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Monofunctionalized Fluorinated Bambusurils and their Conjugates for Anion Transport and Extraction

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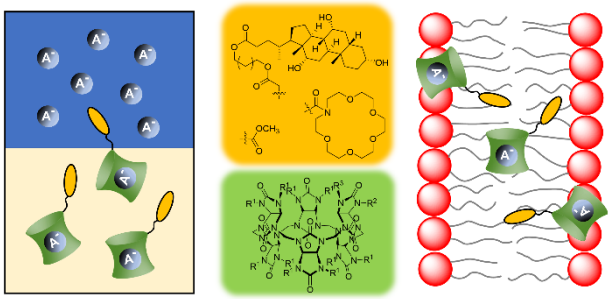
ABSTRACT



Bambusurils are macrocyclic molecules that are known for their high binding affinity and selectivity toward anions. Here we present the preparation of two bambusurils bearing fluorinated substituents and one carboxylic function. These monofunctionalized bambusurils were conjugated with crown ether and cholesterol units. The resulting conjugates were successfully tested in liquid–liquid extraction of inorganic salts and chloride/bicarbonate transport across lipid bilayers.

INTRODUCTION

Macrocycles are an important class of molecules in the field of supramolecular chemistry due to their ability to selectively interact with guest molecules under formation of stable host-guest inclusion complexes. Macrocyclic scaffolds are often functionalized to incorporate macrocycles into more complex structures, allowing a wide range of applications in many different fields, including biomedicine, analytical chemistry, material science, and catalysis.[1–9] Among all functionalized

macrocycles, monofunctionalized macrocycles have proven useful in creating libraries of compounds without altering the key supramolecular properties of the parent macrocyclic hosts. Many different classes of monofunctionalized macrocyclic molecules, such as calixarenes,[10] calixpyrroles,[11,12] pillararenes,[13,14] cyclodextrins[15] and cucurbiturils[16–21] have been successfully prepared by either selective modification of the macrocycle, or by reacting a functionalized monomer with non-functionalized ones during macrocyclization. Bambus[6]urils[22] (hereinafter referred to as bambusurils) are a class of supramolecular anion receptors consisting of six 2,4-substituted glycoluril units linked by one row of methylene bridges (Figure 1). Glycoluril units alternate within the macrocycle with their methine protons pointing inside the cavity. This makes bambusurils preorganized for binding of anions inside their cavity with twelve C-H···A^- interactions.[23] The first bambusuril, bearing twelve methyl groups at the portals of the macrocycle, was prepared in 2010 by a condensation of 2,4-dimethylglycoluril and paraformaldehyde.[24] The reaction was carried out in aqueous HCl, which acted both as an acid catalyst and as an anionic template, inducing the formation of a six- instead of a four-membered ring. During the following years, different reaction conditions for the preparation of bambus[6]urils were investigated, including use of various organic solvents and applying conventional as well as microwave heating.[22,25] The majority of the bambus[6]urils reported so far consist of six identical 2,4-disubstituted glycoluril units. Exceptions are semithio- and semiaza-bambusurils, made of 3-thio- and 3-azaglycolurils,[26–28] and chiral bambusurils, having different substituents in the 2,4-positions of the glycolurils.[29–31] Moreover, recently we reported the synthesis of the first monofunctionalized bambusuril using a statistically driven condensation of two different glycolurils.[32] Bambusuril properties such as solubility, lipophilicity, and binding affinity towards anions could be significantly influenced by the type of substituents on their portals. For example, the bambusuril bearing twelve benzyl groups is soluble in nonpolar solvents such as chloroform, while those containing twelve alkyl carboxylate or 3,6,9-trioxadecyl substituents are soluble in water.[22] Recently, bambus[6]urils **1a** and **1b** (Figure 1) bearing fluorinated benzyl groups were prepared.[33,34] These electron withdrawing and lipophilic groups provide bambusurils with very high binding affinities towards small anions ($K_a > 10^{11}$ M^{-1} for NO_3^- in acetonitrile) and also unprecedented high activity in Cl^-/HCO_3^- transport (antiport) across lipid membranes.

Transport of Cl^- and HCO_3^- anions through cell membranes plays a crucial role in living organisms. Malfunctions in these mechanisms manifest in channelopathies such as cystic fibrosis, Pendred syndrome, or Dent's disease.[35,36] Recent examples in the literature showcase several types of synthetic anion carriers which can be potentially used to treat these channelopathies.[37–39] Expanding the library

of fluorinated bambusurils by preparing monofunctionalized derivatives, which would be easy to further modify, could be used to improve their properties for specific biomedical applications.

Herein, we report the synthesis of fluorinated monofunctionalized bambusuril derivatives **2a**, and **2b** (Figure 1). The single carboxylic acid group in **2a** and **2b** allowed their selective modification. Therefore, these derivatives were used for the synthesis of a library of compounds tested as anionophores in transmembrane transport of anions and liquid-liquid extractions of inorganic salts.

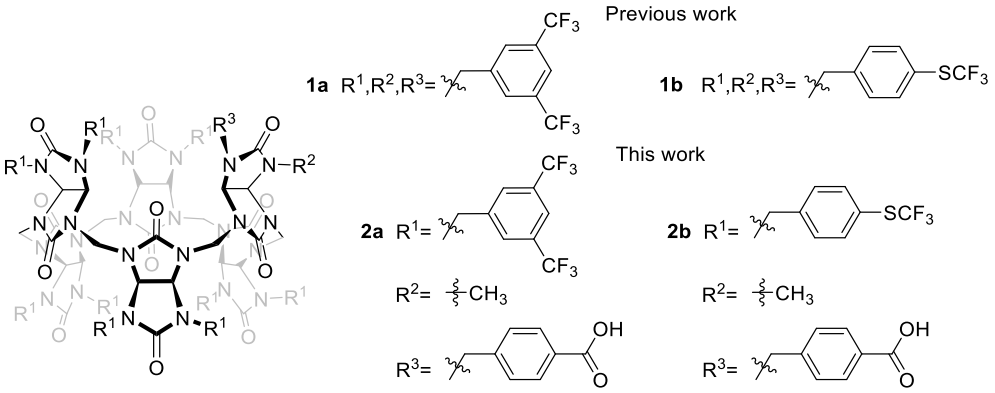
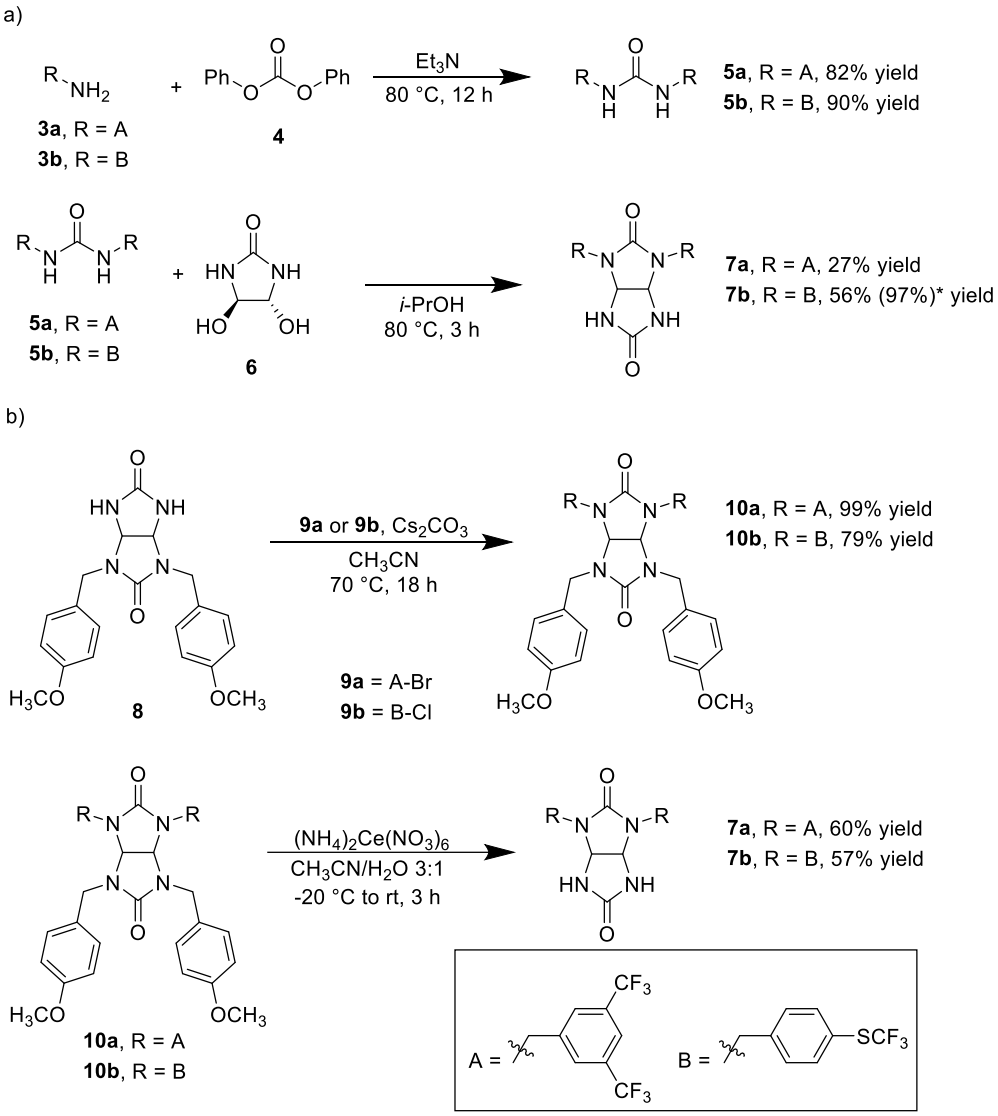


Figure 1: Previously prepared fluorinated bambusurils **1a** and **1b**[33] and new monofunctionalized derivatives **2a** and **2b.**

RESULTS AND DISCUSSION

Synthesis of bambusuril derivatives

The synthesis of monofunctionalized fluorinated bambusurils **2a** and **2b** is based on the 2,4-disubstituted glycolurils **7a** and **7b**. Until now, all reported 2,4-disubstituted glycolurils, have been prepared by the reaction of corresponding disubstituted ureas and 4,5-dihydroxyimidazolidin-2-one **6** (Scheme 1a).[22,33]



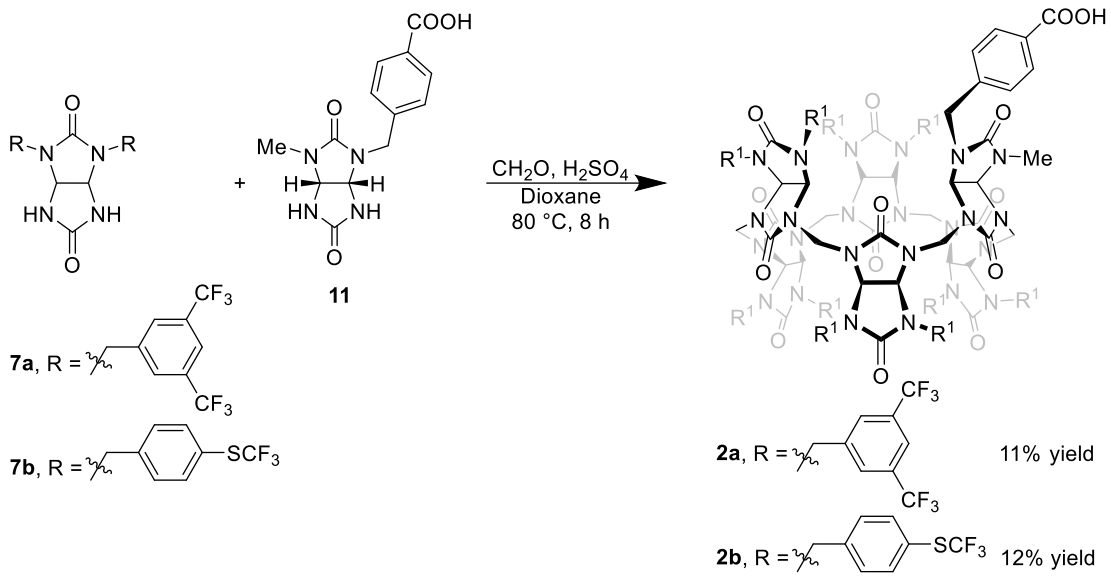
Scheme 1: a) Previously applied synthesis of fluorinated glycolurils.[33] b) Novel approach for the preparation of fluorinated glycolurils. *The yield achieved by the modification of the previously applied synthesis using portionwise additions of **6**.

This strategy was also previously applied for the synthesis of glycolurils **7a** and **7b**, which were obtained in 22% and 50% overall yields with respect to the fluorinated amines **3a** and **3b**.[33] We were able to

significantly improve the yield of **7b** up to 97% by using portionwise additions of an even larger excess of **6**. However, the same strategy did not improve the yield of **7a**. Moreover, the synthesis of glycoluril **7a** was accompanied by the formation of many impurities (particularly hydantoins) which were difficult to remove from the product. The problems discussed above led us to investigate a different strategy for the synthesis of **7a**. We used previously reported 2,4-bis(4-methoxybenzyl)glycoluril **8**[40] and performed its alkylation with 3,5-bis(trifluoromethyl)benzyl bromide **9a** in the presence of Cs_2CO_3 in CH_3CN at 70 °C yielding tetrasubstituted glycoluril **10a** (Scheme 1b). The 4-methoxybenzyl groups of **10a** were subsequently removed by oxidation using ceric ammonium nitrate (CAN)[41] to obtain 2,4-disubstituted glycoluril **7a** in 59% yield with respect to **10a**. Trifluoroacetic acid (TFA) was also successfully tested for the deprotection, but lower yields were obtained, and the work up was more complicated than in the case of CAN. In comparison with the original method, the newly tested approach resulted in a higher yield of **7a**. Moreover, the new approach allowed easier isolation of the final product relying just on precipitation. The new strategy was also applied to prepare glycoluril **7b** in 45% yield with respect to **8**. Thus, the newly developed method is an alternative to the original procedure and can be used for the preparation of various 2,4-disubstituted glycolurils. Monofunctionalized glycoluril **11** (Scheme 2) the second necessary component for the synthesis of the monofunctionalized bambusurils, was prepared according to the previously reported procedure.[31]

With glycolurils **7a**, **7b**, and **11** in hand, we were able to prepare the monofunctionalized fluorinated bambusurils **2a** and **2b** using the statistic approach previously reported for the preparation of monofunctionalized bambusurils.[32] This approach is based on the reaction of **7a** (or **7b**) with **11** in the presence of formaldehyde resulting in a mixture of bambusurils differing in number of glycoluril units of **11** (that is, the number of functional groups) in the macrocycle. We assumed that the reactivity of the two glycolurils **7a** (or **7b**) and **11** is the same and that only six-membered bambusuril homologues are formed. Under this assumption, we used a binomial distribution to estimate that the highest possible amount of monofunctionalized macrocycle could be obtained when the molar ratio of **7a** (or **7b**) and **11** is 5 : 1. Nevertheless, we chose a 6 : 1 ratio in order to decrease the amount of undesired di- and trifunctionalized macrocycles, which might be difficult to separate from the desired product. For the synthesis of bambusuril **2a**, a mixture of 2,4-bis(3,5-bis(trifluoromethyl)benzyl)glycoluril **7a** and (1*S*,5*R*)-2-(4-carboxybenzyl)-4-methylglycoluril **11** was reacted with paraformaldehyde at 80 °C (Scheme 2). The reaction took place in 1,4-dioxane in the presence of sulfuric acid, which acted both as the catalyst (H^+) and the anionic template (HSO_4^-). The monofunctionalized fluorinated bambusuril **2a** was isolated in 11% yield (with respect to glycoluril **11**) as a complex with HSO_4^- after column chromatography. In the same way, monofunctionalized fluorinated bambusuril **2b** was synthesized in

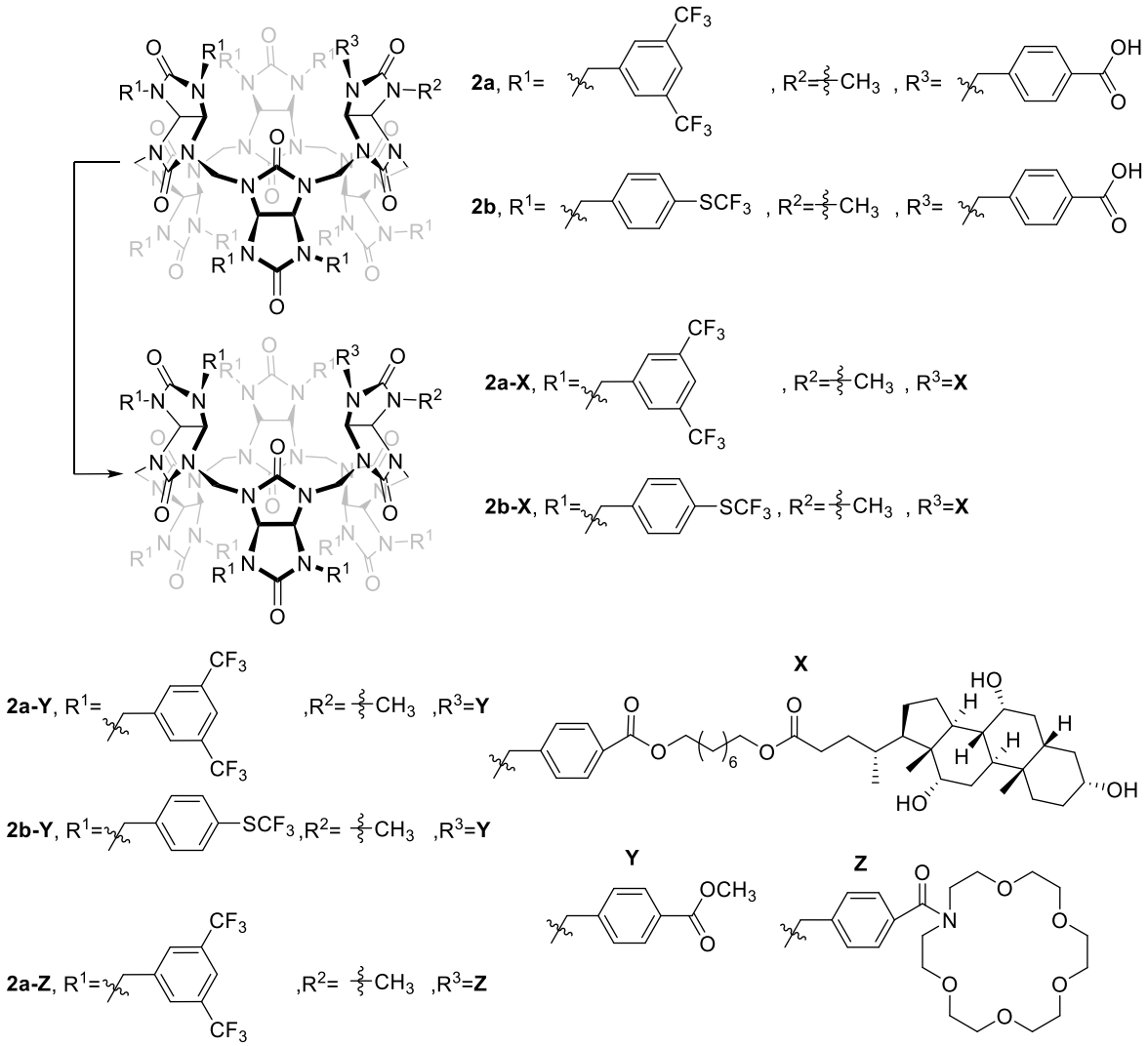
12% yield starting from 2,4-bis(4-((trifluoromethyl)sulfanyl)benzyl)glycoluril **7b** and (1*S*,5*R*)-2-(4-carboxybenzyl)-4-methylglycoluril **11**.



Scheme 2: Synthesis of monofunctionalized fluorinated bambusurils **2a** and **2b**.

The compounds were characterized by NMR spectroscopy and mass spectrometry. The ^{1}H NMR spectrum of the **2a**·HSO_4^- complex recorded in CD_3CN at 30 °C (Figure S14) showed a multitude of signals, as expected for a non-symmetric molecule. However, **2a** was clearly identified by the singlet at 12.79 ppm of the carboxylic acid proton and the singlet at 3.32 ppm of the methyl protons attached to the chiral glycoluril unit. The integral intensities of these signals support the presence of just one unit of the chiral monofunctionalized glycoluril **11** within the macrocycle despite high complexity of the NMR spectra. In addition, MALDI-TOF MS spectrum (Figure S18) showed the major signal at m/z 3355.612, corresponding to the adduct of **2a** with Na^+. Macrocycle **2b** showed a pattern similar to that of **2a** in its ^{1}H NMR spectrum (Figure S32), including the carboxylic acid proton at 12.47 ppm and the characteristic shift of the methyl singlet at 3.28 ppm, and a signal at m/z 2995.422 in the MALDI-TOF MS spectrum (Figure S42) for the adduct of **2b** with Na^+.

The new monofunctionalized fluorinated bambusurils **2a** and **2b** containing a carboxylic acid moiety were coupled with selected substituents through esterification or amidation reactions (Scheme 3). Macrocycles **2a-X** and **2b-X** with cholic ester moieties were prepared as the moiety was reported to enhance the transmembrane ion transport properties of some artificial transporters.[42,43] We also prepared the conjugate of bambusuril and aza-crown **2a-Z** to evaluate the ability of this compound to extract inorganic salts from water to organic media. Methyl esters **2a-Y** and **2b-Y** were prepared to compare them with the other derivatives.



Scheme 3. Synthesis of bambusuril derivatives **2a-X**, **2a-Y**, **2b-X**, **2b-Y**, **2a-Z** from monofunctionalized fluorinated bambusurils **2a** and **2b**.

Liquid – liquid extraction

Conjugate **2a-Z** consists of the bambusuril part with a high affinity towards anions as well as crown ether part, which is known to interact with alkali metals. Thus, we decided to test the ability of **2a-Z** to extract different salts from water to nitrobenzene. Ester **2a-Y** was also studied for the extraction and compared to **2a-Z**. The experiments were performed in an NMR tube filled with 0.5 mL of a 2 mM solution of the ionophore in deuterated nitrobenzene and 0.5 mL of a 2 mM solution of the salt in D_2O. Dichloromethane or chloroform could not be used for the extraction, as resulting complexes were insoluble in these solvents. The tube was vigorously shaken for 5 minutes, and a centrifuge was used to achieve complete separation of both phases. Then, the ^{1}H NMR spectra of the organic phase were recorded. Exchange between anions and bambusurils in nitrobenzene was slow on the NMR time scale,

resulting in the presence of characteristic N-CH_3 signals of bambusuril molecules with and without anion bound at 3.38 and 3.27 ppm respectively (Figure 2).

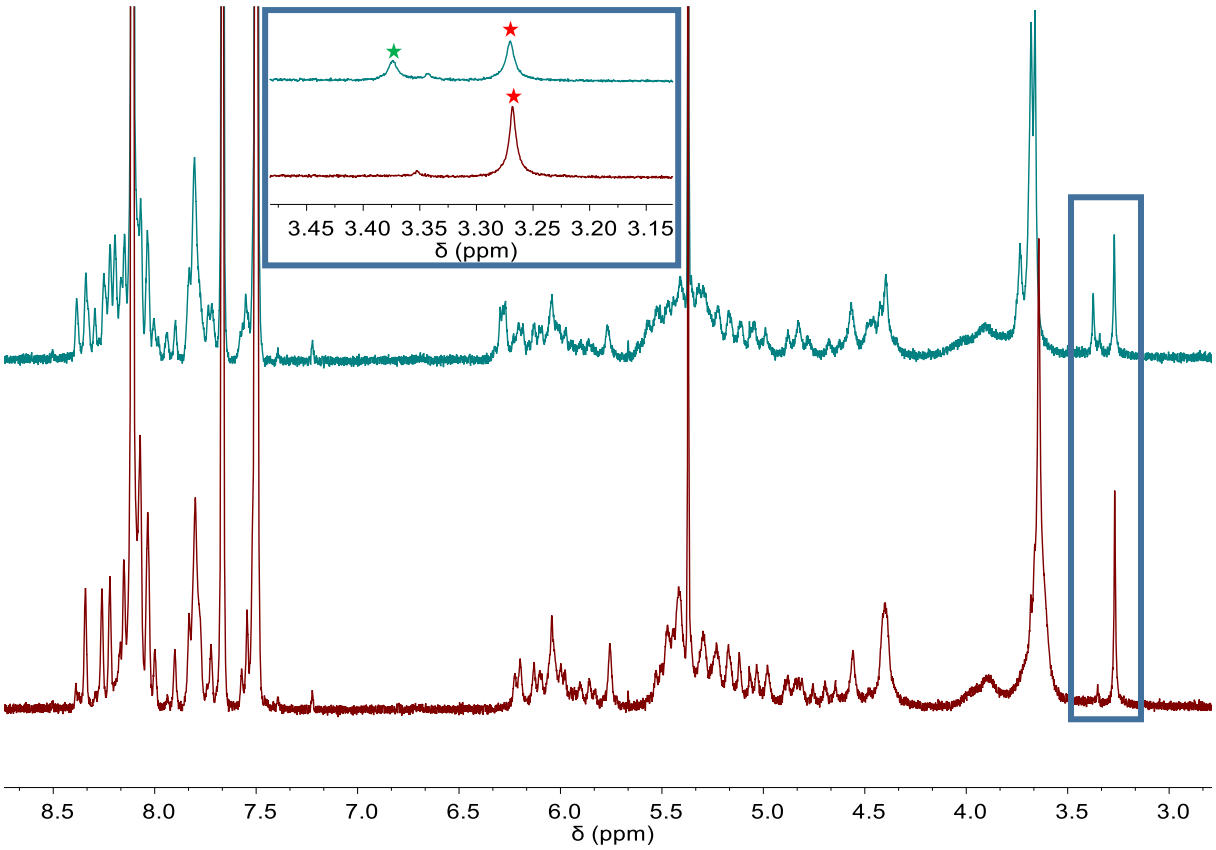


Figure 2. Extraction of NaCl using **2a-Z**. ^{1}H NMR spectra (nitrobenzene-d_5, 300 MHz, 25 °C) of **2a-Z** (0.5 mL, 2mM) after exposure to D_2O (control experiment, bottom) and after exposure to NaCl solution (0.5 mL, 2mM) in D_2O (top); inset: detail of the N-CH_3 signals used for determination of the extraction efficiency; anion free **2a-Z** (red asterisk), **2a-Z**·Cl^- complex (green asterisk).

Therefore, the amount of extracted salt was obtained from integral intensities of these signals. The results summarized in the Table 1 show that the salts containing tetrabutylammonium (TBA^+) cations were extracted quantitatively independently on the type of anion (Cl^- or $H_2PO_4^-$) or the macrocycle. This is due to favorable transfer energy (-19.7 kJ mol^{-1}) for the TBA^+ cation from water into nitrobenzene. On the other hand, Na^+ contributes a penalty to extraction (38.5 kJ mol^{-1}).[44] Macrocycle **2a-Y** was not able to overcome this penalty, showing no extraction for $NaHCO_3$, NaH_2PO_4, and NaCl. However, **2a-Y** allowed efficient extraction of $NaNO_3$ (68%). The observed differences are the result of a significantly higher binding affinity of the macrocycle to NO_3^- compared to other three anions.[33] The situation is different for **2a-Z**, which allowed extraction of NaCl (36%) and quantitative extraction of $NaNO_3$. This showed the positive contribution of crown ether units to the extraction of inorganic salts. However, even **2a-Z** did not extract $NaHCO_3$ and NaH_2PO_4 due to low binding affinity of these anions to bambusurils in water, as result of the high hydration energy of these anions.. The higher extraction

efficiency for KCl (41%) compared to NaCl (36%) could be due to a higher affinity of the aza-crown ether unit to K^+ over Na^+, but also because of the lower phase-transfer penalty of K^+ (27.6 kJ mol^{-1})[44] compared to Na^+. It should be noted that the aza-crown ether alone does not extract any of studied salts as reported previously.[32]

Table 1. Extraction efficiencies[a] (%) of receptors **2a-Y** and **2a-Z** for liquid-liquid extraction of different salts from D_2O to nitrobenzene-d_5.

	2a-Y		**2a-Z**		
	Na^+	TBA^+	Na^+	K^+	TBA^+
HCO_3^-	0	n.d. [b]	traces	traces	n.d. [b]
$H_2PO_4^-$	0	quant.	0	0	quant.
Cl^-	0	quant.	36	41	quant.
NO_3^-	68	quant.	quant.	quant.	quant.

[a]Extraction efficiency is the percentage of receptor molecules occupied by anion in the organic phase, as calculated by integration of the ^{1}H NMR signals of N-CH_3 protons. [b]n.d.-not determined.

Anion transport measurements

Next, we were interested how the monofunctionalization and attachment of various substituents would affect the anion transport activity of the efficient parent bambusurils **1a** and **1b**. We have investigated the exchange of chloride and bicarbonate in large unilamellar vesicles (LUVs) using lucigenin[33] and $[Eu.L1]^+$[34] assays by fluorescence spectroscopy (Figure 3a,d). LUVs of diameter 200 nm were prepared from 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC) and cholesterol (7:3) with bambusurils pre-incorporated in the membranes. Since the fluorescence of lucigenin is quenched in the presence of halide anions, the lucigenin assay was used to monitor the transport of chloride into the LUVs. LUVs with encapsulated lucigenin were dispersed in $NaHCO_3$ solution (225 mM interior and exterior). The experiment was initiated by the addition of NaCl solution (25 mM) into the outer solution, and quenching of the fluorescence was observed. The transport of bicarbonate into LUVs by bambusurils was monitored by our recently developed assay[45] with the europium(III) complex $[Eu.L1]^+$ as emissive probe. LUVs with this probe encapsulated in were dispersed in NaCl/HEPES solution (225 mM and 5 mM; interior and exterior) at pH 7. The experiment was initiated by addition of $NaHCO_3$ solution (10 mM) into the outer solution, and an increase of emission intensity was observed upon binding of bicarbonate to the $[Eu.L1]^+$ complex inside the LUVs.

The experiments in the lucigenin assay to study Cl^-/HCO_3^- antiport by derivatives **2a-X**, **2a-Y**, **2a-Z** showed that transport activities of these bambusurils are nearly identical to the parent macrocycle **1a** (Figure 3b). A difference was observed only for derivative **2a**, which gave slower transport than the other anionophores. A similar trend was observed for the less active series **2b**, **2b-X**, **2b-Y**, for which

we did the transport studies at a 10-fold higher anionophore concentration (Figure 3c). Again, derivatives **2b-X** and **2b-Y** exhibited similar activity to parent macrocycle **1b**, while derivative **2b** showed much slower transport. Exchanging a glycoluril building block in original bambusurils did not cause a significant change in anion binding capabilities or the lipophilicity (see Section 5 in the SI), which was reflected by the similar transport rates. The difference for the derivatives **2a** and **2b** may be caused by the deprotonation of the -COOH group at neutral pH, as the presence of an additional negative charge at the anionophore would slow down its diffusion through the membrane. The possible interaction of the carboxylate group with the headgroups of lipids could also be the cause for the poorer transport, as this interaction would hinder the detachment of anionophore from membrane-buffer interface.

Compared to the lucigenin assay, slightly different behavior was observed when performing the $[Eu.L1]^+$ assay to measure HCO_3^-/Cl^- antiport (Figure 3d-f). For the **1a** derivatives **2a**, **2a-X**, **2a-Y**, **2a-Z**, only the **2a-Z** exhibited similar activity to the parent macrocycle **1a**, while **2a**, **2a-Y**, and also **2a-X** are slightly less active. A different trend in comparison to the lucigenin assay was also found for the derivatives of **1b**. Similarly to the derivatives **2a** and **2a-Y** (Figure 3e), the derivative **2b** was as active as **2b-Y** and, additionally, both of them showed the same rate of transport as the parent macrocycle **1b** (Figure 3f). However, under the conditions of the $[Eu.L1]^+$ assay, **2b-X** was slightly more active.

It is not clear why **2a** and **2b** show significantly different behavior in the lucigenin and $[Eu.L1]^+$ assays. These assays are not carried out under the same experimental conditions: in the lucigenin assay, there is a higher concentration of HCO_3^- (225 mM) and transport is driven by a Cl^- gradient (25 mM), while it is opposite in $[Eu.L1]^+$ assay, which has a higher concentration of Cl^- (225 mM) and where transport is driven by a HCO_3^- gradient (10 mM). Additionally, the lucigenin assay is conducted at pH 7.5–8, while $[Eu.L1]^+$ assay is done at pH 7–7.5. Previously we have concluded that bambusurils **1a** and **1b** act as mobile carriers instead of forming channels.[33] We assume the same for compounds **2a** and **2b** and their derivatives, since their activities are similar or lower to the parent macrocycles and they do not bear a structural moiety which would favor stacking in the membrane as required for channel formation.

While only a minor impact of a methyl ester on the transport of fluorinated bambusurils was anticipated, it was surprising that attaching larger moieties such as a cholesterol or aza-crown ether group did not have a significant impact on the rates of anion exchange. These moieties are likely to affect the diffusion of the bambusurils-anion complexes through the membrane more significantly than the binding and release of the anions by the macrocycle. The minor impact of the appending

moieties could thus indicate that binding and release of anions, rather than the diffusion across the lipid bilayer, is determining the overall rate of transport by fluorinated bambusurils.

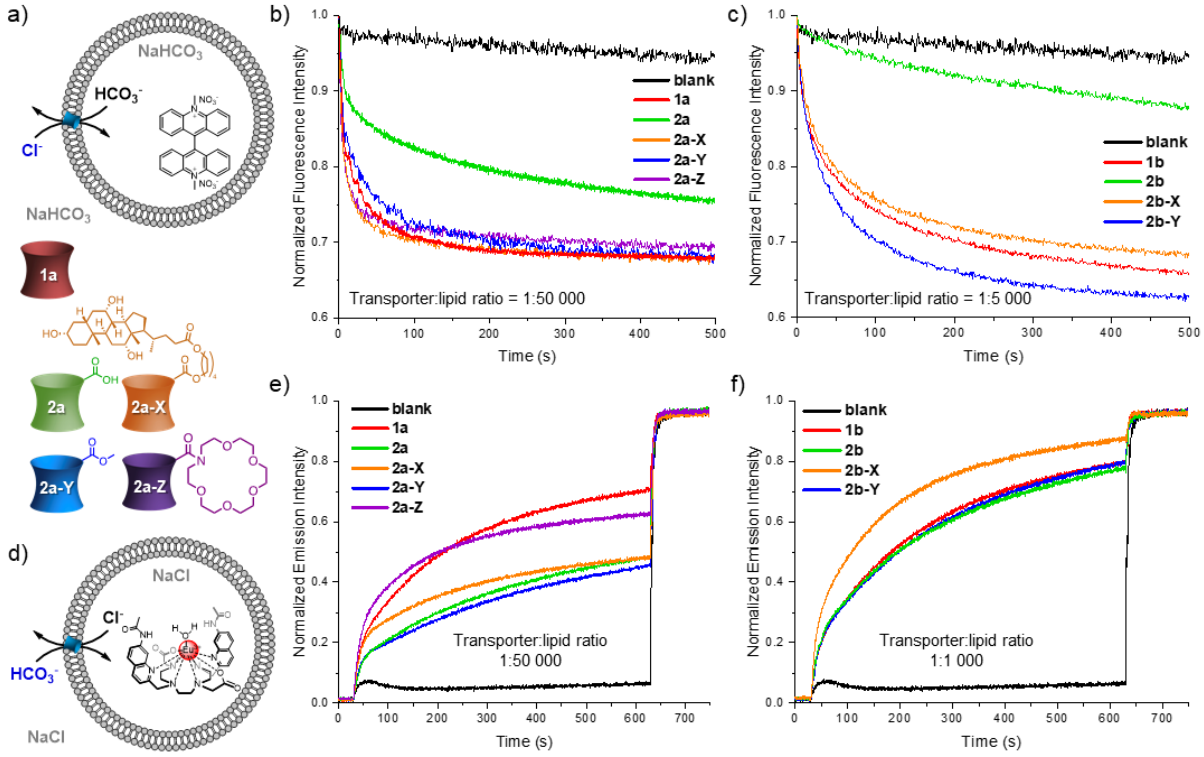


Figure 3: a) Schematic representation of the lucigenin assay used to monitor chloride transport via Cl^-/HCO_3^- antiport by b) **1a**, **2a**, **2a-X**, **2a-Y**, **2a-Z** (pre-incorporated at 1:50000 transporter to lipid ratio) and by c) **1b**, **2b**, **2b-X**, **2b-Y** (1:5000 ratio) as monitored by lucigenin assay (exc. 430 nm; em. 505 nm) in 225 mM $NaHCO_3$ at pH 7.5, upon addition of 25 mM NaCl to the liposomes (0.4 mM lipids); d) schematic representation of $[Eu.L1]^+$ assay used to monitor bicarbonate transport via HCO_3^-/Cl^- antiport by e) **1a**, **2a**, **2a-X**, **2a-Y**, **2a-Z** (pre-incorporated at 1:50000 transporter to lipid ratio) and by f) **1b**, **2b**, **2b-X**, **2b-Y** (1:1000 ratio) as monitored by $[Eu.L1]^+$ assay (exc. 330 nm; em 615 nm) in 225 mM NaCl with 5 mM HEPES at pH 7.0, upon addition of 10 mM $NaHCO_3$ to the liposomes (0.4 mM lipids)

CONCLUSION

Two fluorinated bambusuril macrocycles bearing a single carboxylic acid group were prepared from a functionalized glycoluril monomer and fluorinated glycoluril monomers, synthesized by a modified procedure. The carboxylic acid group on the bambusurils was utilized to covalently attach different moieties, including cholesterol and aza-crown ether. The resulting conjugates were tested for the extraction of various salts from water to nitrobenzene. The compound **2a-Z**, containing an aza-crown ether moiety, showed extraction of NaCl while **2a-Y**, lacking such a cation binding site, did not extract

this salt. Transport experiments with the prepared derivatives revealed that all of them can act as potent chloride/bicarbonate transporters through lipid bilayers. Only the derivatives with carboxylic acid groups show significantly different behavior. It is quite surprising that other moieties (which are very different from each other) have very little impact on the transport activity of fluorinated bambusurils. This opens further possibilities to append a variety of other functionalities which might favor the use of fluorinated bambusurils for biomedical applications, by, for example, improving deliverability to cell membranes or targeting of specific cells.

EXPERIMENTAL SECTION

Materials. All reagents were purchased from Merck, Acros, TCI, abcr or Fluorochem and used without further purification. 4,5-Dihydroxyimidazolidin-2-one **6**, 2,4-bis(4-methoxybenzyl)glycoluril **8** and (1*S*,5*R*)-2-(4-carboxybenzyl)-4-methylglycoluril **11** were prepared according to previously published procedures.[23,31,40] Deuterated solvents were purchased from Acros (acetonitrile, water) and Sigma-Aldrich (nitrobenzene) and used as received. Ultrapure water was prepared by Barnstead™ MicroPure™ Water Purification System.

Instruments and methods. The NMR spectra were measured on Bruker Avance III (^{1}H: 300 MHz, ^{13}C: 75 MHz, ^{19}F: 282 MHz) or Bruker Avance III (^{1}H: 500 MHz, ^{13}C: 126 MHz, ^{19}F 471 MHz), as specified. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz). The NMR spectra were referenced to the solvent residual signal (^{1}H: $\delta_{acetonitrile}$ = 1.94 ppm, $\delta_{nitrobenzene}$ = 8.11 ppm, 7.67 ppm, 7.50 ppm; ^{13}C: $\delta_{acetonitrile}$ = 118.26 ppm, 1.32 ppm).[46,47] Data are reported as follows: chemical shift, multiplicity (s – singlet, d – doublet, t – triplet, q – quadruplet, b – broad, m – multiplet, o – overlapping signals), coupling constant, and integration.

MALDI-TOF mass spectra were recorded on a MALDI-TOF Axima CFR spectrometer. Samples were ionized with the aid of a nitrogen laser (wavelength 337 nm, maximum power 6 MW). Gentisic acid (DHB) or α-cyano-4-hydroxycinnamic acid (HCCA) were used as matrices. HRMS spectra were recorded on an Agilent 6224 Accurate-Mass TOF mass spectrometer. Samples were ionized by electrospray ionization (ESI) or atmospheric-pressure chemical ionization (APCI).

TLC was carried out on VWR aluminum backed sheets coated with silica gel with a fluorescent indicator. The analyte was detected by UV light (wavelength 254 nm) or by staining with ceric ammonium molybdate stain. Preparative chromatographic separations were performed using silica gel (40 – 60 µm particles, pore size 60 Å) supplied by Acros or VWR. Dry column vacuum chromatography was done using silica gel (6 – 35 µm particles, pore size 60 Å) supplied by fluorochem. Preparative

chromatographic separations on reverse phase were performed using Reveleris® X2 Flash Chromatography System with Reveleris® C18-WP 12g Flash Cartridge.

All reactions that require increased temperature were heated with a DrySyn heating block on an electromagnetic stirrer.

Fluorescence measurements were carried out on a FluoroMax-4 (Horiba) (lucigenin and $[Eu.L1]^+$ assays) or SLM8000 (lucigenin assay) spectrofluorometers equipped with a water-thermostatted cell holder with stirring and an injection port.

*Preparation of **10a***. A mixture of glycoluril **8** (23.93 g, 62.58 mmol), Cs_2CO_3 (85.66 g, 262.9 mmol) and CH_3CN (840 mL) is stirred at 70 °C for 1 hour, then 3,5-bis(trifluoromethyl)benzyl bromide (24.10 mL, 40.36 g, 131.5 mmol) is added. The mixture is stirred at 70 °C for 17 hours. Then the reaction mixture is filtered through celite pad. The filtrate is evaporated yielding glycoluril **10a** as a white-yellowish solid (51.73 g, 99% yield). ^{1}H NMR (500 MHz, CD_3CN) δ 7.88 (b, 2H), 7.68 (b, 4 H), 7.03-7.00 (m, 4H), 6.80-6.67 (m, 4H), 5.06 (s, 2H), 4.59-4.55 (o, 4H), 4.44 (d, J = 16.5 Hz, 2H), 4.07 (d, J = 16.0 Hz, 2H), 3.73 (s, 6H). ^{13}C NMR{^{1}H} (125 MHz, CD_3CN) δ 160.4, 160.2, 160.1, 141.9, 132.2 (q, $^2J_{CF}$ = 32.9 Hz), 129.8, 129.7, 128.8, 124.5 (q, $^1J_{CF}$ = 270.4 Hz), 122.3 (t, $^3J_{CF}$ = 3.75 Hz), 115.0, 70.1, 55.9, 47.4, 47.2. ^{19}F NMR (471 MHz, CD_3CN) δ −63.39. HRMS (APCI+): m/z $[C_{38}H_{30}F_{12}N_4O_4 + H]^+$ observed: 835.2144, calculated: 835.2148.

*Preparation of **7a***. A cold solution of $(NH_4)_2Ce(NO_3)_6$ (135.96 g, 248.00 mmol) in H_2O (308 mL) is added dropwise over 30 minutes to a solution of glycoluril **10a** (51.73 g, 61.98 mmol) in CH_3CN (923 mL) at −20 °C. The mixture is stirred at RT for 3 hours, then CH_3CN is removed via evaporation under reduced pressure. H_2O (150 mL) is added and the aqueous phase is extracted with AcOEt (3 x 150 mL). The collected organic layers are washed with brine (150 mL), dried over $MgSO_4$, filtered and evaporated. The resulting yellow oil is sonicated in CH_2Cl_2 until a precipitate forms, which is collected via filtration yielding glycoluril **7a** as a white solid (22.46 g, 61% yield). Spectral features of compound **7a** correspond to those previously published.[33]

*Preparation of **10b***. Glycoluril **10b** was prepared according to the procedure for glycoluril **10a** using 4-((trifluoromethyl)sulfanyl)benzyl chloride as alkylating agent. Glycoluril **8** (1.91 g, 5.00 mmol), Cs_2CO_3 (6.52 g, 20.0 mmol), 4-((trifluoromethyl)sulfanyl)benzyl chloride (2.45 g, 10.5 mmol), CH_3CN (75 ml). glycoluril **10b** was isolated after dry column vacuum chromatography (SiO_2, cyclohexane/EtOAc 9:1 to 1:9, 100 mL fraction volume). White solid (3.03 g 79% yield). ^{1}H NMR (500 MHz, CD_3CN) δ 7.65 (d, J = 8.2 Hz, 4H), 7.29 (d, J = 8.2 Hz, 4H), 6.99 (d, J = 9.0 Hz, 4H), 6.82 (d, J = 9.0 Hz, 4H), 4.93 (s, 2H), 4.60 (d, J = 16.0 Hz, 2H), 4.59, (d, J = 16.5 Hz, 2H), 4.31 (d, J = 16.5 Hz, 2H), 3.94 (d, J = 16.0 Hz, 2H), 3.75 (s, 6H). ^{13}C NMR{^{1}H} (125 MHz, CD_3CN) δ 160.3, 160.2, 160.0, 142.3, 137.6, 130.9 (q, $^1J_{CF}$ = 305.0 Hz) 129.9,

129.7, 129.6, 123.6, 115.0, 69.2, 55.9, 47.2, 47.1. ^{19}F NMR (471 MHz, CD_3CN) δ −43.86. HRMS (APCI+): m/z $[C_{36}H_{32}F_6N_4O_4S_2 + H]^+$ observed: 763.1847, calculated: 763.1842.

*Preparation of **7b**.* Method A. 4,5-Dihydroxyimidazolidin-2-one **6** (10.6 g, 90.0 mmol) is added portion-wise at 30 minutes intervals over 4.5 hours to a stirring solution of **5b** (8.86 g, 20.0 mmol) and **6** (3.54 g, 30.0 mmol) in isopropanol (250 mL) and concentrated HCl (5 mL) at 80 °C. The reaction mixture is filtered. The filtrate is evaporated. The residue is pulverized in water (100 mL) and collected via filtration. Pale yellow solid (10.1 g, 97% yield).

Method B. Glycoluril **7b** was prepared according to the procedure for glycoluril **7a**. Glycoluril **10b** (2.45 g, 3.11 mmol), $(NH_4)_2Ce(NO_3)_6$ (6.83 g, 12.5 mmol), CH_3CN (46.7 mL), H_2O (15.5 mL). A yellow solid precipitated from the reaction mixture after addition of H_2O (250 mL). The solid was filtered, washed with H_2O (2×40 mL), cold Et_2O (20 mL) and hexane (2×10 mL) yielding glycoluril **7b** as a white solid (0.933 g, 57% yield). Spectral features of compound **7b** correspond to those previously published.[33]

***Compound 2a**.* A mixture of glycoluril **7a** (15.56 g, 26.3 mmol), glycoluril **11** (1.239 g, 4.27 mmol) and paraformaldehyde (0.984 g 32.8 mmol) is stirred in 1,4-dioxane (85 mL) at RT. Concentrated H_2SO_4 (2.4 mL) is added. The resulting mixture is stirred at 80 °C for 8 hours, then cooled to RT and Et_2O (150 mL) is added. The resulting white precipitate is collected via filtration and washed with Et_2O (2 x 25 mL). The mixture of bambusurils is separated by column chromatography (eluent: hexane/acetone 1/1) to give bambusuril **2a·H_2SO_4** as a white solid (1.573 g, 11% yield assuming hydrogen sulfate complex). ^{1}H NMR (500 MHz, CD_3CN) δ 12.79 (s, 1H), 8.05 (s, 2H), 7.97 (s, 2H), 7.88-7.73 (o, 17H), 7.58 (s, 2H), 7.52 (s, 1H), 7.47-7.40 (s, 6 H), 7.37 (s, 2H), 7.24 (d, J = 8.0 Hz, 2H), 6.21 (d, J = 8.5 Hz, 1H), 5.94 (d, J = 8.5 Hz, 1H), 5.88 (d, J = 8.5 Hz, 1H), 5.82 (d, J = 8.5 Hz, 1H), 5.79 (d, J = 8.5 Hz, 1H), 5.72-5.68 (o, 2 H), 5.53-5.49 (o, 3H), 5.42-5.38 (o, 2H), 5.33-5.30 (o, 2H), 5.27 (b, 1H), 5.23-5.18 (o, 2H), 5.16-4.62 (o, 16H), 4.54 (d, J = 14.5 Hz, 1H), 4.20 (d, J = 15.0 Hz, 1H), 4.13 (d, J = 15.0 Hz, 1H), 4.08-4.03 (o, 2H), 3.97-3.86 (o, 5H), 3.81 (d, J = 15.0, 1H), 3.74 (d, J = 15.0 Hz, 1H), 3.56 (d, J = 16.0 Hz, 1H), 3.32 (s, 3H). ^{13}C NMR{^{1}H} (125 MHz, CD_3CN) δ 167.2, 161.1, 160.9, 160.8, 160.8, 160.1, 160.0, 159.8, 159.8, 159.4, 159.1, 159.1, 158.9, 143.7, 143.5, 143.5, 143.5, 143.4, 143.4, 143.3, 143.1, 143.0, 142.9, 142.6, 142.3, 132.4 (q, $^2J_{CF}$ = 33.3 Hz), 132.4 (q, $^2J_{CF}$ = 32.9 Hz), 132.3 (q, $^2J_{CF}$ = 32.9 Hz), 132.3 (q, $^2J_{CF}$ = 33.0 Hz), 132.1 (q, $^2J_{CF}$ = 32.9 Hz), 128.3, 128.3, 128.1, 128.1, 128.0, 127.9, 127.9, 127.2, 126.4, 125.9, 125.8, 124.4 (q, $^1J_{CF}$ = 270.0 Hz), 124.4 (q, $^1J_{CF}$ = 270.4 Hz), 122.3, 122.2, 122.1, 122.1, 122.1, 122.0, 122.0, 122.0, 121.4, 121.4, 121.3, 71.3, 70.9, 70.8, 70.7, 70.4, 70.3, 70.1, 70.0, 69.9, 69.4, 69.3, 67.8, 49.5, 49.1, 49.1, 48.8, 48.8, 48.8, 48.7, 48.5, 48.5, 48.4, 48.3, 48.2, 48.2, 47.9, 47.6, 47.6, 47.4, 30.9. ^{19}F NMR (471 MHz, CD_3CN) δ −63.26, −63.29, −63.34, −63.42, −63.46, −63.54, −63.56, −63.59, −63.61, −63.64, −63.67, −63.69,

−63.71, −63.76, −63.79, −63.91, −63.94, −64.14, −64.21, −64.43. MALDI-TOF-MS: m/z [$C_{129}H_{84}F_{60}N_{24}O_{14}$ + Na]$^+$ observed: 3355.612, calculated: 3355.554.

Compound 2a-X. A mixture of **2a·H_2SO_4** (0.100 g, 0.0291 mmol), K_2CO_3 (0.008 g, 0.06 mmol) and **12**[48] (0.019 g, 0.032 mmol) in DMF (2 mL) is stirred at 70 °C under argon for 18 hours. The solvent is evaporated and the residue is transferred into a separatory funnel using ethyl methyl ketone (2 mL). The organic layer is washed with deionized water (4 mL). The aqueous layer is extracted with ethyl methyl ketone 2 x 2mL). The collected organic layers are dried over Na_2SO_4, filtered and evaporated. The crude product is purified using column chromatography (eluent: hexane/acetone 42/58) yielding **2a-X** as a brownish solid (0.012 g 11% yield). ^{1}H NMR (500 MHz, CD_3CN) δ 7.96-7.77 (o, 32H), 7.35 (d, J = 8.0 Hz, 2H), 5.81-5.63 (o, 10H), 5.52 (d, J = 8.5 Hz, 1H), 5.45 (d, J = 8.0 Hz, 1H), 5.11-4.70 (o, 22H), 4.59-4.54 (o, 2H), 4.41 (d, J = 15.5 Hz, 1H), 4.33-4.24 (m, 2H), 4.20 (d, J = 15.0 Hz, 1H), 4.13-3.90 (o, 10H), 3.85 (b, 1H), 3.70 (b, 1H), 3.31-3.22 (m, 1H), 3.04 (s, 3H), 2.31-2.17 (o, 4H), 1.91-1.88 (o, 2H), 1.83-1.19 (o, 28H), 1.11-0.99 (m, 1H), 0.93-0.89 (o, 4H), 0.84 (s, 3H), 0.63 (s, 3H). ^{13}C NMR{^{1}H} (125 MHz, CD_3CN) δ 174.8, 167.0, 160.5, 160.1, 159.8, 159.8, 159.7, 159.6, 143.7, 143.6, 143.6, 143.5, 143.5, 143.5, 143.4, 143.4, 143,4, 132.4 (q, $^2J_{CF}$ = 33.3 Hz), 132.4 (q, $^2J_{CF}$ = 32.9 Hz), 132.4 (q, $^2J_{CF}$ = 32.9 Hz), 130.3, 128.1, 128.0, 127.4, 124.5 (q, $^1J_{CF}$ = 271.3 Hz), 124.4 (q, $^1J_{CF}$ = 271.3 Hz), 124.4 (q, $^1J_{CF}$ = 271.25 Hz), 124.4 (q, $^1J_{CF}$ = 270.8 Hz), 124.4 (q, $^1J_{CF}$ = 270.0 Hz), 122.1, 122.1, 122.1, 122.1, 122.0, 122.0, 122.0, 122.0, 121.9, 121.9, 73.1, 72.2, 70.5, 70.5, 70.5, 70.4, 70.4, 70.4, 70.3, 70.3, 70.2, 70.1, 68.5, 65.9, 64.9, 49.3, 48.9, 48.5, 48.4, 48.3, 48.3, 48.2, 48.2, 48.2, 48.2, 48.0, 48.0, 48.0, 47.9, 47.8, 47.6, 47.2, 42.8, 42.7, 40.7, 40.7, 36.1, 36.1, 35.5, 32.0, 31.9, 31.6, 31.5, 29.9, 29.8, 29.4, 29.4, 28.2, 27.6, 26.6, 23.9, 23.1, 17.6, 12.9. ^{19}F NMR (471 MHz, CD_3CN) δ −63.45, −63.50, −63.63, −63.66, −63.71, −63.78, −63.80. HRMS (ESI−): m/z [$C_{161}H_{138}F_{60}N_{24}O_{19}Br$]$^-$ observed: 3932.8825, calculated: 3932.8842.

Compound 2a-Y. $SOCl_2$ (0.5 mL, 0.819 g, 6.88 mmol) is slowly added to a solution of bambusuril **2a·H_2SO_4** (0.100 g, 0.0291 mmol) in methanol (10 mL) at 0 °C. The mixture is stirred at 60 °C for 15 hours, then the volatiles are evaporated. The solid residue is suspended in ultrapure H_2O (5 mL), collected via centrifugation and dried in vacuo. CH_2Cl_2 (5 mL) is added to the dry solid. The suspension is filtered and the filtrate is evaporated yielding anion free bambusuril **2a-Y** (0.070 g, 71% yield). ^{1}H NMR (500 MHz, CD_3CN) δ 7.97-7.81 (o, 32H), 7.27 (d, J = 8 Hz, 2H), 5.68-5.18 (o, 12H), 5.09-4.59 (o, 21H), 4.32 (d, J = 15.5 Hz, 1H), 4.12-3.84 (o, 15H), 3.07 (s, 3H). ^{13}C NMR{^{1}H} (125 MHz, CD_3CN) δ 161.4, 161.3, 161.3, 159.9, 159.8, 159.7, 159.5, 143.7, 142.8, 142.7, 142.6, 132.4 (q, $^2J_{CF}$ = 33.3 Hz), 132.4 (q, $^2J_{CF}$ = 33.3 Hz), 132.3 (q, $^2J_{CF}$ = 32.9 Hz), 132.2 (q, $^2J_{CF}$ = 33.3 Hz), 130.5, 128.7, 128.1, 124.6 (q, $^1J_{CF}$ = 270.0 Hz), 124.5 (q, $^1J_{CF}$ = 270.8 Hz), 124.4 (q, $^1J_{CF}$ = 270.0 Hz), 122.2, 71.4, 52.7, 49.0, 49.0, 49.0, 49.0, 48.9, 48.7, 48.4, 48.3, 30.4. ^{19}F NMR (471 MHz, CD_3CN) δ −63.27, −63.34, −63.39, −63.41, −63.47,

−63.57, −63.58, −63.60, −63.62, −63.65, −63.66, −63.69, −63.73, −63.75, −63.78, −63.79, −63.80, −63.82. MALDI-TOF-MS: m/z $[C_{130}H_{86}F_{60}N_{24}O_{14} + Na]^+$ observed: 3369.620, calculated: 3369.570.

Compound 2a-Z. Coupling reagent HATU (0.0133 g, 0.0349 mmol) and *N*,*N*-diisopropylethylamine (0.020 mL, 0.0150 g, 0.116 mmol) are added to a solution of bambusuril **2a·H_2SO_4** (0.100 g, 0.0291 mmol) in DMF (2 mL). The mixture is stirred under argon at RT for 1.5 hours, then 1-aza-18-crown-6 (0.0077 g, 0.0291 mmol) is added at 0 °C. The mixture is then stirred under argon at RT overnight. The solvent is removed and the residue dissolved in 5 mL of CH_2Cl_2. The organic phase is washed with ultrapure H_2O (3 x 5 mL). The collected aqueous layers are extracted with CH_2Cl_2 (3 x 5 mL). The collected organic layers are dried over Na_2SO_4, filtered and evaporated. The crude product is purified using reverse phase liquid chromatography (C12 column, eluent: H_2O/CH_3CN from 55/45 to 0/100) giving **2a-Z** as a white solid (0.0371 g, 36%). ^{1}H NMR (500 MHz, CD_3CN) δ 7.99 (s, 1H), 7.96 (s, 3H), 7.93 (s, 2H), 7.89-7.82 (o, 24H), 7.30 (b, 4H), 5.48, (d, J = 8.0 Hz, 1H), 5.43 (d, J = 8.0 Hz, 1H), 5.42 (d, J = 8.5 Hz, 1H), 5.37-5.26 (o, 8H), 5.19 (d, J = 8.5 Hz, 1H), 5.07-5.01 (o, 9H), 4.96 (d, J = 17.0 Hz, 2H), 4.91 (d, J = 17.0 Hz, 1H), 4.85-4.68 (o, 10H), 4.62 (d, J = 15.5 Hz, 1H), 4.55 (d, J = 17.0 Hz, 1H), 4.38 (d, J = 15.5 Hz, 1H), 4.32 (d, J = 15.5 Hz, 1H), 4.16 (d, J = 15.5 Hz, 1H), 4.04 (d, J = 7.0 Hz, 1H), 3.92-3.89 (o, 6H), 3.67-3.53 (o, 24H), 3.07 (s, 3H). ^{13}C NMR{^{1}H} (125 MHz, CD_3CN) δ 172.2, 161.5, 161.4, 161.4, 161.3, 160.4, 159.0, 159.7, 159.7, 159.7, 159.4, 159.4, 142.9, 142.8, 142.8, 142.7, 142.6, 142.4, 142.4, 140.1, 137.6, 132.4 (q, $^2J_{CF}$ = 32.8 Hz), 132.4 (q, $^2J_{CF}$ = 33.8 Hz), 132.4 (q, $^2J_{CF}$ = 33.3 Hz), 132.3 (q, $^2J_{CF}$ = 32.8 Hz), 132.3 (q, $^2J_{CF}$ = 32.4 Hz), 128.9, 128.7, 128.7, 128.7, 128.6, 128.5, 128.5, 128.3, 128.2, 128.1, 127.8, 124.6 (q, $^1J_{CF}$ = 270.8 Hz), 124.5 (q, $^1J_{CF}$ = 270.8 Hz), 124.4 (q, $^1J_{CF}$ = 270.4 Hz), 124.4 (q, $^1J_{CF}$ = 270.0 Hz), 122.7, 122.6, 122.2, 71.7, 71.6, 71.6, 71.4, 71.3, 71.3, 71.2, 71.2, 71.2, 70.2, 49.8, 49.4, 49.1, 49.1, 49.0, 49.0, 48.8, 48.7, 48.7, 48.6, 48.4, 32.0. ^{19}F NMR (471 MHz, CD_3CN) δ −63.23, −63.25, −63.29, −63.38, −63.40, −63.48, −63.54, −63.57, −63.62, −63.65, −63.67, −63.69, −63.72, −63.73, −63.76, −63.78, −63.80. MALDI-TOF-MS: m/z $[C_{141}H_{107}F_{60}N_{25}O_{18} + H]^+$ observed: 3578.727, calculated: 3578.735, m/z $[C_{141}H_{107}F_{60}N_{25}O_{18} + Na]^+$ observed: 3600.707, calculated: 3600.717.

Compound 2b. **2b** was prepared according to the procedure for **2a:** Glycoluril **7b** (1.00 g, 1.91 mmol), glycoluril **11** (0.0929 g, 0.319 mmol) and paraformaldehyde (0.0862 g, 2.87 mmol). The mixture of bambusurils is separated by column chromatography (eluent: DCM/Acetone 4/1) to give bambusuril **2b·H_2SO_4** as a white solid (0.112 g, 12% yield assuming hydrogen sulfate complex). ^{1}H NMR (500 MHz, CD_3CN) δ 12.47 (s, 1H), 7.93-7.90 (o, 1H), 7.69 – 7.02 (o, 43H), 6.16 (d, 1H, *J* = 8.8 Hz), 5.90 (d, 2H, *J* = 8.4 Hz), 5.79 (d, 2H, *J* = 8.8 Hz), 5.65 (d, 1H, *J* = 8.8 Hz), 5.50 – 4.53 (o, 26H), 4.39 – 3.88 (o, 12H), 3.28 (s, 3H). ^{13}C NMR{^{1}H} (126 MHz, CD_3CN) δ 207.0, 160.3, 160.1, 159.9, 159.8, 159.4, 158.8, 158.8, 144.1, 143.8, 143.7, 143.4, 143.1, 143.0, 130.5, 130.5 ($^1J_{CF}$ = 307.6 Hz), 129.5, 129.0, 128.7, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.4, 123.1, 122.7, 70.7, 69.9, 69.6, 69.5, 69.3, 48.8, 48.3, 48.0,

47.9, 47.4, 29.3. ^{19}F NMR (471 MHz, CD_3CN) δ -43.70, -43.71, -43.73, -43.79, -43.87, -43.88, -43.90, -43.97, -44.01, -44.02. HRMS (ESI-): m/z $[C_{119}H_{94}F_{30}N_{24}O_{14}S_{10} + Cl]^-$ observed: 3009.3804 calculated: 3009.3821.

Compound 2b-X. **2b-X** was prepared according to the procedure for **2a-X: 2b·H_2SO_4** (0.101 g, 0.0327 mmol), K_2CO_3 (0.009 g, 0.07 mmol), **12**[48] (0.0195 g, 0.0326 mmol), DMF (2 mL). The crude product is purified using column chromatography (eluent: DCM/acetone 4/1) yielding **2b-X** (0.0869 g 75% yield). ^{1}H NMR (500 MHz, CD_3CN) δ 7.91 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.67 – 7.60 (o, 18H), 7.49 (d, J = 7.5 Hz, 2H), 7.46 – 7.40 (o, 18H), 7.32 (d, J = 8.0 Hz, 2H), 5.81 (b, 7H), 5.67 – 5.54 (o 5H), 5.03 – 4.45 (o, 22H), 4.31 – 4.29 (o 6H), 4.21 (b, 6H), 4.15 (b, 2H), 4.04 (t, J = 5.8 Hz, 2H), 3.90 – 3.89 (m, 1H), 3.74 – 3.73 (m, 1H), 3.32 – 3.28 (m, 1H), 3.02 (s, 3H), 2.36 – 2.14 (o, 4H), 1.98 – 1.89 (o, 2H), 1.84 – 1.26 (o, 28 H), 1.12 – 1.06 (m, 1H), 1.00 – 0.94 (o, 4H), 0.87 (s, 3H), 0.67 (s, 3H). ^{13}C NMR{^{1}H} (125 MHz, CD_3CN) δ 174.4, 166.5, 160.1, 159.7, 159.5, 159.4, 159.3, 158.4, 144.0, 143.9, 143.8, 143.8, 143.8, 137.2, 137.0, 137.0, 131.7, 130.0, 129.3, 128.3, 128.2, 128.1, 126.9, 122.8, 72.8, 71.1, 70.0, 69.9, 69.9, 69.9, 69.9. 69.8, 69.8, 69.8, 68.0, 66.2, 65.0, 48.0, 48.0, 47.8, 47.8, 42.4, 42.3, 40.3, 40.2, 35.8, 35.7, 35.2, 35.1, 31.7, 31.7, 31.6, 31.6, 27.9, 27.6, 26.6, 23.5, 22.7, 17.2, 12.5. ^{19}F NMR (282 MHz, CD_3CN) δ −43.87, −43.88, −43.89, −43.92, −43.92. MALDI-TOF-MS: m/z $[C_{151}H_{148}F_{30}N_{24}O_{19}S_{10} + Na]^+$ observed: 3513.814, calculated: 3513.797.

Compound 2b-Y. **2b-Y** was prepared according to the procedure for **2a-Y: 2b·H_2SO_4** (0.0200 g, 6.51 µmol), methanol (2.0 mL). $SOCl_2$ (0.100 mL, 0.163 g, 1.17 mmol). A solid precipitates from the reaction mixture. The solid is collected via centrifugation, washed with MeOH (2 mL) and dried *in vacuo* to obtain **2b-Y** (8.0 mg, 41% as complex with HCl). ^{1}H NMR (500 MHz, CD_3CN) δ 7.88 (d, J = 8.4 Hz, 2H), 7.72 – 7.23 (o, 42H), 5.74 – 5.34 (o, 12H), 5.02 – 4.40 (o, 24H), 4.37 – 4.02 (o, 12H), 3.86 (s, 3H), 3.02 (s, 3H). ^{13}C NMR{^{1}H} (126 MHz, CD_3CN) δ 167.4, 160.5, 160.3, 160.2, 160.2, 159.8, 159.7, 159.7, 159.5, 145.8, 144.2, 144.1, 144.0, 137.6, 137.5, 137.4, 134.6, 132.2, 130.4, 130.1, 129.7, 128.7, 128.7, 128.7, 128.6, 127.3, 123.2, 70.2, 70.1, 70.0, 69.7, 52.7, 49.2, 48.5, 48.3, 48.2, 48.2, 48.1, 31.7. ^{19}F NMR (282 MHz, CD_3CN) δ -43.84, -43.86, -43.95. MALDI-TOF-MS: m/z $[C_{120}H_{96}F_{30}N_{24}O_{14}S_{10} + Cl^-]$ observed: 3021.472, calculated: 3021.396, m/z $[C_{120}H_{96}F_{30}N_{24}O_{14}S_{10} + NO_3^-]$ observed: 3048.582, calculated: 3048.415.

Extraction experiments. The experimental setup consists of an NMR tube filled with 0.5 mL of a 2 mM solution of the ionophore in deuterated nitrobenzene and 0.5 mL of a 2 mM solution of the salt in D_2O. The tube is vigorously shaken for 5 minutes, then is centrifuged until the two phases separate. The ^{1}H NMR spectrum of the organic phase is recorded. Extraction percentage is calculated comparing the

intensity of the N-methyl signal of the ionophore in the anion-free and complexed form. Blank experiments were performed in the same way, but there was no salt present in the D_2O.

ASSOCIATED CONTENT

The Supporting Information is available free of charge at https://pubs.acs.org/doi/…

^{1}H, ^{19}F, and $^{13}C\{^{1}H\}$ NMR spectra, MS spectra of new compounds. Details of extraction and anion transport experiments.

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(48) The preparation of **12** is described in the Supporting Information.