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Increasing Fluorous Partition Coefficients by Solvent Tuning

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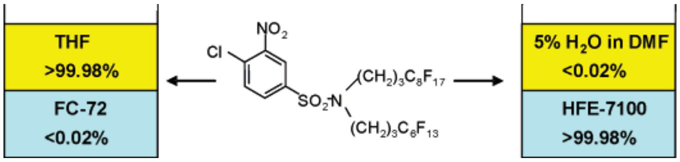
ABSTRACT



Low partition coefficients of fluorous components have been a persistent problem in liquid–liquid separations using perfluoroalkanes as the fluorous phase. Solvent tuning of both the nonfluorous and the fluorous phase dramatically enhances the partitioning of light or polar fluorous molecules into the fluorous liquid phase, while minimally effecting partition coefficients of nonfluorous molecules. These findings suggest an expanded scope for liquid-based separations in fluorous biphasic catalysis, fluorous-tagged reagents, fluorous-supported oligomer synthesis, and related areas.

Since Horvath's seminal 1994 paper[1] describing the use of an organic solvent with an immiscible fluorous solvent in catalysis, fluorous chemistry has found a wide range of applications, including biphasic catalysis,[2] chiral separations,[3] combinatorial chemistry,[4] and peptide and oligosaccharide synthesis.[5] Fluorous systems are appealing because reactions are homogeneous, separations are easy and reliable, and fluorous tags (also called ponytails) are inert.

For liquid−liquid fluorous separations, the efficient partitioning of fluorous reaction components out of the organic phase and into the immiscible fluorous phase is critical. Biphasic separations generally rely on a fluorophobic organic solvent (for example, MeOH, CH_3CN, or toluene) and a perfluoroalkane (perfluoromethylcyclohexane or perfluorohexanes).[6] In these systems, low partition coefficients of fluorous compounds into the fluorous phase have been a persistent problem. The conventional strategy to solve this problem has been to increase the number and length of fluorous tag "ponytails". This "substrate tuning" approach increases synthetic complexity, cost, and molecular mass.

Increasing fluorous partition coefficients by tuning the fluorous solvent is an important option that has been little investigated. Castedo used perfluorocarboxylic acids as

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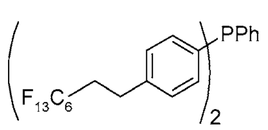
additives to draw ureas into fluorocarbons,[7] while Ryu used the nonvolatile amphiphilic compound F-262 (2-perfluoroethyl-1,3-dimethylbutyl ether) to immobilize a fluorous palladium catalyst.[8] We now report that perfluorobutyl methyl ether, used either alone or in combination with a perfluoroalkane, can significantly increase partition coefficients of fluorous molecules.

Perfluorobutyl methyl ether is sold as HFE-7100[9] and is a mixture of n-$C_4F_9OCH_3$ and i-$C_4F_9OCH_3$ (bp 61 °C). It is non-ozone depleting, is not classified as a volatile organic compound (VOC), and is approved without restrictions under the US EPA Significant New Alternatives Program (SNAP). Inazu and co-workers have used fluoroalkyl alkyl ethers as amphiphilic reaction solvents[10] for fluorous peptide and oligosaccharide synthesis, but they used FC-72 (perfluorohexanes) for the separations.[11] Under ambient conditions, HFE-7100 is miscible with most organic solvents, including MeOH, DMF, toluene, hexane, Et_2O, THF, CH_3CN, and CH_2Cl_2. However, addition of small amounts of water results in phase separation. For example, HFE-7100 is miscible with dry DMF but not with DMF containing a few percent water. To quickly gauge the potential of HFE-7100 as an extraction (co)solvent, we contrasted the partition coefficients of less polar fluorous phosphine **1**[12] and more polar fluorous sulfonamide **2** with nonfluorous controls, triphenylphosphine (Ph_3P) and sulfonamide **3**.[13] As usual, p is defined as the % analyte in the fluorous phase divided by the % analyte in the organic phase. Data from the partitioning experiments of the two phosphines as summarized in Table 1 show that significant solvent tuning is possible with both the organic and fluorous phases.



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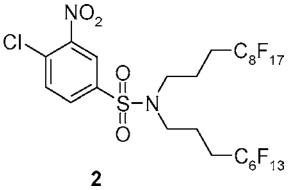

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Standard partitioning of **1** between FC-72 and organic solvents resulted in poor (DMF, THF) to moderate (CH_3CN) distribution for phosphine **1**, as expected for a compound with only 51.8% fluorine content (entries 1−3). In contrast, PPh_3 partitions essentially completely out of the fluorous phase (entry 4). Cutting the organic solvent with water makes the organic phase more fluorophobic and increases the partition coefficients of fluorous molecules in all three solvents (entries 5, 7, and 9). For example, extraction of **1** between FC-72 and 5% aqueous DMF increased its partition coefficient by 2 orders of magnitude from 0.12 to 15 compared to dry DMF (entries 3 and 9). However, PPh_3 still remained in the DMF/water phase (entry 10).

Table 1. Partitioning Coefficients for Phosphine **1** and PPh_3 in Various Fluorous/Organic Systems[a]

entry	solvent system	compound	p[b]
1	FC-72/THF	**1**	<0.02
2	FC-72/CH_3CN	**1**	2.48
3	FC-72/DMF	**1**	0.12
4	FC-72/DMF	PPh_3	<0.02
5	FC-72/5% H_2O in THF	**1**	0.11
6	FC-72/5% H_2O in THF	PPh_3	<0.02
7	FC-72/5% H_2O in CH_3CN	**1**	9.50
8	FC-72/5% H_2O in CH_3CN	PPh_3	na[c]
9	FC-72/5% H_2O in DMF	**1**	15.11
10	FC-72/5% H_2O in DMF	PPh_3	<0.02
11	HFE-7100/5% H_2O in DMF	**1**	>100
12	HFE-7100/5% H_2O in DMF	PPh_3	0.12

[a] Performed with a 1:1 v/v mixture of fluorous and organic solvent. [b] p = [fluorous]/[organic] as measured by GC. [c] PPh_3 was not solvated completely.

Increasing the solvating power of the fluorous phase through use of HFE-7100 (entry 11) resulted in at least another order of magnitude improvement, leading to complete partitioning of **1** into the fluorous phase. The increased solvating power of HFE-7100 is also reflected by the control (entry 12); PPh_3 now partitions to a small extent into the fluorous phase. Similar effects were found for THF and CH_3CN using HFE-7100.

Partition coefficients of the more polar fluorous and nonfluorous sulfonamides **2** and **3** are summarized in Table 2. Despite having more fluorines than phosphine **1**, sulfonamide **2** (53.9% fluorine content) resists partitioning into FC-72, even when the organic solvent is cut with water (entries 1−3, 5, and 6). As expected, the control **3** also partitions into the organic phase (entries 4 and 7). Replacing the FC-72 with HFE-7100 results in a dramatic increase in partitioning of **2** into the fluorous phase against 5% H_2O in DMF (compare entries 6 and 8): indeed, p increases from 0.09 to >100! However, HFE-7100 also begins to extract a small amount of the nonfluorous control **3** into the fluorous layer (entry 9, $p = 0.05$).

Tuning of the fluorous solvent system by using mixtures of FC-72 and HFE-7100 provided a method by which the fluorous solvent could be modulated. A 2:1 FC-72−HFE-7100 mixture resulted in $p = 8.8$ (entry 10), while increasing the amount of HFE-7100 further gave an even higher partition coefficient for **2** into the fluorous phase (entry 12, $p = 42$).

Tables 1 and 2 demonstrate that solvent tuning can produce widely differing partition coefficients for the same com-

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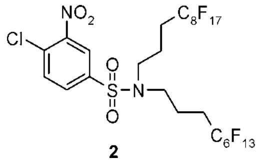
(13) General Protocol: 50 mg of compound was dissolved in 1 mL each of the organic solvent and the fluorous solvent. The mixture was stirred for 15 min, and the phases were allowed to separate. Each phase was analyzed by either GC or LC (254 nm) by dissolving 50 μL in 1 mL of THF. Partition coefficients were determined by comparing the absolute area counts for each phase.

Table 2. Partitioning Coefficients for Sulfonamides **2** and **3** in Various Fluorous/Organic Systems[a]



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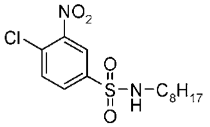

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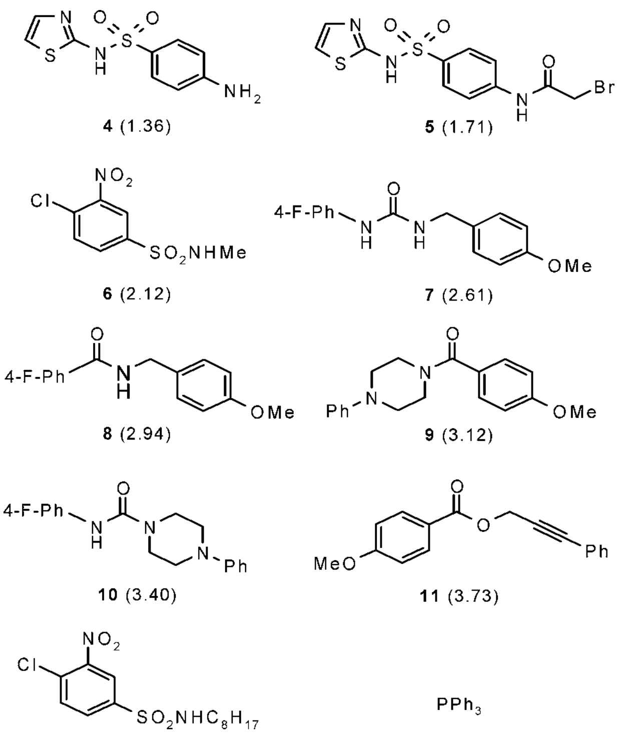
entry	solvent system	compound	p^b
1	FC-72/CH$_3$CN	**2**	0.11
2	FC-72/MeOH	**2**	na[c]
3	FC-72/DMF	**2**	<0.02
4	FC-72/DMF	**3**	<0.02
5	FC-72/5% H_2O in CH$_3$CN	**2**	0.35
6	FC-72/5% H_2O in DMF	**2**	0.09
7	FC-72/5% H_2O in DMF	**3**	<0.02
8	HFE-7100/5% H_2O in DMF	**2**	>100
9	HFE-7100/5% H_2O in DMF	**3**	0.05
10	FC-72−HFE-7100 (2:1)/5% H_2O in DMF	**2**	8.8
11	FC-72−HFE-7100 (2:1)/5% H_2O in DMF	**3**	<0.02
12	FC-72−HFE-7100 (1:1)/5% H_2O in DMF	**2**	42
13	FC-72−HFE-7100 (1:1)/5% H_2O in DMF	**3**	<0.02

[a] Performed with a 1:1 v/v mixture of fluorous and organic solvent. [b] p = [fluorous]/[organic] as measured by GC. [c] Sulfonamide **2** was not solvated completely.



4 (1.36) **5** (1.71) **6** (2.12) **7** (2.61) **8** (2.94) **9** (3.12) **10** (3.40) **11** (3.73) **3** (5.15) (5.69)

Figure 1. Organic compounds (c log P) partitioned between FC-72−HFE-7100 (1:1) and 5% H_2O in DMF.

pound. For example, fluorous compound **1** or **2** can be induced to partition completely in the organic phase (Table 1, entry 1, and Table 2, entry 3) or completely into the fluorous phase (Table 1, entry 11, and Table 2, entry 8); a $>10^3$ change in the partition coefficient.

Equally important to the large effects that solvent tuning have on fluorous compounds are the relatively small effects that they have on the partitioning coefficients of the nonfluorous compounds. This suggests that the major mechanism of separation remains fluorous in nature with polarity playing only a secondary role. To test the generality of the fluorous−organic separation using 5% H_2O in DMF and FC-72/HFE-7100, partition coefficients were measured for 10 organic compounds (Figure 1) with varying lipophilicities as determined by calculated log P, where P in this instance is the traditional octanol−water partitioning. All 10 of the compounds were soluble in the 5% H_2O/DMF in at least 50 mg/1 mL, and in all cases <0.5% of the organic compound leached into the fluorous solvent.

On the basis of these results, we suggest that solvent tuning is a simple and powerful alternative approach to substrate tuning for obtaining suitable fluorous partitioning coefficients. Both fluorophobicity and polarity of the extraction solvents play important roles in determining the partition coefficients. The polarity of a perfluorocarbon liquid phase can be increased by adding perfluoroalkyl alkyl ethers such as HFE-7100 without destroying the inherent fluorous nature of the phase, while the fluorophobicity of polar organic solvents can be increased with even small amounts of water.

It has long been known that certain combinations of polar and nonpolar organic liquids are immiscible, and conducting reactions with the aid of “polar/nonpolar” separations is the subject of lively recent research efforts.[14] Qualitative one-dimensional scales of “polar/nonpolar” solvents and “fluorophilic/fluorophobic” solvents are commonly used today in these two apparently separate areas. We suggest that these scales should be united into a single two-dimensional scale, as illustrated by the diagram in Figure 2. The upper left quadrant is occupied by perfluoroalkanes and related molecules, which are extraordinarily nonpolar and highly fluorous. Moving to the right by removing all fluorines and adding heteroatoms results in solvents that are increasingly polar. Moving down by gradually replacing fluorines with hydrogens and other elements results in more fluorophobic (more organic) solvents. The two lower quadrants, therefore, represent traditional lipophilic and hydrophilic areas. The two upper quadrants represent fluorous nonpolar and fluorous polar regions.

The miscibility of two solvents in a biphasic system is a function of the distance between them within Figure 2. The further apart two solvent systems are, the more likely that a biphasic system will form. The partition coefficient for a molecule in a given biphasic system will be a function of the distances of the two solvent systems to the given molecule. For example, if a molecule’s position in Figure 2 was equidistant from the two solvents used in a biphasic system, it is reasonable to assume a partition coefficient near unity. Since most fluorous separations to date have been conducted using solvents occupying only the extreme upper

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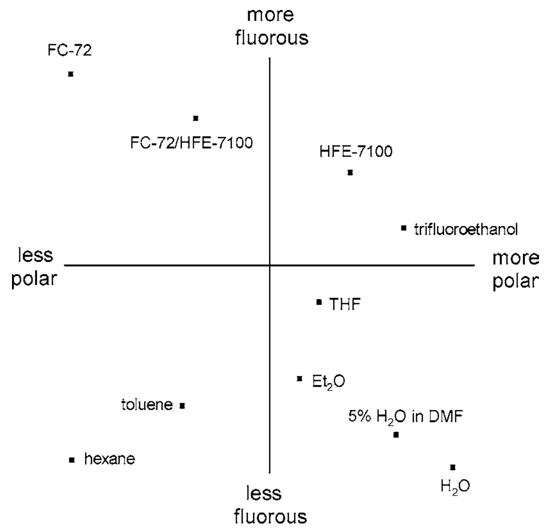

Figure 2. Qualitative representation of various solvent systems used in fluorous biphasic separations.

left corner of Figure 2, it is not surprising that fluorous liquid separations have been plagued by low partition coefficients.

While this qualitative approach is surely oversimplified, thinking of optimizing liquid extractions as one two-dimensional problem rather than two one-dimensional problems provides many more options for tuning. For example, in this work we have optimized the partition coefficients of a polar fluorous molecule by making the fluorous phase more polar without compromising its essential fluorous character. Likewise, a “polar/nonpolar” process might be optimized by introducing fluorines to the nonpolar component and at the same time making the nonpolar liquid phase more fluorophilic. These are just two among many possibilities.

The ability to broadly tune partition coefficients has important implications in those areas of fluorous chemistry that rely on biphasic separation or liquid−liquid extraction. An expanded scope is projected for fluorous biphasic catalysis, fluorous triphasic reactions, supported peptide and oligosaccharide synthesis, and fluorous synthetic methods, including reagents and scavengers. In each of these areas, the ability to use fewer and smaller fluorous tags increases the practicality. On a large scale, the replacement of persistent perfluoroalkyl solvents with perfluoroalkyl alkyl fluorinated ethers results in a more environmentally friendly process.

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Supporting Information Available: Experimental procedures and spectroscopic data of new compounds and all GC and LC data from partitioning experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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