, 2H, ArH), 7.04 (s, 4H, ArH), 7.22 (s, 2H, ArH), 729–735 (m, 10H, ArH); ^{13}C NMR: 27.0, 29.3, 29.5, 29.7 [$(\text{CH}_2)_{10}$], 30.1, 30.2, 30.7 (ArCH_2Ar), 30.8, 30.9, 31.3 [$\text{C}(\text{CH}_3)_3$], 33.4, 33.43, 33.5 [$\text{C}(\text{CH}_3)_3$], 40.1 (CH_2NH), 50.4 (CH_2NCH_2), 59.5, 59.53, 59.9 (OCH_3), 68.8 (OCH_2CO_2), 69.7, 69.9 ($\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2$), 74.8 (OCH_2Ar), 123.8, 124.2, 124.5, 126.5, 126.7, 132.0 (ArH) 123.9, 131.5, 132.3, 132.4, 132.7, 132.9, 134.5, 145.2, 145.6, 145.65, 153.0, 153.2 (ArC), 159.8, 167.1 (CO); MALDI-TOF MS m/z (Ditranol + NaI), 2126.5 [$\text{M} + \text{H}$] $^+$, 2148.0 [$\text{M} + \text{Na}$] $^+$. Anal. (%): Calc. for $\text{C}_{132}\text{H}_{198}\text{N}_6\text{O}_{16}$: C, 74.71; H, 9.39; N, 3.95. Found: C, 75.01; H, 9.57; N, 4.10.

Calix[4]arene channel 7—This was prepared by the general procedure, from **18** (50 mg, 0.065 mmol) and **12DA12** (31 mg, 0.15 mmol). Yield: 107 mg, 77% (oil). *Asymmetric partial cone*: ^1H NMR: 0.99 [s, 9H, $\text{C}(\text{CH}_3)_3$], 1.22 [s, 9H, $\text{C}(\text{CH}_3)_3$], 1.30 [m, 36H, $(\text{CH}_2)_9$], 1.41 [s, 9H, $\text{C}(\text{CH}_3)_3$], 1.64 (m, 4H, CH_2), 2.69 (m, 8H, $\text{CH}_2\text{-N-CH}_2$), 2.73 (s, 8H, $\text{OCH}_3 + \text{ArCH}_2\text{Ar}$), 3.02 (s, 3H, OCH_3), 3.13 (d, 1H, $J = 13.5$ Hz, ArCH_2Ar), 3.15 (d, 1H, $J = 13.3$ Hz, ArCH_2Ar), 3.71–3.79 (m, 4H, ArCH_2Ar), 3.72 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.08 (d, 1H, $J = 13.5$ Hz, ArCH_2Ar), 4.17 (d, 1H, $J = 13.3$ Hz, ArCH_2Ar), 4.78 (d, 1H, $J = 8.0$ Hz, OCH_2Ar), 4.85 (d, 1H, $J = 8.0$ Hz, OCH_2Ar), 5.81 (br s, 2H, NH), 6.33 (d, 1H, $J = 2.1$ Hz, ArH), 6.92 (d, 1H, $J = 2.1$ Hz, ArH), 7.07 (d, 1H, $J = 2.2$ Hz, ArH), 7.13 (d, 1H, $J = 2.2$ Hz, ArH), 7.15 (d, 1H, $J = 2.1$ Hz, ArH), 7.27–7.28 (m, 2H, ArH), 7.30–7.38 (m, 3H, ArH), 7.41–7.45 (m, 2H, ArH), 7.80 (d, 1H, $J = 2.1$ Hz, ArH); ^{13}C NMR: 27.0, 29.3, 29.5, 29.7 [$(\text{CH}_2)_{10}$], 30.9, 31.2, 36.5, 36.9 (ArCH_2Ar), 31.1, 31.5, 31.7 [$\text{C}(\text{CH}_3)_3$], 33.4, 33.8, 34.3 [$\text{C}(\text{CH}_3)_3$], 40.1 (CH_2NH), 50.4 (CH_2NCH_2), 58.4, 59.8, 60.6 (OCH_3), 69.7, 69.9 ($\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2$), 76.7 (OCH_2Ar), 124.9, 125.2, 126.2, 126.4, 127.3, 128.2, 128.3, 128.6, 128.61, 130.4, 131.8 (ArH), 132.0, 132.7, 132.8, 133.2, 134.6, 134.8, 135.8, 136.4, 137.3, 143.5, 144.2, 145.4, 151.6, 154.8, 155.3, 155.7 (Ar), 161.0 (CO). *Cone*: ^1H NMR: 0.69 [s, 9H, $\text{C}(\text{CH}_3)_3$], 1.30 [m, 36H, $(\text{CH}_2)_9$], 1.43 [s, 18H, $\text{C}(\text{CH}_3)_3$], 1.64 (m, 4H, CH_2), 2.69 (m, 8H, $\text{CH}_2\text{-N-CH}_2$), 3.18 (d, 2H, $J = 13.1$ Hz, ArCH_2Ar), 3.20 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar), 3.73 (s, 3H, OCH_3), 3.85 (s, 6H, OCH_3), 4.38 (d, 2H, $J = 13.1$ Hz, ArCH_2Ar), 4.41 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar), 4.86 (s, 2H, OCH_2Ar), 5.81 (2H, NH), 6.24 (s, 2H, ArH), 7.21 (br s, 6H, ArH), 7.27–7.28 (m, 2H, ArH), 7.41–7.45 (m, 3H, ArH); ^{13}C NMR: 29.7, 30.0 (ArCH_2Ar), 30.8, 31.3 [$\text{C}(\text{CH}_3)_3$], 34.2, 34.3 [$\text{C}(\text{CH}_3)_3$], 60.6, 62.4 (OCH_3), 76.8 (OCH_2Ar), 160.0 (CO); MALDI-TOF MS m/z (Ditranol + NaI), 2131.0 [M] $^+$, 2154.0 [$\text{M} + \text{Na}$] $^+$. Anal. (%): Calc. for $\text{C}_{138}\text{H}_{192}\text{N}_4\text{O}_{14}$: C, 77.78; H, 9.08; N, 2.63. Found: C, 77.53; H, 9.19; N, 2.83.

Calix[6]arene channel, 8—This was prepared by general the procedure, from **19** (100 mg, 0.089 mmol) and **12DA12** (42 mg, 0.067 mmol). Yield: 189 mg, 75%, mp 254 °C; ^1H NMR: 1.07 [s, 18H, $\text{C}(\text{CH}_3)_3$], 1.13 [s, 9H, $\text{C}(\text{CH}_3)_3$], 1.26 [s, 18H, $\text{C}(\text{CH}_3)_3$], 1.30 [m, 36H, $(\text{CH}_2)_9$], 1.64 (m, 4H, CH_2), 2.69 (m, 8H, $\text{CH}_2\text{-N-CH}_2$), 2.73 (s, 8H, $\text{OCH}_3 + \text{ArCH}_2\text{Ar}$), 3.04 (s, 3H, OCH_3), 3.07 (4H, CH_2NHCO), 3.29 (s, 6H, OCH_3), 3.38 (m, 8H,

CH₂NHCO + ArCH₂Ar), 3.64 (m, 16H, CH₂OCH₂CH₂OCH₂), 3.83 (m, 4H, ArCH₂Ar), 4.36 (m, 2H, ArCH₂Ar), 4.91 (s, 2H, OCH₂Ar), 5.81 (2H, NH), 6.81 (d, *J* = 2.4 Hz, 2H, ArH), 6.98 (d, *J* = 2.4 Hz, 2H, ArH), 7.02 (s, 2H, ArH), 7.18 (d, *J* = 2.4 Hz, 2H, ArH), 7.26 (d, *J* = 2.4 Hz, 2H, ArH), 7.31–7.40 (m, 3H, ArH), 7.47–7.49 (m, 2H, ArH), 7.48 (s, 2H, ArH); ¹³C NMR: 27.0, 29.3, 29.5, 29.7 [(CH₂)₁₀], 29.7, 30.2, 31.2 (ArCH₂Ar), 31.3, 31.5, 31.6 [C(CH₃)₃], 34.0, 34.1, 34.2 [C(CH₃)₃], 40.1 (CH₂NH), 50.4 (CH₂NCH₂), 59.9, 58.0, 60.0 (OCH₃), 69.7, 69.9 (CH₂OCH₂-CH₂OCH₂), 74.8 (OCH₂Ar), 124.8, 124.9, 126.8, 127.2, 127.7, 127.8, 128.0, 128.2, 128.5, 128.6, 129.7 (ArH), 132.2, 133.4, 133.5, 133.8, 135.9, 145.8, 146.2, 153.4, 154.3, 158.8 (ArC), 168.5 (CO); MALDI-TOF MS *m/z* (Ditranol + NaI), 2836.0 [M + H]⁺, 2859.0 [M + Na]⁺. Anal. (%): Calc. for C₁₈₆H₂₅₆N₄O₁₈: C, 78.77; H, 9.10; N, 1.98. Found: C, 78.95; H, 9.29; N, 2.09.

4-Carboxymethoxybenzoic acid, 9—A suspension of ethyl 4-hydroxybenzoate (300 mg, 1.81 mmol) and K₂CO₃ (500 mg, 3.61 mmol) in Me₂CO (25 mL) was stirred at rt (1 h) and methyl bromoacetate (0.25 mL, 2.72 mmol) was added. After stirring an additional 4 h, the solvent was removed *in vacuo* and the residue was partitioned between CH₂Cl₂ and HCl (1 M). The organic layer was washed with H₂O, dried (MgSO₄) and evaporated. The residue was dissolved in THF, then KOH (50 mg) was added, and the mixture was heated under reflux for 24 h. The solvent was evaporated, the residue was partitioned between CH₂Cl₂ and HCl (1 M), and the organic layer was washed (H₂O), dried (MgSO₄), and evaporated. The residue was purified by flash column chromatography with (hexane–THF 9 : 1) to give **9** (340 mg, 83%) as a colorless solid, mp 97 °C. ¹H NMR (DMSO-*d*₆): 4.77 [s, 2H, OCH₂CO), 7.02 (d, 2H, *J* = 7.5 Hz, Ar), 8.00 (d, 2H, *J* = 7.5 Hz, Ar); ¹³C NMR (DMSO-*d*₆): 64.4 (OCH₂CO), 113.9, 131.4 (ArH), 123.5, 161.9 (Ar), 168.2, 170.7 (CO); electrospray MS *m/z*, 196.0 [M]⁺. Anal. (%): Calc. for C₉H₈O₅: C, 55.11; H, 4.11. Found: C, 55.07; H, 4.08.

4-Benzyloxybenzoic acid (10)—A suspension of ethyl 4-hydroxybenzoate (300 mg, 1.81 mmol) and NaH 60% (87 mg, 3.61 mmol) in DMF (20 mL) was stirred at rt for 1 h and benzyl bromide (0.32 mL, 2.72 mmol) was added. The mixture was stirred for 4 h, evaporated, and the residue was partitioned between CH₂Cl₂ and HCl (1 M). The organic layer was washed (H₂O), dried (MgSO₄), and evaporated. The residue was dissolved in THF, KOH (50 mg) was added, and the mixture was heated under reflux for 24 h. The solvent was evaporated, the residue was partitioned between CH₂Cl₂ and HCl (1 M), the organic layer was washed with H₂O, dried (MgSO₄) and evaporated. The residue chromatographed (flash, hexane–THF 9 : 1) to give **10**, (320 mg, 78%) as a colorless solid, mp 89 °C. ¹H NMR: 5.14 [s, 2H, OCH₂Ar), 7.02 (d, 2H, *J* = 7.8 Hz, Ar), 7.36–7.44 (m, 5H, Ar), 8.06 (d, 2H, *J* = 7.8 Hz, Ar); ¹³C NMR: 70.8 (OCH₂Ar), 114.2, 127.3, 127.5, 128.8, 131.9 (ArH), 121.9, 136.4, 162.3 (Ar), 169.3 (CO); electrospray MS *m/z*, 229.2 [M]⁺. Anal. (%): Calc. for C₁₄H₁₂O₃: C, 73.67; H, 5.30. Found: C, 73.62; H, 5.27.

26-Benzyloxy-11,17,23-tri-*tert*-butyl-25,27,28-trihydroxycalix[4]arene, 11 (cone)—A suspension of 25,27,28-tribenzoyloxy-11,17,23-tri-*tert*-butyl-26-hydroxycalix[4]arene **12,31** (0.5 mg, 0.55 mmol) and NaH 60% (27 mg, 0.66 mmol) in DMF (200 mL) was stirred for 1 h at rt, benzyl bromide (0.79 mL, 0.66 mmol) was added, and the mixture was stirred for 4 h. After evaporation of the solvent, the residue was partitioned between CH₂Cl₂ and HCl (1 M), the organic layer was washed (H₂O), dried (MgSO₄) and evaporated. The residue was dissolved in THF, KOH (100 mg) was added, and the mixture was heated (reflux) for 24 h. The solvent was evaporated, the residue was partitioned between CH₂Cl₂ and HCl (1 M), the organic layer was washed (H₂O) dried (MgSO₄), and evaporated. Chromatography (flash, hexane–THF 9 : 1) gave **11** (cone), (350 mg, 93%) as a colorless solid, mp 221 °C. ¹H NMR: 1.23 [s, 9H, C(CH₃)₃], 1.26 [s, 18H, C(CH₃)₃], 3.43 (d, 2H, *J*

= 13.7 Hz, ArCH₂Ar), 3.45 (d, 2H, *J* = 13.1 Hz, ArCH₂Ar), 4.24 (d, 2H, *J* = 13.7 Hz, ArCH₂Ar), 4.38 (d, 2H, *J* = 13.1 Hz, ArCH₂Ar), 5.23 (s, 2H, OCH₂Ar), 6.95 (t, 1H, *J* = 7.5 Hz, ArH), 7.02 (s, 2H, ArH), 7.04 (d, 2H, *J* = 2.4 Hz, ArH), 7.07 (d, 2H, *J* = 2.4 Hz, ArH), 7.14 (s, 1H, ArH), 7.16 (s, 1H, ArH), 7.49–7.56 (m, 3H, ArH), 7.73–7.75 (m, 2H, ArH), 9.28 (s, 2H, OH), 9.69 (s, 1H, OH). ¹³C NMR: 31.4, 31.5 [C(CH₃)₃], 32.1, 32.8 (ArCH₂Ar), 33.9 [C(CH₃)₃], 79.3 (OCH₂Ar), 125.2, 125.7, 125.9, 126.2, 128.95, 129.0, 129.1, 129.3 (ArH), 127.4, 127.9, 128.1, 134.7, 135.6, 143.1, 143.8, 147.0, 148.6, 151.5 (Ar); MALDI-TOF MS *m/z* (Ditranol + NaI), 682.4 [M]⁺, 705.4 [M + Na]⁺. Anal. (%): Calc. for C₄₇H₅₄O₄: C, 82.66; H, 7.97. Found: C, 82.34; H, 7.98.

25,27,28-Tribenzoyloxy-11,17,23-tri-*tert*-butyl-26-hydroxycalix[4]arene 12—This was prepared as previously reported.³¹

26-Benzyloxy-11, 17, 23-tri-*tert*-butyl-25, 27, 28-trimethoxycalix[4]arene, 13 (asymmetric partial cone : cone 3 : 1)—A suspension of **11** (200 mg, 2.9 mmol) and NaH 60% (70 mg, 1.74 mmol) in DMF (15 mL) was stirred for 20 min at rt, CH₃I (0.11 mL, 1.74 mmol) was added, and the mixture was stirred for 2 h. The solvent was evaporated, the residue was partitioned between CH₂Cl₂ and HCl (1 M), the organic layer was washed (H₂O), dried (MgSO₄) and evaporated. Chromatography (flash, hexane–THF 95 : 5) gave **13**, (233 mg, 90%). *Asymmetric partial cone*: ¹H NMR: 1.07 [s, 9H, C(CH₃)₃], 1.19 [s, 9H, C(CH₃)₃], 1.38 [s, 9H, C(CH₃)₃], 3.04 (s, 3H, OCH₃), 3.05 (d, 1H, *J* = 13.3 Hz, ArCH₂Ar), 3.10 (d, 1H, *J* = 13.8 Hz, ArCH₂Ar), 3.65–3.75 (m, 4H, ArCH₂Ar), 3.65 (s, 3H, OCH₃), 3.70 (s, 3H, OCH₃), 4.06 (d, 1H, *J* = 13.8 Hz, ArCH₂Ar), 4.17 (d, 1H, *J* = 13.3 Hz, ArCH₂Ar), 4.73 (d, 1H, *J* = 10.7 Hz, OCH₂Ar), 4.82 (d, 1H, *J* = 10.7 Hz, OCH₂Ar), 6.23 (s, 2H, ArH), 6.34 (d, 1H, *J* = 7.2 Hz, ArH), 6.44 (t, 1H, *J* = 7.2 Hz, ArH), 6.81 (d, 1H, *J* = 2.4 Hz, ArH), 6.88 (d, 1H, *J* = 7.2 Hz, ArH), 6.94 (d, 1H, *J* = 2.4 Hz, ArH), 7.01 (d, 1H, *J* = 2.4 Hz, ArH), 7.13 (d, 1H, *J* = 2.4 Hz, ArH), 7.36–7.44 (m, 3H, ArH), 7.51–7.53 (m, 2H, ArH). ¹³C NMR: 30.7, 31.1, 36.2, 36.6 (ArCH₂Ar), 31.1, 31.2, 31.4 [C(CH₃)₃], 34.0, 34.2, 34.3 [C(CH₃)₃], 58.7, 59.7, 60.3 (OCH₃), 76.0 (OCH₂Ar), 122.0, 124.5, 124.9, 126.2, 126.3, 127.9, 128.4, 128.5, 130.7, 131.2 (ArH), 131.9, 132.5, 133.1, 134.7, 135.9, 136.2, 136.7, 137.6, 144.2, 144.5, 145.2, 154.9, 155.5 (Ar). *Cone*: ¹H NMR: 0.77 [s, 9H, C(CH₃)₃], 1.41 [s, 18H, C(CH₃)₃], 3.18–3.19 (m, 4H, ArCH₂Ar), 3.75 (s, 3H, OCH₃), 3.84 (s, 6H, OCH₃), 4.36 (d, 2H, *J* = 14.0 Hz, ArCH₂Ar), 4.42 (d, 2H, *J* = 14.0 Hz, ArCH₂Ar), 4.81 (s, 2H, OCH₂Ar), 6.10 (s, 2H, ArH), 6.98 (m, 3H, ArH), 7.01 (s, 2H, ArH), 7.04 (s, 1H, ArH), 7.08 (s, 1H, ArH), 7.36–7.37 (m, 3H, ArH), 7.48–7.49 (m, 2H, ArH). ¹³C NMR: 31.4, 31.5 [C(CH₃)₃], 32.1, 32.7 (ArCH₂Ar), 34.2, 34.3 [C(CH₃)₃], 60.5, 62.3 (OCH₃), 79.8 (OCH₂Ar), 125.3, 125.7, 125.8, 126.3, 128.8, 129.0, 129.1, 129.3 (ArH), 127.4, 127.8, 128.3, 134.9, 135.4, 143.2, 143.7, 146.8, 148.4, 151.5 (Ar); MALDI-TOF MS *m/z* (Ditranol + NaI), 724.4 [M]⁺, 747.4 [M + Na]⁺. Anal. (%): Calc. for C₅₀H₆₀O₄: C, 82.83; H, 8.34. Found: C, 82.99; H, 8.20.

5-Bromo-11,17, 23, 29, 35-penta-*tert*-butyl-38-hydroxy-37,39,-40,41,42-pentamethoxycalix[6]arene, 14—Br₂ (0.13 mL, 2.5 mmol) was added dropwise to a 0 °C solution of **5, 11, 17, 23, 29-penta-*tert*-butyl-37-hydroxy-38, 39, 40, 41,42-pentamethoxycalix[6]arene, 15**, (500 mg, 0.50 mmol) in CHCl₃ (50 mL). The solution was allowed to warm to ambient temperature while stirring for 1 h, whereupon 10% aq. NaHSO₃ (10 mL) was added to quench the reaction. The organic layer was washed with water, dried (MgSO₄), and evaporated. The residue was triturated with MeOH to give **14**, (490 mg, 92%) as a colorless solid, mp 190 °C. ¹H NMR: 0.95 [s, 9H, C(CH₃)₃], 1.07 [s, 18H, C(CH₃)₃], 1.11 [s, 18H, C(CH₃)₃], 2.93 (s, 6H, OCH₃), 3.14 (s, 6H, OCH₃), 3.41 (s, 3H, OCH₃), 3.69 (br s, 4H, ArCH₂Ar), 3.85 (br s, 8H, ArCH₂Ar), 6.83 (s, 2H, ArH), 6.86 (d, *J* = 2.4 Hz, 2H,

ArH), 6.91 (s, 2H, ArH), 6.94 (s, 4H, ArH), 6.99 (d, $J = 2.4$ Hz, 2H, ArH), 7.73 (s, 1H, OH). MALDI-TOF MS m/z (Ditranol + NaI), 1064.6 $[M + H]^+$, 1087.6 $[M + Na]^+$.

5, 11, 17, 23, 29-Penta-*tert*-butyl-37-hydroxy-38,39,40,41,42-pentamethoxycalix[6]arene, 15—This was prepared as previously reported.³²

26-Benzyloxy-5-bromo-11, 17, 23-tri-*tert*-butyl-25, 27, 28-trimethoxycalix[4]arene, 16 (asymmetric partial cone : cone 5 : 1)—Br₂ (0.13 mL, 2.5 mmol) was added dropwise to a cooled solution of **13** (500 mg, 0.67 mmol) in CHCl₃ (50 mL) at 0 °C and stirring was continued for 1 h. NaHSO₃ (20 mL, 10% aq.) was added to quench the reaction. The organic layer was washed (H₂O), dried (MgSO₄), and evaporated. The residue was precipitated from CHCl₃–MeOH (3 : 1) to give **16** (498 mg, 90%).

Asymmetric partial cone: ¹H NMR: 1.07 [s, 9H, C(CH₃)₃], 1.10 [s, 9H, C(CH₃)₃], 1.33 [s, 9H, C(CH₃)₃], 2.94 (s, 3H, OCH₃), 3.05 (d, 1H, $J = 13.4$ Hz, ArCH₂Ar), 3.09 (d, 1H, $J = 13.4$ Hz, ArCH₂Ar), 3.62–3.64 (m, 4H, ArCH₂Ar), 3.63 (s, 3H, OCH₃), 3.64 (s, 3H, OCH₃), 4.01 (d, 1H, $J = 13.4$ Hz, ArCH₂Ar), 4.05 (d, 1H, $J = 13.4$ Hz, ArCH₂Ar), 4.66 (d, 1H, $J = 10.8$ Hz, OCH₂Ar), 4.73 (d, 1H, $J = 10.8$ Hz, OCH₂Ar), 6.38 (d, 1H, $J = 2.4$ Hz, ArH), 6.58 (d, 1H, $J = 2.6$ Hz, ArH), 6.93 (d, 1H, $J = 2.4$ Hz, ArH), 6.97 (d, 1H, $J = 2.6$ Hz, ArH), 7.03 (d, 1H, $J = 2.4$ Hz, ArH), 7.08 (d, 1H, $J = 2.4$ Hz, ArH), 7.13 (d, 1H, $J = 2.4$ Hz, ArH), 7.24 (d, 1H, $J = 2.4$ Hz, ArH), 7.36–7.44 (m, 3H, ArH), 7.51–7.53 (m, 2H, ArH). ¹³C NMR: 30.9, 31.1, 36.3, 36.8 (ArCH₂Ar), 31.2, 31.3, 31.5 [C(CH₃)₃], 34.1, 34.2, 34.4 [C(CH₃)₃], 58.6, 60.0, 60.8 (OCH₃), 76.5 (OCH₂Ar), 124.8, 125.2, 126.2, 126.5, 127.9, 128.4, 128.5, 130.2, 131.6 (ArH), 114.3, 131.9, 132.7, 133.1, 134.6, 134.9, 136.2, 136.3, 137.6, 143.2, 144.0, 145.2, 154.9, 155.3 (Ar). **Cone:** ¹H NMR: 0.89 [s, 9H, C(CH₃)₃], 1.31 [s, 18H, C(CH₃)₃], 3.14 (d, 2H, $J = 7.8$ Hz, ArCH₂Ar), 3.18 (d, 2H, $J = 8.0$ Hz, ArCH₂Ar), 3.77 (s, 3H, OCH₃), 3.80 (s, 6H, OCH₃), 4.29 (d, 2H, $J = 8.0$ Hz, ArCH₂Ar), 4.31 (d, 2H, $J = 8.00$ Hz, ArCH₂Ar), 4.75 (s, 2H, OCH₂Ar), 6.50 (s, 2H, ArH), 6.69 (s, 2H, ArH), 7.08 (d, 2H, $J = 2.4$ Hz, ArH), 7.18 (d, 2H, $J = 2.4$ Hz, ArH), 7.36–7.44 (m, 3H, ArH), 7.58–7.60 (m, 2H, ArH). ¹³C NMR: 29.9, 30.1 (ArCH₂Ar), 31.2, 31.5 [C(CH₃)₃], 34.2, 34.3 [C(CH₃)₃], 60.5, 62.7 (OCH₃), 77.8 (OCH₂Ar), 124.6, 124.7, 127.2, 127.7, 129.0, 131.5 (ArH), 115.0, 128.1, 130.7, 141.2, 143.3, 152.2, 153.1 (Ar); MALDI-TOF MS m/z (Ditranol + NaI), 802.4 $[M]^+$, 825.3 $[M + Na]^+$. Anal. (%): Calc. for C₅₀H₅₉O₄; C, 74.70; H, 7.40. Found: C, 74.79; H, 7.43.

38- Benzyloxy- 5- bromo-11, 17, 23, 29, 35- penta-*tert*- butyl-37,39,40,41,42-pentamethoxycalix[6]arene, 17—A suspension of **14** (630 mg, 0.59 mmol) and NaH 60% (36 mg, 0.88 mmol) in THF (40 mL) was heated at 80 °C for 1 h. Benzyl bromide (0.11 mL, 0.88 mmol) was added and the mixture was refluxed for 5 h. The solvent was evaporated and the residue was partitioned between CH₂Cl₂ and HCl (1 M). The organic layer was washed (H₂O), dried (MgSO₄) and evaporated. The residue was precipitated from MeOH to give **17** (439 mg, 65%), mp 205 °C. ¹H NMR: 1.06 [s, 18H, C(CH₃)₃], 1.28 [s, 9H, C(CH₃)₃], 1.32 [s, 18H, C(CH₃)₃], 2.63 (s, 6H, OCH₃), 2.77 (s, 3H, OCH₃), 3.41 (s, 6H, OCH₃), 3.53 (br s, 6H, ArCH₂Ar), 3.86–4.00 (br s, 6H, ArCH₂Ar), 4.97 (s, 2H, OCH₂Ar), 6.77 (d, $J = 2.2$ Hz, 2H, ArH), 6.87 (br s, 2H, ArH), 6.91 (d, $J = 2.2$ Hz, 2H, ArH), 7.15 (s, 2H, ArH), 7.17 (d, $J = 2.2$ Hz, 2H, ArH), 7.20 (d, $J = 2.2$ Hz, 2H, ArH), 7.38–7.44 (m, 3H, ArH), 7.51–7.55 (m, 2H, ArH). ¹³C NMR: 30.9 (ArCH₂Ar), 31.3, 31.5 [C(CH₃)₃], 34.1, 34.2 [C(CH₃)₃], 59.9, 60.0 (OCH₃), 74.7 (OCH₂Ar), 124.9, 126.6, 127.7, 127.9, 128.1, 128.6, 130.2 (ArH), 132.5, 133.4, 133.60, 133.64, 137.7, 145.8, 146.2, 153.4, 154.2 (ArC). MALDI-TOF MS m/z (Ditranol + NaI), 1155.5 $[M + H]^+$, 1177.4 $[M + Na]^+$. Anal. (%): Calc. for C₇₄H₉₁BrO₆·MeOH: C, 75.80; H, 8.06. Found: C, 75.92; H, 8.14.

26-Benzyloxy-11,17,23-tri-*tert*-butyl-5-hydroxycarbonyl-25,27,-28-trimethoxycalix[4]arene, 18,(asymmetric partial cone : cone 9 : 1)—*tert*-Butyllithium (1.5 M solution in pentane) (0.96 mL, 1.3 mmol) was added dropwise to a -78 °C solution of **16** (0.5 mg, 0.63 mmol) in dry THF (10 mL). The resulting yellow solution was stirred at -78 °C for 20 min. Cooling was continued at 0 °C and CO₂ gas was bubbled in during 30 min. The solvent was evaporated and the residue was partitioned between CH₂Cl₂ and HCl (1 M). The organic layer was washed (H₂O), dried (MgSO₄) and evaporated. The residue chromatographed (flash, hexane–THF 8 : 1) to give **18** (395 mg, 82%). *Asymmetric partial cone*: ¹H NMR: 0.99 [s, 9H, C(CH₃)₃], 1.22 [s, 9H, C(CH₃)₃], 1.41 [s, 9H, C(CH₃)₃], 3.02 (s, 3H, OCH₃), 3.13 (d, 1H, *J* = 13.5 Hz, ArCH₂Ar), 3.15 (d, 1H, *J* = 13.3 Hz, ArCH₂Ar), 3.71–3.79 (m, 4H, ArCH₂Ar), 3.72 (s, 3H, OCH₃), 3.74 (s, 3H, OCH₃), 4.08 (d, 1H, *J* = 13.5 Hz, ArCH₂Ar), 4.17 (d, 1H, *J* = 13.3 Hz, ArCH₂Ar), 4.78 (d, 1H, *J* = 8.0 Hz, OCH₂Ar), 4.85 (d, 1H, *J* = 8.0 Hz, OCH₂Ar), 6.33 (d, 1H, *J* = 2.1 Hz, ArH), 6.92 (d, 1H, *J* = 2.1 Hz, ArH), 7.07 (d, 1H, *J* = 2.2 Hz, ArH), 7.13 (d, 1H, *J* = 2.2 Hz, ArH), 7.15 (d, 1H, *J* = 2.1 Hz, ArH), 7.27–7.28 (m, 2H, ArH), 7.30–7.38 (m, 3H, ArH), 7.41–7.45 (m, 2H, ArH), 7.80 (d, 1H, *J* = 2.1 Hz, ArH). ¹³C NMR: 30.9, 31.2, 36.5, 36.9 (ArCH₂Ar), 31.1, 31.5, 31.7 [C(CH₃)₃], 33.4, 33.8, 34.3 [C(CH₃)₃], 58.4, 59.8, 60.6 (OCH₃), 76.7 (OCH₂Ar), 124.9, 125.2, 126.2, 126.4, 127.3, 128.2, 128.3, 128.6, 128.61, 130.4, 131.8 (ArH), 132.0, 132.7, 132.8, 133.2, 134.6, 134.8, 135.8, 136.4, 137.3, 143.5, 144.2, 145.4, 151.6, 154.8, 155.3, 155.7 (Ar), 161.0 (CO). *Cone*: ¹H NMR: 0.69 [s, 9H, C(CH₃)₃], 1.43 [s, 18H, C(CH₃)₃], 3.18 (d, 2H, *J* = 13.1 Hz, ArCH₂Ar), 3.20 (d, 2H, *J* = 13.0 Hz, ArCH₂Ar), 3.73 (s, 3H, OCH₃), 3.85 (s, 6H, OCH₃), 4.38 (d, 2H, *J* = 13.1 Hz, ArCH₂Ar), 4.41 (d, 2H, *J* = 13.0 Hz, ArCH₂Ar), 4.86 (s, 2H, OCH₂Ar), 6.24 (s, 2H, ArH), 7.21 (br s, 6H, ArH), 7.27–7.28 (m, 2H, ArH), 7.41–7.45 (m, 3H, ArH). ¹³C NMR: 29.7, 30.0 (ArCH₂Ar), 30.8, 31.3 [C(CH₃)₃], 34.2, 34.3 [C(CH₃)₃], 60.6, 62.4 (OCH₃), 76.8 (OCH₂Ar), 160.0 (CO); MALDI-TOF MS *m/z* (Ditranol + NaI), 768.4 [M]⁺, 791.4 [M + Na]⁺. Anal. (%): Calc. for C₅₁H₆₀O₆: C, 79.65; H, 7.86. Found: C, 79.05; H, 7.62.

38-Benzyloxy-11,17,23,29,35-penta-*tert*-butyl-5-hydroxycarbonyl-37,39,40,41,42-pentamethoxycalix[6]arene, 19—*tert*-Butyllithium (0.15 mL, 0.16 mmol) was added dropwise at -78 °C to a solution of **17** (150 mg, 0.13 mmol) in dry THF (10 mL). The resulting yellow solution was stirred at -78 °C for 20 min, cooling was changed to an ice bath, and CO₂ gas was bubbled in during 30 min (0 °C). The solvent was evaporated and the residue was partitioned between CH₂Cl₂ and HCl (1 M). The organic layer was washed (H₂O), dried (MgSO₄) and evaporated. The residue was chromatographed (flash, hexane–THF 8 : 1) to give **19** (110 mg, 76%) as a white solid, mp 220 °C. ¹H NMR (C₂D₂Cl₄, 403 K (130 °C)): 0.99 [s, 18H, C(CH₃)₃], 1.20 [s, 9H, C(CH₃)₃], 1.25 [s, 18H, C(CH₃)₃], 2.69 (s, 6H, OCH₃), 2.88 (s, 3H, OCH₃), 3.29 (s, 6H, OCH₃), 3.90 (s, 12H, ArCH₂Ar), 4.97 (s, 2H, OCH₂Ar), 6.72 (d, *J* = 2.4 Hz, 2H, ArH), 6.85 (d, *J* = 2.4 Hz, 2H, ArH), 7.04 (s, 2H, ArH), 7.07 (d, *J* = 2.4 Hz, 2H, ArH), 7.15 (d, *J* = 2.4 Hz, 2H, ArH), 7.31–7.40 (m, 3H, ArH), 7.47–7.49 (m, 2H, ArH), 7.50 (s, 2H, ArH). ¹³C NMR: 29.7, 30.2, 31.2 (ArCH₂Ar), 31.3, 31.5, 31.6 [C(CH₃)₃], 34.0, 34.1, 34.2 [C(CH₃)₃], 59.9, 59.96, 60.01 (OCH₃), 74.8 (OCH₂Ar), 124.8, 124.9, 126.8, 127.2, 127.7, 127.8, 128.0, 128.2, 128.5, 128.6, 129.7 (ArH), 132.4, 133.4, 133.5, 133.6, 135.7, 145.8, 146.2, 153.4, 154.3, 158.9 (ArC), 166.2 (CO). MALDI-TOF MS *m/z* (Ditranol + NaI), 1143.8 [M + Na]⁺. Anal. (%): Calc. for C₇₅H₉₂O₈: C, 80.32; H, 8.27. Found: C, 80.21; H, 8.49.

26-Benzyloxy-11,17,23-tri-*tert*-butyl-25,27,28-trimethoxy-5-methoxycarbonylcalix[4]arene, 20,(asymmetric partial cone : cone 9 : 1)—A suspension of **18** (250 mg, 0.33 mmol), Cs₂CO₃ (530 mg, 1.63 mmol) and CH₃I (1 mL, 16.3 mmol) in THF (25 mL) was stirred for 12 hours at rt, the mixture was evaporated, and the residue was partitioned between CH₂Cl₂ and HCl (1M). The organic layer was washed

(H₂O), dried (MgSO₄) and evaporated. The residue was chromatographed (flash, hexane–THF 95 : 5) to give **20** (200 mg, 81%). *Asymmetric partial cone*: ¹H NMR: 0.86 [s, 9H, C(CH₃)₃], 1.10 [s, 9H, C(CH₃)₃], 1.28 [s, 9H, C(CH₃)₃], 2.91 (s, 3H, OCH₃), 2.98–3.03 (m, 2H, ArCH₂Ar), 3.55–3.64 (m, 4H, ArCH₂Ar), 3.58 (s, 3H, OCH₃), 3.61 (s, 3H, OCH₃), 3.66 (s, 3H, CO₂CH₃), 3.96 (d, 1H, *J* = 13.9 Hz, ArCH₂Ar), 4.04 (d, 1H, *J* = 13.9 Hz, ArCH₂Ar), 4.64 (d, 1H, *J* = 11.1 Hz, OCH₂Ar), 4.72 (d, 1H, *J* = 11.0 Hz, OCH₂Ar), 6.22 (d, 1H, *J* = 2.0 Hz, ArH), 6.79 (d, 1H, *J* = 2.0 Hz, ArH), 6.96 (d, 1H, *J* = 2.2 Hz, ArH), 7.01 (d, 1H, *J* = 2.2 Hz, ArH), 7.02 (d, 1H, *J* = 2.1 Hz, ArH), 7.08 (s, 1H, ArH), 7.15 (s, 1H, ArH), 7.29–7.31 (m, 3H, ArH), 7.39–7.42 (m, 2H, ArH), 7.60 (d, 1H, *J* = 2.1 Hz, ArH). ¹³C NMR: 30.9, 31.5, 31.7 [C(CH₃)₃], 30.9, 31.2, 36.6, 37.0 (ArCH₂Ar), 33.4, 33.8, 34.2 [C(CH₃)₃], 51.4 (CO₂CH₃), 58.3, 59.8, 60.6 (OCH₃), 76.6 (OCH₂Ar), 124.9, 125.2, 126.2, 126.4, 127.3, 128.2, 128.3, 128.6, 128.61, 130.4, 131.8 (ArH), 132.0, 132.7, 132.8, 133.2, 134.6, 134.8, 135.8, 136.4, 137.3, 143.5, 144.2, 145.4, 151.6, 154.8, 155.3, 155.7 (Ar), 160.2 (CO). *Cone*: ¹H NMR: 0.56 [s, 9H, C(CH₃)₃], 1.31 [s, 18H, C(CH₃)₃], 3.06–3.09 (m, 4H, ArCH₂Ar), 3.51 (s, 3H, CO₂CH₃), 3.64 (s, 3H, OCH₃), 3.73 (s, 6H, OCH₃), 4.24 (d, 2H, *J* = 9.8 Hz, ArCH₂Ar), 4.29 (d, 2H, *J* = 9.6 Hz, ArCH₂Ar), 4.73 (s, 2H, OCH₂Ar), 6.12 (s, 2H, ArH), 7.01 (s, 2H, ArH), 7.08 (s, 4H, ArH), 7.26–7.31 (m, 3H, ArH), 7.39–7.41 (m, 2H, ArH). ¹³C NMR: 30.7, 31.4 [C(CH₃)₃], 30.9, 31.0 (ArCH₂Ar), 33.8, 34.2 [C(CH₃)₃], 51.3 (CO₂CH₃), 58.3, 60.5 (OCH₃), 76.8 (OCH₂Ar), 160.2 (CO); MALDI-TOF MS *m/z* (Ditranol + NaI) 783.4 [M + H]⁺, 805.4 [M + Na]⁺. Anal. (%): Calc. for C₅₂H₆₂O₆: C, 79.76; H, 7.98. Found: C, 79.55; H, 7.72.

38-Benzyloxy-11, 17, 23, 29, 35-penta-*tert*-butyl-37, 39,40,41,42-

pentamethoxy-5-methoxycarbonylcalix[6]arene, 21—A solution of **19** (230 mg, 0.21 mmol) and DCC (64 mg, 0.31 mmol) was stirred at rt (5 h) in dry MeOH (5 mL), the solvent was evaporated, and the residue was partitioned between CH₂Cl₂ and HCl (1 M). The organic layer was washed (H₂O) dried (MgSO₄), evaporated, and chromatographed (flash, hexane–THF 9 : 1) to give **21** (175 mg, 75%) as a white solid, mp 190 °C. ¹H NMR: 0.98 [s, 18H, C(CH₃)₃], 1.27 [s, 9H, C(CH₃)₃], 1.33 [s, 18H, C(CH₃)₃], 2.55 (s, 6H, OCH₃), 2.78 (s, 3H, OCH₃), 3.42 (s, 6H, OCH₃), 3.52 (s, *J* = 16.0 Hz, 2H, ArCH₂Ar), 3.71 (s, 3H, CO₂Me), 3.76 (s, *J* = 15.6 Hz, 2H, ArCH₂Ar), 3.80 (s, *J* = 14.0 Hz, 2H, ArCH₂Ar), 4.17 (s, *J* = 14.0 Hz, 2H, ArCH₂Ar), 4.20 (s, *J* = 15.6 Hz, 2H, ArCH₂Ar), 4.50 (s, *J* = 16.0 Hz, 2H, ArCH₂Ar), 5.00 (s, 2H, OCH₂Ar), 6.71 (d, *J* = 2.3 Hz, 2H, ArH), 6.87 (d, *J* = 2.3 Hz, 2H, ArH), 7.15 (s, 2H, ArH), 7.16 (d, *J* = 2.5 Hz, 2H, ArH), 7.26 (d, *J* = 2.5 Hz, 2H, ArH), 7.35–7.44 (m, 5H, ArH), 7.54 (s, 2H, ArH). ¹³C NMR: 29.7, 30.5, 31.1 (ArCH₂Ar), 30.2, 30.8, 31.5 [C(CH₃)₃], 34.0, 34.15, 34.2 [C(CH₃)₃], 51.7 (CO₂Me) 59.9, 60.0 (OCH₃), 74.8 (OCH₂Ar), 124.7, 124.9, 126.8, 127.3, 128.0, 128.1 (ArH), 125.4, 128.6, 132.5, 133.4, 133.6, 135.4, 137.1, 145.7, 146.1, 153.4, 154.3 (ArC), 166.0 (CO). MALDI-TOF MS *m/z* (Ditranol + NaI), 1157.6 [M + Na]⁺, 1233.6 [M + Na]⁺. Anal. (%): Calc. for C₇₆H₉₄O₈: C, 80.38; H, 8.34. Found: C, 80.84; H, 8.12.

11, 17, 23- Tri-*tert*- butyl-26-hydroxy-25,27,28-trimethoxy-5-methoxycarbonylcalix[4]arene, 22 (cone : symmetric partial cone 10 : 1)—

Hydrogen was bubbled into a suspension of **20** (0.5 g, 0.38 mmol), Pd/C (50 mg) in THF (50 mL) during 30 min. The mixture was filtered (celite), evaporated, and the solid was triturated with EtOH, filtered, and dried to give **22** (262 mg, 100%). *Cone*: ¹H NMR: 0.87 [s, 18H, C(CH₃)₃], 1.39 [s, 9H, C(CH₃)₃], 3.28 (d, 2H, *J* = 12.9 Hz, ArCH₂Ar), 3.44 (d, 2H, *J* = 13.6 Hz, ArCH₂Ar), 3.90 (s, 6H, OCH₃), 3.96 (s, 3H, CO₂Me), 4.01 (s, 3H, OCH₃), 4.33 (d, 2H, *J* = 13.6 Hz, ArCH₂Ar), 4.35 (d, 2H, *J* = 12.9 Hz, ArCH₂Ar), 6.56 (d, 2H, *J* = 2.5 Hz, ArH), 6.63 (d, 2H, *J* = 2.5 Hz, ArH), 7.21 (s, 2H, ArH), 7.30 (s, 1H, OH), 7.87 (s, 2H, ArH). ¹³C NMR: 31.1, 31.7 [C(CH₃)₃], 31.2, 31.3 (ArCH₂Ar), 33.8, 34.2 [C(CH₃)₃], 51.7 (CO₂CH₃), 60.4, 63.0 (OCH₃), 124.7, 125.4, 125.5, 130.3 (ArH), 120.2, 129.1, 130.8, 132.3,

135.7, 146.0, 152.9, 155.3, 158.3 (Ar), 167.7 (CO). *Symmetric partial cone*: $^1\text{H NMR}$: 1.14 [s, 18H, C(CH₃)₃], 1.47 [s, 9H, C(CH₃)₃], 2.59 (s, 3H, OCH₃), 3.39 (d, 2H, $J = 13.9$ Hz, ArCH₂Ar), 3.77 (s, 6H, OCH₃), 3.89 (s, 4H, ArCH₂Ar), 3.95 (s, 3H, CO₂Me), 4.06 (d, 2H, $J = 13.9$ Hz, ArCH₂Ar), 6.83 (d, 2H, $J = 2.5$ Hz, ArH), 7.08 (d, 2H, $J = 2.5$ Hz, ArH), 7.33 (s, 2H, ArH), 7.82 (s, 1H, OH), 7.84 (s, 2H, ArH). $^{13}\text{C NMR}$: 31.1, 31.7 [C(CH₃)₃], 31.1, 38.4 (ArCH₂Ar), 33.9, 34.2 [C(CH₃)₃], 50.9 (CO₂CH₃), 58.2, 60.8 (OCH₃), 125.6, 127.0, 127.2, 130.3 (ArH), 120.2, 128.3, 131.7, 133.1, 133.5, 146.1, 146.3, 153.4 (Ar), 167.7 (CO); MALDI-TOF MS m/z (Ditranol + NaI), 693.4 [M + H]⁺, 715.4 [M + Na]⁺. Anal. (%): Calc. for C₄₅H₅₆O₆: C, 78.00; H, 8.15. Found: C, 77.89; H, 8.03.

5, 11, 17, 23, 29-Penta-*tert*-butyl-38-hydroxy-37,39,40,41,42-pentamethoxy-5-methoxycarbonylcalix[6]arene, 23—Hydrogen was bubbled into a suspension of **21** (200 mg, 0.18 mmol), Pd/C (20 mg) in THF (20 mL) during 30 min. The mixture was filtered (celite), evaporated, and the solid was triturated with EtOH. The mixture was filtered to give **23** (187 mg, 100%) as a white solid, mp 193–196 °C. $^1\text{H NMR}$: 1.06 [s, 9H, C(CH₃)₃], 1.17 [s, 18H, C(CH₃)₃], 1.19 [s, 18H, C(CH₃)₃], 3.02 (s, 6H, OCH₃), 3.32 (s, 6H, OCH₃), 3.57 (s, 3H, OCH₃), 3.83 (s, 3H, CO₂Me), 3.87 (s, 4H, ArCH₂Ar), 3.98 (s, 8H, ArCH₂Ar), 6.94 (s, 2H, ArH), 6.96 (d, $J = 2.4$ Hz, 2H, ArH), 7.02 (d, $J = 2.5$, 2H, ArH), 7.06 (d, $J = 2.5$ Hz, 2H, ArH), 7.11 (d, $J = 2.4$ Hz, 2H, ArH), 7.71 (s, 2H, ArH), 8.41 (s, 1H, OH). $^{13}\text{C NMR}$: 29.7, 30.9 (ArCH₂Ar), 30.4, 31.3, 31.4 [C(CH₃)₃], 34.0, 34.1, 34.2 [C(CH₃)₃], 51.6 (CO₂Me), 60.4, 60.42, 60.8 (OCH₃), 125.4, 125.5, 125.9, 126.2, 126.5, 133.3 (ArH) 126.2, 130.3, 131.8, 132.9, 133.6, 133.7, 145.3, 145.7, 146.9, 152.8, 154.0, 154.4, 156.8 (ArC) 167.3 (CO). MALDI-TOF MS m/z (Ditranol + NaI), 1067.6 [M + Na]⁺. Anal. (%): Calc. for C₆₉H₈₈O₈: C, 79.27; H, 8.48. Found: C, 79.57; H, 8.89.

11,17,23-Tri-*tert*-butyl-25, 27, 28-trimethoxy-5-methoxycarbonyl-26-methoxycarbonylmethyloxycalix[4]arene, 24 (asymmetric partial cone : cone 9 : 1)—A suspension of **22** (300 mg, 0.43 mmol) and K₂CO₃ (120 mg, 0.87 mmol) in CH₃CN (50 mL) was heated at 80 °C for 1 h. Methyl bromoacetate (0.8 mL, 0.87 mmol) was added and heating continued for 3 h. The solvent was evaporated, the residue was partitioned between CH₂Cl₂ and HCl (1 M), the organic layer was washed (H₂O), dried (MgSO₄), evaporated, and the residue was chromatographed (flash, hexane–THF 8 : 2) to give **24** (190 mg, 69%). *Asymmetric partial cone*: $^1\text{H NMR}$: 0.87 [s, 9H, C(CH₃)₃], 1.08 [s, 9H, C(CH₃)₃], 1.28 [s, 9H, C(CH₃)₃], 2.71 (s, 3H, OCH₃), 3.12–3.15 (m, 1H, ArCH₂Ar), 3.16–3.21 (m, 1H, ArCH₂Ar), 3.62 (s, 3H, OCH₃), 3.65 (s, 3H, OCH₃), 3.61 (s, 3H, CO₂CH₃), 3.70–3.80 (m, 4H, ArCH₂Ar), 3.72 (s, 3H, CO₂CH₃), 4.11 (d, 1H, $J = 13.9$ Hz, ArCH₂Ar), 4.19 (d, 1H, $J = 13.9$ Hz, ArCH₂Ar), 4.35 (d, 1H, $J = 11.1$ Hz, OCH₂CO), 4.57 (d, 1H, $J = 11.0$ Hz, OCH₂CO), 6.34 (d, 1H, $J = 2.0$ Hz, ArH), 6.92 (d, 1H, $J = 2.0$ Hz, ArH), 7.13 (br s, 2H, ArH), 7.18 (s, 1H, $J = 1.9$ Hz, ArH), 7.34 (br s, 2H, ArH), 7.68 (d, 1H, $J = 1.9$ Hz, ArH). $^{13}\text{C NMR}$: 30.8, 31.6, 31.7 [C(CH₃)₃], 30.9, 31.2, 36.3, 36.9 (ArCH₂Ar), 33.4, 33.8, 34.2 [C(CH₃)₃], 51.5, 51.9 (CO₂CH₃), 58.4, 59.8, 60.6 (OCH₃), 70.8 (OCH₂CO), 124.9, 126.2, 126.4, 127.3, 128.2, 128.3, 128.6, 130.4, 131.8 (ArH), 132.0, 132.7, 132.8, 134.6, 134.8, 135.8, 136.4, 137.3, 143.5, 144.2, 145.4, 151.6, 154.8, 155.3, 155.7 (Ar), 159.8, 166.9 (CO). *Cone*: $^1\text{H NMR}$: 0.66 [s, 9H, C(CH₃)₃], 1.31 [s, 18H, C(CH₃)₃], 3.20 (d, 2H, $J = 10.0$ Hz, ArCH₂Ar), 3.23 (d, 2H, $J = 9.8$ Hz, ArCH₂Ar), 3.19 (s, 3H, CO₂CH₃), 3.61 (s, 3H, OCH₃), 3.73 (s, 6H, OCH₃), 3.79 (s, 3H, CO₂CH₃), 4.40 (d, 2H, $J = 9.8$ Hz, ArCH₂Ar), 4.42 (d, 2H, $J = 10.0$ Hz, ArCH₂Ar), 4.49 (s, 2H, OCH₂CO), 6.26 (s, 2H, ArH), 7.02 (s, 2H, ArH), 7.14 (s, 2H, ArH), 7.24 (s, 2H, ArH). $^{13}\text{C NMR}$: 30.7, 31.4 [C(CH₃)₃], 30.9, 31.1 (ArCH₂Ar), 33.8, 34.2 [C(CH₃)₃], 51.4, 51.9 (CO₂CH₃), 58.3, 60.5 (OCH₃), 71.3 (OCH₂CO), 159.8, 166.9 (CO); MALDI-TOF MS m/z (Ditranol + NaI), 764.5 [M + H]⁺, 787.5 [M + Na]⁺. Anal. (%): Calc. for C₅₂H₆₂O₆: C, 75.36; H, 7.91. Found: C, 75.56; H, 7.99.

11,17,23,29,35-Penta-*tert*-butyl-37,39,40,41,42-pentamethoxy-5-methoxycarbonyl-38-methoxycarbonylmethyloxycalix[6]arene, 25—A

suspension of **23** (150 mg, 0.14 mmol) and K₂CO₃ (29 mg, 0.21 mmol) in Me₂CO (20 mL) was heated at 80 °C for 1 h. Methyl bromoacetate (19 μL, 0.21 mmol) was added and heating continued for 5 h. The solvent was evaporated, the residue was partitioned between CH₂Cl₂ and HCl (1 M), the organic layer was washed (H₂O), dried (MgSO₄), evaporated, and the residue was precipitated from MeOH to give **25** (135 mg, 87%) as a white solid mp 197 °C; ¹H NMR: 1.03 [s, 18H, C(CH₃)₃], 1.26 [s, 9H, C(CH₃)₃], 1.33 [s, 18H, C(CH₃)₃], 2.72 (s, 6H, OCH₃), 2.84 (s, 3H, OCH₃), 3.33 (s, 6H, OCH₃), 3.74 (s, 3H, CO₂Me), 3.79 (s, 3H, CO₂Me), 3.98 (br s, 12H, ArCH₂Ar), 4.39 (s, 2H, OCH₂CO₂), 6.77 (s, 2H, ArH), 6.93 (s, 2H, ArH), 7.13 (s, 2H, ArH), 7.14 (s, 2H, ArH), 7.26 (s, 2H, ArH), 7.58 (s, 2H, ArH). ¹³C NMR: 29.7, 30.1, 30.9 (ArCH₂Ar), 29.5, 30.2, 31.4 [C(CH₃)₃], 34.0, 34.2, 34.2 [C(CH₃)₃], 51.8, 52.0 (CO₂Me), 59.9, 60.0 (OCH₃), 69.2 (OCH₂CO₂), 125.1, 126.6, 127.0, 127.5, 129.7 (ArH), 125.2, 125.8, 132.4, 133.3, 133.5, 133.6, 135.1, 145.6, 145.7, 146.3, 153.6, 154.2, 154.3, 157.7 (ArC), 166.3, 169.2 (CO); MALDI-TOF MS *m/z* (Ditranol + NaI), 1139.7 [M + Na]⁺. Anal. (%): Calc. for C₇₂H₉₂O₁₀: C, 77.38; H, 8.30. Found: C, 77.05; H, 8.15.

11,17,23-Tri-*tert*-butyl-5-hydroxycarbonyl-26-hydroxycarbonylmethyloxy-25,27,28-trimethoxycalix[4]arene, 26 (asymmetric partial cone : cone 9 : 1)—A suspension of **24** (200 mg, 0.26 mmol) and KOH (50 mg) in THF (50 mL) was heated at 80 °C for 5 h. The solvent was evaporated, the residue was partitioned between CH₂Cl₂ and HCl (1 M), the organic layer was washed (H₂O), dried (MgSO₄), evaporated, and then precipitated from MeOH to give **26** (175 mg, 92%).

Asymmetric partial cone: ¹H NMR: 0.84 [s, 9H, C(CH₃)₃], 1.12 [s, 9H, C(CH₃)₃], 1.25 [s, 9H, C(CH₃)₃], 2.75 (s, 3H, OCH₃), 3.15–3.25 (m, 2H, ArCH₂Ar), 3.62 (s, 3H, OCH₃), 3.74 (s, 3H, OCH₃), 3.70–3.80 (m, 4H, ArCH₂Ar), 4.17 (m, 1H, ArCH₂Ar), 4.23 (m, 1H, ArCH₂Ar), 4.35 (s, 2H, OCH₂CO), 6.34 (d, 1H, *J* = 2.0 Hz, ArH), 6.92 (d, 1H, *J* = 2.0 Hz, ArH), 7.13 (br s, 2H, ArH), 7.18 (s, 1H, *J* = 1.9 Hz, ArH), 7.34 (br s, 2H, ArH), 7.68 (d, 1H, *J* = 1.9 Hz, ArH). ¹³C NMR: 30.8, 31.6, 31.7 [C(CH₃)₃], 30.9, 31.2, 37.7, 38.4 (ArCH₂Ar), 33.4, 33.8, 34.2 [C(CH₃)₃], 58.4, 59.8, 60.6 (OCH₃), 70.4 (OCH₂CO), 124.9, 126.2, 126.4, 127.3, 128.2, 128.3, 128.6, 130.4, 131.8 (ArH), 132.0, 132.7, 132.8, 134.6, 134.8, 135.8, 136.4, 137.3, 143.5, 144.2, 145.4, 151.6, 154.8, 155.3, 155.7 (Ar), 169.0, 170.5 (CO). *Cone*: ¹H NMR: 0.72 [s, 9H, C(CH₃)₃], 1.35 [s, 18H, C(CH₃)₃], 3.27 (m, 2H, ArCH₂Ar), 3.29 (m, 2H, ArCH₂Ar), 3.61 (s, 3H, OCH₃), 3.73 (s, 6H, OCH₃), 4.40 (d, 2H, *J* = 9.8 Hz, ArCH₂Ar), 4.42 (d, 2H, *J* = 10.0 Hz, ArCH₂Ar), 4.62 (s, 2H, OCH₂CO), 6.26 (s, 2H, ArH), 7.02 (s, 2H, ArH), 7.14 (s, 2H, ArH), 7.24 (s, 2H, ArH). ¹³C NMR: 30.7, 31.4 [C(CH₃)₃], 30.9, 31.1 (ArCH₂Ar), 33.8, 34.2 [C(CH₃)₃], 51.4, 51.9 (CO₂CH₃), 58.3, 60.5 (OCH₃), 71.2 (OCH₂CO), 169.0, 170.5 (CO). MALDI-TOF MS *m/z* (Ditranol + NaI), 736.5 [M]⁺, 759.4 [M + Na]⁺. Anal. (%): Calc. for C₄₆H₅₆O₈: C, 74.97; H, 7.66. Found: C, 74.80; H, 7.51.

11,17,23,29,35-Penta(*tert*-butyl-5-hydroxycarbonyl-38-hydroxycarbonylmethyloxy-37,39,40,41,42-pentamethoxycalix[6]arene, 27—A

suspension of **25** (150 mg, 0.13 mmol) and KOH (200 mg) in THF (20 mL) was heated at 80 °C for 5 h, the solvent was evaporated, the residue was partitioned between CH₂Cl₂ and HCl (1 M), the organic layer was washed (H₂O), dried (MgSO₄), evaporated, and the residue was precipitated from MeOH to give **27** (140 mg, 99%) as a white solid, mp 220 °C. ¹H NMR (C₂D₂Cl₄, 388 K (115 °C)): 0.95 [s, 9H, C(CH₃)₃], 1.00 [s, 18H, C(CH₃)₃], 1.22 [s, 18H, C(CH₃)₃], 3.16 (s, 2H, OCH₂CO₂), 3.26 (s, 6H, OCH₃), 3.41 (s, 6H, OCH₃), 3.46 (s, 3H, OCH₃), 3.92 (s, 8H, ArCH₂Ar), 3.98 (s, 4H, ArCH₂Ar), 6.71 (s, 2H, ArH), 6.73 (s, 2H, ArH), 6.85 (s, 2H, ArH), 7.04 (s, 4H, ArH), 7.84 (s, 2H, ArH). ¹³C NMR: 30.1, 30.2, 30.7 (ArCH₂Ar), 30.8, 30.9, 31.3 [C(CH₃)₃], 33.4, 33.43, 33.5 [C(CH₃)₃], 59.5, 59.53, 59.9

(OCH₃), 68.8 (OCH₂-CO₂), 123.8, 124.2, 124.5, 126.5, 126.7, 132.0 (ArH), 123.9, 131.5, 132.3, 132.4, 132.7, 132.9, 134.5, 145.2, 145.6, 145.65, 153.0, 153.2 (ArC), 159.8, 167.1 (CO). MALDI-TOF MS *m/z* (Ditranol + NaI), 1111.7 [M + Na]⁺. Anal. (%): Calc. for C₇₀H₈₈O₁₀: C, 77.17; H, 8.14. Found: C, 77.32; H, 8.41.

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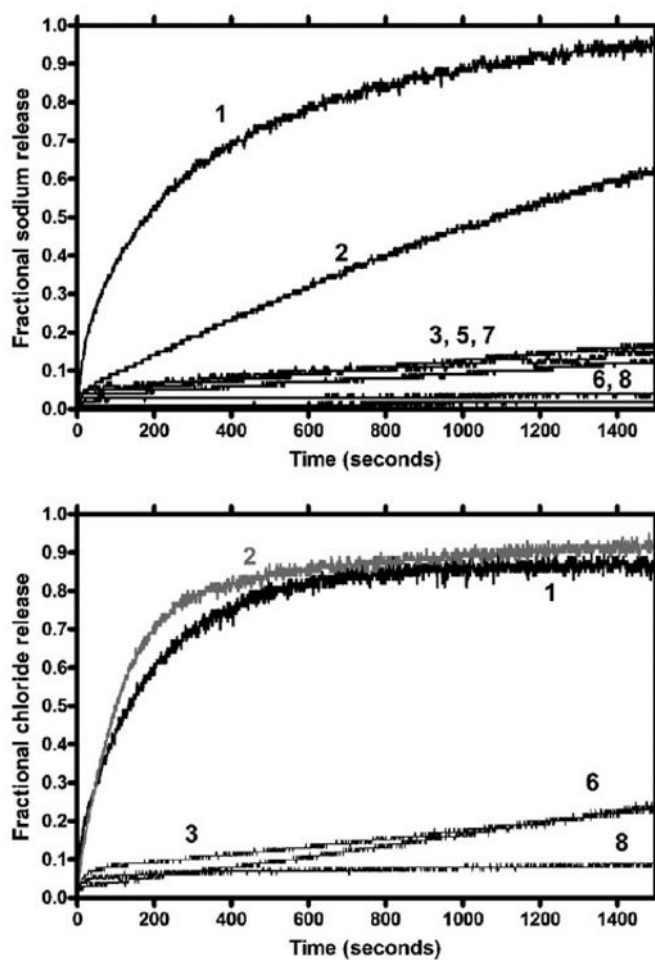


Fig. 1. Sodium (upper panel) and chloride (lower panel) release from DOPC:DOPA liposomes mediated by synthetic ionophores.

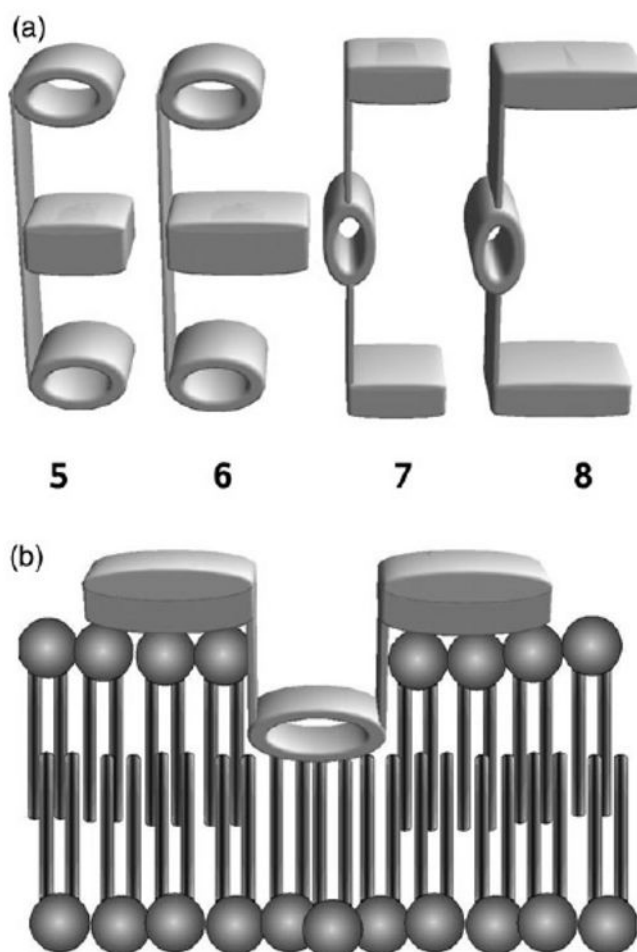


Fig. 2. Schematic representations of compounds (left to right) **5**, **6**, **7** and **8**. Postulated non-conducting structure for calixarene derivative **8**.

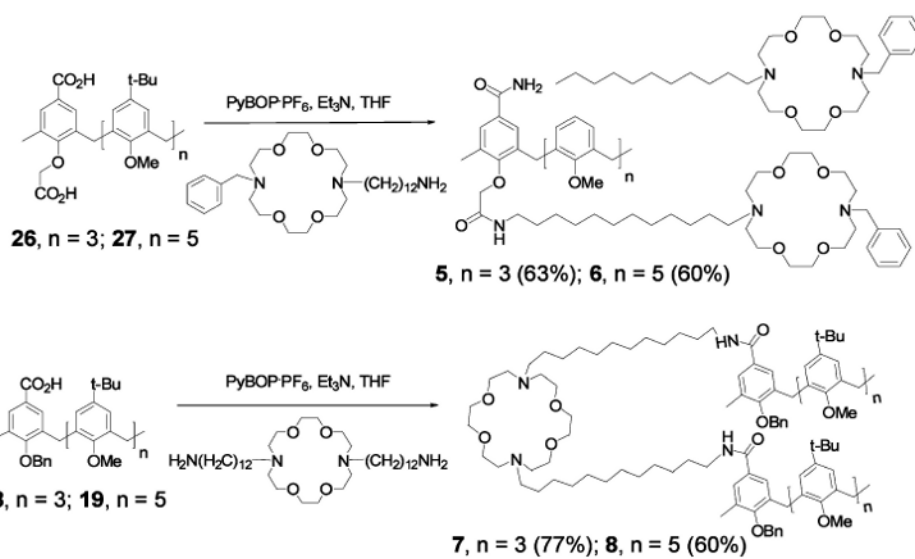


Chart 1.
Final coupling steps to form calixarene derivatives **5**, **6**, **7** and **8**.