Journal of Chromatography A, 1217 (2010) 2287–2295

Contents lists available at ScienceDirect

Journal of Chromatography A

journal homepage: www.elsevier.com/locate/chroma

Review

Fluorous media for extraction and transport

Kristi L. O'Neal, Hong Zhang, Yanhong Yang, Lei Hong, Dujuan Lu, Stephen G. Weber*

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA

ARTICLE INFO

Article history:
Available online 3 December 2009

Keywords:
Fluorophilicity
Teflon AF
Molecular recognition
Selectivity

ABSTRACT

Selective partitioning can be useful for sample cleanup or the isolation and purification of desired compounds. Fluorocarbon solvents and polymers, and solvents or polymers with similar properties that are not composed solely of carbon and fluorine (so-called 'fluorous' solvents or polymers) have a low ability to dissolve or sorb solutes or penetrants. This lack of solvating ability can lead to selective extractions. Fluorous phases will solvate, and therefore extract or transport, fluorous solutes, or non-fluorous solutes that are stabilized in the fluorous phase by non-covalent interactions with a 'host' or 'receptor' molecule that is in the fluorous phase. In this review, there is a brief discussion of molecular recognition as applied to selective extraction. Fluorous solvents are introduced, and there is a description of some recent applications, chiefly in synthetic organic chemistry. In particular, it is important to understand solute partitioning behavior and methods to predict it when one of the solvents is fluorous. Fluorous polymers Teflon AF1600 and AF2400 have been used in separations. Their rather complex and still not completely understood properties in separations and transport are described. There is a discussion of molecular recognition in fluorous phases as well as a brief discussion of efficient methods of carrying out extractions for analytical or physicochemical purposes.

Contents

1. Introduction

Despite the rapid development of analytical instrumentation, most analytical methods still incorporate some kind of pretreatment step or sample preparation. Sample preparation methods typically involve a separation step in which analytes and other species are removed from the sample and concentrated with the overall goal of increasing the signal-to-noise ratio of the measurement. Despite the significant impact that sample preparation methods have on the success of the overall analytical process, they have traditionally been laborious, time consuming, waste generating, and practically neglected by the research community [1]. Today, because of developments in high-throughput measurements, sample preparation is often the rate determining step in the analytical process, thus driving the need for improvement. In addition, increasing awareness of our impact on the environment has placed a greater emphasis on analytical methods that produce less waste.

Extraction and adsorption/elution are the most widely used sample preparation techniques. The goal of any such operation is the selective removal of a target analyte from the sample matrix. Liquid–liquid extraction (LLE) is a method to separate compounds based on their distribution between two immiscible liquid phases. LLE is an equilibrium process, thermodynamically driven by a difference in chemical potential of the solute in each phase. Concentration is achieved when the analyte, *x*, has a high distribution

* Corresponding author. Tel.: +1 412 624 8520; fax: +1 412 624 1688.
E-mail address: sweber@pitt.edu (S.G. Weber).

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doi:10.1016/j.chroma.2009.11.077

coefficient (D_c) between phase *a* and *b*. D_c, given by Eq. (1), is the ratio of the sums of the concentrations (C_x) of all forms of the analyte in each phase.

$$D_c = \frac{C_{x,b}}{C_{x,a}} \quad (1)$$

D_c is distinguished from a partition coefficient (K_c) in that D_c includes all forms of the sample component (i.e. free, complexed, ionized, dimerized, etc.) while K_c only considers one particular form.

Solid phase extraction (SPE) is one of the most common sampling techniques in environmental, pharmaceutical, clinical, and food chemistry [2]. In SPE, analytes are exhaustively removed from a flowing sample matrix by transfer and sorption to a solid phase. Solid phase microextraction (SPME) is another widely accepted technique that was later developed by the Pawliszyn group [3,4]. SPME most often involves the non-equilibrium removal of chemical constituents from a sample matrix by retention on a sorbent or in a film with subsequent desorption of target analytes. SPME differs from SPE in that the sorbent material is coated on a fine rod which makes the approach particularly suitable for analysis by gas chromatography. Selection of the sorbent material can be crucial to the success of the separation. It must be able to sorb sample constituents rapidly and reproducibly [5] yet components must be easily eluted from the sorbent [6], meaning that the sorption process must be reversible. Many materials are used as the solid phase in SPE and SPME, however there is no universal sorbent for all applications [7] and retention behavior can vary dramatically among sorbent materials. Therefore, it is necessary to continue to explore new materials for SPE and SPME applications and design sorbents for specific analyte/matrix systems.

2. The selectivity of an extraction

The selectivity of an extraction is defined as the ratio of the relative concentrations of the analyte and interfering species in the two phases. Approaches to altering or improving the selectivity of an extraction include the choice of the extraction solvent, manipulation of the properties of the extracting solvent (i.e. temperature and pressure if the extracting medium is compressible, e.g. CO_2) or adsorbent (e.g. an adsorbent's activity), and by the application of restricted access media (RAM) and molecularly imprinted polymers (MIPs) [8]. It has also been shown that extraction selectivity is enhanced through incorporating an artificial molecular receptor into the receiving phase [9,10].

Artificial receptors work based on molecular recognition, a chemical phenomenon involving non-covalent interactions between a receptor and substrate. It is one of the most fundamental phenomena in chemistry. Selectivity is attained by arranging non-covalent forces (e.g. electrostatic and van der Waals interactions) between substrate and receptor to occur in a sterically and geometrically defined way. Selective molecular recognition plays an essential role in many life processes, including DNA base pairing, tRNA binding to amino acids, enzyme-substrate binding, neurotransmitter and neuropeptide binding at receptors, cell organelle self-assembly, and pheromone-mediated chemical communication [11]. Many novel approaches to analytical chemistry are based on molecular recognition, or host–guest chemistry such as chiral separations, immunoassays, aptamer-based systems, ionophores, and sensors.

Our group has been interested in combining molecular recognition processes with separation and sample preparation methods. It is interesting to contrast *molecular* recognition with *metal ion* recognition that has been used for selective extraction and analysis for decades. Metal ion recognition typically involves multidentate ligands that are of one type—Lewis base. Although the geometry

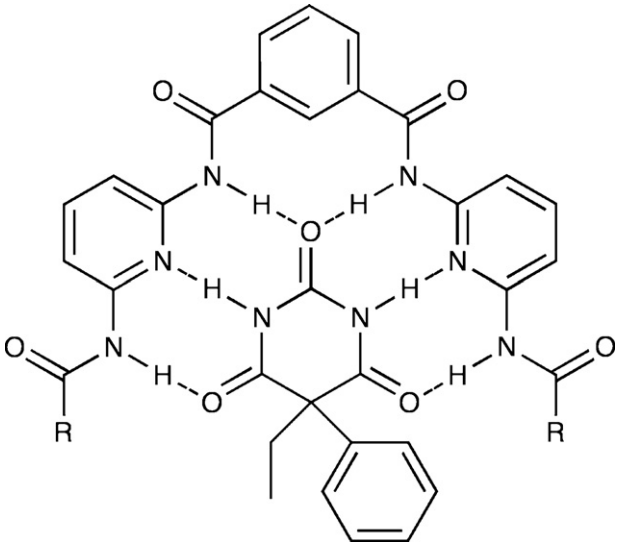


Fig. 1. Artificial molecular receptor (R = 1-propyl) binding with phenobarbital.

may vary, they are always capable of being arranged convergently, pointing to a central metal ion. The Lewis base/Lewis acid interactions are often very strong. When applied in extractions, it is almost always the case that the partitioning of the metal ion to the organic phase in the absence of a chelator is negligible. Thus, the selectivity of the extraction is completely defined by the selectivity of the chelating agent and the partition coefficients of the complexes. In *molecular* recognition, the receptor or host may have a variety of functional groups—acidic, basic, hydrophobic, aromatic. The interaction energies are not necessarily large. When applied in extractions, the natural tendency of solutes (both desired solutes, i.e. analytes and undesired solutes, i.e. interferences) to partition in part controls the selectivity of the molecular-recognition-assisted extraction. Valenta et al. [12] observed a 40-fold increase in extraction yield when they incorporated an artificial molecular receptor (Fig. 1) into a chloroform receiving phase in the extraction of phenobarbital from human control serum compared with receptor-free chloroform. This work was pivotal in demonstrating the effectiveness of artificial receptors in analytical applications.

With suitable modification of the receptor (R = 2-ethylhexyl) it can be made soluble in plasticized poly(vinyl chloride) (PVC). Li et al. [10] developed a plasticized PVC extraction medium coated on a fine rod for SPME with capillary electrophoresis (CE) detection of barbiturates (Fig. 2) [10].

In a series of investigations on the influence of the plasticizer, which acts as a solvent [9,13–15], it became clear that the solvent plays a strong role in the selectivity of the receptor-based extraction. Among the plasticizers used for PVC in extractions with the receptor (Fig. 1), chloroparaffin had the lowest polarity (as determined by its values for Kamlet-Taft solvatochromic parameters). It showed the highest selectivity for a series of barbiturates. Here, selectivity is defined as the ratio of the distribution coefficient of the drug in the presence of receptor to the same quantity in the absence of the receptor. This demonstrates the general premise that in molecular recognition-based extractions, selectivity for a target is high if non-covalent intermolecular interactions between receptor and target dominate the standard-state free energy change for the extraction process. The most selective extractions are those in which the receptor is completely responsible for the partitioning or distribution of the analyte into the extracting phase. Thus a matrix that is a poor solvent will provide a more selective environment for molecular recognition interactions [10,16]. It makes sense, then, to consider the worst possible solvents as matrices for selective

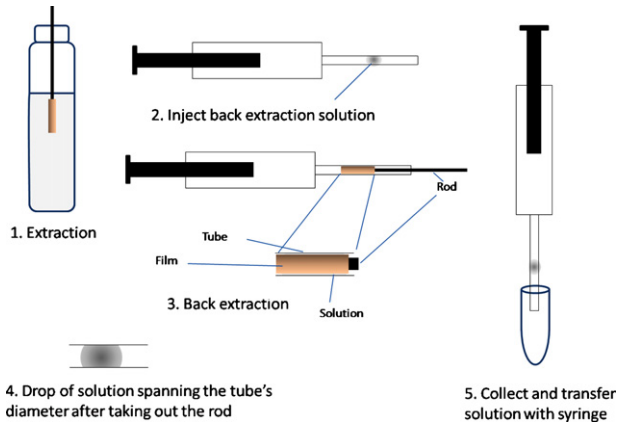


Fig. 2. Reproduced from Li et al. [10], device and operation. (1) Place rod in sample solution for a designated amount of time. (2) Inject 5 μL of back extraction solution into the Teflon tube. (3) Remove rod, wipe clean, place in Teflon tube, and (4) remove after a set time. (5) Collect the solution by moving the droplet spanning the diameter as a piston and transfer the drop to an injection vial.

extractions. We turn to a description of a class of materials known for its poor solvating ability.

3. Fluorous liquids and polymers as transport and extraction media

Fluorous or 'fluorophilic' liquids are highly non-polar and notoriously poor solvents [17]. Recently, the synthetic organic community has recognized the possibility of using fluorous solvents in organic synthesis and related unit operations [18]. An appealing property to the field of separation science is the simultaneous hydrophobic and oleophobic nature of these media, often leading to poor solubility of non-fluorinated molecules in them. Horvath and Rabai [19] first suggested that the affinity of a molecule for a fluorous phase can be manipulated by attaching varying numbers and lengths of 'pony tails' in the form of $(CH_2)_m(CF_2)_{n-1}CF_3$. This led to interest in the field of fluorous biphasic chemistry for synthesis and purification. Curran [20] and Wipf and Reeves [21] developed fluorous tagging strategies to selectively isolate target analytes from complicated sample matrices. Curran and co-workers [22] also developed the fluorous triphasic reaction in which a liquid–liquid separation is directly coupled with a chemical reaction to produce a pure product from the reaction mixture. In addition to separations and derivatization, recent innovations suggest a wide range of potential applications of fluorinated tags for identification resulting from distinctive signatures in mass spectrometry and ^{19}F NMR spectroscopy.

There have been many measurements of the partitioning of fluoro-tagged molecules particularly between the solvents perfluoromethylcyclohexane (PFMCH) and toluene [18]. These partition coefficients have become the basis for a measure of 'fluorophilicity' [23]. However, the term 'fluorophilicity' can be a little misleading if it is thought of literally. To paraphrase Goss and Bronner [24], considering air/solvent partitioning, compounds with high fluorine content have the same, or even lower, preference for fluorous solvents in comparison to an organic compound of equal molar volume, but they have a far lower preference for an organic solvent. This is due to the weaker van der Waals interactions experienced by fluorinated compounds/solvents in comparison to their organic counterparts with a similar molar volume. Thus, increasing the number of $-CF_2-$ groups in a molecule does not increase fluorophilicity literally. Rather, it increases 'oleophobicity'. Although increasing the number of $-CF_2-$ groups in a molecule generally increases its partition coefficient (higher concentration in the fluorous phase), at least in theory, it is not always the case. de Wolf has theoretically investigated the partitioning behavior in fluorous biphasic systems [25]. They calculated partitioning behavior for a number of molecules that had an organic moiety with a molar volume of 400 cm^3/mol and a $-CF_3$ group. Several sets of partitioning data were calculated based on organic moieties with different polarity, and a range of numbers of $-CF_2-$ groups between the organic moiety and the $-CF_3$ group. Only the non-specific vaporization energy (E_v) was considered in the determination of solute polarity, since specific interactions are not important in aprotic fluorous biphasic systems. If the non-specific vaporization energy of the organic moiety is lower than 120 kJ/mol, then $\log P_{OF}$, the logarithm of the partition coefficient for the solute going from organic phase to fluorous phase, linearly increases with n, the number of $-CF_2-$ groups. For organic solutes with a non-specific vaporization energy in the range of 120–280 kJ/mol, $\log P_{OF}$ increases with n, but there is increasing curvature as the solute becomes more polar. When solutes have a highly polar organic moiety, with a non-specific vaporization energy over 360 kJ/mol, $\log P_{OF}$ actually decreases with n when n is small. This can be understood from the simplified solubility parameter picture shown in Fig. 3. If the solubility parameter of the organic solute (δ_b) is between those of the organic (δ_O) and fluorous (δ_F) solvents (Fig. 3a), the addition of $-CF_2-$ decreases the solubility parameter of the solutes, resulting in increased $\log P_{OF}$. For example, the derivatives of cinnamyl alcohol (Fig. 4) with 2H,2H,3H,3H-perfluoroalkanoic acids ($HOOC-(CH_2)_2-(CF_2)_{n-1}CF_3$, $n = 2, 4, 6, 8$) show a linear relationship of $\log P_{OF}$ vs. n [26]. In this case the E_v for the ester, $Ph-CH{=}CH-CH_2-OC(O)-CH_2-CH_2-CF_3$, is 59.96 kJ/mol, while the molar volume is 234.5 cm^3/mol. To compare to the work of de Wolf

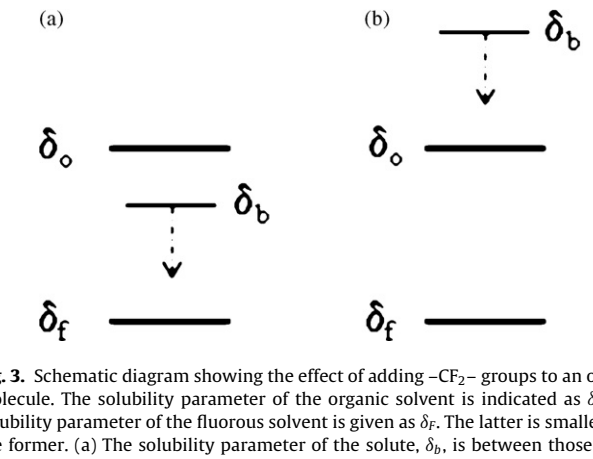
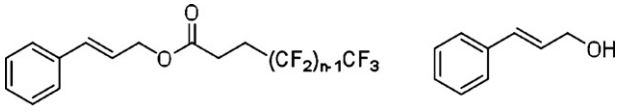


Fig. 3. Schematic diagram showing the effect of adding $-CF_2-$ groups to an organic molecule. The solubility parameter of the organic solvent is indicated as δ_O. The solubility parameter of the fluorous solvent is given as δ_F. The latter is smaller than the former. (a) The solubility parameter of the solute, δ_b, is between those of the two solvents. It partitions between the solvents. As more $-CF_2-$ groups are added (arrow) the solute's solubility parameter becomes closer to δ_F and the partitioning favors the fluorous phase more. (b) If the organic moiety is more polar, its solubility parameter is larger than in the previous case. In this case, adding $-CF_2-$ groups makes the solute more similar to the organic solvent, leading to the prediction that the effect of adding $-CF_2-$ groups in this case is to make the partition coefficient favor the organic phase more.



1a ($n = 2$)
1b ($n = 4$)
1c ($n = 6$)
1d ($n = 8$)

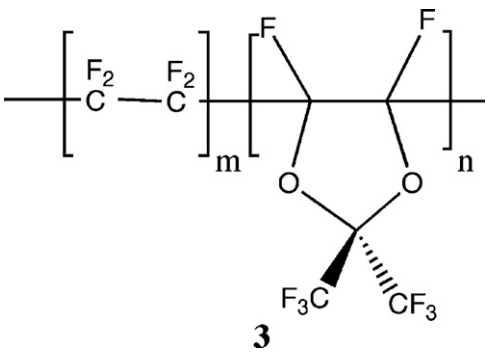
2

Fig. 4. Structures of fluorous solutes **1**, and cinnamyl alcohol **2**.

et al. the E_v corresponding to the larger molar volume in de Wolf's work (400 cm^3/mol) would be 102 kJ/mol. The results of Yang et al. [26] are thus in accord with the theory of de Wolf. If on the other hand the organic moiety is highly polar with a solubility parameter larger than the organic solvent (Fig. 3b), the decrease of the solubility parameter from the addition of $–CF_2–$ groups does not increase P_{OF} until the solubility parameter of the solute reaches that of the organic solvent. This interesting prediction may be difficult to realize in practice. Using group contribution approaches [27] we were unable to 'create' a hypothetical organic moiety with a 400 cm^3 mol^{-1} molar volume and a non-specific vaporization energy near 360 kJ/mol. In practice, such a molecule would likely be insoluble in both organic and fluorous solvents, and such a molecule with a long perfluorinated tail would likely be a surfactant.

Aside from PMFCH, another commonly used fluorous solvent is FC-72, perfluorohexanes. FC-72 is clear and colorless, thermally and chemically stable, compatible with sensitive materials, non-flammable, non-toxic, and leaves no residue upon evaporation. This unique combination of properties makes FC-72 ideal for many electronic applications and its inertness makes it a useful reaction medium [28].

Liquids can be used in supported liquid membranes (SLMs) as well as bulk extraction. Yang et al. have developed supported liquid membranes based on modified porous alumina to meet this need [26,29]. Porous alumina membranes can be rendered fluorophobic by reaction with perfluoroalkanoic acids. Modified porous alumina membranes demonstrate their hydrophobic nature by the very large initial contact angles which equal or exceed 130°. The pores of these membranes can be filled with fluorous solvents forming fluorous SLMs or FSLMs. These FSLMs show high transport selectivity for fluorinated molecules over organic molecules. The membranes achieved a transport selectivity of 100 for transport of a fluorinated ester (**1c**) in comparison to the alcohol (**2**). Independent measurements of the partition coefficients of a series of fluorinated esters (**1a–d**) between the source/receiving phase solvent, ethanol, and the fluorous solvents reveal that the selectivity behavior is dominated by partitioning rather than diffusion. Several equations have been developed to predict partition coefficients in fluorous biphasic systems [23,25,30–32]. As briefly mentioned above, de Wolf et al. have established a general predictive equation for any fluorous biphasic system in which the organic phase does not contain proton-donor or -acceptor sites, according to the MOD (mobile order and disorder) universal log *P* model [25]. In the predictive equation, the partition coefficient is estimated using the molar volumes and the non-specific cohesion parameters of the solute, pure organic and pure fluorous solvents. These parameters are readily calculated by group increment methods. A good correlation was achieved in estimating 88 solutes' (fluorinated and non-fluorinated) partition coefficients in two biphasic systems, PFMCH/toluene and FC-72/benzene. For FC-72, the experimental mutual solubility data were employed by de Wolf to calculate the cohesion parameters. A potential difficulty arises because most commercially available fluorous solvents such as FC-72, FC-77, and FC-3283 are mixtures. In principle, group increment methods apply to single compounds, not mixtures. This would severely limit the application of this approach to fluorous solvents because many commercially available solvents are mixtures. Yang et al. recently adopted some assumptions to apply group contribution methods to four fluorous solvents (FC-77, PF-5080, FC-3283 and FC-43), and compare the predicted to the experimental partition coefficients. For example, FC-3283 is a mixture of perfluorononanes. The value for its molar volume was estimated based on that of perfluoro-*n*-nonane. Parameters for perfluoro-*n*-nonane were also used to calculate the values of non-specific cohesion parameter for FC-3283. Similar assumptions were made for the other fluorous solvents. The resulting excellent correlation between the predicted and measured values of partition coefficients demonstrates the validity and applicability of the general predictive equation to fluorous solvents that are mixtures. Furthermore, these results were for partitioning between fluorous solvent and ethanol, an associating solvent. Despite being outside of the scope of the MOD theory, at least in this case, the theory worked well for a system with an associating solvent. Yang et al. also determined that the diffusion coefficients of the four solutes in the four fluorous solvents were well described by the Stokes–Einstein equation.



3

Fig. 5. Structure of Teflon AF.

For practical reasons, polymer films or coatings are preferred over liquids as an extraction medium. Teflon AFs (**3**) are chemically inert and thermally stable amorphous fluorinated polymers with potential applications in fluorous SPME for example. Teflon AF 2400 (Fig. 5) is a copolymer of tetrafluoroethylene (TFE, 13 mol%) and 2,2-bistrifluoromethyl-4,5-difluoro-1,3 dioxole (BDD, 87 mol%), whereas Teflon AF 1600 contains 35% TFE and 65% BDD. Thin Teflon AF films are easily prepared through solvent casting. The films are transparent through a wide UV–vis and IR range, which makes them ideal for studying intermolecular interactions in films. Current applications are mainly for gas separation and ion-selective electrodes (ISEs). Table 1 shows some important physical properties of Teflon AF2400 [33–35].

Sorption and permeation of light gases, C1–C12 hydrocarbons, C1–C7 perfluorocarbons and chlorinated hydrocarbons in Teflon AFs (AF 2400 and AF 1600) have been studied by Pinnau, Yampolskii and their co-workers [36–41]. Due to the larger fractional free volume (FFVs) in view of the increased bulky BDD portion, the solubility, permeability and diffusivity are systematically higher in Teflon AF 2400 than Teflon AF 1600 [37]. As penetrant size (as measured by critical volume) increases, both permeability and diffusion coefficients decrease in Teflon AFs, resulting a sieving effect [36,37]. The dependence of diffusion coefficients on penetrant concentration for poorly sorbed gases (e.g. O_2, N_2, CO_2, CH_4, CF_4) and highly sorbed gases (e.g. C_2H_6, C_3H_8, C_2F_6, C_3F_8) exhibit different patterns, which indicates that Teflon AF 2400 is plasticized when exposed to highly sorbed gases [39]. The dependence of permeability on pressure is more pronounced for fluorocarbons than hydrocarbons, indicating better plasticization by fluorocarbons [37]. The enthalpies of sorption in Teflon AF 2400 of fluorocar-

Table 1
The physical properties of Teflon AF 2400.

Properties	Values
Dielectric constant (@22 °C)	1.9
M_n	3×10^5
Density (g/mL)	1.7
Refractive index (λ = 589 nm)	1.291
Glass transition temperature (°C)	240
Molding temperature (°C)	340–360
Thermal conductivity (W/mK)	0.05

bons at infinite dilution are significantly more negative than those of the analogous hydrocarbons (same number of carbons) [39]. However, evaluating the enthalpies of sorption per molar volume based on Goss's perspective makes a great difference [24]. The hydrocarbons have more negative enthalpies of sorption per molar volume than fluorocarbons due to their stronger van der Waals interaction with the Teflon matrix when there is no plasticization (e.g. $\left|\Delta H_S/V\right|_{CH_4} > \left|\Delta H_S/V\right|_{CF_4}$). For penetrants that can plasticize Teflon, the penetrant-induced changes in the matrix could alter the physical properties of the matrix such as the cohesive energy density. Thus, unlike for the CH_4/CF_4 pair, the enthalpies of sorption per molar volume of C_2F_6 and C_3F_8 are more negative than those of C_2H_6 and C_3H_8. Yampolskii and co-workers also developed amorphous Teflon AFs as pervaporation materials [35,42,43]. Pervaporation is a method in which components of a solution pass through a selective membrane into a vapor phase. The Teflon AF membranes exhibit an attractive combination of stability, permeability, and selectivity. The temperature dependence of the permeability and solubility indicates that solutes have similar enthalpies of sorption in the two Teflon AFs. However, the activation energy of diffusion is much smaller in AF2400 due to the larger FFV [42]. Thus, the effects of temperature on permeability and selectivity are mainly controlled by the change in the penetrants/solutes diffusivity [43]. In both Teflon AF2400 and 1600, there is a correlation between the solubility coefficients of organic compounds, a ratio of their concentrations in film over gaseous pressure, and the square of those compounds' critical temperatures [37,39,42].

Transport studies of larger organic solutes from a chloroform source through films of Teflon AF2400 to a chloroform receiving phase have shown that the logarithm of the solute permeability decreases linearly as the molar volume of the solute increases [44,45]. In addition, the films demonstrated selectivity for fluorinated solutes in comparison to the hydrogen-containing control. It was also noted that films of Teflon AF2400 (containing no additives or plasticizers) imbibed a significant quantity of chloroform. In fact, films at equilibrium with chloroform are about 1 M chloroform! Thus, the environment in a Teflon AF2400 film that is exposed to solvent may not be very fluorous.

Zhang et al. [46] hypothesized that if the film were more fluorous-liquid-like, then the effect of organic solvent would be minimized, and performance would be better. They prepared defect-free, clear Teflon AF 2400 films doped with various concentrations of FC-70 (perfluortripentyl amine). FC-70 does not plasticize Teflon AF 2400. Zhang et al. view the composite as a supported liquid membrane [46]. The transport rates (permeabilities) of a fluorous/non-fluorous pair of solutes show dramatic changes with composition, passing through a minimum in the 15 wt% FC-70 region. Measurements of fractional free volume (FFV, from density measurements) showed a similar trend (Fig. 6).

Selectivity (expressed as the ratio of the permeabilities of a fluorine-containing solute to the hydrogen containing analog) tends to increase as the volume fraction of FC-70 increases. For the Teflon AF membranes that contain a significant amount of FC-70 (>15%), both high FFV and large fluorophilicity favors the permeation of fluorine-containing solutes.

Zhang et al. concluded that Teflon AF2400 in the films containing small weight fractions of FC-70 is antiplasticized [47–50]. This is interesting, as the rationale for antiplasticization is that strong interactions between additive and polymer lead to a loss in FFV and an increase in storage modulus. Of course, fluorocarbons are not known for strong intermolecular interactions, yet antiplasticization occurs anyway. Despite antiplasticization, one key objective was attained by Zhang et al. The films with high FC-70 content (>25% (w/w)) transport solutes well, and with selectivity.

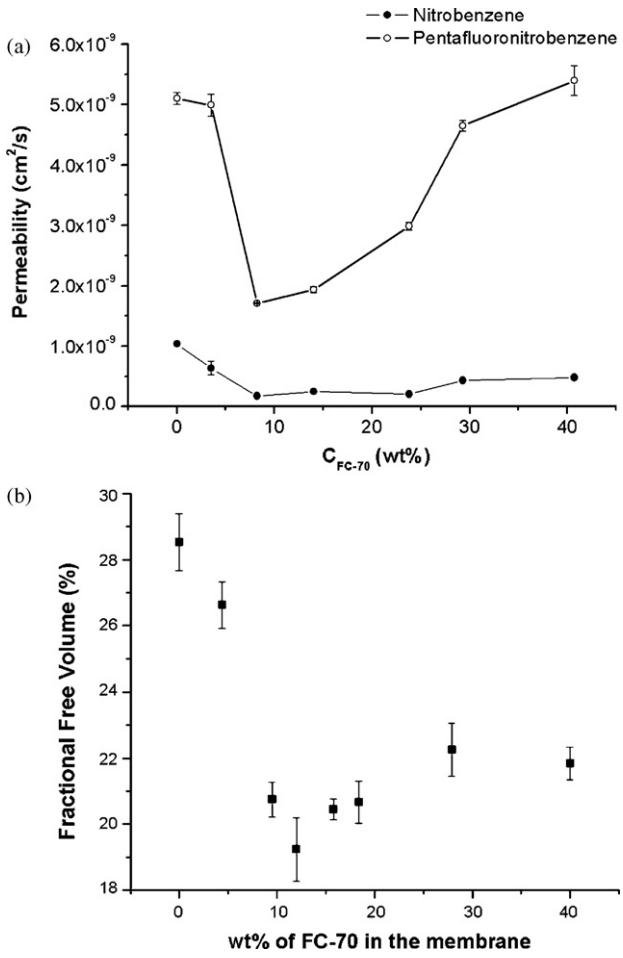


Fig. 6. (a) Permeability of a fluorinated solute, pentafluoronitrobenzene (○) compared to an analogous H-containing solute, nitrobenzene (●) through Teflon AF2400 films containing various weight % FC-70 and (b) fractional free volume as a function of FC-70 concentration (weight %) in Teflon AF-2400 films.

Besides the applications in the field of membrane separations, Teflon AFs have been developed as gas sensors due their permeability, low refractive index ($n = 1.29$), wide range of transparency (200–2000 nm), and excellent stability. A Teflon AF tube filled with reagent is highly permeable to gases of environmental interest. Sensors capable of on-line monitoring designed for specific gases based on selective chromogenic reactions have been developed by the Dasgupta group [51]. Buhlmann and co-workers reported ion-selective electrodes (ISE) based on fluorous sensing membranes [52–55]. The first generation of such fluorous liquid membrane-based ISEs is based on a fluorous bulk membrane containing an ion exchange site, sodium tetrakis [3,5-bis(perfluorohyxyl)phenyl]-borate, in perfluoroperhydrophenanthrene as sensing phase [52]. This ISE showed remarkably high potentiometric selectivity which exceeds previously reported values in conventional plasticized PVC membranes by more than 5 orders of magnitude. Moreover, the selectivity was not compromised by the coordinative properties of the ether group in the fluorous media. The basicity of perfluoroethers, long assumed to be weak, was experimentally determined to be weak enough to be neglected in the presence of strongly binding ionophores [53]. Recently, the same group developed a second generation of fluorous membrane ISEs for pH measurements with membranes composed of **3** containing a linear perfluorooligoether (14.3 ether groups per molecule) plasticizer, sodium tetrakis [3,5-bis(perfluorohexyl)phenyl]borate for ionic sites, and bis[(perfluorooctyl)propyl]-2,2,2-trifluoroethylamine as an H^+ ionophore [55]. These perfluorinated polymer-based elec-

trodes exhibited high potentiometric selectivities, Nernstian responses to H^+ over a wide pH range, and good mechanical stability. Interestingly, potentiometric and spectroscopic evidence showed that **3** contains –COOH functional groups (one per 854 monomer units) formed by hydrolysis of carboxylic acid fluoride groups originally present in Teflon AF 2400, resulting in undesirable side effects. Fortunately for this application, the use of higher ionophore concentrations removed the undesirable effects of the –COOH groups almost completely. Also, the existence of such functional groups provides opportunities for the chemical modification of Teflon AFs for specific purposes.

4. Partitioning with the aid of molecular receptors in the fluorous phase

In the realm of synthetic chemistry, fluorous separations are made possible through covalent labeling or tagging of a product, precursor, or catalyst with a fluorinated tag. The result is easy separation of the tagged entities through extraction with fluorous liquids or adsorption onto a fluorous phase (fluorous SPE or F-SPE). Approaches based on non-covalent complex formation between a receptor in the fluorous phase and an analyte do not require tagging and thus have wider applicability outside of the synthetic community. In addition, we described above the prediction of De Wolf et al. [27] that very polar organic molecules could not easily be made fluoro-soluble by adding perfluorinated tails. However, if the free energy of the partitioning of the organic moiety into the fluorous phase was decreased by non-covalent interactions with a receptor, then adding a perfluorinated tail would have the desired effect of making the molecule even more fluoro-soluble. Molecular recognition in combination with fluorous matrices should improve the selectivity of extractions by (1) reducing the amount and number of interfering species extracted and (2) increasing the strength of substrate-receptor interactions by making the free energy of solute-solvent interactions less favorable [19,56]. Thus, a fluorous-solvent- or polymer-based extraction with a molecular receptor component should be quite selective.

The subject of non-covalent interactions in fluorous phases has recently been reviewed [57]. The work of El Bakkari in the group of Jean-Marc Vincent [58–63] is interesting. They have exploited the Lewis acid property of a dicopper carboxylate complex in fluorous solvents. The complex is soluble in fluorous solvents because the acids are themselves fluorous. The complex extracts (from, e.g. chloroform) molecules with pyridine attached to them, for example, 5, 10, 15, 20 tetra(4-pyridyl) porphyrin (TPyP). Tetrahydrofuran (THF) competes with the pyridyl moiety on the target, liberating it. This group has also shown that a sensing system for ethanol can be created based on this competitive chemistry. Early work by Palomo et al. [64] is also important as it showed binding of a fluorinated urea to a fluorinated carboxylic acid in the fluorous phase. Recently, a set of perfluoroalkyl-tagged calix-4-arenes was prepared [65]. They were not highly soluble in fluorous media, limiting their applicability.

Perfluorocarboxylic acids are among the limited number of perfluorinated compounds available to act as simple, single functional group receptors. Carboxylic acids play an important role in molecular recognition and have been used as receptors for aminopyridines [66] and for the self-assembly of pyrazine carboxylic acid [67]. A wide variety of perfluoroalkanoic acids of varying lengths are commercially available; however, the rigidity of the perfluorinated chain results in low solubility in both fluorous and organic liquids. Krytox 157FS*x* (where *x* = L, M, or H corresponding to nominal molecular weights of 2500, 5000, and 7500 Da) is a perfluoropolyether whose ether oxygen give the chain much more flexibility than the perfluoro-*n*-alkyl chains and, abundant ether oxygen notwithstanding [53], is extremely hydrophobic and soluble only in highly fluorinated solvents [68]. A carboxylic acid terminated Krytox 157FSH (**4**) at the high molecular weight range would be an excellent choice for a fluorous-soluble receptor based on complementary hydrogen bond accepting functional groups (Fig. 7).

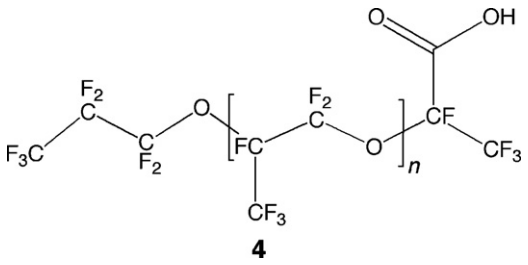


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Fig. 7. Structure of Krytox FS series.

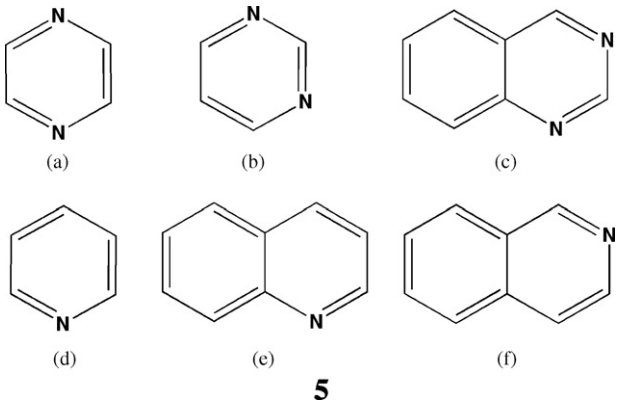

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Fig. 8. Structures of basic solutes.

Fluorinated carboxylic acids (Krytox 157 FSH, measured M_n ~5–6000) (**4**) and perfluordecanoic acid (PFDA)) bind to heterocyclic nitrogen bases in FC-72 (Fig. 8). O'Neal et al. studied a series of related bases (**5**) as solutes [69,70]. The three stronger bases, **5d–f**, bind three molecules of **4** in the fluorous solvent FC-72. O'Neal et al. found surprisingly that the proton is transferred from **4** to **5d–f** in these complexes. Based mostly on IR evidence, they postulated that the ionic complex involves a pair of acid molecules stabilizing the acid associating with the base (**6**, Fig. 9). Bases **3a–c** form molecular complexes (no proton transfer) and have 1:1 stoichiometry. Because of **4**'s H bond dimer formation and the stoichiometry of the ionic complexes, they were not able to determine a simple, single H bond formation free energy. Their thermodynamic analysis for pyridine-$\mathbf{2}_3$ is shown in Fig. 9. Numbers are free energies in kJ/mol at room temperature (22+/− 1 °C). Complex formation is driven by a considerable free energy.

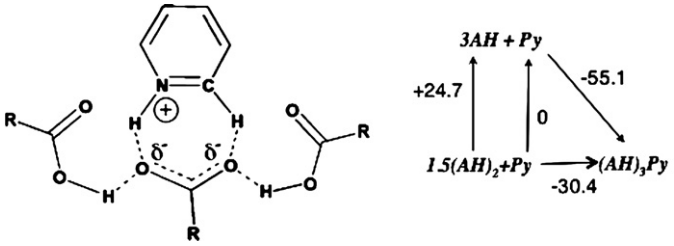

Fig. 9. Left: proposed structure (**6**) for the complex between pyridine and **4** which includes proton transfer. Right: thermodynamics of complex formation. Numbers are Gibbs free energies in kJ/mol.

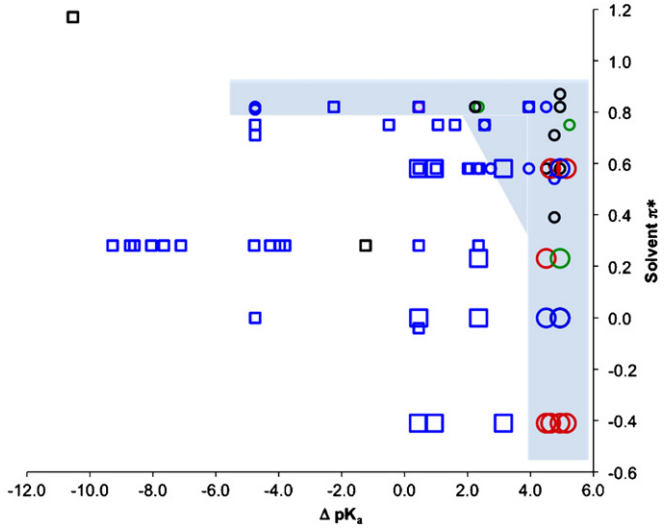

Fig. 10. A survey of complexation between N-heterocyclic bases with carboxylic acids in a variety of solvents. Squares and circles represent molecular and ionic complexes, respectively; small symbols (○,□) are literature data and large symbols (○,□) are data reported here. 1:1 complexes are shown in blue, 1:2 (base:acid) in green, and 1:3 in red. Complexes with unknown stoichiometry are shown in black. The shaded zone is where proton transfer has been observed. See the Supporting Information in the original publication [72] for the data table. $\Delta pK_a = pK_a(BH^+) - pK_a(AH)$; π^* = Kamlet – Taft dipolarity/polarizability parameter (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article).

Table 2
Fraction of solute (starting concentration 1.0 mM in $CHCl_3$) extracted into an equal volume of fluorous solvent containing 1.0 mM Krytox FSH.

Solute	Fraction extracted
2-Hydroxypyridine	0.41
3-Hydroxypyridine	0.96
4-Hydroxypyridine	0.82
2-Aminopyridine	0.98
3-Aminopyridine	0.98
4-Aminopyridine	0.99
Pyridine	0.72
Aniline	0.05
Nicotinamide	0.09
Phenol	0.01

The literature has many examples of carboxylic acid—N-heterocycle non-covalent association but very few in poor solvents. O'Neal and Weber made measurements in fluorous solvents and other weak solvents in an attempt to make an empirical generalization about ionic vs. molecular complex formation. Their data (shown as large symbols) and all the existing literature data (smaller symbols) are shown in Fig. 10 [70]. The difference in aqueous pK_a between the protonated N-heterocycle and the acid is plotted vs. the Kamlet-Taft dipolarity of the solvent. The difference in pK_as represents the relative acidity of the acid and the protonated base. When this number is positive, in an aqueous solution at any pH there would be relatively more protonated base than undissociated acid. The Kamlet-Taft dipolarity, π^*, roughly corresponds to solvent strength. It is a fair measure of solvent strength for solvents without hydrogen bond donating or accepting functional groups. This is because there are other parameters related to hydrogen bond accepting and donating ability that relate to a solvent's strength but which do not contribute to dipolarity. In Fig. 10, circles represent ionic and squares represent molecular complexes. The colors represent stoichiometry: red is 1:3, green is 1:2, blue is 1:1, and black is unreported. FC-72 is at $\pi^* \sim -0.4$. Note that the ionic complexes are found only in the shaded region. Ionic complexes form in polar solvents or where the driving force for proton transfer is high enough. The formation of 1:3 complexes is not unique to fluorous solvents but it is rare. Ionic complexes in poor solvents tend to involve more than one acid per base, supporting the idea represented by Fig. 10. As a practical matter, it is striking to note that 1 mM solutions of **4** in FC-72 can extract a significant fraction of equimolar basic solutes from an equal volume of $CHCl_3$ as shown in Table 2 [69]. Fluorous extractions of polar organic molecules with the aid of a molecular receptor are thus possible.

Recall that El Bakkari had demonstrated the extraction of pyridyl compounds with the aid of a perfluorinated dicopper complex. As the much simpler **4** extracts pyridine, it might also extract molecules with pyridyl tags. O'Neal and Weber found that not only was TPyP extracted into FC-72 through non-covalent interactions with **4** [71], but that 5,10,15,20-tetraphenylporphyrin (TPhP) was also extracted. Compound **4** transfers two protons to the TPhP tetrapyrrole ring to create the porphyrin dication (H_2TPhP^{2+}) in FC-72 while up to six protons are transferred to the TPyP pyridyl and tetrapyrrole nitrogen to create a hexavalent cation macrocycle in the fluorous phase! The total charge on TPyP is controlled by adjusting the concentration of **4** in the fluorous phase. In addition, ZnTPyP can be extracted from $CDCl_3$ with **4**/FC-72. The Zn salt of **4** extracts (from $CDCl_3$) and metalates TPyP. The reaction product,

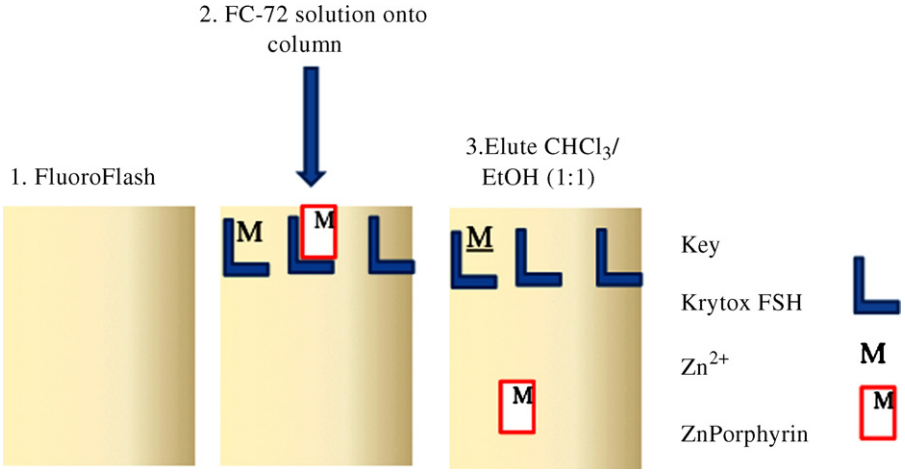

Fig. 11. Schematic diagram showing the use of FSPE to recover a product held in the fluorous phase based on H-bonding. An FC-72 solution of metalloporphyrin bound to **4**, metal ion (Zn^{2+}) bound to **4** and free **4** is introduced to an FSPE column. The solvent evaporates. Elution with an organic solvent removes the metalloporphyrin, leaving behind **4** and its metal salt.

ZnTPyP, is easily recovered from the fluorous phase using fluorous solid phase extraction (F-SPE) as shown in Fig. 11.

It is well known that metals form acetyl acetonates. Recently, Nakashima et al. [72] used the analogous 1,1,1,5,5,6,6,6-octafluoro-2,4-hexanedione, which is soluble in FC-72, to extract transition metals from aqueous and nonaqueous solvents into the fluorous phase. Nitric acid released the extracted metals.

5. Related technologies

It is noteworthy that there is a considerable amount of activity in using fluorous-modified glass to adsorb perfluoroalkyl tagged compounds for screening, binding, and synthesis [73,74]. Glass is modified with a fluoroalkyl silane, giving the glass surface a fluorous nature. Following modification, the surface will adsorb molecules with an eight-carbon perfluoroalkyl tail. The non-covalently modified surface is capable of binding complementary biomolecules. The surface is stable against multiple exposures to aqueous solvents.

Another area which in the future will overlap with analyte extractions and separations is electrowetting. Teflon AF is often used as a coating that is not 'wetted' by an aqueous (or other polar liquid) droplet in the absence of an electric field, but is wetted in the presence of an electric field. This phenomenon can be used to move droplets, creating a type of microfluidics that is distinct from the more standard channels-in-a-nonconducting-material type [75–78].

Solute distribution measurements are tedious and require significant amounts of solvent. Advances in partitioning into fluorous media will undoubtedly take advantage of newer, more efficient approaches. In particular, 96-well methods have been developed for partitioning measurements [79–83]. Chen et al. [79–81] and Vuckovic and Pawliszyn [83] measure the distribution coefficient of a solute between a polymer phase and an aqueous phase (P_{pw}) in a 96-well format with the intention of discovering or measuring solute partitioning or binding properties. For example, chiral recognition, drug/cyclodextrin binding, and drug/serum albumin binding have been quantitatively assessed with these methods. An advantage is that many repeats can be done, e.g. 8 replications of each measurement. This permits the measurement of small changes in concentration (less than 1%) in the liquid phase. Moreover, Chen et al. use micoplates, with only a few hundred microliters needed in each well. Thus, these methods require only a very small amount of material. The methods are also time and labor saving due to automation. Cudjoe and Pawliszyn have applied a similar system for the extraction of drugs from samples [82]. For purification of perfluoro-labeled compounds, a simple gravity operated fluorous SPE system based on the 96-well format is effective [84].

6. Toxicity

Fluorinated compounds can be persistent in the environment. This has led to concern. Many fluorinated compounds are nontoxic. Indeed, there are abundant biomedical applications of fluorinated compounds as blood substitutes, imaging agents for ultrasound and magnetic resonance, and many applications in drug delivery on the horizon [85–89]. Small (few thousand Dalton) perfluoroethers (Krytoxes, Fomblins) are widely used in industry and consumer products (cosmetics). On the other hand, perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are toxic at high enough concentrations [90–92]. The lifetime of perfluorotributylamine in the body is hundreds of days. Despite the fact that it is not toxic (http://www.sisweb.com/referenc/msds/fc43.pdf) it is not favored for biomedical use because the long lifetime in the body may give the opportunity for metabolic reactions to create toxic species. A pragmatic observation is that high molecular weight fluorocarbons (so-called 'heavy' fluorous compounds) are so insoluble that they are not transported readily in the environment. While there is concern, it is clear that fluorocarbons and related fluorinated compounds will continue to be used.

Acknowledgement

This work was supported by NSF Grant CHE 0615952.

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