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Mixing behavior of 10-(perfluorohexyl)-decanol and DPPC

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Abstract

Fluorocarbon alcohol such as 10-(perfluorohexyl)-decanol are of interest for novel pulmonary drug delivery approaches. The purpose of this study was to investigate the mixing behavior of 10-(perfluorohexyl)-decanol with dipalmitoylphosphatidylcholine (DPPC), the major component of lung surfactant, as an aid in assessing usefulness for this and other biomedical applications. The impact of 10-(perfluorohexyl)-decanol on the phase transitions of DPPC bilayers fully hydrated with a 0.15 M sodium chloride solution were studied using differential scanning calorimetry (DSC). No peak corresponding to excess alcohol was observed. The fluorinated alcohol caused DPPC peak broadening, especially below $X_{\text{DPPC}} < 0.95$, and elimination of the pretransition of DPPC at $X_{\text{DPPC}} \sim 0.91$. The onset of the main phase transition remains constant down to $X_{\text{DPPC}} \sim 0.91$, suggesting limited miscibility in the gel phase. Hydration of the 10-(perfluorohexyl)-decanol-DPPC mixtures with calcium chloride (2 mM) in place of sodium chloride did not alter the macroscopic phase behavior. In addition to the thermal properties, the miscibility of 10-(perfluorohexyl)-decanol in DPPC in monolayers at the air water interface was investigated on water, sodium chloride (0.15 M), calcium chloride (2 mM) or hydrochloric acid (pH=1.9) subphases. The concentration dependence of the onset pressure of the liquid-expanded to liquid condensed phase transition of DPPC showed a slight change with increasing mole fraction on all four subphases. The surface area-mole fraction diagrams of 10-(perfluorohexyl)-decanol and DPPC on water, sodium chloride and calcium chloride showed near ideal behavior with slight negative deviations at higher surface pressure. A more significant negative deviation was observed for the hydrochloric acid subphase. Overall, both the DSC and the monolayer studies suggest that 10-(perfluorohexyl)-decanol and DPPC are partially miscible in biological mono- and bilayers. The macroscopic phase behavior 10-(perfluorohexyl)-decanol-DPPC system is significantly different from the analogous hydrocarbon system, which is attributed to a less favorable packing of the partially fluorinated hydrophobic tails in the mono- and bilayer.

Keywords

Differential scanning calorimetry; liposomes; Langmuir monolayer; air-water interface; fluorinated alcohol

1. Introduction

Fluorine is the most electronegative of the elements and, as a result, the replacement of a hydrogen atom with fluorine in an organic molecule alters its properties significantly. The fluorine-carbon bond is very strong, but intramolecular interactions of fluorocarbons are weak. This dichotomy results in an exceptional combination of properties of fluorocarbons, such as

thermal, chemical and biological inertness, low solubility in water as well as polar and non-polar organic solvents, and high density, fluidity, compressibility and dielectric constants. Available toxicological data suggest that most fluorinated compounds show only little or no toxicity. Because of these chemical and biological properties there is growing interest in partially fluorinated amphiphiles for pharmaceutical and medical applications [1-3] as well as for fluorinated prodrugs for pulmonary drug delivery [4,5].

A significant number of fluorinated compounds are under investigation for pulmonary administration [4-7]. A better understanding of the physicochemical properties of these compounds at interfaces, i.e. the air-water interface, is needed to fully assess their usefulness and to assist in the design of compounds for novel pulmonary drug delivery approaches [4,5]. Partially fluorinated alcohols with the general structure $F_nC_{2n+1}(CH_2)_mOH$ are valuable starting materials for many fluorinated amphiphiles [6,7] and prodrugs [4,5] for biomedical applications. One compound of particular interest is 10-(perfluorohexyl)-decanol (Figure 1) [8]. This terminally fluorinated alcohol is an analog of hexadecanol, a detergent alcohol that is an important component of formulations such as Exosurf® used for pulmonary surfactant replacement therapy. The behavior of hexadecanol and its mixtures with other amphiphiles, for example phospholipids, have been studied extensively at interfaces [9-12]. A comparison of the mixing behavior of a 10-(perfluorohexyl)-decanol-lipid system with the corresponding hexadecanol-lipid system is, therefore, expected to provide additional insight in how introducing a perfluorinated tail into an alkyl alcohol alters interactions with biological structures such as lipid mono- and bilayer.

Towards this goal this study employs a combination of monolayer and DSC studies to gain a better insight into the interaction of 10-(perfluorohexyl)-decanol and dipalmitoylphosphatidylcholine (DPPC), an important biological phospholipid and the major component of pulmonary surfactant. DSC is a straightforward tool to investigate the effect of increasing incorporation of organic compounds, e.g. 10-(perfluorohexyl)-decanol, in organic bilayers [13,14]. This technique allows the study of the effect of a compound dispersed in a model membrane on the main transition characteristic for fully hydrated phospholipids [15, 16]. Changes in the onset of the so-called pretransition of phosphatidylcholines are another sensitive way to assess the interaction of an organic compound with a model lipid bilayer of phospholipids. Monolayer studies using DPPC at the air-water interface were chosen as a model of the pulmonary surfactant. This method allows the direct investigation of the miscibility of DPPC-fluorinated alcohol mixtures at the air-water interface. Overall, the combination of these two different approaches will further our understanding of interactions of DPPC and fluorinated alcohols and, thus, contribute to the rational design of compounds for pulmonary administration.

2. Experimental

2.1. Chemicals

10-(Perfluorohexyl)-decanol was synthesized by free radical coupling of perfluorohexyliodide and 9-decenoic acid methyl ester [17-19]. Its characterization and purity has been described previously [8]. Dipalmitoylphosphatidylcholine (DPPC) was obtained from Avanti Polar Lipids (Alabaster, Alabama, U.S.A.) in >99% purity and used without further purification. All solvents and chemicals were of HPLC or ACS grade purity and were purchased from Fisher Scientific (Pittsburgh, Pennsylvania, U.S.A.) or VWR (West Chester, Pennsylvania, U.S.A.). Deionized water for the DSC experiments was obtained from a PURELAB Plus water system and had a resistance ≥ 18 meg Ω [13,14] whereas deionized water for the monolayer studies was distilled first from basic potassium permanganate followed by distillation from sulfuric acid [13,14,20].

2.2. Differential scanning calorimetry experiments

DPPC and 10-(perfluorohexyl)-decanol were dissolved in chloroform – methanol (3:1, v/v) at the appropriate mole fractions [21]. The solvent was removed under a stream of nitrogen, and the mixtures were further dried under vacuum for at least 3 hours. The samples (a mixture of phospholipid and 10-(perfluorohexyl)-decanol or pure phospholipid) were hydrated in an excess of water, sodium chloride (0.15 M) or calcium chloride (2 mM) (three times by weight). Samples were heated above the lipid transition temperature of DPPC for 5 minutes and vortexed for 2 minutes. This process was repeated eight times and the hydrated samples were stored at 4°. Hydration of samples was always carried out the day before collecting the DSC scans.

A Thermal Analysis 2920 differential scanning instrument was used for the DSC studies. The hydrated samples were weighed into DSC aluminum pans. The DSC cell and the refrigerated cooling system were purged with 60 mL/min and 120 mL/min of dry nitrogen, respectively. Samples were cooled to 4°C at a heating rate of 10°C/min and then heated from 4°C to 80°C with a heating rate of 5°C/min [13,14,21,22]. All samples were subjected to two subsequent heating cycles. All experiments were carried out in triplicates. Onset, maximum and offset temperatures, as well as peak width of the pre-transition and the main phase transition, were determined for the second DSC run using the Universal Analysis NT software [8,13,14,23].

2.3. Monolayer studies at the air-water interface

All monolayer experiments were carried out as described previously using a rectangular Teflon trough (306 × 150 mm) held at $37 \pm 2^\circ\text{C}$ (KSV-3000, Finland). The surface pressure was measured by the Wilhelmy plate method using paper plates (15 × 58 mm) [8,13,14,20,23,24]. Every surface area-surface pressure isotherm was determined on a freshly poured subphase of water, hydrochloric acid (pH = 1.9 to 2.1), sodium chloride (0.15 M) or calcium chloride (2 mM). The subphase was allowed to equilibrate for 10 min at $37 \pm 2^\circ\text{C}$. Surface-active impurities were removed from the air-water interface with a slight vacuum after compression of the barrier. 10-(Perfluorohexyl)-decanol, DPPC, and 10-(perfluorohexyl)-decanol-DPPC solutions with a concentration of 1-2 mg/mL were freshly prepared every day in *n*-hexanes:2-propanol = 9:1 v/v. A known quantity of solutions was spread on the surface, and 10 minutes at $37 \pm 2^\circ\text{C}$ was allowed to elapse for solvent evaporation before the start of the compression at a constant compression speed of 15 cm²/min (10 mm/min).

3. Results and Discussion

3.1. Mixing behavior in fully hydrated bilayers

The interactions of 10-(perfluorohexyl)-decanol and DPPC were studied in lipid bilayers fully hydrated with a 0.15 M sodium chloride solution. Representative thermograms of hydrated 10-(perfluorohexyl)-decanol-DPPC mixtures are shown in Figure 2. A partial phase diagram is shown in Figure 3. Within the experimental error, the phase behavior of the 10-(perfluorohexyl)-decanol-DPPC system did not depend on the solution employed to hydrate the mixtures (water, 0.15 M sodium chloride or 2 mM calcium chloride; data not shown). This observation is in agreement with previous studies that have shown these concentrations of sodium and calcium chloride have little or no effect on the macroscopic phase behavior of phosphatidylcholines such as DPPC [25-28]. We therefore only present the results from mixtures hydrated with the sodium chloride solution.

As shown in Figure 2, pure hydrated DPPC shows two thermal events, the main phase transition at about 42°C and a smaller pretransition at about 34°C. The main transition represents melting of the hydrocarbon chains, while the pretransition represents a shift from a tilted to vertical configuration of the chains [29]. For mixtures of DPPC and 10-(perfluorohexyl)-decanol, alternations in both of the thermal events are evident. At low amounts of the alcohol added,

$X_{\text{DPPC}} \sim 0.97$, the pretransition of DPPC appears to have merged with the main phase transition and appears to be still present as a shoulder at $X_{\text{DPPC}} > 0.91$. This change can be interpreted as an increase in the offset temperature and a significant peak broadening of the pretransition caused by increasing concentrations of 10-(perfluorohexyl)-decanol.

Figure 3 shows the onset and offset temperatures of the main transition as well as the onset temperature of the pretransition as a function of mole fraction of DPPC. Figure 4 shows the main transition band width relative to that of pure DDPC alone. Both sets of data were determined directly from the thermograms in Figure 2. In the 10-(perfluorohexyl)-decanol-DPPC system the onset and the offset temperatures and the peak width of the main phase transition remains approximately constant down to $X_{\text{DPPC}} \sim 0.95$, which suggest immiscibilities in the gel phase in this mole fraction range. At $X_{\text{DPPC}} = 0.91$ a significant increase both in transition temperature and peak width can be observed. Close examination of Figure 2 at $X_{\text{DPPC}} = 0.91$ shows that a shoulder is evident that corresponds to the maximum temperature (42.2 to 41.8 °C) for the main phase transition at lower mole fractions. This suggests that at $X_{\text{DPPC}} = 0.91$ two phase transitions are present, one transition close to that of pure DPPC and the other at a higher temperature. Up to $X_{\text{DPPC}} \sim 0.81$ the onset temperature of this phase transition shows an increase with increasing concentration of 10-(perfluorohexyl)-decanol, but decreases at $X_{\text{DPPC}} = 0.62$. This change in the onset temperature is reflected in changes in the peak width (Figure 4). The peak width shows a maximum at $X_{\text{DPPC}} \sim 0.91$, a projected minimum at $X_{\text{DPPC}} \sim 0.85$ and increases again at $X_{\text{DPPC}} < 0.70$.

The thermograms as well as the partial phase diagram presented in Figures 2 and 3 provide an indication of the miscibility of 10-(perfluorohexyl)-decanol and DPPC in the bilayer. At no mole fraction investigated (i.e., mole fraction of DPPC between 1 and 0.6) was a peak corresponding to excess alcohol (melting point = 48.8 °C [8]) observed which suggests that all of the added 10-(perfluorohexyl)-decanol is associated with the phospholipid. Similar observation have been reported for fully hydrated bilayers of mixtures of a partially fluorinated acid [13] and other simple linear alcohols and carboxylic acids [9] with phosphatidylcholines. The OH-group will likely be located at the lipid-water interface, while the partially fluorinated tail is assumed to be aligned with the alkyl chains of DPPC.

The pretransition of DPPC is considered very sensitive to the incorporation of various small molecules into the DPPC bilayer [9]. Similar to alcohols and carboxylic acids with a chain length of ≥ 12 carbon atoms, the pretransition is completely eliminated after addition of only a small amount of 10-(perfluorohexyl)-decanol, i.e. at a mole fraction of $X_{\text{DPPC}} \sim 0.91$. The elimination of the pretransition after addition of the fluorinated alcohol also suggests it is incorporated into the DPPC bilayer. The tilted arrangement of the hydrophobic chains below the pretransition temperature of DPPC results from packaging constraints caused by the mismatch of the area of its tails and its headgroup. A more optimal, that is, vertical, alignment of the tails of DPPC is possible in the presence of small quantities of other small molecules, e.g. (partially fluorinated) carboxylic acids [9,13], thus resulting in an elimination of the tilted gel phase and, hence, the pretransition. Most likely the incorporation of 10-(perfluorohexyl)-decanol into the DPPC bilayer causes a similar change in tilt angle.

Longer chain alcohols (12-18 carbon atoms) cause an increase in the onset temperature of the main phase transition of DPPC as a result of the formation of a 2:1 compound [9,30]. This drastic increase in the temperature of the phase transition in the perhydrocarbon system has been explained by the more optimal packing of the alkyl chains in the 2:1 mixture and, hence, an increase in chain-chain interactions. In contrast to long-chain perhydrocarbon alcohols, 10-(perfluorohexyl)-decanol only slightly increases the temperature of the phase transition of DPPC. Obviously, the partially fluorinated tail of 10-(perfluorohexyl)-decanol, similar to the structurally related 11-(perfluorohexyl)-undecanoic acid [13], would not be expected to favor

improved packing of the bilayer and, thus, not to lead to a significant increase in the melting point of the mixture due to the formation of a 2:1 complex.

3.2. Mixing behavior in monolayers at the air-water interface

In addition to the DSC studies we investigated the mixing behavior of 10-(perfluorohexyl)-decanol and DPPC at the air-water interface. The compression isotherms of different mixtures of 10-(perfluorohexyl)-decanol and DPPC on four different subphases, water, sodium chloride (0.15 M), calcium chloride (2 mM), and HCl (pH = 1.9) are shown in Figure 5. Solutions with these concentrations of sodium chloride and calcium chloride are typically used to isolate pulmonary surfactant from lungs. In addition, monolayer studies at the air-water interface frequently employ a 0.15 M sodium chloride solution as subphase [31,32]. The compression on hydrochloric acid was studied to allow a comparison with previous work on fluorinated carboxylic acids-phosphatidylcholines mixtures at the air-water interface [13,14,24].

To assess the miscibility of 10-(perfluorohexyl)-decanol and DPPC on the four subphases the concentration dependence of the surface pressure of onset of the liquid expanded-liquid condensed phase transition of the compression isotherms was employed [13,20,24,33,34]. In general, a concentration-dependent surface pressure of the phase transition is indicative of complete miscibility of the two components, whereas concentration independence is a sign of immiscibility of the components [33]. In Figure 5, the onset of the liquid expanded-liquid condensed transition of DPPC can be observed down to $X_{\text{DPPC}} = 0.4$ and shows only minor changes in its onset pressure over this mole fraction range. This suggests limited miscibility of both components in Langmuir monolayer on all four subphases. On the other hand, the phase transition of 10-(perfluorohexyl)-decanol [8] disappears at a mole fraction of DPPC of 0.2, suggesting that both components are miscible at high mole fractions of the alcohol.

The concentration dependence of the average molecular area at a constant film pressure was used as a second criterion to assess the miscibility of both components at the air-water interface. In ideal behavior the two components follow the “additivity rule”, i.e. the average area per molecule of any mixture is the sum of the areas occupied by each species at the surface

$$A(\pi) = X_{10-(\text{perfluorohexyl})-\text{decanol}} \cdot A_{10-(\text{perfluorohexyl})-\text{decanol}} + X_{\text{DPPC}} \cdot A_{\text{DPPC}} \quad \text{Eq. 1}$$

(X is the mole fraction of each component present at the air-water interface, A is the average area per molecule of the pure component, and DPPC is dipalmitoylphosphatidylcholine). Mixtures of two components that follow Eq. 1 show either ideal mixing or complete phase separation. Binary mixtures that do not follow Eq. 1 exhibit partial miscibility resulting from interactions between the two components. An attractive interaction will lead to a negative deviation, and a repulsive interaction will lead to a positive deviation from ideal behavior. Plots of area per molecule versus mole fraction (A - X_{DPPC} diagrams) are typically used to investigate whether a two component system follows Eq. 1.

The A - X_{DPPC} diagrams of 10-(perfluorohexyl)-decanol-DPPC mixtures on all four subphases are shown at several surface pressures in Figure 6. The A - X_{DPPC} diagrams on water shows a significant negative deviation from Eq. 1 at 3 mN/m and only a moderate deviation at 7 mN/m. At higher surface pressures of 20 or 30 mN/m, the experimental results follow Eq. 1. Similar to the water subphase, the A - X_{DPPC} diagrams on the calcium chloride and sodium chloride subphases show a negative deviation from Eq. 1 at 3 mN/m. This negative deviation becomes smaller with increasing surface pressure and the A - X_{DPPC} diagram approximately follows Eq. 1 at a surface pressure of 30 mN/m. The A - X_{DPPC} diagram of the hydrochloric acid subphase exhibits characteristics different from the other three A - X_{DPPC} diagrams in that a negative deviation from Eq. 1 can be observed at all surface pressures investigated. The extent of this deviation appears to decrease with increasing surface pressure. Especially at higher surface pressures the deviation displays a maximum at high mole fractions of DPPC ($X_{\text{DPPC}} \sim 0.6$ to

0.8). Overall, the (slight) concentration dependence of the phase transitions as well as the negative deviation apparent in the $A-X_{\text{DPPC}}$ diagram suggest partial miscibility of 10-(perfluorohexyl)-decanol and DPPC on all four subphases investigated. This finding is also in agreement with the results from the DSC study and appears to be typical for all binary mixtures of single chain alcohols and carboxylic acids with phosphatidyl cholines investigated to date at the air-water interface [10,24,35-39].

Our finding that 10-(perfluorohexyl)-decanol-DPPC mixtures are partially miscible on water parallels the mixing behavior of related long-chain alcohol-DPPC systems [10-12]. However, there are significant differences to be noted in the macroscopic mixing behavior of the fluorocarbon versus the hydrocarbon system. In the hexadecanol-DPPC system the surface pressure of the onset of the phase transition drastically decreases with decreasing mole fraction of DPPC on a water subphase at 37°C [12]. The phase transition completely disappears at $X_{\text{DPPC}} < 0.5$ under these experimental conditions. Such a change in the onset of the phase transition is characteristic for systems of the “modified cigar type” [35], where the components are not miscible in the region without a phase transition. Such immiscibility has been suggested for the hexadecanol-DPPC system at 30°C [10]. In contrast, the 10-(perfluorohexyl)-decanol-DPPC system shows only minor changes in the onset of DPPC's phase transition from a liquid-expanded to a liquid-condensed phase. This behavior suggests that 10-(perfluorohexyl)-decanol is miscible with DPPC to a lesser degree than its hydrocarbon analog.

Analogous to our findings from the DSC studies the differences between the fluorocarbon and the hydrocarbon systems are due to the differences in the structure of the hydrophobic tail. The perfluorinated terminus of 10-(perfluorohexyl)-decanol is lipophobic, significantly larger compared to an alkyl chain, and the $-\text{CF}_2\text{-CH}_2-$ linkage is highly polar. We and others have suggested that such a structure results in less dense packing at the air-water interface and, thus, weaker chain-chain interactions in monolayers of partially fluorinated amphiphiles [8,20,23, 24,40]. This ultimately results in differences in the macroscopic phase behavior of the fluorinated versus the hydrocarbon system at the air-water interface.

It is well established that the presence of electrolytes dissolved in the subphase can significantly alter the phase behavior of phospholipids [41] and other amphiphiles [8] at the air-water interface. Electrolytes such as sodium and calcium chloride also modulate the domain formation of membranes consisting of lipid mixtures [42,43]; however, much less is known about how electrolytes influence the miscibility of phospholipids and simple, single tail amphiphiles. In the present study the subphase composition did not significantly alter the macroscopic phase behavior of 10-(perfluorohexyl)-decanol-DPPC mixtures at the air-water interface. This observation is similar to the results from the DSC study which suggests that, analogous to the DSC studies, the concentration of sodium and calcium chloride were too low to significantly affect the macroscopic miscibility of the two-component bilayer. Indeed, the compression isotherms of DPPC on 0.1 M sodium chloride solution are practically identical with isotherms of DPPC on water [44]. The only exception from this observation is the hydrochloric acid subphase. As shown in the $A-X$ diagrams in Figure 6, the 10-(perfluorohexyl)-decanol-DPPC mixture displays a more significant deviation from Equation 1 than on the other three subphases. The difference in the macroscopic phase behavior at $\text{pH} \sim 2$ is most likely the result of the partial protonation of DPPC at this pH [30].

4. Conclusions

The mixing behavior of 10-(perfluorohexyl)-decanol with DPPC was studied in fully hydrated DPPC bilayers and in monolayers at the air–water interface to provide an insight into the interaction of fluorinated alcohols with biological systems such as cell membranes. The fluorinated alcohol was incorporated into both the DPPC mono- and bilayers. However, both

mono- and bilayers show some evidence for partial miscibility. In the DSC study the onset temperature of the main phase transition hardly increases in the presence of the fluorinated alcohol, which suggests limited miscibility in the gel phase. The monolayer studies show a negative deviation from Eq. 1, especially at lower surface pressures, which is also indicative of partial miscibility. Such limited miscibility could give rise to the formation of domains within a mono- or bilayer where the concentration of the partially fluorinated acid are particularly high. Such domains could locally cause an enrichment of the alcohol and, thus, alter the functions of biological phospholipids mono- or bilayers.

The differences in the macroscopic phase behavior of the 10-(perfluorohexyl)-decanol-DPPC compared to the hexadecanol-DPPC system are the result of the different chemical structure of the hydrophobic tail, i.e. the large size and the lipophobic/hydrophobic character of the perfluoroalkyl terminus as well as the dipole moment resulting from the CF₂CH₂-linkage, which prevent the optimal packaging of the partially fluorinated tails of 10-(perfluorohexyl)-decanol in the DPPC mono- and bilayers. Although the changes in the macroscopic phase behavior caused by the introduction of a perfluoroalkyl group, especially the putative formation of alcohol-rich domains, may alter the function of biological membranes, there is little evidence that partially fluorinated surfactants are toxic. Thus, 10-(perfluorohexyl)-decanol and related compounds represent as highly promising and versatile class of novel compounds for a large variety of biomedical application including pulmonary drug delivery.

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Figure 1.
Chemical structure of 10-(perfluorohexyl)-decanol.

Figure 2.

Typical calorimetric scans for mixtures of DPPC and 10-(perfluorohexyl)-decanol in excess aqueous NaCl (0.15 M). The mole fraction of DPPC is indicated besides each scan. The heating rate was 5°/minute from 4°C to 80°C (only the part of the curve with a phase transition is shown).

Figure 3. Partial phase diagram of mixtures of DPPC and 10-(perfluorohexyl)-decanol in excess aqueous NaCl (0.15 M). (■) Onset temperature of pre-transition, (◆) onset temperature of main transition, and (▲) offset temperature of a main transition. All data points are averages of at least three experiments $\pm$ one standard deviation.

Figure 4. Changes in the ratio of half-widths of the main phase transition of DPPC and 10-(perfluorohexyl)-decanol in excess aqueous NaCl (0.15 M). The ratio of the half-width is defined as the ratio between the half-width of the main transition of the mixed system and that of pure phospholipid. All data points are averages of at least three experiments $\pm$ one standard deviation.

Figure 5.

Representative compression isotherms of mixtures of DPPC with 10-(perfluorohexyl)-decanol ($X_{\text{DPPC}} = 0, 0.2, 0.4, 0.6, 0.8, 1$ from left to right) at $37 \pm 2^\circ\text{C}$ on (a) water, (b) hydrochloric acid ($\text{pH} = 1.9$ to 2.1), (c) sodium chloride (0.15M), and (d) calcium chloride.

Figure 6.

A - X_{DPPC} diagrams of mixtures of DPPC and 10-(perfluorohexyl)-decanol at $37 (\pm 2)^\circ\text{C}$ on (a) water, (b) sodium chloride (0.15M), (c) hydrochloric acid (pH = 1.9 to 2.1) and (d) calcium chloride. All data points are averages of at least three experiments $\pm$ one standard deviation.