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Fluorous Effects in Amide-Based Receptors for Anions

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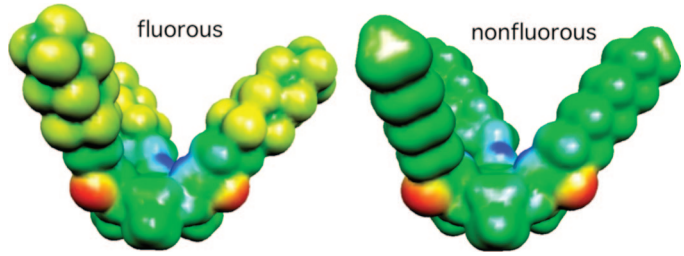

Hybrid receptors designed to recognize both the sulfonate headgroup and the fluorous tail of perfluorooctanesulfonate ($CF_3(CF_2)_7SO_3^-$, "PFOS") were prepared by coupling fluorinated carboxylic acids onto poly(aminomethyl)benzene scaffolds. Binding to PFOS, $CF_3SO_3^-$, *p*-TsO^-, and Cl^- was monitored by ^1H NMR and isothermal titration calorimetry (ITC). In chloroform solvent, hydrogen-bonding to anions is accompanied by downfield shifts in the amide N*H* protons of the fluorinated receptors and by evolution of heat. Association constants for 1:1 complexation (K_{assoc}) are $>1000\ M^{-1}$. An analogous hydrocarbon receptor binds weakly to anionic guests ($K_{assoc} < 50\ M^{-1}$). Ab initio calculations indicate that the differences in 1:1 binding strengths between fluorous and nonfluorous hosts cannot be ascribed to differences in N*H* donor acidities.

Introduction

Highly fluorinated organic compounds tend to partition into solvents and stationary phases that are likewise "fluorous", making it possible to separate the components of a mixture on the basis of their degree of fluorine content.[1] In the field of supramolecular chemistry, fluorous interactions have been used to control large-scale assembly. Targeted replacement of leucine residues with hexafluoroleucines imparts stability to peptide oligomers,[2] fluorinated dendrimers can assume columnar shapes that are not observed in their hydrocarbon analogues,[3] and a "teflon-footed" resorcinarene forms hexameric capsules in wet fluorous media.[4] To examine whether these effects can enhance anion binding in organic solvents, we have chosen to target perfluorooctanesulfonate ($CF_3(CF_2)_7SO_3^-$, "PFOS"), a surfactant that has gained notoriety as a globally dispersed persistent organic pollutant.[5,6] Synthetic receptors for anions typically present an array of hydrogen-bond donor atoms to their intended guests.[7] The sulfonate headgroup of PFOS is expected to be a poor acceptor of H-bonds, however, because resonance stabilization within the SO_3^- moiety and inductive electron withdrawal (by F atoms) limit the negative charge density at each oxygen. The hybrid receptors described here feature perfluorocarbon arms in proximity to amidic NH donor units. They are designed to weakly anchor the oxoanionic portion of PFOS by H-bonding, allowing any subtle contributions from host−guest fluorous contacts to be observed. At present, none of the

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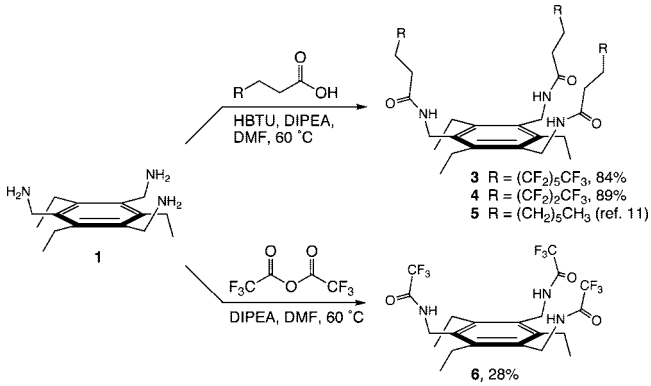
TABLE 1. Association Constants from ^{1}H NMR Titrations in $CDCl_3$ at 295 K[a]

	3	4	5	6	7
PFOS	4.0×10^6 M^{-2b}	3.1×10^6 M^{-2b}	39 M^{-1}	1400 M^{-1}	130 M^{-1}
$CF_3SO_3^-$	2.4×10^6 M^{-2b}	4.0×10^6 M^{-2b}	41 M^{-1c}	nd	nd
p-TsO$^-$	2.0×10^6 M^{-2b}	8.2×10^6 M^{-2b}	36 M^{-1}	5500 M^{-1}	190 M^{-1}
Cl$^-$	1500 M^{-1}	8.9×10^5 M^{-2b}	12 M^{-1c}	1000 M^{-1}	60 M^{-1}

[a] Values represent averages of at least two replicate titrations. Anions were added as TEA salts. [b] Binding stoichiometry of 2 hosts per 1 guest. [c] From ref 11. nd = not determined.

SCHEME 1



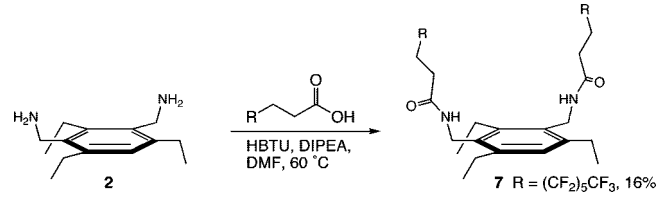
methods to detect[5] or decompose[6] PFOS rely upon its selective binding by organic hosts.

Results

Synthesis. Steric gearing predisposes the functional arms of 1,3,5-trisubstituted 2,4,6-triethylbenzenes to lie on the same face of the central arene,[8] and several anion receptors that take advantage of such preorganization have been described.[9] Here, two tripodal hosts with >40% fluorine content by weight were prepared by coupling fluorinated carboxylic acids onto tris(aminomethyl) scaffold **1**[10] (Scheme 1) using standard amidation conditions.[11] Upon cooling of the reaction mixtures and/or adding water, **3** and **4** precipitated as analytically pure powders in good yield. Hydrocarbon control compound **5**[11] was synthesized from **1** and nonanoic acid. As expected, the coupling strategy was unsuccessful when applied to trifluoroacetic acid. Short-armed host **6** was instead obtained by reaction of **1** with the corresponding anhydride. Diamine **2**[12] served as starting material for bidentate molecule **7** (Scheme 2), which was isolated via column chromatography using standard silica gel and a nonfluorous eluent (CH_2Cl_2/EtOAc).

Anion Binding in Solution: NMR. In preparation for NMR titrations, the behavior of fluorous hosts **3**, **4**, and **7** was examined in deuterated chloroform. These compounds can be dissolved in $CDCl_3$ to concentrations approaching 0.005 M, though such samples tend to flow poorly and to foam. Solutions

SCHEME 2



of 0.0003−0.0005 M are freely mobile and yield sharp ^{1}H NMR spectra. Six signals are observed in the ^{19}F NMR spectrum of **3** (CF_3 at −81.7 ppm, CF_2 units from −115.5 to −127.0 ppm).[13] ^{19}F-based measurements could not be used in quantitative determinations of anion binding, however, as the presence of putative guests induced negligible shifts in these peaks. Two equivalents of PFOS (as tetraethylammonium (TEA) salt) caused the signal assigned to $CH_2CF_2CF_2$ to move upfield by 0.08 ppm, while 2 equiv of *p*-toluenesulfonate (*p*-TsO$^-$) induced a downfield shift of 0.03 ppm.

Association constants with PFOS, *p*-TsO$^-$, $CF_3SO_3^-$, and Cl$^-$ (Table 1) were derived from graphs of receptor δ_{NH} vs $[\text{anion}]_{\text{total}}$.[14,15] A single set of peaks appeared throughout each experiment, indicative of fast exchange on the NMR time scale. Although the presence of perfluorocarbon arms in a host enhances anion affinities (e.g., fluorous, bidentate **7** forms more robust complexes than nonfluorous, tridentate **5**), it does not impart selectivity for PFOS in chloroform. For **3** and **4**, fitting of sulfonate binding isotherms to a 1:1 stoichiometry model led to large errors. A continuous variations plot for **3** with TEAPFOS (Figure 1) confirmed that higher-order species are formed.[16] Reliable fits for δ_{NH} vs [sulfonate] were ultimately obtained by assuming that all complexes in solution have 2:1 host−guest composition. The simple 1:1 binding behavior of **7**, which is 51% fluorine by weight, suggests that high F content alone is not sufficient to promote higher-order complexation.

Chloride binding stoichiometry is sensitive to the structure of the host and the tetraalkylammonium countercation.[17] The ratio of **3**/Cl$^-$, verified by continuous variations analysis to be 1:1 when TEACl is the chloride source (see the Supporting Information), is 2:1 for titrations performed using the tetrabutylammonium (TBA) salt. The β value for 2:1 complexes of **3**

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(14) Hynes, M. J. *J. Chem. Soc., Dalton Trans.* **1993**, 311–312.

(15) When ^{1}H NMR binding experiments were conducted at higher receptor concentrations ([**3**] or [**4**] = 0.004 M) the resultant isotherms were not smoothly hyperbolic and the β values obtained from them were not reproducible. See the Supporting Information.

(16) Both 1:1 and 2:1 complexes containing **3** were observed by electrospray ionization mass spectrometry. In negative ion mode, the base peak for chloroform solutions of **3** and TEAPFOS in molar ratios of 10:1, 2:1, and 1:8 appears at m/z = 1870, corresponding to **3**·PFOS. The 10:1 samples also have a low-abundance (< 1%) signal at m/z = 3242 assigned to **3**·**3**·PFOS.

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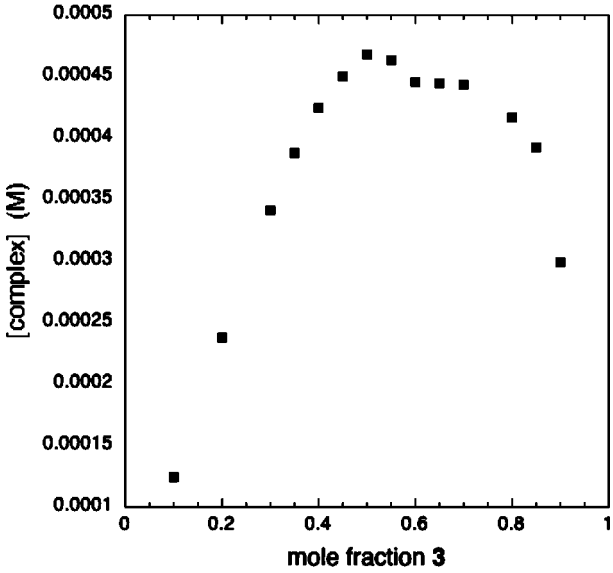

FIGURE 1. Continuous variations plot for **3** with TEAPFOS in $CDCl_3$.

TABLE 2. Thermodynamic Parameters from ITC in $CDCl_3$ at 298 K[a]

	K (M^{-1})	ΔH (kcal/mol)	$T\Delta S$ (kcal/mol)	N(anion/host stoichiometry)
3 + PFOS	3500	−11.0	−6.1	0.54
3 + $CF_3SO_3^-$	1600	−10.1	−5.7	0.54
3 + Cl^-	1200	−3.4	0.8	0.99
6 + PFOS	1200	−6.9	−2.6	0.76

[a] Values represent averages of at least two replicate titrations. Anions were added as TEA salts.

and TBACl (8.2×10^5 M^{-2}) is of the same order of magnitude as that measured for **4** + TEACl.

Anion Binding in Solution: ITC. Selected combinations from Table 1 were analyzed by isothermal titration calorimetry (ITC). To facilitate comparison with NMR results, host molecules in the sample cell were prepared to concentrations of 0.0003−0.0005 M in $CDCl_3$. Interactions between **3** and PFOS or $CF_3SO_3^-$ are driven entirely by enthalpy (Table 2), and their similar thermodynamic profiles are indicative of a common mode of complexation. Chloride binding is characterized by a positive, albeit small, $T\Delta S$ term. Positive entropies have been observed previously for calix[4]pyrrole-chloride complexes in DMSO[17] and for binding of sulfate ion by ditopic guanidinium receptors in methanol[18] and are associated with release of ordered solvent into the bulk solution. Host **3** was unresponsive to the TEA salt of a weakly coordinating anion (PF_6^-). Thus, the data in Table 2 do not arise from binding of the countercation. Stoichiometries, N, for complexes containing **3** follow those determined by NMR. In the case of **3** + TBACl (data not shown), N tended toward zero during the curve fitting process. Fixing N at either 1.00 or 0.500 allowed for convergence, but the latter fit had significantly lower error. A representative plot for a 2:1 interaction is shown in Figure 2.

"Reversed" ITC experiments were conducted by injecting chloroform solutions of **3** into the instrument cell containing TEAPFOS. Endothermic peaks were observed when the concentration of **3** in the syringe exceeded 0.002 M. This finding

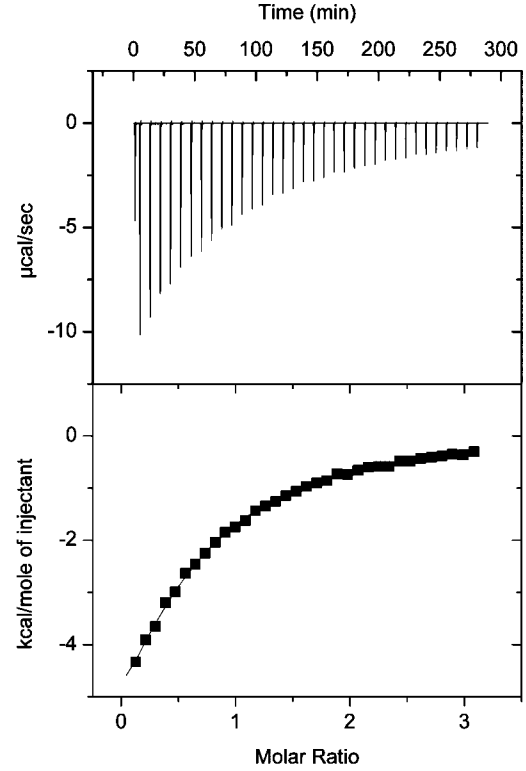

FIGURE 2. ITC response during addition of TEAPFOS (12.5 mM in chloroform) to **3** (0.401 mM in chloroform). The fit line corresponds to $K = 3400$ M^{-1}, $\Delta H = -11.6$ kcal/mol, $T\Delta S = -6.8$ kcal/mol, $N = 0.50$.

is consistent with aggregates of **3** undergoing disassociation. Exothermic behavior was restored by using more dilute titrant solutions ([**3**] < 0.001 M), and thermodynamic parameters derived from these runs were statistically identical to those obtained by "forward" titrations.

Discussion

Inductive Effects. For synthetic hosts that operate via H-bond donation, anion affinities are enhanced by the presence of electron-withdrawing groups near the donor atoms. Halogenation of the β-positions of pyrrole-based receptors, for example, makes the NH groups more acidic.[19] A similar effect is observed when the aromatic ring of phenyl-substituted amides is substituted.[20] In the case of **3**, **4**, and **7**, two CH_2 units separate the donor amides from $(CF_2)_nCF_3$. Previous studies showed that phosphine[21] and 2,2′-bipyridine[22] ligands require eight or more methylene spacers to be fully insulated from perfluoroalkyl groups, but for the present systems, ^{1}H NMR data indicate that $-CH_2CH_2-$ is almost as effective. In chloroform, the N*H* resonances of **3** and **4** appear at 5.28 and 5.29 ppm, only slightly downfield of that observed for nonfluorous **5** (5.23 ppm).[11] Natural population analyses of charges on the amide N*H* atoms, at the B3LYP/6-31+G* level of theory, further support that the

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TABLE 3. Calculated Binding Energies and Hydrogen-Bond Lengths for 1:1 Complexes[a]

	$\Delta E_{\text{gas phase}}$ (kcal/mol)	$\Delta E_{\text{chloroform}}$[b] (kcal/mol)	N*H*···acceptor (Å, av)	O=CC*H*···acceptor (Å, av)
3·PFOS	−31.4	−13.6	2.07	2.74
3·$CF_3SO_3^-$	−35.0	−15.4	2.04	2.73
3·Cl^-	−45.3	−16.2	2.59	3.58
4·$CF_3SO_3^-$	−34.8	nd	2.05	2.70
5·PFOS	−24.9	−11.1	2.18	2.80
5·$CF_3SO_3^-$	−27.4	nd	2.13	2.79
5·Cl^-	−34.7	nd	2.71	3.71

[a] Computations employed the Becke−Tsuneda−Hirao gradient-corrected exchange-correlation functional[24] and a double numerical plus polarization basis set. [b] COSMO solvent model[25] applied. nd = not determined.

binding atoms of **3**, **4**, and **5** are electronically similar. These calculations predict average values of +0.428, +0.429, and +0.426 per hydrogen atom, respectively, for the three hosts.

Although the perfluoroalkyl groups in **3** have negligible local impact on amide acidity, they have a pronounced influence on the global distribution of charge density, relative to hydrocarbon **5**. The calculated dipole moment of **3** is 4.43 D, with its positive end located near the aromatic scaffold of the host and its negative end directed toward the perfluorocarbon arms. Therefore, from a "dipole-engineering"[23] perspective, **3** is properly matched to its intended PFOS guest. For **5** the dipole is of similar magnitude (5.28 D) but in the opposite direction. DFT-calculated models of PFOS, $CF_3SO_3^-$, and Cl^- were docked to the lowest-energy conformations of receptors **3**, **4**, and **5** and the resultant 1:1 systems were optimized.[24] Binding energies follow the trend **3** > **5** for all three guests, and average N*H*···anion distances are about 0.1 Å shorter for complexes of **3** (Table 3). Application of a solvent field[25] corresponding to chloroform renders anion binding less favorable.

Countercation Effects. DFT was further applied to two complexes with included countercations, **3**·TEACl and **3**·$TEACF_3SO_3$. Figure 3 shows the lowest-energy gas-phase structures for each. In Figure 3a, the spherical Cl^- ion forms three hydrogen-bonds to **3** while remaining tightly paired to TEA. Desolvation of both salt components would be required for binding in this manner in solution and may give rise to the favorable entropic term observed by ITC. Such close approach between charges is impossible for a directional species like $CF_3SO_3^-$ once it has bound to a tripodal receptor. Thus, the cation resides outside of the cleft (Figure 3b). We propose that an "outer-sphere" cation is probable for the larger sulfonates PFOS and *p*-TsO^-, which occupy more space than $CF_3SO_3^-$ in the binding pocket, but also for chloride complexes when the cation cannot comfortably fit within the receptor cleft (e.g., **3** + TBACl). If so, the interaction stoichiometries observed for **3** by NMR and ITC are correlated with cation location.

Solvent Effects. Perfluorocarbons are hydrophobic.[26] As such, the affinity between the fluorous regions of host and guest should

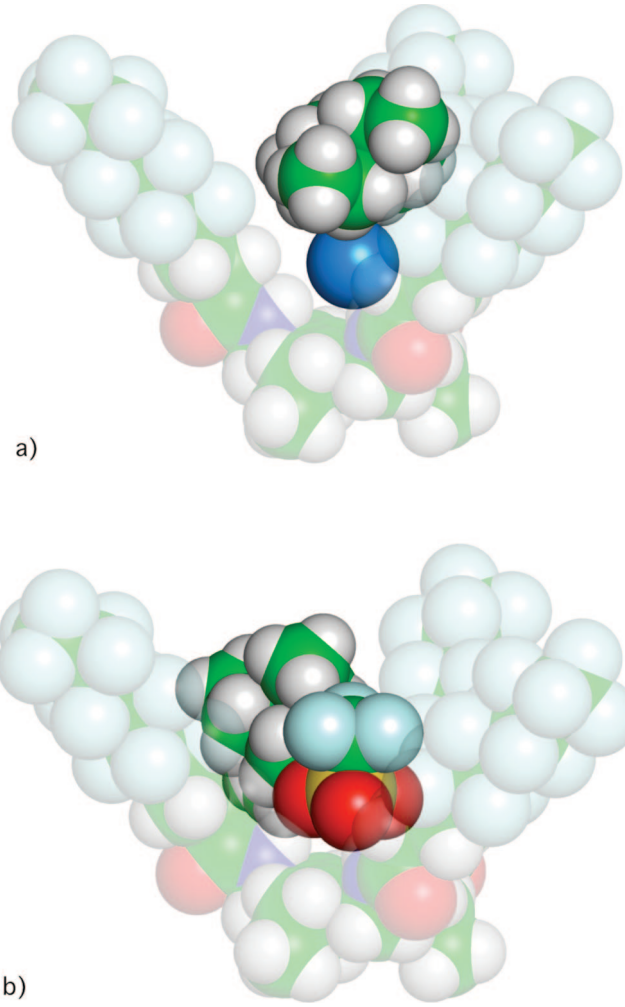

FIGURE 3. (a) DFT-optimized view of **3**·TEACl, showing the countercation inside of the binding pocket. The $N_{TEA}\cdots Cl^-$ separation is 4.21 Å, and the average $NH\cdots Cl^-$ hydrogen-bond length is 2.99 Å. (b) DFT-optimized view of **3**·$TEACF_3SO_3$, showing the countercation outside of the binding pocket. The $N_{TEA}\cdots S_{triflate}$ separation is 6.42 Å, the closest $N_{TEA}\cdots O_{triflate}$ approach is 5.52 Å, and the average $NH\cdots O_{triflate}$ hydrogen-bond length is 2.16 Å.

be enhanced in solvents of higher polarity. In acetone-d_6, the NMR-derived β values for 2:1 binding[27] of **3** + PFOS and **3** + $CF_3SO_3^-$ are 1.3×10^4 and 8.6×10^2 M^{-2}, respectively, indicating that **3** can distinguish between sulfonates that have a long fluorinated chain or a short one. Furthermore, selectivity for PFOS over $CF_3SO_3^-$ is predicted to disappear in a solvent-free environment (Table 3). Comparing absolute binding strengths in acetone and chloroform, any stabilization from fluorous interactions in the former solvent is apparently overwhelmed by acetone's ability to compete for H-bonding sites on the host. In the absence of guests, hydrogen-bonding between acetone-d_6 and the N*H* protons of **3** causes them to resonate at 7.18 ppm (vs 5.28 ppm in $CDCl_3$, see above). The limited solubility of **3** in DMSO-d_6, CD_3CN, and perfluorohexane prevented measurement of β values in these solvents.

Conclusions

The presence of multiple fluorine atoms in tripodal anion receptors enhances binding affinities without significantly alter-

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(27) The maximum in the continuous variations plot for **3** + TEAPFOS in acetone-d_6 appears at ≥0.6 mol fraction **3**. See the Supporting Information.

ing the acidity of their H-bond donor groups. Such hosts form 2:1 complexes with sulfonates, complicating direct comparison with nonfluorous analogues. Efforts are underway to obtain binding data in fluorous solvents,[28] using systems with greater fluorine content than those described here.

Experimental Section

***N,N′,N″*-(2,4,6-Triethylbenzene-1,3,5-triyl)tris(methylene)tris-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononanamide) (3).** Triamine **1**[10] (0.125 g, 0.501 mmol), 4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononanoic acid (0.609 g, 1.55 mmol), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU, 0.664 g, 1.75 mmol), and *N*,*N*-diisopropylethylamine (DIPEA, 0.259 g, 2.00 mmol) were combined in 8 mL of DMF. Under N_2, the mixture was heated to 60 °C for 2 h with stirring, during which time it became red-brown. Upon cooling, the mixture deposited a precipitate. The solid was collected by filtration, washed with water, and dried under vacuum to afford 0.575 g (84%) of **3** as a faintly pink powder. mp = 208−210 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 9H), 2.44 (t, 6H), 2.58 (m, 6H), 2.69 (q, 6H), 4.50 (d, 6H), 5.28 (t, 3H);^{13}C NMR (acetone-d_6) δ 16.5, 23.4, 26.8, 27.2, 27.4, 38.4, 108.4, 112.0, 116.1, 119.6, 123.1, 133.2, 144.6, 169.8;^{19}F NMR ($CDCl_3$, neat CF_3COOH (−78.5 ppm) as external reference) δ −81.7, −115.5, −122.8, −123.8, −124.4, −127.0; IR (film) ν_{max} 3306, 1644, 1548 cm^{-1}; Anal. Calcd for $C_{42}H_{36}F_{39}N_3O_3$: C, 36.78; H, 2.65; N, 3.06. Found: C, 36.91; H, 2.67; N, 3.08.

***N,N′,N″*-(2,4,6-Triethylbenzene-1,3,5-triyl)tris(methylene)tris-(4,4,5,5,6,6,6-heptafluorohexanamide) (4).** The procedure described for **3** was followed, using 4,4,5,5,6,6,6-heptafluorohexanoic acid (0.389 g, 1.61 mmol). After 24 h, the mixture was allowed to cool with stirring. Dropwise addition of cold water precipitated the crude product, which was collected by filtration and washed with water. Drying under vacuum yielded 0.412 g (89%) of **4** as a light orange solid. mp = 212−213 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 9H), 2.46 (t, 6H), 2.52 (m, 6H), 2.69 (q, 6H), 4.50 (d, 6H), 5.29 (t, 3H); ^{13}C NMR (acetone-d_6) δ 16.5, 23.4, 26.8, 26.9, 38.4, 133.2, 144.6, 169.8; IR (film) ν_{max} 3320, 1643 cm^{-1}; Anal. Calcd for $C_{33}H_{36}F_{21}N_3O_3$: C, 43.01; H, 3.94; N, 4.56. Found: C, 43.26; H, 3.96; N, 4.58.

***N,N′,N″*-(2,4,6-Triethylbenzene-1,3,5-triyl)tris(methylene)tris-(2,2,2-trifluoroacetamide) (6).** Triamine **1**[10] (0.173 g, 0.694 mmol) and DIPEA (1.49 g, 11.5 mmol) were combined in 10 mL of DMF. While the mixture was stirred, a solution of trifluoroacetic anhydride (0.468 g, 2.22 mmol) in 10 mL of DMF was added dropwise over several minutes. A condenser was affixed to the flask, and the contents were heated to 60 °C under N_2 for 24 h. Upon cooling, the reaction was quenched by dropwise addition of 10 mL of water. The solvents were removed under reduced pressure, and the crude product was dissolved in CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, filtered, and evaporated to afford 0.103 g (28%) of **6** as a white solid. mp = 216−218 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 9H), 2.72 (q, 6H), 4.63 (d, 6H), 6.14 (s, 3H); ^{13}C (CD_3CN) δ 16.3, 24.0, 39.1, 111.5, 115.3, 119.1, 122.9, 131.5, 146.1, 156.9, 157.4, 157.9, 158.3; IR (film) ν_{max} 3284, 1695 cm^{-1}; Anal. Calcd for $C_{21}H_{24}N_3O_3F_9$: C, 46.93; H, 4.50; N, 7.82. Found: C, 47.26; H, 4.59; N, 7.69.

***N,N′*-(2,4,6-Triethyl-1,3-phenylene)bis(methylene)bis-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononanamide) (7).** Diamine **2**[12] (0.125 g, 0.567 mmol), 4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononanoic acid (0.455 g, 1.16 mmol), HBTU (0.530 g, 1.40 mmol), and DIPEA (0.220 g, 1.70 mmol) were combined in 6 mL of DMF. Under N_2, the flask was heated to 60 °C with stirring. After 3 h, the reaction mixture was poured into 100 mL of water and extracted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, filtered, and evaporated to give a brown oil, which solidified while standing under vacuum. The crude product was purified by flash column chromatography over silica gel using CH_2Cl_2/EtOAc (2:1, v:v) as the eluent, affording 90 mg (16%) of **7** as an off-white solid. mp = 198−200 °C; TLC (CH_2Cl_2/EtOAc, 2:1) R_f = 0.65; ^{1}H NMR ($CDCl_3$) δ 1.18 (t, 3H), 1.23 (t, 6H), 2.43 (t, 4H), 2.46−2.60 (m, 4H), 2.65 (q, 4H), 2.70 (q, 2H), 4.48 (d, 4H), 5.30 (s, 2H), 7.02 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.9, 16.6, 22.7, 26.2, 26.5, 26.8, 27.0, 37.9, 128.0, 130.7, 143.4, 144.3, 169.3; Anal. Calcd for $C_{32}H_{30}F_{26}N_2O_2$: C, 39.68; H, 3.12; N, 2.89. Found: C, 39.68; H, 3.15; N, 2.85.

ITC. Samples of **3** or **6** were dissolved in freshly opened $CDCl_3$ to concentrations of 0.0004−0.0005 M then transferred into the calorimetry cell. A solution of the appropriate anion (as tetraalkylammonium salt), prepared to be ∼30× more concentrated than that of the host, was injected in 4 μL aliquots until [anion] was at least 3[host]. To determine the enthalpies of solution for TEAPFOS, $TEACF_3SO_3$, TEACl, and TBACl, the anion salt in question was titrated into an equilibrated 1:6 mixture of host and anion salt. The heat changes associated with the last four injections of these titrations were averaged. The resulting background values were subtracted from the original binding data, then iterative fitting to a "single set of identical binding sites" model was performed. Values of K, ΔH, and N (interaction stoichiometry) were allowed to vary freely.

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Supporting Information Available: ^{1}H/^{13}C NMR spectra for all new compounds, representative binding curves from ^{1}H NMR and ITC, Job plots, views of DFT-calculated structures and associated atomic coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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