Synthesis, characterization, and applications of fluorous resorcin[4]arenes†‡

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Three fluorous resorcin[4]arenes (1a-c) were synthesized and characterized for their potential application in separation science. A crystal structure of 1b confirmed its ring size and conformation. The fluorous resorcin[4]arenes are soluble in hybrid fluorous solvents. Preliminary studies demonstrated that 1a immobilized in a fluorous bulk membrane is capable of transporting tetramethylammonium cation from an aqueous source phase into an aqueous receiving phase.

The selective transport of a target compound from a mixture source phase into a receiving phase is a ubiquitous phenomenon in bio-systems[1] and has practical application in separation science.[2] Commonly used solvents for liquid transport are organic solvents such as $CHCl_3$, CCl_4, and toluene. Transport targets are limited with such solvents because of background transport (simple diffusion).

Fluorous solvents are both hydrophobic and lipophobic which make them immiscible with most organic and aqueous solutions.[3] A recent study on fluorous biphasic extraction demonstrated that fluorous compounds selectively retained in a fluorous phase can enhance partitioning organic molecules into fluorous solvents by hydrogen bonding.[4] Furthermore, triphasic reactions have successfully used fluorous solvents as bulk membranes that block both organic and inorganic species from partitioning out of an organic source phase while allowing fluorophilic compounds to partition through the fluorous bulk membrane.[5] Fluorous hosts can encapsulate guest molecules that exhibit both electronic and steric complementarities[6] and thereby enhance partitioning into a fluorous phase.[7] Thus, we hypothesized that synthetic fluorous hosts immobilized in a fluorous bulk membrane could serve as carrier in a triphase system to selectively transport a guest molecule from a source phase to a receiving phase. This transport expands the application of fluorous separations since guest molecules can even be fluorophobic.

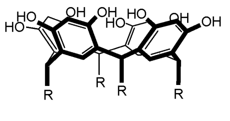
Although several fluorous hosts have been synthesized and studied,[7,8] there are no reports of using them for transport. Because of the cavity and special matrix of hydroxyl groups, resorcinarenes have been used in the transport of both ionic and neutral species such as K^+ and carbohydrates.[9] Herein we report the synthesis, characterization and preliminary transport applications of fluorous resorcinarenes (**1a–c**, Scheme 1).

The difference between fluorous resorcin[4]arenes (**1a–c**) and their organic counterpart **2** is the R groups attached to the lower rim. The perfluoroalkyl groups are insulated from the recognition moieties (aromatic rings and hydroxyl groups) by three sp^3 hybridized carbons to reduce the electron withdrawing effects of the fluorous tags.[10] Moreover, the eight unmodified hydroxyl groups of resorcin[4]arene on the upper rim can be functionalized to increase the size of the cavity and install new groups for molecular recognition of different guests.

The fluorous resorcin[4]arenes (**1a–c**) were synthesized starting from perfluoroalkyklethyl iodides (Scheme 2). The iodides $F(CF_2)_nCH_2CH_2I$ were treated with BuLi, and then reacted with DMF to give aldehydes $F(CF_2)_nCH_2CH_2CHO$. Acid-catalyzed condensation of 1,3-dihydroxybenzene (resorcinol) with equivalent amount of fluorous alkanals offered the targeted fluorous resorcin[4]arenes (**1a–c**) in good yields (68–76%). Resorcin[4]arene **2** with long alkyl (undecyl) "ponytails", widely used in supramolecular chemistry because of its solubility in organic solvents,[11] was synthesized as a control.

While all synthesized fluorous resorcin[4]arenes have four fluorous "ponytails", their fluorous contents differentiate them from each other. Compounds **1a**, **1b** and **1c** contain 46%, 53%, and 57% fluorine by molecular weight, respectively. That is 36, 52, and 68 fluorine atoms, respectively. Just as with their organic variant **2**, these fluorous resorcin[4]arenes were purified by column chromatography (silica sorbent, hexane and ethyl acetate eluant), and isolated as white solids.

The electron-withdrawing effect of the fluorous tags was assessed by ^1H and ^{13}C NMR spectroscopy.[12] Based on the chemical shifts of the hydrogens and carbons on the recognition moieties as compared to the control, the electron



1: R = $-CH_2CH_2(CF_2)_nF$, (**1a**, n = 4; **1b**, n = 6; **1c**, n = 8), **2**: R = $-C_{11}H_{23}$

Scheme 1 Fluorous Resorcin[4]arenes **1a–c** and their organic variant **2**.

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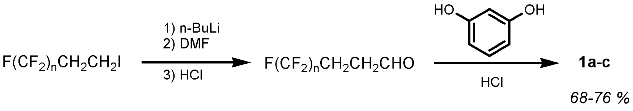

Scheme 2 Synthesis of fluorous resorcin[4]arenes **1a–c**.

withdrawing effects of fluorous alkyl chains were significantly reduced by the sp^3 C spacers. The X-ray structure of **1b** confirms the ring size and cone conformation.§ In the crystalline state, three of the four fluorous chains have all antibonds while the fourth chain has one gauche bond (Fig. 1). The distances between opposite aromatic protons on the upper rim are 8.23 and 10.78 Å, respectively.

Fluorous host **1b** crystallizes with an ethyl acetate guest between the cavity and the neighboring host molecule as shown in Fig. 1c. This demonstrates the potential application of the fluorous resorcin[4]arenes as transport hosts.

The fluorous resorcin[4]arenes synthesized in this work are insoluble in perfluorohexane, however, they are soluble in wet hydrofluoroether (HFE, *e.g.* C$_4$F$_9$OCH$_3$)[13] and other hybrid fluorous solvents such as perfluorohexylethyl-1,3-dimethylbutyl ether (F-626).[4b,14]

To demonstrate the application of the fluorous hosts, fluorous resorcin[4]arene **1a** was used as a carrier in fluorous triphasic transport experiments shown in Fig. 2 (left).[15] Tetramethylammonium cation (TMA$^+$), which is a known guest of resorcin[4]arenes, was selected for this study. The mechanism of transport is illustrated in Fig. 2 (right). A fluorous layer (F-626) is placed between two aqueous layers. The source phase is an aqueous layer with 0.5 N NaOH and the receiving phase containing 0.5 N HCl. The pK_a of the resorcinarenes[16] is about 10 therefore **1a** is deprotonated at the interface of the fluorous transport layer and the basic feeding layer. The negatively charged **1a** picks up the positively charged ammonium guest, transports the guest to the interface between the fluorous transport layer and the acidic receiving phase. There the host is re-protonated and the guest is released to the receiving phase. The transport process is driven by neutralization reaction between the basic source phase and acidic receiving phase.[16,17]

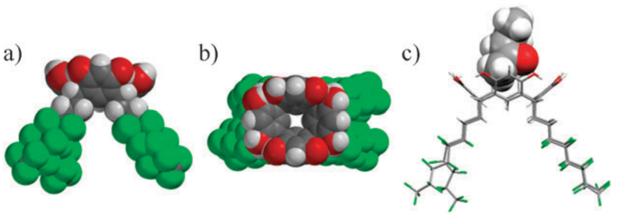

Fig. 1 Crystal structure of **1b**. (a) side view of **1b** in space filling style; (b) top view of **1b** in space filling style showing the cavity; (c) ethyl acetate (in space filling style) was hosted in the cavity of **1b** (in stick style) and space between neighboring molecules in the crystal.

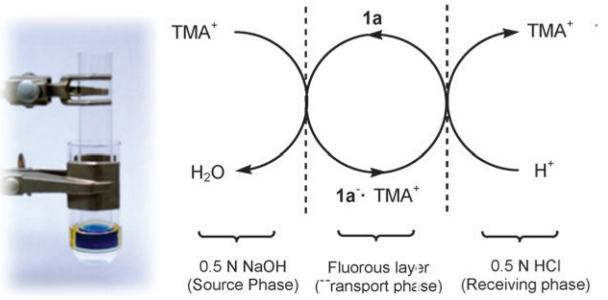

Fig. 2 The double-tube triphasic system used for transport of TMA$^+$ cation through fluorous bulk membrane by **1a** (left);[17] The proposed tranport model (right).

The triphasic transport experiments were carried out in a double-tube system as shown in Fig. 2a.[18] The transport phase is the colorless layer in the bottom with 0.01 mmol fluorous resorcinarene **1a** dissolved in 2 mL of F-626. Meanwhile, 0.5 mmol TMACl was dissolved in 2 mL of D$_2$O with 0.5 N NaOH serving as the source phase (blue layer inside the open-end small tube), and the receiving phase consisted of 2 mL D$_2$O with 0.5 N HCl (yellow layer between the two tubes). Transport was monitored by ^{1}H NMR. The TMA$^+$ cation was detected in the receiving phase within 1 h. After 4 days, 0.1 mmol pure TMACl was isolated in the receiving phase by evaporating the D$_2$O and excess HCl. Although the efficiency of transport still needs to be improved, this result is encouraging for further investigation.

Two control experiments were also performed to support the model in Fig. 2. When there was no resorcinarene in the transport phase, no TMA$^+$ cation was detected by ^{1}H NMR spectroscopy even after 4 days. This demonstrates that the transport of the cation is facilitated by the fluorous host. When fluorous resorcinarene **1a** was replaced with fluorous phenol **3** (p-C$_8$F$_{17}$CH$_2$CH$_2$SC$_6$H$_4$OH), again no transport was observed. It was detected from this experiment that the cavity and the hydroxyl group matrix created by the resorcinarene are critical for transport because the fluorous phenol **3** is soluble in F-626 and contains a hydroxyl group with similar pK_a to **1**.

In summary, we have synthesized and characterized three fluorous resorcin[4]arenes with different fluorous content. The limited electron withdrawing effect of the fluorous alkyl "ponytails" to the resorcin[4]arenes was demonstrated using by ^{1}H and ^{13}C NMR spectroscopy. A crystal structure of **1b** confirmed the ring size, conformation and showed the potential of fluorous resorcin[4]arenes as hosts. The fluorous resorcin[4]arenes (**1a–c**) studied within were soluble in hybrid fluorous solvents. Preliminary experiments show that fluorous host **1a** can transport the non-fluorous tetramethylammonium cation through a bulk fluorous layer into an aqueous receiving layer. Our study showed the potential application of fluorous hosts in separation.

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Notes and references

§ Crystal data for compound **1b**: colourless, 0.12 × 0.12 × 0.25 mm, C80H72F52O12, M = 2213.38, Triclinic, P-1, a = 10.6231(15) Å, b = 18.888(3) Å, c = 24.412(3) Å, α = 72.853(3)°, β = 86.220(3)°, γ = 76.854(3)°, V = 4557.9(11) Å^3; T = 150 (2) K, Dcalc = 1.613 g cm^{-3}, Z = 2, reflections collected = 36 782, independent reflections = 16 051 (R_{int} = 0.0798), R values [$I > 2\sigma(I)$, 7254 reflections]: R_1 = 0.1203, wR_2 = 0.3165; S = 1.032; CCDC 770495.†

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12 A comparison of ^{1}H, ^{13}C and ^{19}F NMR of resorcin[4]arenes **1a–c** and **2** are shown in supporting information.

13 The solubility in HFE increases by addition of small amount of MeOH or H_2O. It might be becausesmall amount of protic solvent is able to disturb the hydrogen bond between the resorcinarene in its solid state and stabilize its soluble forms (*e.g.* dimeric and hexameric capsules) in solution.

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