# Fluorous chemistry and its application perspectives in the field of fluoroorganic and fluoroinorganic compounds

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The unique properties of perfluorinated solvents and of fluorous structural fragments (*F*-domains), like hydrophobicity and lipophobicity, inertness, non-toxicity, and easy phase separation play key role in the development of effective separation and synthesis techniques. The fluorous phase has been involved in several innovative catalyst and reagent immobilization protocols, isolation techniques, and seems to alter the way of our thinking about chemistry. In this respect not only chemical reactions, but product separations should also be designed for a chemical synthesis. Then the actual phase behavior of the reaction components will control their separation. Thus, fluorous extraction can effectively be used for fluorophilic compounds, while flash chromatography over *F*-SiO$_2$ is highly suitable for the separation of untagged and *F*-tagged molecules (Scheme 1).[1]
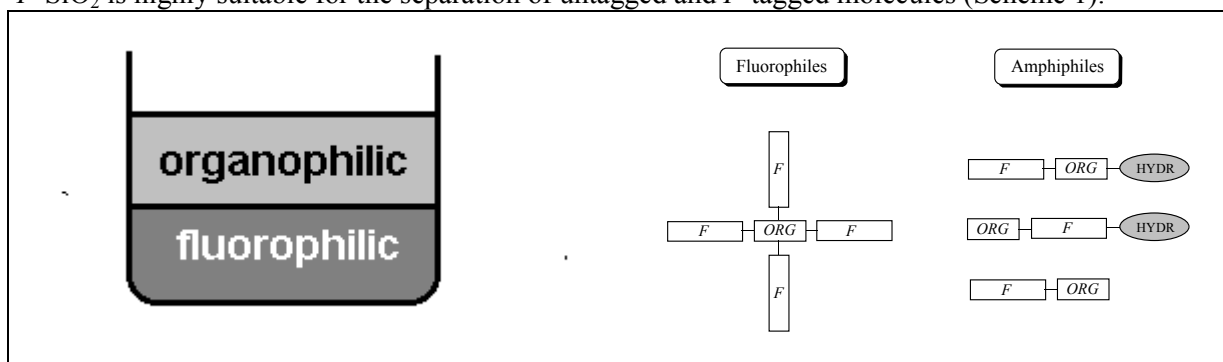

Scheme 1. Structural motifs and types of entities involved in fluorous-organic phase separations (e.g.: liquid organic/liquid fluorous, liquid organic/solid fluorous, *ORG*/*F-ORG*-amphiphile-*F*-SiO$_2$, etc.).

Fluorous chemistry now encompasses diverse fields of chemistry: (a) synthesis of fluorous ligands and catalysts; (b) application of fluorous reagents and scavengers; (c) use of fluorous catalysts in hydroformylation, hydrogenation, enantioselective transformation, and oxidation; etc. (d) fluorous supramolecular, polymer and materials chemistry; (e) fluorine chemistry syntheses and fluorous solvent development; and (f) has also been applied in bioorganic and biological chemistry.[2] An entry to fluorous chemistry has been provided by the launching of the fluorous biphasic system (FBS) concept in 1994, involving one-phase catalysis coupled with biphase catalyst separation using a fluorous soluble HRh(CO)$\{$P[CH$_2$CH$_2$(CF$_2$)$_5$CF$_3$]$_3\}_3$ hydroformylation system.[3] At that time the word 'fluorous' was reserved for the identification of the C$_{sp3}$-F bond rich part of a multiphase system, which consisted of perfluorinated and other solvents, fluorous ligands, catalysts, and reagents. The synthesis of fluorous phase compatible catalysts and ligands were achieved by appending fluorous ponytails (e.g. linear perfluoroalkyl group, R$_{fn}$ = F(CF$_2$)$_n$-) of appropriate number, length and shape as demonstrated by the early examples of the FBS concept. Moreover, attention was called upon, that the strong electron withdrawing effect of the perfluoroalkyl groups on the reaction centers can be insulated by the insertion of an -(CH$_2$)$_n$- fragment in-between the fluorous ponytail and parent compound.[4] The temperature dependent miscibility of perfluorocarbons with standard organic solvents allowed to apply homogeneous reaction conditions at higher temperatures (one phase regime), while facile catalyst recovery by phase separation at lower temperatures (two phase regime).[5] This concept was immediately followed by the introduction of fluorous synthesis (FS), where target molecules are rendered selectively soluble in the fluorous phase by the permanent or temporary attachment of adequate fluorous phase labels.[6] Here fluorous-organic liquid-liquid and fluorous solid-phase extraction techniques (SPE, filtration over *F*-SiO$_2$) served to facilitate product isolation. The evolution of FS soon resulted in the introduction of fluorous reagents, protecting groups, and scavengers.[7]

Since 'heavily' fluorous compounds have low solubility in organic solvents, like organic compounds in fluorous solvents, benzotrifluoride, a solvent with fluorous-organic amphiphilic character was introduced to conduct liquid phase syntheses under homogeneous conditions. In 'light' fluorous synthesis, where fluorous components have shorter fluorous tags, standard organic solvents are suitable for reactions and provide effective product separation with fluorous SPE.[8] Fluorous mixture synthesis (FMS) is a recent application of the power of fluorous-tagging coupled with F-SiO$_2$ chromatography, where a mixture of related fluorous compounds are separated in the order of their 'fluorine content'.[9] In a synthesis design, besides chemical reactions *solvent selection* and the purposeful tuning/switching of *phasephilicities* of the reaction components are the key elements.

Solvents can also be arranged according to their elution power (ε^o/Al$_2$O$_3$), which show the same trend as their Hildebrand solubility parameters.[10] It is worth to mention, that perfluorinated solvents have the least cohesion energy density, thus they are poor solvents for most of organic solvents/compounds (Scheme 2). The question 'What makes a compound particularly soluble in the fluorous phase?' is still unanswered. However, it is a fact, that molecules rendered soluble in the fluorous phase usually do not have exposed functional groups capable for attractive intermolecular interactions via directional forces; only non-directional forces are appearing.[11] Thus, a C$_6$F$_5$-group is non-fluorous, and consequently increases organic phase preference.
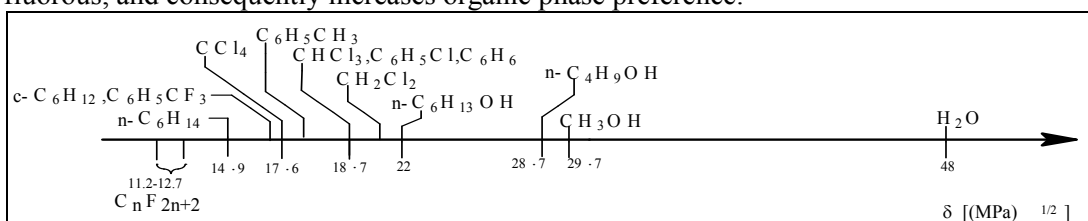
Scheme 2. Hildebrand parameter as a measure of solvent polarity and strength, as well as of solute-solvent likeness. Perfluoroalkanes are immiscible at ~20 °C with solvents appearing right from CCl$_4$.

One of the major problems of homogeneous catalysis is the separation and recycling of catalysts from products. Fluorous biphasic techniques could be devised for the solution of these problems and than result in the development of FBC processes for large scale production, if (1) the fluorous version retains the original catalyst activity and selectivity, and (2) and the extent of leaching of fluorous components into the product phase is controlled.

In some Rh/phosphine catalysed reactions ligands such as P(CH$_2$CH$_2$R$_{fn}$)$_3$, P(C$_6$H$_4$R$_{fn}$)$_3$, P(C$_6$H$_4$CH$_2$CH$_2$R$_{fn}$)$_3$, and P(C$_6$H$_4$Si(CH$_3$)$_2$CH$_2$CH$_2$R$_{fn}$)$_3$ were tested, and their reactivity and selectivity were compared to that of P(C$_6$H$_5$)$_3$. Results indicated that the Si(CH$_3$)$_2$CH$_2$CH$_2$ fragment is a perfect insulator for the electronic effect of the perfluroalkyl group.[12] To keep leaching at the lowest possible value, however, more fluorophilic *catalyst rest states* have to be designed, synthesised and tested.[13]

By principle, catalyst leaching can be kept at an acceptable level, if the fluorous partition coefficient ($P_{FBS} = c_{C6F11CF3}/c_{C6H5CH3}$) of the actual catalytic species is enough high. Thus, the development of prediction models for $\ln P_{FBS}$ is of high importance in FBC. Fluorophilicity ($f = \ln P$) is a convenient measure of phase preference.[14,15] Now compounds with one fluorous domain are called as 'light' fluorous ($f = \ln P_{FBS} < 0$), while others as 'heavy' fluorous (fluorophilic, $f = \ln P_{FBS} > 0$) ones.

Recently, specific fluorophilicity has been defined for compound 'i', as the product of its experimental fluorophilicity value and of the ratio of the van der Waals volumes of the expelled fluorous solvent and of the entering solute molecules (Eq.1.).

$$f_{spec(i)} = f_{(i)} [V_{vdw(CF3C6F11)}]/[V_{vdw(i)}] \qquad \text{Eq.1.}$$

Linear correlation was found between the specific fluorophilicity values and calculated Hildebrand parameters for compounds (i) within a compound family (Eq.2.).

$$f_{spec(i)} = a - b\delta_{calcd(i)} \qquad (a, b \text{ are contants and } a, b > 0) \qquad \text{Eq.2.}$$

Thus, a 'design protocol' for fluorophilic molecules consists of assembling several structural fragments to a molecule in a way that allows the required chemistry, while keeping δ_{calcd} of the final constitution at the lowest value possible (Scheme 3). Both calculations and experiments indicate, that this goal can be achieved by incorporating CF$_3$ groups and branching in the fluorous ponytails, and other building blocks with low cohesive increments. It must emphasize here, that the shortest ponytail (CF$_3$) is the most effective one for increasing compounds' fluorophilicity.[15]

| n	f	P_{FBS}	n	f	P_{FBS}
6	-2.03	0.13	6	-1.29	0.28
8	-1.13	0.32	8	-0.15	0.86
10	-0.47	0.63	10	1.16	3.19

Scheme 3. Effect of molecular structure on fluorophilicity.[16]

While fluorophilic molecules can be designed according to the above thermodynamic model, little information was available on solubility/structure correlation until now. A thesis just appeared, presents an improved model for prediction of ln$P$, which is based on the *Mobile Order Disorder* theory and furthermore, disclose another model for estimation absolute solubility values for solutes in different solvents. Molar volume and cohesion parameter of the solute/solvent pair and the melting point and enthalpy of fusion of solute play key role here.[17]

A program was initiated in our laboratories to explore the potential of trifluoromethyl-group chemistry for the synthesis of novel generation fluorophilic compounds and we aimed at studying the effect of molecular structure on some physical properties, which could have high influence on fluoruos techniques and applications (e.g.: melting point, boiling point, density, partition coefficient, and absolute solubility).[18]

We applied Mitsunobu conditions for the synthesis of fluorophilic ketals and amines.[18,19] Thus, a mixture of $R_{fn}(CH_2)_3OH$ (n = 4,6,8,10; 1.0 mmol of each) and $(CF_3)_2C(OH)_2$ (2.0 mmol) was reacted with Ph_3P/DIAD in ether to afford a library of $(CF_3)_2C[O(CH_2)_3R_{fn}]_2$ type ketals in high yield and purity, easily separated by fluoruos extraction (FC-72/CH_3OH). As a result of statistical combination, diagonal members of the product matrix (4-4, 6-6, 8-8, 10-10) were formed in 1/16, while the off-diagonal ones (4-6, 4-8, 6-8, 4-10, 6-10, 8-10) in 1/8 ratios. This result is in agreement with their calculated probabilities. The unique volatility of these compounds allowed to use GC for their analytical separation (PONA, 50 m). This capillary column has a nonpolar stationary phase, which is very effective in the separation of highly fluorinated compounds. Compound pairs even with the same fluorinated carbon number (6-6/4-8, 6-8/4-10, 8-8/6-10) showed base-line separation here.

Furthermore, we used triflic amide as a two basic N-H acid precursor for the synthesis of symmetrical fluorophilic secondary amines. All polar products (DIADH$_2$ and Ph$_3$P=O) were easily dissolved in boiling methanol, while the solid N.N-bis(perfluoroalkylpropyl)trifluoromethane sulfonamide precipitate was isolated by filtration in high yield (92%) and purity (98% by GC). Finally, its deprotection gave the secondary amine in 65% yield.[20]
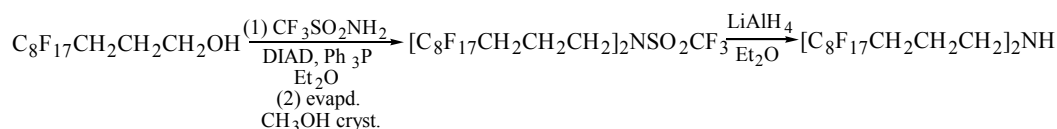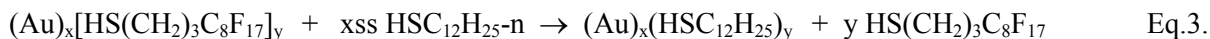

Scheme 4. 'Ideal synthesis' of fluorous secondary amines by a Mitsunobu reaction.

Where is fluorous chemistry going to? What size the involved fluorous entities could have? How the selectivity/activity profile looks like, if catalytic reactions were performed in patterned fluorous monolayers immobilized onto nanosized entities instead of using bulk fluorous phases?

To answer some of these questions, we devised syntheses of perfluorocarbon soluble fluorous self-assembled-monolayer (SAM) protected gold nanoclusters for the first time. Thus a solution of $(C_8H_{17})_4NAuCl_4$ and of $C_8F_{17}CH_2CH_2CH_2SH$ in $CF_3C_6H_5$ was treated with NaBH$_4$ dissolved in water at room temperature. The separated organic phase was concentrated in vacuum and the residue was treated with dioxane. A black solid, $(Au)_x(HSCH_2CH_2CH_2C_8F_{17})_y$, was isolated by filtration, which showed fluorophilic character: soluble in fluorous solvents, benzotrifluoride, but insoluble in dioxane, toluene, methanol and dichloromethane.

An interesting reaction occurs, when the above fluorophilic SAM protected gold nanoparticle is treated with an excess of an organophilic thiol (e.g.: dodecyl mercaptane); due to a place exchange reaction the latter particle become organophilic (i.e. soluble in organic solvents) (Eq. 3.).

$$(Au)_x[HS(CH_2)_3C_8F_{17}]_y \; + \; xss \; HSC_{12}H_{25}\text{-}n \; \rightarrow \; (Au)_x(HSC_{12}H_{25})_y \; + \; y \; HS(CH_2)_3C_8F_{17} \qquad Eq.3.$$

Thus, if a two liquid phase system composed of a dilute solution F-(Au_x) in perfluoromethyl-cyclohexane (tan coloured) and of a solution of excess of $C_{12}H_{15}SH$ in toluene (colourless) is stirred for overnight, all gold clusters migrate into the upper toluene phase as indicated by the colour changes of the liquid phases; resulting in colurless lower and tan coloured upper phases ('Gold Fever'). The physical and chemical properties of these novel F-(Au_x) clusters are under investigation.

In conclusion, the phase behavior of F-(Au_x) and ORG-(Au_x) nanoclusters is controlled by their outward layers accessible for intermoleculer contacts with the molecules of the bulk phases.

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