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Review

# Noncovalent associations in fluorous fluids

Jean-Marc Vincent *

*Université de Bordeaux, Institut des Sciences Moléculaires, CNRS, 351 cours de la Libération, 33405 Talence Cedex, France*

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ABSTRACT

Perfluorocarbons (PFCs) are emerging as a new type of liquid phase in which molecular recognition processes can effectively take place. The combination of perfluorocarbons (PFCs) and noncovalent associations, mostly hydrogen bonds, ion pairing, halogen bonds or coordination bonds, has already been successfully exploited for applications in organic synthesis (catalyst recycling, by-product removal), electrochemical sensing, selective extraction/titration processes or to prepare gels. Due to the extreme solvophobic effect in PFCs, the least polar existing fluids, noncovalent associations tend to be enhanced. For instance, quantitative data on the increase in association strength occurring in PFCs have recently been reported for ion-pairing interactions or encapsulation processes. Moreover, several examples show that confining a receptor in a fluorous phase leads to recognition processes with improved selectivity.


**Contents**



Because of the extremely low polarizability of the C–F bond, perfluorocarbons (PFCs) are the least polar existing fluids [1]. Consequently, PFCs form liquid/liquid biphasic systems at room temperature, not only with water, but also with most of commonly employed organic solvents including alkanes. This unique property was first exploited in synthetic chemistry by Horváth and Rábai who developed the Fluorous Biphasic Catalysis concept for catalysts recycling through liquid/liquid separation process [2]. Since this seminal work, PFCs have been extensively employed for the separation/recovery of catalysts, reactants and reaction products [3]. The important requirement for such methodologies is that the extracted molecule is fluorophilic enough to ensure a high partition coefficient (preferably >99%) for the fluorous phase. This is usually achieved by covalently attaching several perfluoroalkyl tags [4], typically perfluorooctyl chains ($C_8F_{17}$).

Rather surprisingly, much less work has been reported dealing with systems exploiting noncovalent interactions in PFCs. Indeed, due to the extremely nonpolar and aprotic character of PFCs, it is anticipated that such interactions should be reinforced in these ultimate noncompetitive solvents. It is only very recently, thanks to the groups of Bühlmann, Shimizu, Weber or Metrangolo and Resnati, that preliminary data quantifying the strength of noncovalent associations in fluorous liquids were made available. These data demonstrate that indeed, larger association constants could be observed in a fluorous phase compared to aqueous or organic phases. Moreover, several examples now clearly show that

* Fax: +33 540006158.
*E-mail address:* jm.vincent@ism.u-bordeaux1.fr.

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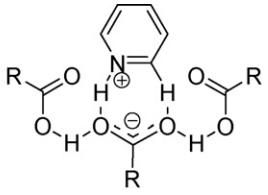
a molecular receptor confined in a PFC will exhibit a higher selectivity for its guest.

In this review we will focus on the works that have studied and/or exploited noncovalent associations (mostly hydrogen bonding, ion pairing, halogen bonding and coordination to metals) taking place in fluorous fluids. Applications of this approach to liquid/liquid phase-switching procedures, catalyst recycling and by-product removal, sensing or selective extraction processes will be discussed. We wish also to highlight the few reports dealing with the gelation of PFCs, the gelation process arising from the self-association of amphiphilic molecules through noncovalent interactions.

## 1. Hydrogen bonding and/or ion pairing in PFCs

In 1997, an IR spectroscopic study on the dimerization of fluorous carboxylic acids and their salts in perfluoropolyethers (PFPEs) was reported by Kasai and coworkers [5]. They postulated that the PFPEs carboxylic acids **1**–**3** would provide, due to the extreme hydrophobicity of the PFPE chains, an anhydrous fluid medium to study the naked interactions between the acids and their sodium salts (Scheme 1). They showed that the acids **1**–**3** exist exclusively under the hydrogen bonded cyclic dimeric form **4** in the fluorous medium with the carbonyl band at 1775–1782 $cm^{-1}$. The Rf–COONa salts **5** give rise to a shift of ~100 $cm^{-1}$ to shorter wavelengths. Interestingly, when mixing equimolar amounts of the acids with their corresponding sodium salts, a third species attributed to the mixed acid–salt dimer **6** was formed (Scheme 1), giving rise to two new broad carbonyl bands at 1740 and 1640 $cm^{-1}$. Enthalpies of dimerization of 19.5, 34.1 and 53.1 kcal/mol for the acid–acid, acid–salt and salt–salt were obtained by ab initio calculations.

In 2007, Weber and coworkers reported a detailed study on the interactions between pyridine/substituted pyridines and the fluorous carboxylic acids **2** (Krytox) or the perfluorodecanoic acid in perfluorohexanes (FC-72) [6]. They showed that Krytox was acting as an effective receptor for the pyridines allowing their efficient extraction (up to 99%) from chloroform into the fluorous phase containing equimolar **2**. Aniline was poorly extracted (5%) under the same conditions, demonstrating that the pyridyl nitrogen was primarily responsible for the binding to the carboxylic acid. Titration experiments (continuous variation method) afforded an acid–pyridine complex stoichiometry of 3:1. Based on IR studies and comparison with previous work, a structure for the 3:1 complex in which the pyridinium is interacting with the carboxylate through OH–N and CH–O hydrogen bonds was proposed. Two additional carboxylic acids would be H-bonded with the carboxylate giving rise to a hydrogen-bonded relay "chain" which should favor the solvation of the polar pyridinium in the fluorous phase (Scheme 2). The OH–N and CH–O



$CF_3CF_2CF_2O[CF(CF_3)CF_2O]_{33}CF(CF_3)$ = R

**Scheme 2.**

hydrogen bonds motif is supported by the crystal structure of the pyridine/perfluorodecanoic acid complex in which such interactions are found. A free energy of formation for the cyclic dimer ($\mathbf{2}_2$) of $-16.5$ kJ $mol^{-1}$ ($K_a$ = 755 $M^{-1}$) in FC-72 was estimated by IR spectroscopy titration experiments, whilst the overall free energy of formation for the 3:1 complex from the monomeric acid **2** and the pyridine was estimated at around $-39$ kJ $mol^{-1}$.

In 2000, Crooks and coworkers reported what might be considered as the first example of application in synthetic chemistry which exploits hydrogen bonding and/or ions pair interactions in PFCs [7]. Thus, a poly(amidoamine) (PAMAM) dendrimer in which nanoparticles of Pd were encapsulated was made highly soluble in PFCs by complexing noncovalently the final dendrimer amine groups with the carboxylic end group of **7** (Scheme 3). Whether the acidic proton is partially or totally transferred to the amino group in such a poorly solvating medium for ion pairs has not been addressed. The high fluorophilicity of **7** ensured a quantitative extraction of the dendrimer-encapsulated nanoparticles into the fluorous phase. Interestingly, long perfluoroalkanoic acids $CF_3(CF_2)_nCO_2H$ ($n$ = 11, 17) failed to solubilize the dendrimer in the PFCs. The fluorous Pd/dendrimers proved to be good catalysts for hydrogenation reactions under fluorous biphasic conditions (tetrahydrofuran/perfluoro-2-butyltetrahydrofuran FC-75) under vigorous agitation at room temperature. The catalyst was recycled 12 times without appreciable loss of catalytic activity by simply recovering the fluorous phase at the end of the reaction. Interestingly, the dendrimer-encapsulated Pd nanoparticles were found to be more selective than conventional polymer-bound Pd(0) particles. This improved selectivity was attributed mostly to the polar nanoenvironment within the dendrimer thus favoring the reactivity of the more polar substrates. It was also proposed that steric hindrance might play a role by limiting the diffusion of the larger substrates into the core of the dendrimers.

In 2001, Palomo et al. reported an original strategy to scavenge fluorinated *N*,*N*′-dialkylureas in PFCs through the formation of the heteromeric hydrogen-bonded urea-perfluoroalkanoic acid complexes [8]. Indeed, they discovered that the fluorophilicity of fluorous ureas **8** was dramatically improved in the presence of

$CF_3$-$CF_2$-$CF_2$-O-[$CF_2$-$CF_2$-$CF_2$-O]$_m$-$CF_2$-$CF_2$-$CO_2H$

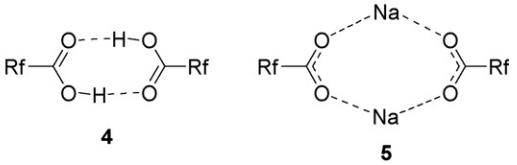
**1** (Demnum)

$CF_3$-$CF_2$-$CF_2$-O-[$CF(CF_3)$-$CF_2$-O]$_m$-$CF(CF_3)$-$CO_2H$

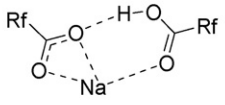
**2** (Krytox)

$HO_2C$-$CF_2$-O-[$CF_2$-$CF_2$-O]$_m$-[$CF_2$-O]$_n$-$CF_2$-$CO_2H$

**3** (Fomblin Z)



**4** **5**



**6**

**Scheme 1.**

$CF_3$-O-[$CF(CF_3)$-$CF_2$-O]$_m$-[$CF_2$-O]$_n$-$CF_2$-$CO_2H$

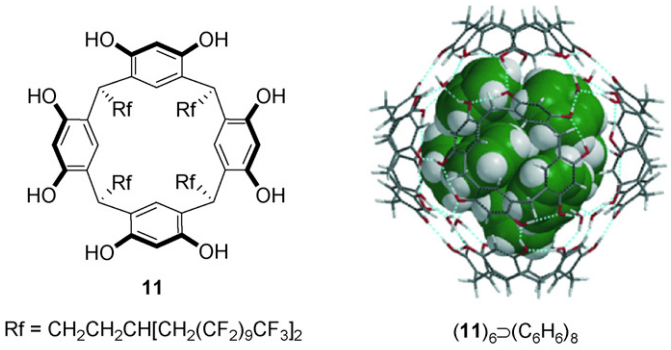
**7** (MW ~ 550)

**Scheme 3.**

stoichiometric amounts of the perfluoroalkanoic acids **9** (Scheme 4). For instance, an increase of the partition coefficient $P$ ($C_6F_{14}$/$CH_2Cl_2$) of the urea **8c** from 30:70 as high as 99:1 was observed upon formation of the **8c**.**9a** complex bearing medium-size fluorinated chains (Scheme 4). The replacement of dichloromethane by more coordinating solvents such as acetonitrile led to a significantly less efficient extraction process ($P$ ($C_6F_{14}$/$CH_3CN$) = 90:10 for **8c**.**9a**). The weaker acids **9b** and **9c**, that are expected not to be as good hydrogen bond donors, were found to be less efficient extracting agents than **9a** ($P$ ($C_6F_{14}$/$CH_2Cl_2$) = 98:2 and 95:5 for **8c**.**9b** and **8c**.**9c**, respectively). FTIR studies coupled with NMR titrations confirmed the formation of the heteromeric 1:1 complexes with the tentative structure presented in Scheme 4. The extraction process was successfully applied to the purification step of dipeptides and ester synthesis. By employing the fluorous carbodiimide **10** as the coupling agent, the urea by-product **8c** was efficiently removed from the organic reacting phase (DCM) by washing with a $C_6F_{14}$ solution containing **9a**.

In 2007, Shimizu et al. reported on the encapsulation properties of the hexameric fluorous supramolecular capsule (**11**)$_6$ formed by the self-assembly of six "Teflon-footed" resorcinarenes **11** (Fig. 1) [9]. The structure is held in solution by a network of hydrogen bonds between the resorcinol OH groups and around eight additional water molecules. Accordingly, the fluorous resorcinarene **11** was found to be mostly soluble in wet perfluorobutylmetlyl ether (HFE-7100) and in wet FC-72.

The fluorophilicity of **11** was reflected by the large partition coefficients in biphasic FC-72/organic solvents systems (99, 124 and 332 for $CH_3CN$, EtOAc and MeOH, respectively). NMR experiments showed that in wet HFE-7100 an average of 4.3 molecules of solvent were encapsulated within (**11**)$_6$, whilst encapsulation of benzene (up to 7.2 molecules/(**11**)$_6$) was favored in HFE-7100/benzene mixtures, most probably because of fluorophobic effects. Interestingly, the association constants ($K_a$) for the encapsulation of 3,3-dimethyl-1-1-butanol **12** and *tert*-butyl benzene **13** in HFE-7100 were found to be respectively 330- and 49-fold larger than that measured in $CHCl_3$ using the non-fluorinated analog *C*-undecyl resorcinarene. Moreover, a much higher $K_a$ was obtained for the encapsulation of **12** ($K_a = 1.8 \times 10^4\ M^{-1}$) compared to that of **13** ($K_a = 54\ M^{-1}$), pointing to two types of interactions (CH–π and hydrogen bonding) that occur with **12** whereas only one type of interaction (CH–π or π–π) is present for **13**. Overall, the work by Shimizu and coworkers nicely demonstrates that thanks to the fluorophobic




**11**

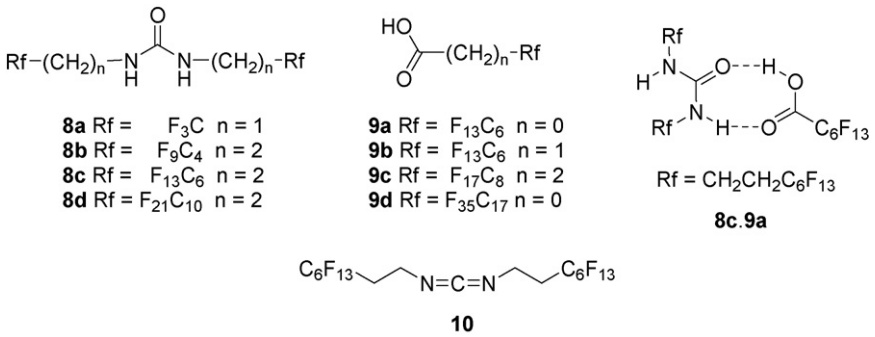
Rf = $CH_2CH_2CH[CH_2(CF_2)_9CF_3]_2$

$(\mathbf{11})_6 \supset (C_6H_6)_8$

**Fig. 1.** Structure of the resorcinarene **11** and model of the hexameric hydrogen-bonded supramolecular assembly which encapsulates eight benzene molecules. (Adapted from Ref. [9]).

effect, both stronger non-covalent associations and enhanced selectivities can be obtained by embedding a supramolecular receptor in a PFC.

In 2005, Bühlmann and coworkers reported the first quantitative data demonstrating that the strength of noncovalent associations, in particular ion pairing, can be greatly enhanced in fluorous media [10]. Their objective is to develop Ion-Selective-Electrodes (ISEs) exploiting fluorous matrices (both fluorous membranes and fluorous solvents). It was anticipated that the unwanted adsorption of lipids and proteins onto such membranes (biofouling) would be prevented or limited due to their extremely low polarity. The sensing membranes (porous Teflon) were prepared by impregnation with a perfluoroperhydrophenanthrene solution of the highly fluorophilic tetrakis[3,5-bis(perfluorohexyl)phenyl]borate anion **14**, employed as an anionic site for cations (Scheme 5). Association constants for the ion pair formation ($K_{ip}$) were determined by measuring the resistivities of the resulting fluorous membranes at various concentrations of the salts. The log $K_{ip}$ values measured for a range of cations including $Li^+$, $Na^+$, $Cs^+$, $NH_4^+$ or $H_3O^+$ (values falling between 20.1 and 20.7) exceeded those previously reported in organic media for similar ion pairs by at least 5 orders of magnitude. Maybe more importantly, it has been shown that these ionophore-free sensing membranes exhibit exceptionally high selectivities due to the low extent of solvation of the interfering ions in the fluorous phase. Logarithmic selectivity coefficients ($\log K^{pot}_{Cs,J}$, determined using $Cs^+$ as the reference point) spanning a range of 16 orders of magnitude between the extremes of the scale $Ca^{2+}$ ($\log K^{pot}_{Cs,J} = -4.35$, high selectivity for $Cs^+$ over $Ca^{2+}$) and $N(Bu)_4^+$ ($\log K^{pot}_{Cs,J} = +11.41$, high selectivity for $N(Bu)_4^+$ over $Cs^+$) were observed. The selectivity range proved to be 8 orders of magnitude higher than that of non-fluorous membranes




**8a** Rf = $F_3C$ n = 1
**8b** Rf = $F_9C_4$ n = 2
**8c** Rf = $F_{13}C_6$ n = 2
**8d** Rf = $F_{21}C_{10}$ n = 2

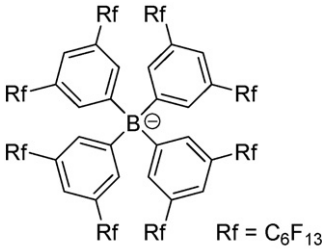
**9a** Rf = $F_{13}C_6$ n = 0
**9b** Rf = $F_{13}C_6$ n = 1
**9c** Rf = $F_{17}C_8$ n = 2
**9d** Rf = $F_{35}C_{17}$ n = 0

Rf = $CH_2CH_2C_6F_{13}$

**8c**.**9a**

**10**

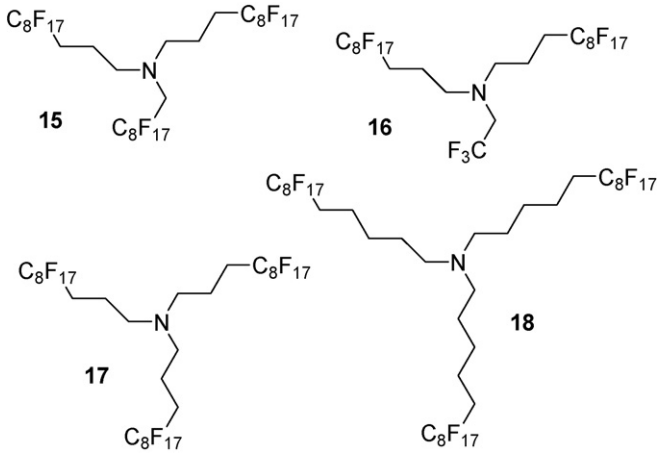
**Scheme 4.**




Scheme 5.

doped with **14**. Remarkably, the selectivity was comparable to that of membranes doped with selective ionophores for $Cs^+$ based on crown ethers.

Very recently, the same group reported the first examples of ionophore-doped ISEs based on fluorous matrices [11]. The fluorophilic amines **15**–**18** were employed as ionophores for $H^+$ (Scheme 6). Not surprisingly the most selective pH sensor was obtained from the most basic amine **18** possessing spacers with five methylene units. The fluorous membrane pH sensor based on **18** proved to discriminate $H^+$ over $K^+$ ($\log K^{pot}_{H^+,K^+} < -12.8$) more effectively than the best ISEs reported so far which are based on poly(vinyl chloride)membranes doped with tridodecylamine. For the first time, it has been possible to determine the p$K_a$s of the amines in a PFC. This was achieved by comparing the selectivities of the non-doped and ionophores-doped membranes for $K^+$, $Na^+$, and $H^+$ ions over $PPh_4^+$ (the anionic site **14** being always present in the membranes). The $PPh_4^+$ ion was chosen because it was expected that it would not interact with the ionophores. p$K_a$ values of 3.6, 3.8, 9.8, and 15.4 ± 0.3 were determined in perfluoroperhydrophenanthrene for the amines **15**–**18**, respectively. Interestingly, the value of 15.4 obtained for **18** is much higher than the p$K_a$s of trialkylamines in water (~10.6).



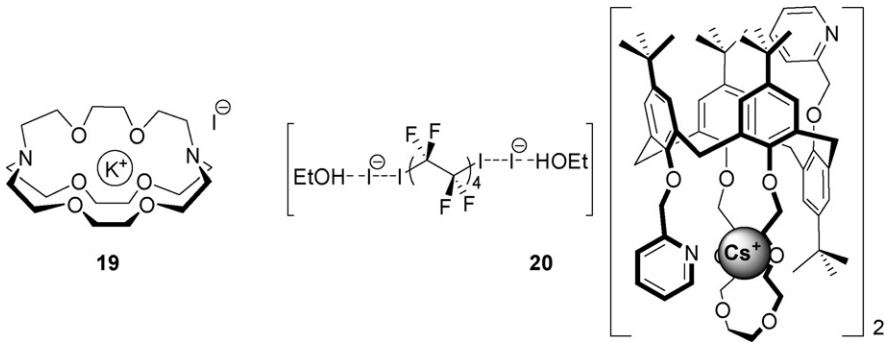

Scheme 6.

## 2. Halogen bonding in PFCs

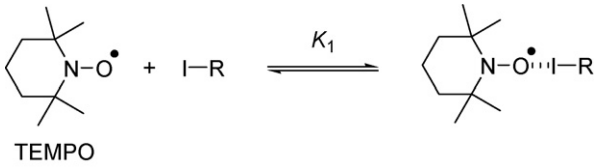
The extensive and pioneering work of Metrangolo, Resnati and coworkers on halogen bonding (XB), the attractive interactions involving halogen atoms as electron acceptors, has clearly demonstrated that IodoPFCs (I–PFCs) are powerful XB donors [12]. Whilst most of their work tends to exploit XB interactions for crystal engineering, they reported a few studies dealing with XB in fluorous fluids. For instance, they showed that the very strong $I^-$...I–PFC halogen bond could be used as a powerful tool to increase the fluorophilicity of highly polar ionic compounds such as the cryptate K.2.2.2.⊂KI **19** or the tetrabutylammonium iodide **20** [13]. Indeed, **19** and **20** were found to be more soluble in 1-iodoperfluorohexane (>500 mg/mL) than in water (>200 mg/L). From $^{19}F$ NMR studies it has been established that the strength of the $I^-$...I–PFC interaction is significantly higher than N...I–PFC, confirming theoretical calculations predicting bond strengths of 41 and 13 kcal/mol for $I^-...I_2$ and N...$I_2$, respectively.

Owing to the strength of the $I^-$...I–PFC interaction, the same group demonstrated in 2007, that CsI can be selectively extracted from an aqueous into a fluorous phase by combining a selective receptor for $Cs^+$ ions and a diiodoperfluoroalkane [14]. A calixcrown was selected as the ionophore affording, upon complexation of CsI, an ionic complex in which the naked $I^-$ anion has become an excellent XB acceptor. Addition of the 1,8-diiodoperfluorooctane affords the hybrid supramolecular charged-separated salt **20**, whose structure was confirmed by X-ray analysis. The extraction experiments were conducted using 1,4-dioodoperfluorobutane as both the fluorous liquid phase and the XB donor. Their experiments confirmed that indeed, CsI (2 mM) can be efficiently extracted from an aqueous phase into a solution of the crown ether (10 mM) in 1,4-dioodoperfluorobutane by simple stirring of the biphasic system. Moreover, because of the synergic effect of the ionophore and the 1,4-dioodoperfluoroalkane, this system is selective for both $Cs^+$ and $I^-$. Neither, $CsNO_3$, NaI or KI was extracted in the fluorous phase under the same conditions. Such selectivity was attributed to the poor ability of $NO_3^-$ to act as an XB acceptor and the high energetic cost of the solvation/desolvation associated with $K^+$ and $Na^+$ ions (Scheme 7).

Finally, ESR studies by Lucarini and coworkers, have shown that the oxygen atom of persistent nitroxide radicals such as TEMPO, behave as good XB acceptors in halogen bonding [15]. Starting from aliphatic and aromatic I-PFCs, quite stable halogen-bonded paramagnetic complexes can be formed in solution (Scheme 8). The highest equilibration constant ($K_1$ = 15.4 ± 0.6 $M^{-1}$ at 298 K,




Scheme 7.




**Scheme 8.**

assessed by ESR) was measured in *n*-$C_8F_{18}$ for the TEMPO/*n*-$C_8F_{17}I$ complex. An enthalpy of formation of 7 kcal/mol was determined for this complex, a value which is similar to those reported for the interaction between TEMPO and strong hydrogen-bond donors.

## 3. Coordination bonds in PFCs

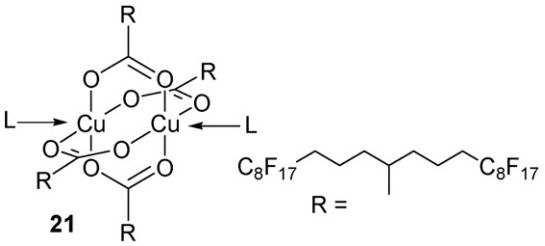
In this section we would like to highlight the works exploiting the reversibility of kinetically labile coordination bonds, the reversibility being a fundamental characteristic of association processes occuring through noncovalent interactions.

In 2002, our group reported the first example of a hydrocarbon/perfluorocarbon reversible phase-switching process for non-fluorinated compounds [16]. This process relies on the reversible coordination of pyridyl groups to the highly fluorophilic copper(II)–carboxylate complex **21** that is soluble only in PFCs (Scheme 9) [17].

As shown in the photographs of Fig. 2, pyridyl tagged molecules such as porphyrins, metalloporphyrins or a $C_{60}$-dipyridyl derivative can be very efficiently extracted in a PFC that contains the complex **21** upon stirring of a HC/PFC biphasic system. Perhaps more importantly, due to the lability of the monopyridyl ligands, instantaneous and quantitative release of tetrapyridylporphyrin TPyP was possible by adding a large excess of chelating solvents such as THF, EtOH or MeOH to the biphasic system, which are competitive ligands for the copper ion [16,18].

This unique liquid/liquid reversible phase-switching process was successfully applied for the rapid purification of reaction products in a multi-step synthesis [19]. The non fluorous bis-monopyridyl benzyl alcohol tag **22** was prepared and engaged in the synthesis reported in Fig. 3. The liquid/liquid purification process employed in the first, third and last steps proved to be straightforward and highly efficient, the hydantoin **23** being obtained in 86% overall yield.

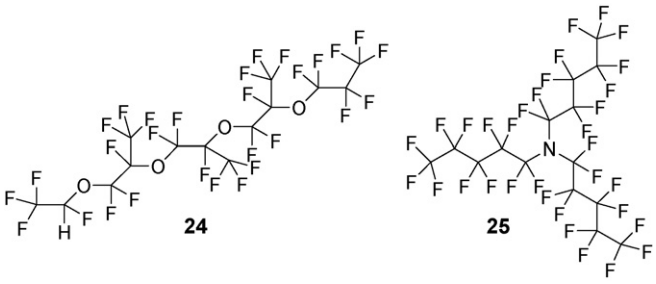
The peculiarity of this reversible phase-switching system is its extreme efficiency and sensitivity. Importantly, while water and EtOH are expected to exhibit a similar affinity for copper(II) ions, it was found that TPyP was poorly released by water (1–2% compared to that of EtOH in the same conditions) [20]. This result is attributed to the very low solubility of water in $C_6F_{14}$, the




**Scheme 9.**

perfluorocarbon providing an anhydrous environment for the [**21**-TPyP] assembly. The remarkable selectivity for ethanol over $H_2O$ was exploited to develop a colorimetric assay for ethanol [20]. It has to be noted that the competitive role of water is very often a severe limitation for the sensing/detection methodologies based on supramolecular interactions. In the multiphasic Indicator–Displacement–Assay (IDA) we proposed, the [**21**-TPyP] receptor-indicator complex is confined in the anhydrous fluorous phase (Fig. 4). The assay was successfully applied to the accurate titration of ethanol in hydroalcoholic beverages and ethanol-gasoline blends using calibration curves obtained from standard ethanolic solutions. Overall, our study demonstrates that PFCs provide an effective anhydrous environment for a receptor. This allowed the titration of EtOH in a vast amount of water thanks to an IDA based on coordination chemistry.

In 2005, Bühlmann and coworkers reported the first quantitative data on the coordinative properties of perfluoroethers and perfluoralkylamines towards monocations [21]. They have shown that the selectivity (potentiometric measurement and referenced to $Cs^+$) of a fluorous-liquid membrane loaded with **14** for the small ions $Na^+$ and $Li^+$ was modified when using the perfluoroether **24** (Scheme 10) as the fluorous liquid phase instead of the perfluorodecalin or perfluoroperhydrophenanthrene. On the other hand, the same selectivity was observed when comparing the Teflon membranes




**Scheme 10.**

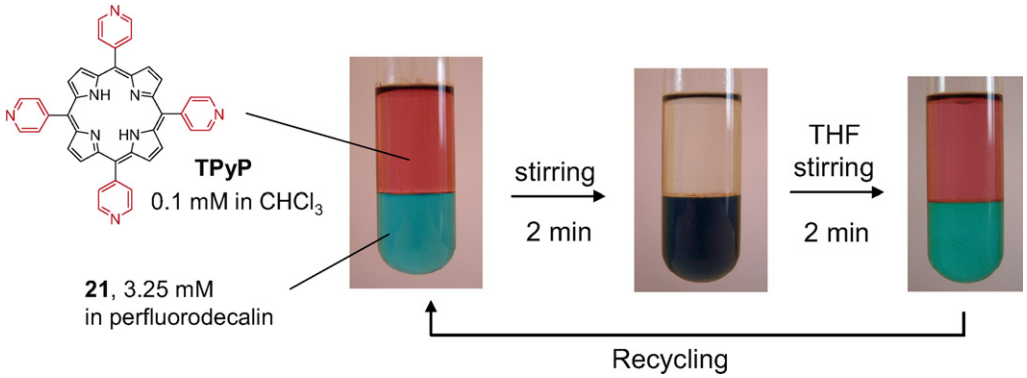



**Fig. 2.** Photographs of a liquid/liquid reversible phase-switching experiment (adapted from Ref. [18]).

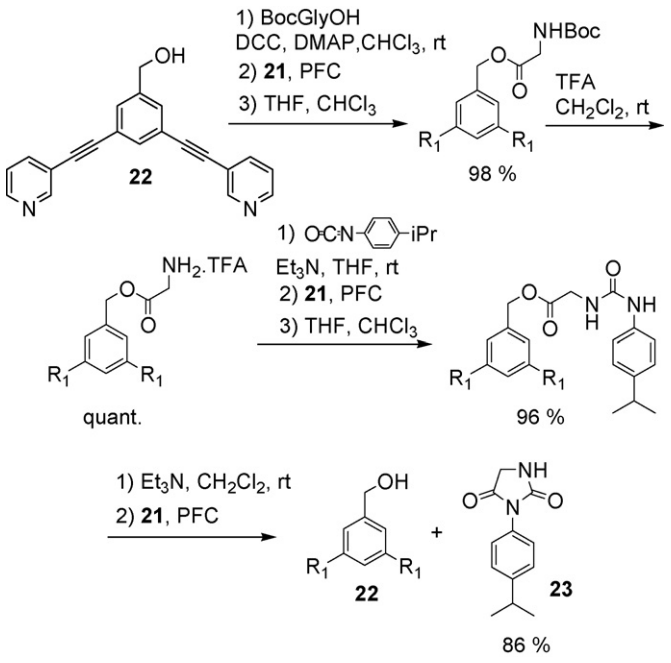
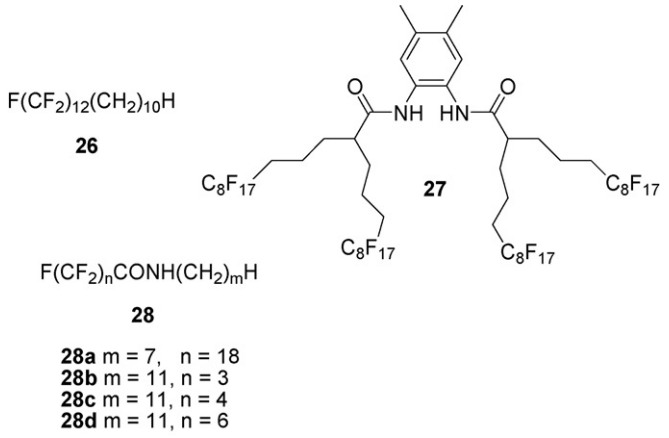



**Fig. 3.** Synthesis of a hydantoin using a reversible phase-switching procedure as purification steps (adapted from Ref. [19]).

impregnated either with perfluorotripentylamine **25** or with perfluoroperhydrophenanthrene. These results represent the first experimental evidence that perfluoroethers exhibit weak but clearly detectable coordinating properties towards $Na^+$ and $Li^+$ whilst the association of perfluoroalkylamines for the tested cations, and in particular $H^+$, is too low to be measured. From the potentiometric selectivity values and the determination of the single ion distribution coefficients for the various ions and solvents, complexation constants of $2.3 \pm 0.8\ M^{-1}$ for $Na^+$ and $1.5 \pm 0.6\ M^{-1}$ for $Li^+$ were obtained for the binding with the tetraperfluoroether **24** (assuming a 1:1 ion–solvent complex stoichiometry). Interestingly, it can be estimated that 17% of the sodium ions (23% for lithium ions) present in the perfluoroether membrane were not interacting with a solvent molecule, even though solvent molecules are in 1000-fold excess toward cations (Scheme 11).




**Scheme 11.**

## 4. Gels of PFCs

Finally, we wish to highlight the few reports dealing with the gelation of PFCs by low molecular weight organogelators (LMOGs). The gelation process results from the self-assembly of a gelling agent into a 3D network of fibers which entraps the solvent molecules [22]. The network structure is held together by attractive noncovalent forces such as hydrogen bonding, π–stacking and van der Waals interactions. PFC gels are a class of fluorous colloids that are of interest due to potential applications as corporal delivery cream, *in vivo* oxygen delivery or as lubricants [23]. To date most of the PFC gels were obtained using fluorous surfactants in the presence of 1–20% water. Only a few examples of compounds were shown to gelate "pure PFCs". For instance, Möller and coworkers showed that the diblock perfluoroalkylalkane **26** at high concentration (12 wt%) was able to gelate perfluorodecalin [24]. Optical micrographs revealed that the gelation process was occuring through the formation of interdigitated crystallites (long needles) which trap large amount of solvent in the cavities. In 2002, our group reported that the fluorous diamide **27** could gelate the perfluorotributylamine at low concentration (1 wt%), the gel being stable at 4 °C but melted at 20 °C [25]. Electron microscopy clearly revealed that the formation of ribbon-like fibers was responsible for the gelation. The most efficient gelators for PFCs

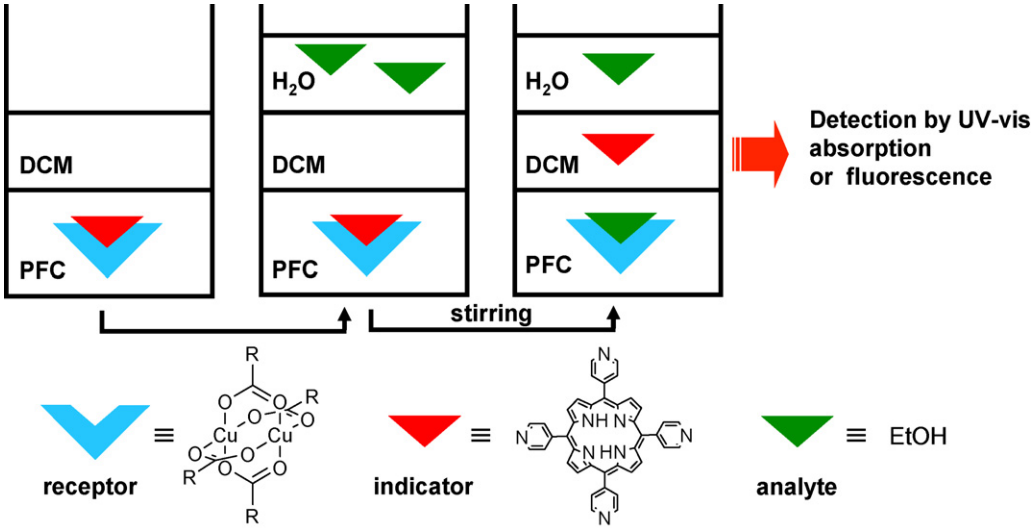



**Fig. 4.** Schematic representation of the fluorous IDA for EtOH.

reported to date are the *N*-alkyl perfluoroalkanamides **28** developed by Weiss and coworkers [26]. These compounds gelate at low concentration (2 wt%) a range of perfluorinated fluids including *n*-perfluorooctane, FC-72, FC-77, FC-43 and L-18543. The resulting gels are thermoreversible and stable for months at room temperature. Extensive studies by optical microscopy, X-ray diffraction and small-angle neutron scattering revealed that the PFCs are encaged in a network of fibrils of very small cross-sectional dimensions (in the nanometer range). The role of H-bonding among the central amide groups to increase the stability of the supramolecular assembly has been clearly established. For instance, the analog of **28b** possessing a central ester group instead of the amide failed to gelate the PFCs.

## 5. Conclusion

As highlighted in this review, fluorous fluids are receiving an increasing interest as a potential liquid phase in which molecular recognition processes can be studied and exploited. There are now a few examples that have established that noncovalent associations are reinforced in these extremely apolar non-competitive media and that higher selectivities can be attained by confining a receptor into PFCs. These attractive features have already been successfully exploited to develop practical "real-life" applications such as the electrochemical sensors developed by Bühlmann and coworkers which are based on receptor-doped fluorous liquid membranes. Among the potential important applications, it has been suggested that drugs could be directly delivered in lungs thanks to XB interactions with perfluorooctyl bromide which is used for liquid ventilation in lung diseases [27]. Considering that many synthetic strategies are now available to prepare fluorophilic receptors, the combination of fluorous liquid phases and recognition processes should provide many opportunities to develop further innovative applications, in particular for sensing and selective extraction processes.

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