Amphiphiles containing aromatic groups in the hydrophobic part
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Chapter 6
Epilogue

The main topic of this thesis is the aggregation behaviour and aggregate properties of mono- and di-n-alkyl phosphates containing an aromatic moiety in the hydrophobic tail. The background described in Chapter 1 serves as a basis to interpret the results described in the subsequent four experimental chapters. Together with an evaluation of the conclusions drawn in these chapters, the question whether the aim presented in Chapter 1 has been reached will be discussed. Also some recommendations for future research will be presented.

6.1 Achievements and outlook

In Chapter 1 it was explained that we wanted to incorporate aromatic units in the hydrophobic part of anionic amphiphiles and study the effect of this incorporation on the aggregation behaviour and aggregate properties of these amphiphiles. The main issue involved the question whether $\pi-\pi$ interactions are present and if so, how their presence influences aggregate properties and whether it is possible to increase the interactions between the hydrophobic tails via $\pi-\pi$ interactions.

In Chapter 2 it was found that the replacement of three methylene groups at the end of the hydrophobic chain in a single-tailed phosphate surfactant by a phenoxy group ($\text{C}_{11}\text{OphenPO}_4$) increased the CMC compared to that of the fully aliphatic tail ($\text{C}_{14}\text{PO}_4$) (Section 2.4, 2.5 and 2.7). If chain–chain interactions were increased via $\pi-\pi$ interactions, a decrease in CMC would be expected.

Instead of participating in $\pi-\pi$ interactions, we observed that the phenoxy group was, at least partially, located near the head group. This preferential positioning influenced the pKa of the phosphate head group. In bidistilled water the pKa of the head group of $\text{C}_{11}\text{OphenPO}_4$ in micelles is lower than that of the head group of $\text{C}_{14}\text{PO}_4$ in micelles (Section 2.6 and 2.7). It would be informative to study the influence of the position of the phenoxy group along the chain on both the aggregation behaviour and to what extent this variation of the position would affect the bending of the phenoxy group towards the micellar interface. Also a more detailed study of the influence of the position on the protonation state of the phosphate head group would be an interesting topic for further investigation.

Another possibility for further research would be adding various aromatic molecules to micelles composed of $\text{C}_{14}\text{PO}_4$ and to study the effect of this addition on the protonation state of the head group and the CMC. Aromatic molecules can bind to the micellar interface, but can also be located in the micellar core, depending on their substituents. In addition, binding of aromatic molecules to
micelles formed from C_{11}OphenPO_{4} could be investigated, in particular whether this binding differs from binding to micelles composed of C_{14}PO_{4}. Unfortunately, the \textit{n}-alkyl phosphates containing a biphen oxy or naphthoxy group at the end of the hydrophobic chain did not sufficiently dissolve in water.

\textbf{Figure 6.1} Representation of the packing in a leaflet of a bilayer composed of C_{11}phen with the methylene chain \textit{all-trans} (left), C_{14}P (middle) and C_{11}phen with the methylene chain containing \textit{gauche} conformations (right).

In order to investigate the effect of a larger aromatic group at the end of the hydrophobic chain of an amphiphilic molecule on its aggregation behaviour and aggregate properties, another head group is proposed. As described in Section 1.3, the Krafft temperature of \textit{n}-tetradecyl phosphate is 45 °C, which is relatively high. It could be that incorporating a biphenoxy or naphthoxy group increases the Krafft temperature even more. It is therefore better to select a surfactant with a lower Krafft point than \textit{n}-tetradecyl phosphate to serve as a basis for incorporating aromatic units. Surfactants containing a trimethylammonium head group have lower Krafft temperatures than \textit{n}-alkyl phosphates with a similar tail length. The same holds for \textit{n}-alkyl sulfates (e.g. the Krafft temperature of cetyltrimethylammonium bromide is 26°C and the Krafft temperature of sodium tetradecyl sulphate is 21 °C). It is known that ammonium amphiphiles containing biphenoxy and azobenzoxy units dissolve in water and form aggregates in water.

In Chapter 3 and 4 the aggregation behaviour and properties of aggregates of \textit{di-}n-alkyl phosphates are described. The absence of a significantly large increase in T_{m} for an amphiphile containing a phenoxy group at the end of the hydrophobic chain (C_{11}Ophen) and the decrease in T_{m} for an amphiphile containing a phenyl group at the end of the hydrophobic chain (C_{11}phen) suggests that possible π–π interactions do not increase the interactions between the hydrophobic tails.
reduction of $T_m$ is even larger when the phenyl or phenoxy moiety is located in the middle of the hydrophobic chain. All measurements described in Chapters 3 and 4 point towards a reduced packing of the tails in the bilayer of aggregates composed of di-$\pi$-alkyl phosphates containing an aromatic moiety. The reduced packing probably has its origin in the large space that the rigid phenyl group occupies. As a consequence, the phenyl group induces a change in conformation of the alkyl chain. Without this change the packing would be even worse. This is illustrated by Figure 6.1, in which we see that a C$_{11}$phen molecule that has its alkyl chains in an all-$\text{trans}$ conformation takes up more space than a C$_{14}$P molecule that has its alkyl chains in an all-$\text{trans}$ conformation. A C$_{11}$phen molecule that contains gauche conformers in its alkyl chains has a better packing in the bilayer compared to a C$_{11}$phen molecule that has its alkyl chains in an all-$\text{trans}$ conformation. (See also Figure 4.11).

It can be concluded that the possible $\pi$-$\pi$ inter-actions do not compensate for the loss of interchain interactions due to conformational changes upon introducing an aromatic moiety in the chain. As a consequence, the amphiphiles described in Chapters 3 and 4 are not suitable for a study of $\pi$-$\pi$ interactions in a bilayer, because the presence of the aromatic units significantly disturbs the packing of the bilayer. In order to examine $\pi$-$\pi$ interactions, a system is needed in which the aromatic unit does not interfere with the packing in the alkyl. It seems reasonable that this could be attained by incorporating the aromatic group directly attached to the head group. This would leave the alkyl tail free to adopt an all-$\text{trans}$ conformation.

Another possible system consists of amphiphiles that have an aromatic unit attached to only one of the two tails. This is illustrated in Figure 6.2. These amphiphiles could form an interdigitated bilayer; this would force the head groups...
further apart than in the non-interdigitated bilayer. Biphenoxy units and azobenzoxy units have been attached to ammonium amphiphiles in this fashion.\(^3\) Another disadvantage of the phosphates described in this thesis is that vesicles formed from these amphiphiles do not form closed vesicles below \(T_m\) in contrast to many phospholipids, which form closed, faceted vesicles below \(T_m\).\(^4\) The same observations have been made for di-\(n\)-hexadecyl phosphate and di-\(n\)-octadecyl dimethylammonium bromide.\(^5,6\) It could be a general feature of a certain kind of synthetic vesicle-forming amphiphiles that they do not form closed vesicles below \(T_m\). We believe this is caused by the fact that the tails in the synthetic amphiphile molecule cannot move as independently from each other compared to the tails in a phospholipid molecule. This hampers the ability to accommodate bilayer curvature, especially below \(T_m\) because the alkyl chains have less possibility to adapt to the curvature below \(T_m\) via gauche conformers. In a phospholipid molecule the tails are connected to each other via three bonds. In many synthetic amphiphiles the tails are connected via two bonds. This means that a molecule has one rotational degree of freedom more than the synthetic amphiphiles di-\(n\)-hexadecyl phosphate and di-\(n\)-octadecyl dimethylammonium bromide.

An interesting goal would be to develop synthetic amphiphiles that form closed vesicles below \(T_m\). Some molecular structures are proposed in Figure 6.3. The common characteristic is that more than two bonds connect the hydrophobic tails of the amphiphile. We expect that the increased number of degrees of freedom resulting from this structural change makes the amphiphiles capable of accommodating to the curvature at a temperature below \(T_m\).

We also expect that amphiphiles with this structural feature will enable a study of the effect of aromatic units of different sizes on the aggregation behaviour and aggregate properties. The di-\(n\)-alkyl phosphates containing a biphenyl and naphthyl unit did not dissolve sufficiently in water, probably because of efficient crystal packing. We suppose that the crystal packing of amphiphiles

![Proposed amphiphile structures to form spherical vesicles below \(T_m\).](image-url)

Figure 6.3 Proposed amphiphile structures to form spherical vesicles below \(T_m\). \(R\) is an alkyl chain or an alkyl chain derivatised with an aromatic moiety.
proposed in Figure 6.3 is less efficient due to the change in molecular structure and as a result, these amphiphiles might dissolve more readily.

In Chapter 5 the design and synthesis of oligomerisable derivatives containing aromatic moieties was described, with the objective to serve as a tool in the study of membrane fusion. Preliminary measurements on the biphenyl derivative showed, however, that this system is not suitable for the preparation of vesicles of which the inner leaflet is selectively oligomerised. In order to improve the system developed by Ravoo et al., a different strategy might be better. The main problem in Ravoo’s ‘slow motion’ fusion system in the cryo-TEM investigations was the lens shape of the vesicles, which gives rise to a complicated projection view and hampers the study of possible fusion intermediates.

An improvement would be to employ a system that gives spherical vesicles. A possible approach could be mixing of the oligomerisable lipids with phospholipids. Upon oligomerisation, the distance between the head groups in the bilayer changes. This could lead to domain formation of oligomerised amphiphiles and consequently have an undesired effect on the morphology of the vesicles. Another option is to use oligomerisable lipid derivatives with one or two tails containing an unsaturation. In Chapter 4 it was shown that a synthetic amphiphile containing unsaturated tails forms spherical vesicles, so it is likely that use of the oligomerisable lipid derivatives with one or two tails containing an unsaturation will form spherical vesicles. Another advantage of amphiphiles containing unsaturated tails is that their $T_m$ is below room temperature. This would make the study of the fusion process easier, because measurements have to be performed above $T_m$.

In retrospect it is obvious that the influence of the space requirements of the phenyl group on the packing of the bilayer has been initially underestimated. In $\text{di-}n$-alkyl phosphates, the two tails are relatively close together. This is inherent to its molecular structure. The incorporation of an aromatic unit could only lead to a disruption of the packing of the bilayer, due to the lack of available space in the bilayer. The effect of possible $\pi-\pi$ interactions was more than compensated by the disturbance of the packing. One must therefore be careful with introducing moieties to increase interactions in supramolecular systems. Beforehand the possibilities of additional effects must be evaluated.
6.2 References


