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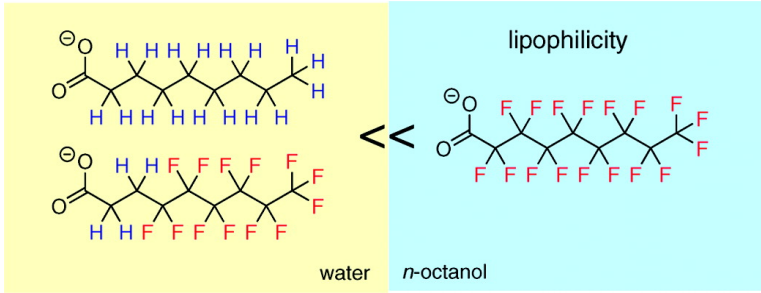

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High Lipophilicity of Perfluoroalkyl Carboxylate and Sulfonate: Implications for Their Membrane Permeability

Ping Jing, Patrick J. Rodgers, and Shigeru Amemiya*

Department of Chemistry, University of Pittsburgh, Pennsylvania 15260

Received October 8, 2008; E-mail: amemiya@pitt.edu

Abstract: Here we report on remarkably high lipophilicity of perfluoroalkyl carboxylate and sulfonate. A lipophilic nature of this emerging class of organic pollutants has been hypothesized as an origin of their bioaccumulation and toxicity. Both carboxylate and sulfonate, however, are considered hydrophilic while perfluroalkyl groups are not only hydrophobic but also oleophobic. Partition coefficients of a homologous series of perfluoroalkyl and alkyl carboxylates between water and *n*-octanol were determined as a measure of their lipophilicity by ion-transfer cyclic voltammetry. Very similar lipophilicity of perfluoroalkyl and alkyl chains with the same length is demonstrated experimentally for the first time by fragment analysis of the partition coefficients. This finding is important for pharmaceutical and biomedical applications of perfluoroalkyl compounds. Interestingly, ~2 orders of magnitude higher lipophilicity of a perfluoroalkyl carboxylate or sulfonate in comparison to its alkyl counterpart is ascribed nearly exclusively to their oxoanion groups. The higher lipophilicity originates from a strong electron-withdrawing effect of the perfluoroalkyl group on the adjacent oxoanion group, which is weakly hydrated to decrease its hydrophilicity. In fact, the inductive effect is dramatically reduced for a fluorotelomer with an ethylene spacer between perfluorohexyl and carboxylate groups, which is only as lipophilic as its alkyl counterpart, nonanoate, and is 400 times less lipophilic than perfluorononanoate. The high lipophilicity of perfluoroalkyl carboxylate and sulfonate implies that their permeation across such a thin lipophilic membrane as a bilayer lipid membrane is limited by their transfer at a membrane/water interface. The limiting permeability is lower and less dependent on their lipophilicity than the permeability controlled by their diffusion in the membrane interior as assumed in the classical solubility-diffusion model.

Introduction

Widespread accumulation of perfluoroalkyl acids such as perfluoroalkyl carboxylic and sulfonic acids in wildlife and humans is an emerging environmental problem worldwide.[1] These synthetic acids with a perfluorinated alkyl group are chemically stable, resistive to biodegradation, and persistent in the environment.[2] More recently, their adverse health effects such as developmental toxicity, immunotoxicity, hepatotoxicity, and carcinogenicity were reported.[3] The bioaccumulation and toxicity of the perfluoroalkyl acids suggest their high lipophilicity. In fact, perfluorooctyl carboxylic and sulfonic acids were detected in umbilical cord blood and brain, indicating that they are lipophilic enough to cross the placental and blood−brain barriers, respectively.[4] Recent in vitro toxicology studies also show that the perfluoroalkyl acids not only interact with cell membranes but also cross the membranes to inhibit intracellular events, cause oxidative stress, and induce apoptosis.[5] Lipophilicity of perfluoroalkyl acids, however, is not well understood. On one hand, these acids are dissociated under most aqueous environments to carry a net negative charge to enhance their hydrophilicity.[6] This strong acidity is due to an electron-withdrawing effect of the perfluoroalkyl group on the adjacent acid group. On the other hand, a perfluoroalkyl group is considered not only hydrophobic, but also oleophobic.[7] More quantitative understanding of the lipophilicity of perfluoroalkyl groups is significant beyond environmental sciences because perfluoroalkyl compounds have found a wide range of applications as drugs,[8] vehicles for drug and oxygen delivery,[9] and tags for high-throughput synthesis, separation, and identification of biological and organic molecules based on their two-phase partitioning.[7,10]

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Lipophilicity of an organic molecule is a key physicochemical property for assessment of its environmental and human-health risks[11] as well as for its pharmaceutical and biomedical applications.[8,9,12] A more lipophilic molecule is more permeable across a biological membrane as governed qualitatively by the so-called Overton rule.[13] Quantitatively, the solubility-diffusion model relates a membrane permeability, P_m, of a molecule to its partition coefficient, P, between the aqueous and membrane phases as a measure of its lipophilicity, thereby yielding[13]

$$P_m = \frac{D_m P}{d} \quad (1)$$

where the partition coefficient represents the membrane concentration of the molecule with respect to its aqueous concentration, D_m is the diffusion coefficient of the molecule in the membrane, and d is the membrane thickness. In practice, a partition coefficient of an electrically neutral molecule is measured experimentally by using water and a water-immiscible organic solvent,[14] most typically *n*-octanol,[15] as a model of a bilayer lipid membrane (BLM). So far, partition coefficients of perfluoroalkyl carboxylic acids between *n*-octanol and water have been estimated empirically and theoretically without experimental assessment.[16] No partition coefficient of a perfluoroalkyl carboxylate or sulfonate has been reported although perfluorooctyl carboxylate and sulfonate partition favorably from water into an organic solvent. The perfluorooctyl oxoanions can be extracted from biological matrices into methyl *tert*-butyl ether as tetrabutylammonium salts for subsequent mass spectrometric detection.[17] Selective partition of the perfluorooctyl species against chloride from water into lipophilic polymer membranes or a fluorous solvent was also demonstrated by potentiometry.[18]

Partition coefficients of nonfluorinated alkyl oxoanions between water and various organic solvents[19] including *n*-octanol[19k] were measured by ion-transfer voltammetry. With this approach, an external potential is applied to a liquid/liquid interface to drive interfacial transfer of an ion, which is monitored as a flow of an ionic current. In contrast to a neutral molecule, a partition coefficient of an ion depends on the Galvani potential difference between the aqueous and organic phases, $\Delta_w^o\phi$, as given by[20]

$$\log P = -\frac{z_i F(\Delta_w^o\phi - \Delta_w^o\phi^{0\prime})}{2.303RT} \quad (2)$$

1. $CF_3(CF_2)_{n-2}CO_2^-$ $(n = 4–10)$

2. $CH_3(CH_2)_{n-2}CO_2^-$ $(n = 7–12$

3. $CF_3(CF_2)_7SO_3^-$

4. $CH_3(CH_2)_7SO_3^-$

5. $CF_3(CF_2)_5(CH_2)_2CO_2^-$

Figure 1. Molecular formula of oxoanionic surfactants studied in this work.

where z_i is the charge of the ion, and $\Delta_w^o\phi^{0\prime}$ is a formal ion-transfer potential as measured voltammetrically. This potential-dependence of ion partition was considered in recent models for ion permeation across a lipophilic liquid membrane sandwiched between two aqueous electrolyte solutions by Kihara and co-workers[21] and others,[22] thereby extending the original solubility-diffusion model. It is assumed in both original and new models that overall ion permeability of a membrane is limited by ion translocation in the interior of the membrane rather than by ion transfer at the membrane/water interface while Murtomäki and co-workers considered kinetic effects of interfacial ion transfer on membrane permeability.[22d]

Here we report on remarkably higher lipophilicity of perfluoroalkyl carboxylate and sulfonate in comparison to their alkyl counterparts. Partition coefficients of various carboxylates and sulfonates with a fully-, non-, or partially fluorinated alkyl chain (Figure 1) between *n*-octanol and water are determined systematically by ion-transfer cyclic voltammetry to identify a main origin of 2 orders of magnitude different lipophilicities of perfluoroalkyl and alkyl oxoanions with the same chain length. Also, this study is the first to experimentally quantify lipophilicity of perfluoroalkyl chains with different lengths, which is required for estimating lipophilicity of perfluoroalkyl compounds with environmental, biomedical, or pharmaceutical importance. In addition, kinetic parameters as obtained from a transient cyclic voltammogram at micrometer-sized interfaces[23]

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enabled us to model permeability of a lipophilic membrane to the perfluoroalkyl oxoanions without the constraint of rapid partition equilibrium at the membrane/water interface.

Experimental Section

Chemicals. All perfluoroalkyl and alkyl carboxylic acids, sodium octyl sulfonate, tetradodecylammonium (TDDA) bromide, sodium tetraphenylborate (TPB), tetraphenylarsonium (TPA) chloride, and *n*-octanol (>99%) were obtained from Aldrich (Milwaukee, WI). Potassium perfluorooctyl sulfonate was obtained from Synquest Laboratories (Alachua, FL). Potassium tetrakis(pentafluorophenyl)borate (TFAB) was from Boulder Scientific Company (Mead, CO). All reagents were used as received. Preparation of various salts employed for electrochemical measurements is described in Supporting Information. All aqueous solutions were prepared with 18.3 MΩ cm^{-1} deionized water (Nanopure, Barnstead, Dubuque, IA).

Electrochemical Measurements. A computer-controlled CHI 660B electrochemical workstation equipped with CHI 200 picoampere booster and Faraday cage (CH Instruments, Austin, TX) was used for CV measurements with the following electrochemical cell:

Ag | AgCl | 3 M NaCl || 1 mM $MgSO_4$ in water || 10 μM carboxylate or sulfonate **1**−**5** and 1 mM $MgSO_4$ in water | 40 mM TDDATFAB in *n*-octanol | Ag

An Ohmic potential drop in the *n*-octanol phase was maintained negligibly low in the presence of TDDATFAB as an organic supporting electrolyte, which is highly soluble in *n*-octanol in contrast to other organic supporting electrolyte salts.[19k,24] A $Mg(OH)_2$ solution was used to adjust the aqueous pH at 6−7 so that the carboxylates and sulfonates are present as monoanions in either *n*-octanol or water phase.[19d]

A micrometer-sized interface was formed at the tip of a glass micropipet filled with a *n*-octanol solution.[25] An inner-wall silanized micropipet was fabricated and characterized as reported elsewhere.[23] The inner diameters of the tips were 3.5−10 μm while the outer diameter was 1.3 times larger than the inner diameter. Estimated tip inner angles were 3−6° while an outer tip angle was 12°. A double junction Ag/AgCl electrode (BASi, West Lafayette, IN) was used as a reference/counter electrode. The potential of the *n*-octanol phase with respect to the aqueous phase was calibrated by employing tetrabutylammonium as a reference ion and defined on the basis of the nonthermodynamic hypothesis, i.e., TPA-TPB assumption (see Supporting Information).[20,26] A current carried by a negative charge from the aqueous phase to the organic phase was defined to be negative. Supplemental thermodynamic data were obtained by potentiometry (see Supporting Information), which is less limited by a narrow potential window at the *n*-octanol/water interface and a high resistance of a *n*-octanol solution with a low supporting electrolyte concentration. All electrochemical experiments were performed at 22 ± 3 °C.

Results and Discussion

Lipophilicity of Perfluoroalkyl and Alkyl Oxoanions. Lipophilicity of oxoanions **1**−**5** with various chains (Figure 1) was investigated by employing cyclic voltammetry at *n*-octanol/water microinterfaces formed at the tip of a glass micropipet electrode.[25] During a potential cycle, an oxoanionic surfactant, which was initially present only in the outer aqueous phase, was transferred across the interface between the two bulk liquid phases. The simple transfer of an ion, i^{z_i}, is defined as

$$i^{z_i}\,(\text{outer aqueous phase}) \rightleftharpoons i^{z_i}\,(\text{inner } n\text{-octanol phase}) \quad (3)$$

All surfactants **1**−**5** give well-defined CVs without a voltammetric feature of their adsorption or emulsification or instability of the interfaces.[19g,i,27] In a typical CV as obtained with perfluorohexanoate (Figure 2A), a sigmoidal anodic wave corresponds to ingress transfer of the carboxylate coupled with its nonlinear diffusion from the outer aqueous phase to the micrometer-sized interface. The transfer of the carboxylate into the bulk *n*-octanol phase was confirmed by the broad cathodic peak, indicating transient diffusion of the carboxylate from the inner *n*-octanol phase to the interface. A CV with a similar feature was also obtained with nonanoate, which requires more positive potentials (Figure 2B). This result indicates that nonanoate with a longer chain is less lipophilic than perfluorohexanoate.

Partition coefficients of surfactants **1**−**5** between aqueous and *n*-octanol phases were determined by numerical analysis of their CVs. Figures 2A and 2B exemplify that experimental CVs fit very well with quasi-reversible CVs simulated for simple, one-step ion transfer (eq 3; see Supporting Information).[23] A value of $\Delta^{\circ}_{w}\phi^{0'}$ for an oxoanion thus obtained from a CV corresponds to its formal partition coefficient, $P^{0'}$, as given by[28]

$$\log P^{0'} = \frac{z_i F \Delta^{\circ}_{w}\phi^{0'}}{2.303RT} \quad (4)$$

where $\Delta^{\circ}_{w}\phi^{0'}$ is standardized on the basis of the nonthermodynamic TPA-TPB assumption (see Supporting Information).[20,26] The values of $\Delta^{\circ}_{w}\phi^{0'} = -41 \pm 6$ and -4 ± 4 mV for perfluorohexanoate and nonanoate, respectively, in Figure 2 correspond to the values of log $P^{0'} = 0.7 \pm 0.1$ and 0.07 ± 0.07, respectively, in eq 4, indicating that perfluorohexanoate is 4 times more lipophilic than nonanoate. A ∼100 mV anodic shift of a half-wave potential with respect to $\Delta^{\circ}_{w}\phi^{0'}$ (Figure 2) is mainly due to asymmetric diffusion in the inner and outer solutions at a micropipet electrode, which contrasts to conventional steady-state voltammetry at a solid ultramicroelectrode.[23] Diffusion of the carboxylates is more efficient in the outer aqueous phase than in the inner *n*-octanol phase, which is not only more viscous (see Supporting Information) but also surrounded by the pipet wall. The anodic shift is partially due to a kinetic limitation in the CVs, which significantly deviate from a nernstian behavior (Figure 2).

Higher lipophilicity of perfluoroalkyl carboxylates **1** in comparison to alkyl carboxylates **2** was systematically confirmed by using log $P^{0'}$ (Figure 3). Plots of log $P^{0'}$ versus the number of carbon atoms, *n*, demonstrate that a perfluoroalkyl carboxylate is ∼2 orders of magnitude more lipophilic than the alkyl carboxylate with the same value of *n*. The higher lipophilicity of perfluoroalkyl carboxylates is remarkable. A perfluoroalkyl carboxylate with a net negative charge is only ∼15 times less lipophilic than the electrically neutral, alkyl carboxylic acid with the same carbon number[29] ($n = 4-10$ in Figure 3), which is $\sim 2.5 \times 10^3$ times more lipophilic than the corresponding alkyl

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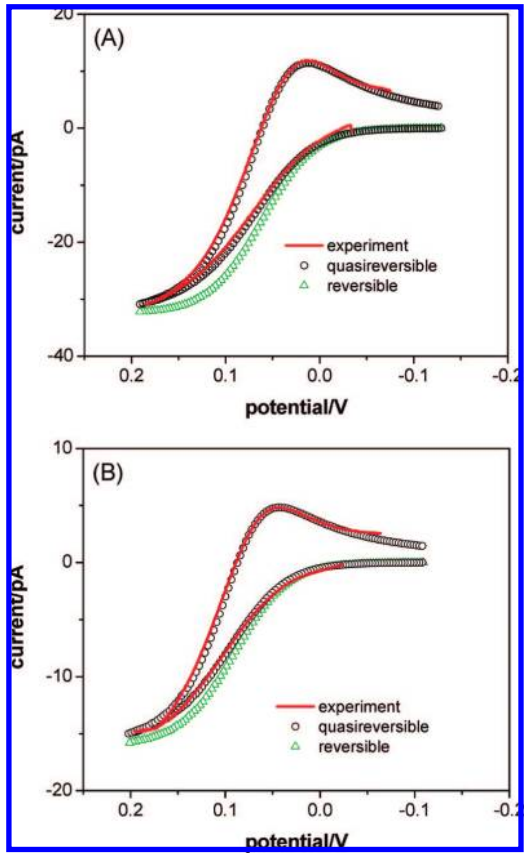

Figure 2. Background-subtracted CVs of (A) perfluorohexanoate and (B) nonanoate at *n*-octanol/water microinterfaces formed at the tip of glass micropipets with diameters of 10 and 6.8 μm, respectively.

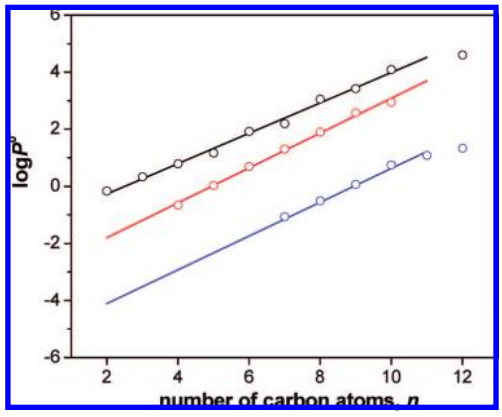

Figure 3. Plots of the formal partition coefficient, $P^{0'}$, versus the number of carbon atoms for perfluoroalkyl carboxylates **1** (red circles), alkyl carboxylates **2** (blue circles), and alkyl carboxylic acids (black circles). The value of $P^{0'}$ for perfluorodecanoate was determined by potentiometry (see Supporting Information). The values of $P^{0'}$ for the acids correspond to partition coefficients reported in the literature.[29] The solid lines represent eq 5.

carboxylate ($n = 7-12$). Moreover, perfluorodecanoate (log $P^{0'} = 2.9 \pm 0.1$) is as lipophilic as TPB (log $P^{0'} = 2.89 \pm 0.07$), where the central ionic entity is effectively shielded by the four phenyl groups. Importantly, the larger $P^{0'}$ for perfluoroalkyl carboxylates in comparison to alkyl carboxylates is not due to stronger ion pairing of the perfluoroalkyl carboxylates with the bulky organic cation, TDDA, in the *n*-octanol phase. A difference in log $P^{0'}$ for perfluoroalkyl and alkyl carboxylates is independent of the concentration of the organic cation as demonstrated by potentiometry (see Supporting Information).

Perfluorooctyl sulfonate **3**, which is another major environmental contaminant, is also ~2 orders of magnitude more lipophilic than octyl sulfonate **4**. CVs of the respective sulfonates with an octyl group give log $P^{0'} = 2.45 \pm 0.08$ and 0.6 ± 0.1. Perfluorooctyl sulfonate is nearly as lipophilic as perfluorononanoate with the same perfluorooctyl group (log $P^{0'} = 2.57 \pm 0.07$) while octyl sulfonate is three times more lipophilic than nonanoate. The latter result is consistent with the previous observation that an alkyl sulfonate with a larger ionic radius is more lipophilic than the carboxylate with the same alkyl group at water/1,2-dichloroethane or nitrobenzene interfaces.[19a]

The Origin of Higher Lipophilicity of Perfluoroalkyl Oxoanions. The higher lipophilicity of perfluoroalkyl carboxylates in comparison to the corresponding alkyl carboxylates was assessed by using a fragment method[15] to identify its origin. A plot of log $P^{0'}$ versus n is linear for perfluoroalkyl or alkyl carboxylates or alkyl carboxylic acids[30] except dodecanoate and dodecanoic acid[19h] (Figure 3), thereby yielding

$$\log P^{0'} = (n-2)f(\mathrm{CX_2}) + f(\mathrm{CX_3}) + f(\mathrm{COY}) \qquad (5)$$

where f is a fragmental contribution of each unit to the total log $P^{0'}$, X = H or F, and Y = O^- or OH. The slope of the linear plots corresponds to $f(CX_2)$ while the sum of $f(CX_3)$ and f(COY) is equivalent to log $P^{0'}$ extrapolated to $n = 2$. This analysis clearly demonstrates that the ~2 orders of magnitude higher lipophilicity of perfluoroalkyl carboxylates is ascribed to the difference between $f(CF_3) + f(COO^-)$ and $f(CH_3) + f(COO^-)$, which are equal to -1.9 and -4.1, respectively. On the other hand, a perfluoroalkyl chain is as lipophilic as the alkyl chain with the same length. A value of $f(CF_2) = 0.61$ is very close to values of $f(CH_2) = 0.59$ and 0.53 as obtained for alkyl carboxylates and carboxylic acids, respectively. This result suggests that $f(CF_3)$ and $f(CH_3)$ are also very similar, which is confirmed in the following. Overall, the different lipophilicities of perfluoroalkyl and alkyl carboxylates are mainly ascribed to the carboxylate groups.

We hypothesize that the higher lipophilicity of a carboxylate group attached to a perfluoroalkyl group is due to a strong electron-withdrawing effect of the perfluoroalkyl group on the oxoanion group. The oxoanion group with a reduced net negative charge is weakly hydrated to be partitioned favorably into a lipophilic *n*-octanol phase although water-saturated *n*-octanol contains a large mole fraction of water.[15] To test this hypothesis, we examined lipophilicity of fluorotelomer **5**. The ethylene spacer between the perfluorohexyl and carboxylate groups dramatically reduces the electron-withdrawing effect on acidity of perfluorohexanoic acid to raise pK_a by 2.32 units in 50% aqueous ethanol although a hexyl spacer is required for further increasing pK_a by 1.14 units to eliminate this inductive effect.[30] In fact, our hypothesis was confirmed by much lower lipophilicity of fluorotelomer **5** (log $P^{0'} = -0.05 \pm 0.07$), which is 4.0×10^2 times lower than perfluorononanoate with the same number of carbon atoms. Moreover, the value of log $P^{0'}$ for fluorotelomer **5** is nearly identical to the value for nonanoate. Apparently, the substitution of hydrogen atoms with fluorine atoms in an alkyl group does not affect lipophilicity of the alkyl group. Thus, the different lipophilicities of perfluorooctyl and octyl sulfonates are also ascribed to the sulfonate groups.

Lipophilicity of Perfluoroalkyl Chains. This work is the first to systematically determine an experimental $f(CF_2)$ value

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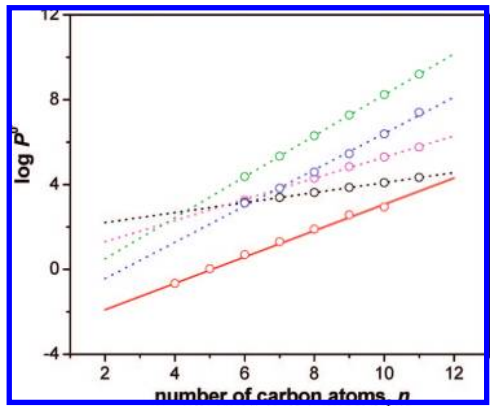

Figure 4. Plots of the formal partition coefficient, $P^{0\prime}$, versus the number of carbon atoms for perfluoroalkyl carboxylate **1** (red circles), and perfluoroalkyl carboxylic acids. The values of $P^{0\prime}$ for the acids correspond to partition coefficients estimated empirically by U.S. EPA's EPI suite and ClogP (green and black circles, respectively) and theoretically by COSMOtherm C2.1 and SPARC (purple and blue circles, respectively).[16] The solid lines represent eq 5.

between *n*-octanol and water phases. This unique opportunity is given by the carboxylate group, which not only solubilizes relatively long perfluoroalkyl chains in water but also serves as a probe to monitor their partitioning processes by ion-transfer voltammetry.

Our value of $f(CF_2) = 0.61$ is equivalent to a difference in free energy of −0.83 kcal/mol, which is close to the free energy of transfer of a CF_2 group from water to a micelle environment[31] or sediments[32] (−0.95 and −0.75 kcal/mol, respectively). We also compare our value of $f(CF_2)$ with the values that are estimated empirically or theoretically for perfluoroalkyl carboxylic acids between *n*-octanol and water. Figure 4 shows logarithmic plots of empirical and theoretical partition coefficients[16] versus *n* together with the corresponding plot for perfluoroalkyl carboxylates as obtained experimentally in this work. Our value is relatively close to a value of $f(CF_2) = 0.50$ as calculated with COSMOtherm C2.1 based on density functional quantum calculation while a larger value of 0.80 was obtained using the SPARC solvation model. Two common programs based on empirical fragment methods, i.e., the U.S. EPA's EPI suite and ClogP, give much larger or smaller values of 0.90, and 0.20, respectively. This result casts doubt on reliability of the original partition coefficients used in these programs. Moreover, a negative $f(CF_2)$ value of −0.097 has been reported for calculation of drug lipophlicity,[12] indicating significance of our experimental assessment of the fragmental partition coefficient.

It should be noted that the similar lipophilicity of perfluoroalkyl and alkyl chains results from the convolution of their different properties. A C−F bond is much more polar than a C−H bond, while a trifluoromethyl group is at least as isosteric as an isopropyl group.[33] Also, a perfluoroalkyl chain is harder and less flexible and changes from a linear to a helical structure as chain length increases.[34]

Permeability of a Thin Lipophilic Membrane to Perfluoroalkyl Oxoanions. A noticeable finding in this work is the very high lipophilicity of oxoanion groups of the perfluoroalkyl surfactants. The high lipophilicity is important in permeation of the perfluoroalkyl oxoanions across a BLM with a lipophilic inner environment. Permeability of such thin lipophilic membranes to the perfluoroalkyl oxoanions was assessed by considering a thin *n*-octanol layer sandwiched between two aqueous phases as a model of a BLM (Figure 5).[21,22] For simplification, identical and constant potentials at both *n*-octanol/water interfaces, $\Delta_w^o\phi$, were assumed, thereby resulting in no potential difference between the two aqueous phases. Heterogeneous rate constants, k_f and k_b, are defined for the forward and backward transfers of an ion at the *n*-octanol/water interfaces (eq 3) by employing a Butler−Volmer-type model as[20,23a,35]

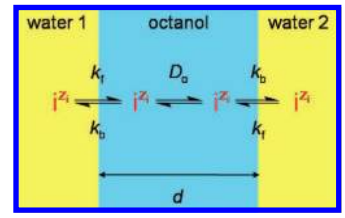

Figure 5. Scheme of a thin *n*-octanol layer sandwiched between two aqueous electrolyte solutions.

$$k_f = k^0 P^{\alpha} \tag{6}$$

$$k_b = k^0 P^{\alpha-1} \tag{7}$$

where k^0 is the standard ion-transfer rate constant, and α is the transfer coefficient. These kinetic parameters as well as diffusion coefficients in *n*-octanol, D_o, were obtained from CVs of perfluoroalkyl and alkyl oxoanions at *n*-octanol/water microinterfaces (Table S1, Supporting Information).

Permeability of this symmetric membrane is given by (see Supporting Information)

$$P_m = \frac{k_f}{2 + k_b d/D_o} \tag{8}$$

Equation 8 indicates that as a membrane becomes thinner, its permeability increases toward a limiting value as given by

$$P_m^{lim} = \frac{k^0 P^{\alpha}}{2} \tag{9}$$

This limiting permeability is independent of a membrane thickness and is equivalent to $k_f/2$. This result indicates that permeability of such a thin membrane is limited by interfacial ion transfer rather than by ion diffusion in the interior of the membrane as assumed in the solubility-diffusion model (eq 1). Eq 8 is equivalent to eq 1 only when a membrane is thick enough to satisfy $2 \ll k_b d/D_o$.

Equation 8 predicts that membrane permeability to a more lipophilic ion is more amenable to the interfacial transfer control. For instance, the interfacial control is dominant at a thicker membrane for a more lipophilic anion with negative $\Delta_w^o\phi^{0\prime}$, where smaller k_b results in $k_b d/D_o \ll 2$ in eq 8 even at positive potentials. In other words, a more lipophilic ion, which is more favorably transferred into a lipophilic membrane, prefers staying in the membrane to being transferred from the membrane phase to the aqueous phase, thereby reaching the interfacial transfer

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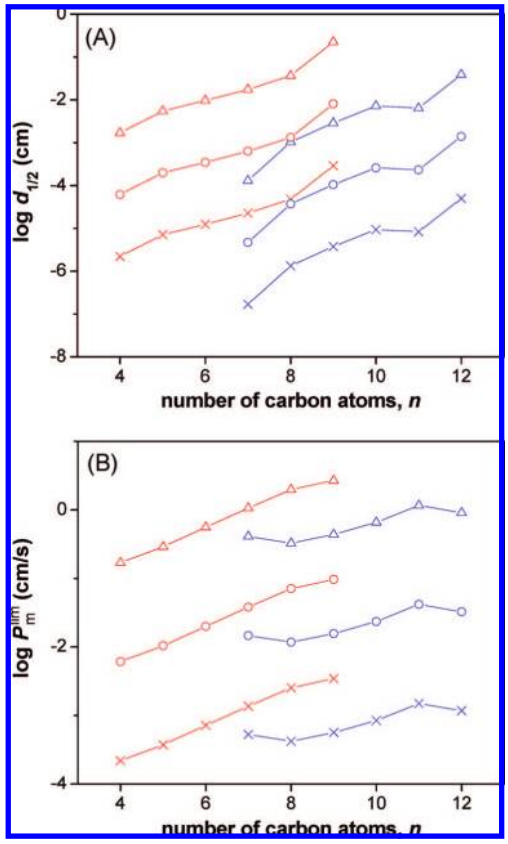

Figure 6. (A) The characteristic membrane thickness, $d_{1/2}$ (eq 10), and (B) limiting permeability, P_m^{lim} (eq 9), as calculated for perfluoroalkyl carboxylates **1** (red symbols and lines) and alkyl carboxylates **2** (blue symbols and lines) at $\Delta_w^o\phi = 171$, 0, and -171 mV (triangles, circles, and crosses, respectively).

control. This prediction was quantitatively evaluated by using a characteristic membrane thickness, $d_{1/2}$, as given by

$$d_{1/2} = \frac{2D_o}{k^0 P^{\alpha-1}} \tag{10}$$

A membrane with this thickness gives a half of the limiting permeability, P_m^{lim} (see eq 8). The characteristic membrane thickness calculated using parameters obtained from CVs is larger for a perfluoroalkyl carboxylate than for the alkyl carboxylate with the same chain length (Figure 6A), corresponding to different lipophilicities. The calculated thickness strongly depends on the interfacial potential, $\Delta_w^o\phi$, as shown in the range between -171 and $+171$ mV, which are equal to $\Delta_w^o\phi^{0\prime}$ for TPB and TPA, respectively. Moreover, eq 10 indicates that an ion with larger k^0 requires a thinner membrane for limiting permeability. The values of $k^0 = 0.1-0.01$ cm/s as obtained for carboxylates **1** and **2** are relatively large although larger k^0 values of $\sim$1 cm/s[35b,c] have been reported for facilitated transfer of alkaline cations at 1,2-dichloroethane/water interfaces. Nevertheless, the characteristic membrane thickness as obtained in the potential range of $\pm$171 mV predicts that a micrometer- or nanometer-thick *n*-octanol membrane is thin enough to give in the limiting permeability to the perfluoroalkyl carboxylates with high lipophilicity.

An important prediction of eq 9 is the weak dependence of limiting permeability on ion lipophilicity. With $\alpha = 0.5$ in eq 9, the permeability under interfacial transfer control depends only on the square root of a partition coefficient in contrast to the direct proportionality under membrane diffusion control (eq 1). The limiting permeability calculated using eq 9 with experimentally determined parameters confirms the weaker lipophilicity dependence (Figure 6B). The limiting permeability at $\Delta_w^o\phi = 0$ mV varies only from 0.006 to 0.1 cm/s for all perfluoroalkyl and alkyl carboxylates while their $P^{0\prime}$ values vary by 4 orders of magnitude. In contrast, diffusion-controlled permeability (eq 1) depends on ion lipophilicity much more strongly and subsequently varies in a wider range by 4 orders of magnitude (Figure S3, Supporting Information).

An application of eqs 8 and 9 to a BLM implies that permeability of this ultrathin lipophilic membrane to a highly lipophilic perfluoroalkyl oxoanion is limited by its interfacial transfer. In fact, this implication is supported by a classical model that was proposed to explain experimental permeability of a BLM to highly lipophilic ions such as tetraphenyl borate,[36] which is as lipophilic as perfluorodecanoate. Ion diffusion in the membrane interior was not considered in this model, where the transfer of an ion adsorbed just inside the membrane/water interface into the membrane interior limits membrane permeability to the rates given by equations that are equivalent to eqs 6 and 7 for k_f and k_b.

It should be noted that, in addition to their high lipophilicity, an ionic nature of perfluoroalkyl oxoanions render them advantageous as a probe to investigate whether their membrane transport is controlled by interfacial transfer (eq 9) or membrane diffusion (eq 1). These two mechanisms demonstrate different dependences of ion permeability on the interfacial potential, which can be modulated by externally applying a membrane potential or chemically depolarizing the membrane. Such a discrimination of the two permeation mechanisms based on their potential dependences is not feasible with an electrically neutral probe molecule although the permeability of a BLM to neutral molecules deviate from the solubility-diffusion model as demonstrated experimentally for a homologous series of alkyl carboxylic acids[13b] and also suggested theoretically using partition parameters for various nonelectrolytes between *n*-octanol and water phases.[37]

Conclusions

Our finding of the remarkably high lipophilicity of perfluoroalkyl carboxylate and sulfonate is significant. This finding quantitatively supports the hypothesis that bioaccumulation and toxicity of these perfluoroalkyl surfactants originate from their lipophilic nature. Interestingly, we found that the high lipophilicity is due not to a perfluoroalkyl group itself but to its electron-withdrawing effect on the adjacent oxoanion group. Understanding of this finding at a molecular level requires more studies about the structure of the oxoanion groups and their interactions with lipophilic and aqueous environments while such studies have been focused on the perfluoroalkyl group.[34]

Ionic nature and high lipophilicity of perfluoroalkyl oxoanions are advantageous to experimentally address the long-standing question: how does permeability of a BLM depend on the lipophilicity of a permeating species? Membrane diffusion versus interfacial transfer control in permeation of a perfluoroalkyl oxoanion across a BLM will be distinguishable by studying potential dependence of its permeability. Such a study will be facilitated by using a highly stable BLM formed at the tip opening of a nanopore electrode, thereby yielding a surpris-

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ingly large breakdown voltage of 800 mV.[38] Greater understanding of a lipophilicity−permeability relationship of ions at BLMs will be significant for environmental, pharmaceutical, and biomedical sciences.

This work exemplifies powerfulness of voltammetric approaches that were recently reinforced for the study of ion transfer at liquid/liquid interfaces. Transient cyclic voltammetry at a micropipet electrode provides a more comprehensive set of parameters for ion transfer at liquid/liquid interfaces in comparison to steady-state voltammetry.[23] Importantly, both thermodynamic and kinetic parameters are necessary to comprehensively model the permeability of a lipophilic liquid membrane as demonstrated in this work and also by Murtomäki et al.[22d] Moreover, the high lipophilicity of perfluoroalkyl oxoanions will enable sensitive and selective detection of these environmentally important analytes by employing ion-transfer stripping voltammetry with a thin lipophilic polymer membrane.[39]

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Supporting Information Available: Details of electrolyte preparation, CV simulations, parameters determined by cyclic voltammetry and potentiometry, derivation of eq 8, and numerical evaluations of eq 1. These materials are available free of charge via the Internet at http://pubs.acs.org.

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