PCCP

Cite this: *Phys. Chem. Chem. Phys.*, 2012, **14**, 3909–3914

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PAPER

Generation of (nonafluoro-*tert*-butoxy)methyl ponytails for enhanced fluorous partition of aromatics and heterocycles†

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Received 2nd October 2011, Accepted 5th December 2011
DOI: 10.1039/c2cp23113a

The reaction of sodium perfluoro-*tert*-butoxide with benzylic carbon–bromide bond(s) leads to the formation of (nonafluoro-*tert*-butoxy)methyl ponytail(s), which can enhance the fluorous solubility and partition of aromatics and heterocycles.

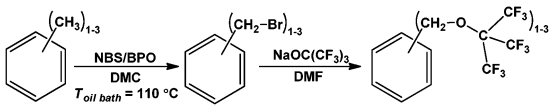
Introduction

One of the most important objectives of sustainable chemistry is the development of efficient catalysts which can be readily separated from the products. Liquid–liquid biphasic homogeneous catalysts could combine the molecular control of the active site with facile catalyst recycling.[1] Since the formation of a liquid–liquid biphasic system is due to the sufficiently different intermolecular forces of two liquids,[2] the selection of the catalyst phase depends primarily on the solvent properties of the product phase at a high conversion level.[3] For example, if the product is apolar the reagent or catalyst phase should be polar such as water, alcohols, and ionic liquids, and *vice versa*, if the product is polar the reagent or catalyst phase should be apolar like supercritical carbon dioxide and fluorous liquids. The most apolar solvents are the perfluorinated alkanes, perfluorinated dialkylethers, and perfluorinated trialkylamines.[2] Their miscibility even with common organic solvents is low at room temperature, thus these materials could form fluorous biphasic systems.[3]

The fluorous biphasic concept,[4] which led to the evolution of fluorous chemistry,[5] was based on the attachment of long perfluoroalkyl-chains to reagents and catalysts in appropriate numbers. The preferred size of the fluorous ponytails was in the range of C_6–C_{12} in order to achieve efficient product separation.[6] Unfortunately, the sustainability of fluorous chemistry has been limited by the persistency, toxicity, and long half-lives in humans of compounds containing longer fluorous ponytails. The appearance of perfluorooctyl sulfonate and perfluorooctanoic acid (PFOA) in the environment,[7] combined with their toxicity,[8] have resulted in global concerns and controls.[9] The negative environmental and health impacts of PFOA and related higher homologues have slowed down the initial interests in fluorous chemistry, as reagents or catalysts containing longer perfluoroalkyl-chains can decompose to perfluoroalkyl acids by entering the environment.[10] While limiting the exposure could lower the risks, the replacement of the longer perfluoroalkyl-chains with C_{1-4}-perfluoroalkyl-groups was proposed[11] to limit accumulation potential and toxicity.[12] The combination of shorter perfluoroalkyl groups attached to the backbone of reagents and catalysts in appropriate number and size has been shown to provide the necessary fluorous cover leading to high fluorous solubility and partition.[13] The perfluoro-*tert*-butyl group is one of the best shorter perfluoroalkyl-chains to provide high fluorous partition or fluorophilicity[14] and several fluorous compounds were prepared by using the sodium or potassium salts of perfluoro-*tert*-butanol.[13,15] Since the reactivity of the perfluoro-*tert*-butoxide is rather limited, we have developed an alternative approach by reacting it with benzylic carbon–bromine bonds of aromatic or heterocyclic compounds to form (nonafluoro-*tert*-butoxy)-methyl ponytails at preferred positions.

Results and discussions

During the search for a new synthetic use of the readily available sodium or potassium perfluoro-*tert*-butoxide, we have confirmed that the basicity of the perfluoro-*tert*-butoxide is too low to react with aryl-bromides due to the strong electron withdrawing effect of the perfluoromethyl groups. Next, we have introduced one methylene (–CH_2–) group between the bromine and the carbon atom(s) of the aromatic ring to shift the reaction to the more reactive benzylic carbon atoms.



Indeed, we were able to prepare aromatic compounds containing different numbers of (nonafluoro-*tert*-butoxy)methyl groups in various positions, which were used to measure the fluorous partition coefficients and fluorophilicity for fluorous reagents and catalyst designers.

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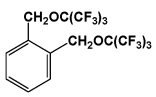
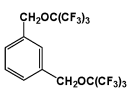
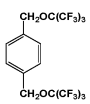
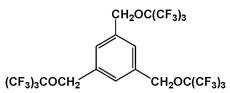
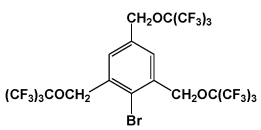
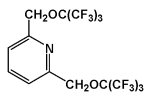
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c2cp23113a

The bromination of the methyl groups of toluene,[16a–c] *o*-,[16a] *m*-,[16a] *p*-xylenes,[16a] 1,3,5-trimethylbenzene,[16d,e] 4-bromo-1,3,5-trimethyl-benzene[16f] was performed by using *N*-bromo-succinimide (NBS) in stoichiometric amounts with respect to the methyl groups in the presence of 0.5 mol% initiators, either benzoyl peroxide (BPO) or azobisisobutyronitrile (AIBN), in the green solvent dimethyl carbonate (DMC) at 110 °C. The reactions were complete in 15 minutes and the isolated yields were between 40–80%. The expected structures of these compounds were confirmed by elemental analysis, IR and NMR spectroscopy. The reaction of **1a–f** and 2,6-bis(bromomethyl)pyridine with sodium perfluoro-*tert*-butoxide was performed in DMF at 110 °C.[13] After 2 hours the product(s) were isolated in 30–60% isolated yields by using an aqueous-fluorous biphasic workup. The expected structures of the new compounds **2a–g** were established by MS, IR and NMR spectroscopy.

The partition coefficients of **2a–g** were established by dissolving a given compound in a fluorous biphasic system consisting of 2 mL of c-$C_6F_{11}CF_3$ and 2 mL of toluene. The resulting mixture was stirred for several minutes, let to stand for 24 hours at 25 °C, and samples of the two phases were taken at 25 °C. The concentration of the compounds in the lower fluorous phase and the upper toluene rich phase was established by GC/MS analysis (Table 1).

The fluorous partition coefficient increases from 0.55 to 25.41 by increasing the number of (nonafluoro-*tert*-butoxy)-methyl from one to three, as expected (Table 1). There are

Table 1 Partition coefficient (P) and fluorophilicity (ln P) of fluorous compounds in 2 mL c-$C_6F_{11}CF_3$ and 2 mL toluene

Fluorous compounds		wt% F	P	ln P
2a		52.4	0.55	−0.598
2b		59.6	4.14	1.421
2c		59.6	3.88	1.356
2d		59.6	4.57	1.520
2e		62.4	25.41	3.235
2f		56.9	20.96	3.043
2g		59.5	7.21	1.975

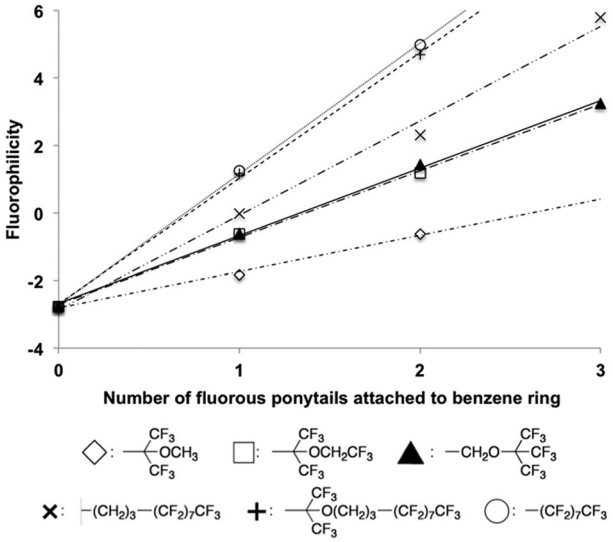


Fig. 1 Fluorophilicity of fluorous aromatic compounds.

small differences between the disubstituted benzenes (P = 4.14 for **2b**, 3.88 for **2c**, 4.57 for **2d**), among which the fluorous ponytails in the 1,3-positions seem to be the least effective, similarly to –$(CH_2)_3$–$(CF_2)_7CF_3$ ponytails.[17] Interestingly, the replacement of the "CH" between the 1,3-positions in **2c** with the N-atom in **2g** increases the partition coefficient from 3.88 to 7.21. These and other previously reported data on analogous fluorous aromatics show that the exact structure of the fluorous ponytails has a significant effect on fluorophilicity (Fig. 1).

Deelman *et al.*[19] have developed an empirical mobile order and disorder theory to estimate the distribution of substances in a fluorous biphasic system. However, this theory is not applicable to our biphasic system because the molar non-specific vaporization energy and molar volume parameters for perfluoro-*tert*-butoxy groups is not available. In order to shed light on the partition equilibria of fluorous compounds in c-$C_6F_{11}CF_3$ and toluene solvents, density functional theory calculations were performed to predict structures and energetics of selected fluorous compounds. A polarizable continuum model[20] (PCM) was used to account for the solvent effect. The geometrical optimizations and vibrational frequencies calculations were carried out at the B3LYP level[21] with the 6-31G(d) basis set in the presence of the solvent effect

Table 2 Partition coefficient (P) and predicted partition coefficient (P_{pred}) of selected fluorous compounds in c-$C_6F_{11}CF_3$ and toluene

Fluorous compounds and their oligomers		P	P_{pred}
2a	Monomer	0.55	0.95
2c	Monomer	3.88	1.34
	Dimer		4.16
2e	Monomer	25.41	1.84
	Dimer		6.54
	Trimer		9.51
	Tetramer		27.0
2g	Monomer	7.21	1.92
	Dimer		3.82
	Trimer		4.18
	Tetramer		5.57

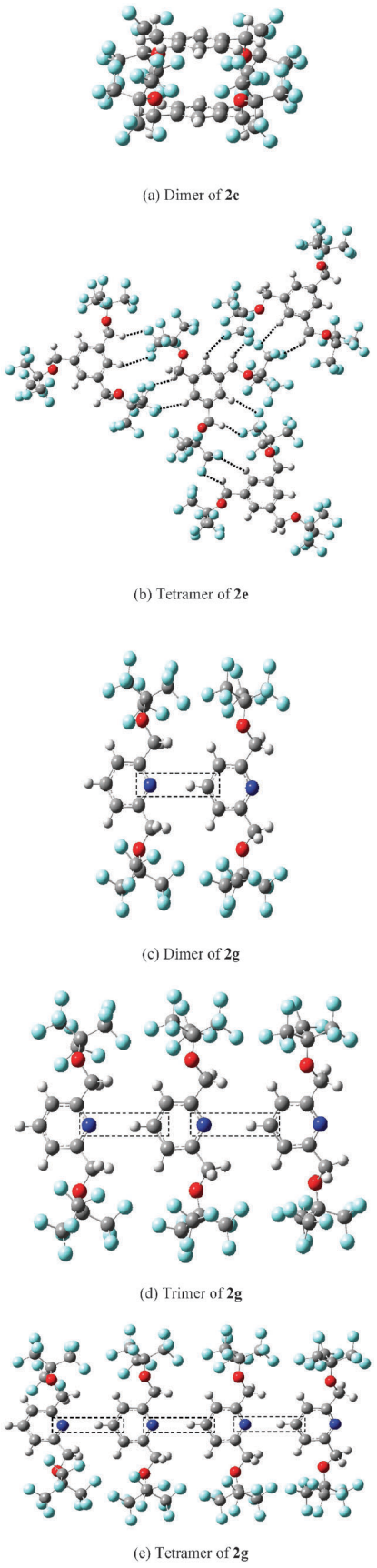


Fig. 2 Optimized structures of (a) dimer of **2c**; (b) tetramer of **2e**; (c) dimer of **2g**; (d) trimer of **2g** and (e) tetramer of **2g**.

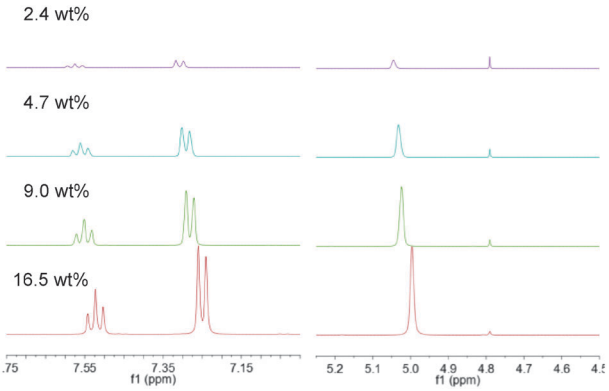


Fig. 3 Concentration dependence ^{1}H-NMR of **2g** in $C_6F_{11}CF_3$ (using D_2O in a capillary tube as external reference).

using Gaussian 09 program.[22] Based on the mathematical relationship:

$$P_{\text{pred}} = e^{-\frac{\Delta G^{\circ}}{RT}} \quad (1)$$

where P_{pred} is the predicted partition coefficient (or equilibrium constant), ΔG° is the molar Gibbs free energy change for partition equilibria of fluorous compounds in c-$C_6F_{11}CF_3$ and toluene at 298 K (T) and R is 8.314 J mol^{-1} K^{-1}, we have predicted the partition coefficients of compounds **2a**, **2c**, **2e** and **2g** in c-$C_6F_{11}CF_3$ and toluene (Table 2).

The predicted partition coefficients of monomeric **2a**, **2c**, **2e** and **2g** range from 0.95 to 1.92. Except **2a**, all other three predictions deviate from the measured partition coefficients significantly. Examining the structures of **2c**, **2e** and **2g**, the monomer may aggregate to form oligomers due to the formation of intermolecular hydrogen bonds and/or π–π stacking between aromatic rings. The dimer form of **2c** yields a partition coefficient of 4.16, which is in good accord with the measured value (3.88). The dimer structure of **2c** is found to be held by π–π interaction and intermolecular hydrogen bonds between the fluorous ponytails and aromatic hydrogens (Fig. 2(a)).

For compound **2e**, the respective partition coefficients of its monomer, dimer, trimer and tetramer are 1.84, 6.54, 9.51 and 27.0 while the measured partition coefficient is 25.41. Based on theoretical prediction, it is expected that **2e** should exist as a tetramer in the c-$C_6F_{11}CF_3$ and toluene due to strong intermolecular interactions between fluorous ponytails and aromatic or methylenic hydrogens. The intermolecular interactions (dashed lines) existing in the tetramer of **2e** are shown in Fig. 2(b). The partition coefficients of compound **2g** increase from 1.92 (monomer) to 3.82 (dimer) to 4.18 (trimer) to 5.57 (tetramer). Examining the structures of the dimer, trimer and tetramer of **2g**, we see a striking feature in which the intermolecular hydrogen bonding units N···HC (shown in dashed boxes in Fig. 2(c)–(e)) are arranged in a near-perfect linear manner.

The formation of oligomers of **2g** was experimentally supported by its concentration and temperature dependence ^{1}H-NMR in c-$C_6F_{11}CF_3$ using an external deuterium source in a capillary tube as a reference. When the concentration of **2g** was increased from 2.4 to 16.5 wt%, the resonances at 7.58, 7.36, and 5.05 ppm shifted 0.05 ppm upfield (Fig. 3).

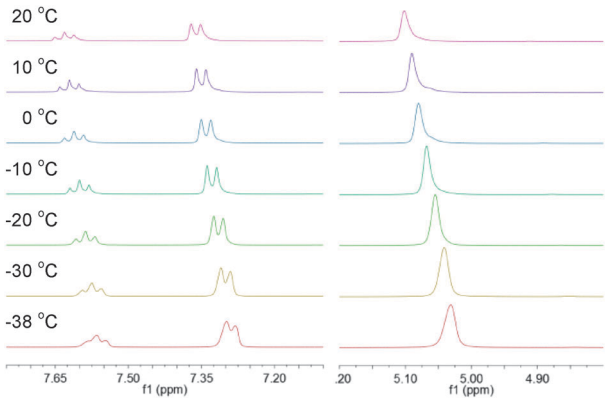


Fig. 4 Low temperature ^{1}H-NMR of **2g** (4 wt%) in $C_6F_{11}CF_3$ (using CD_2Cl_2 in a capillary tube as external reference).

Similarly, the temperature dependence ^{1}H-NMR spectra of **2g** have shown an upfield shift of about 0.05 ppm for the resonances at 7.63, 7.35, and 5.05 ppm (Fig. 4).

Conclusions

We have demonstrated that the (nonafluoro-*tert*-butoxy)-methyl ponytails can be readily assembled on aromatic compounds to provide high fluorous solubility and partition. We have confirmed again that besides having the total fluorine content above 60%, the number of perfluoroalkyl groups is an important factor for controlling fluorous partition. This is in agreement with the original proposal that appropriate shielding of the hydrocarbon domain, which could have attractive interaction between each other or with the constituents of the non-fluorous phase, leads to higher fluorous solubility and higher fluorous partition coefficients.[4] The theoretical predictions of the partition coefficients of selected fluorous compounds are in good agreement with the measured values and suggest that the (nonafluoro-*tert*-butoxy)methyl substituted aromatics aggregate to form oligomers in c-$C_6F_{11}CF_3$ and toluene. The formation of aggregates of **2g** was supported by its concentration and temperature dependent ^{1}H-NMR.

Experimental

General

NBS, BPO, AIBN, DMC, sodium, xylenes, and mesitylenes were purchased from Aldrich. Bromomesitylene and 2,6-bis(hydroxymethyl)pyridine were purchased from Acros. While DMF and toluene were supplied by VWR, chloroform was purchased from RCI Labscan. Perfluoro-*tert*-butanol and perfluoro(methylcyclohexane) were products of Fluorochem. All purchased chemicals and solvents were used without any purification. Sodium perfluoro-*tert*-butoxide[13] and 2,6-bis(bromomethyl)pyridine[18] were synthesized according to the literature. ^{1}H, ^{13}C, ^{19}F NMR spectra were recorded on a Bruker AV400 FT-NMR spectrometer at room temperature. ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC correlation experiments were also applied in some cases. Data were expressed as chemical shifts in ppm relative to residual chloroform (^{1}H δ = 7.26, ^{13}C δ = 77.2) or dichloromethane (^{1}H δ = 5.32, ^{13}C δ = 54.0) or an external standard for ^{19}F (perfluorobenzene, δ = −64.9). EIMS were recorded on a Hewlett Packard 6890 GC instrument coupled with a 5973 mass selective detector. Fourier transform infrared spectra in the range of 500–4000 cm^{-1} using a Nujol matrix or KBr plates were recorded on a Perkin-Elmer Model FTIR-1600 spectrometer. Melting points were measured by an electrothermal digital apparatus and are uncorrected.

General procedure for benzylic bromination

A 100 mL 2-neck rounded bottom flask equipped with a magnetic stirrer, a condenser and a gas-inlet adaptor was evacuated and filled with nitrogen 3 times. The arene compound (10 mmol), *N*-bromosuccinimide (1 equivalent per methyl group in the arene compound), benzoyl peroxide (0.5 mol% of NBS) in dimethyl carbonate (30 mL) were added under nitrogen. The flask was placed into an oil bath preheated to 110 °C. After stirring the reaction mixture for 15 minutes, the flask was removed and cooled to room temperature in a water bath. It was transferred to a separation funnel, washed with water (3 × 20 mL) and dried over Na_2SO_4. After filtration, the solution was concentrated and the product was purified by distilling at 79–82 °C/15 mm Hg (**1a**) or by column chromatography (**1b–f**) using ethyl acetate/petroleum ether on a silica column. The raw product was recrystallized by slow evaporation of a chloroform solution at room temperature to give the final product.

General procedure for the synthesis of compounds 2a–2g

A 50 mL 2-neck rounded bottom flask equipped with a magnetic stirrer, a condenser and a gas-inlet adaptor was evacuated and filled with N_2 three times. A sample of compound **1a–g** (10 mmol) and pyridine (2.00 g), $NaOC(CF_3)_3$ (1.1 equivalent with respect to each bromomethyl group) in DMF (10 mL) was added under N_2. The reaction mixture was heated to 110 °C by an oil bath for 2 hours, then cooled to room temperature. Distilled water (50 mL) was added and the fluorous and aqueous phases were separated in a separatory funnel. The aqueous phase was extracted with 10 mL of perfluoromethylcyclohexane. The combined fluorous phase was washed with water (3 × 30 mL) and toluene (3 × 30 mL) and evaporated to afford the products. While **2a** and **2g** were pure after washing with toluene, **2b–f** were purified by silica column chromatography using CH_2Cl_2.

((Nonafluoro-*tert*-butoxy)methyl)benzene (2a)

Yield: 1.29 g (34%) colorless oil. ^{1}H-NMR (CD_2Cl_2): δ 5.06 (2H, s, PhCH_2O), 7.37–7.44 (5H, m, C*H*); ^{13}C-NMR (CD_2Cl_2): δ 72.2 (m, $^{4}J_{C-F}$ = 2 Hz, Ph*C*H$_2$O), 80.6 (m, $^{2}J_{C-F}$ = 30 Hz, C(CF$_3$)$_3$), 121.2 (q, $^{1}J_{C-F}$ = 292.9 Hz, *C*F$_3$), 128.6 (*C*H-2,6), 129.3 (*C*H-3,5), 129.5 (*C*H-4), 135.54 (*C*-1); ^{19}F NMR (CD_2Cl_2): δ −72.64. GC-MS (EI): *m*/*z* 326 (M$^+$). IR (Nujol): 1461 (vs), 1376 (s), 1274 (vs), 1252 (vs), 1152 (s), 1018 (s), 973 (s), 729 (s) cm^{-1}.

o-Bis((nonafluoro-*tert*-butoxy)methyl)benzene (2b)

Yield: 1.65 g (38%) white solid, mp: 61.5–63.2 °C. ^{1}H-NMR (CD_2Cl_2): δ 5.15 (4H, s, PhCH_2O), 7.45 (4H, s, C*H*); ^{13}C-NMR (CD_2Cl_2): δ 69.6 (brs, Ph*C*H$_2$O), 80.5 (m, $^{2}J_{C-F}$ = 30 Hz,

$C(CF_3)_3$), 121.0 (q, $^1J_{C-F}$ = 292.7 Hz, CF_3), 130.0 (*C*H-4,5), 130.1 (*C*H-3,6), 133.9 (*C*-1,2); ^{19}F-NMR (CD_2Cl_2): δ −72.71. GC-MS (EI): *m*/*z* 574 (M^+). IR (KBr): 1302 (s), 1258 (vs), 1143 (s), 1016 (s), 972 (s), 730 (s) cm^{-1}.

m-Bis((nonafluoro-*tert*-butoxy)methyl)benzene (2c)

Yield: 1.83 g (42%) white solid, mp: 44.7–45.9 °C. Purity: >99%. ^{1}H NMR (CD_2Cl_2): δ 5.09 (4H, s, PhCH_2O), 7.36–7.40 (3H, m, PhC*H*), 7.43–7.46 (1H, m, PhC*H*); ^{13}C NMR (CD_2Cl_2): δ 71.8 (m, $^4J_{C-F}$ = 2 Hz, Ph*C*H$_2$O), 80.8 (m, $^2J_{C-F}$ = 30 Hz, *C*(CF_3)$_3$), 121.3 (q, $^1J_{C-F}$ = 293.5 Hz, *C*F_3), 127.6 (*C*H-4,6), 128.8 (*C*H-5), 129.8 (*C*H-2), 136.4 (*C*-1,3); ^{19}F NMR (CD_2Cl_2): δ −72.54. GC-MS (EI): *m*/*z* 574 (M^+). IR (KBr): 1300 (s), 1269 (vs), 1253 (vs), 1148 (s), 1018 (s), 972 (s), 730 (s) cm^{-1}.

p-Bis((nonafluoro-*tert*-butoxy)methyl)benzene (2d)

Yield: 1.79 g (41%) white solid, mp: 93.2–95.8 °C. Purity: >99%. ^{1}H NMR (CD_2Cl_2): δ 5.07 (4H, s, PhCH_2O), 7.41 (4H, s, C*H*); ^{13}C NMR (CD_2Cl_2): δ 71.7 (m, $^4J_{C-F}$ = 2 Hz, Ph*C*H$_2$O), 80.6 (m, $^2J_{C-F}$ = 30 Hz, *C*(CF_3)$_3$), 121.1 (q, $^1J_{C-F}$ = 292.4 Hz, *C*F_3), 128.8 (*C*H-2,3,5,6), 136.2 (*C*-1,4); ^{19}F NMR (CD_2Cl_2): δ −72.66. GC-MS (EI): *m*/*z* 574 (M^+). IR (KBr): 1304 (s), 1269 (vs), 1243 (vs), 1145 (s), 1017 (s), 972 (s), 730 (s) cm^{-1}.

1,3,5-Tris((nonafluoro-*tert*-butoxy)methyl)benzene (2e)

Yield: 2.73 g (59%) white solid, mp: 46.8–49.4 °C. Purity: >99%. ^{1}H NMR (CD_2Cl_2): δ 5.01 (6H, s, PhCH_2O), 7.37 (3H, s, C*H*); ^{13}C NMR (CD_2Cl_2): δ 71.3 (m, $^4J_{C-F}$ = 2 Hz, Ph*C*H$_2$O), 80.6 (m, $^2J_{C-F}$ = 30 Hz, *C*(CF_3)$_3$), 121.1 (q, $^1J_{C-F}$ = 293.6 Hz, CF_3), 127.4 (*C*H-2,4,6), 136.9 (*C*-1,3,5); ^{19}F NMR (CD_2Cl_2): δ −72.75. GC-MS (EI): *m*/*z* 822 (M^+). IR (KBr): 1256 (vs), 1152 (s), 1026 (s), 973 (s), 727 (s) cm^{-1}.

1-Bromo-2,4,6-tris((nonafluoro-*tert*-butoxy)methyl)benzene (2f)

Yield: 2.14 g (52%) white solid, mp: 47.2–48.3 °C. Purity: >99%. ^{1}H NMR (CD_2Cl_2): δ 5.11 (2H, s, Ph-4-CH_2O), 5.20 (4H, s, Ph-2,6-CH_2O), 7.50 (2H, s, C*H*); ^{13}C NMR (CD_2Cl_2): δ 70.8 (m, $^4J_{C-F}$ = 2 Hz, Ph*C*H$_2$O), 80.6 (m, $^2J_{C-F}$ = 30 Hz, *C*(CF_3)$_3$), 121.0 (q, $^1J_{C-F}$ = 293.5 Hz, *C*F_3), 122.2 (*C*-1), 127.7 (CH-3,5), 136.1 (C-2,6), 136.5 (*C*-4); ^{19}F NMR (CD_2Cl_2): δ −72.68 (2,6-$CH_2OC(CF_3)$), −72.81 (CF_3). GC-MS (EI): *m*/*z* 900 (M^+). IR (KBr): 1262 (vs), 1156 (s), 1027 (s), 973 (s), 729 (s) cm^{-1}.

2,6-Bis((nonafluoro-*tert*-butoxy)methyl)pyridine (2g)

Yield: 3.19 g (73%) white solid, mp: 69.2–70.6 °C. Purity: >99%. ^{1}H NMR (CD_2Cl_2): δ 5.15 (4H, s, PyCH_2O), 7.43 (2H, d, $^3J_{H-H}$ = 7.8 Hz, C*H*-3,5), 7.85 (1H, t, $^3J_{H-H}$ = 7.8 Hz, C*H*-4); ^{13}C NMR (CD_2Cl_2): δ 72.2 (m, $^4J_{C-F}$ = 2 Hz, Py*C*H$_2$O), 80.6 (m, $^2J_{C-F}$ = 30 Hz, C(CF_3)$_3$), 121.0 (q, $^1J_{C-F}$ = 293.1 Hz, *C*F_3), 121.1 (*C*H-3,5), 138.7 (*C*H-4), 155.3 (*C*-2,6); ^{19}F NMR (CD_2Cl_2): δ −72.79. GC-MS (EI): *m*/*z* 575 (M^+). IR (KBr): 1302 (s), 1263 (vs), 1160 (s), 1026 (s), 971 (s), 729 (s) cm^{-1}.

Measurement of the partition coefficients

A 7 mL vial was used to partition 0.010–0.030 mmol of **2a–g** in a well established biphasic system,[6] which was prepared by mixing 2.000 mL perfluoromethyl-cyclohexane and 2.000 mL toluene. The vial was sealed and vigorously mixed for several minutes. After standing at 25.0 °C for 24 hours, samples (0.500 mL) were taken from both phases, which were analyzed by GC using 1,4-dioxane in xylene as the internal standard. All partition experiments were done in triplicate.

NMR measurements

The temperature and concentration dependence ^{1}H-NMR experiments of **2g** in c-$C_6F_{11}CF_3$ were expressed using an external deuterium source of D_2O (^{1}H δ = 4.79) for concentration dependence and CD_2Cl_2 for the low temperature study.

Acknowledgements

We are grateful for the continuous support and help of the Technical Officers of the Department of Biology and Chemistry of City University of Hong Kong. We would like to thank Ka Chung Tong for his assistance in some of the synthetic work. This work was funded by the City University of Hong Kong, project number 7002604 (2010).

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