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Fluorophilicity Switch by Solvation

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"Fluorophilicity"[1] is a key issue in fluorous biphase technology, which has witnessed rapid advances in the past decade.[2] In this technology, the innately immiscible fluorous and organic phases are made miscible at elevated temperatures so as to conduct the reaction efficiently under homogeneous conditions. After completion of the reaction, the solution is cooled usually to room temperature, resetting the original two-phase situation. The organic product and fluorous catalyst are recovered from the organic and fluorous phases, respectively. As such, the catalyst partition behaviors between the two phases play a pivotal role.

Previously, we reported that fluorous distannoxanes, $[XR^f_2SnOSnR^f_2Y]_2$ ($R^f = C_6F_{13}C_2H_4$; X, Y = halogens) exhibited greater preference for fluorocarbon solvents than for organic solvents,[3] resulting in much higher partition coefficients for fluorous solvents over usual organic solvents than simple mononuclear fluorous organotin compounds.[4] These unique properties led us to the development of nearly ideal (trans)esterification under fluorous biphasic conditions. We, then, supposed that replacement of the chlorines in **1**[3f] with perfluorooctanesulfonate (PFOS) or bis(perfluorooctanesulfonyl)amide (PFOSA) groups would further heighten the fluorophilicity because the fluorine content is increased by incorporation of these groups (Scheme 1).[5] Treatment of **1** with 4 equiv of AgPFOS afforded the desired compound **2** as a hydrate. By contrast, one-half of the chlorine atoms was replaced by reaction with AgPFOSA to give **3** also as a hydrate. Both **2** and **3** were purified by recrystallization as described later.

To our surprise, however, these compounds were found to be completely insoluble in fluorocarbon solvents, such as FC-72, FC-77, $CF_3C_6F_{11}$, etc. They are also insoluble in hydrocarbons, such as toluene and hexane, as well as halo alkanes, such as CH_2Cl_2 and $CHCl_3$. By contrast, quite unexpected solubility was found in polar organic solvents. They exhibited extremely low or no solubility in CH_3CN, while they showed good solubility in other polar organic solvents, such as EtOAc, acetone, THF, and MeOH ($1.5-6.3 \times 10^{-2}$ mmol/mL).[6] Despite the insolubility in both FC-72 and CH_3CN (Figure 1a, (i) and (ii)), when **2•hyd** or **3•hyd** (100 mg) was added into a two-phase mixture of these solvents (each 2 mL), the organotin compounds were dissolved completely (Figure 1a, (iii)). More remarkably, **2** and **3** were partitioned in favor of FC-72 in a 95:5 or 96:4 ratio, respectively (Table 1). Obviously, the solvophobicity (or solvophilicity) of these compounds was switched from *non-fluorophilic* to *fluorophilic*. It should be noted that "selective solvation, by which dipolar solutes are preferentially solvated at two different loci by two different organic solvents" occasionally induces dissolution of the solutes in a mixture of the two solvents, even though they are either not soluble or less soluble in the respective pure solvents.[7] The terms "co-solvency" and "blending" were also used for the similar phenomena of some polymers and soaps.[8] However, these two solvents, to our knowledge, are miscible with each other in most cases, and no change of the solvophilicity is involved in these cases.

Further, remarkably, upon dissolution in a 1:1 mixture of FC-72 and EtOAc, these compounds were partitioned in a 93:7 or 94:6 ratio in favor of FC-72 (Table 1), completely opposite to their innate solubility in the pure solvents, and hence, the solvophilicity was switched from *lipophilic* to *fluorophilic* in this case. The similar enhancement of fluorophilicity was observed in mixtures with THF and methanol, but to a lesser extent.[9] ^{1}H NMR spectra revealed that some portions of the organic solvents were transferred into the fluorous phase, but the water that had been used for hydration was not detected in the fluorous phase. The concentrations of the distannoxanes and the organic solvents in the FC-72 layer together with their molar ratios as determined by ^{1}H NMR are given in Table 1. These results led us to a rationale which follows. The fluorous distannoxane hydrates are not soluble in fluoro- and hydrocarbons as well as halo alkanes because the coordinated water molecules prevent these hydrophobic solvents from approaching the distan-

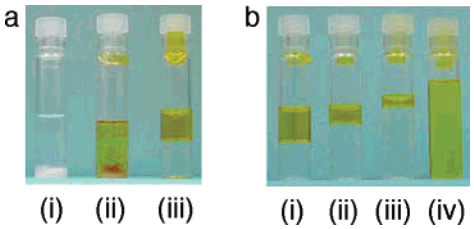

Figure 1. (a) Solubility of **2•hyd**: (i) in FC-72, (ii) in CH_3CN, and (iii) in a mixture of FC-72 and CH_3CN. (b) Change of miscibility of EtOAc and FC-72 (each 0.25 mL) depending on the amount of **2•hyd**: (i) 0.00 g; (ii) 0.10 g; (iii) 0.30 g; (iv) 0.55 g. The CH_3CN and EtOAc layers are colored by β-carotene.

Scheme 1

$$[ClR^f_2SnOSnR^f_2Cl]_2 \;(\mathbf{1},\ \%F\ 57.68) + 4\ AgOSO_2C_8F_{17}\ (AgPFOS) \longrightarrow [(PFOS)R^f_2SnOSnR^f_2(PFOS)]_2\cdot 10H_2O\ (\mathbf{2\cdot hyd},\ \%F\ 59.85)$$

$$\mathbf{1} + 2\ AgN(SO_2C_8F_{17})_2\ (AgPFOSA) \longrightarrow [ClR^f_2SnOSnR^f_2(PFOSA)]_2\cdot 11H_2O\ (\mathbf{3\cdot hyd},\ \%F\ 59.27)$$

$R^f = C_6F_{13}C_2H_4$

Table 1. Partition of **2** and **3** between FC-72 and Organic Solvent[a]

organic solvent	partition[b] FC-72:org. solv	concn of **2** or **3**[c] in FC-72 (mmol/mL)	concn of org. solv[c] in FC-72 (mmol/mL)	molar ratio in FC-72 **2** or **3**/org. solv
CH_3CN				
2	95:5	9.15×10^{-3}	1.50×10^{-1}	1:16
3	96:4	9.06×10^{-3}	1.23×10^{-1}	1:14
EtOAc				
2	93:7	9.18×10^{-3}	7.71×10^{-1}	1:84
3	94:6	9.06×10^{-3}	7.59×10^{-1}	1:84
THF				
2	86:14	7.29×10^{-3}	8.65×10^{-1}	1:119
3	80:20	7.50×10^{-3}	8.59×10^{-1}	1:115
MeOH				
2	56:44	5.06×10^{-3}	8.11×10^{-2}	1:16
3	54:47	5.63×10^{-3}	9.25×10^{-2}	1:16

[a] **2•hyd** or **3•hyd** (100 mg) in FC-72 (2 mL)/organic solvent (2 mL). [b] Determined by isolation of **2** or **3** from the respective layers. [c] Determined by ^{1}H NMR.

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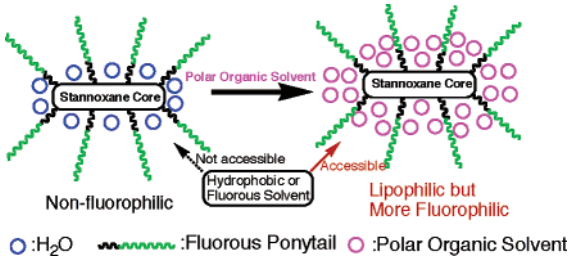

Figure 2. Fluorophilicity switch by solvation.

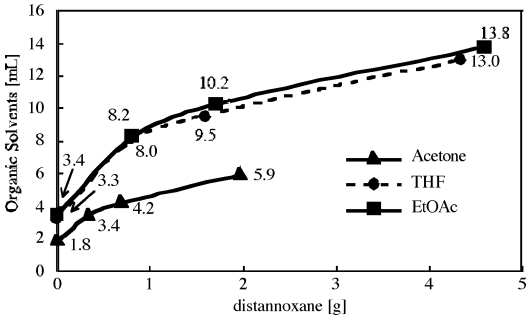

Figure 3. The maximum amount of organic solvent to be dissolved in 100 mL of FC-72 versus concentration of **2•hyd**.

noxane core (Figure 2). On the other hand, water-miscible polar solvents are able to replace the water molecules. The solvation may be assisted by the relatively strong Lewis acid character of the cationic tin atoms[10] and hydrophobic interactions with the ethylene moieties in the fluorous ponytails. The solvation mechanism by polar solvents is compatible with the failure of the mixtures of FC-72/hydrocarbons or halo alkanes to dissolve the distannoxanes. The newly generated solvated species are lipophilic but more strongly fluorophilic because the surface of these species is covered by fluoroalkyl chains, giving rise to a triply layered structure consisting of the stannoxane core wrapped by an inner lipophilic layer with the fluorophilic surface.

As **2•hyd** was added gradually to a 1:1 mixture of EtOAc and FC-72 (each 0.25 mL), the EtOAc layer became thinner with increased amount of **2•hyd**, and a homogeneous solution finally resulted when the amount of **2•hyd** reached 0.55 g (Figure 1b). Furthermore, the unique capability of **2** to homogenize the two phases is shown in Figure 3, in which the maximum amounts of EtOAc that can be dissolved in 100 mL of FC-72 are plotted at various levels of distannoxane concentration.[6] Apparently, **2** is effective for increasing the solubility of EtOAc in FC-72; for example, the solubility (mL/100 mL FC-72) increased from 3.48 (without **2**)[11] to 8.22 and 10.2 upon addition of 0.82 and 1.71 g of **2•hyd**, respectively. The similar effect was observed with THF and acetone. Probably, the blending effect is induced by enclosure of the polar solvent molecules in the hydrophobic pockets in the distannoxane templates.

The present unique solubility served for purification of **2** and **3**. The crude products obtained according to the equations in Scheme 1 were contaminated by both organic and fluorous impurities. The organic impurities could be removed by reprecipitation from acetone/CH_2Cl_2, but the precipitates thus formed were contaminated by the fluorous impurities, which were soluble only in fluorocarbon solvents. Hence, a mixture of acetone and FC-72 was employed to dissolve the crude product. The acetone layers containing the organic impurities were separated off, and the FC-72 layer was kept standing in open air for 24 h. Pure **2** or **3** was crystallized as hydrates in ca. 80% yield,[12] while the fluorous impurities stayed in FC-72. Standing of the FC-72 solution in open air is crucial to allow slow and mild hydration. When water was added to the solution with the aim of accelerating the crystallization rate, the distannoxanes were partially hydrolyzed. When the solution was kept under nitrogen, no precipitates appeared even after more than 2 weeks because the solvated species remained dissolved in FC-72.

In conclusion, hydrated **2** and **3** are non-fluorophilic due to the coordinated water, replacement of which with polar solvents, on the other hand, turns the compounds fluorophilic. Mixing of organic solvents and fluorocarbons by use of fluorous homogenizers will find a variety of applications in fluorous biphase technology. The switch of fluorophobicity is ascribable to the triply layered structure of the fluorous distannoxanes. The molecules that can be caught in the lipophilic pockets are not restricted to organic solvents, but many other organic substrates may be accommodated. Further studies on other fluorous homogenizers as well as their utilization are now in progress.

Supporting Information Available: Experimental procedures and characterization of **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) For the influence of the fluorine content on the fluorophilicity, see: Herrera, V.; de Rege, P. J. F.; Horváth, I. T.; Huseo, T. H.; Hughes, R. P. *Inorg. Chem. Commun.* **1998**, *1*, 197.
(6) For detailed data, see Supporting Information.
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(9) The biased partition was also observed by use of FC-77 or perfluoromethylcyclohexane in place of FC-72; see Supporting Information.
(10) The partial ionization to ionic species, such as $[(PFOS)R^f_2SnOSnR^f_2]_2^{2+}\cdot 2PFOS^-\cdot 10H_2O$ and $[ClR^f_2SnOSnR^f_2]_2^{2+}\cdot 2PFOSA^-\cdot 11H_2O$, is suggested by conductivity measurements: $\Lambda = 129.5$ and 121.0 μS cm^{-1} in MeOH (0.5 mmol/L) for **2** and **3**, respectively.
(11) The solubility of pure EtOAc in pure FC-72 was determined by ^{1}H NMR.
(12) Unfortunately, no suitable crystals for X-ray analysis have been available.

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