# Novel Resorcin[4]arenes as Potassium-Selective Ion-Channel and Transporter Mimics

**Angela J. Wright,[a] Susan E. Matthews,[a] Wolfgang B. Fischer,[b] and Paul D. Beer*[a]**

**Abstract:** A series of novel resorcin[4]arenes with extended π systems have been synthesised and developed as potassium-selective transporters. Resorcin[4]arenes that feature crown ether moieties function as efficient carriers of $K^+$ across bulk liquid membranes showing enhanced selectivity over the other alkali metal ions relative to a model system (benzo[15]crown-5). Incorporation of functionalities suitable for pore formation, in addition to an extra annulus of aromatic residues, gives molecules which have remarkable ion-channel-mimicking behaviour in a biological lipid bilayer with outstanding $K^+/Na^+$ selectivity.

**Keywords:** alkali metals · ion channels · ionophores · planar lipid bilayer · resorcin[4]arenes

## Introduction

Cations play a number of crucial roles in biology, including the involvement of potassium and sodium in nerve impulse transmission, which depends upon the efficient transport of cations across cellular membranes. However, the lipid bilayer of biological membranes is intrinsically impermeable to ions and polar molecules, and permeability is only conferred by integral membrane proteins such as channels, pumps and transporters. Understanding the functions and mechanisms underlying these transport processes is of paramount importance to chemistry and biochemistry.[1]

Over the past decade considerable research effort has been directed towards the proteins responsible for transport. The structure of the acetylcholine-gated sodium/potassium channel was elucidated by cryoelectron microscopy by Unwin in 1995,[2] and the first X-ray structure of a potassium channel (from *Streptomyces lividans*) was reported three years later.[3] Such discoveries of structural features have sparked intensive investigation into the mechanistic details concerning transport and selectivity. Ion-channel proteins are difficult to isolate and handle,[4] therefore a number of model systems have been developed that are based on naturally occurring channel-forming peptide sequences and synthetic ion-channel models.

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Many different synthetic architectures have been exploited in the development of ion channel mimics: some composed of two half-channels,[5, 6] others of a selective core derived from macrocycles such as cyclodextrins,[7] crown ethers[8] and calixarenes.[9] In these last approaches the core is presumed to reside within the bilayer, and ion conduction to occur through the central unit. There are few examples of model systems that exhibit cation selectivity. Such systems have potential applications as sensors and cell-permeabilising agents, allowing laboratory testing of channel-blocking agents and facilitating drug delivery.[10]

Resorcin[4]arenes form complexes with both cations and polar organic molecules, but are also capable of solubilising simple sugars such as glucose and ribose into non-polar solvents,[11] and transporting simple hexoses and pentoses across a lipid bilayer.[12] Tanaka and Kobuke[6] have reported transport of cations across a bilayer, with discrimination between potassium and sodium, by using simple alkyl resorcin[4]arenes. They postulated that the residues self-assemble into tail-to-tail dimers within a phospholipid bilayer by interdigitation of the alkyl chains, to form a channel pore that allows the passage of cations. Resorcin[4]arenes share similar architectural motifs with the recently solved structure of the potassium channel.[3] Notably, the channel structure includes an array of four aromatic groups at the membrane face and carbonyl oxygens, directed into the selectivity filter, which are arranged to differentiate between potassium and other cations.

Here we report the synthesis of a novel class of resorcin[4]arenes that are capable of transporting potassium through bulk liquid membranes and across planar lipid bilayers. Incorporation of functionalities designed for pore formation has allowed us to develop potassium-selective molecules;

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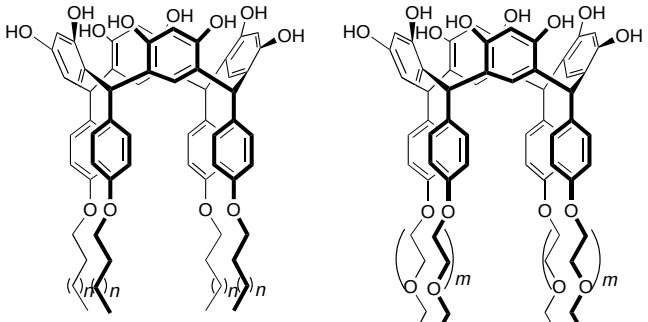
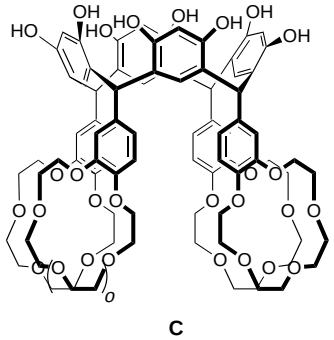
these exhibit remarkable ion-channel-like behaviour in model membranes. Furthermore, inclusion of specific binding sites (e.g. crown ethers) has enabled the design of bulk liquid membrane transport molecules that can be fine-tuned for the selective transport of potassium over sodium and caesium.

## Results

**Synthesis**: Resorcin[4]arenes were chosen for development as they include two key features required by potential ion channels: amphiphilicity to enable effective orientation in the bilayer and an annulus of the correct dimensions to allow the passage of ions. Inclusion of an extra ring of aromatic groups at the lower rim was intended to both rigidify the structure to facilitate pore functioning and allow additional weak cation–π interactions[13, 14] within the pore to enhance both kinetics and selectivity.

Three approaches were developed to investigate the structural requirements for transport across bulk liquid or supported liquid membranes. A series of new resorcin[4]-arenes with phenoxyalkyl substituents (**A**) were initially pre-




pared in which the carbon chain length at the lower rim was systematically varied in order to provide evidence of a mechanism involving interdigitation of the two resorcin[4]-arenes within the bilayer and to identify an optimal chain length, which could be correlated with the known width of the bilayer (~50 Å).

Alternatively pre-organised binding sites were provided by using monoether and crown ether moieties (**C**) whose selective complexation and transport properties are well documented.[15, 16] Acyclic analogues of crown-ether-derived species (**B**) were also synthesised that have been proposed to provide a series of binding sites allowing cation "hopping".[17]

The new resorcin[4]arenes were prepared by using modifications of previously reported synthetic procedures.[18] Condensation of resorcinol with an appropriately functionalised aldehyde in absolute ethanol at 80 °C yielded the all *cis* isomers in high yield (70–91%). For both the alkyl and polyether resorcin[4]arenes (**1**–**8**; Scheme 1) the desired isomer precipitated from the reaction mixture and recrystallisation or trituration from hot ethanol gave the pure product. However, with the benzocrown ether derived resorcin[4]-arenes (**9, 10**; Scheme 2), the products were obtained as a mixtures of isomers; their low solubility precluded purification.

The low solubility of the simple resorcin[4]arenes (**1**–**10**) in halogenated solvents lead to the synthesis of octaacyl derivatives (**11**–**16**) suitable for study using bulk liquid membrane techniques (Scheme 1). Acylation was achieved through heating the resorcin[4]arenes to 110 °C in acetic anhydride using pyridine as base.[18] With both the alkyl and polyether derivatives the product was isolated as a flattened cone structure, with inequivalent adjacent aromatic units. In the case of the benzocrown ether derivatives this method enabled isolation of the resorcin[4]arenes as a single isomer in the $C_{4v}$ symmetrical crown conformation.

## Discussion

A combination of bulk liquid membrane and planar lipid bilayer techniques were used to identify resorcin[4]arene-based molecules with potential as both transporter molecules and channel mimics. Bulk liquid systems were initially used to provide a qualitative picture of carrier-function and selectivities. Detailed conductimetric studies were then performed by insertion of the resorcin[4]arenes into planar lipid bilayers. This latter technique yielded useful information regarding the mechanistic details of resorcin[4]arene behaviour for analogy with natural systems.

**U-tube studies**: To gain an understanding of the general transport abilities and selectivities of the molecules towards alkali metal cations, initial crude bulk liquid membrane studies in chloroform were performed by using a modification of the technique of Rebek, Jr. et al.[19]

**Comparison of resorcin[4]arenes with known transporter systems (crown ethers):** U-tube studies with potassium picrate were carried out on an example of each type of resorcin[4]-arene synthesised: phenoxy-alkyl, -polyether, and -crown ether. Resorcin[4]arenes (**15, 16**), which feature the well-known crown ether pre-organised unit,[16] demonstrated efficient carrier-mediated transport over the seven hour study period although the rate of transport was reduced relative to that of the model compound benzo[15]crown-5 (Figure 1).

In contrast, the acylated derivatives (**11, 14**) of alkyl and polyether resorcin[4]arenes show negligible transport comparable to the blank experiment with no carrier in the membrane phase. Comparison of the concentration of potas-

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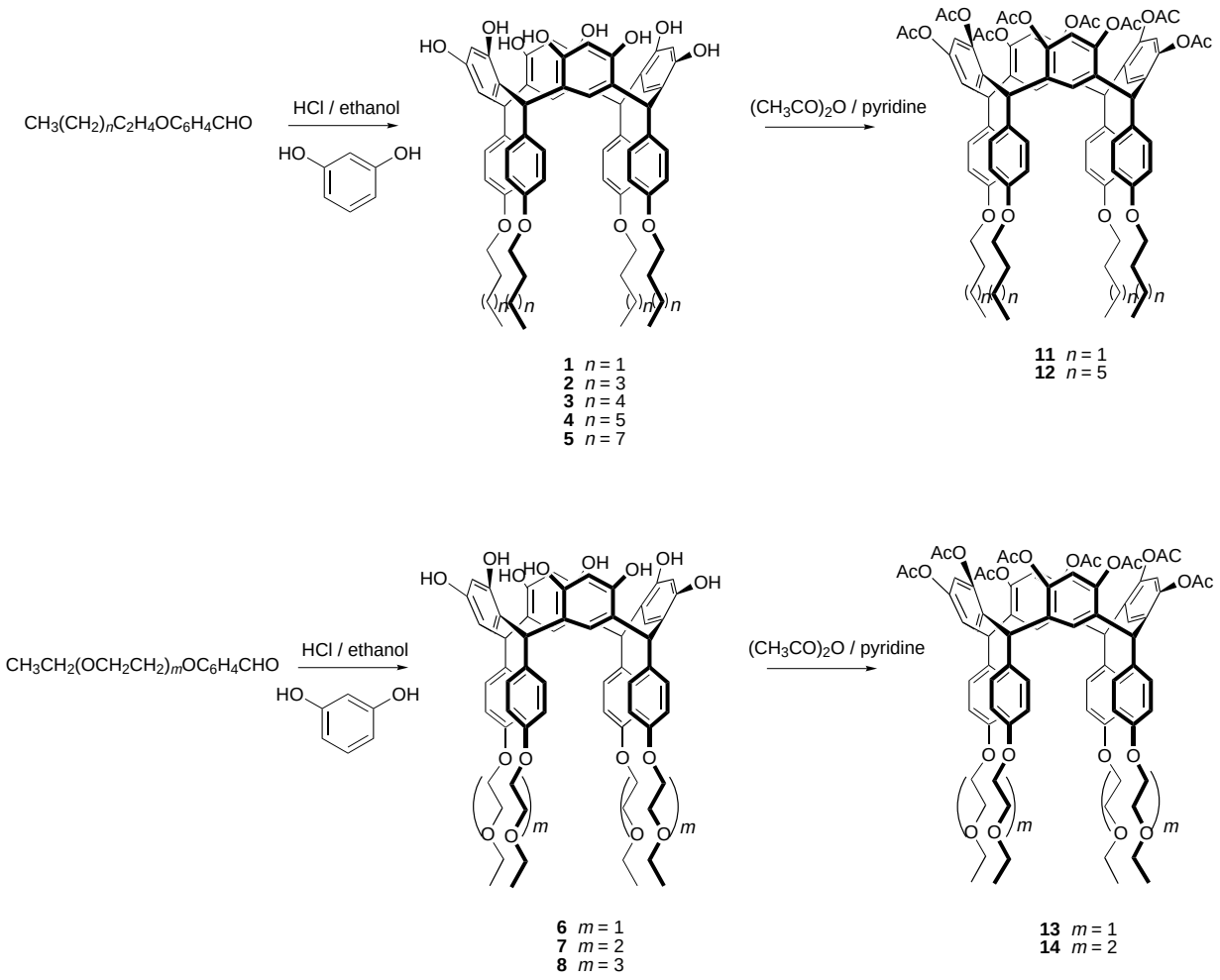
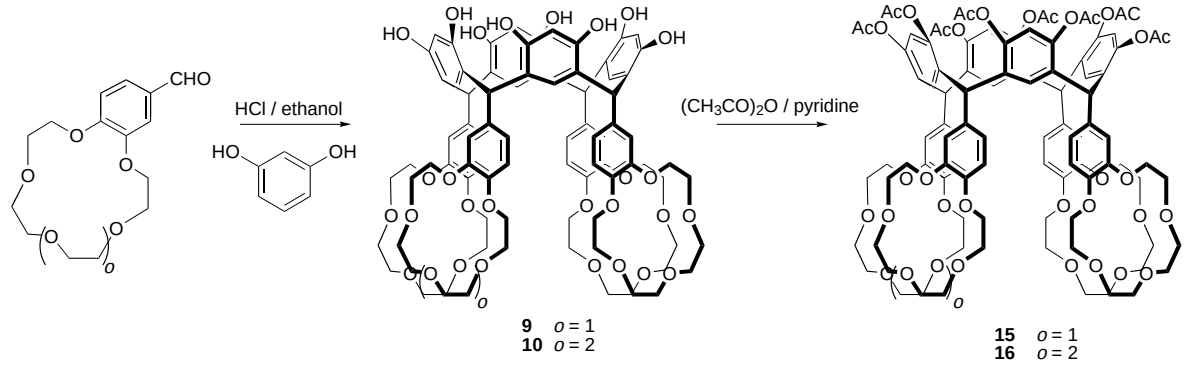



Scheme 1. Synthesis of polyalkyl and polyether resorcin[4]arenes and their acylated derivatives.




Scheme 2. Synthesis of crown ether resorcin[4]arenes and their acylated derivatives

sium picrate (KPic) in the receiving phase after 24 hours (Table 1) reflects the requirement for a pre-organised binding site. Mean fluxes of only $10^{-9}$ mol h$^{-1}$ were observed for the alkyl and polyether resorcin[4]arenes, whereas the crown resorcin[4]arenes exhibited fluxes of $10^{-6}$ mol h$^{-1}$.

**Cation selectivity**: After suitable transporter molecules had been identified, Group 1 metal ion selectivity studies were undertaken through variation of the source phase (10 mM aq.

Table 1. Transport of potassium across a chloroform bulk liquid membrane ($T = 20\,^{\circ}$C).

| Resorcin[4]arene | [KPic] in receiving phase [mM][a] | Mean flux [mol h$^{-1}$] |
|---|---|---|
| **11** | 0.01 | $2.10 \times 10^{-9}$ |
| **14** | 0.04 | $8.96 \times 10^{-9}$ |
| **15** | 5.30 | $1.10 \times 10^{-6}$ |
| **16** | 5.12 | $1.05 \times 10^{-6}$ |

[a] After 24 h.



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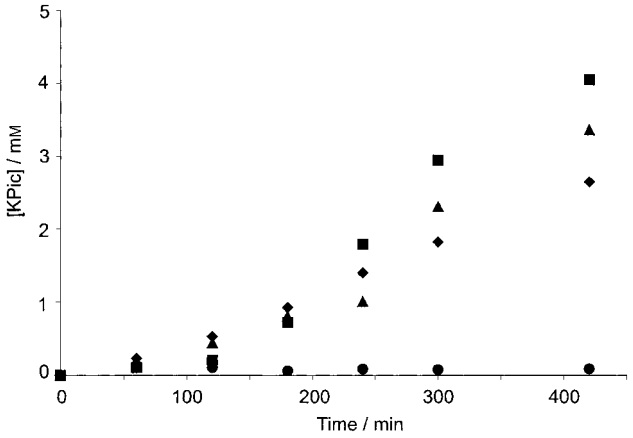



Figure 1. Transport of potassium picrate across a chloroform bulk liquid membrane at 20 °C by resorcin[4]arenes **14** (●), **15** (◆), **16** (▲) and benzo[15]crown-5 (■)

sodium picrate, potassium picrate and caesium picrate). Under these conditions, the model compound benzo[15]-crown-5 shows considerable transport of both sodium and potassium, but is unable to distinguish between these two cations (Table 2).

Table 2. Comparison of alkali metal transport across a chloroform bulk liquid membrane ($T = 20\,^{\circ}C$).

| Resorcin[4]arene | Mean flux $Na^+$ [mol h$^{-1}$] | Mean flux $K^+$ [mol h$^{-1}$] | Mean flux $Cs^+$ [mol h$^{-1}$] |
|---|---|---|---|
| **15** | $8.30 \times 10^{-7}$ | $1.10 \times 10^{-6}$ | $8.50 \times 10^{-7}$ |
| **16** | $4.04 \times 10^{-7}$ | $1.05 \times 10^{-6}$ | $1.04 \times 10^{-6}$ |
| benzo[15]crown-5 | $1.03 \times 10^{-6}$ | $1.09 \times 10^{-6}$ | $6.20 \times 10^{-7}$ |

In contrast when the same unit is incorporated onto a resorcin[4]arene scaffold (**15**), selectivity is enhanced with potassium being transported faster than both sodium and caesium (Figure 2). With resorcin[4]arene **16**, which features four benzo[18]crown-6 units, more complex selectivity trends are observed (Table 2). Transport of sodium is slow, whereas both caesium and potassium are transported at similar rates.

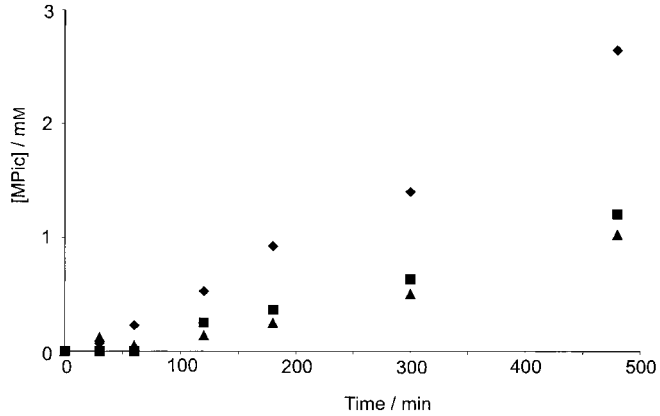



Figure 2. Cation selectivity profile for bulk liquid membrane transport of picrate salts by resorcin[4]arene (**15**) at 20 °C. potassium (◆), sodium (■) and caesium (▲)

These results may be rationalised by considering the balance between the rates of complexation at the source phase and decomplexation at the receiver phase, which is itself influenced by the complementarity between the metal cation and the crown ether binding site. For the benzo[15]-crown-5 derivative **15**,[15] sodium is bound most strongly and, therefore, transport is limited by de-complexation, whereas caesium is too large to be bound tightly and complexation may be the rate-limiting step. In contrast, it can be proposed that potassium is bound efficiently but not so as to disfavour de-complexation and hence the highest fluxes are exhibited with this cation.

**Planar lipid bilayer studies**: These preliminary U-tube studies do not reveal any conclusive evidence regarding transport abilities. However, they may be used in combination with planar lipid bilayer studies to infer mechanism. Inactivity in liquid membranes and activity in lipid bilayers implies a channel-type mechanism, as only carrier-mediated transport is possible in a bulk liquid membrane.[1, 4] Pore sizes calculated from conductance levels can be used to determine the mode of ion conductance through the lipid bilayer.

**Potassium ion transport**: Five alkyl resorcin[4]arenes (**1**–**5**) were tested for ion channel activity by using the planar lipid bilayer technique of Montal and Müller.[20] Rectangular current patterns, indicating channel-like ion flux, were observed for **4** and **5** at an applied membrane potential of $\pm 150$ mV (Figure 3a and b). Lowering the membrane poten-

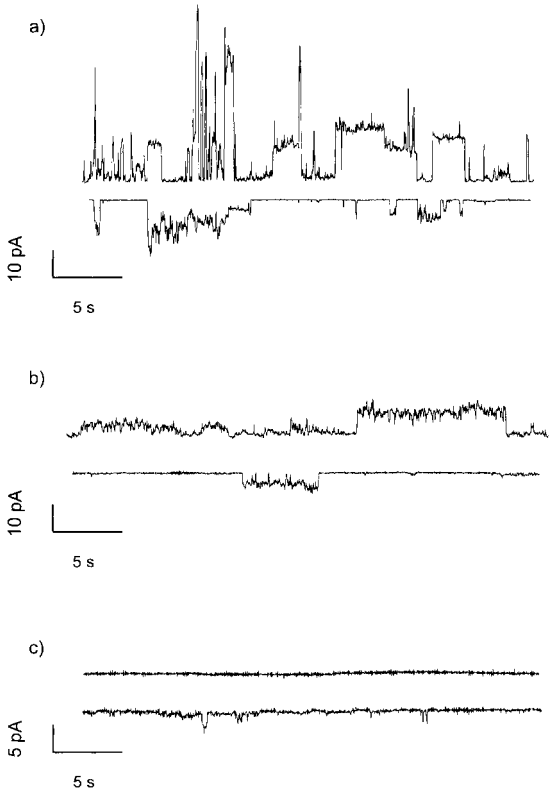



Figure 3. Current activity of resorcin[4]arenes **5** (a), **4** (b), and **2** (c) reconstituted in a lipid bilayer (L-$\alpha$-phosphatidylcholine) at $\pm 150$ mV applied membrane potential. Data were filtered, resulting in a cut off frequency of 50 Hz.

tial below ±150 mV leads to a decrease in the current amplitudes, a reduced number of events and an increase in non-rectangular current patterns, all of which indicate reduced ion flux. In the case of resorcin[4]arenes with shorter chain lengths (**1** and **2**), no current was observed regardless of the applied potential. In contrast, the polyether resorcin[4]-arene **8** simply perturbs the electrical properties of the membrane resulting in only short burst-like channel activity (Figure 4).

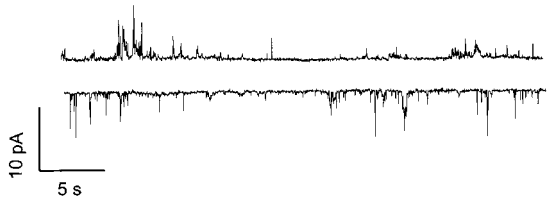
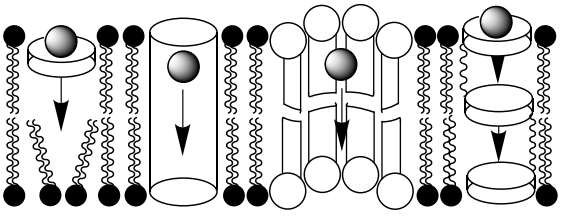



Figure 4. Current activity of **8** reconstituted in a lipid bilayer (L-α-Phosphatidylcholine) at ±150 mV applied membrane potential. Data were filtered, resulting in a cut off frequency of 50 Hz.

This dependence of the channel recordings on the length of the aliphatic chains is in agreement with the proposed concept[6] that two resorcin[4]arenes firstly must co-align across the membrane to allow the ion flux (**E** and **F**). A similar




mechanism has been postulated previously for gramicidine.[10, 25] If the aliphatic chain length is too short, and the ends cannot meet within the lipid membrane to allow the formation of a water filled pore, then no current can be observed. Addition of ether oxygens within the chains appears, in these preliminary studies, to be detrimental to ion flux.

The recordings indicate open times of over several seconds for the resorcin[4]arenes **4** and **5**. On expanding a particular section of the channel recordings for **5** it is possible to resolve channel fluctuations in the ms range indicating fast conformational changes of the molecules (Figure 5). Similar flickering has also been observed with pore-forming membrane peptides.[21, 22]

With resorcin[4]arene **5** well-resolved, irregularly spaced conductance levels [2, 13, 18 and 21 pA (13, 87, 120, 140 pS)] were observed at −150 mV (Figure 6). Whereas for **4** levels at 3 and 10 pA (20 and 67 pS) were found. The pore radius has been estimated from these values, using standard methods,[23] to be between approximately 0.5 and 1.7 Å. This pore diameter is large enough to allow for the passage of potassium

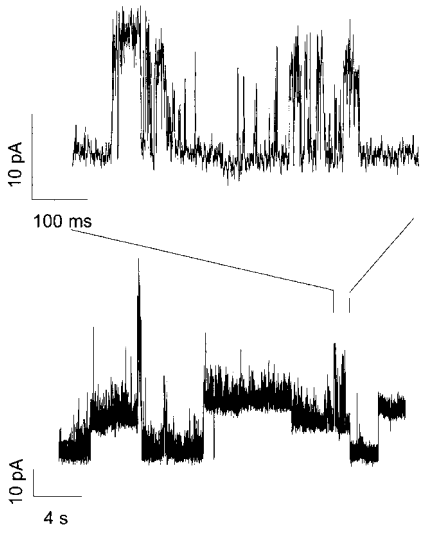



Figure 5. Extended view of a section of the unfiltered trace for resorcin[4]-arene **5**.

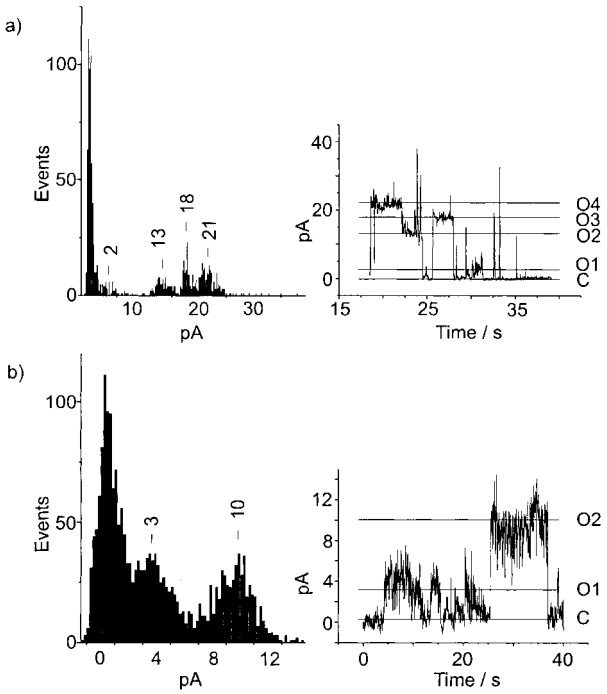



Figure 6. Current histogram of current recordings from the data shown in Figure 3. a) Based on a selected section from recordings for resorcin[4]-arene **5**. b) Based on the complete trace for resorcin[4]arene **4**. Values in histograms (shown in pA) refer to the centres of the peaks fitted onto the data. C: closed state; O1 to O4: open states 1 to 4 at 2, 13, 18 and 21 pA respectively.

ions and is smaller than the annulus of the resorcin[4]arenes (≈5.3 Å C−C distance[24]).

The current levels observed in all cases are of a similar size to those of peptide-based ion channels; however, a number of mechanisms can be proposed (**D**–**G**). Currents from the aliphatic resorcinarenes (**4** and **5**) tend towards those seen for peptide pores featuring hydrophilic residues on the interior of the pore.[21]

Although the dependence of current flux on chain length tends towards an interdigitation based mechanism (**E**), the



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estimated pore sizes, irregularly spaced conductance levels and current levels observed are somewhat inconsistent with an annular transport mechanism. Thus, our current study does not rule out a mechanism for ion transport by the assembly of the molecules around a pseudosymmetrical axis forming an internal water-filled pore (**F**).

**Cation selectivity studies**: The selectivity of the alkyl resorcin[4]arenes for potassium was evaluated through a comparison with conductance using a sodium chloride based electrolyte of identical ionic strength and pH.

No conductance was observed with an identical concentration of resorcin[4]arene (**4** and **5**; $3 \times 10^{-9}$ mol) as in the studies with potassium. In addition, application of up to 150 μL of a tenfold more concentrated solution (1 mM) in 10 μL aliquots resulted in no conductance. The permeability ratios ($P_{K+}/P_{Na+}$) exceed 50 in both cases, a value considerably higher than that obtained with resorcin[4]arenes that feature only one annulus of aromatic residues.[6] It can be concluded that incorporation of further aromatic residues at the lower rim both enhances the ion flux and increases the ion selectivity ($K^+/Na^+$) of the resorcin[4]arene architecture.

## Conclusion

Through the synthesis of a variety of novel resorcin[4]arene-derived molecules, potassium selectivity in both bulk liquid membranes and planar lipid bilayer conditions has been established. Long-chain phenoxyalkyl resorcin[4]arenes have a conductance of potassium ions across a lipid bilayer of a level comparable to that of natural systems (e.g., gramicidin) and outstanding $K^+/Na^+$ flux selectivity. Evidence for a channel or aggregate pore mechanism has been demonstrated. The incorporation of a crown ether pre-organised binding site resulted in molecules capable of demonstrating enhanced transportation and selectivity for potassium across a bulk liquid membrane when compared with a model system (benzo[15]crown-5).

## Experimental Section

All chemicals were commercial grade and used without further purification unless otherwise stated. Solvents were pre-dried, purified by distillation and stored under nitrogen where appropriate. Dichloromethane was distilled from calcium hydride, tetrahydrofuran was distilled from sodium wire with benzophenone as indicator and triethylamine was distilled from potassium hydroxide.

Nuclear magnetic resonance spectra were recorded with either a 300 MHz Varian VXWorks spectrometer or a 500 MHz Varian Unity spectrometer. Ultraviolet-visible spectra were recorded on a Perkin–Elmer Lambda 6 spectrophotometer. Mass spectral analyses were carried out by the EPSRC mass spectrometry service of University College, Swansea.[26]

Simple aldehyde precursors were prepared according to literature procedures.[27] 4′-formylbenzo[15]crown-5 and 4′-formylbenzo[18]crown-6 were synthesised by following the method of Reinhoudt.[28]

**General procedure for the synthesis of resorcin[4]arenes**: Concentrated hydrochloric acid (3 mL, 35 mmol) was added dropwise to a stirred mixture of 1,3-dihydroxybenzene (1.65g, 15 mmol) and the corresponding aldehyde (15 mmol) in absolute ethanol (12 mL). The red solution was stirred at 75 °C for 10 h then cooled over ice. The resulting precipitate was isolated by Büchner filtration, washed with cold ethanol and dried. The crude product was recrystallised from hot ethanol to give the desired resorcin[4]arene. The numbering scheme for NMR assignments of resorcin[4]arenes is given in Figure 7.

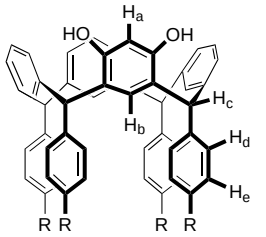

Figure 7. Numbering scheme for NMR assignment of resorcin[4]arenes.

**2,8,14,20-Tetra(4-butyloxyphenyl)pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]tetracosa-1(25),2,4,7(26),8,10,13(27),14,16,19-(28),20,22-dodecaene-4,6,10,12,16,18,22,24-octol (1)**: Yield: 79 %; $^1$H NMR (500 MHz, [D]DMF, 18 °C): $\delta = 8.47$ (s, 8H; ArO*H*), 6.58 (d, $^3J$(H,H) = 8.6 Hz, 8H; $H_d$), 6.49 (d, $^3J$(H,H) = 8.6 Hz, 8H; $H_e$), 6.27 (br s, 4H; $H_b$), 6.08 (s, 4H; $H_a$), 5.54 (s, 4H; $H_c$), 3.86 (t, $^3J$(H,H) = 6.2 Hz, 8H; OC$H_2$), 1.67 (m, 8H; OCH$_2$C$H_2$), 1.43 (m, 8H; C$H_2$CH$_3$), 0.93 (t, $^3J$(H,H) = 7.4 Hz, 12H; C$H_3$); $^{13}$C NMR (75 MHz, [D]DMF, 18 °C): $\delta = 156.21$, 153.00, 137.87, 131.09, 129.28, 120.78, 112.81, 101.69, 66.77, 40.50, 31.18, 18.80, 13.13; MS (FAB): *m/z*: 1081 $[M]^+$, 1104 $[M+Na]^+$.

**2,8,14,20-Tetra(4-hexyloxyphenyl)pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]tetracosa-1(25),2,4,7(26),8,10,13(27),14,16,19(28),20,22-dodecaene-4,6,10,12,16,18,22,24-octol (2)**: Yield: 80 %; $^1$H NMR (500 MHz, [D]DMF, 18 °C): $\delta =$ 8.55 (s, 8H; ArO*H*), 6.61 (d, $^3J$(H,H) = 8 Hz, 8H; $H_d$), 6.52 (d, $^3J$(H,H) = 8 Hz, 8H; $H_e$), 6.26 (br s, 4H; $H_b$), 6.11 (s, 4H; $H_a$), 5.86 (s, 4H; $H_c$), 3.87 (t, $^3J$(H,H) = 5.5 Hz, 8H; OC$H_2$), 1.67 (m, 8H; OCH$_2$C$H_2$), 1.41 (m, 8H; OCH$_2$CH$_2$C$H_2$), 1.29 (m, 16H; C$H_2$), 0.86 (t, $^3J$(H,H) = 8.3 Hz, 12H; C$H_3$); $^{13}$C NMR (75 MHz, [D]DMF, 18 °C): $\delta = 156.02$, 152.87, 137.79, 131.02, 129.17, 120.68, 112.70, 101.59, 67.00, 40.41, 31.16, 29.03, 25.29, 22.03, 13.16; MS (FAB): *m/z*: 1193 $[M]^+$, 1215 $[M+Na]^+$.

**2,8,14,20-Tetra(4-heptyloxyphenyl)pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]tetracosa-1(25),2,4,7(26),8,10,13(27),14,16,19(28),20,22-dodecaene-4,6,10,12,16,18,22,24-octol (3)**: Yield: 85 %; $^1$H NMR (500 MHz, [D]DMF, 18 °C): $\delta =$ 8.50 (s, 8H; ArO*H*), 6.59 (d, $^3J$(H,H) = 8.7 Hz, 8H; $H_d$), 6.50 (d, $^3J$(H,H) = 8.7 Hz, 8H; $H_e$), 6.27 (br s, 4H; $H_b$), 6.09 (s, 4H; $H_a$), 5.55 (s, 4H; $H_c$), 3.86 (t, $^3J$(H,H) = 6.6 Hz, 8H; OC$H_2$), 1.70 (m, 8H; OCH$_2$C$H_2$), 1.41 (m, 8H; OCH$_2$CH$_2$C$H_2$), 1.29 (m, 24H; C$H_2$), 0.85 (t, $^3J$(H,H) = 6.9 Hz, 3H; C$H_3$); $^{13}$C NMR (75 MHz, [D]DMF, 18 °C): $\delta = 155.64$, 152.44, 137.42, 130.65, 128.81, 120.29, 112.34, 101.21, 66.67, 39.97, 30.94, 28.72, 28.29, 25.22, 21.64, 12.84; MS (FAB): *m/z*: 1249 $[M]^+$.

**2,8,14,20-Tetra(4-octyloxyphenyl)pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]tetracosa-1(25),2,4,7(26),8,10,13(27),14,16,19(28),20,22-dodecaene-4,6,10,12,16,18,22,24-octol (4)**: Yield: 72 %; $^1$H NMR (500 MHz, [D]DMF, 18 °C): $\delta = 8.52$ (s, 8H; ArO*H*), 6.61 (d, $^3J$(H,H) = 9.5 Hz, 8H; $H_d$), 6.51 (d, $^3J$(H,H) = 9.5 Hz, 8H; $H_e$), 6.29 (br s, 4H; $H_b$), 6.11 (s, 4H; $H_a$), 5.57 (s, 4H; $H_c$), 3.87 (t, $^3J$(H,H) = 3.1 Hz, 8H; OC$H_2$), 1.68 (m, 8H; OCH$_2$C$H_2$), 1.40 (m, 8H; OCH$_2$CH$_2$C$H_2$), 1.24 (br s, 32H; C$H_2$), 0.82 (t, $^3J$(H,H) = 6.75 Hz, 12H; C$H_3$); $^{13}$C NMR (75 MHz, [D]DMF, 18 °C): $\delta = 156.00$, 152.84, 137.77, 131.01, 129.16, 120.66, 112.67, 101.57, 66.96, 40.37, 31.27, 29.10, 28.77, 25.64, 22.00, 13.16; MS (FAB): *m/z*: 1305 $[M]^+$, 1328 $[M+Na]^+$; HRMS: calcd for $C_{84}H_{104}O_{12}Na$: 1327.7425; found 1327.7429 $[M+Na]^+$.

**2,8,14,20-Tetra(4-decyloxyphenyl)pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]tetracosa-1(25),2,4,7(26),8,10,13(27),14,16,19(28),20,22-dodecaene-4,6,10,12,16,18,22,24-octol (5)**: Yield: 85 %; $^1$H NMR (500 MHz, [D]DMF, 18 °C): $\delta =$ 8.51 (s, 8H; ArO*H*), 6.59 (d, $^3J$(H,H) = 8.9 Hz, 8H; $H_d$), 6.49 (d, $^3J$(H,H) = 8.9 Hz, 8H; $H_e$), 6.27 (br s, 4H; $H_b$), 6.09 (s, 4H; $H_a$), 5.57 (s, 4H; $H_c$), 8.86 (t, $^3J$(H,H) = 5.9 Hz, 8H; OC$H_2$), 1.70 (m, 8H; OCH$_2$C$H_2$), 1.42 (m, 8H; OCH$_2$CH$_2$C$H_2$), 1.25 (m, 48H; C$H_2$), 0.83 (t, $^3J$(H,H) = 6.5 Hz, 12H; C$H_3$); $^{13}$C NMR (75 MHz, [D]DMF, 18 °C): $\delta = 156.03$, 152.86, 137.78, 131.06, 129.19, 120.69, 112.69, 101.61, 67.03, 40.40, 31.30, 29.16, 29.07, 28.77, 25.67, 22.00, 13.16; MS (FAB): *m/z*: 1417 $[M]^+$, 1440 $[M+Na]^+$.

**2,8,14,20-Tetra[4-(2-ethoxyethoxy)phenyl]pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]-octacosa-1(25),2,4,7(26),8,10,13(27),14,16,19(28),20,22-dodecaene-4,6,10,12,16,18,22,24-octol (6)** : Yield: 84 %; $^1$H NMR (500 MHz, [D]DMF, 18 °C): $\delta =$ [*rccc*-crown] 8.52 (s, 8H; ArO*H*), 6.61 (d, $^3J$(H,H) = 8.5 Hz, 8H; $H_d$), 6.56 (d, $^3J$(H,H) = 8.5 Hz, 8H; $H_e$), 6.27 (br s, 4H; $H_b$), 6.12 (s, 4H; $H_a$), 5.58 (s, 4H; $H_c$), 4.01 (t, $^3J$(H,H) = 4.7 Hz, 8H; ArOC$H_2$), 3.69 (t, $^3J$(H,H) = 4.7 Hz, 8H; ArOCH$_2$C$H_2$), 3.51 (q, $^3J$(H,H) = 6.5 Hz, 12H; OC$H_2$CH$_3$); [*rccc*-flattened cone] 8.50 (s, 4H; (ArO*H*)$_2$), 8.43 (s, 4H; (ArO*H*)$_1$), 6.51 (d, $^3J$(H,H) = 8.8 Hz, 8H; $H_d$), 6.46 (d, $^3J$(H,H) = 8.8 Hz, 8H; $H_e$), 6.31 (s, 2H;

$H_{a1}$), 6.29 (s, 2H; $H_{a2}$), 6.12 (s, 2H; $H_{b2}$), 5.68 (s, 2H; $H_{b1}$), 5.46 (s, 4H; $H_c$), 3.92 (t, $^3J$(H,H) = 4.7 Hz, 8H; ArOC$H_2$), 3.65 (t, $^3J$(H,H) = 4.7 Hz, 8H; ArOCH$_2$C$H_2$), 3.49 (q, $^3J$(H,H) = 6.5 Hz, 8H; OC$H_2$CH$_3$), 1.11 (t, $^3J$(H,H) = 6.5 Hz, 12H; OCH$_2$C$H_3$); $^{13}$C NMR (75 MHz, [D]DMF, 18 °C): $\delta$ = 155.68, 155.57, 152.91, 152.83, 152.77, 137.90, 136.34, 131.98, 130.94, 129.48, 129.07, 112.66, 112.50, 101.47, 101.16, 68.48, 68.43, 66.71, 66.55, 65.49, 41.08, 40.35, 14.27; MS (FAB): *m/z*: 1143 $[M]^+$, 1165 $[M+Na]^+$.

**2,8,14,20-Tetra{4-[2-(2-ethoxyethoxy)ethoxy]phenyl}pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]tetracosa-1(25),2,4,7(26),8,10,13(27),14,16,19(28),20,22-dodecaene-4,6,10,12,16,18,22,24-octol (7)**: Yield: 91%; $^1$H NMR (500 MHz, [D]DMSO, 18 °C): $\delta$ = 8.48 (s, 4H; (ArO$H$)$_2$), 8.41 (s, 4H; (ArO$H$)$_2$), 6.48 (d, $^3J$(H,H) = 8.7 Hz, 8H; $H_d$), 6.43 (d, $^3J$(H,H) = 8.7 Hz, 8H; $H_e$), 6.28 (s, 2H; $H_{a1}$), 6.26 (s, 2H; $H_{a2}$), 6.10 (s, 2H; $H_{b2}$), 5.65 (s, 2H; $H_{b1}$), 5.44 (s, 4H; $H_c$), 3.91 (t, $^3J$(H,H) = 4.6 Hz, 8H; ArOC$H_2$), 3.69 (t, $^3J$(H,H) = 4.6 Hz, 8H; ArOCH$_2$C$H_2$), 3.56 (t, $^3J$ = 4.8 Hz, 8H; ArCH$_2$CH$_2$OC$H_2$), 3.49 (t, $^3J$(H,H) = 4.8 Hz, 8H; ArOCH$_2$CH$_2$OCH$_2$C$H_2$), 3.42 (q, $^3J$(H,H) = 7.3 Hz, 8H; OC$H_2$CH$_3$), 1.08 (t, $^3J$(H,H) = 7.3 Hz, 12H; OCH$_2$C$H_3$); $^{13}$C NMR (75 MHz, [D]DMF, 18 °C): $\delta$ = 155.43, 152.77, 152.69, 136.22, 131.86, 129.37, 128.92, 120.83, 112.41, 101.25, 101.03, 69.751, 68.99, 68.91, 66.44, 65.26, 40.982, 14.12; MS (ES): *m/z*: 1321 $[M]^+$, 1343 $[M+Na]^+$.

**2,8,14,20-Tetra{4-[2-[2-(2-ethoxyethoxy)ethoxy]ethoxy}phenyl}pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]tetracosa-1(25),2,4,7(26),8,10,13(27),14,16,19(28),20,22-dodecaene-4,6,10,12,16,18,22,24-octol (8)**: Yield: 70%; $^1$H NMR (500 MHz, [D]DMSO, 18 °C): $\delta$ = 8.52 (s, 4H; (ArO$H$)$_2$), 8.45 (s, 4H; (ArO$H$)$_1$), 6.50 (d, $^3J$(H,H) = 8.8 Hz, 8H; $H_d$), 6.45 (d, $^3J$(H,H) = 8.8 Hz, 8H; $H_e$), 6.30 (s, 2H; $H_{a1}$), 6.28 (s, 2H; $H_{a2}$), 6.11 (s, 2H; $H_{b2}$), 5.66 (s, 2H; $H_{b1}$), 5.45 (s, 4H; $H_c$), 3.92 (t, $^3J$(H,H) = 4.8 Hz, 8H; ArOC$H_2$), 3.67 (t, $^3J$(H,H) = 4.8 Hz, 8H; ArOCH$_2$C$H_2$), 3.57 – 3.49 (m, 48H; OC$H_2$), 3.32 (q, $^3J$(H,H) = 7.0 Hz, 8H; OC$H_2$CH$_3$), 1.06 (t, $^3J$(H,H) = 7.0 Hz, 12H; OCH$_2$C$H_3$); MS (FAB): *m/z*: 1498 $[M]^+$, 1520 $[M+Na]^+$; HRMS: calcd for $C_{84}H_{104}O_{24}Na$: 1519.6815; found 1519.6812 $[M+Na]^+$.

**2,8,14,20-Tetra(1,4,7,10,13-pentaoxabenzo[*b*]cyclopentadecan-15-yl)pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]tetracosa-1(25),2,4,7(26),8,10,13(27),14,16,19(28),20,22-dodecaene-4,6,10,12,16,18,22,24-octol (9):**[29] Yield: 73%; $^1$H NMR (500 MHz, [D]DMSO, 18 °C): $\delta$ = 8.50 (s, 4H; ArO$H$), 8.46 (s, 4H; ArO$H$), 6.51 – 6.02 (2m and 2s, 20H; Ar$H$), 5.61 – 5.46 (2s, 4H; $H_c$), 3.89 – 3.78 (2m, 16H; ArOC$H_2$), 3.72 (m, 16H; ArOCH$_2$C$H_2$), 3.64 (m, 32H; OC$H_2$); MS (FAB): *m/z*: 1553 $[M]^+$, 1575 $[M+Na]^+$.

**2,8,14,20-Tetra(1,4,7,10,13,16-hexaoxabenzo[*b*]cyclooctadecan-18-yl)pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]tetracosa-1(25),2,4,7(26),8,10,13(27),14,16,19(28),20,22-dodecaene-4,6,10,12,16,18,22,24-octol (10)**: Yield: 93%; $^1$H NMR (300 MHz, [D]DMSO, 18 °C): $\delta$ = 8.45 (s, 8H; ArO$H$), 6.50 – 5.94 (2m and 3s, 20H; Ar$H$), 5.45 (s, 4H; $H_c$), 3.94 – 3.78 (2m, 16H; ArOC$H_2$), 3.65 (m, 16H; ArOCH$_2$C$H_2$), 3.56 (m, 40H; OC$H_2$); MS (FAB): *m/z*: 1731 $[M+H]^+$.

**General procedure for the preparation of acylated resorcin[4]arenes**: A solution of resorcin[4]arene (1 g, 0.95 mmol) in acetic anyhydride (7.2 mL, 76.3 mmol) and pyridine (1.3 mL, 16.3 mmol) was stirred at 110 °C for 3 h. Methanol (30 mL) was added and the reaction mixture cooled overnight to − 23 °C. The resulting precipitate was isolated by Büchner filtration and recrystallised from 1:2 chloroform/methanol to yield a white crystalline solid. The numbering scheme for NMR assignments of resorcin[4]arenes is given in Figure 8.

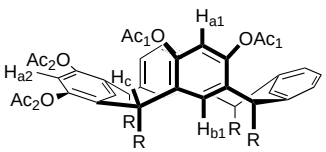


Figure 8. Numbering scheme for NMR assignment of the flattened cone acylated derivatives of resorcin[4]arenes.

**2,8,14,20-Tetra(4-butyloxyphenyl)pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]tetracosa-1(25),2,4,7(26),8,10,13(27),14,16,19(28),20,22-dodecaene-4,6,10,12,16,18,22,24-octayl octaacetate (11)**: Yield: 70%; $^1$H NMR (500 MHz, [D]CHCl$_3$, 18 °C): $\delta$ = 7.07 (s, 2H; $H_{a1}$), 6.82 (s, 2H; $H_{a2}$), 6.60 (s, 16H; $H_d$, $H_e$), 6.09 (s, 2H; $H_{b2}$), 6.04 (s, 2H; $H_{b1}$), 5.30 (s, 4H; $H_c$), 3.91 (t, $^3J$(H,H) = 6.3 Hz, 8H; ArOC$H_2$), 2.03 (s, 12H; (COC$H_3$)$_2$), 1.98 (s, 12H; (COC$H_3$)$_1$), 1.78 (m, 8H; OCH$_2$C$H_2$), 1.56 (m, 8H; C$H_2$CH$_3$), 1.00 (t, $^3J$(H,H) = 7.4 Hz, 12H; C$H_3$); $^{13}$C NMR (75 MHz, [D]CHCl$_3$, 18 °C): $\delta$ = 168.33, 157.68, 146.92, 146.82, 132.40, 132.34, 132.16, 130.71, 129.44, 128.58, 117.35, 116.19, 114.07, 67.50, 44.06, 31.49, 20.62, 20.52, 19.26, 13.93; MS (FAB): *m/z*: 1417 $[M]^+$, 1440 $[M+Na]^+$.

**2,8,14,20-Tetra(4-octyloxyphenyl)pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]tetracosa-1(25),2,4,7(26),8,10,13(27),14,16,19(28),20,22-dodecaene-4,6,10,12,16,18,22,24-octayl octaacetate (12)**: Yield: 66%; $^1$H NMR (500 MHz, [D]CHCl$_3$, 18 °C): $\delta$ = 7.07 (s, 2H; $H_{a1}$), 6.83 (s, 2H; $H_{a2}$), 6.60 (s, 16H; $H_d$, $H_e$), 6.09 (s, 2H; $H_{b2}$), 6.03 (s, 2H; $H_{b1}$), 5.31 (s, 4H; $H_c$), 3.90 (t, $^3J$(H,H) = 6.9 Hz, 8H; OC$H_2$), 2.04 (s, 12H; (COC$H_3$)$_2$), 1.98 (s, 12H; (COC$H_3$)$_1$), 1.79 (m, 8H; OCH$_2$C$H_2$), 1.48 (m, 8H; OCH$_2$CH$_2$C$H_2$), 1.33 (m, 32H; C$H_2$), 0.90 (t, $^3J$(H,H) = 6.8 Hz, 12H; C$H_3$); $^{13}$C NMR (75 MHz, [D]CHCl$_3$, 18 °C): $\delta$ = 168.37, 157.70, 146.93, 146.84, 132.43, 132.35, 132.14, 130.74, 129.45, 128.60, 117.37, 116.19, 114.07, 67.85, 44.08, 31.86, 29.55, 29.53, 29.32, 26.14, 22.67, 20.65, 20.56, 14.10; :MS (FAB): *m/z*: 1642 $[M+H]^+$, 1664 $[M+Na]^+$.

**2,8,14,20-Tetra[4-(2-ethoxyethoxy)phenyl]pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]-tetracosa-1(25),2,4,7(26),8,10,13(27),14,16,19(28),20,22 – 4,6,10,12,16,18,22,24-octayl octaacetate (13)**: Yield: 70%; $^1$H NMR (500 MHz, [D]CHCl$_3$, 18 °C): $\delta$ = 7.10 (s, 2H; $H_{a1}$), 6.87 (s, 2H; $H_{a2}$), 6.61 (s, 16H; $H_d$, $H_e$), 6.23 (s, 2H; $H_{b2}$), 6.07 (s, 2H; $H_{b1}$), 5.41 (s, 4H; $H_c$), 4.05 (t, $^3J$(H,H) = 5.0 Hz, 8H; ArOC$H_2$), 3.77 (t, $^3J$(H,H) = 5.0 Hz, 8H; ArOCH$_2$C$H_2$), 3.69 (m, 8H; OC$H_2$CH$_2$OEt), 3.60 (m, 8H; OCH$_2$C$H_2$OEt), 3.56 (q, $^3J$(H,H) = 7.1 Hz, 8H; OC$H_2$CH$_3$), 2.05 (s, 12H; (COC$H_3$)$_2$), 2.00 (s, 12H; (COC$H_3$)$_1$), 1.24 (t, $^3J$(H,H) = 7.1 Hz, 12H; OCH$_2$C$H_3$); $^{13}$C NMR (75 MHz, [D]CHCl$_3$, 18 °C): $\delta$ = 168.52, 168.23, 157.33, 146.76, 146.40, 132.56, 131.91, 131.15, 129.89, 129.11, 117.02, 116.81, 114.33, 69.03, 67.17, 66.75, 43.76, 20.62, 20.54, 15.18; MS (FAB): *m/z*: 1480 $[M]^+$, 1503 $[M+Na]^+$; HRMS: calcd for $C_{84}H_{89}O_{24}$: 1481.5744; found 1481.5743 $[M+H]^+$.

**2,8,14,20-Tetra{4-[2-(2-ethoxyethoxy)ethoxy]phenyl}pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]tetracosa-1(25),2,4,7(26),8,10,13(27),14,16,19(28),20,22-dodecaene-4,6,10,12,16,18,22,24-octayl octaacetate (14)**: Yield: 72%; $^1$H NMR (500 MHz, [D]CHCl$_3$, 18 °C): $\delta$ = 7.10 (s, 2H; $H_{a1}$), 6.87 (s, 2H; $H_{a2}$), 6.60 (s, 16H; $H_d$, $H_e$), 6.23 (s, 2H; $H_{b2}$), 6.05 (s, 2H; $H_{b1}$), 5.41 (s, 4H; $H_c$), 4.07 (t, $^3J$(H,H) = 5.2 Hz, 8H; ArOC$H_2$), 3.83 (t, $^3J$(H,H) = 5.2 Hz, 8H; ArOCH$_2$C$H_2$), 3.71 (t, $^3J$ = 4.7 Hz, 8H; ArOCH$_2$CH$_2$OC$H_2$), 3.61 (t, $^3J$(H,H) = 4.7 Hz, 8H; ArOCH$_2$CH$_2$OCH$_2$C$H_2$), 3.54 (q, $^3J$ = 7.0 Hz, 8H; OC$H_2$CH$_3$), 2.05 (s, 12H; (COC$H_3$)$_2$), 2.00 (s, 12H; (COC$H_3$)$_1$), 1.21 (t, $^3J$(H,H) = 7.0 Hz, 12H; OCH$_2$C$H_3$); $^{13}$C NMR (75 MHz, [D]CHCl$_3$, 18 °C): $\delta$ = 168.49, 168.22, 157.26, 146.75, 146.38, 132.51, 131.90, 131.17, 129.88, 129.13, 117.00, 116.80, 114.29, 70.79, 69.82, 69.75, 67.13, 66.64, 43.75, 20.62, 20.51, 15.14; MS (FAB): *m/z*: 1658 $[M+Na]^+$, 1694 $[M+K]^+$.

**2,8,14,20-Tetra(1,4,7,10,13-pentaoxabenzo[*b*]cyclopentadecan-15-yl)pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]tetracosa-1(25),2,4,7(26),8,10,13(27),14,16,19(28),20,22-dodecaene-4,6,10,12,16,18,22,24-octayl octaacetate (15)**: Yield: 66%; $^1$H NMR (500 MHz, [D]CHCl$_3$, 18 °C): $\delta$ = 6.90 (s, 4H; $H_a$), 6.56 (d, $^3J$(H,H) = 7.5 Hz, 4H; $H_d$), 6.21 (d, $^3J$(H,H) = 7.5 Hz, 4H; $H_e$), 6.21 (brs, 4H; $H_b$), 6.21 (s, 4H; $H_{d'}$), 5.38 (brs, 4H; $H_c$), 4.08 (s, 8H; ArOC$H_{2a}$), 3.89 (s, 8H; ArOC$H_{2b}$), 3.85 (s, 16H; ArOCH$_2$C$H_2$), 3.74 (s, 32H; OC$H_2$), 2.05 (s, 24H; COC$H_3$); MS (FAB): *m/z*: 1889 $[M]^+$, 1912 $[M+Na]^+$.

**2,8,14,20-Tetra(1,4,7,10,13,16-hexaoxabenzo[*b*]cyclooctadecan-18-yl)pentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]tetracosa-1(25),2,4,7(26),8,10,13(27),14,16,19(28),20,22-dodecaene-4,6,10,12,16,18,22,24-octayl octaacetate (16)**: Yield: 74%; $^1$H NMR (300 MHz, [D]CHCl$_3$, 18 °C): $\delta$ = 6.97 (s, 4H; $H_a$), 6.91 (s, 4H; $H_{d'}$), 6.55 (d, $^3J$(H,H) = 10.6 Hz, 4H; $H_d$), 6.19 (d, $^3J$(H,H) = 10.6 Hz, 4H; $H_e$), 6.19 (brs, 4H; $H_b$), 5.36 (brs, 4H; $H_c$), 4.10 (s, 8H; ArOC$H_{2a}$), 3.90 (s, 8H; ArOC$H_{2b}$), 3.86 (s, 16H; ArOCH$_2$C$H_2$), 3.68 (s, 48H; OC$H_2$), 2.06 (s, 24H; COC$H_3$).

**U-tube studies**:[19] The source phase comprised a 10 mM aqueous solution of an alkali metal picrate salt and the receiving phase was distilled water. The liquid membrane was a 1.0 mM solution of the resorcin[4]arene under study in chloroform. The temperature was maintained at 20 °C throughout. Aliquots were taken from both aqueous phases at periodic intervals and analysed by UV/Vis spectroscopy, monitoring the absorbance at 206 nm.

**Planar lipid bilayer studies:** Planar lipid bilayers were formed across an elliptical aperture (ca. 100 μm diameter on the long axis) in a thin (25 μm) teflon film (Yellow Springs Instruments, OH, USA).[20] About 40 μL of lipid L-α-phosphatidylcholine (Type II-s) and cholesterol (10:1 w/w) (Sigma), in pentane were layered on top of a buffer solution (0.5 M KCl, 10 mM BES, pH 7.0). After allowing the solvent to evaporate, the buffer level was raised across the aperture. This resulted in approximately 0.2 mg



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lipid on each side. The resorcin[4]arenes were dissolved in ethanol (1 mM) and added to both the *cis* and *trans* sides (amplifier) either by injection under the aqueous surface near the bilayer or onto the aqueous surface once the buffer level was lowered (temporarily destroying the bilayer). The temperature was maintained at 20 °C throughout the measurements. Electrical currents were recorded with an Axopatch 1D amplifier at a rate of 5 kHz and filtered with 1 kHz by using a Digi Data 1200 interface (Axon Instruments, CA, USA). Currents were generated by using a Function Generator TG 302 (LEVELL, Barnet, UK). Histograms were calculated by using Origin 5.0. A step size of 0.2 pA was applied and the data were fitted with Gaussian curves. The numbers in the histograms reflect the peak centres of the curves in pA.

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