Partition coefficients in mixed surfactant systems

Application of multicomponent surfactant solutions in separation processes

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Abstract

It is their unique surface activity and self-assembly properties that make surfactants suitable for a wide range of applications. Though, the relevant phase equilibria are not yet described sufficiently. Of particular interest are the surfactant/ water phase behavior and the partition coefficient of the target compound between the micelles and the surrounding aqueous phase. Therefore, in this work different methods for the determination of micelle/ water partition coefficients are evaluated. Based on the partition coefficients and considering the surfactant/ water phase behavior the optimization of the decisive process parameters is aimed. The main focus is on the description of the effect of surfactant mixtures, the pH value, and additives to provide the basis for an effective control of processes, utilizing surfactants.

It is shown that with the chosen experimental methods, namely the micellar liquid chromatography (MLC), the micellar enhanced ultrafiltration, molar solubilization ratio measurements, and cloud point extraction, micelle/ water partition coefficients in various surfactant systems are determined reliably. Each of these methods is limited regarding the surfactant type and the magnitude of the partition coefficient. Yet, combining different methods, partition coefficients are measured with a high quality in a variety of mixed surfactant solutions. Thus, appropriate techniques for the evaluation of partition coefficients in mixed micellar systems are provided.

Further, the thermodynamic model COSMO-RS is evaluated for the prediction of partition coefficients in multicomponent surfactant solutions. It is demonstrated, that the composition of the micelles is the essential parameter for the successful prediction of partition coefficients in mixed surfactant systems. Since these data are difficult to measure, COSMO-RS based methods are introduced, to evaluate the micellar composition. Based on the applied experimental methods and the *a priori* prediction surfactant based processes can now be designed and optimized, as demonstrated by the following potential implementations:

- Application of the introduced methods to unknown systems, which are challenging to handle: the partition coefficient of retinol (vitamin A) in a lipid derived surfactant is determined for possible food applications.
- Optimizing the operating conditions in MLC: based on predicted partition coefficients, the retention behavior of the solutes is determined for different mobile phase compositions.
- Reactive separation of sugars from an aqueous solution: phenylboronic acid was used as carrier to solubilize sugars in the micelles. Optimized parameters are defined to increase the separation efficiency.

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1 Introduction

„It‘s more effective, it’s more efficient, it’s more elegant, it’s simply better chemistry.” That is how Paul Anastas describes the term ”green chemistry“, which he introduced in the early 1990th.[1] Since then green chemistry became the buzzword for sustainability in chemical research and industry. Its relevance becomes obvious considering the increasing amount of publications related to green chemistry in recent years.[2] Even the implementation in industry was realized, in particular the pharmaceutical industry reduced the environmental factor (E-factor) significantly and thus successfully met Anastas’ slogan. However, green chemistry is still ”in it’s embryonic at best“, as stated from Eric Beckman.[1] Especially the production of bulk chemicals with well-established procedures requires economic equivalent and efficient but also sustainable alternatives which provide the basis for redesigning the state of the art processes. Implementing green chemistry can and should take place in each production step, e.g. using renewable feedstocks, biological catalysts and replace the used solvents by less toxic and hazardous alternatives. As promising green solvents supercritical carbon dioxide and ionic liquids were proposed, their use in real applications is still rare for reasons of cost.

Besides, it was shown, that surfactants are similar effective and efficient, and are certainly more elegant than organic solvents.[3,4] Surfactants are versatile, readily available, less toxic and non-hazardous compared to organic solvents.[5] The amphiphilic molecules with ionic, nonionic or zwitterionic head groups and different types of hydrophobic moieties aggregate in aqueous solution, the aggregates are designated as micelles. The efficiency of surfactant based processes is attributed to the solubilization of the target components within the micelles. Accordingly, surfactants have been proved useful in a wide range of applications. For example, the stabilization of vitamins and drugs in micellar systems was demonstrated.[6,7] Besides, the use of micelles as target specific drug delivery vehicles and as model for biomembranes were reported.[8–10] Moreover, the use of micellar systems for analytical purposes, the separation and recovery of contaminants or valuable products was described.[11,12] The efficiency of micellar systems was proven for the preconcentration of metal ions for subsequent analysis[13] and the extraction of organic compounds, including polycyclic aromatic hydrocarbons (PAHs), pesticides, bioactive compounds, dyes, etc. from liquid and solid samples.[12,14,15] Furthermore, surfactants were used beneficially in processes involving chemical and enzymatic catalyzed reactions.[16–21]

The potential applications for micellar systems are versatile. However, the transfer of the scientific studies to industrial applications is still in its beginning. For an actual implementation, the dominant phenomena need to be known in detail. In particular, the knowledge of the binary surfactant/ water liquid-liquid-equilibrium (LLE) and the distribution of the target compound between the micelles and the aqueous bulk phase provide valuable information. While the LLEs, especially in pure aqueous surfactant solutions are relatively well studied,[14] the partitioning in micellar solutions is not yet understood sufficiently. This is particularly true for mixed surfactant solutions, containing e.g. contaminants, additives or more than one type of surfactant. The distribution of the solute between the micelles and the aqueous bulk phase is quantified by the partition coefficient P_i^{MW}, which is defined as the ratio of the concentrations of the target component in the micelles and the water phase. Since the composition of the respective phases is taken into account, the partition coefficient is a crucial parameter to evaluate the relevant influences on the desired application.

Predictive methods can support the investigations of the decisive parameters, affecting the partition coefficient. Furthermore, thermodynamic models can make a significant contribution to the detailed description and understanding of the mechanisms on a molecular level. Thus, based on a profound thermodynamic prediction the implementation of novel, green solvents, like surfactants, can be promoted considerably.

The aim of this work is to investigate the applicability of surfactants as alternative solvents in separation processes. Therefore, the relevant process parameters need to be defined and quantified. The knowledge of both, the LLE and the partition coefficients provide fundamental information for the process design. The data currently available is not sufficient, especially regarding the influence of additives on the equilibria. Thus, in this work, special importance is given to the phase equilibria in mixed surfactant systems. Of particular interest is the influence of the pH value, organic additives and surfactant mixtures on the partition equilibria. In addition to available literature data, LLEs in mixed surfactant solutions are investigated. For the determination of micelle/ water partition coefficients and influencing parameters, several experimental methods, namely the micellar liquid chromatography (MLC), micellar enhanced ultrafiltration (MEUF), molar solubilization ratio (MSR), and cloud point extraction (CPE) are evaluated. For the first time, different experimental methods are compared for the same system, exploring their respective limits. Moreover, the predictability of the influence of additives on the partitioning is investigated with the thermodynamic model COSMO-RS based on own experimental data. Thereby, different kinds of surfactants are considered, that is, cationic, anionic, and nonionic, species, including their mixtures. The applicability of the introduced methods for the design and optimization of surfactant based processes will be demonstrated for selected analytical and separation techniques.

Accordingly, in the following sections the thermodynamic basics and the fundamentals of the COSMO-RS model are described. Subsequently an overview of the current knowledge about surfactant systems is given. Of particular importance are:

- the liquid-liquid-equilibria (LLE) in binary surfactant/ water solutions,
- relevant parameters affecting the LLE,
- partition coefficients (P_i^{MW}) in binary surfactant/ water solutions, and
- relevant parameters influencing the P_i^{MW}.

Each of these topics includes the consideration of experimental and thermodynamic (and predictive) aspects. Finally, different applications of surfactants as proposed in literature are introduced.

2 State of the Art

2.1 Thermodynamic Fundamentals

2.1.1 Phase Equilibria in Liquid Systems

The knowledge of thermodynamic data is required for the design of virtually any chemical and biochemical process.[22] Basically, this data is the phase equilibrium of a certain mixture, or in other cases can be derived thereof. The phase equilibrium in a heterogeneous closed system is accompanied by the system's minimum of the internal energy U at constant volume V and entropy S.[23] In this state the thermal, mechanical, and chemical equilibria are reached, which are characterized by the temperature (T), pressure (P), and chemical potentials μ_i of all components (i=1…n) in the corresponding phases (φ=1…π) as given in equation 2.1.

$$\mu_i^{\alpha}=\mu_i^{\beta}=\cdots=\mu_i^{\varphi}=\cdots=\mu_i^{\pi} \quad \text{for } i=1\ldots n \tag{2.1}$$

The chemical potential is defined as the partial molar derivative of the Gibbs energy. Considering an ideal mixture, μ_i is calculated according to equation 2.2, based on μ_i^0, the chemical potential of the chosen standard state.

$$\mu_i^{ideal}=\mu_i^0+RT\cdot\ln(x_i) \tag{2.2}$$

In equation 2.2, the temperature and mole fraction (x_i) dependency of the chemical potential is accounted for. However, for the description of real mixtures, the non-ideality needs to be considered. Therefore, the activity a_i is introduced, an auxiliary property, describing the non-ideal correlation between the chemical potential and the mole fraction of component i. Thus, the chemical potential for a real mixture is expressed as

$$\mu_i^{real}=\mu_i^0+RT\cdot\ln(a_i). \tag{2.3}$$

To quantify the degree of non-ideality, the activity coefficient γ_i is defined as given in equation 2.4.

$$\gamma_i = \frac{a_i}{x_i} \qquad 2.4$$

Assuming an identical standard state for component i in all phases and combining equation 2.1 and 2.3 leads to the equality of the activities a_i in all phases:

$$a_i^{\alpha} = a_i^{\beta} = \cdots = a_i^{\varphi} = \cdots = a_i^{\pi} \qquad \text{for i=1…n} \qquad 2.5$$

Considering the correlation between the activity of the components and their mole fraction (equation 2.4), the general equilibrium relationship is derived, as usually used for the description of liquid-liquid-equilibria (LLE):[23]

$$x_i^{\alpha}\gamma_i^{\alpha} = x_i^{\beta}\gamma_i^{\beta} = \ldots = x_i^{\varphi}\gamma_i^{\varphi} = \ldots = x_i^{\pi}\gamma_i^{\pi} \qquad 2.6$$

2.1.2 Calculation of Partition Coefficients

The distribution of a compound between two immiscible phases α and β results from the thermodynamic equilibrium, as derived in the previous section. The ratio of the mole fractions x_i^{φ} of the solute i in the two corresponding phases α and β is designated as partition coefficient K_i:

$$K_i^{\alpha\beta} = \frac{x_i^{\alpha}}{x_i^{\beta}} = \frac{\gamma_i^{\beta}}{\gamma_i^{\alpha}} \qquad 2.7$$

According to equation 2.6, $K_i^{\alpha\beta}$ can be expressed as the ratio of mole fractions or activity coefficients. In agreement with the common approach, α is defined as organic, β as aqueous phase throughout this work. The partition coefficient most studied is the octanol/ water partition coefficient.[24] Usually, the distribution of the solutes between the aqueous and octanol rich phase is given as ratio of molar concentrations, which in general is depicted as partition coefficient $P_i^{\alpha\beta}$:

$$P_i^{\alpha\beta} = \frac{c_i^{\alpha}}{c_i^{\beta}} = \frac{x_i^{\alpha}}{x_i^{\beta}} \cdot \frac{v^{\beta}}{v^{\alpha}} = K_i^{\alpha\beta} \cdot \frac{v^{\beta}}{v^{\alpha}} \qquad 2.8$$

The partition coefficients $K_i^{\alpha\beta}$ and $P_i^{\alpha\beta}$ are directly connected by the ratio of the molar volumes v^{φ} of the phases α and β, as indicated in equation 2.8.

2.1.3 Partitioning of Dissociable Solutes

The partitioning of the solutes between two immiscible phases depends on its molecular characteristics. These characteristics are determined by the nature of the solute, but can also be influenced by external parameters. The influence of the pH value is particularly significant, regarding the partition coefficients of dissociable components. With the knowledge of the partition coefficient of the non-dissociated and the dissociated state, the pH-dependent partitioning, that is the lipophilicity profile, can be described. Analogues to equation 2.8, the partition coefficient of the non-dissociated solute $P_N^{\alpha\beta}$ is defined as the ratio of the corresponding concentrations, as given in equation 2.9 for a monoacid (HA) as an example.

$$P_N^{\alpha\beta} = \frac{c_{HA}^{\alpha}}{c_{HA}^{\beta}} \qquad 2.9$$

For the determination of the partition coefficient of the dissociated acid, the ionic species (I) A^- as well as the formation of ion pairs (IP) A^-X^+ need to be considered. The corresponding partition coefficients $P_I^{\alpha\beta}$ and $P_{IP}^{\alpha\beta}$ can be written as

$$P_I^{\alpha\beta} = \frac{c_{A^-}^{\alpha}}{c_{A^-}^{\beta}} \qquad 2.10$$

$$P_{IP}^{\alpha\beta} = \frac{c_{A^-X^+}^{\alpha}}{c_{A^-X^+}^{\beta}} \qquad 2.11$$

The pH-dependent partition coefficient $D_i^{\alpha\beta}$ is defined as the ratio of the concentrations of all species in the phases α and β:

$$D_i^{\alpha\beta} = \frac{c_{HA}^{\alpha} + c_{A^-}^{\alpha} + c_{A^-X^+}^{\alpha}}{c_{HA}^{\beta} + c_{A^-}^{\beta} + c_{A^-X^+}^{\beta}} \qquad 2.12$$

The respective proportion of each species is determined by the degree of dissociation and association, according to the corresponding dissociation and ion pair formation constant, expressed by the apparent pK_a and pK_{IP} values. Combining the ionic and ion pair species formally as dissociated solute (I;IP), the pH-dependent partition coefficient $D_i^{\alpha\beta}$ of acids is calculated as follows

$$D_{acid}^{\alpha\beta} = \frac{P_N^{\alpha\beta} \cdot 10^{(pK_a - pH)} + P_{I;IP}^{\alpha\beta}}{1 + 10^{(pK_a - pH)}} \qquad 2.13$$

A detailed derivation of equation 2.13 is included in Appendix A 1.1. Analogues, $D_i^{\alpha\beta}$ can be derived for basic components:

$$D_{base}^{\alpha\beta} = \frac{P_N^{\alpha\beta} \cdot 10^{(pH-pK_a)} + P_{I;IP}^{\alpha\beta}}{1+10^{(pH-pK_a)}} \qquad 2.14$$

2.2 The COSMO-RS Model

Many different thermodynamic models are already implemented in industry.[22] They can be divided into two approaches: equations of state (EoS) and activity coefficient (g^E) models. Basically, none of the models can describe all types of equilibria at all conditions equally successful. The preferred applicability of EoS are less complex mixtures in a wide pressure range, while g^E models are more appropriate for complex mixtures in a limited, low pressure range. Thus, for the description of mixed surfactant solutions at ambient pressure, g^E models are preferred in this work. Their potential for the predictive calculation of thermodynamic equilibria was proven recently.[22] Among those, the conductor-like screening model for realistic solvation (COSMO-RS) is characterized by the ability to predict thermodynamic data based on a limited number of element specific parameters.[25–28] The COSMO-RS model combines quantum chemical calculations with statistical thermodynamics.[28,29]

2.2.1 The Conductor-like Screening Model

As a first step in every COSMO-RS prediction, quantum chemical methods are applied to calculate the screening charge density on the surface of a molecule. The molecular surface is defined by the cavity, surrounding the particular molecular structure. The cavity is based on the element specific radii of the enclosed atoms. The quantum chemical calculation is performed in a virtual conductor environment, simulated by means of the conductor-like screening model COSMO, a variant of the continuum solvation models. In this environment a polarization charge density σ is induced at the interface of the molecule to the conductor.[22] All interactions between the molecules are completely screened on the interface to the perfect conductor. Thus, in an ensemble of molecules within the conductor environment, there are no intermolecular interactions.[30]

2.2.2 The Conductor-like Screening Model for Realistic Solvation

For the further calculation, the state of the molecule in the conductor environment is considered as reference state. However, for the description of realistic solutions the intermolecular interactions need to be considered. This development is provided by the application of statistical thermodynamics, which are combined with the COSMO method in the COSMO-RS approach.[25] In particular, the three-dimensional cavity around the molecule is discretized to surface segments, each with its local average polarization charge density σ. A molecule is uniquely defined by its σ-profile, which represents the distribution of the charge

densities of all surface segments. Based on the σ-profile, the interaction energy of pairwise interacting surface segments is quantified in the COSMO-RS calculation.

Different contributions to the interaction energy are considered, which are summarized briefly in the following. A detailed explanation of the COSMO-RS methodology and the underlying thermodynamic descriptions can be found in the references [25–28,30,31].

The electrostatic contribution to the intermolecular interactions is described by the misfit energy term. The misfit energy e_{misfit} is attributed to the difference of the local polarization charge densities of the two contacting segments σ and σ', which is scaled with the misfit energy factor α', an empirical factor, fitted to experimental data.

$$e_{misfit}(\sigma,\sigma') = \frac{\alpha'}{2}(\sigma+\sigma')^2 \qquad 2.15$$

In case of an interaction of segments with high surface charge densities, a hydrogen bonding contribution e_{hb} needs to be considered. Both screening charge densities, of the hydrogen bond acceptor and donor, need to exceed a certain, empirical threshold value σ_{hb}. The hydrogen bonding energy parameter c_{hb} is derived empirically.

$$e_{hb}(\sigma,\sigma') = c_{hb}(T)\min(0;\sigma_{don}+\sigma_{hb})\max(0;\sigma_{acc}-\sigma_{hb}) \qquad 2.16$$

A third contribution is due to van der Waals interactions, caused by the induction of dipols, based on the polarizability of the present molecules. The van der Waals contribution e_{vdW} cannot be described based on the screening charge density of the surface segments. Instead, element (e) specific parameters τ_{vdW}, derived from experimental data are employed.

$$e_{vdW}(e,e') = \tau_{vdW}(e)+\tau_{vdW}(e') \qquad 2.17$$

Thus, the overall interaction energy e_{int} between two contacting surface segments is calculated as the sum of the described contributions (equations 2.15-2.17):[28]

$$e_{int}(\sigma,\sigma') = e_{misfit}(\sigma,\sigma')+e_{hb}(\sigma,\sigma')+e_{vdW}(e,e') \qquad 2.18$$

The chemical potential μ'(σ) of a surface segment σ, as determined from the interaction with all segments in the ensemble is given in equation 2.19.

$$\mu'(\sigma) = -\frac{k_B T}{a_{eff}}\cdot\ln\left(\int p'_s(\sigma')\cdot\exp\left(\frac{-a_{eff}(e_{int}(\sigma,\sigma')-\mu'(\sigma'))}{k_B T}\right)\cdot d\sigma'\right) \qquad 2.19$$

with a_{eff} and k_B being the effective thermodynamic contact area and the Boltzmann constant, respectively; $p'_s(\sigma')$ is the normalized σ-profile of the system. From the chemical potential of the surface segments of a molecule, the residual contribution to the chemical potential $\mu_{i,res}$ of the compound i is calculated, as given in the following equation.

$$\mu_{i,res} = \int p_i(\sigma)\mu'(\sigma)d\sigma \qquad 2.20$$

The chemical potential of the component i is then calculated with

$$\mu_i = \mu_{i,res} + \mu_{i,comb} + k_B T \cdot \ln(x_i), \qquad 2.21$$

considering the combinatorial contribution $\mu_{i,comb}$, described by the Staverman-Guggenheim expression, and the component's mole fraction x_i in the mixture. The activity coefficient γ_i for the component i in the mixture is then derived, with regard to the chemical potential μ_i^0 of the standard state:

$$\gamma_i = \exp\left(\frac{\mu_i - \mu_i^0 - k_B T \cdot \ln(x_i)}{k_B T}\right) \qquad 2.22$$

Finally, thermodynamic data, such as the LLE (equation 2.6) and partition coefficients (equation 2.7) can be derived from the activity coefficient.

2.2.3 Prediction of Thermodynamic Data with COSMO-RS

In previous works the predictive power of the COSMO-RS model (and models based on COSMO-RS), and thus its potential for industrial applications was demonstrated. Besides the prediction of activity coefficients, LLEs, and partition coefficients, various vapor-liquid-equilibria, gas solubilities, pK_a values, soil sorption coefficients, vapor pressures, Setschenow coefficients, and enthalpies of vaporization were calculated for systems, containing such different components as pharmaceuticals, hydrocarbons, ionic liquids, polymer, and aqueous solutions.[22,27,30,32,33] Moreover, partition coefficients between water and octanol, micelles, or membranes were predicted in good agreement with experimental data.[25,34–37] It was shown, that even the salting in and salting out effect as well as the influence of the pH value in the system octanol/ water can quantitatively be predicted.[38,39] Combining molecular dynamics simulations with COSMO-RS, known as COSMOmic, the anisotropy of complex structures like micelles and lipid bilayers is explicitly accounted for.[36] Initial studies revealed an improvement of the predictive quality for anisotropic structures compared to the pseudo phase approach, assuming isotropic phases.[36,40,41]

Nevertheless, the COSMO-RS model is a comparatively young approach and obviously has its limitations.[22,30,42] However, the model proved to give reliable predictions for a variety of

properties and is distinguished from other approaches by its predictiveness and flexibility concerning the involved molecules and complexity of the investigated mixtures. The development of the COSMO-RS model and its extensions and variants persists; e.g. recently improvements of the hydrogen bonding term and for the prediction of free energies of hydration were implemented and an enhanced modeling of electrolyte solutions was described.[43–45] In this work the currently available version of the model is applied to mixed surfactant systems, to evaluate the limits of the predictability regarding surfactant systems.

2.3 Surfactants and Micelles

Surfactants (surface active agents) are used traditionally as soaps and detergents.[46] Nowadays, the applications of surfactants are numerous and versatile. They include historically important areas like dyeing of textiles and fibers, are economically significant as in cosmetics and personal care products and comprise processes in papermaking, mining, metal-processing, food-related, chemical and pharmaceutical industries, among others.[46]

The surface active characteristics of surfactants are due to their amphiphilic structure. The hydrophobic moieties usually are long-chain hydrocarbon residues, which can be straight-chained or branch-chained, may contain alkylbenzene and alkylnaphthalene residues, perfluoroalkyl or polysiloxane groups.[47] However, the classification of surfactants is made according to the nature of their hydrophilic groups. Basically, anionic, cationic, zwitterionic, and nonionic polar moieties are distinguished and dominate the surfactants characteristics. To correlate the molecular structure with the surfactants nature, the hydrophilic-lipophilic balance (HLB) number was introduced, initially to quantify the efficiency in emulsion systems.[46,47] Originally developed on an empirical basis,[48] the HLB can be defined based on the molar hydrophilic fraction of the surfactant molecule or comprises contributions of the associated hydrophilic and lipophilic molecular groups.[46] A detailed description of the various classes along with their main application areas can be found in the references [14,49–51].

2.3.1 Phase Behavior of Surfactants in Aqueous Solution

Due to their amphiphilic structure, surfactants tend to concentrate at interfaces, reducing the system's interfacial free energy.[46] Once the saturation of the interfaces is approached, the system's free energy may be further reduced by the formation of solid or liquid crystals, bilayers, vesicles or micelles.[46] With increasing surfactant concentration in aqueous solution, micelles are formed as soon as the surfactant specific threshold value, the critical micelle concentration (cmc) is reached. The formation of the surfactant aggregates is accompanied by characteristic changes of the physical properties of the solution, like the osmotic pressure, the surface and interfacial tension.[47] Thus, the cmc is a decisive value for assessing the solution properties, which significantly affect the application of surfactant solutions. Besides external effects, the cmc value is highly influenced by the surfactants molecular structure.[14,46,52] A major effect is attributed to the hydrophobic group, which is reflected by a decrease of the cmc value as the number of carbons in the hydrocarbon chain increases.[53,54]

This effect can be explained, considering that the reduction of the interaction between water and the hydrocarbon chain is the driving force in the micelle formation process.[46] A comparatively small effect, namely an increase of the cmc, is caused as the number of ethylene oxide groups in nonionic surfactants increases. However, ionic head groups counteract the aggregation and thus comparatively high cmc values are observed. The degree of ionization of the ionic group greatly influences the electrostatic repulsion. Depending on the polarizability and valence of the counterion the degree of ion binding and thus the cmc is influenced.

The micelle formation itself is characterized as the self-assembly of surfactant monomers. The particular evolution of the surfactant aggregates depends on the characteristics of the surfactant and its concentration. The micelles can be categorized according to their aggregation number and shape, most common is the spherical aggregate next to cylindrical, worm-like, lamellar, disk-like, and cylindrical micelles.[46,47] Micellar aqueous solutions are macroscopically homogeneous phases, although on a molecular scale heterogeneity needs to be considered. The description of the micelles usually is based on the pseudo phase approach, assuming the micelles to be a separated phase (cf. section 2.3.3).[55]

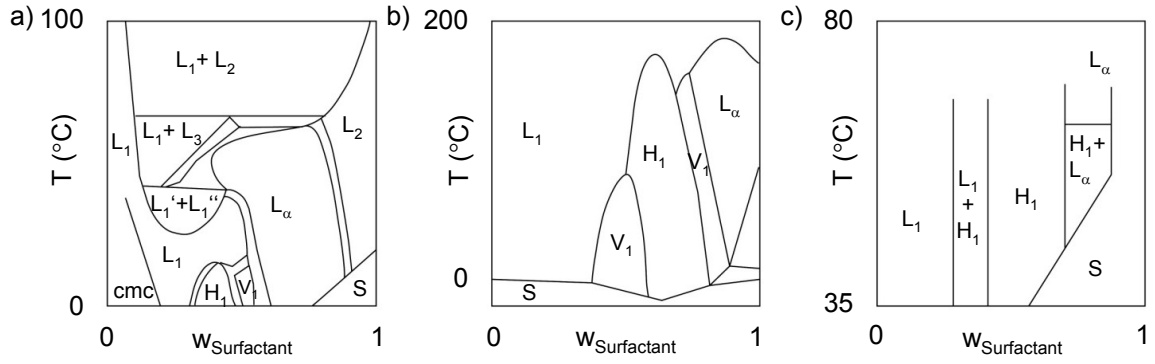


Figure 2.1: Representative phase diagrams for a) nonionic surfactants (here: $C_{12}E_5$, adopted from reference [56]) b) anionic surfactant (adopted from reference [57]) and c) zwitterionic surfactants (here: hexadecaldimethylammoniopropanesulfonate (LPC) adopted from reference [58]); L_1, L_2, and L_3 denote normal and reverse micellar and an isotropic solution containing bilayers, respectively; L_1' and L_1'' are the surfactant-lean and surfactant-rich phase; H_1 is a hexagonal, V_1 a cubic and L_α a lamellar liquid crystalline phase, and S represents the solid surfactant/ hydrated crystals.

With increasing surfactant concentration more complex mesophases can be distinguished: hexagonal, bicontinuous, lamellar, and inverse structures occur, the particular arrangement depends on a variety of parameters.[6,46,58] Representative phase diagrams are shown in Figure 2.1 for the different types of surfactants. The solubility of ionic surfactants often is poor at low temperatures, but increases dramatically at temperatures above the so called Krafft temperature.[47] For nonionic surfactants a characteristic phase separation is observed at elevated temperatures exceeding the cloud point temperature.[14] Thus, a surfactant-lean, aqueous phase and a surfactant-rich phase, also referred to as micellar phase, coexist. Zwitterionic surfactants can exhibit an upper and a lower consolute boundary concurrently.[58]

The knowledge of the phase behavior is essential for any process. If it is aimed, to solubilize a specific component in a macroscopically homogenous aqueous solution, conditions assuring the presence of the L_1 phase (cf. Figure 2.1) are indispensable. Regarding separation processes, two coexisting phases, differing in their microstructure, like L_1' and L_2' are required. However, for the actual application of surfactants in industrial processes, additional factors need to be taken into account. Above all, contaminants or additives influence the surfactant/ water equilibrium and make the implementation more challenging. A brief overview of the relevant effects is given in the following section.

2.3.2 Phase Equilibria in Mixed Surfactant Systems

The presence of a third component affects the cmc value (transition to L_1 phase) as well as the binary surfactant/ water liquid-liquid-equilibrium (LLE, coexisting phases L_1' and L_2').[58] Both effects might contribute to or against the intended use of the surfactant solution. Thus, a detailed knowledge of the influence of the particular additive and a description of the expected impact is absolutely necessary. Especially considering sustainable and bio-based processes, complex mixtures are to be expected, originating from e.g. fermentations of varying feedstock and composition. The most relevant components influencing the cmc and LLE are electrolytes and organic molecules, which are considered in detail in the following sections.

Influence of Electrolytes on the Phase Equilibria

The influence of electrolytes on the cmc value has been investigated extensively. For nonionic surfactants, this effect can be summarized as the well-known salting in/ salting out effect.[53] Depending on the nature of the added electrolyte, the properties of the aqueous pseudo phase, as well as the degree of solvation of the surfactants' hydrophilic groups are altered.[59] As a result, the micelle formation is affected and the cmc value changes. In case of ionic surfactants the impact of electrolytes on the cmc value is more pronounced. Due to a reduction of the electrostatic repulsion between the ionic head groups, the cmc value decreases significantly upon the addition of electrolytes.[60,61] Also acids and bases influence the equilibrium according to the salting in/ salting out effect, the actual pH value rarely has an additional impact.[46] However, some carboxylate soap and amphoteric surfactants can exhibit pH-dependent micellization behavior, which needs to be considered.

Similar to the cmc value, the binary phase behavior is influenced by electrolytes. Again, the LLE of aqueous solutions of nonionic surfactants is basically determined by the salting in/ salting out phenomenon.[6,58,62,63] It appears, that the cloud point temperature (CPT), the temperature at which phase separation at a given surfactant concentration occurs,[14] and consequently the consolute boundary is shifted. For ionic surfactants the strong electrostatic interactions need to be considered. These cause an increase of the Krafft temperature, that is, a reduction of the surfactant solubility at lower temperatures. Provided, that the solubility is maintained, a phase separation can be induced with increasing temperature, similar to nonionic surfactants.[6]

Influence of Organic Compounds on the Phase Equilibria

Also regarding organic compounds, the influence of diverse species was investigated, differing significantly in their characteristic properties. Accordingly, different interactions with the surfactants and the micelles are distinguished. Concerning the cmc, a differentiation of the additives between low and high water solubility seems appropriate.[46] Water soluble compounds include sugars, amides, and short-chain alcohols such as glycols, methanol, and ethanol. These polar components basically change the cmc value by modifying the structure of water (structure breaking or promoting), its dielectric constant or solubility parameter.[47] The net effect on the cmc finally depends on the magnitude of these opposing effects, and thus also depends on the additive concentration.[46,64]

Non-polar and thus poor water soluble components reduce the cmc value due to incorporation in the micellar aggregate. Thereby, it can be distinguished between different solubilization loci, as demonstrated in Figure 2.2.[9] Hydrophobic molecules are located basically in the micellar core and the less hydrophobic the molecule, the further it is located in the vicinity of the surfactant head groups. Hydrophilic components (also sugars, short-chain alcohols, etc. preferably at high concentrations) adsorb on the surface of the micelle. Located in the micellar core, hydrophobic molecules reduce the surface energy of the surfactants hydrocarbon chains and thus promote micellization.[47] Material solubilized in the area of the head groups, the palisade layer, reduces the electrostatic repulsion between the ionic head groups and consequently the cmc decreases.[65,66] Molecules, which are present primarily within the interfacial layer[67] are characterized by their amphiphilic structure, like e.g. alcohols.[64,65,68,69] Due to their poor hydrophilicity, they do not self-aggregate and form micelles. However, they highly influence the micelle formation of surfactants and act as co-surfactants.[6,70]

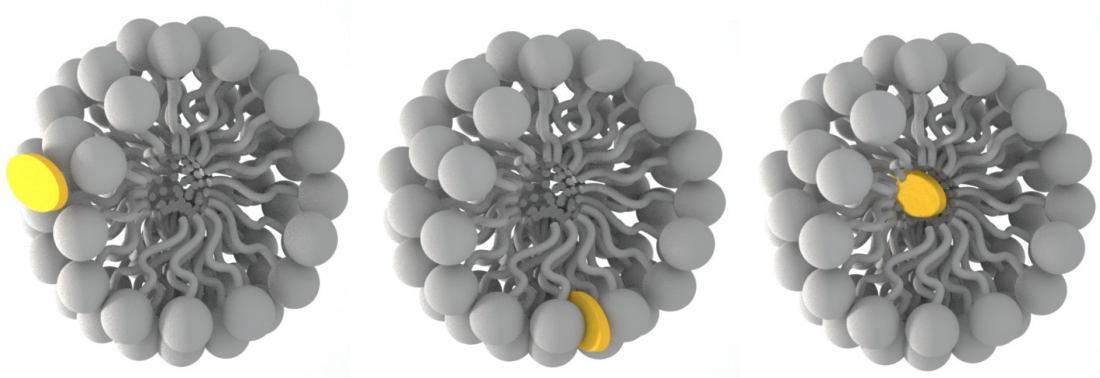


Figure 2.2: Locations for the solubilization of solutes with increasing hydrophobicity (left to right) within the micellar aggregates.

The influence of the various organic compounds also becomes evident, regarding the entire phase behavior.[58] Alcohols are the most studied organic additives, the short and long-chain species being representative for different types of organic additives. In solutions containing nonionic surfactant, an increase of the cloud point temperature upon the addition of short-chain alcohols (such as methanol, ethanol and n-propanol) is observed, while long-chain

alcohols, glycerol and phenol decrease the CPT.[14,62,63,71–76] As for the cmc value, the different effects of the alcohols on the CPT can be explained by their influence on the properties of the aqueous bulk phase and their location within the micellar structure. At elevated content of water-soluble organics, a disaggregation of the micelles occurs, since the surfactant monomer solubility is enhanced;[77] also the dimension of the mesophases is reduced or even disappears.[6] In contrast, the formation of mesophases is enhanced upon the addition of non-polar organic additives.[6,78] In that case, also the possible formation of (micro)emulsions needs to be considered.[67] Thus, the effect of organic additives on the phase equilibria is highly dependent on the kind of additive and its interaction with the micelles.

Phase Equilibria in Solutions Containing Surfactant Mixtures

The presence of third components like electrolytes and organic compounds highly influences the characteristics of surfactant solutions. Moreover, in practical applications, like in cosmetics, detergency and enhanced oil recovery, surfactants are mostly used in mixtures, since they have improved characteristics compared to single surfactant solutions.[79–81] Thus, in recent years much effort was spent in the investigation of the dominant effects. The cmc is the most studied characteristic in mixed surfactant systems. Other relevant properties of mixed micelles are the micelle size, its composition and the aggregation number. The experimental methods to study these properties are versatile, they include surface tension and conductivity measurements. Furthermore, light scattering, ultrafiltration, NMR self-diffusion, fluorescence quenching and surfactant specific electrodes as well as analytical ultracentrifuges are applied, to name a few.[82,83] The most relevant findings are summarized in the following.

The actual cmc value for a binary surfactant mixture (cmc_{12}) might deviate significantly from the behavior of an ideal mixture. The more both, the hydrophilic as well as hydrophobic groups of the two surfactants resemble each other, the less is the deviation from ideality.[84] The cmc_{12} value of the surfactant mixture ranges between the single surfactants cmc_1 and cmc_2. It is possible, however, that the mixture cmc is less or larger than either single surfactant cmc.[47,84] These cases are referred to as synergism and antagonism (negative synergism), respectively. Antagonism is less described, but was reported for e.g. ionic/ nonionic surfactant mixtures.[85] Also conditions for synergism are rarely satisfied, whereas negative deviation from ideality was observed for several ionic/ nonionic surfactant mixtures.[84,86–89] Speaking of synergism implies the negative deviation from ideality and additionally the compliance of the condition that $cmc_{12}<cmc_1$ and $cmc_{12}<cmc_2$ at any mixture composition.[82] However, synergistic effects in micellization are observed for zwitterionic/ anionic but are most pronounced in anionic/ cationic surfactant mixtures.[90–92] In Figure 2.3, the cmc_{12} for two types of surfactant mixtures (cationic/ nonionic and cationic/ anionic) are compared. Both kinds of mixtures showing negative deviation from ideality, while just the cationic/ anionic mixture exhibits synergistic behavior.

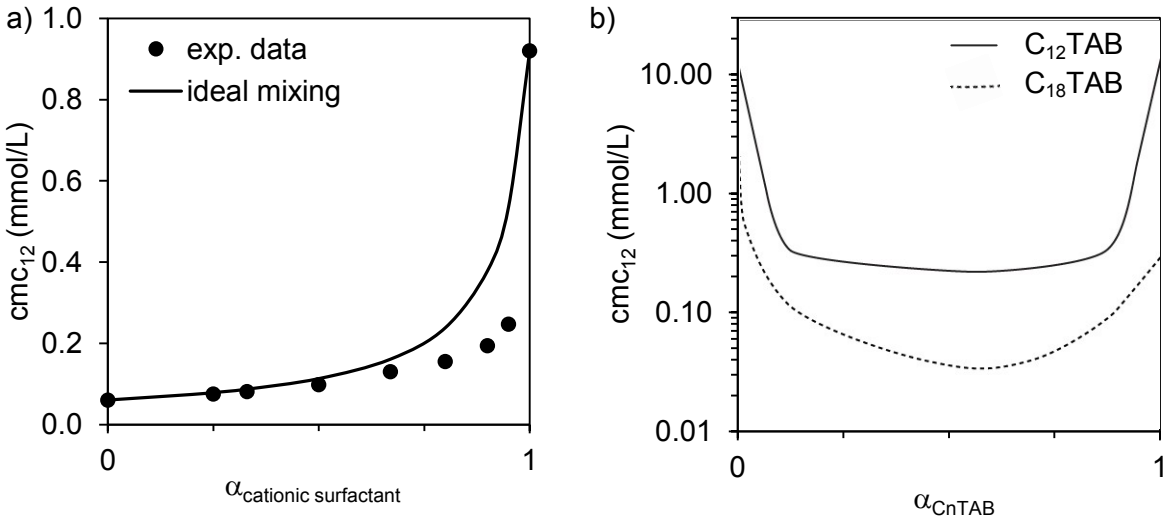


Figure 2.3: Cmc_{12} value in mixed micellar systems with increasing cationic surfactant content a) ideal mixing compared to experimental data in a cationic/ nonionic mixture, showing negative deviation from ideality[93] b) synergistic micelle formation for cationic/ anionic surfactant mixtures: $C_{12}TAB$/ sodium dodecylsulfonate and $C_{18}TAB$/ sodium dodecylsulfonate.[92]

Besides the cmc value, the addition of ionic surfactants highly affects the CPT of nonionic surfactants.[63,94–96] In Figure 2.4 the typical increase of the CPT due to the presence of a small quantity of ionic surfactant, far below its cmc, is depicted.[97]

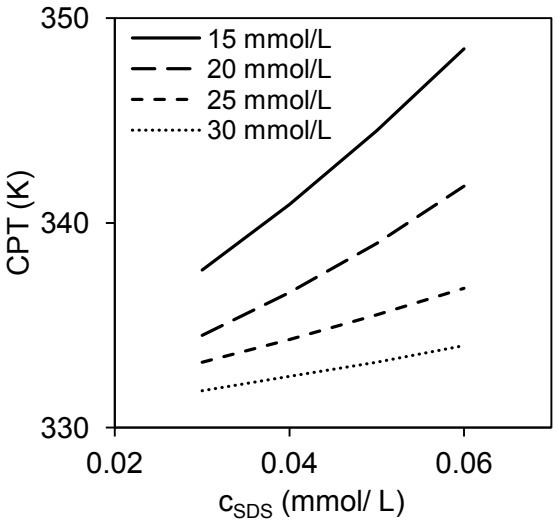


Figure 2.4: Cloud point temperature (CPT) for various concentrations of the nonionic surfactant Brij 97 with an increasing content of anionic surfactant SDS, adopted from reference [97].

Consequently, the phase behavior is highly influenced, resulting in a considerable change of the solubility and the LLE.[83] Due to the addition of small amounts of ionic surfactant to an aqueous solution of nonionic surfactant, the apparently open miscibility loop becomes a closed loop LLE. Moreover, the miscibility loop decreases with increasing ionic surfactant content, until it vanishes.[98] With the incorporation of ionic surfactants within the nonionic micelles, the electrostatic repulsion predominates the attractive interactions between the

hydrophilic head groups and thus mixed nonionic/ ionic surfactant solutions reveal a behavior increasingly similar to the pure ionic micellar solution.[83,99]

In this subchapter, it was demonstrated that micelle formation and phase equilibria in surfactant solutions are highly influenced by the particular solution's composition. Depending on the kind and concentration of the additive, different effects are caused. If various additives are present simultaneously, these effects might be either countervailing or enhance each other. The basic mechanisms underlying these phenomena are largely understood, although a limited number of systems are investigated so far. The thermodynamic description of these processes can contribute in gaining an even more detailed understanding of the prevailing effects, and in transferring the knowledge to not yet investigated systems.

2.3.3 Thermodynamic Characterization of Surfactant Solutions

Thermodynamics of Micellization

The micellization is thermodynamically characterized basically by either the mass action model (MAM) or the pseudo phase separation approximation (PSA).[100] The PSA suggests the micelle formation to be represented as a phase separation, analogues to the liquid-liquid phase equilibrium in e.g. water/ organic solvent mixtures. On the basis of this approach the formation of just one type of micelle is assumed, considering a fixed aggregation number N_{agg}, according the following equation:[101]

$$N_{agg}S \overset{K_N}{\leftrightarrow} S_{N_{agg}} \qquad 2.23$$

with S representing the surfactant monomer and K_N the equilibrium constant. Thus, the PSA is a comparatively simple approach, which works well for the micellization of nonionic surfactants at high aggregation numbers. In contrast, the micelle formation is regarded as the actual aggregation of surfactant monomers applying the MAM, allowing for the consideration of the polydispersity, as a result of multiple equilibria:

$$\begin{aligned} S+S &\overset{K_2}{\leftrightarrow} S_2 \\ S_2+S &\overset{K_3}{\leftrightarrow} S_3 \\ &\dots \end{aligned} \qquad 2.24$$

In general terms, for all aggregation numbers that are relevant:

$$S_{N_{agg}-1}+S \overset{K_N}{\leftrightarrow} S_{N_{agg}} \qquad 2.25$$

The MAM allows an accurate description of the micellization. However, usually, the information about the equilibrium constants K_N as function of the aggregation number N_{agg} is

not available.[101] Moreover, for very high aggregation numbers ($N_{agg}\rightarrow\infty$) the mass action model approaches the phase separation model. Thus, usually the equilibrium constant is defined by the ratio of the mole fraction of micellar x_m and monomer surfactants x_S according to the PSA:

$$K_N=\frac{x_m}{x_S^{N_{agg}}} \qquad 2.26$$

Accordingly, the standard Gibbs energy change of micellization ΔG^0_{mic}, expressing the tendency of the formation of micelles, is calculated with equation 2.27.[101]

$$\Delta G^0_{mic}=-RT\cdot\ln(K_N)=-RT\cdot\ln(x_m)+N_{agg}\cdot RT\cdot\ln(x_S) \qquad 2.27$$

Assuming a surfactant concentration around the cmc ($x_S=x_{cmc}$), at which the formation of micelles is initiated, and describing the Gibbs energy change per mole of surfactant monomer, equation 2.27 becomes:

$$\Delta g^0_{mic}=\frac{\Delta G^0_{mic}}{N_{agg}}=-\frac{RT}{N_{agg}}\cdot\ln(x_m)+RT\cdot\ln(x_{cmc}) \qquad 2.28$$

Considering a large aggregation number N_{agg}, equation 2.28 is simplified to

$$\Delta g^0_{mic}=RT\cdot\ln(x_{cmc}) \qquad 2.29$$

for nonionic surfactants.[47,101] Considering charged surfactants with monovalent counterions, the degree of dissociation ($1-\beta$) and binding of the counterions (β), respectively is accounted for according to equation 2.30.

$$\Delta g^0_{mic}=(1+\beta)\cdot RT\cdot\ln(x_{cmc}) \qquad 2.30$$

Equation 2.30 can further be extended for surfactants with divalent counterions[47] and for the consideration of added electrolytes.[101] From the measurement of the cmc values at different temperatures or amounts of electrolyte Δg^0_{mic} can be determined experimentally, as is summarized for a comprehensive list of various surfactants in e.g. reference [47] (Δg^0_{mic} along with its contributions Δh^0_{mic} and Δs^0_{mic}).

Besides the experimental determination, the Gibbs energy of micellization can be approximated using a correlation with the surfactants molecular structure in the form:[102]

$$-\Delta g^0_{mic} = r \cdot n_C + s \qquad 2.31$$

Based on the empirical parameters r and s, the dependency of Δg^0_{mic} on the number of carbon atoms n_C can be described for a homologues series at a given temperature. In contrast, derived from thermodynamic fundamentals, molecular thermodynamic models e.g. based on the phenomenological theory of Tanford,[103] define the Gibbs energy of micellization as the combination of a hydrophobic and a repulsive part:

$$\Delta g^0_{mic} = \Delta u^0_{mic} + w_{mic} \qquad 2.32$$

Δu^0_{mic} represents the energy change due to the transfer of the alkyl chain from the aqueous medium to the core of the micelle, while w_{mic} quantifies the contribution of the repulsion between the head groups. The two parts can be estimated from experimental data, simple empirical or thermodynamically derived equations.[103] Nagarajan and Ruckstein[104,105] developed a statistical thermodynamic theory to specify these hydrophobic and repulsive contributions on a physical basis.[106] According to their approach, the attractive component of the free energy change is attributed to[105]

- the van der Waals interactions between the hydrocarbon tails and
- the changes in the structure of water and the interactions between the surfactants and water caused by the aggregation.

The repulsive contribution is ascribed to

- the interfacial tension arising from the contact of the hydrocarbon core with the aqueous medium and
- the reduction of the translational and rotational degrees of freedom.[105]

In case of ionic and zwitterionic surfactants the electrostatic interactions between the head groups need to be considered additionally.[105] Δg^0_{mic} is calculated as the sum of the single contributions, and further employed for the derivation of the cmc value next to the size and shape of the micelles.[107]

Blankschtein and coworkers[106,108–110] however, decomposed the Gibbs energy of micellization into of a transfer, interfacial, packing and steric contribution. Accordingly, the formation of micelles is hypothetically divided into

- the transfer of the surfactant tail from an aqueous phase to a bulk tail-like environment (transfer),
- the formation of a tail drop in water (interfacial),
- the conformational constrains in the micelle core (packing), and
- the localization of the surfactant heads (steric).

Taking into account all the contributions, the Gibbs energy of micellization can be modeled. Additional contributions need to be considered, for e.g. ionic surfactants and ellipsoid micelles. Based on this "molecular thermodynamic" model the cmc, the critical surfactant concentration for phase separation and the osmotic compressibility can be derived, as demonstrated recently.[106,108,109] To apply the molecular thermodynamic model, the position and orientation of the surfactant within the micelle need to be known. For surfactants with more complex chemical structures, this information is provided by molecular dynamics (MD) simulations.[111] MD simulations were alternatively used to calculate the free energy of perturbation of the surfactant molecules. From the derived solvation free energy, the Gibbs energy of micellization can be approximated directly.[112,113]

As illustrated in equation 2.29 and 2.30 the cmc value is the decisive measurable quantity for the derivation of the Gibbs energy of micellization. Thus, information about micellization can be derived directly from the cmc data. Similar as described for the Gibbs energy of micellization, correlations that allow for the calculation of cmc values were developed. Besides correlations of the cmc to the carbon number of an homologue series, a more general QSPR (Quantitative Structure–Property Relationship) method was introduced.[114,115] For nonionic surfactants e.g. equation 2.33 was proposed.[114]

$$\log(x_{cmc}) = a + b \cdot KH + c \cdot AI + d \cdot RNNO \qquad 2.33$$

The factors a, b, c, and d represent empirically derived constants. KH, the Kier & Hall Index gives information about the size of the hydrophobic fragment, while its complexity is expressed by the average information content AI. RNNO is defined as the relative number of nitrogen and oxygen atoms and represents the size of the hydrophilic fragment. The three descriptors in equation 2.33 are determined on an empirical basis and need to be evaluated system specific. Alternatively, a semi empirical correlation was developed based on the COSMO-RS model (cf. chapter 2.2), as expressed in the following equation:[116]

$$\log(x_{cmc}) = a \cdot r_m^3 + b \cdot \hat{S} + \sum_i \left(\frac{c_i H_i^{diff}}{\hat{S}} \right) + d \cdot H_{ring} + e \qquad 2.34$$

While a - e are empirical constants, r_m, the molecular radius of the surfactant and $\hat{S}$, its solvent accessible surface are the descriptors along with different enthalpies H_i^{diff}, calculated with COSMO-RS. Besides a correction for ring size (H_{ring}), the hydrogen bonding, van der Waals and misfit contribution to the enthalpy are considered.[116] Using equation 2.34, the cmc values for a variety of surfactants are calculated in accordance with experimental data.

Furthermore, thermodynamic models such as g^E models were used for the prediction of cmc data.[22,117–119] Based on the assumptions of the PSA, the micellar aggregates are represented as a pseudo phase, which is considered to be a pure liquid phase. Hence, the chemical potential of the surfactant monomer within the micelle corresponds to its reference state and

the activity equals unity (cf. equation 2.3). From the equality of the surfactant's activity in both (pseudo) phases (cf. equation 2.5) it follows:

$$a_S^W = a_S^M = 1 \qquad 2.35$$

where a_S^W and a_S^M are the activity of the surfactant monomers in the water phase and the micelle, respectively. Based on the definition of the activity the relation between the activity coefficient and the mole fraction is specified (cf. equation 2.4). Applying g^E models, the cmc value can be derived from the calculation of the concentration dependent activity coefficients, considering the requirements of equation 2.35. One of the first to apply this procedure was Chen,[117] who combined a contribution for the local composition with a description of the configurational entropy of mixing water with surfactant monomers. These contributions are represented by the activity coefficient as calculated with the NRTL (Non-Random-Two-Liquid) model and a Flory-Huggins (FH) contribution, respectively, as illustrated in equation 2.36.

$$\gamma_i = \gamma_i^{NRTL} + \gamma_i^{FH} \qquad 2.36$$

By adjusting the relevant parameters, the cmc values can be calculated in agreement with experimental data.[117] A similar procedure was applied based on the group contribution model UNIFAC.[118] By introducing a new group, which allows for the description of the hydrophilic moiety and appropriate adjustment of the corresponding parameters, cmc values are calculated qualitatively correct.

In an alternative approach, also based on the UNIFAC model, the cmc of nonionic surfactants was determined by calculating the surfactant/ water LLE, assuming a surfactant-lean and a surfactant-rich phase (not a pure surfactant phase).[119] Obviously, the isoactivity criterion is accounted for, but the value of the activity is not equal to unity and needs to be derived for the particular system. Based on the definition of appropriate structural groups and the adjustment of the relevant parameters, cmc values can be predicted.[119]

Both, the Gibbs energy of micellization as well as the cmc value, which are the decisive state variable and measurable quantity describing the micellization process, can be correlated based on empirical equations. Besides, more general approaches, based on thermodynamic fundamentals were applied, such as molecular thermodynamic and g^E models. Thus, the micellization in pure surfactant/ water systems are described successfully with the presented approaches.

Influence of Additives on the Micellization

Like described for additive free surfactant solutions, the influence of additional components on the micellization can be quantified based on Δg^0_{mic} or the cmc values. The Gibbs energy of micellization in solutions containing additives is calculated with e.g. the models introduced in the previous section, such as the model of Naragajan and Ruckenstein or the Blankschtein group.[120] As demonstrated exemplarily for the effect of urea, the influence of an additive on the Gibbs energy of micellization can quantitatively be described with the molecular thermodynamic model of Blankschtein and coworkers.[121,122] Of the four contributions (cf. the previous section), only the packing part is independent of the additive concentration. Regarding the interfacial and steric contribution, the influence of the additive is accounted for by concentration dependent parameters (interfacial tension and average cross-sectional area of the surfactant head group, respectively). In contrast, an additional term for the calculation of the transfer from the additive containing solution to an additive free aqueous bulk phase needs to be considered in order to satisfy the transfer contribution. However, for a reliable description, the necessary molecular parameters need to be available for the surfactant as well as the additive. To overcome this limitation, a complementary model was introduced, based on the molecular thermodynamic approach.[120] Thereby the ordering and interaction energies of the head groups within the micelle as well as information about the interaction with additives is provided by Monte Carlo simulations. Thus, especially considering larger, penetrating additives, the description of the micellization behavior is improved considerably.

Next to the Gibbs energy of micellization, the influence of a specific additive on the micellization can be quantified based on the cmc data.[123–126] For a specific surfactant, the influence of a particular additive on the cmc value can be correlated empirically, like given exemplarily in equation 2.37.[47,127]

$$\log(x_{cmc}) = -KC_S + \text{constant} \qquad 2.37$$

Using that specific equation, the influence of electrolytes on the cmc value of nonionic and zwitterionic surfactants is accounted for. C_S is the electrolyte concentration, while K represents a surfactant, electrolyte as well as temperature specific constant. Beside the empirical correlations of the cmc value with the additive concentration, the calculation based on thermodynamic models, like g^E models was not described, previously.

Finally, MD simulations can give information about the influence of additives on the micellization, as was shown for the effect of electrolytes on the formation of ionic surfactants micelles.[128] However, extensive calculations for a particular system are required; up to now MD calculations have not been considered notably.

The Formation of Mixed Micelles

The formation of mixed micelles, consisting of two types of surfactants, was described based on experimental data.[83,129] As for single surfactant systems, the MAM and PSA are the most studied approaches.[83,130] Especially the PSA in combination with the regular solution theory (RST) was applied extensively and successfully for the description of intramicellar interactions.[131,132]

In the case of minimal interactions between the different kinds of surfactants, an ideal mixture is assumed for the calculation of the mixture cmc_{12}, as given in equation 2.38.[47]

$$\frac{1}{cmc_{12}} = \frac{\alpha_1}{cmc_1} + \frac{(1-\alpha_1)}{cmc_2} \qquad 2.38$$

Cmc_1 and cmc_2 are the cmc values for the single surfactant systems. α_1 is the ratio of the mole fraction of surfactant 1 in the solution $x_1^{solution}$, compared to the total surfactant mole fraction, according to equation 2.39.

$$\alpha_1 = \frac{x_1^{solution}}{x_1^{solution} + x_2^{solution}} \qquad 2.39$$

Considering the interactions between the surfactants, the non-ideality (cf. Figure 2.3) is expressed by the activity coefficients of the surfactants in the micelle, as depicted in equation 2.40.[47]

$$\frac{1}{cmc_{12}} = \frac{\alpha_1}{\gamma_1 cmc_1} + \frac{(1-\alpha_1)}{\gamma_2 cmc_2} \qquad 2.40$$

The mole fraction x_1 of surfactant 1 in the micelle at the surfactant bulk composition α_1 and total concentration c_S is calculated as:[133]

$$x_1 = \frac{\alpha_1 c_S - cmc_1^*}{c_S - cmc_{12}} \qquad 2.41$$

Cmc_1^* indicates the cmc of surfactant 1 in the mixture at the composition α_1. At high overall surfactant concentrations ($c_S >> cmc_{12}$), the micellar (x_1) is approaching the bulk (α_1) composition, whereas significant deviations at surfactant concentrations close to the mixture cmc ($c_S \approx cmc_{12}$) may occur.[133–136] Several recent studies investigated the effect of the surfactant concentration, as well as the surfactant's molecular structure on the composition of ionic/ nonionic mixed micelles.[82,83,88,89,93,97,137–147] In Figure 2.5 examples for ionic/ nonionic surfactant mixtures are given to demonstrate the influence of the surfactant's molecular structure and concentration on the micellar composition.

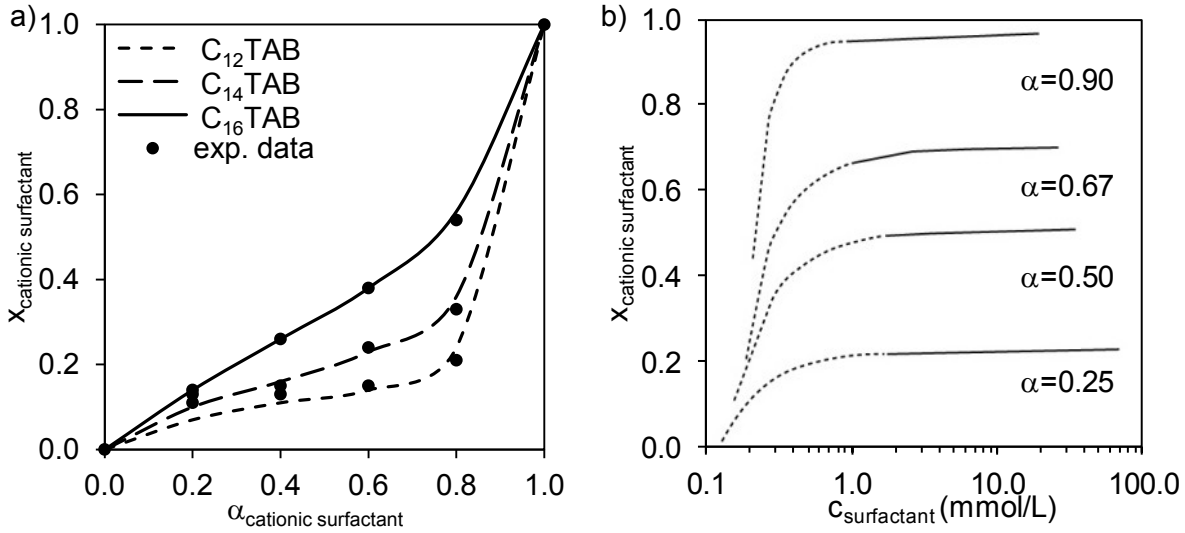


Figure 2.5: Composition of cationic/ nonionic mixed micelles at different bulk surfactant compositions a) influence of the hydrophobic chain length of the cationic surfactant in C_nTAB/ TritionX-100 mixtures, adopted from reference [88] b) influence of the overall surfactant concentration in CTAB/ Brij 35 mixtures of different compositions, as determined by self diffusion experiments (solid line) and from equation 2.41 (dotted line); adopted from reference [93].

The micellar composition is not directly accessible by experimental investigations. Especially at low surfactant bulk concentrations around the cmc value, deviations between the bulk α_1 and the micellar composition x_1 arise (cf. Figure 2.5). Assuming ideal micellization, the relation between x_1 and α_1 is given as:[47]

$$x_1 = \frac{\alpha_1 \cdot cmc_2}{\alpha_1 \cdot cmc_2 + (1-\alpha_1) \cdot cmc_1} \qquad 2.42$$

Accounting for the non-ideality, and thus considering the interaction between the different surfactants within the micelles, x_1 can be derived from the RST.[83] Therefore, the chemical potential of the surfactant monomers is calculated according to equation 2.3. Assuming the activity coefficient to be unity it follows:[148]

$$\mu_i = \mu_i^0 + RT \cdot \ln(cmc_i^*). \qquad 2.43$$

In contrast, the chemical potential μ_i^{MM} of the respective surfactant monomer in the mixed micelle is calculated from:

$$\mu_i^{MM} = \mu_i^M + RT \cdot \ln(x_i \cdot \gamma_i) \qquad 2.44$$

with x_i and γ_i, the mole fraction and activity coefficient of the surfactant in the mixed micelle, and μ_i^M, the chemical potential of the solute in the corresponding single surfactant micelle. From the pseudo phase approach, μ_i^M is derived from the single surfactant system:

$$\mu_i^M=\mu_i^0+RT\cdot\ln(cmc_i) \quad 2.45$$

Considering the equality of the chemical potential at equilibrium conditions ($\mu_i^{MM}=\mu_i$), the following relation can be derived, combining the equations 2.43 - 2.45:

$$cmc_i^*=x_i\cdot\gamma_i\cdot cmc_i \quad 2.46$$

According to the RST, the activity coefficients γ_i in a binary surfactant mixture can be approximated as follows:

$$\ln(\gamma_1)=\beta\cdot(1-x_1)^2 \quad 2.47$$

$$\ln(\gamma_2)=\beta\cdot(x_1)^2 \quad 2.48$$

where the parameter β is related to the interaction of the two surfactants within the micelle. At a surfactant concentration close to the mixture cmc_{12} at the composition α_1, the corresponding single surfactant cmc_i^* is calculated as follows:

$$cmc_1^*=\alpha_1\cdot cmc_{12} \quad 2.49$$

$$cmc_2^*=(1-\alpha_1)\cdot cmc_{12} \quad 2.50$$

Combining equations 2.46 - 2.50, equation 2.51 can be derived, from which x_1 is calculated numerically.

$$\frac{x_1^2\cdot\ln((cmc_{12}\cdot\alpha_1)/(cmc_1\cdot x_1))}{(1-x_1)^2\cdot\ln((cmc_{12}\cdot(1-\alpha_1))/(cmc_2\cdot(1-x_1)))}=1 \quad 2.51$$

Thus, based on experimental data of the cmc of the single surfactants and the mixture, the composition of the micelles and subsequently the interaction parameter β is calculated:[47,83,149]

$$\beta=\frac{\ln\left[\frac{\alpha_1 cmc_{12}}{x_1 cmc_1}\right]}{(1-x_1)^2}=\frac{\ln\left[\frac{(1-\alpha_1)cmc_{12}}{(1-x_1)cmc_2}\right]}{x_1{}^2} \quad 2.52$$

β is an empirical parameter, which quantifies the interaction between the surfactants within the micelle, thus the non-ideality of the system is accounted for. Based on the interaction parameter conclusions concerning the contribution of the surfactants' head groups or the length of the alkyl chain were drawn.[82,132,150] However, due to its undifferentiated description of the interaction and lacking thermodynamic fundamentals, the RST is often questioned.[80,83,131,151]

Besides the RST, predictive models based on thermodynamic fundamentals were suggested for the description of the formation of mixed micelles. Different energetic contributions are considered, in a similar way as for single surfactant micelles.[137,140,152] These models give more detailed information about the different influences, like the steric, hydrophobic, and electrostatic contributions on the formation of the micelles. It was also shown, that the micellization of mixed micelles can be studied at an atomic level with molecular dynamic simulations. Though, the feasibility was demonstrates for bile salt/ fatty acid mixtures, further investigations were not yet reported.[153–155] Nevertheless, these results promise further clarification of the micellization in mixed surfactants systems in future.

In the preceding section it was shown, that the micellization in single surfactant systems can be described fairly well. Also the influence of additives and surfactant mixtures can be accounted for, provided that the relevant parameters are known. These parameters are specific for an investigated system and thus need to be fitted accordingly or are derived from computational expensive simulations. Hence, the prevailing mechanisms are not fully understood. But especially due to an increasing computational power more detailed insights can be expected in the future.

2.4 Partition Coefficients in Surfactant Solutions

According to the pseudo phase approximation, micelles and the aqueous bulk phase are considered as two separated phases. Thus, by analogy with binary two phase systems, like octanol/ water, the distribution of solutes between water and the micelles follows the equilibrium conditions, as described in chapter 2.1.

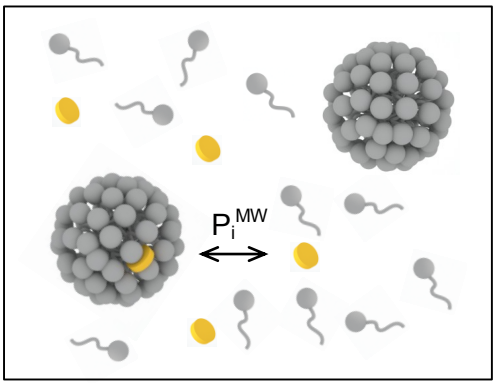


Figure 2.6: Schematic representation of the micelle/ water partition coefficient.

In contrast to the octanol/ water system, the micelle/ water partition coefficient P_i^{MW} is characterized by the distribution of a solute in a macroscopically homogeneous solution, as illustrated in Figure 2.6. The partition coefficient between micelles and water quantifies the tendency of the solute to partition in either pseudo phase. Consequently, the micelle/ water partition coefficient is a measure for the solubilization capacity of micellar solutions and furthermore a decisive parameter, evaluating the efficiency of a process where surfactants are applied.

2.4.1 Micelle/ Water Partition Coefficients in Single Surfactant Systems

Several experimental methods were used, to determine micelle/ water partition coefficients (or binding constants), like micellar enhanced ultrafiltration[156,157] (MEUF), solid phase microextraction[158] (SPME), solubility determination,[159] micellar liquid chromatography[160] (MLC) and micellar electrokinetic chromatography[161] (MEKC). Each technique has its limitations, so that an appropriate method needs to be chosen for a particular system, in order to provide reliable results. Especially the partition coefficients of hydrophobic components are estimated frequently from its solubility in micellar solutions.[162–166]

The main factors influencing the solubilization, and with it the partition coefficient, are the interactions between solute and surfactant. The surfactants cmc value and hydrophobic chain length, and the micellar aggregation number were described as parameters that correlate with these interactions.[167] Thus, besides the solute's hydrophobicity, the characteristics of the surfactant highly affect the partitioning.[168] Considering a limited range of solutes, correlations between the surfactant structure (of a homologues series) and the solubilization behavior can be drawn, as to the surfactants HLB value.[164,169]

Furthermore, the solubilization of a component in micellar solution is influenced by the temperature, which is connected to the changes in the micellar structure.[170] While with increasing temperature an increase in micellar size (or rather the aggregation number) is accompanied by a reduced amount of micelles in the case of nonionic surfactants, micelles formed from ionic surfactants show enhanced thermal agitation, and thus a better accessibility for solutes.[47,169] Besides the micellar characteristics, the nature of the solute and its interactions with the surfactant influence the micelle/ water partition coefficient. Thus, the effect of temperature on the micelle/ water partition coefficient is multiple, contrary trends were reported in literature.[171–174]

An even more pronounced effect is ascribed to the presence of additives, as in the case of the extraction of products in biorefinery processes[175] or the recovery of pharmaceuticals from a fermentation broth.[176] A summary of the most important aspects is given in the following section.

2.4.2 Micelle/ Water Partition Coefficients in Mixed Surfactant Solutions

Additives like salts and organics affect the partition equilibria of the system and change the partition coefficients of all components (water, surfactant and target solute) and hence e.g. the selectivity of the separation process.[14,173] Furthermore, in the case of biomolecules, like proteins, specific parameters in a narrow process window need to be met, to maintain the functionality or activity.[177] Thus, the knowledge of the specific impact of the present additives, and the possibilities to adjust these parameters is crucial for the design and optimization of a process. The main impact factors are reviewed in the following.

Influence of Electrolytes on the Micelle/ Water Partition Coefficient

The influence of electrolytes on the partition coefficient is basically attributed to the salting in/ salting out effect.[172,178] Moreover, effects like changes in the micellar structure,[169,179] counter ion binding in case of ionic micelles,[167] interactions with the EO groups of nonionic surfactants,[169] and the incorporation of hydrophobic salts and mixed micelle formation,[178,180] are discussed in literature. The resulting partition coefficient is influenced by different effects of the electrolyte and needs to be evaluated for the particular salt.

The solution's pH value also influences the micellar properties with increasing ionic strength. The partition equilibria of very non-polar, non-dissociable components like polycyclic aromatic hydrocarbons (PAHs) are not further affected by the pH value.[179] In contrast, significant dependence from the pH value for dissociable components was described. For selected hydroxybenzoic acids and their esters it was shown, that with increasing dissociation of the solute, the binding to nonionic and anionic micelles decreases significantly.[181] However, as stated before, organic salts, like sodium salicylate and tetrabutylammonium bromide, are incorporated within the micelles, in spite of e.g. expected electrostatic repulsion.[172,178] Especially in the case of drugs and their applications, these effects are of major importance, since many pharmaceuticals are characterized by a moderate pK_a value and are exposed to a broad physiological pH range[182] (pH 1 (stomach) to 8 (intestine); blood: pH 7.4). As an example, it was shown, that the solubility of flavopiridol (pK_a 5.68), a drug for the treatment of cancer, is increased dramatically in the acid pH range, thus in the dissociated state.[183] Despite the increased solubility in water, the dissociated drug still preferentially partitions into the nonionic micelle, though less distinctly compared to the non-dissociated form. The same trend, namely a decrease of the partition coefficient, but still a higher concentration of drug in the nonionic micelle, compared to the aqueous bulk phase, was observed for carvedilol phosphate (pK_a 7.8), a drug used to treat high blood pressure and heart failure.[167] In contrast, strong electrostatic interactions affect the partitioning, when ionic surfactants are involved. Likely charge of solute and surfactant results in repulsion, while at opposite charge high binding of the solute to the micelle is observed, which can lead to the formation of stable, insoluble salts.[167] The knowledge of the pH-dependent partitioning helps e.g. to estimate the transport and resorption characteristics of drugs in the body. Therefore, different effects, namely the salt effect, the degree of dissociation and the incorporation of the solute in the micelles need to be considered.

Influence of Organic Additives on the Micelle/ Water Partition Coefficient

In technical applications, such as fermentations or extractions of natural products, the presence of organic additives or contaminants needs to be considered. Especially in bioseparations, a high content of versatile organic compounds is expected. The influence of organic modifiers on the partition coefficient was investigated for a variety of solutes.[173,184] Thereby, the influence of alcohols is most frequently analyzed. It was shown, that the partition coefficients decrease, as the carbon chain length of the alcohol and its concentration increases.[158,185] In case of e.g. toluene, however, an increase of the partition coefficient is observed, which is explained by an expansion of the micellar structure, due to the toluene concentration in the micellar core of the nonionic micelles.[157] The kind and concentration of organic additive effects the partition coefficients, due to its influence on the microenvironment in both, aqueous pseudo phase and micelles. Hence, the assessment of the particular component needs to be considered.

Partition Coefficients between Water and Mixed Surfactant Micelles

Besides the influence of additives on the partition coefficients, the kind of the surfactant itself is crucial, due to its impact on the characteristics of the micelles. Significant changes of the micellar properties are observed for binary ionic/ nonionic surfactant mixtures compared to the single surfactant micelles (cf. section 2.3.2). While the formation of mixed micelles has intensively been studied experimentally as well as theoretically in the past (mainly based on the cmc_{12} data), the partitioning of solutes between ionic/ nonionic mixed micelles and the aqueous bulk phase is far less researched. Yet, the partition behavior is the decisive factor for practical applications. The available experimental data is basically determined by the molar solubilization ratio (MSR) method (cf. section 3.2.4), thus giving the partition coefficients for non-infinite dilution.[147,165,166] The partitioning for infinite dilution in mixed micellar systems is rarely investigated. Analogues to the micelle formation non-ideal behavior for the partition coefficients and, more frequently for the solubilization, in ionic/ nonionic mixed micellar systems was observed.[47,138,139,145,147,165,166,186] The effects can be explained by considerable changes of the microenvironment in the mixed micelles in comparison to the single surfactant aggregates[165] and the interactions of the surfactants' head groups.[186] In addition, the partition behavior can be affected by electrolytes and organic components, as described before.[165] Besides the surfactant composition, additionally influencing parameters were rarely considered in previous studies. Although, especially in pharmaceutical applications the solubilization of dissociable components in single and mixed micelles is of particular interest to mimic physiological processes,[150,187–190] the degree of dissociation was not accounted for in particular.

The micelle/ water partition coefficients in mixed surfactant systems (containing electrolytes, organic additives or surfactant mixtures) differ from, and cannot be derived directly from the ones in single surfactant systems. While the influence of organic additives and electrolytes on the partition coefficient was determined in a few studies, the partitioning in mixed micellar systems was even less studied. The combined effect of these parameters is virtually not investigated, though e.g. as depicted recently, the pH value is a relevant factor to prevent

denaturation of proteins during extraction by means of mixed surfactant systems.[191,192] Besides the experimental evaluation, the description of the partition coefficients, in particular in mixed surfactant solutions and considering the influence of multiple parameters can contribute in an enhanced understanding of the mechanisms.

2.4.3 Modeling Partition Coefficients in Micellar Systems

As was shown in the previous section, the factors influencing micelle/ water partition coefficients are numerous. The experimental investigation of a new system is laborious, thus methods were developed to predict partition coefficients in order to reduce the experimental effort. Most widespread and best studied is the partition coefficient in the two phase system octanol/ water, accordingly the applied models are versatile, ranging from quantitative structure-property relationships (QSPR) to g^E models, to molecular dynamics simulations.[193–200]

Since both, the octanol/ water as well as the micelle/ water partition coefficient are closely related to the solute's hydrophobicity, correlations were suggested to determine the latter partition coefficient, based on the former.[164,169,181] These correlations usually are represented as:

$$\log(P_i^{MW}) = a \cdot \log(P_i^{OW}) + b \qquad 2.53$$

with the system specific constants a and b. Apart from the octanol system, a purely empirical correlation can be used for the partitioning in surfactant solutions. For example, the partitioning of a protein in aqueous surfactant systems was correlated to the difference of the compositions of the coexisting phases.[201] The composition of these phases can be derived from a modified virial model, originally developed for polymer systems.

Furthermore, similar to the octanol/ water system, linear solvation free energy relationships were used for the calculation of micelle/ water partition coefficients.[164,202,203] Therefore, the partition coefficient is correlated with solute-dependent parameters expressing its excess molar refraction (E), polarizability/ dipolarity (S), hydrogen bond acidity (A) and basicity (B) and molecular volume (V). The system specific coefficients (c, e, s, a, b, v) are used to fit equation 2.54.

$$\log K_i^{MW} = c + eE + sS + aA + bB + vV \qquad 2.54$$

Based on the introduced correlations, micelle/ water partition coefficients are calculated reliably. The necessary parameters are fitted to a particular system, comprising the specific surfactant type and temperature; for some approaches the parameters are limited to a specific class of solutes. This determines the drawback of the correlations, which is its restricted flexibility regarding the description of surfactant systems. In contrast, there is no need in fitting the system specific parameters using g^E models such as UNIFAC and

COSMO-RS (cf. chapter 2.2). As was shown recently, these models were applied successfully for the prediction of the partition behavior of various solutes between water and octanol, hydrocarbons, polymers or micelles.[34,37,204,205] Based on the molecules' functional groups and their appropriate parameterization (UNIFAC) and the molecular structure (COSMO-RS), respectively, the partitioning in an unlimited number of different systems can be calculated. The temperature dependency is taken into account explicitly and the influence of additives can be considered in principle.

The description of the influence of a specific additive on the partition equilibrium is also feasible with the before mentioned approaches. For the correlations and relationships, the solvent specific descriptors need to be readjusted or redefined. Therefore, an extensive experimental data set is required. However, especially in mixed micellar systems, partition coefficients have rarely been correlated nor predicted, not least because of the lack of experimental data. It was shown though, that using the geometric mean equation, good agreement with experimental data for non-polar components in single and mixed surfactant systems is achieved (cf. Figure 2.7).[150] According the geometric mean equation, the partition coefficient in micellar systems is defined as:

$$\log K_i^{MW} = \left(\frac{N}{2.3RT}\right) \cdot (\pi_{20} \cdot \pi_{cmc})^{1/2} (TSA) \qquad 2.55$$

with the Avogadro's constant N, the product of the geometric mean, $(\pi_{20}\pi_{cmc})^{1/2}$, of the two surface tension reductions (π_{cmc} is surface pressure at cmc and π_{20} is the surface tension reduction equal to 20 dyn/cm) by the surfactant solution and the total molecular surface area (TSA) of the solute.

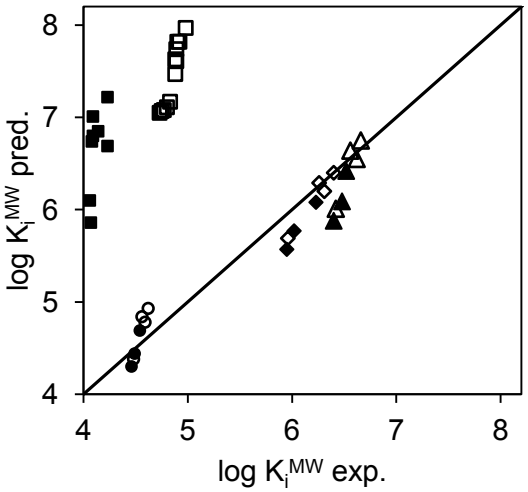


Figure 2.7: Prediction of micelle/ water partition coefficients in single (closed symbols) and mixed (open symbols) surfactant systems based on the geometric mean equation (equation 2.55) for anthracene (♦), naphthalene (●), naproxen (■), and pyrene (▲); data from reference [150]; the line shows perfect agreement of experimental with predicted data.

Nevertheless, for more polar components like naproxen, this approach reveals significant deviations, as is visualized in Figure 2.7. Thus, up to now, the prediction of partition coefficients in mixed micellar systems has still not been satisfactorily resolved.

Among the approaches mentioned for the description of micelle/ water partition coefficients, the COSMO-RS model stands out, due to its predictivness (no adjusting/ fitting necessary) and flexibility. It was shown previously, that even the salting in and salting out effect as well as the influence of the pH value in the system octanol/ water can be quantitatively predicted.[38,39] Thus, COSMO-RS is a promising tool for the determination of partition coefficients in complex mixtures, comprising various kinds of surfactants and their mixtures. Further, the predictions could give valuable information for the design of processes, determining optimal conditions for any application.

2.5 Applications of Surfactants in Separation Processes

Surfactant solutions are proposed in a variety of application fields, from industrial to household use, from cosmetics and food to oil production and waste water treatment.[6,206] Being a major component in processes involving foams, emulsions or suspensions,[46,67,207] and being model for “materials that heal themselves”[208] surfactant solutions were proven to be highly potential systems. The efficiency of surfactant solutions is basically due to the solubilization mechanism, which was mentioned before. Therefore, one takes advantage in terms of enhancing the solubility of hydrophobic components in aqueous solution. Moreover, separating the micelles from the solution is accompanied by the separation of the solutes incorporated within the micelles, and can thus be applied in purification processes. Some promising applications of micellar solutions and their major principles will be introduced in the following sections.

2.5.1 Cloud Point Extraction

The cloud point extraction (CPE) is a surfactant based separation process; the separation mechanism is due to the surfactants phase behavior (cf. section 2.3.1). A phase separation in solutions of nonionic surfactants is observed, if the temperature is increased above the cloud point temperature (CPT) or upon the addition of an appropriate, CPT decreasing additive. Also for zwitterionic and ionic surfactant solutions a phase separation is observed under specific conditions.[12,14] However, nonionic surfactants are used in the majority of the described CPE processes. It was shown previously, that the CPE can be implemented in a continuous extraction column, and thus provides the potential for industrial application.[209–211]

The separation effect is based on the solubilization of the (hydrophobic) target solute within the micelles; components solubilized within the micelles will concentrate in the surfactant-rich phase, while the aqueous phase is characterized by lean concentrations of surfactant and solute, as illustrated in Figure 2.8.

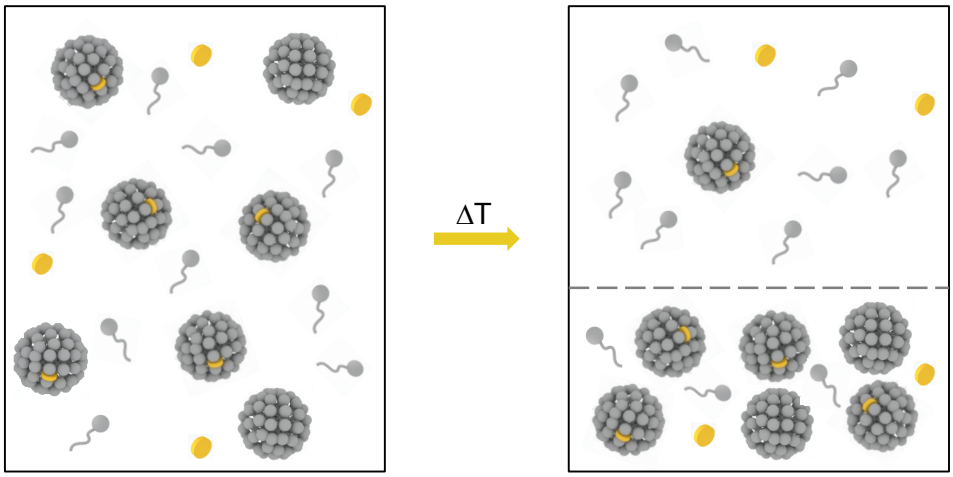


Figure 2.8: Schematic illustration of the cloud point extraction: temperature induced phase separation in a surfactant solution.

The enriched phase (solute and surfactant-rich) can be used for further process operations like subsequent purification, analytics or is handled within a manufacturing process. The CPE method was employed for extracting such diverse solutes as metals,[13,212,213] various organic compounds,[12,214–216] and bioactive materials[191,217–220] from aqueous solutions.[14] Furthermore, it was shown, that cloud point systems can be used, for the in situ extraction of products from biotransformations and in bioseparations.[5,177]

For the evaluation of CPEs, the extraction efficiency and partition coefficients between the surfactant-rich and surfactant-lean phase are usually analyzed. Optimized conditions for the extraction are defined, investigating parameters like the kind of surfactant, operating temperature, additives and solute concentration.[221]

The CPE can also be applied for the evaluation of micelle/ water partition coefficients. It must be considered, however, that the structure and the properties of the surfactant aggregates in the surfactant-rich phase might deviate from the micelles in dilute aqueous solution. Nevertheless, it was suggested, that the surfactant-rich phase is “micelle-like in structure”.[174] For some chlorinated alkanes it was shown,[174] that only minor deviations from the partition equilibrium are observed, if the solute concentration in the water of the surfactant-rich phase (not incorporated in the surfactant aggregates) is assumed equal to the concentration in the aqueous phase. Therefore, it can be expected, that the micelle/ water partition coefficient is a crucial value for the evaluation of CPEs.

2.5.2 Micellar Enhanced Ultrafiltration

In contrast to the CPE, the micellar enhanced ultrafiltration (MEUF) is operated with macroscopically homogeneous micellar solutions, i.e. in the one phase region (cf. Figure 2.1 for the respective surfactant types). Thus, the MEUF is characterized by its enormous flexibility concerning the usable surfactant types and blends, its high tolerance range concerning additives and is restricted mainly by the surfactant’s temperature dependent solubility (Krafft and cloud point temperature). Characteristic of the MEUF is the removal of

the aqueous bulk phase using a membrane; the micelles are retained and thus are concentrated within the retentate, as indicated in Figure 2.9 schematically.

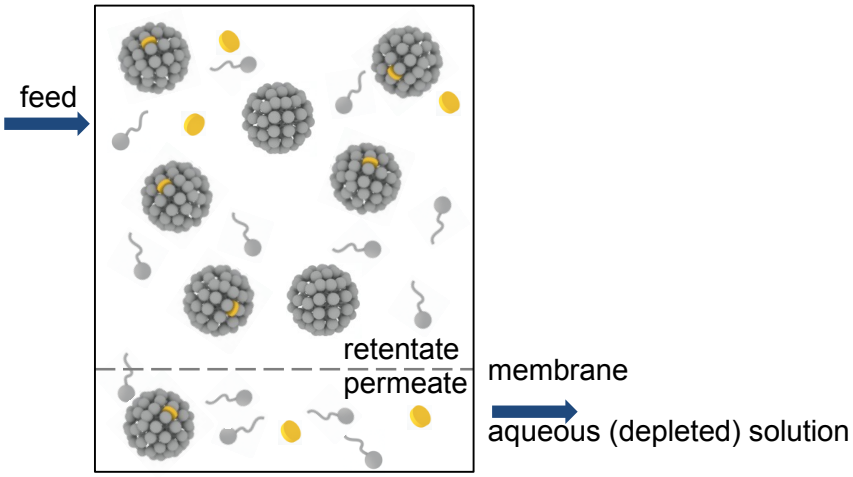


Figure 2.9: Schematic view of the micellar enhanced ultrafiltration (MEUF).

Accordingly, solutes solubilized within or adsorbed on the surface of the micelles are enriched in the retentate; hence, the removed aqueous solution is purified. The MEUF technique was introduced by Dunn et al.[222] in the 1980s. Since then it was proposed for the purification of waste water,[223–225] the efficient separation of organic and inorganic components (such as phenol[156] and metal ions[226,227]) and the simultaneous removal of lipophilic and hydrophilic components.[228]

Moreover, the MEUF can be applied for the combined product recovery and enhancement of a chemical reaction due to the presence of surfactants.[229] The MEUF is already successfully applied for the recycling of catalysts in systems, where micelles are used as a medium for catalytic reactions.[230–232] Thus, a simultaneous separation of the products and recovery of the catalyst is enabled based on the MEUF technique.[233]

As was described for the cloud point system, the effectiveness of MEUF processes is significantly influenced by the solubilization capacity of the used micellar system concerning the target molecules. Hence, the MEUF is assessed by means of micelle/ water partition coefficients or the rejection R of the respective components i, as determined from the weight fractions w in the feed and permeate, respectively.

$$R_i = 1 - \frac{w_i^{Permeate}}{w_i^{Feed}} \qquad 2.56$$

2.5.3 Further Applications of Surfactants in Separation Processes

Besides CPE and MEUF, surfactants are applied in several other unit operations. In the following table, a brief overview is given to demonstrate the versatility of surfactant applications. For detailed information it is referred to the cited references.

Table 2.1: Overview of suggested applications of surfactants in separation processes.

Application	Characteristics and examples of use	References
Microemulsion based separations	• Oil in water and water in oil emulsions are controllable by the addition of surfactants • Tertiary oil recovery; separation of enantiomers	[46,206,234,235]
Separations based on adsorption	• Surfactant is adsorbed on solid phase or particles • Enhance solubilization of target compounds on solid phase/ the solubility of the particles in solution	[46,206]
Separations based on foams/ aphrons	• Solute is adsorbed at the interface between dispersed phase (bubble) and continuous phase • Flotation	[46,47,206,236]
Reverse micellar extraction	• Reverse micelles (hydrophilic, water containing core) in nonpolar solvent • Extraction of proteins	[206,237–240]
Separations based on precipitation	• Precipitation of ionic surfactant by the addition of corresponding counterions • Recovery of surfactant and target compound, following the separation process	[206]

2.5.4 Surfactants in Analytics

The described surfactant based methods in separation processes are applied e.g. for the preconcentration of solutes prior to analysis. For example, metal ions and proteins are concentrated and preseparated prior to quantification.[191,214,241–245] Besides, chromatographic methods using surfactants for the direct analysis were developed. Firstly used in ion-pair chromatography, surfactants at low concentration (c_S < cmc) are added to the polar hydro-organic mobile phase and thus modify the retention due to adsorbing on the stationary phase and associating with the analytes.[173,246] Higher concentrations of surfactants, hence micellar solutions were originally used for size exclusion and thin layer chromatography.[246,247] Shortly thereafter, micellar mobile phases were employed in reverse-phase liquid chromatography (RPLC), operated as Micellar Liquid Chromatography (MLC).[173,248] Almost concurrently, micelles were used in capillary electrophoresis.[249] In the so called micellar electrokinetic capillary chromatography (MECC) or micellar electrokinetic chromatography (MEKC) micelles act as a pseudo stationary phase in a buffer based mobile phase, migrating in a strong electric field.[250] The migration of ionic micelles along the electroosmotic flow is retarded according to their electrophoretic velocity.[250] Analytes partition between the micelles and the buffered aqueous bulk phase according to their partition coefficient P_i^{MW}, hence

components can be separated due to their different hydrophobicity and specific interactions with the micelles.[250,251] In Figure 2.10 the principle of the MEKC is illustrated schematically. Nowadays MEKC is the main application area of surfactants for analytical purposes, which is attributed to its high efficiency (in the range hundreds of thousands plates/ m).[173] Ionic surfactants are applied for the separation of uncharged solutes, while nonionic and zwitterionic surfactants are basically used for charged analytes. Utilizing mixtures of ionic and nonionic surfactants enhances the applicability of the MEKC technique; it is applied for the separation of organic, inorganic, and biochemical compounds, innumerable examples are given in the references [250,252–261].

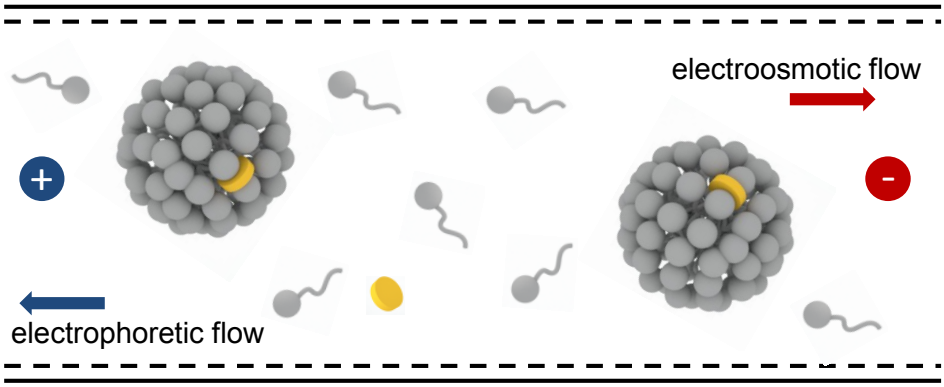


Figure 2.10: Illustration of the separation principle in micellar electrokinetic chromatography, adopted from reference [262].

In the microemulsion electrokinetic chromatography (MEEKC) surfactants are used as microemulsion forming agents. The MEEKC is based on the same principles as described for the MEKC, but micelles are replaced by microemulsion droplets.[263] Thus, MEEKC can be operated with water in oil (seldom) and oil in water (common) emulsions. The separation of highly lipophilic analytes with MEEKC is enhanced compared to MEKC and is thus applied for e.g. flavonoids and vitamins.[252,263,264] In analogy, the microemulsion liquid chromatography (MELC) was developed, following the basic principles of the MLC.[265–267]

In contrast to the electrokinetic techniques, the MLC is a mode of the conventional reverse-phase liquid chromatography (RPLC), expanding the spectrum of the latter. MLC and RPLC share the basic assumptions, however, in MLC the versatile interactions with the surfactants result in a comparatively high complexity.

Application of the Micellar Liquid Chromatography

The number of interactions between surfactants and analytes gave rise to numerous applications of the MLC for analytical purposes (as well as MEKC and MEEKC, as addressed briefly in the previous section). The following paragraph will give a short overview of recent studies and applications involving MLC, to emphasis its impact and distribution among scientific and industrial sectors.

The MLC proved to be an adequate technique for the separation of sugars, aromatic amines, parabens, phenolic compounds, alkaloids, PAHs, and their coumarin derivatives.[185,246,268–274]

Samples of biological origin and with environmental impact were analyzed successfully.[246,275–277] More common, however, is the application of the MLC for the analysis of pharmaceutical and biomedical samples.[173,246,250,252,278–280] Amino acids, proteins, peptides as well as enantiomers are separated selectively.[281–286]

The anionic surfactant sodium dodecyl sulfate (SDS) is the most commonly used surfactant in MLC.[173,246] But also other anionic, as well as cationic (especially CTAB: cetyltrimethylammonium bromide), nonionic (Brij 35: polyoxyethylene (23) lauryl ether) and zwitterionic (like betaine) surfactants were applied recently, several more are applicable.[173,246,287]

A major benefit of the MLC for most of these applications is the fact, that complex samples can be injected directly, without any sample preparation. Thus, a fast and reliable analysis of physiological fluids, like serum and urine, food and cosmetic samples or waste water is provided.[246,274,288] The detection of performance-enhancing drugs, screening and monitoring of therapeutic drugs and corresponding metabolites was proposed.[279,280,289,290] Thus, the MLC technique proved not only to be a possible alternative to conventional RPLC, but also meets the requirements of “green chemistry”, since there is no need in preparing the samples prior to analysis.[246,278,291]

The major drawback of the MLC is the reduced efficiency compared to the RPLC.[173,246] Significant improvements are achieved by the addition of modifiers to the mobile phase.[66,270,271,292] In most of the cited studies in this paragraph such a hybrid mobile phase was used, where mainly small amounts of short-chain alcohols are added to the micellar mobile phase, more recently acetonitrile is suggested.[185,246,293] Besides the modification of the mobile phase by the addition of organic modifier, it was shown, that the selectivity is enhanced using nonionic/ ionic mixed micellar mobile phases.[268,294,295] By combining different surfactant types, the molecular interactions can be adjusted, increasing the selectivity of the separation.[272]

Adjusting the composition of the micellar phase, the MLC can be used as an efficient, indirect method for the determination of octanol/ water partition coefficients.[296,297] Moreover, micelle/ water partition coefficients and micelle binding constants are determined reliably, as was demonstrated for a number of surfactants and solutes.[160,173,184,185] With the appropriate settings, the partitioning into bilayers of a biological membrane can be simulated.[298] This specific mode of the MLC, designated as biopartitioning micellar chromatography (BMC) aims to elucidate phenomena, involved in the pharmacokinetic behavior of drugs, their activity as well as permeability across the intestinal and blood-brain barrier.[298–305] It was shown, that the retention of the solutes is correlated to the corresponding property (quantitative retention–activity relationships (QRAR)) with a higher accuracy compared to the correlation with the octanol/ water partition coefficient (quantitative structure–activity relationships (QSAR)), which is mainly used for the estimation of bioactivity parameters.[300,306,307] The mobile phases applied for BMC contain the nonionic surfactant Brij 35, which exhibits structural resemblance to the membranous hydrocarbons.[307]

Frequently, the correlation between retention and activity is improved by the addition of the anionic surfactant SDS and organic or inorganic additives.[308,309]

The possible applications of MLC are versatile. For the improvement of the technique and targeted optimization, the basic mechanisms need to be known. Thus, the basic assumptions, covering the retention are addressed in the following paragraphs.

Retention in Micellar Liquid Chromatography

As in any chromatographic process, the separation in MLC is based on the interactions of the analytes with the stationary and mobile phase. In contrast to most other techniques, in MLC both phases are modified by the surfactant. The characteristics of the stationary phase are modified due to adsorption of surfactant monomers; the mobile phase is a microscopically heterogeneous solution, composed of the micellar aggregates and the aqueous bulk phase.[173] The analyte, or solute, partitions between the three coexisting phases, the surfactant modified stationary phase (S), the micelles (M), and the aqueous bulk phase (W), according to its partition equilibria. This is quantifiable by the corresponding partition coefficients $P_i^{\alpha\beta}$. The three phase model was introduced by Armstrong and Nome in the early 1980s, to explain the chromatographic behavior in MLC.[173,310] In Figure 2.11 the relevant partition equilibria in MLC are shown schematically.

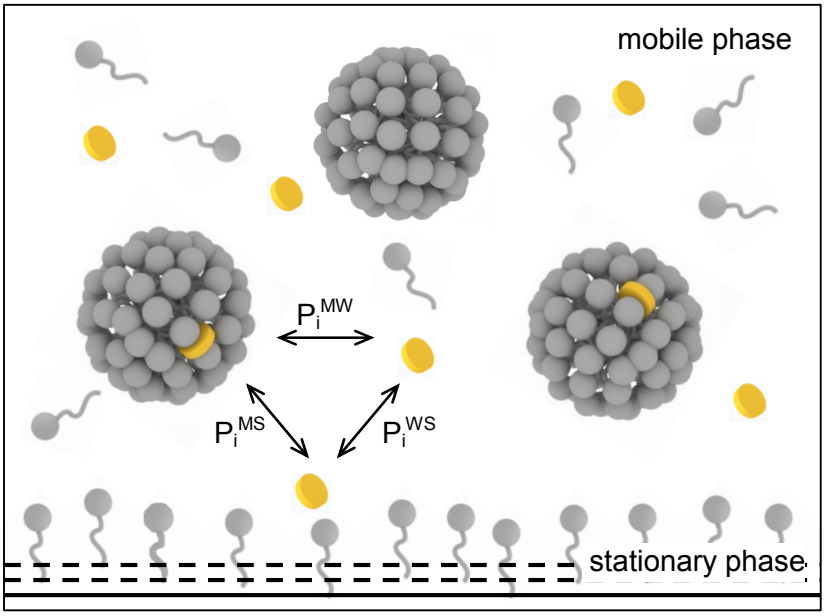


Figure 2.11: Partition equilibria in MLC according to the three phase model,[310] adopted from reference [311]; where P_i^{MW}, P_i^{MS}, and P_i^{WS} represent the solute's partition coefficient between the micelles and the aqueous bulk phase, micelles and stationary phase, and aqueous bulk and stationary phase, respectively.

The retention in MLC depends on the partition equilibria between the three coexisting phases, and thus is influenced by a considerable number of possible interactions. The partition coefficient P_i^{MW} between the micelles and the aqueous bulk phase is highly sensitive to modifications of the mobile phase composition, such as the addition of alcohols for efficiency improvements.[246] In section 2.4.2 factors influencing partition coefficients were

discussed and can be transferred to the partition equilibrium within the mobile phase. The partition coefficients P_i^{MS} and P_i^{SW} are influenced significantly by the type of stationary phase involved, while P_i^{MW} basically remains constant.[173,312–315] By means of the targeted modification of the partition equilibria, the selectivity and efficiency can be enhanced significantly.

Basically, hydrophobic, electrostatic, and dipole interactions of the solute with the micelles and the surfactant modified stationary phase influence its elution. Hence, depending on the analyte's retention behavior, a classification into three species, according to the binding of the solute to the micelle was suggested:[173,316]

(1) Solutes binding to the micelles are characterized by a decreasing retention at increasing micelle concentration in the mobile phase.
(2) Non-binding solutes show constant retention, independent from the micelle content, since they do not associate with the micelles.
(3) Antibinding analytes elute retarded as the micelle content is increased, which is rarely observed, only if surfactant and analyte are likely charged (electrostatic repulsion).

In the case of very strong interactions between the solute and surfactant, the retention is very high, due to strong binding to the stationary phase, even irreversible adsorption may occur.[173,185] Thus, the partition behavior deviates from the presented three-phase model. The solute is hardly present in the aqueous bulk phase, but a direct transfer between the micelles and the stationary phase is required, as illustrated in Figure 2.12.

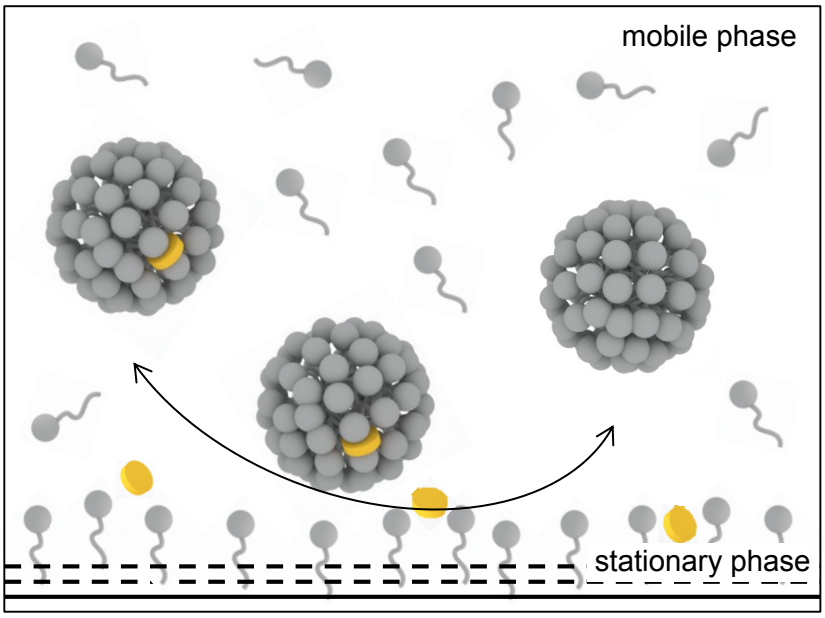


Figure 2.12: Partition behavior in MLC for very hydrophobic, highly retarded analytes; compared to Figure 2.11, a direct transfer of the solute from the stationary phase to the micelles is illustrated; adopted from reference [311].

Based on the retention of a solute, the binding behavior can be determined using the MLC technique. The binding of the solute is influenced by the environment, and is thus sensitive to

additives within the mobile phase. Consequently, the influence of an additive on the binding behavior can be monitored by means of MLC.

Description of the Retention in Micellar Liquid Chromatography

Provided, that the investigated solute exhibits binding behavior, and furthermore, assuming, that the cmc and the aggregation number is not altered due to the presence of the solute nor with increasing surfactant concentration, a relation between the retention and the partition equilibria can be formulated.[246] In 1981, Armstrong and Nome[310] were the first to establish the link between the retention behavior and the partitioning of the analyte between the three phases. Later in the 1980s Arunyanart and Cline-Love[317] introduced a model, that describes the influence of the solute/ micelle and the solute/ stationary phase binding constants based on the retention factor of the solute. A third equation was introduced and comprehensively evaluated by Foley in 1990.[318] While Armstrong and Nome derived the equation based on partition equilibria, Arunyanart and Cline-Love as well as Foley used an equilibrium approach.[173] Although derived with different approaches, the three models give equivalent connections between the partition equilibria and the retention behavior and are widely accepted.[173] A detailed derivation of the respective equations can be looked up in the corresponding publications and are summarized in reference [319] and in the Appendix A 1.2.

The equation derived by Armstrong and Nome[310] is used in the following expression.

$$\frac{V_s}{V_e - V_0} = \frac{v(P_i^{MW}\text{-}1)}{P_i^{SW}} \cdot c_m + \frac{1}{P_i^{SW}} \qquad 2.57$$

where v and c_m are the surfactant molar volume and micellar concentration (c_m=c_S-cmc) in the mobile phase, V_S and V_0 are the volume of the stationary phase and the void volume. Based on the determination of the solute's elution volume V_e with varying micellar concentration the partition coefficients P_i^{SW} and P_i^{MW} can be determined.

The approach of Arunyanart and Cline-Love[317] connects the retention factor k with the equilibrium constants K_1 and K_2 as given in equation 2.58.

$$\frac{1}{k} = \frac{K_2}{\Phi\,[L_s]\,K_1} \cdot c_m + \frac{1}{\Phi\,[L_s]\,K_1} \qquad 2.58$$

While the Armstrong and Nome equation (2.57) allows the direct determination of the partitioning between aqueous bulk phase and the stationary phase (P_i^{SW}) and between aqueous bulk phase and the micelles (P_i^{MW}), the Arunyanart and Cline-Love equation (2.58) calculates the solute/ stationary phase association constant K_1, linked to the volume ratio of the stationary to the mobile phase Φ and the concentration of the stationary phase sites [L_S].

From the solute/ micelle association constant K_2 the micelle/ water partition coefficient can be calculated:[173]

$$P_i^{MW} = \frac{K_2}{v} + 1 \qquad 2.59$$

Finally, the equation derived by Foley[318] links the retention factor to the solute/ micelle association constant according to equation 2.60.

$$\frac{1}{k} = \frac{K_2}{k_0} \cdot c_m + \frac{1}{k_0} \qquad 2.60$$

Thereby, k_0 describes the retention factor of the free solute, that is, in a micelle-free mobile phase.

All the introduced approaches can be used equivalently. They were evaluated for nonionic, anionic, cationic, and zwitterionic surfactants and are well established for the evaluation of micelle/ water partition coefficients.[173] The described retention models are also valid for hybrid micellar eluents.[173] Hence, the influence of organic modifier on the retention and partitioning can be quantified.

The described retention models are limited to components, not having very large nor very small binding constants.[173] On the one hand, retention in a reasonable time needs to be achieved for moderate surfactant concentrations. On the other hand retention times need to be sufficiently different in the presence or absence of micelles in the mobile phase.[173] Both circumstances can be enhanced, choosing an appropriate stationary phase. However, compounds with an important hydrophobic character and consequently high retention in the MLC experience high uncertainties in the evaluation. Borgerding et al.[320] derived a relation between k and c_m from the equation of Armstrong and Nome (equation 2.57) to describe the elution of such hydrophobic compounds:[173]

$$k = \frac{\Phi \cdot P_i^{SM}}{v \cdot c_m} \qquad 2.61$$

Furthermore, Jandera and Fischer[321] derived an approach for anti-binding solutes, considering a reduced stationary and mobile phase volume, since close contact is hindered due to repulsive interactions. Four different cases were described, considering the exclusion of the solute from the stationary phase, the micelle, both or neither. Equation 2.62 was depicted, which describes the retention factor in case of the solute exclusion from stationary phase as well as the micelles:

$$\frac{1}{k} = \frac{1\text{-}f_m \cdot c_m}{\Phi \cdot K_1 - \Phi \cdot K_1 \cdot f_S \cdot Q_{cmc}} \qquad 2.62$$

where f_S and f_m are the fraction of stationary and mobile phase inaccessible to the solute and Q_{cmc} the amount of adsorbed surfactant, which is assumed to be constant above the cmc.

In the case of dissociable components, the pH value of the mobile phase becomes a crucial factor for the elution, since the partition behavior is influenced significantly by the apparent charge of the analyte (cf. section 2.4.2).[311,322] Considering the mass action law and the pK_a value, the pH-dependent retention of dissociable solutes can be described by the model of Arunyanart and Cline-Love:[323,324]

$$k = \frac{k_0(1+K_2 \cdot c_m) + k_1(1+K_4 \cdot c_m) \cdot \frac{K_a}{[H^+]}}{1+K_2 \cdot c_m + (1+K_4 \cdot c_m) \cdot \frac{K_a}{[H^+]}} + 1 \qquad 2.63$$

where k_0 and k_1 are the capacity factor of the non-dissociated and the dissociated solute, respectively. Accordingly, K_2 and K_4 are defined as the micelle-binding constants of the non-dissociated and the dissociated solute. The degree of dissociation is accounted for by considering the dissociation constant K_a and the particular pH value, that is, the concentration of the hydrogen ions $[H^+]$. Further extensions were introduced by Rodgers et al.[325,326] and Torres-Lapasió et al.[322] for zwitterionic solutes and the combined description of the influence of pH and organic modifier, respectively.[311]

All in all there are a variety of equations describing the correlation between the retention and the binding of the solute to the micelles and the stationary phase. Although some of them were derived for a specific case, the equations can be used equivalently, provided that the met assumptions are true.

Besides the empirical description of the retention behavior in MLC, efforts for the modeling and prediction were made, which are summarized in the following section.

Modeling of the Retention Behavior in MLC

As described above, the retention in MLC is influenced by a number of parameters. These factors should be treated simultaneously, to assure an appropriate description of the retention. However, these variables, including pH value and kind and content of organic modifier can be interdependent and nonlinear, hence the prediction of the chromatographic behavior is a challenging task.[268]

Therefore, empirical correlations, e.g. considering the explicit changes in the microenvironment due to the addition of organic modifiers were introduced recently.[311,327–329] Starting in the late 1980s, it was attempted to describe the retention behavior in a more

general way. At that time, quantitative structure-retention relationships (QSRR) were developed, which correlate the retention in MLC measurements with e.g. the homologue carbon number of the solute[320] or its octanol/ water partition coefficient.[330,331] The QSRR correlation is based on parameters (descriptors), which are fitted for a specific micellar or hybrid (contains micelles and usually an alcohol as modifier) mobile phase. The descriptors need to be determined by the evaluation of a sufficiently large number of experimental data, to ensure reliable parameters. With the QSRR approaches, the retention of the solutes can be predicted, however, its applicability is limited to systems, where almost exclusively hydrophobic interactions need to be considered. Moreover, the inclusion of ionic solutes is a huge challenge, since the electrostatic interactions become dominant.[173] In more complex QSRR approaches a higher number of descriptors is considered, e.g. Rodriguez-Delgado et al.[332,333] introduced an additional parameter to account for the polarity to adequately describe the retention of PAHs. The most common and widely accepted approach for the description of the retention behavior in MLC and other chromatographic methods are the linear solvation energy relationships (LSER).[311,334–339] The most studied LSER is the model developed by Abraham[340] which correlates the solute's properties like the retention factor or partition coefficient (cf. equation 2.54) with solute dependent parameters expressing its excess molar refraction (E), polarizability/ dipolarity (S), hydrogen bond acidity (A) and basicity (B), and molecular volume (V) together with several solvent/ stationary phase specific regression coefficients (c, e, s, a, b, v), as shown in equation 2.64.

$$\log k = c + eE + sS + aA + bB + vV \qquad 2.64$$

The evaluation of LSER data reveals valuable information about the quality and quantity of specific interactions between the solute and mobile and stationary phase.[295,299] Descriptors are available for many different solutes, but still, the system specific regression coefficients need to be determined by performing a multiple parameter linear least square fit, based on a sufficient number of measurements.[335] Concerning the MLC, numerous measurements for each system, that is the specific mobile phase composition in combination with the used stationary phase, need to be evaluated.

To enhance the determination of the molecular descriptors, several theoretical approaches for their calculation were suggested.[341] Many of these approaches deal with a huge amount of descriptors to select the most appropriate for the given system. Previously, a reduced amount of descriptors was predicted with the COSMO-RS model, being consistent with the Abraham descriptors.[340,341] The COSMO-RS model was used before, to facilitate the solvent system selection in centrifugal partition chromatography and counter-current chromatography[342,343] and to predict retention in classical RPLC by simulating the stationary phase as pseudo-liquid molecules.[344] Also the UNIFAC model was used to predict the retention in various chromatographic processes.[345–347] Partition coefficients, which are linked to the retention factor, are predicted as the ratio of the activity coefficients of the solute in the corresponding phases. However, the drawback of the UNIFAC approach is its empiric

parameterization and the shortcoming of chemical insights provided.[335] Nevertheless, it was shown, that the chromatographic behavior can be described by means of g^E-models. Applying these methods to the MLC can contribute to a prediction of the retention behavior without the necessity of adjusting parameters.

2.5.5 Reactions in Micellar Solution

Not only from the (technical) separation point of view, but also considering biological processes, micelles are of great scientific interest. Micelles have been used for some time, to determine hydrophobic interactions, which are of central interest in biology.[16] Besides, micelles were used as comparatively simple models for a living cell component, to understand reactions and their kinetics in biological systems.[9,348,349] The publication of Menger and Portnoy in 1967[348] was pioneering in relation to the investigation of chemical and biological reactions in micelles. Its 700 citations by 2013 (according to the web of science[350]) deal with such different topics like nucleophilic substitutions,[351] oxidations,[352–355] hydrolysis,[356] electron transfer reactions,[172] phytochemical reactions,[357] and complex formation[358] in micellar media.[47,359] Due to the different environments coexisting in micellar solutions (polar nature in the aqueous bulk phase, non-polar in the micellar core, and intermediated in the transition region), all reactants, products, and eventually catalyst are solubilized, and thus favorable conditions for many chemical reactions are provided.[46] The catalytic effect of the micelles is attributed to the hydrophobic and electrostatic interactions, which also mainly influence the solubilization.[47] Depending on the kind and magnitude of these interactions and the resulting locus of solubilization, reactions can be enhanced and retarded, respectively. Since educts and products partition between the micelles and the aqueous bulk phase, the separation can be conducted subsequent or parallel to the reaction, depending on the particular separation technique (e.g. MEUF, cf. section 2.5.2). The efficiency of this reactive separation process is determined by the reaction kinetics and the partition coefficients of educts and products. Recently it was shown, that based on the formation of a complex with a preferably hydrophobic molecule, hydrophilic compounds like amino acids are solubilized within the micelles, and provided that a chiral selector is applied, racemic mixtures can be separated.[286]

The reactive separation in micellar systems is one example, to demonstrate the potential of surfactant solutions. It was shown, that analytical and separation processes can be combined with other unit operations or integrated in a multi-step process.[13,360,361] Numerous applications are conceivable, and they are all based on the selective solubilization of the compounds in micellar solutions.

In this work the applicability of surfactants is investigated for selected processes. From the areas mentioned, the focus is on the enhanced description of

(1) novel surfactant systems,
(2) the retention of analytes in MLC, and
(3) the separation efficiency in reactive separation processes.

Fundamental information for the process design and optimization arises from the LLE and the partition coefficients in multicomponent surfactant solutions. Therefore, it is aimed to provide reliable experimental techniques for the evaluation of micelle/ water partition coefficients, considering relevant parameters such as the influence of additives. For this purpose several methods are compared and their limits are evaluated. The obtained experimental data is further used for the validation of the COSMO-RS model for the prediction of partition coefficients in multicomponent surfactant systems.

Accordingly the presentation of the results of this work is structured as illustrated in Figure 2.13. The detailed description of the procedures is given in the following chapter.

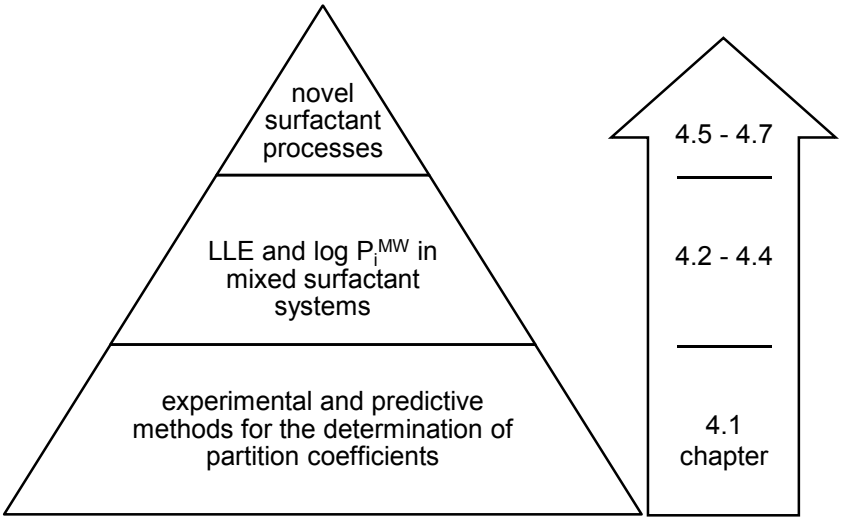


Figure 2.13: Graphic representation of the structure of the result section.

3 Material and Methods

3.1 Chemicals

Different kinds of surfactants were investigated in this work. The nonionic TritonX-100 is an octylphenol ethoxylate type surfactant with a cloud point temperature of 64-67°C,[14,362] the nonionic Brij 35 (polyoxyethylene (23) lauryl ether) has a CPT > 100°C.[14] Furthermore, the cationic cetyltrimethylammonium bromide (CTAB, Krafft temperature 22°C[363]) and methyl trioctyl ammonium chloride (Aliquat 336), and the anionic sodium dodecyl sulfate (SDS, 16°C[363]) were used. The zwitterionic 18:0 lysophosphatidylcholine (LPC transition temperature 27°C[364]) was kindly donated by the Nestlé Research Center, Lausanne, Switzerland. The characteristic data of all used surfactants is summarized in Table 3.1.

Table 3.1: Characteristic data for the surfactants investigated within this work.

Surfactant	CAS-Nr.	Formula	cmc (mmol/ L)	v (L/ mol)	Supplier	Purity
TritonX-100	9002-93-1	$C_{14}H_{21}(C_2H_4O)_nOH$	0.17-0.24[14]	0.587	Merck	≥ 98%
Brij 35	9002-92-0	$C_{58}H_{118}O_{24}$	0.09	1.12	J.T. Baker	≥ 98%
Aliquat 336	63393-96-4	$C_{25}H_{54}ClN$	0.12[365]	0.457	Alfa Aesar	99%
CTAB	57-09-0	$C_{19}H_{42}BrN$	0.92[366]	0.364	Serva	≥ 98%
SDS	151-21-3	$C_{12}H_{25}NaO_4S$	8.3[363]	0.246	Sigma-Aldrich	≥ 98.5%
LPC	19420-57-6	$C_{26}H_{54}NO_7P$	0.4µmol/ L[367]	0.524	Avanti Polar Lipids	≥ 99%

For adjusting the pH value NaOH (CAS 1310-73-2, Sigma-Aldrich, purity ≥ 99%), KOH (1310-58-3, Fluka, ≥ 86%), and HCl (7647-01-0, Sigma-Aldrich, 37%) were used. For analytics and for rinsing the ultrafiltration membrane and HPLC column acetonitrile (75-05-8, Roth, ≥ 99%), KH_2PO_4 (7778-77-0, Berud Kraft, ≥ 99%), ethanol (64-17-5, Roth, ≥ 99.8%) and methanol (67-56-1, Sigma-Aldrich) were employed. Methanol and potassium iodide (7687-11-0, Merck) were used for the determination of the void volume in the chromatographic measurements. Tetrahydrofuran (THF, 109-99-9, purity ≥ 99.8%) and n-butanol (71-36-3, ≥ 95%) were purchased from Merck, butylated hydroxytoluene (BHT, 128-37-0, ≥99%) from Fluka, phenylboronic acid (98-80-6, 97%) from ABCR and cyclooctylamine (5452-37-9, 97%) from Sigma Aldrich. All chemicals were used as received. An overview of the investigated solutes is given in Table 3.2.

Table 3.2: Solutes studied in this work.

Solute	CAS-Nr.	Formula	pK_a	Supplier	Purity
2-vanillin	148-53-8	$C_8H_8O_3$	7.91	Sigma-Aldrich	99%
3-methoxyphenol	150-19-6	$C_7H_8O_2$	9.65	Alfa Aesar	≥ 97%
4-hydroxybenzaldehyde	123-08-0	$C_7H_6O_2$	7.61	Sigma-Aldrich	≥ 98%
4-hydroxybenzoic acid	99-96-7	$C_7H_6O_3$	4.54	Sigma-Aldrich	≥ 99%
acetone	67-64-1	C_3H_6O	-	Riedel-de-Haen	≥ 99.9%
acetophenone	98-86-2	C_8H_8O	-	Sigma-Aldrich	99%
arabinose	147-81-9	$C_5H_{10}O_5$	-	Sigma-Aldrich	≥ 99%
benzaldehyde	100-52-7	C_7H_6O	-	Sigma-Aldrich	99%
benzyl alcohol	100-51-6	C_7H_8O	-	Sigma-Aldrich	99%
cellobiose	528-50-7	$C_{12}H_{22}O_{11}$	-	Alfa Aesar	98%
coumarin	91-64-5	$C_9H_6O_2$	-	Sigma-Aldrich	≥ 97%
diclofenac sodium salt	15307-79-6	$C_{14}H_{10}C_{l2}NNaO_2$	4.18	Sigma-Aldrich	≥ 99%
dopamine hydrochloride	62-31-7	$C_8H_{11}NO_2 \cdot HCl$	9.39	Alfa Aesar	99%
ephedrine hydrochlorid	50-98-6	$C_{10}H_{15}NO \cdot HCl$	10.25	Sigma Aldrich	99%
ethyl vanillin	121-32-4	$C_9H_{10}O_3$	7.6	Sigma-Aldrich	≥ 98%
ferulic acid	1135-24-6	$C_{10}H_{10}O_4$	4.7	Sigma-Aldrich	99%
glucose	50-99-7	$C_6H_{12}O_6$	-	Merck	≥ 99%
ibuprofen sodium salt	31121-93-4	$C_{13}H_{17}NaO_2$	4.41	Sigma-Aldrich	≥ 98%
isovanillin	621-59-0	$C_8H_8O_3$	8.89	Sigma-Aldrich	≥ 99.5%
lidocaine hydrochloride	73-78-9	$C_{14}H_{22}N_2O \cdot HCl$	7.96	AppliChem	≥ 99%
naphthalene	91-20-3	$C_{10}H_8$	-	Fluka	≥ 97%
p-coumaric acid	501-98-4	$C_9H_8O_3$	4.64	Sigma-Aldrich	≥ 98%
phenanthrene	85-01-8	$C_{14}H_{10}$	-	Fluka	≥ 97%
phenol	108-95-2	C_6H_6O	9.99	Riedel-de-Haen	≥ 99.5%
propranolol hydrochloride	3506-09-0	$C_{16}H_{21}NO_2 \cdot HCl$	9.5	CALBIOCHEM	≥ 98%
pyrene	129-00-0	$C_{16}H_{10}$	-	Fluka	≥ 97%
retinol	68-26-8	$C_{20}H_{30}O$	-	Sigma Aldrich	99%
salicylic acid	69-72-7	$C_7H_6O_3$	2.97	Sigma-Aldrich	99%
sodium salicylate	54-21-7	$C_7H_5NaO_3$	2.97	Sigma-Aldrich	≥ 99.5%
sucrose	57-50-1	$C_{12}H_{22}O_{11}$	-	Merck	≥ 99%
syringic acid	530-57-4	$C_9H_{10}O_5$	4.34	Sigma-Aldrich	97%
toluene	108-88-3	C_7H_8	-	Merck	≥ 99.9%
vanillic acid	121-34-6	$C_8H_8O_4$	4.51	Sigma-Aldrich	≥ 97%
vanillin	121-33-5	$C_8H_8O_3$	7.39	Sigma-Aldrich	≥ 98%

3.2 Experimental Methods

3.2.1 Cloud Point Extraction

For the cloud point extraction (CPE) experiments, the surfactant, solute, and additive were mixed with water and homogenized according to the desired concentration. On heating, the solution separates into two phases, an aqueous and a surfactant-rich phase. The phase separation was performed in the oven (Memmert from OMNILAB), the solutions were equilibrated for 65 hours.[368] The surfactant-lean phase as well as the surfactant-rich phase was analyzed as described below. The measurements were carried out three times; the error was calculated according to the t-distribution (confidence level 95%).

Both, the partition coefficient between surfactant-rich and aqueous phase $P_i^{MP/WP}$ and between the micelles and water P_i^{MW} can be derived from the CPE experiments. In Figure 3.1 $P_i^{MP/WP}$ and P_i^{MW} are represented graphically, to highlight the difference. Within this work, $P_i^{MP/WP}$ is not considered, all partition coefficients shown in the result section are P_i^{MW} values.

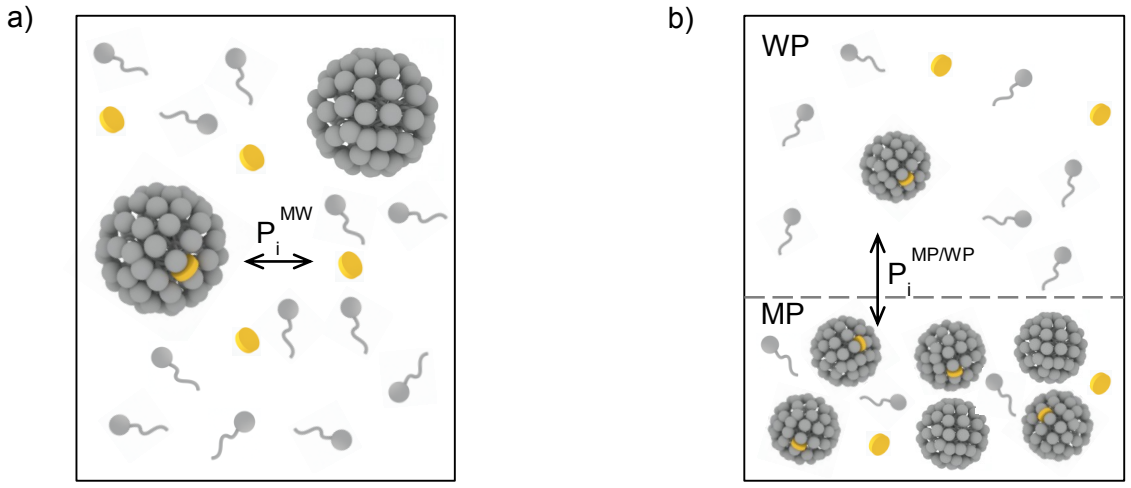


Figure 3.1: Schematic comparison of a) the micelle/ water partition coefficient P_i^{MW} with b) the surfactant-rich/ aqueous phase partition coefficient $P_i^{MP/WP}$.

The measured solute (x_i) and surfactant mole fractions (x_{Surf}) in the surfactant-rich (MP) and the surfactant-lean (WP) phase were used to calculate micelle/ water partition coefficients according to the following procedure. The solute content in the surfactant-rich phase (x_i^{MP}) was virtually separated into solute dissolved in water (according to the composition of the aqueous phase (x_i^{WP})) on the one hand and solute solubilized by the water free surfactant aggregates (x_i^{M}) on the other hand. According to the definition of the micelle/ water partition coefficient, the mole fraction of solute in the surfactant aggregates x_i^M was divided by the mole fraction of solute in water x_i^W. The respective molar fractions are calculated as:

$$x_i^M = \frac{(1-x_{Surf}^{WP}+cmc)\cdot x_i^{MP} - (1-x_{Surf}^{MP}+cmc)\cdot x_i^{WP}}{(1-x_{Surf}^{WP}+cmc)\cdot(x_{Surf}^{MP} - cmc) - (1-x_{Surf}^{MP}+cmc)\cdot(x_{Surf}^{WP} - cmc)} \qquad 3.1$$

and

$$x_i^W = \frac{x_i^{WP} - (x_{Surf}^{WP} - cmc)x_i^M}{1 - x_{Surf}^{WP} + cmc} \qquad 3.2$$

The influence of the alcohols was investigated in detail at 85°C. Therefore, the content of the alcohols in the surfactant-rich and the aqueous phase and hence the partitioning between micelles and water was analyzed. Experiments were performed as described above, the surfactant concentration was determined with HPLC, the alcohol content with GC. From the surfactant and alcohol concentration the water content was calculated by means of the mass balance.

3.2.2 Micellar Liquid Chromatography

For the determination of partition coefficients by means of the micellar liquid chromatography (MLC) an Agilent 1200 Series HPLC, equipped with a quaternary pump, tempered autosampler, column thermostat, and diode array detector was used. Data was acquired and processed with the software ChemStation (B.04.01 © Agilent 2008). Nucleodur C18 Gravity columns (Macherey Nagel, 4x125 mm, 5 µm, 100 Å) with corresponding pre-columns were employed, which are applicable for a broad pH range (pH 1-11). The mobile phase flow rate was 0.5 and 1 ml/ min, depending on the pressure drop. The pH value of the mobile phase was adjusted with NaOH and HCl, respectively. At the beginning of a series, the column was equilibrated with the surfactant solution. Subsequently, the void volume was determined by the injection of KI or methanol, before the retention of the solute was determined. The injection volume was 2 and 20 µl, the solutes were dissolved in water (retinol was dissolved in 60% ethanol, due to its low solubility in water), the column was kept at 25°C and 33°C in case of LPC. The retention volume of the solutes in single and mixed surfactant mobile phases was measured for at least five different surfactant concentrations in the mobile phase. The retention data was evaluated with the models of Armstrong and Nome[310] and Arunyanart and Cline-Love,[317] as introduced in chapter 2.5.4. A detailed list of the solute and surfactant specific parameters, including injection volume and mobile phase composition is given in the Appendix A 2.

3.2.3 Micellar Enhanced Ultrafiltration

A temperature-controlled dead end ultrafiltration cell was employed for the micellar enhanced ultrafiltration (MEUF) experiments at a transmembrane pressure drop of 4.5 bar, adjusted with nitrogen. The membranes PL-1 and YM-10 (Millipore, regenerated cellulose) with a molecular weight cut off of 1 and 10 kDa and Biomax-5 membranes (Millipore, polysulfone, 5 kDa) were used. It is assumed, that the micelles are rejected completely. For the solutes a pH-dependent rejection in the surfactant free medium was observed, and is accounted for in the calculations. The detailed rejection of solutes and surfactants is summarized in the Appendix A 3.

For the determination of the partition coefficients P_N^{MW} and $P_{I;IP}^{MW}$, the concentrations of the solute (non-dissociated and dissociated) in the feed and permeate were measured at the corresponding pH value. The composition of the retentate was determined after the filtration process, to consider the mass balance. The partition coefficient is calculated as the ratio of the solute (i) concentration in the micelle (M) and the aqueous bulk phase (W) according to the equations (2.8-2.12). c_i^W is calculated with equation 3.3, taking the rejection R_i^0 (equation 3.4) in the surfactant free solution (0) into account:

$$c_i^W = \frac{c_i^P}{1-R_i^0} \tag{3.3}$$

$$R_i^0 = 1 - \frac{c_i^{P,0}}{c_i^{F,0}} \tag{3.4}$$

with the measured concentration of the solute in the feed c_i^F and the permeate c_i^P. Based on the mass balance the solute concentration in the micelles c_i^M is calculated:

$$c_i^M = \frac{c_i^F - c_i^P \cdot (1 - c_i^F - c_S^F(V))}{c_S^F(V) - cmc} \tag{3.5}$$

considering the following assumptions: the surfactant concentration in the permeate equals the cmc; the solute concentration in the feed c_i^F changes insignificantly during the filtration process; the increasing surfactant concentration in the feed is accounted for according to equation 3.6:

$$c_S^F(V) = \frac{n_S^F - cmc \cdot \Delta V}{(n_S^F - cmc \cdot \Delta V) \cdot v^S + (n_W^F - (1 - cmc - c_i^P) \cdot \Delta V) \cdot v^W + (n_i^F - c_i^P \cdot \Delta V) \cdot v^i} \tag{3.6}$$

where ΔV is the volume of the permeate at the time of sampling (equals up to 25% of the initial feed volume) and n the amount (mole) of surfactant (S), solute (i) and water (W) in the feed (F) and permeate (P), with the corresponding molar volume v.

The separation efficiency E_i was calculated according to the work of Brennan et al.:[369]

$$E_i = \frac{(n_i^0 / V_W^0) - (n_i^1 / V_W^1)}{(n_i^0 / V_W^0)} \cdot 100\% \tag{3.7}$$

n_i^0, n_i^1, V_i^0 and V_i^1 are defined as the amount and volume of solute i and water W prior (0) and after (1) the extraction, respectively.[369]

The pH value is adjusted with NaOH (KOH in case of the sugar recovery, cf. section 4.7) and HCl. All experiments were performed at least three times (two times in case of the sugar recovery), mean values are shown as the results, the deviations are calculated according to the t-distribution, with a 90% confidence level. After each filtration the membrane was rinsed with deionsed water and ethanol.

3.2.4 Molar Solubilization Ratio

The partition coefficient of retinol was determined by means of the MSR method, which is an established method for lipophilic components. For the evaluation of the partition coefficient, the MSR is defined as given in equation 3.8:[370]

$$MSR = \frac{S - S_{cmc}}{c_S - cmc} \qquad 3.8$$

where S and S_{cmc} are the apparent solubility of the solute at the given surfactant concentration (c_S and the cmc), respectively. The MSR can be obtained graphically from the plot of the solubilized solute against the surfactant concentration. The partition coefficient can then be calculated according to equation 3.9:

$$K_i^{MW} = \frac{x_i^M}{x_i^W} = \frac{\frac{MSR}{1+MSR}}{S_{cmc} \cdot v^W} \qquad 3.9$$

with the mole fraction of solute i in the aqueous bulk phase x_i^W and in the micelles x_i^M and the molar volume of water v^W=0.018 L/ mol. S_{cmc} can be represented by the solubility of the solute in pure water.[163] In this work, the solubility of retinol in pure water of $6.2 \cdot 10^{-8}$ mol/ L[371] was used for the evaluation of the partition coefficients. In order to measure the solubility S of retinol in aqueous surfactant solutions, LPC and SDS solutions (0.1-0.5 wt%) were prepared and retinol was added in excess. All solutions were sonicated (5 min) and equilibrated (1 h, 100 rpm, 25°C (SDS) or 30°C (LPC) in a shaking water bath (OLS200 by Grant). The retinol concentration in the surfactant solution was determined by absorption measurement at 326 nm (Evolution 300 UV Vis by Thermo Scientific). Prior to the absorption measurement the samples were filtrated with 0.2 µm PTFE syringe filters to remove unsolubilized retinol.

3.2.5 Indirect Measurement, in Presence of an Organic Solvent Phase

An indirect measurement was introduced by Gobas et al.[372] to determine the partition coefficients of very hydrophobic components between water and liposomes. Within the present work this method was applied to micellar systems by the Nestlé Research Center, Lausanne, in the framework of a joint project. Therefore 200-400 mg/L retinol was dissolved in hexane (with 50 mg/L BHT). The hexane solution was mixed with an aqueous micellar

solution (10 wt% SDS and 5 wt% LPC, respectively) in a volume ratio of 1:10 and stirred on a magnetic stirring plate at 1500 rpm at 25 ± 0.5°C until equilibrium was reached (24 h).

The two phases (aqueous micellar solution and hexane) were separated by centrifugation (Rotina 38, Hettich) at 2360 g for 60 min. Samples were taken from both, the aqueous micellar and the hexane phase. From the samples of the aqueous solution, retinol was extracted 4-7 times with a THF/ hexane mixture (volume ratio 1:2) at a volume ratio of 1:3. Retinol was subsequently concentrated by rotary evaporation (Rotavapor R-210, Büchi) at 300 mbar and 40°C and finally filled up to a volume of 5 mL or 10 mL. The concentration of retinol in the samples was analyzed with a UV-spectrometer (Uvikon XS, Flowspek) at 325 nm.

Thus, the micelle/ water partition coefficient P_i^{MW} can be calculated according to the mass balance:[372]

$$P_i^{MW} = \frac{c_i^M}{c_i^W} = \frac{V_{Aq} \cdot \left(c_i^{tot} - \frac{c_i^{hexane}}{P_i^{HW}} \right)}{\frac{m_{Surf.}}{\rho_M} \cdot \frac{c_i^{hexane}}{P_i^{HW}}} \qquad 3.10$$

with the solute concentration c_i^M, c_i^W, c_i^{hexane}, and c_i^{tot} in the micelles, the aqueous bulk phase, the hexane phase, and in the water-micelles-suspension, respectively. V_{Aq} is the volume of the aqueous micellar solution, $m_{Surf.}$ and ρ_M the mass of the surfactant and micelle density, respectively. The hexane/ water partition coefficient P_i^{HW} of retinol ($\log P_i^{HW}$=5.21) was predicted with the COSMO-RS model (see section 2.2).

3.2.6 Analytics

The feed, permeate and retentate of the MEUF experiments as well as the surfactant-rich and surfactant-lean phases from CPE experiments were analyzed for the quantification of the solute (and surfactant) content. Therefore, the aforementioned HPLC apparatus was used or the analysis was performed in the central analytical laboratory, Hamburg University of Technology. The main parameters of the analytical procedures are summarized in Table 3.3.

Table 3.3: Parameters of the analytical procedures, as determined in our lab and the central analytical laboratory (CL), using the columns Zorbax Eclipse XDB-C18 column (Agilent, 4.6x150 mm, 5 µm, 80 Å), Nucleosil C18 column (Macherey Nagel, 4x125 mm, 5 µm, 100 Å), Superspher RP 18 , and a sugar Na-column (Machery-Nagel); gradient (grad.) and isocratic (isocr.) mobile phases were applied, containing acetonitrile (ACN) and different buffers (50 mmol/ L H_3PO_4, 50 mmol/ L $HClO_4$, and 20 mmol/ L KH_2PO_4). Analytes were detected with DAD, RI and FI detectors.

Analyte	Method	Column	Detecion wavelength (nm)	Mobile phase	Injection volume (µL)
3-methoxyphenol	HPLC	Zorbax	220	ACN/ water grad.	2
arabinose	HPLC_CL	Sugar	RI	water	
acetone	GC _CL		FI		
cellobiose	HPLC_CL	Sugar	RI	water	
dopamine	HPLC_CL	Superspher	275 and 317	$HClO_4$, isocr.	
ephedrin HCl	HPLC	Nucleosil	216	ACN/ KH_2PO_4 grad., pH 4.0	20
ethanol	GC _CL		FI		
glucose	HPLC_CL	Sugar	RI	water	
lidocaine	HPLC	Nucleosil	216	ACN/ KH_2PO_4 grad. pH 4.0	20
n-butanol	GC _CL		FI		
naphthalene	HPLC	Zorbax	275	ACN/ water grad.	2
phenanthrene	HPLC	Zorbax	244	ACN/ water grad.	2
phenol	HPLC	Zorbax	277	ACN/ water grad.	2
phenylboronic acid	HPLC	Zorbax	275	ACN/ water grad.	2
propranolol	HPLC	Zorbax	216 and 254	ACN/ KH_2PO_4 grad., pH 2.8	2
	HPLC_CL	Superspher	225 and 350	ACN/ H_3PO_4.isocr.	
pyrene	HPLC	Zorbax	344	ACN/ water grad.	2
sucrose	HPLC_CL	Sugar	RI	water	
TritonX-100	HPLC	Zorbax	244 and 275	ACN/ water grad.	2
toluene	HPLC	Zorbax	216 and 254	ACN/ water grad.	2
vanillic acid	HPLC	Zorbax	216 and 254	ACN/ KH_2PO_4 grad., pH 4.5	2
vanillin	HPLC	Zorbax	275	ACN/ water grad.	2

3.3 Prediction with COSMO-RS

3.3.1 Prediction of Micelle/ Water Partition Coefficients

In this work the software HyperChem (release 8.0) was used, to generate the molecular structures of all compounds, including a representative amount of conformers. The COSMO polarization charge density of all molecular structures was calculated with a full DFT optimization, performed with Turbomole 5.10,[373] a triple zeta valence polarized basis set (TZVP) and the resolution of identity (RI) approximation was used.[374–377] Using the software COSMO*therm*X (Version C21_0111_a)[378] the activity coefficients γ_i of the compounds for a defined phase composition are calculated. Based on the pseudo phase approach, a pure micellar phase and an aqueous phase containing surfactant at the cmc are assumed. The partition coefficient of the solutes can be derived from the activity coefficients as shown in equation 2.7 and 2.8.

For the evaluation of the prediction the root mean square error (RMSE) was calculated:

$$RMSE=\sqrt{\frac{1}{n}\cdot\sum_{i=1}^{n}\left(\log P_i^{COSMO\text{-}RS}-\log P_i^{exp}\right)^2} \qquad 3.11$$

Predicting partition coefficients in mixed surfactant systems, the deviation for the single surfactant systems (α=0 and α=1) $\Delta\log P_i=\log P_i^{COSMO\text{-}RS}-\log P_i^{exp}$ was considered. Therefore, the prediction at the respective composition was corrected according to the deviation of the nonionic surfactant system ($\Delta\log P_i(\alpha=0)$) and the deviation of the pure ionic surfactant according to its content x_1, as given in equation 3.12.

$$\Delta\log P_i=\Delta\log P_i(\alpha=0)+x_1\cdot[\Delta\log P_i(\alpha=1)-\Delta\log P_i(\alpha=0)] \qquad 3.12$$

3.3.2 Determination of the Micellar Composition

Alcohol Distribution

For the prediction of the distribution at finite dilution as in the case of the alcohols, an in house developed program was used for the iterative calculation of the alcohol content in the micelles and the water phase. The corresponding procedure is shown schematically in Figure 3.2.

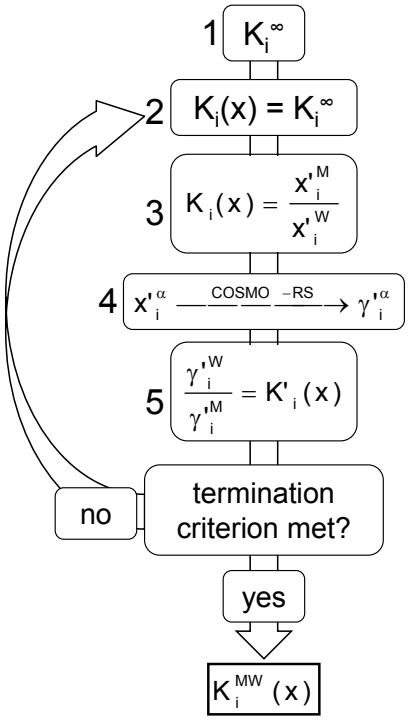


Figure 3.2: Workflow for the prediction of micelle/ water partition coefficients $K_i^{MW}(x)$ at finite concentration; 1. calculation of K_i^{∞} with COSMO-RS, 2. assumption: $K_i(x) = K_i^{\infty}$, 3. derivation of x'^{M}_i and x'^{W}_i, 4. calculation of corresponding γ'^{M}_i and γ'^{W}_i, 5. calculation of $K'_i(x)$ from γ'^{M}_i and γ'^{W}_i; termination criteria as defined in equation 3.13 and 3.14.

In the first calculation step (1), the partition coefficient K_i^{∞} was predicted with the COSMO-RS model for infinite dilution, as described in the previous chapter. Following the assumption (2), that the partition coefficient of the alcohol at a given overall concentration (0.2, 0.4, 0.6, 0.8, and 1.0 mol/ L) is equal to K_i^{∞}, the mole fractions of the solute in the micelles and the water phase $x_i'^{M}$ and $x_i'^{W}$ can be estimated (3). Therefore it is assumed, that the micelles are free of water and the surfactant concentration in the water phase is equal to the cmc. These phase compositions were further used as input for the COSMO-RS prediction (4) of the respective activity coefficients. A new partition coefficient $K_i'(x)$ was calculated from the activity coefficients (5) and compared to the initial value. The procedure was repeated until either of the following criteria is met:

$$\frac{(K_n - K_{n-1})^2}{(K_{n-1} - K_{n-2})^2} \leq 1\% \qquad 3.13$$

$$\frac{|K_n - K_{n-1}|}{|K_{n-1}|} \leq 1\% \qquad 3.14$$

where n denotes the number of the iteration steps. Based on the calculated alcohol distribution, the compositions of the surfactant-rich and surfactant-lean phase were

calculated and furthermore used as input for the calculation of the micelle/ water partition coefficients of the solutes.

Composition of the Mixed Micelles

In order to predict the partition coefficients in mixed surfactant systems, the composition of the micelles needs to be known. In this work several approaches to determine the micellar composition are evaluated and compared.

(1) Micellar Composition in an Ideal System

Considering the micelle formation as an ideal process, the mole fraction of ionic surfactant within the micelle x_1 is calculated based on the cmc of the single surfactants (cmc_1 and cmc_2) as:[47]

$$x_1 = \frac{\alpha_1 \cdot cmc_2}{\alpha_1 \cdot cmc_2 + (1-\alpha_1) \cdot cmc_1} \qquad 2.42$$

the indices 1 and 2 referring to the ionic and nonionic surfactant, respectively.

(2) Micellar Composition from the Real Solution Theory (RST)

A simple and common approach to account for the non-ideality of mixed micelles is the regular solution theory (RST). The composition can be determined iteratively with equation 2.51, based on the measured cmc data of the surfactant mixture cmc_{12}, as derived in section 2.3.3.

$$\frac{x_1^2 \cdot \ln((cmc_{12} \cdot \alpha_1)/(cmc_1 \cdot x_1))}{(1-x_1)^2 \cdot \ln((cmc_{12} \cdot (1-\alpha_1))/(cmc_2 \cdot (1-x_1))} = 1 \qquad 2.51$$

In this work, the composition for Brij 35/ CTAB and Brij 35/ SDS mixed micelles as derived from the RST were collected from literature and are summarized in the Appendix 0.[93,97,379]

(3) Approach I: Micellar Composition Derived from Experimental Cmc_{12} Data

Based on the pseudo phase approach, the cmc of a non-ideal mixture is derived as:[148]

$$\frac{1}{cmc_{12}} = \frac{\alpha_1}{\gamma_1 cmc_1} + \frac{(1-\alpha_1)}{\gamma_2 cmc_2} \qquad 2.40$$

γ_1 and γ_2 are the activity coefficients of the ionic and nonionic surfactants in the micelle. The cmc values of the single surfactants (cmc_1 and cmc_2) and the mixture (cmc_{12}) at the given surfactant composition α_1 can be determined experimentally.

In this work the activity coefficients were determined iteratively with the COSMO-RS model ($\gamma_i^{COSMO\text{-}RS}$). Therefore, the micellar composition (x_1) for the calculation of the activity coefficients was adjusted to minimize the objective function (OF) for each experimental data point (α_1/ cmc_{12}).

$$OF = \frac{1}{cmc_{12}^{exp}} - \frac{1}{cmc_{12}^{COSMO\text{-}RS}} \quad 3.15$$

with

$$\frac{1}{cmc_{12}^{COSMO\text{-}RS}} = \frac{\alpha_1}{\gamma_1^{COSMO\text{-}RS} cmc_1} + \frac{(1-\alpha_1)}{\gamma_2^{COSMO\text{-}RS} cmc_2} \quad 3.16$$

Experimental cmc data for single and mixed surfactant solutions were collected from literature.[93,97,380] A summary of the data used in this work is enclosed in Appendix A 4.

(4) Approach II: Micellar Composition Derived from Experimental Partition Coefficients

The composition of the micelles influences the solubilization capacity and thus the partition coefficient between the bulk aqueous phase and the micelles. For Approach II the composition of the micelles was calculated based on the partition coefficients of several solutes.

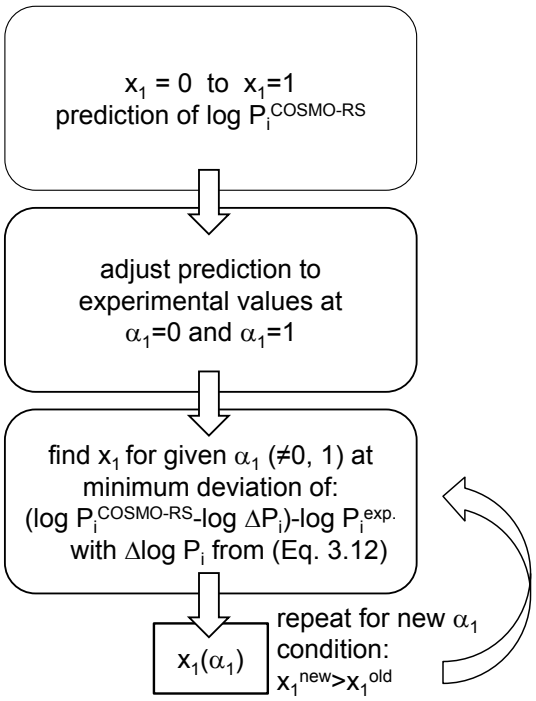


Figure 3.3: Determination of the micellar composition x_1 for a given surfactant composition α_1 as derived from experimental partition coefficients (Approach II), process is repeated for each solute, $x_1(\alpha_1)$ is calculated as mean value.

Therefore, the composition of the micelles used as the input for the prediction (with COSMO-RS) was optimized for each value, to reach a minimum deviation from the experimentally determined partition coefficient of the given solute (MLC and MEUF method). The deviation of the prediction for the single surfactant systems were considered as offset value. The final composition of the micelles was then defined as the mean value of all investigated solutes; the deviation is presented with the results. The procedure is illustrated in Figure 3.3.

3.3.3 Description of the Retention Behavior

Based on the predicted partition coefficients, the retention data can be determined by measuring the retention volume at a single surfactant concentration. Therefore, predicted partition coefficients were used in equation 2.57, together with the elution volume at a given micellar concentration of the mobile phase. Based on a single experimental data point (retention at a given surfactant concentration c_S), the surfactant concentration dependent retention is determined for selected solutes. The predicted values are evaluated based on the standard error SE:

$$SE(A)=\sqrt{\frac{1}{n-2}\cdot\sum_{i=1}^{n}\left(A_{pred.}-A_{exp.}\right)^2} \qquad 3.17$$

with A representing the quantity of interest.

3.3.4 Calculation of pK_a Values

The software COSMO*therm*X is also used for the calculation of the pK_a values. For the component i, the pK_a value is calculated with the empirical equation from the Gibbs energies of the non-dissociated and the dissociated species:[378]

$$pK_a(i)=c_0+c_1\cdot(\Delta G^{(i)}_{non\text{-}diss.}-\Delta G^{(i)}_{diss.}) \qquad 3.18$$

where c_0 and c_1 are solvent specific constants.

4 Results and Discussion

To evaluate the applicability of surfactant systems for a given process, reliable methods for the determination of micelle/ water partition coefficients are required. Furthermore, the LLE data needs to be known, in particular for processes involving a phase separation, such as the cloud point extraction. In the following chapters several techniques for the determination of partition coefficients are described and their limits are explored. For the first time, several methods are used for the same systems and the results are compared among each other. It is aimed, to investigate relevant parameters, in particular the temperature, alcohol content, pH value, and the partitioning in surfactant mixtures. Based on the experimental data, the COSMO-RS model is evaluated for the prediction of partition coefficients in multicomponent surfactant solutions. All partition coefficients presented in this chapter quantify the distribution between the pseudo phases, i. e. micelles and water, as illustrated in Figure 2.6. The individual partition coefficients are defined as summarized in the following table and described in detail in chapter 2.1.

Table 4.1: Definition of the different partition coefficients as used in this work.

Symbol	Description of the partition coefficient
P_i	Concentration based partition coefficient (mol/L)
P_N	Partition coefficient of non-dissociated solutes (mol/L)
$P_{I;IP}$	Partition coefficient of dissociated solutes (mol/L)
D_i	Partition coefficient in dependence of the pH value (mol/L)

Considering the apparent LLE and based on the introduced methods, it is intended to demonstrate the applicability of surfactant systems for selected processes. The presented results were partly published in the references [381–385].

4.1 Determination of Partition Coefficients in Surfactant Solutions

4.1.1 Evaluation of the Experimental Methods

Several experimental methods for the determination of micelle/ water partition coefficients were applied in this work. These were compared among each other as well as to literature data, if available. In the following section, the reliability of the applied methods for the

determination of micelle/ water partition coefficients is investigated. In this context, nonionic and ionic surfactants are considered.

Cloud Point Extraction

In cloud point extraction (CPE) processes, the target solute distributes between the surfactant-rich and the surfactant-lean phase according to its affinity to the micelles. For the evaluation of micelle/ water partition coefficients, the assumptions referred to in the description of the technique (section 2.5.1) need to be considered. The nonionic octylphenol ethoxylate type surfactant TritonX-100 exhibits a CPT below 100°C, and thus can be used for CPEs. To validate the CPE method, the partition coefficients of three polycyclic aromatic hydrocarbons were determined. The results are presented in Table 4.2 together with MSR measurements from different research groups, which are available in literature.

Table 4.2: Partition coefficients log P_i^{MW} of some polycyclic aromatic hydrocarbons (PAHs), different experimental methods are applied (CPE, this work and molar solubilization (MSR) method from literature); n.a.: not applicable, due to CPT limitations.

	pyrene		naphthalene		phenanthrene	
T (°C)	log P_{MSR}	log P_{CPE}	log P_{MSR}	log P_{CPE}	log P_{MSR}	log P_{CPE}
25	4.49[370] 4.36[165] 5.04[166] 5.06[163]	n. a.	3.10[370] 3.07[165]	n. a.	4.16[370] 4.03[165] 4.56[163]	n. a.
70	n. a.	4.17 ± 0.17	n. a.	2.94 ± 0.03	n. a.	3.70 ± 0.05
85	n. a.	4.15 ± 0.22	n. a.	2.96 ± 0.06	n. a.	3.43 ± 0.10

Although all referred literature data were determined by the same method, the deviation between the partition coefficients are quite high (up to $\Delta \log P_i^{MW}$=0.7). Generally, the partition coefficients of such hydrophobic solutes as PAHs are difficult to determine, since their water solubility is quite low. The data determined in this work was measured at higher temperature, since the cloud point extraction is applicable for temperatures above the CPT only. For temperatures above the CPT partition coefficients have not yet been measured. The partition coefficients, as determined in this work, were calculated from the solute concentrations in the surfactant-rich and the aqueous phase. Although in CPE experiments the structure of the surfactant aggregates (surfactant-rich phase) might deviate from the micellar structure in aqueous solution (MSR experiments), the partition coefficients between micelles and water are well comparable to the MSR method, considering, that the partition coefficient decreases with increasing temperature[173] (cf. section 2.4.1). These results demonstrate, that the micelle/ water partition coefficients can be adequately evaluated from the CPE measurements based on the assumption, that surfactants in the surfactant-rich phase aggregate in micelle-like structures.[174]

Micellar Liquid Chromatography

The micellar liquid chromatography (MLC) is a well-established method for the determination of partition coefficients and has been applied frequently.[173] For the validation of the method within this work, partition coefficients are compared to literature data in Table 4.3. All partition coefficients were evaluated with the equations of Armstrong and Nome (equation 2.57) and Arunyanart and Cline-Love (equation 2.58). Furthermore, different columns were compared for the determination of partition coefficients for selected systems. In general, the type of column and the applied equation for the evaluation did not influence the partition coefficient, as expected. However, the comparison was used as an additional proof of the reliability of the measurements. The detailed results are shown in the Appendix A 5.

Table 4.3: Comparison of partition coefficients as determined by MLC in this work and from different working groups for the nonionic surfactant Brij 35 and the cationic surfactant CTAB at 25°C.

Surfactant	Solute	log P_i^{MW} (this work)	log P_i^{MW} (literature data)
Brij 35	benzyl alcohol	1.18 ± 0.01	1.00 - 1.28[173,330,386]
Brij 35	benzaldehyd	1.36 ± 0.01	1.21 - 1.26[173,330,386]
Brij 35	acetophenon	1.46 ± 0.01	1.31 - 1.39[173,330,386]
CTAB	phenol	2.40 ± 0.25	1.83 - 2.34[156,173]

The partition coefficients are determined with a low experimental error and in good agreement with the data from literature, as demonstrated in Table 4.3. Thus, the MLC method was validated and implemented successfully as a technique for the evaluation of partition coefficients in systems with ionic and nonionic surfactants.

Micellar Enhanced Ultrafiltration

Like the MLC, the micellar enhanced ultrafiltration (MEUF) is used for macroscopically homogeneous micellar solutions. Within this work, the MEUF is applied for systems containing ionic as well as nonionic surfactants. Membranes from regenerated cellulose and polysulfone with different molecular weight cut-offs were investigated. The membrane for a particular solute/ surfactant was chosen according to the rejection as defined in equation 3.4. While the optimum membrane neither rejects the solute (i) nor the surfactant monomers (S), micelles (M) should be rejected completely, that is $R_i=R_S=0$ and $R_M=1$. In case of the micelles, that criterion was met for all experiments within this work. For some solutes, however, a pH-dependent rejection in the aqueous, micelle-free solution was observed (cf. Appendix A 3), which was considered in the calculations of the rejection due to the solubilization in the micelles, according to equation 3.3. The determined partition coefficients are compared to literature data in Table 4.4, and furthermore to the MLC and CPE method in Table 4.5.

Table 4.4: Partition coefficients $\log P_i^{MW}$ between ionic surfactant micelles and the aqueous bulk phase; comparison of the MEUF experiments with literature data.

Surfactant	Solute	$\log P_i^{MW}$ (this work)	$\log P_i^{MW}$ (literature)
SDS	toluene	2.12 ± 0.02	2.35[173]
SDS	phenol	1.63 ± 0.04	1.58[173]
CTAB	phenol	2.17 ± 0.10	1.83 - 2.34[156,173]

As illustrated by the comparison to literature data, the determination of partition coefficients with the MEUF method was implemented successfully and is performed with a small experimental error.

Table 4.5: Partition coefficients $\log P_i^{MW}$ of some phenolic compounds in the nonionic surfactant TritonX-100; comparison of experimental methods: micellar liquid chromatography MLC, cloud point extraction CPE, and micellar enhanced ultrafiltration MEUF; n.a.: not applicable, due to CPT limitations.

	phenol			3-methoxyphenol		vanillin		
T (°C)	$\log P_{MLC}$	$\log P_{CPE}$	$\log P_{MEUF}$	$\log P_{MLC}$	$\log P_{CPE}$	$\log P_{MLC}$	$\log P_{CPE}$	$\log P_{MEUF}$
10	-	n. a.	1.86±0.02	-	n. a.	-	n. a.	1.81±0.02
20	1.79±0.10	n. a.	1.83±0.05	1.96±0.10	n. a.	1.90±0.13	n. a.	-
25	-	n. a.	-	-	n. a.	-	n. a.	1.56±0.07
50	1.61±0.10	n. a.	1.54±0.06	1.76±0.09	n. a.	1.77±0.08	n. a.	1.39±0.05
70	n. a.	1.45±0.02	n. a.	n. a.	1.58±0.03	n. a.	1.37±0.12	n. a.
85	n. a.	1.40±0.01	n. a.	n. a.	1.51±0.01	n. a.	1.36±0.02	n. a.

Taking the influence of temperature into account,[173] the applied experimental methods show good agreement with each other, as compared in Table 4.5. This is especially remarkable, taking the particular structural properties into account. While the MLC, MEUF, and MSR (cf. Table 4.2) are applied in homogeneous solutions, for the CPE method a phase separation (aqueous phase and surfactant-rich phase) is required. Despite the considerable structural differences, these methods can be used equivalently for the determination of micelle/ water partition coefficients. Thus, based on the four introduced methods, partition coefficients in a wide temperature range can be determined, including ionic and nonionic surfactants. A larger deviation can be observed for vanillin at 50°C (cf. Table 4.5). Since vanillin is the most hydrophilic of the investigated compounds ($\log P_i^{OW}$=1.21), it can be assumed, that the micelle/ water partition coefficient should be smaller than for phenol ($\log P_i^{OW}$=1.46) and 3-methoxyphenol ($\log P_i^{OW}$=1.58). Thus, in case of vanillin the values obtained with MEUF seem to be more reliable. However, since the general principle of the MLC and MEUF methods differs significantly, the differences of the partition coefficients $\Delta\log P_i^{MW}$<0.4 can be regarded as moderate. Thus, for each temperature range a suitable method is provided. Partition coefficients can be determined equivalently with either method, as is done regarding the following results. In this work, the MLC was used as the main technique, since it stands out

due to automatism and robustness.[173] Therefore, the MLC was investigated in more detail, as described in the next section.

4.1.2 Determination of Partition Coefficients with MLC

For 21 solutes, which are considered as model components for food related, pharmaceutical or sewage relevant applications, partition coefficients between water and micelles were determined by means of MLC. With the chosen solutes a broad pK_a and log P_i^{OW} range is covered. In Table 4.6 the micelle/ water partition coefficients in the nonionic surfactant Brij 35 and the cationic surfactant CTAB are summarized for all solutes as measured in the non-dissociated form.

Table 4.6: Partition coefficients of non-dissociated solutes log P_N^{MW} between the aqueous bulk phase and Brij 35 and CTAB micelles, respectively; MLC retention data evaluated with the model of Armstrong and Nome[310] at 25°C; ob.: "overbinding" characteristics observed; nb.: "non-binding" characteristics observed.

	log P_N^{MW}	
Solute	Brij 35	CTAB
2-vanillin	1.53 ± 0.06	2.11 ± 0.22
4-hydroxybenzaldehyde	1.62 ± 0.09	2.12 ± 0.22
4-hydroxybenzoic acid	2.01 ± 0.05	2.59 ± 0.27
acetophenone	1.46 ± 0.02	-
benzaldehyde	1.36 ± 0.03	-
benzyl alcohol	1.18 ± 0.07	-
coumarin	1.55 ± 0.13	2.18 ± 0.07
diclofenac sodium salt	3.42 ± 0.32	ob.
dopamine hydrochloride	nb.	2.73 ± 0.28
ethyl vanillin	1.73 ± 0.12	2.35 ± 0.25
ferulic acid	2.37 ± 0.10	2.91 ± 0.10
ibuprofen sodium salt	4.00 ± 0.38	ob.
isovanillin	1.54 ± 0.06	2.36 ± 0.07
lidocaine hydrochloride	1.81 ± 0.03	2.99 ± 0.12
p-coumaric acid	2.47 ± 0.08	2.92 ± 0.12
phenol	1.68 ± 0.11	2.40 ± 0.09
salicylic acid	2.22 ± 0.09	3.77 ± 0.15
sodium salicylate	2.27 ± 0.21	3.78 ± 0.15
syringic acid	1.90 ± 0.07	2.34 ± 0.04
vanillic acid	1.89 ± 0.08	2.49 ± 0.02
vanillin	1.62 ± 0.05	2.28 ± 0.24

Generally, the measured partition coefficients are higher in the CTAB system compared to Brij 35, which can be attributed to stronger electrostatic interactions and the longer alkyl chain of CTAB compared to Brij 35.[47] For solutes, having a comparatively high partition coefficient in Brij 35 (like diclofenac and ibuprofen), a reliable determination of the partitioning in the cationic system is not possible, since the binding behavior is too strong to apply the corresponding retention models for the evaluation (here designated as “overbinding”). For the evaluation of the retention data binding behavior is mandatory.[173] Thus, partition coefficients of non-binding (weak interactions between micelles and solute), antibinding (repulsive interactions between even charged solute and surfactant) and “overbinding” (very strong attractive interactions) solutes cannot be determined with the MLC method. Alternatively, the MEUF can be applied, provided, that the concentration (and concentration differences) in the depleted aqueous solution is detectable (cf. chapter 3.2.3), or the MSR, as suggested for very hydrophobic solutes.[370]

However, in the range evaluable with the given retention models, various partition coefficients were determined and thus the potential of the MLC as an efficient technique for the determination of partition coefficients was proven. Considering the relevance of partition coefficients, the MLC is a useful tool in designing e.g. separation processes or to assess the solubilization capacity for a particular solute. Nevertheless, it was shown, that the determination of partition coefficients, in particular for very hydrophobic components is challenging and high uncertainties arise. A reliable prediction of the data can help to enhance the development and optimization of the process design. In this work the COSMO-RS model was used for the prediction of micelle/ water partition coefficients; the results are described in the following section.

4.1.3 Validation of the Prediction with COSMO-RS

In general, the predictions of micelle/ water partition coefficients with the COSMO-RS model show good agreement with experimental data, as was shown previously for e.g. SDS and TritonX-100 systems.[204,387,388] In Figure 4.1 the partition coefficients predicted with the COSMO-RS model are compared to literature data and own measurements (cf. Table 4.6) for Brij 35 and CTAB.

The majority of the data is predicted in good agreement with the experimental values. However, a wide scattering of the data is observed, especially for hydrophobic compounds (PAHs), as is particular obvious for Brij 35. The RMSE is 1.16 and 0.78 in case of Brij 35 and CTAB, respectively.

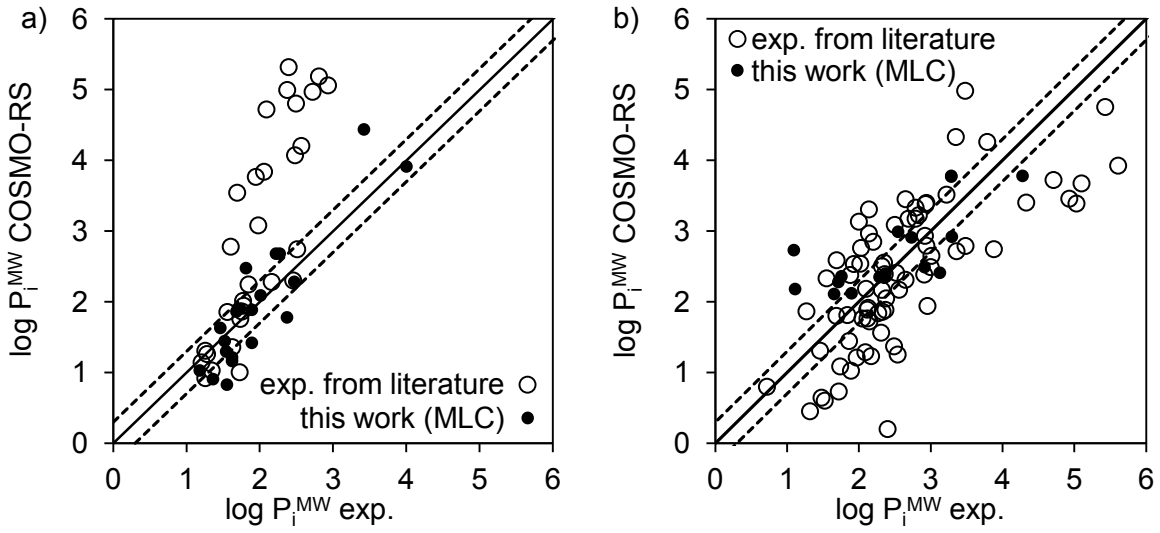


Figure 4.1: Evaluation of COSMO-RS model for the prediction of partition coefficients in a) Brij 35 and b) CTAB solutions; comparison to MLC data as determined in this work (Table 4.2) and from other research groups, summarized in the references [173,389], the dotted lines (above and below the diagonal) represent an average experimental error of 0.3 in the log P_i^{MW} scale.[204]

As was described before (cf. chapter 2.5.4), regarding very hydrophobic components, high uncertainties need to be considered for the evaluation of partition coefficients with the MLC method. In Table 4.7 the partition coefficients for some PAHs as determined by MSR for the TritonX-100 systems (cf. Table 4.2) are compared to the MLC measurements for Brij 35[173] together with the corresponding predictions.

Table 4.7: Comparison of predicted (COSMO-RS) and experimental determined partition coefficients of PAHs; experimental data: average values from literature: MSR measurements in the case of TritonX-100 (cf. Table 4.2) and MLC in the case of Brij 35.[173]

	pyrene		naphthalene		phenanthrene	
Surfactant	log $P_{exp.}$	log $P_{COSMO-RS}$	log $P_{exp.}$	log $P_{COSMO-RS}$	log $P_{exp.}$	log $P_{COSMO-RS}$
TritonX-100	4.74	4.68	3.09	3.26	4.25	4.32
Brij 35	2.48	4.07	1.60	2.78	1.94	3.77

While the prediction for the TritonX-100 micellar solution agrees well with the literature data, high deviations are observed for the Brij 35 micellar system. As was described before, similar partition coefficients are expected for different classes of nonionic surfactants.[211] Thus, one might expect close values in the case of TritonX-100 and Brij 35, as predicted with the COSMO-RS model. Nevertheless, the deviation of the prediction with the COSMO-RS model increases with the solutes' hydrophobicity, as was shown before for SDS.[389] If the PAHs are not considered in the evaluation, the RMSE of e.g. the Brij 35 partition coefficients is reduced significantly to 0.53. Thus, partition coefficients are predicted in agreement with experimental data considering nonionic and ionic surfactants.

As described in section 2.4.1 and shown in Table 4.2 and Table 4.5, besides the characteristics of the surfactant, the temperature affects the partition coefficient. The

predictability of the temperature effect with the COSMO-RS model is discussed in the next section.

4.1.4 Influence of Temperature on the Partition Coefficient as Described by COSMO-RS

In contrast to e.g. the LSER approaches (cf. chapter 2.4.3), g^E models like COSMO-RS and UNIFAC allow the explicit consideration of the effect of the temperature on the interaction energy and thus, on the partition coefficient. For the validation of the predictability of the temperature effect with the COSMO-RS model, partition coefficients were predicted for PAHs and phenolic compounds in TritonX-100. In Table 4.8 the experimental values are compared with the predicted data; in Figure 4.2 the temperature dependency is illustrated graphically for vanillin and pyrene exemplarily.

Table 4.8: Influence of the temperature on the micelle/ water partition coefficient log P_i^{MW} in TritonX-100 solutions, as predicted (pred.) with the COSMO-RS model and mean values of the different experimental methods (exp.), as presented in Table 4.2 and Table 4.5.

	phenol		3-methoxyphenol		vanillin		pyrene		naphthalene		phenanthrene	
T (°C)	exp.	pred.	exp.	pred.	exp.	pred.	exp.	pred.	exp.	pred.	exp.	pred.
10	1.86	2.32	-	2.56	1.81	1.29	-	-	-	-	-	-
20	1.81	2.14	1.96	2.38	1.9	1.28	-	-	-	-	-	-
25	-	2.05	-	2.30	1.56	1.27	4.74	4.68	3.09	3.26	4.25	4.32
50	1.58	1.64	1.76	1.91	1.64	1.21	-	-	-	-	-	-
70	1.45	1.36	1.58	1.63	1.37	1.15	4.17	4.10	2.94	2.84	3.70	3.77
85	1.40	1.18	1.51	1.44	1.36	1.08	4.15	3.90	2.96	2.70	3.43	3.58

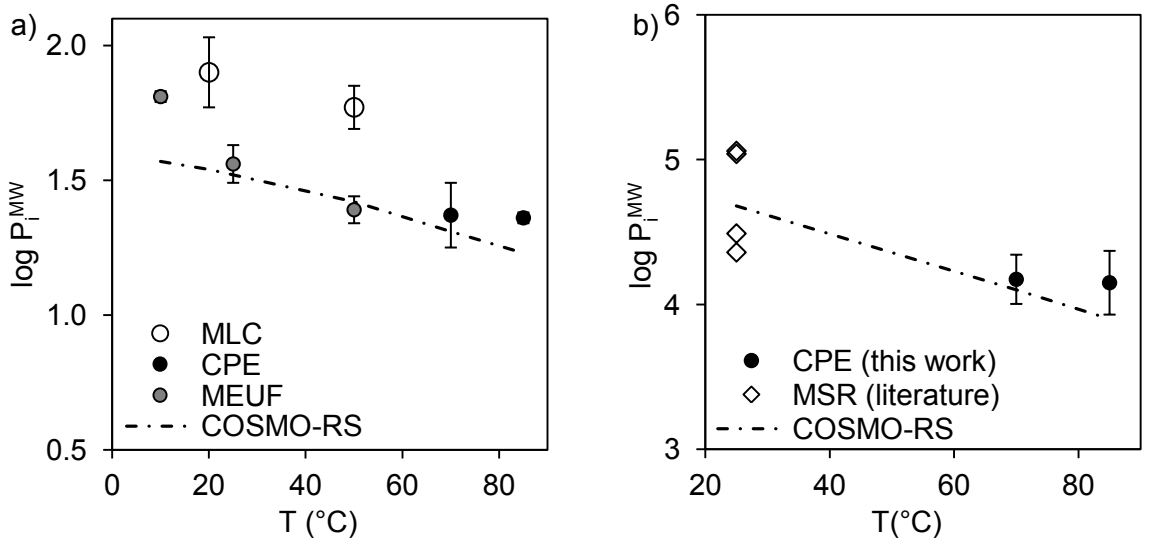


Figure 4.2: Influence of the temperature on the partition coefficient in a) vanillin and b) pyrene; comparison of the prediction with COSMO-RS and experimental data as determined in this work and from literature[163,165,166,370] (cf. Table 4.2 and Table 4.5).

The temperature dependency of the partition coefficients of the investigated compounds is well predicted by the model, although the temperature effect is slightly overestimated. Partition coefficients between the surfactant aggregates and water decrease with increasing temperature, as expected from literature. The values calculated with COSMO-RS are in good agreement with all experimental data, the effect of temperature being reflected.

Thus, in the preceding chapter 4.1 it was shown, that the COSMO-RS model gives reliable predictions for partition coefficients in ionic and nonionic micellar systems. The influence of the surfactant type and the temperature are reflected correctly. Furthermore, all applied experimental methods give reliable results, showing good agreement among each other and to literature data. Among the used techniques, the MLC is a sound method, in particular suitable for the analysis of multi component samples. Partition coefficients in the range $\log P_i^{MW}$=1.2-4.0 were measured by means of MLC with a small experimental error. The experimental error increases with higher affinity of the solutes to the micelle. As a consequence, partition coefficients for solutes showing overbinding characteristics cannot be determined with MLC. However, in combination with the other introduced methods (CPE, MEUF, and MSR), partition coefficients can be determined over a wide range of $\log P_i^{MW}$ values, including temperatures below and above the CPT, and considering ionic and nonionic surfactants. These experimental, as well as the predictive method are applied in the following, to investigate the influence of additives on the partition coefficient.

4.2 Influence of Alcohols on the Partition Equilibrium

Additives in solution will not only influence the partition coefficient of a solute between water and micelles, but will also affect the micellization and the surfactant/ water equilibrium itself (cf. section 2.3.2). In the following chapter, the influence of two different alcohols (short chain and long chain) on the surfactant/ water LLE and subsequently on the partition coefficients is described, as an example for the influence of organic additives. Based on the experimental data, the ability of COSMO-RS to predict the effects of additives on the partition equilibria is studied.

4.2.1 Influence of Alcohols on the Surfactant/ Water Equilibrium

The influence of organic additives on the partition equilibria was investigated using the CPE method (cf. section 3.2.1). In Figure 4.3 the influence of ethanol and n-butanol on the composition of the two coexisting phases is shown. The overall alcohol concentration is 0.5 mol/ L in both cases (corresponds to 2.3 wt% ethanol, 3.7 wt% n-butanol). The lines in Figure 4.3 connecting the measured points are added for better visualization, they should not be interpreted as calculated LLE curves.

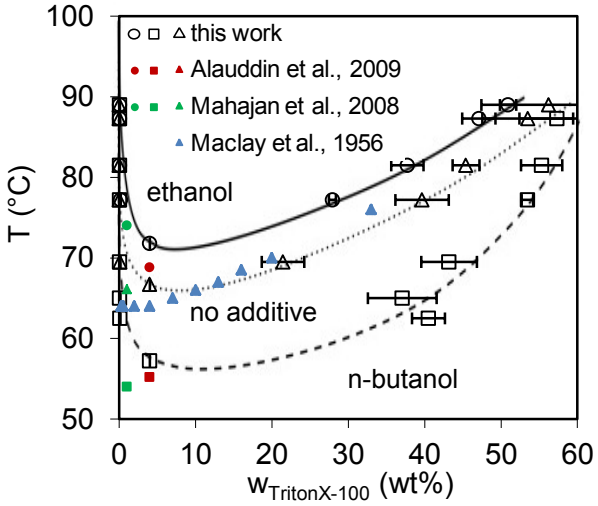


Figure 4.3: LLE of aqueous TritonX-100 solution without and with alcohol; influence of 0.5 mol/ L ethanol (circles) and 0.5 mol/ L butanol (squares) compared to aqueous TritonX-100 solution without additive (triangles); $\Delta w_{TritonX-100} \leq 5$ wt%; comparison with CPT determination experiments according to Alauddin et al., 2009[74], Mahajan et al., 2008,[62] and Maclay et al., 1956;[63] the lines were added to guide the eye.

With increasing temperature the surfactant concentration in the aqueous phase decreases, while it increases in the surfactant-rich phase. The obtained data correlates well with the CPT measurements of Maclay et al.[63] and Mahajan et al.[62] Compared to the TritonX-100 solution without additives, a shift of the LLE to higher temperatures and an increasing surfactant concentration in the surfactant-rich phase can be observed for ethanol, while butanol shows the opposite effect, as expected[62,74] (cf. section 2.3.2). These effects can be explained by different interactions of the alcohols with water, as described before. Thus, the composition of the phases can be controlled and adjusted for a given application by addition of the corresponding additive.

A detailed investigation of the influence of the alcohols on the phase composition was performed at 85°C, at which a sufficient phase separation was observed for all investigated solutions (cf. Figure 4.3). The composition of the surfactant-rich phase with increasing alcohol content is shown in Figure 4.4.

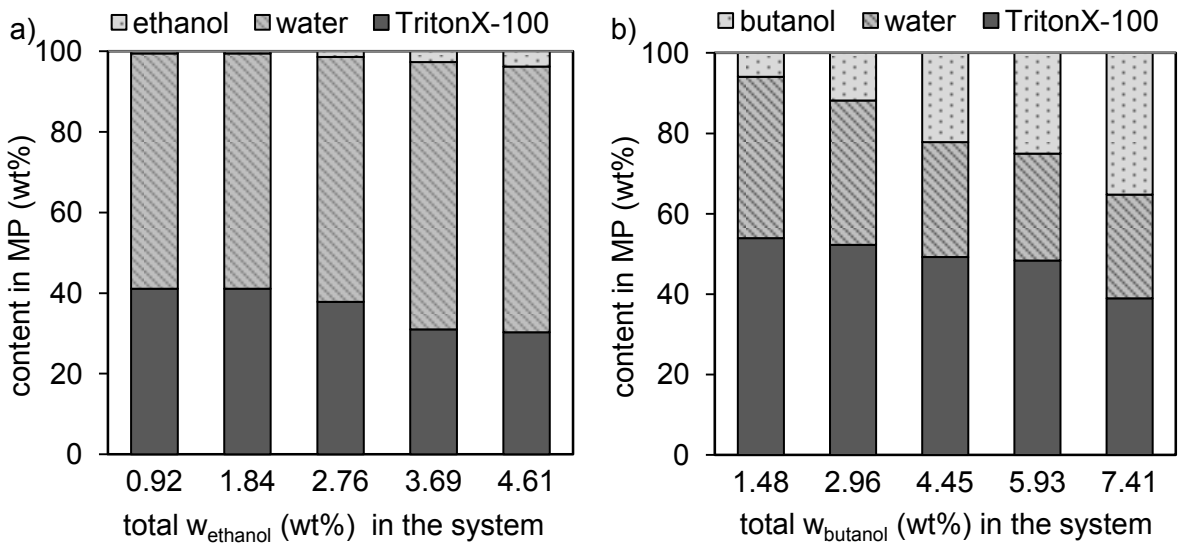


Figure 4.4: Surfactant-rich phase (MP) composition at 85°C, after 65 h equilibration time in the presence of a) ethanol and b) n-butanol; $\Delta w_{TritonX\text{-}100} \leq 1.5$ wt%, $\Delta w_{alcohol} \leq 4$ wt%; the alcohol fractions (wt%) equal 0.2 to 1.0 mol/ L.

For both alcohols, the surfactant content in the surfactant rich phases decreases, while the alcohol content increases with increasing total alcohol concentration. But also an increase of the volume of the surfactant-rich phase (related to the total volume) with increasing alcohol concentration was observed in the experiments. In case of ethanol this can be explained by the elevated water content in the surfactant-rich phase, while in case of butanol it can be attributed to an accumulation of butanol.

While the absolute amount of surfactant in the surfactant-rich phase changes marginally with increasing alcohol concentration, the amount of water depends on the kind and concentration of added alcohol. Upon addition of ethanol the amount of water in the surfactant-rich phase increases, since the polarity of the surfactant-rich phase is increased by the presence of ethanol. On the contrary, in case of butanol the amount of water in the surfactant-rich phase decreases with increasing butanol concentration, due to the reduced hydration of the surfactant head groups.[63]

To further investigate the influence of the alcohols on the respective microenvironment, the alcohol distribution between micelles and the aqueous bulk phase was determined based on the phase compositions, as described in section 3.2.1. The resulting alcohol distribution is shown in Figure 4.5 as a function of the overall alcohol concentration at 85°C. The mass balance was considered for each point. Although the vapor pressure of ethanol is comparably high (~1.3 bar at 85°C) vaporization can be neglected for concentrations up to ~6 wt% ethanol in solution. However, at higher ethanol concentrations the evaporation of ethanol leads to an additional uncertainty, as proven by the mass balance.

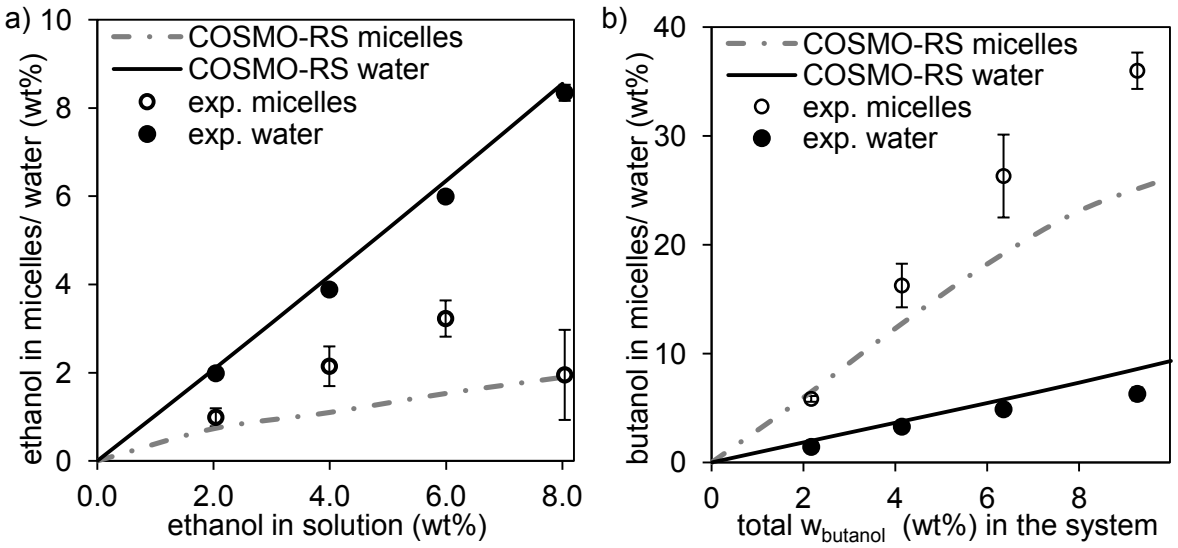


Figure 4.5: Distribution of the organic additive between aqueous bulk phase (aq phase) and (water-free) micelles at 85°C plotted against the additive fraction; comparison of experimental data with predicted values by means of COSMO-RS; influence of a) ethanol $\Delta w \leq 1.0$ wt% and b) n-butanol $\Delta w \leq 3.8$ wt%.

The concentration of additive in the micelles as well as in the bulk phase increases with increasing overall alcohol concentration in solution. As expected, ethanol is concentrated mainly in the water phase, while butanol is enriched in the micelles, due to its ability to incorporate into the micelle interior, whereas ethanol rather adsorbs on the micellar surface, but does not penetrate into the hydrophobic core of the micelle.[75,76]

As seen from Figure 4.5, the prediction with COSMO-RS reproduces the composition of the water phase correctly, whereas the alcohol content in the micelles is underestimated. It was assumed, that the additive distributes between the micelles and water. However, the structural aspects like the destruction of the micelles at high alcohol content[77] and the molecular order of highly concentrated surfactant solutions were not considered. Even so, the COSMO-RS model gives a reasonable approximation for the distribution of the additives between the micelles and the aqueous bulk phase. Hence, valuable information concerning the phase compositions is given, especially taking into account, that no fitting parameters were used.

4.2.2 Influence of Alcohols on the Partition Coefficients

With the knowledge of the phase compositions, depending on the alcohol content, micelle/ water partition coefficients in the surfactant/ water/ alcohol solution can be determined. In this work, the influence of ethanol and butanol on the partitioning of three phenolic compounds was investigated, the results are summarized in Table 4.9.

Table 4.9: Partition coefficients log P_i^{MW} of phenol, vanillin, and 3-methoxyphenol at 85°C in dependence of the ethanol and n-butanol concentration; prediction with COSMO-RS and experimental data from CPE at a surfactant concentration of 4 wt% TritonX-100.

EtOH (wt%)	phenol		3-methoxyphenol		vanillin	
	log $P_{COSMO-RS}$	log P_{CPE}	log $P_{COSMO-RS}$	log P_{CPE}	log $P_{COSMO-RS}$	log P_{CPE}
0	1.18	1.40 ± 0.01	1.44	1.51 ± 0.01	1.08	1.36 ± 0.02
0.92	1.14	1.38 ± 0.02	1.39	1.48 ± 0.01	1.03	1.32 ± 0.01
1.84	1.10	1.36 ± 0.02	1.35	1.44 ± 0.01	0.98	1.30 ± 0.01
2.76	1.07	1.31 ± 0.02	1.31	1.41 ± 0.01	0.94	1.26 ± 0.01
3.68	1.03	1.27 ± 0.02	1.26	1.41 ± 0.01	0.89	1.25 ± 0.01
4.60	1.00	1.23 ± 0.02	1.22	1.39 ± 0.01	0.84	1.23 ± 0.01
	phenol		3-methoxyphenol		vanillin	
BuOH (wt%)	log $P_{COSMO-RS}$	log P_{CPE}	log $P_{COSMO-RS}$	log P_{CPE}	log $P_{COSMO-RS}$	log P_{CPE}
0	1.18	1.43 ± 0.01	1.44	1.54 ± 0.01	1.08	1.39 ± 0.02
1.48	1.17	1.49 ± 0.01	1.42	1.57 ± 0.01	1.07	1.39 ± 0.01
2.96	1.16	1.54 ± 0.01	1.40	1.62 ± 0.01	1.04	1.42 ± 0.01
4.45	1.15	1.60 ± 0.01	1.37	1.66 ± 0.01	1.02	1.45 ± 0.01
5.93	1.12	1.62 ± 0.06	1.33	1.69 ± 0.02	0.98	1.46 ± 0.07
7.41	1.09	1.67 ± 0.03	1.29	1.72 ± 0.01	0.94	1.58 ± 0.44

With increasing alcohol concentration in solution a clear increase in solute concentration (wt%) in the aqueous bulk phase can be observed for ethanol (up to 20%), while it decreases with increasing butanol content (up to 20%). However, the partition coefficients (log P_i^{MW}) of all three solutes change only slightly, which is qualitatively reproduced by COSMO-RS (Table 4.9). Similar results were reported for the nonionic surfactant Brij 35 and the solutes benzaldehyde and benzyl alcohol.[173] For both solutes the partition coefficients decrease around Δlog P_i^{MW}=0.08 upon the addition of 15% (v/ v) (equiv. to approx. 19 wt%) ethanol.[173]

Generally, the predicted values are lower than the experimental data, which can be attributed to the overvalued decrease of the solutes hydrophobicity with increasing temperature as was shown before (section 4.1.4). The highest deviation (Δlog P_i^{MW}=0.31) between the measured and predicted values without alcohol was observed for vanillin. It can be considered as moderate, taking into account the experimental deviation of partition coefficients determined by different working groups (cf. log P_i^{MW} of PAHs in Table 4.2). In the case of n-butanol a very slight influence of the additive concentration on the partition coefficients is observed, the effect of butanol is even smaller than for ethanol. However, COSMO-RS predicts a slight decrease of log P_i^{MW} values with increasing butanol concentration. Although for butanol the trend of the experimental data is not reproduced correctly by COSMO-RS, in general the influence of the length of the alcohol alkyl chain can be predicted by the model. Butanol is a

“short long chain” alcohol, further calculations (Appendix A 6) show, that with increasing chain length, an increase of the micelle/ water partition coefficient is predicted.

In summary, additives like ethanol and butanol can be used to shift the cloud point without causing significant changes on the partition coefficient of the target compound. This could be especially advantageous for the extraction of temperature sensitive compounds with micellar systems. By means of COSMO-RS the influence of an alcohol on the partition equilibrium can be evaluated and thus the model helps to reduce the experimental efforts. Regarding extraction processes, the LLE needs to be known in addition to the partition coefficients. Compared to the partition coefficients, the LLE is strongly influenced by the presence of organic additives.

4.3 Partition Coefficients of Dissociated Solutes

In contrast to organic additives, as described in the previous section, the solution’s pH value hardly affects the LLE of micellar solutions. However, the partition coefficients of acids and bases are highly influenced at pH values close to their pK_a value. Thus, for the reliable description of the partition equilibria, the dissociation behavior of the solute and its resulting partitioning between the micelles and the aqueous bulk phase needs to be known.

4.3.1 Prediction of pK_a Values with COSMO-RS

The partition coefficients of acids and bases are highly influenced by the solutions pH value and the dissociation constant of the particular acid or base. The respective pK_a values are well studied and available from literature. However, to increase the predictive character the predictability of the pK_a values with the COSMO-RS model was evaluated for several acids (cf. section 3.3.4). In Figure 4.6 the predicted values are compared to available data from literature.

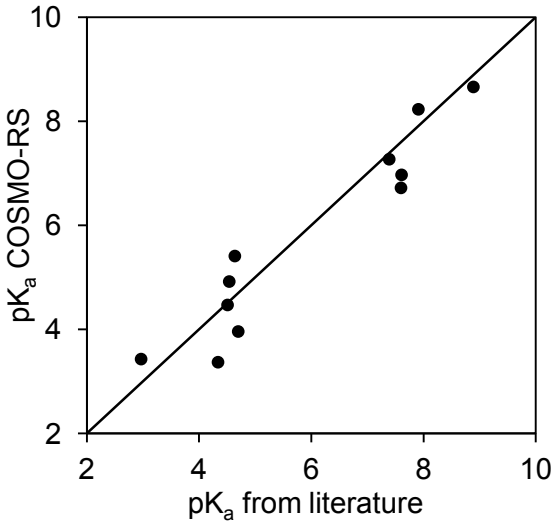


Figure 4.6: Comparison of the pK_a values predicted with the COSMO-RS model with data from literature; solutes considered: 2-vanillin, 4-hydroxybenzaldehyde, 4-hydroxybenzoic acid, ethyl vanillin, ferulic acid, isovanillin, p-coumaric acid, salicylic acid, syringic acid, vanillic acid, and vanillin; literature data from reference [390].

The pK_a values of the investigated acids are generally predicted in good agreement with the literature data. These results indicate a high quality of the description of the non-dissociated as well as the dissociated molecules. Still, the correct reflection of the interaction between the micelles and the solute under the present conditions is decisive for the prediction of the partition coefficients. Thus, in the following section, the influence of the dissociation is investigated in detail.

4.3.2 Lipophilicity Profiles in Micellar Systems

For the description of the pH-dependent partition behavior, both, the partition coefficients of the non-dissociated as well as the dissociated solute need to be determined. Thus, to elucidate the sensitivity of the partition coefficients, the partitioning of the dissociated form was determined for selected solutes in addition to the molecular form, as presented in Table 4.6 in the previous chapter 4.1. In Table 4.10 the partition coefficients of the ionized solutes, determined by MLC, are summarized for Brij 35 and CTAB.

Table 4.10: Partition coefficients of dissociated solutes log $P_{I;IP}^{MW}$ between the aqueous bulk phase and Brij 35 and CTAB micelles, respectively; MLC retention data evaluated at the mobile phase pH 10.5 with the model of Armstrong and Nome;[310] 25°C; ob.: "overbinding" characteristics observed; nb.: "non-binding" characteristics observed.

		log $P_{I;IP}^{MW}$ (dissociated solutes)	
Solute	pK_a	Brij 35	CTAB
diclofenac sodium salt	4.18	2.77 ± 0.71	ob.
ethyl vanillin	7.60	nb.	3.44 ± 0.94[a]
ferulic acid	4.70	nb.	4.06 ± 1.11[a]
ibuprofene sodium salt	4.41	1.69 ± 0.72[a]	ob.
isovanillin	8.89	nb.	3.49 ± 0.96[a, b]
p-coumaric acid	4.64	nb.	4.71 ±1.29[a]
syringic acid	4.34	nb.	3.31 ± 0.91[a]
vanillin	7.39	nb.	3.51 ± 0.96[a]

[a] deviation determined by assuming the highest relative deviation of all measurements instead of multiple determination; [b] at pH 10.5 not completely dissociated.

Using the MLC, the partition coefficients of the dissociated form could be measured only for a few solutes. Among the investigated components, these are basically the hydrophobic solutes (diclofenac and ibuprofen sodium salt) in the Brij 35 micellar solution, and the less hydrophobic components in the CTAB micellar solutions. While the partition coefficient of acidic components decreases in the nonionic surfactant (up to non-binding behavior) as the dissociation increases, the opposite trend can be observed for the cationic surfactant. The decreasing partition coefficient in Brij 35 due to increasing dissociation is attributed to the hydrophilicity of the ionized solute and was observed for the system octanol/ water and liposome/ water before.[391] In case of less hydrophobic compounds, the partition coefficient of

the ionized solute cannot be determined by means of MLC, due to non-binding behavior. In contrast, strong electrostatic interactions between the deprotonated acids and the cationic surfactant CTAB cause a significant increase of the partition coefficients. On a molecular level, the formation of ion pairs or chemical reactions could contribute to an increasing partition coefficient. Further studies are necessary to elucidate the detailed mechanism. However, due to the strong interactions, “overbinding” behavior is observed, and thus the retention data of the ionized hydrophobic components (diclofenac and ibuprofen sodium salt) cannot be evaluated. In Figure 4.7 the influence of the degree of dissociation on the distribution coefficient for selected solutes is shown for Brij 35 (nonionic surfactant) and CTAB (cationic surfactant) solutions. For the validation of the data, partition coefficients at intermediate pH were measured and are shown as well.

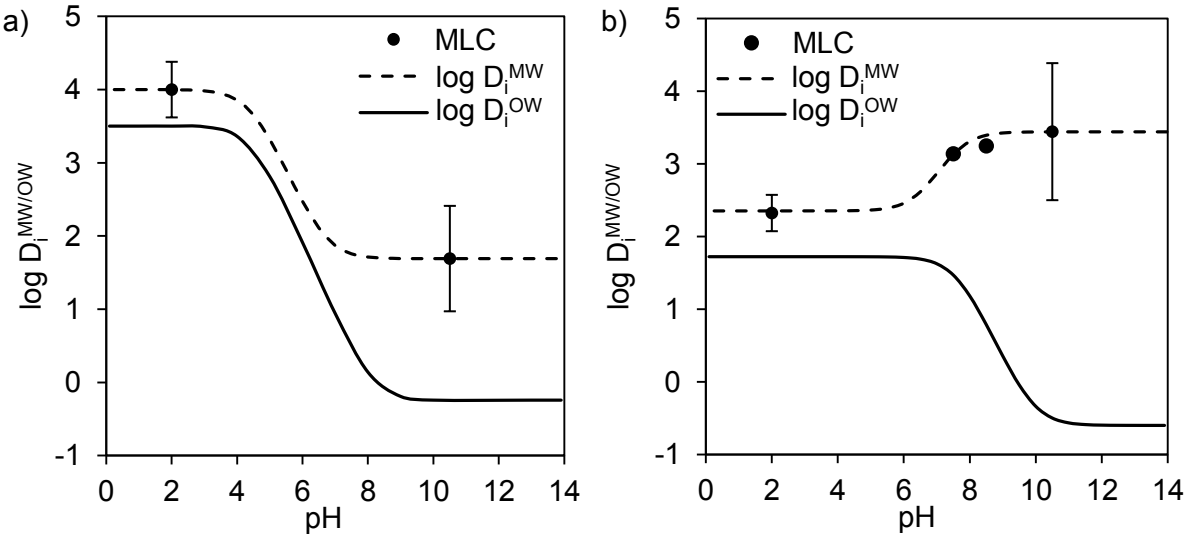


Figure 4.7: Lipophilicity profile of the acids a) ibuprofen in Brij 35 and b) ethylvanillin in CTAB; MLC retention data evaluated with the model of Armstrong and Nome;[310] 25°C; log D_i^{MW} was calculated with equation 2.13; log D_i^{OW} data from reference [390].

In case of the nonionic surfactant the lipophilicity profile resembles the one in the octanol/ water system; hence, with increasing dissociation, the partition coefficient decreases. However, as was shown for the nonionic surfactant TritonX-114, the octanol/ water partition coefficient can be used, to access micelle/ water partition coefficients of the non-dissociated species, but is less suitable to estimate the micelle/ water partition coefficient for the ionized solute.[388] This becomes particular obvious for ionic surfactant systems (compare log D_i^{MW} and log D_i^{OW} in Figure 4.7 b). Thus, the determination of micelle/ water partition coefficients based on a correlation to well-studied octanol/ water partition coefficients is inacceptable. Still, the specific experimental determination is necessary, a prediction is absolutely desirable, but requires further information about the particular molecular properties. For example the incorporation of the solute as co-surfactant and the possible formation of ion-pairs between solutes and surfactants need to be taken into account.

Thus, in the preceding chapter 4.3 the partition coefficients of dissociable solutes were investigated over the entire pH range with the MLC. While the lipophilicity profile in nonionic

surfactant solutions resembles the one in the octanol/ water system, the reverse trend is observed for acids in a cationic surfactant solution due to strong electrostatic interactions. The pK_a value of several acids is well predicted with COSMO-RS. However, the partitioning of ionized solutes cannot be correlated, nor predicted based on the known models (cf. Appendix A 7). Further research is required for the understanding of the complex interactions between ionized solutes and surfactants and micelles.

4.4 Partition Coefficients in Mixed Micellar Solutions

While partition coefficients in single surfactant solutions were determined frequently, micellar solutions containing different kinds of surfactants were far less considered. Regarding the manifold applications of mixed surfactant solutions, the knowledge of the partition equilibria is strongly required. In the following sections, the experimental determination of partition coefficients in a nonionic/ cationic and a nonionic/ anionic surfactant mixture is described over the entire pH range. Furthermore, it is investigated whether partition coefficients in mixed micellar solutions can be predicted.

4.4.1 Partition Coefficients in Nonionic/ Cationic Mixed Micellar Solutions

Only few partition coefficients in mixed micellar systems are available in literature. It was shown before, that the MLC and MEUF methods can equally be applied for the determination of partition coefficients in single surfactant systems (cf. chapter 4.1.1). In this work, both methods are applied for the first time for the evaluation of micelle/ water partition coefficients of several acids and bases at infinite dilution in mixed surfactant solutions. First, the nonionic/ cationic mixture Brij 35/ CTAB is investigated. In Figure 4.8 the partition coefficients of two selected acids at different surfactant compositions α_{CTAB} as determined by MEUF and MLC are compared.

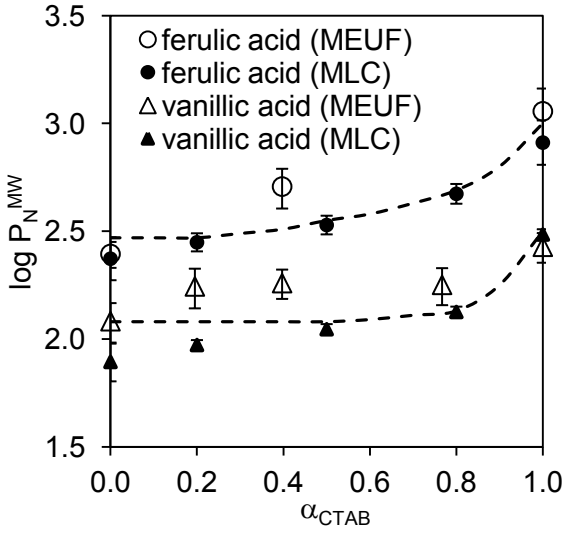


Figure 4.8: Influence of the surfactant composition on the partition coefficient (measured at pH 2) of non-dissociated acids as determined with MLC and MEUF in CTAB/ Brij 35 mixed solutions; the lines are drawn to guide the eye; $\alpha_{CTAB}=x_{CTAB}/(x_{CTAB}+x_{Brij\ 35})$ (equation 2.39).

Both methods agree well with each other, considering the deviations of very different techniques. Thus, MLC and MEUF can be used for the reliable determination of partition coefficients in mixed surfactant systems. However, the evaluation of partition coefficients log P_i^{MW}<1 is quite demanding, due to nonbinding behavior (MLC), as discussed before, and low concentrations in the micelles, which are difficult to quantify (MEUF, cf. equation 3.5). Thus, at log P_i^{MW}<1 higher deviations are expected.

In Figure 4.8 the partition coefficients of both non-dissociated acids increase with the cationic surfactant content (α_{CTAB}), predominantly at α_{CTAB} > 0.6. The influence of the cationic surfactant on the partition coefficient was investigated for several acids, the base lidocaine and the non-dissociating coumarin, to cover a reasonable hydrophobicity range (log P_i^{OW}=1.04 - 2.20; pK_a=4.34 - 9.99). As summarized in Table 4.11, the partition coefficient of all investigated solutes increases with increasing CTAB content.

Table 4.11: Partition coefficients log P_N^{MW} of non-dissociated components at various compositions α_{CTAB} of the Brij 35/ CTAB mixed micellar solutions, determined by MLC at pH 2 in case of the acids and at pH 10.5 in case of lidocaine and coumarin.

	log P_N^{MW}						
α_{CTAB}	lidocaine	coumarin	isovanillin	phenol	syringic acid	ferulic acid	vanillic acid
0.00	1.81 ± 0.03	1.55 ± 0.13	1.54 ± 0.06	1.68 ± 0.11	1.89 ± 0.12	2.37 ± 0.10	1.89 ± 0.09
0.05	1.69 ± 0.15	1.57 ± 0.13	-	-	-	-	-
0.10	1.72 ± 0.15	1.64 ± 0.14	-	-	-	-	-
0.15	1.75 ± 0.15	1.52 ± 0.13	-	-	-	-	-
0.20	1.82 ± 0.16	1.59 ± 0.09	1.60 ± 0.04	1.75 ± 0.01	1.86 ± 0.02	2.45 ± 0.04	1.97 ± 0.02
0.50	2.13 ± 0.18	1.69 ± 0.14	1.65 ± 0.04	1.77 ± 0.01	1.95 ± 0.02	2.53 ± 0.04	2.05 ± 0.02
0.80	2.24 ± 0.19	1.85 ± 0.03	1.86 ± 0.04	2.06 ± 0.01	1.98 ± 0.02	2.67 ± 0.05	2.13 ± 0.02
0.90	2.34 ± 0.20	2.02 ± 0.17	-	-	-	-	-
1.00	2.99 ± 0.04	2.18 ± 0.08	2.36 ± 0.19	2.40 ± 0.25	2.34 ± 0.04	2.91 ± 0.10	2.49 ± 0.02

As was described before (cf. chapter 4.1.2), the partition coefficients in pure CTAB micelles are higher compared to Brij 35 micelles, which can be attributed to stronger electrostatic interactions and the different structure of the micelles. Accordingly, the data reveals, that at higher CTAB content, the partition coefficients increase gradually. However, the correlation between α_{CTAB} and log P_i^{MW} is non-linear, as illustrated in Figure 4.8. Due to the non-ideality of the micelle formation (cf. section 2.3) the composition of ionic/ nonionic micelles (x_1) differs significantly from the surfactant composition in the solution (α_1).[47,84] As the CTAB content in the mixed micelles x_{CTAB} increases less compared to the solution composition α_{CTAB}, (cf. Figure 2.5),[93] a correlation between x_{CTAB} and log P_i^{MW} can be assumed.

4.4.2 Partition Coefficients in Nonionic/ Anionic Mixed Micellar Solutions

Besides CTAB, the influence of the anionic surfactant SDS on the partition coefficients in aqueous Brij 35 solutions was investigated. The partition coefficients for bases, non-dissociable molecules and an acid for various surfactant compositions are summarized in Table 4.12. In Figure 4.9 the influence of the anionic and the cationic surfactant on the partition equilibrium of phenol is compared as an example. As shown in Figure 4.9, good agreement of the partition coefficients to available literature data in all single surfactant micelles was observed.

Table 4.12: Partition coefficients log P_N^{MW} of non-dissociated components for various compositions α_{SDS} of the Brij 35/ SDS mixed micellar systems, determined by MEUF.

	log P_N^{MW}						
α_{SDS}	propranolol	lidocaine	ephedrine	syringic acid	acetone	toluene	phenol
0.00	2.93 ± 0.01	1.66 ± 0.03	1.61 ± 0.02	1.89* ± 0.12	0.79 ± 0.12	2.00 ± 0.02	1.61 ± 0.02
0.20	3.02 ± 0.01	1.73 ± 0.02	-	1.60 ± 0.02	-	-	-
0.40	3.17 ± 0.02	1.83 ± 0.05	1.57 ± 0.01	1.56 ± 0.02	0.77 ± 0.53	2.19 ± 0.03	1.57 ± 0.01
0.75	3.28 ± 0.02	2.05 ± 0.04	1.52 ± 0.01	1.48 ± 0.02	0.72 ± 0.62	2.19 ± 0.02	1.52 ± 0.01
1.00	3.76 ± 0.07	2.97 ± 0.03	1.63 ± 0.04	1.80 ± 0.01	0.59 ± 0.28	2.12 ± 0.02	1.63 ± 0.04

* determined by MLC

The influence of SDS on the partitioning of syringic acid, acetone, toluene and phenol is comparatively small. Similar effects were observed for PAHs and some synthetic perfumes: the partition coefficient log P_i^{MW} changes marginally, and even tends to have a minimum at intermediate nonionic/ anionic surfactant compositions.[139,165,166]

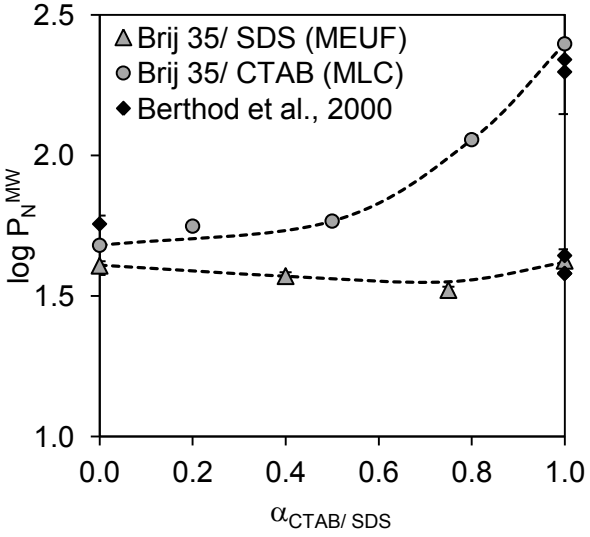


Figure 4.9: Influence of the surfactant composition on the partition coefficient (measured at pH 2) of phenol in anionic (SDS) and cationic (CTAB)/ nonionic (Brij 35) mixed micellar systems; literature data from Berthod et al., 2000;[173] the lines are drawn to guide the eye.

In general, the solubilization characteristics can be attributed to the solutes hydrophobicity, the interaction between the surfactants in the mixed micelle, and micellar characteristics such as its size, density and charge density on the surface of the micelle.[84,139,165,392] Regarding the investigated ionic surfactants, besides the charge of the head group, CTAB and SDS differ in the length of the alkyl chain (C_{16} and C_{12}), which has an impact on the solutes partition coefficient. It was shown, that the structure of Brij 35 micelles remains basically unchanged upon the incorporation of SDS molecules, but its conformation changes due to the addition of CTAB.[393] The hydrocarbon environment remains relatively constant, though, in case of CTAB incorporation the hydrophilic chains become looser, which facilitates the diffusion of water molecules into the palisade layer.[393] Thus, the characteristics of the palisade layer and of the surface of the micelle become dominant concerning the partitioning of the investigated components and result in higher partition coefficients in the CTAB compared to the SDS system. Especially the increased electrostatic interactions between the micelle and the solute's alcohol, ketone, carboxylic acid and ether groups are enhanced significantly due to the incorporation of ionic surfactants. In the case of the bases propranolol, lidocaine, and ephedrine a further increase of the interaction between SDS and the solute due to the additional amine groups, results in higher partition coefficients (cf. Table 4.12). The influence of electrostatic interactions becomes even more pronounced for ionized solutes, as was shown before for single surfactant micelles (cf. section 4.3). A detailed investigation of the effect of the micellar composition on the partition coefficient of dissociated solutes is described in the following section.

4.4.3 Partition Coefficients of Dissociated Solutes

The partition coefficients of the investigated acids and bases are highly influenced by the solution's pH value. For the description of the pH-dependent partition behavior, both, the partition coefficients of the non-dissociated as well as the dissociated solute needs to be determined. In this work the partitioning of the ionized acids (and bases) was determined in the CTAB (and SDS) mixed system only, since a pronounced effect is expected. The measured values are summarized in Table 4.13 and Table 4.14 for the CTAB and SDS mixed system, respectively.

Table 4.13: Partition coefficient $\log P_{I;IP}^{MW}$ of dissociated acids in Brij 35/ CTAB mixed micellar solutions; determined by MLC at pH 10.5; nb.: non binding solute, ob.: "overbinding" effect.

	$\log P_{I;IP}^{MW}$ (dissociated solutes)			
α_{CTAB}	isovanillin	syringic acid	ferulic acid	vanillic acid
0.00	nb.	nb.	nb.	nb.
0.05	1.38 ± 0.04	1.83 ± 0.50	1.90 ± 0.23	1.83 ± 0.50
0.10	1.74 ± 0.05	2.26 ± 0.62	2.63 ± 0.32	2.28 ± 0.63
0.15	1.76 ± 0.06	2.63 ± 0.72	2.98 ± 0.36	2.61 ± 0.71
0.20	2.36 ± 0.07	ob.	ob.	ob.
0.50	2.59 ± 0.08	ob.	ob.	ob.
0.80	2.54 ± 0.08	ob.	ob.	ob.
0.90	2.82 ± 0.09	ob.	ob.	ob.
1.00	3.49 ± 0.96	ob.	ob.	ob.

As expected, the partition coefficients of the dissociated solutes increase significantly with the ionic surfactant content. More than $\Delta\log P_{I;IP}^{MW}=3$, which corresponds to a factor of 1000, was observed comparing ionic with nonionic micelles; the broad range in between is covered by the corresponding mixtures. The MLC method is restricted to solutes with binding characteristics,[173] which does not apply for all ionized solutes investigated in this work. In case of the Brij 35 micelles, nonbinding behavior (nb.) was observed, while at an elevated CTAB content very strong binding, designated as "overbinding" (ob.), permits the evaluation with the retention models, as was described before. The MEUF method covers a broader range of partition coefficients with a small deviation and is limited only due to the detection limits of the analytical methods.

Table 4.14: Partition coefficient $\log P_{I;IP}^{MW}$ of dissociated bases in Brij 35/ SDS mixed micelles; determined by MEUF at pH 2.

	$\log P_{I;IP}^{MW}$ (dissociated solutes)			
α_{SDS}	propranolol	lidocaine	ephedrine	dopamine
0.00	1.66 ± 0.01	0.35 ± 0.20	0.52 ± 0.18	0.44 ± 0.19
0.20	3.02 ± 0.01	1.70 ± 0.03	1.46 ± 0.03	1.42 ± 0.02
0.40	3.84 ± 0.01	2.30 ± 0.03	2.18 ± 0.01	1.92 ± 0.02
0.75	4.77 ± 0.08	3.15 ± 0.01	2.96 ± 0.01	2.51 ± 0.03
1.00	4.78 ± 0.11	3.89 ± 0.06	3.30 ± 0.02	3.15 ± 0.02

For selected solutes (isovanillin and lidocaine) the partition coefficients in Brij 35/ CTAB and Brij 35/ SDS mixed micelles are compared in Figure 4.10 regarding their non-dissociated and dissociated form.

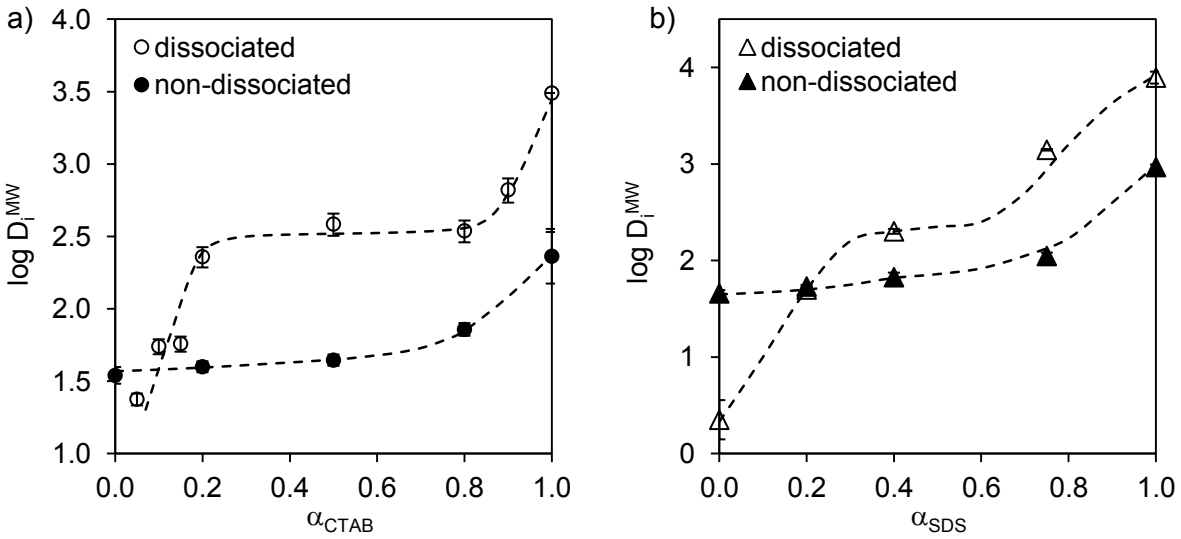


Figure 4.10: Influence of the surfactant composition on the partition coefficient of dissociated and non-dissociated a) isovanillin (Brij 35/ CTAB) determined with MLC (pH 2 and 10.5) and b) lidocaine (Brij 35/ SDS), determined with MEUF (pH 2 and 12); the lines are drawn to guide the eye.

Compared to the non-dissociated solute, the dissociated acid/ base shows two distinctive regions (cf. Figure 4.10). Analogues to the non-dissociated solute an increase in the partition coefficient at high ratios of ionic surfactant $\alpha_1 > 0.6$ can be observed. An additional increase is recognizable at low ratios of ionic surfactant up to $\alpha_1 \approx 0.2$. These effects can be attributed to the strong electrostatic interactions between the ionized solute and the ionic surfactant. Similar effects were observed in recently published studies for single partially dissociated solutes: the solubilization in single[187,190] and mixed surfactant systems[150] is enhanced significantly due to ion/ ion surfactant/ solute interactions. These effects could be attributed to ion pair formation or chemical reactions of the ionized component and the ionic surfactant. However, to fully understand the precise mechanisms and to define influencing factors, apart from the micellar composition, further research is required. The experimental data determined in this work can contribute in illuminating these effects.

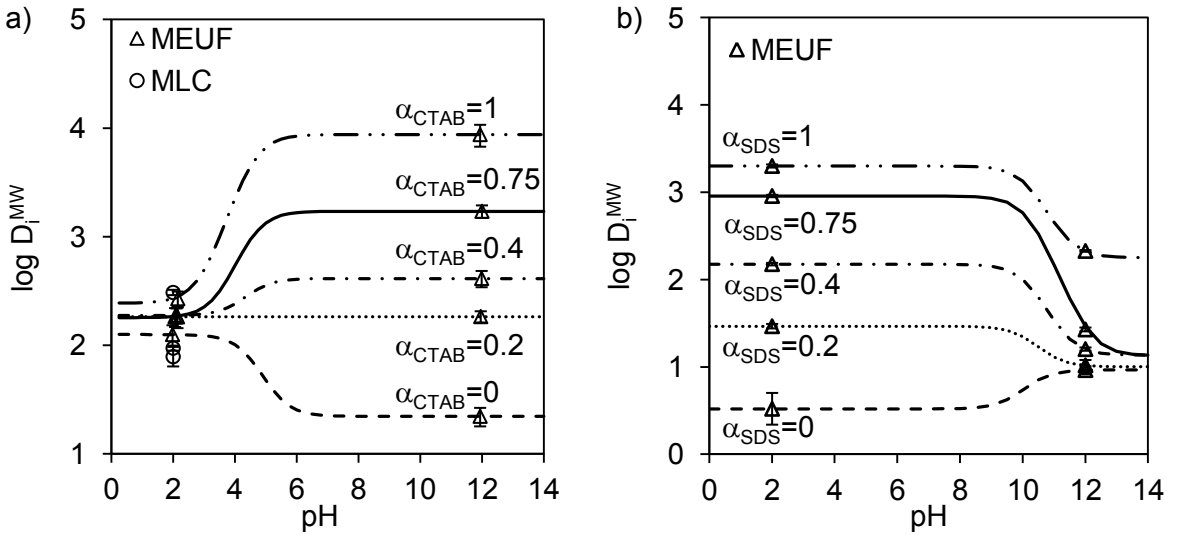


Figure 4.11: Lipophilicity profile of a) vanillic acid in Brij 35/ CTAB mixed system and b) ephedrine in Brij 35/ SDS mixed micelles; the lines are derived from equation 2.13 and 2.14, respectively.

In Figure 4.11 the complete lipophilicity profiles are shown for vanillic acid in the CTAB/ Brij 35 systems and for ephedrine in the SDS/ Brij 35 system. Based on the partitioning of the non-dissociated and the dissociated solute lipophilicity profiles for nonionic/ anionic and nonionic/ cationic surfactant mixtures are provided. In Figure 4.11 the immense variability of micellar systems is illustrated. By adjusting the pH value and the surfactant composition, optimal conditions for e.g. extraction and solubilization processes can be defined. A wide range of partition coefficients is covered, reaching up to three orders of magnitude. The results show, that micellar systems are highly flexible and tunable aqueous solutions, applicable to a variety of practical issues.

4.4.4 Prediction of Partition Coefficients in Mixed Micellar Systems

Composition of the Mixed Micelles

Up to now, only one publication describing the partition coefficients in mixed micellar systems is available, which is based on the geometric mean equation (cf. section 2.4.3).[150] In the present work, the thermodynamic model COSMO-RS is evaluated for the first time for the prediction of partition coefficients in mixed micellar systems. The crucial factor for the prediction of the micelle/ water partition coefficients is the composition of the mixed micelles. However, the composition is not directly accessible by experimental investigations. Thus, several approaches for the description of the micellar composition were compared, as explained in detail in section 3.3 and summarized in Table 4.15. The calculated micellar compositions using the various approaches are illustrated in Figure 4.12.

Table 4.15: Approaches for the determination of the mixed micelles composition evaluated in this work.

Approach	Basic assumptions
$x=\alpha$	Composition of the micelle (x_1) equals the surfactant composition in the solution (α_1)
ideal	cf. equation 2.42
RST	cf. equation 2.51
Approach I	cf. equations 3.15 and 3.16 activity coefficients are predicted with COSMO-RS
Approach II	cf. Figure 3.3 predicted partition coefficients are fitted to experimental data for all investigated solutes (Table 4.11 in case of the CTAB mixed micelle; Table 4.12 in case of the SDS mixed micelles); x_1 is given as average value

The micellar composition depends on the cmc values of the corresponding surfactants (cf. equation 2.42 and 2.51) and the surfactant-surfactant interactions.[82,89,144] The higher values of x_1, as determined by the RST compared to the ideal composition reveals the negative deviation from ideality in micelle formation. This effect is more dominant for the SDS mixed

micelle due to stronger interaction between Brij 35 and SDS compared to Brij 35/ CTAB.[93,97,150,379]

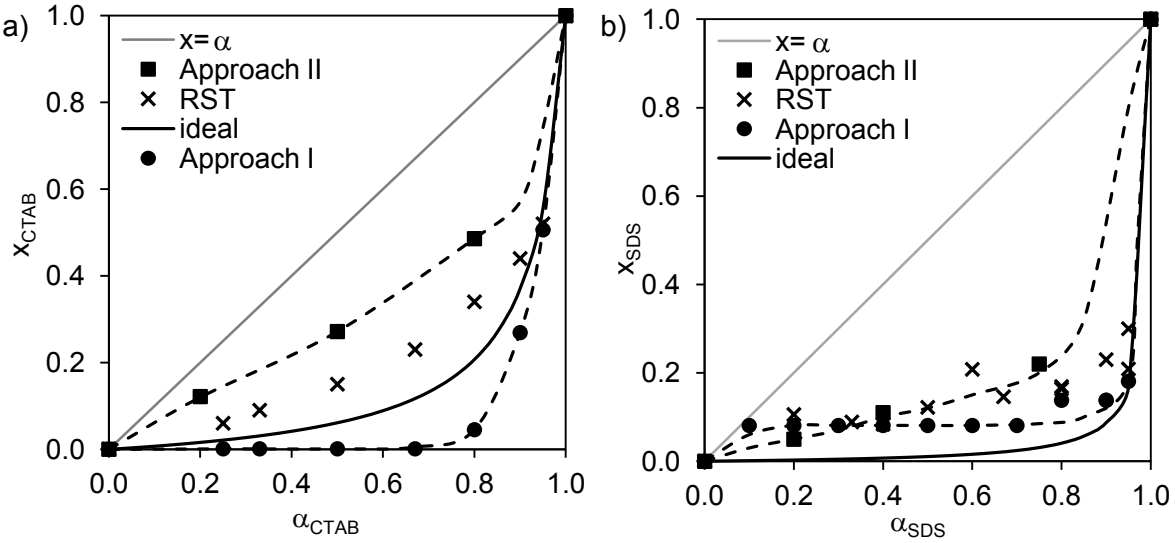


Figure 4.12: Composition of the mixed micelles as determined by the different approaches (cf. Table 4.15) a) Brij 35/ CTAB b) Brij 35/ SDS; cmc_{12}^{exp} (Approach I) and RST data from references [93,97,379,380] as summarized in the Appendix A 4; the dashed lines are drawn to guide the eye.

The values determined with the COSMO-RS based approaches (Approach I and II) are close to the RST values in case of SDS mixed micelles. However, considerable differences are observed for Brij 35/ CTAB mixed micelles. While the prediction based on the cmc data (Approach I) reveals significantly less, the prediction based on the partition coefficients (Approach II) yields considerably increased ionic surfactant content in the micelles. Though, compared to the other procedures, Approach II is not based on cmc data of the single and mixed surfactant systems but on experimental partition coefficients. Thus, provided that partition coefficients in mixed surfactant systems are available, the micellar composition can be determined by adjusting the prediction with COSMO-RS.

Prediction of Partition Coefficients Based on Known Micellar Compositions

The composition of the mixed micelles, as revealed from the different approaches, was used as input to predict the partition coefficients with the COSMO-RS model. Similar trends as described for the micellar composition were observed for the solutes' partitioning, as shown in Figure 4.13.

For a given CTAB composition the partition coefficients increase in the following order: Approach I < ideal < RST < Approach II < (x=α). For the evaluation of the predictions the deviation (RMSE) from the measured data was calculated, taking the deviation of the single surfactant systems into account. It follows the order: (x=α) > Approach I > ideal > RST > Approach II. As for the micellar composition, the partition coefficients in the SDS mixed micelles do not differ significantly, assuming the different approaches. The deviation from the experimental data follows the order (x=α) > ideal > Approach I > RST > Approach II.

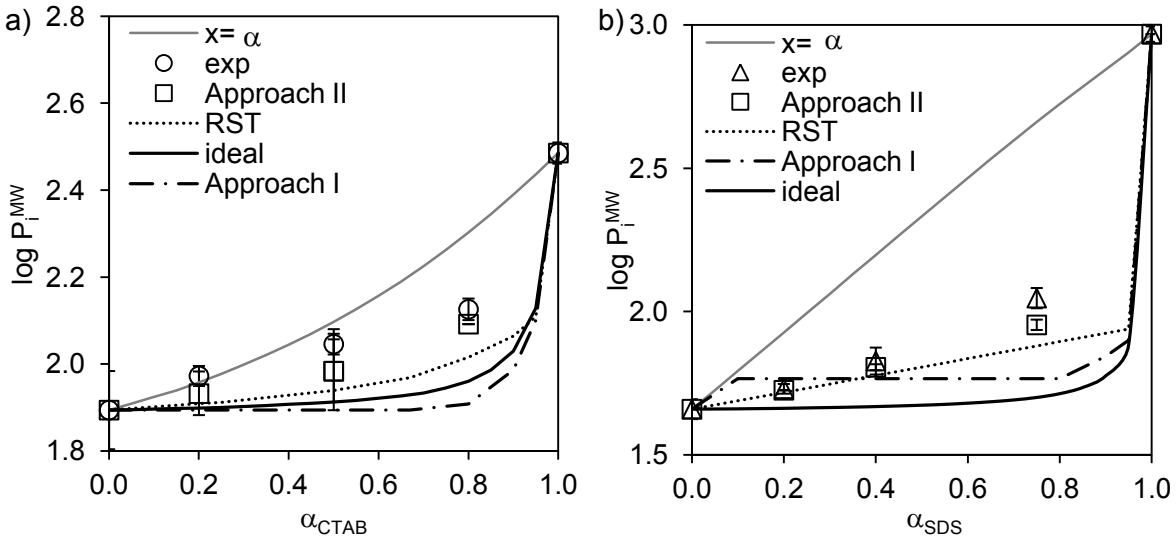


Figure 4.13: Prediction of partition coefficients in mixed micelles based on the different approaches a) vanillic acid in Brij 35/ CTAB micelles b) lidocaine in Brij 35/ SDS; offset for the prediction in single surfactant systems was accounted for (cf. equation 3.12).

As expected, Approach II is very close to the experimental data. But also the RST method gives very good results for the predicted partition coefficients. The composition of mixed micelles, as derived from the RST is already published for a variety of binary surfactant mixtures and can otherwise be determined based on the cmc values of the single surfactants and the corresponding mixture. Thus, the RST provides the necessary accuracy concerning the micellar composition for the reliable prediction of the partitioning of non-dissociated components in mixed micellar systems with models like COSMO-RS. Besides the cmc values no experimental data and no fitted parameters are used for the prediction. Alternatively, the micellar composition can be determined based on experimental partition coefficients (Approach II), as described in the previous section, and subsequently be used for the prediction of further solutes.

In the preceding chapter 4.4, lipophilicity profiles in mixed micellar systems were investigated comprehensively. It was shown, that adjusting the surfactant composition and the pH value, the micelle/ water partition coefficient can be customized in the range of up to three magnitudes. For the non-dissociated solutes these partition coefficients can be predicted successfully with COSMO-RS if the composition of the mixed micelles is known.

Together with the previous chapters 4.1 to 4.3 it was illustrated, that based on the introduced methods, partition coefficients can be determined reliably. The influence of temperature, organic additives, pH value and surfactant composition was analyzed experimentally and predicted with COSMO-RS. In the following chapters, the suitability of surfactant solutions will be investigated for selected applications.

4.5 Partition Coefficients in Food Applications

The solubilization of components like PAHs,[394] but also of e.g. drugs[395] can be increased dramatically in micellar solutions. Moreover, it was shown, that the stability of drugs as well as vitamins is increased in presence of micelles.[6,7] However, especially in pharmaceutical and food industry the use of additives is strictly regulated and the choice of surfactants is limited. For pharmaceutical and food applications, the micelle forming agents should originate from compounds, which are approved for the food industry (e.g. lipids, proteins or polysaccharides).[6] The zwitterionic lipid based lysophosphatidylcholines (LPCs) are hydrolysed lecithins, which are obtained from natural sources[396–399] and are applied for the stabilization of dispersions and the solubilization of biomaterials.[6,400–402] Furthermore, LPC was used to enhance the solubilization and absorption characteristics, and thus proved to be a suitable, food ingredients approved surfactant.[403–407] Within this work, the partitioning of food relevant molecules between water and LPC micelles is investigated based on the introduced methods.

4.5.1 MLC for the Determination of Partition Coefficients in Novel Surfactant Systems

In the previous chapters it was shown, that the micellar liquid chromatography is an efficient and well-established method for the reliable determination of partition coefficients. The evaluation of the data is based on retention models, as described in chapter 2.5.4. However, these equations were applied mainly for the determination of the partition behavior in presence of ionic (SDS, CTAB) and nonionic surfactants (Brij 35); zwitterionic surfactants were rarely used in MLC. Nevertheless, it was shown, that the retention models developed for ionic and nonionic are also applicable for zwitterionic surfactants.[287,408] Lipid derived surfactants were not used in MLC at all. For the evaluation of the MLC for the determination of partition coefficients between LPC and water four natural and artificial flavor compounds were chosen as model solutes for pharmaceutical and food applications (isovanillin, ethylvanillin, 4-hydroxybenzaldehyde, and coumarin). For isovanillin and ethylvanillin the retention data for an increasing LPC concentration in the mobile phase is shown exemplarily in Figure 4.14.

For all four solutes used within this study (isovanillin, ethylvanillin, coumarin and 4-hydroxy-benzaldehyde) a decreased retention with increasing LPC concentration is observed. Thus, the binding of the solutes to the micelles, which is mandatory for the evaluation of partition coefficients, is given.

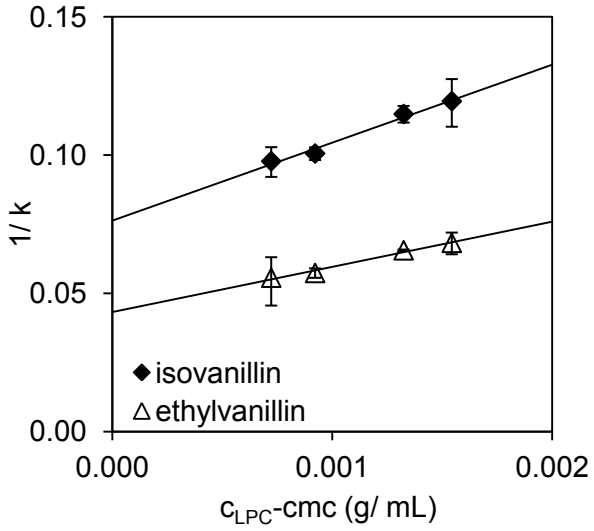
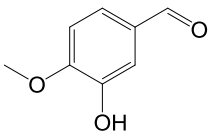
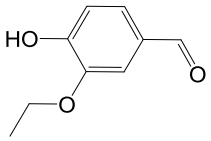
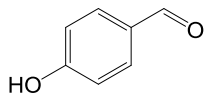
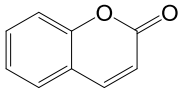


Figure 4.14: Reciprocal of the retention factor ($1/k=V_0/(V_e-V_0)$) of isovanillin and ethylvanillin with increasing LPC concentration.

The partition coefficient increases with increasing slope and decreasing intercept of the linear plot, as shown in Figure 4.14. For all four solutes the partition coefficients in the system LPC/ water can be determined, demonstrating, that the MLC is a reliable method for food and pharmaceutically relevant systems. The results for the four flavor components are compared to partition coefficients between water and the anionic surfactant SDS in Table 4.16.

Table 4.16: Partition coefficients log P_i^{MW} of vanillin flavor compounds between water and LPC micelles (33°C, MLC, this work) and water and SDS micelles (25°C, data from literature).

Solute	Molecular structure	log P_i^{MW} LPC	log P_i^{MW} SDS
isovanillin		2.45 ± 0.26	2.21[173]
ethylvanillin		2.58 ± 0.25	2.23[173]
4-hydroxybenzaldehyde		2.48 ± 0.17	1.73[409]
coumarin		2.48 ± 0.14	2.38[173]

All measured partition coefficients in the system with LPC are higher compared to SDS. The same trend was observed for the zwitterionic surfactants myristyl betaine (MB-14) and sulfo betaine (SB-12).[287] Furthermore, this fact is correlated to the decrease of the free energy of transfer in the presence of ether groups in SDS micelles,[410] while in lipid systems an increase of the free energy of transfer is observed.[411,412] Moreover, in lipid systems the effect of the

ether group on the partition coefficient is small, compared to the influence of e.g. the OH group. The hydrophobicity of coumarin is influenced by its ether and dominated by its ketone group. The data available for SDS and egg PC vesicles indicates, that the presence of the ketone group causes a decrease of the partition coefficient, which is significantly less pronounced in the SDS ($\Delta\log P^{MW}$ (acetophenone - ethylbenzene)=0.57[173]) compared to the lipid system ($\Delta\log P^{PC/W}$ (2-octanone - n-octane)=2.25[40]). Thus, the partition coefficients of the investigated compounds in LPC solutions are consistent with the effects, described in literature, and the MLC is an appropriate method for their determination.

Especially in food applications, very hydrophobic solutes are of particular interest. The partition behavior for such solutes is rarely described in literature. In this work, the partitioning of retinol ($\log P_i^{OW}$=5.68[413]) between water and micelles is examined exemplarily, as described in the following paragraph.

4.5.2 Determination of Micelle/ Water Partition Coefficients of Retinol

The partition coefficients of retinol between water and SDS and LPC micelles, respectively were determined in cooperation with the Nestlé Research Center, Lausanne. The results, as determined with MLC and compared to the MSR measurement and an indirect, organic solvent utilizing method are shown in Table 4.17.

Table 4.17: Partition coefficients $\log P_i^{MW}$ of retinol between water and LPC and SDS micelles, respectively, as determined by different methods.

Surfactant	$\log P_{MLC}$	$\log P_{MSR}$	$\log P^*_{\text{indirect method}}$
LPC	5.91 ± 0.73	6.68 ± 0.02	6.34 ± 0.04
SDS	-	6.66 ± 0.06	6.60 ± 0.08

* data provided by the Nestlé Research Center, Lausanne

In contrast to the values for the flavor components, the partition coefficients of retinol in both surfactant systems are similar. Since retinol is highly hydrophobic, the interaction with the different kinds of head groups is less significant, compared to the flavor components. The partitioning is based mainly on the solute's hydrophobicity, and hence similar for both investigated surfactants. Although the corresponding methods are fundamentally different, (the partition coefficient is determined for unsaturated and saturated solutions, respectively) the values agree fairly well with each other. Regarding the different methods the maximum deviation of the partition coefficient is $\Delta_{max}\log P_i^{MW} \approx 0.8$. Compared to the values determined for the same system (e.g. water/ nonionic surfactant/ PAHs) using the same method (MSR) from different working groups similar deviations for even less hydrophobic solutes are reported (cf. Table 4.2).

When assessing the experimental data, the hydrophobicity of retinol needs to be considered. There is few data available for such hydrophobic components like retinol. Up to now, the highest micelle/ water partition coefficients determined with the corresponding experimental

methods are: $\log P_i^{MW}$=5.97 by MLC[173] and $\log P_i^{MW}$=6.70 by the MSR method.[414] The indirect method, using a second, organic phase was not yet applied for micellar systems. Gobas et al.[372] determined a maximum value of $\log P_i^{DMPC/\ W}$=6.05 in the system DMPC/ water. All methods show a reduced reliability concerning the determination of the partition coefficients of such hydrophobic components. As discussed for the MSR method, measurements of different research groups show significant deviations (cf. Table 4.2). For the evaluation of partition coefficients with MLC, overbinding behavior may occur. For the indirect method uncertainties concerning the influence of hexane on the partition equilibrium cannot be excluded and the partition coefficient between water and hexane needs to be known for the evaluation, or measured in an additional experimental series. However, considering the hydrophobicity of retinol, the three different methods, applied in two different laboratories (TUHH and Nestlé) are in very good agreement. The magnitude of the partition coefficient can be measured very well with all applied methods and the influence of the surfactant is recognizable.

Nevertheless, it was illustrated once more, that the determination of partition coefficients for very hydrophobic components is challenging and high uncertainties arise. In the next section the predictability of these partition coefficients will be examined. Therefore, the prediction with the COSMO-RS model, as introduced before, is compared to an extension of the COSMO-RS model (COSMOmic), taking into account the anisotropy of the surfactant aggregate.[36] It was shown before, that in particular for lipid systems the prediction of partition coefficients can be further improved, considering the actual aggregate's structure.[388]

4.5.3 Prediction of Partition Coefficients in Novel Surfactant Systems

Within this work, two approaches for the *a priori* prediction of partition coefficients are compared for the zwitterionic LPC and the anionic SDS: partition coefficients are calculated with

(1) the COSMO-RS model based on the pseudo phase approach and
(2) considering the anisotropic structure of the aggregates with COSMOmic.

For the second approach (COSMOmic), the three dimensional structure of the micelles is usually obtained from all-atom molecular dynamics (MD) simulations. For this work, the MD simulation of the LPC and SDS micelle, with an aggregation number of 46 and 71, respectively, were provided from reference [415]. In Figure 4.15 the prediction with the two approaches are compared to experimental data in the LPC/ water and SDS/ water solutions (cf. Table 4.16 and Table 4.17).

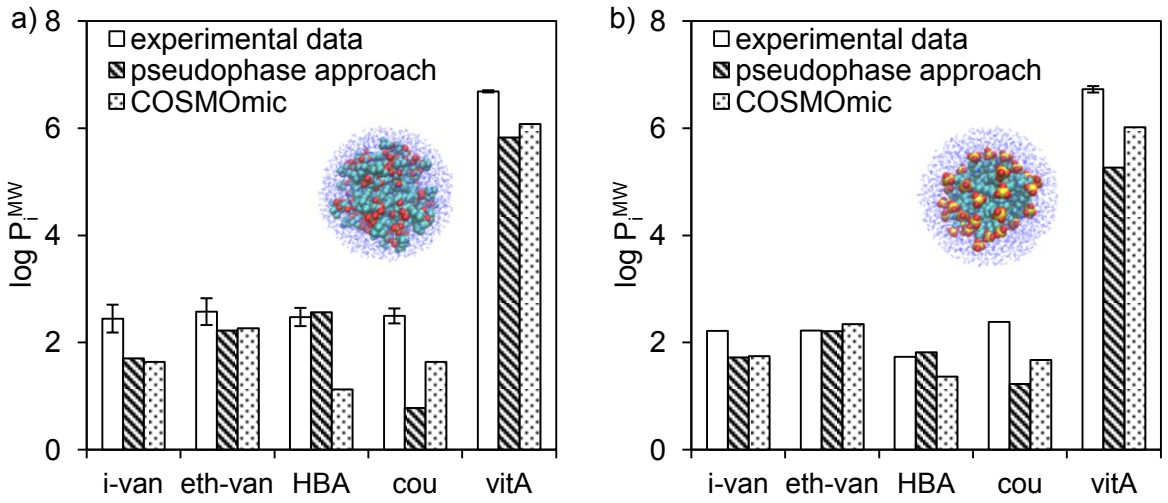


Figure 4.15: Comparison of predicted partition coefficients with experimental data in a) LPC system at 33°C (this work, MSR and MLC method) and b) SDS surfactant system at 25°C;[173,409] prediction with the pseudo phase approach (COSMO-RS; $RMSE_{SDS}$=0.86, $RMSE_{LPC}$=0.93) and considering the anisotropic structure (COSMOmic; $RMSE_{SDS}$=0.53, $RMSE_{LPC}$=0.86); solutes: isovanillin (i-van), ethylvanillin (eth-van), 4-hydroxybenzaldehyde (HBA), coumarin (cou), and retinol (vitA).

The values predicted with COSMO-RS (pseudo phase approach) agree well with the experimental determined partition coefficients, the influence of the surfactant is reflected correctly. This result is in line with the results presented above and in particular with the data published previously by Mokrushina et al.,[204] who reported an excellent agreement between experimental and predicted surfactant/ water partition coefficients for SDS, based on the pseudo phase approach. However, the coefficients predicted for coumarin differ significantly from the experimental data. The predicted partition coefficients of coumarin in both surfactant systems can be improved significantly, when the anisotropic structure of the micelles is accounted for. Though, for 4-hydroxybenzaldehyde the deviance increases, the mean deviation (RMSE) of the predictions for all five components was reduced, using the COSMOmic approach. Both approaches give reliable *a priori* predictions of the partition behavior in novel and innovative systems. Nevertheless, outliers are observed with either approach, whereas the COSMOmic approach reveals less scattering of the data. Especially in the case of the hydrophobic component retinol the consideration of the micellar structure reveals a significant improvement of the predicted partition coefficient, as was shown before for an extensive dataset in lipid and SDS systems.[388] Thus, based on MD simulations and combined with the COSMO-RS model reliable *a priori* predictions make surfactant systems available for new applications in food and pharmaceutical industry.

In this first example for the application of surfactant systems, it was shown, that the introduced methods, in particular the MLC can be applied to unknown systems successfully. Partition coefficients in e.g. food relevant systems, like the lipid derived surfactant LPC can be measured and predicted reliably. Also the partition coefficient of retinol can be evaluated, which demonstrates the applicability as an efficient tool for the determination of partition coefficients for a number of new and enhanced applications. Based on the pseudo phase approach, partition coefficients can qualitatively be predicted with a high efficiency. The

parameters and compositions can be varied easily, without requiring a full MD simulation taking the particular conditions into account. Nevertheless, if a detailed data prediction is required, COSMOmic will be the preferred method.

In the following chapters, the benefit of these methods will be discussed for two more selected applications out of the potential surfactant based processes, as described in section 2.5.

4.6 Prediction of the Retention Behavior in MLC

It was shown previously, that the MLC is a green alternative to conventional RPLC analytics (cf. section 2.5.4).[246,278,291] The retention and thus the efficiency in MLC is highly influenced by the micelle/ water partition coefficient. In the previous sections several possibilities to affect the solutes' partitioning were reported, whereas alcohols being the most used modifiers in MLC analytics.[173,246] The retention is connected to the mobile phase composition according to the retention models (equation 2.57 and 2.58), the micelle/ water partition coefficient being a crucial parameter.

$$\frac{V_s}{V_e - V_0} = \frac{v(P_i^{MW} - 1)}{P_i^{SW}} \cdot c_m + \frac{1}{P_i^{SW}} \qquad 2.57$$

$$\frac{1}{k} = \frac{K_2}{\Phi\,[L_s]\,K_1} \cdot c_m + \frac{1}{\Phi\,[L_s]\,K_1} \qquad 2.58$$

Using the retention models, the retention data (V_e and k), depending on c_m can be determined based on the predicted partition coefficients P_i^{MW} (or binding constant K_2) by measuring the retention volume at a single surfactant concentration. Hence, the experimental effort can be reduced significantly, if the partition coefficients in the relevant systems can be predicted from theoretical models. Therefore, predicted partition coefficients were used in equation 2.57, together with the measured elution volume at any micellar concentration of the mobile phase. Based on a single experimental data point, the surfactant concentration dependent retention is determined, as demonstrated in Figure 4.16.

In Figure 4.16 (a) an example with very good agreement of the predicted and experimental data for all mobile phase compositions is shown, while in Figure 4.16 (b) an example exhibiting significant deviations is demonstrated. All in all, for both surfactants the predicted retention agrees well with the experimental determined data. Even for the "overbinding" solutes a reasonable prediction is observed. For the description of $V_S/(V_e-V_0)$ the overall standard error (SE) for all solutes is 0.057 in case of Brij 35 (at a surfactant concentration of c_S=1.5 wt% in the mobile phase) and 0.005 in case of CTAB (c_S=0.15 wt%).

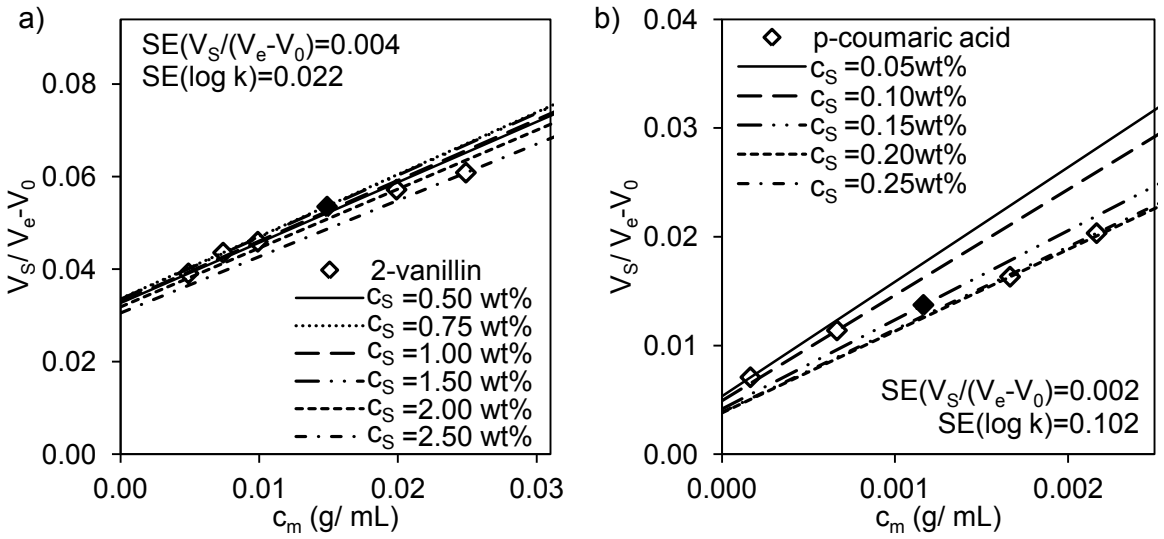


Figure 4.16: Prediction of retention data of a) 2-vanillin depending on the Brij 35 concentration in the mobile phase and b) p-coumaric acid depending on the CTAB concentration in the mobile phase based on the predicted partition coefficient P_i^{MW} with the COSMO-RS model; the retention behavior is determined based on a single measurement (symbols) of the retention at given surfactant concentration c_S; for each measured data point the predicted behavior is shown (lines); the standard error SE is given for the surfactant concentration c_S=1.5wt% and 0.15 wt% in case of Brij 35 an CTAB, respectively, as indicated by the filled symbol.

For the comparison with literature the SE of log k was calculated: SE(log k)=0.098 for the Brij 35 system and SE(log k)=0.110 for CTAB. The error is close to the upper limits for LSER target standards.[335] However, for LSERs in MLC similar deviations were reported.[334,336] Thus, the predictions of the retention data based on the COSMO-RS model and by LSER methods give results of equivalent quality. The SE presented here also considers hydrophobic compounds, for which the reliability is reduced in MLC. It was observed, that the standard error increases with an increasing partition coefficient log P_i^{MW} of the solute. Besides, also the components for which the predicted partition coefficient deviates significantly (cf. Figure 4.1) were considered in the error calculation. With a further enhancement of the prediction, e.g. by combining the COSMO-RS model with MD simulations of the aggregate structure (COSMOmic), it can be assumed, that the prediction of the retention can be improved. However, although there is further potential for optimization, the prediction of the retention data based on the COSMO-RS model yields reasonable results which are comparable to the LSER approach. It can be assumed, that using the COSMO-RS model, the retention of not yet described solutes as well as the influence of mobile phase additives can be determined straightforward. As an example, it was shown in section 4.2, that based on the COSMO-RS approach the distribution of alcohol as well as the influence on the partition coefficient can be predicted, which is of special interest in MLC evaluation since alcohols are frequently used for efficiency improvement. Independently of these results, it was demonstrated, that in RPLC analytics, the interactions between solute and stationary phase can be predicted with COSMO-RS, considering the stationary phase to be a pseudo liquid.[344] If both methods are combined, a fully predictive description of the retention behavior in MLC can be realized.

Thus, the predicted partition coefficients can be used to support the implementation of green solvents in analytical procedures. Provided, that the partition coefficients as well as the influencing parameters are predicted with a sufficient accuracy, the experimental effort for the determination of optimized retention and separation in MLC can be reduced significantly.

4.7 Reactive Micellar Separation of Sugars

Besides for analytical purposes, the applicability of surfactants in separation processes will be demonstrated. Therefore, the recovery of sugars from aqueous solution with single and mixed surfactant micelles is investigated. Sugars are highly water-soluble, and consequently, the separation from aqueous solution is challenging. However, mono- and disaccharides are promising renewable raw materials, representing an alternative to fossil materials.[416] Sugars are used in a variety of applications in food and drug industry as well as a chemical feedstock,[417] therefore, there is an interest in separating sugars from aqueous solution.

It was shown previously, that mono- and disaccharides can be transferred to an organic phase by using a carrier, which forms stable complexes with the sugar at an elevated pH value.[369,418–420] Therefore, different processes were described in literature: ion pair formation,[369,418–420] the extraction with a primary amine[421] or with “sugar-philic” ionic liquids.[422] Among those the ion pair formation in combination with an organic solvent based extraction are the most frequently studied mechanisms. The formation of a complex [PBA - S^{2-} - PBA] between sugar (S) and phenylboronic acid (PBA) was described previously.[369,418,419,423] The corresponding reaction mechanism is:[424]

$$[S] + 2\,[PBA - OH^-] \leftrightarrow [PBA - S^{2-} - PBA] + 4\,H_2O \qquad 4.1$$

A particular advantage of this mechanism is the pH-dependent formation of the complex. At alkaline pH the complex formation is favored, while at low pH values the sugar is released from the complex. Thus, the extraction and recovery of sugars from an organic phase with phenylboronic acid is a process which is comparatively easy to control.

Based on this mechanism, the recovery of mono- and disaccharides from aqueous solution by means of MEUF is proposed in this work. As described before (section 2.5.2), the MEUF is well established for the separation of hydrophobic and ionic hydrophilic components. However, there are only few investigations concerning the recovery of hydrophilic, but nonionic solutes, such as sugars. Therefore, the reaction mechanism described for the extraction with organic solvents is combined with micellar systems. Hence, the feasibility of the recovery of sugars with a surfactant based process will be validated and the crucial process parameters are determined.

4.7.1 Influence of Surfactants on the Rejection of Sugars

The rejection of sugars in aqueous micellar solution was determined by means of MEUF. In the absence of a reactive carrier the sugars are not rejected significantly. Thus, without an additional carrier, the MEUF is not appropriate for the separation of sugars from aqueous streams, as expected from the solubility data.

While the extraction of sugars with carrier and organic solvents has already been described, surfactant systems have not yet been employed for this purpose. In this work a cationic surfactant (CTAB) and mixtures of anionic (SDS)/ cationic (Aliquat 336) and cationic (Aliquat 336, CTAB)/ nonionic (TritonX-100) surfactants were investigated concerning the recovery of sugars from aqueous solution in presence of a carrier. Two different carriers were employed within the study: phenylboronic acid, which proved to be a promising sugar-selective carrier[369,418] and cyclooctylamine as proposed by Hameister et al.[421] The addition of cyclooctylamine to micellar systems did not result in an improved recovery of sugars. Neither was the sugar recovery improved in the anionic/ cationic surfactant mixture, regardless of the used carrier. In the sugar-free solution (contains surfactant and carrier) an increased rejection of cyclooctylamine was observed for all types of surfactant, while in case of phenylboronic acid (PBA) the rejection was enhanced with CTAB, only. This indicates a solubilization of cyclooctylamine in the micellar core, and consequently a restriction of the reactivity, while PBA is adsorbed on the micellar surface due to the electrostatic interactions, maintaining the reactivity. However, for the cationic (CTAB) as well as nonionic/ cationic (TritonX-100/ Aliquat 336) surfactant systems a significant improvement of the rejection of various sugars was observed in presence of the carrier phenylboronic acid as shown in Figure 4.17.

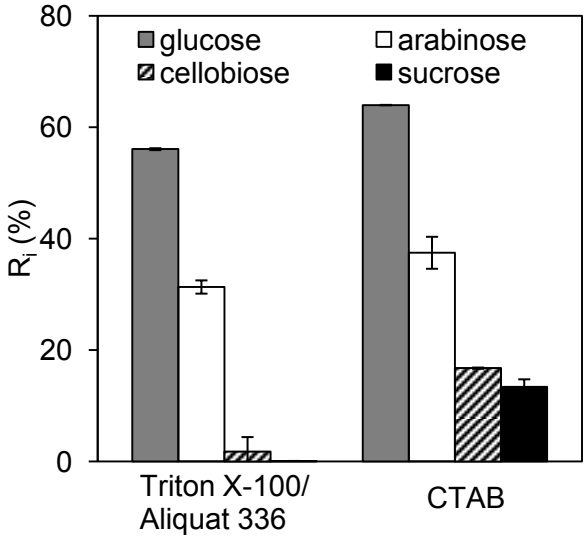


Figure 4.17: Rejection R_i of sugars with different surfactant systems containing phenylboronic acid; experimental conditions: 0.05 wt% sugar, 0.17 wt% phenylboronic acid, 0.2 wt% CTAB, 5 wt% TritonX-100, 0.75 wt% Aliquat 336, 2 h equilibration, T=25°C.

Due to the complex formation the sugar is solubilized in the micelles. The ratio of the complex solubilized in the micelle however, depends on the overall concentration of the

compounds.[425] Thus, the rejection of the sugars as shown in Figure 4.17 will deviate, as the concentration of the components is changed. However, it is shown that the recovery of sugars from aqueous solution using MEUF can be improved significantly in presence of the carrier phenylboronic acid. For the pure cationic surfactant as well as the surfactant mixture high rejections up to 60% are observed. For both surfactant systems the rejection of monosaccharides is significantly higher than for disaccharides. Using the surfactant mixture the rejection of disaccharides is very low, indicating a selective recovery of monosaccharides.

On the one hand the open-chain structure of sugar is favored for the complex formation,[426,427] and hence the monosaccharide complex is more probable than the disaccharide complex. On the other hand it was shown, that the polarity of a sugar/ borate complex decreases in the following order glucose> arabinose>>cellobiose>sucrose[426] which coincides with the degree of solubilization as determined within this work. With increasing charge density of the complex the electrostatic interaction with the micelles and thus the rejection increases. Both effects result in the selective recovery of monosaccharides.

For all investigated sugars, the rejections are higher using CTAB compared to the surfactant mixture. This is significant regarding the used surfactant concentration, which is 5.75 wt% in case of TritonX-100/ Aliquat 336 and 0.2 wt% in the CTAB system. Additional experiments have been performed, investigating the influence of the particular cationic surfactant on the rejection of glucose in the cationic/ nonionic systems Aliquat 336/ TritonX-100 and CTAB/ TritonX-100. The molar concentration of CTAB was equal to the Aliquat 336 concentration. However, the rejection of glucose in the CTAB mixed system (48.06 ± 5.60%) was less than in the Aliquat 336 mixed system (56.16 ± 0.18%) and considerably less than the rejection in the pure cationic system (63.98 ± 0.04%). Even though CTAB and Aliquat 336 are both cationic surfactants their different molecular structure results in a difference concerning the glucose rejection. It was shown for nonionic surfactants of the same type, that the more hydrophilic a surfactant ($HLB_{Aliquat\ 336}$=3.3[428] < HLB_{CTAB}=21.4[429]), the larger the cmc value (cf. Table 3.1) and the lower the aggregation number for single surfactant systems.[430] Furthermore, it was shown, that the formation of mixed ionic/ nonionic surfactants is enhanced at longer alkyl chain length due to an increased interaction between the surfactant molecules.[84] Hence, it can be assumed, that both described effects significantly influence the properties of the mixed micelles and thus affect the solubilization capacity (cf. chapter 4.4).

The sugar/ phenylboronic acid-complex is negatively charged and thus attracted by the positively charged head groups of the surfactants due to electrostatic interactions. The charge density on the surface of mixed micelles is decreased significantly by the addition of nonionic surfactant.[228,431] In the case of pure cationic micelles, the electrostatic interactions between the micelle and the complex are increased and thus the rejection of the sugar complex is higher. Even at low concentrations of cationic surfactant a high recovery of sugar can be achieved.

4.7.2 Comparison of the MEUF with an Organic Solvent Extraction

The efficiency of the proposed extraction of sugars with micellar systems is compared to the state of the art of the corresponding extraction with organic solvents. Considering the organic solvent extraction, the presence of Aliquat 336 is required for the partitioning of the sugar/ phenylboronic acid-complex between water and the organic phase. For the evaluation of the efficiency, the organic solvent extraction and MEUF are compared in Table 4.18 for the sugars glucose and cellobiose. The separation efficiencies were calculated according to equation 3.7. The different concentrations of sugar and PBA in the experiments were not considered, thus the efficiencies are compared qualitatively. For the MEUF the concentration dependence will be described in section 4.7.3.

Table 4.18: Separation efficiency E (%) for glucose and cellobiose using organic solvents and micellar solutions, respectively; micellar solutions (this work): 0.05 wt% glucose and cellobiose, 0.17 wt% (PBA); organic solvents:[369] 0.18 wt% glucose, 0.34 wt% cellobiose, 0.85 wt% PBA. 25°C, 2 h equilibration.

Sugar	CTAB	E_i (%) TritonX-100/ Aliquat 336	hexane/ octanol (85:15)
glucose	64.06 ± 0.03	58.67 ± 0.35	97
cellobiose	16.91 ± 0.12	7.38 ± 2.48	30

The highest extraction efficiency was achieved with a mixture of hexane and octanol.[369] The use of organic solvents seems to be more effective than the use of micellar solutions. However, the extraction efficiency does not consider the amount of solvent used. For the extraction with organic solvent 50 vol% hexane/ octanol were used compared to 0.2 vol% CTAB and 5.6 vol% TritonX-100/ Aliquat 336 in the surfactant systems.

Rather than the extraction efficiency, partition coefficients can be used to compare the efficiency, considering the volume of the extraction solvent. The partition coefficients ($\log P_i^{\alpha\beta}$) of the sugars were calculated according to equation 2.8. Solvent/ water and micelle/ water coefficients are compared, as shown in Table 4.19.

Table 4.19: Partition coefficients $\log P_i^{\alpha\beta}$ of glucose and cellobiose using organic solvents and micellar solutions, respectively; micellar solutions (this work): 0.05 wt% glucose and cellobiose, 0.17 wt% PBA; organic solvents:[369] 0.18 wt% glucose, 0.34 wt% cellobiose, 0.85 wt% PBA, 25°C, 2 h equilibration.

Sugar	CTAB	$\log P_i^{\alpha\beta}$ TritonX-100/ Aliquat 336	hexane/ octanol (85:15)
glucose	3.04 ± 0.04	1.45 ± 0.02	1.51
cellobiose	2.09 ± 0.01	0.20 ± 0.17	-0.36

The $\log P_i^{\alpha\beta}$ values in the CTAB system are higher than those using TritonX-100/ Aliquat 336 and hexane/ octanol. Especially the use of the pure cationic micelles (CTAB) results in high

partition coefficients. Due to the different sugar and carrier concentrations used in the experiments, a quantitative comparison of the methods is not possible based on the available data. However, it was shown, that micellar systems are a promising alternative to the state of the art extraction based on organic solvents. In the following section, the determination of the decisive parameters regarding the efficiency of the MEUF for the extraction of sugars is aimed.

4.7.3 Parameters Affecting the Efficiency of the MEUF for Sugar Extraction

For further improvement of the extraction efficiency the crucial parameters need to be defined. Therefore, the influence of the concentration and the equilibration time on the efficiency was investigated for the system with pure cationic surfactant CTAB.

Influence of the Carrier/ Sugar Ratio

The influence of the carrier/ sugar ratio $\alpha_{PBA/G}$ was investigated at constant glucose concentration and increasing boronic acid concentration. In Figure 4.18 the rejection of glucose and phenylboronic acid in dependence of the ratio $\alpha_{PBA/G}$ is shown.

The rejection of phenylboronic acid decreases with increasing phenylboronic acid/ glucose ratio $\alpha_{PBA/G}$, while the sugar rejection is constant after reaching a maximum value. A 2:1 phenylboronic acid/ glucose ratio $\alpha_{PBA/G}$ is proposed for the complex formation.[369,424] In Figure 4.18 it is shown, that the rejection of the sugar complex is not increased with increasing PBA concentration at ratios exceeding $\alpha_{PBA/G}$=2. Thus, the extraction efficiency is not improved if the carrier content is increased.

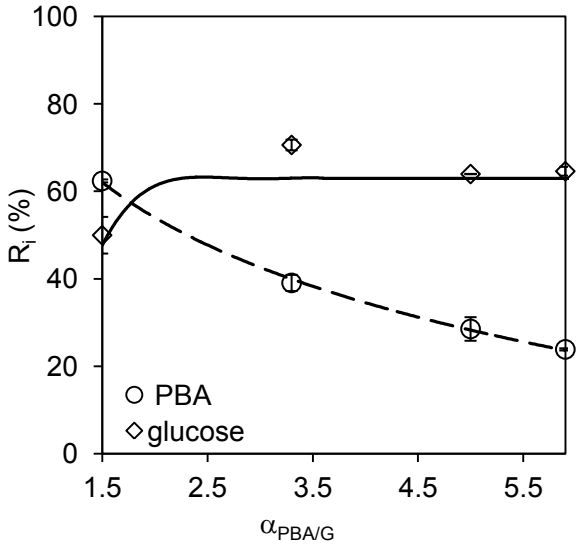


Figure 4.18: Influence of the molar boronic acid/ sugar ratio $\alpha_{PBA/G}$ on the rejection R_i of glucose and PBA; experimental conditions: 0.05 wt% glucose, 0.05-0.2 wt% PBA, 0.2 wt% CTAB, 2 h equilibration, 25°C, lines show trends.

However, at lower ratios ($\alpha_{PBA/G}$<2) the glucose rejection slightly decreases from 60 to 50% at a PBA/ sugar ratio of 1.5. Since the concentration of the carrier is less than is required for

the 2:1 complex formation, the reduced glucose rejection was expected. Still, the reduction is less than might be derived from the apparent carrier/ sugar ratio. Besides the formation of the 2:1 complex, the formation of boronates and boronate esters was described.[423] In aqueous solution boronate is the more stable association of both 1:1 complexes. Under the present conditions (pH 11) boronate might be ionized and thus will interact with the micelles. Compared to the extraction described for organic solvents,[369,424] the carrier/ sugar ratio can be reduced in micellar systems without a significant decrease of the sugar recovery, due to the efficient complexation and the strong electrostatic interactions.

Influence of the Sugar/ CTAB Ratio

The recovery of glucose cannot be increased by an increase of the PBA concentration, once the carrier/ sugar ratio 2:1 is reached. Therefore, the influence of the sugar concentration on its rejection was investigated at constant CTAB concentration. The results are shown in Figure 4.19.

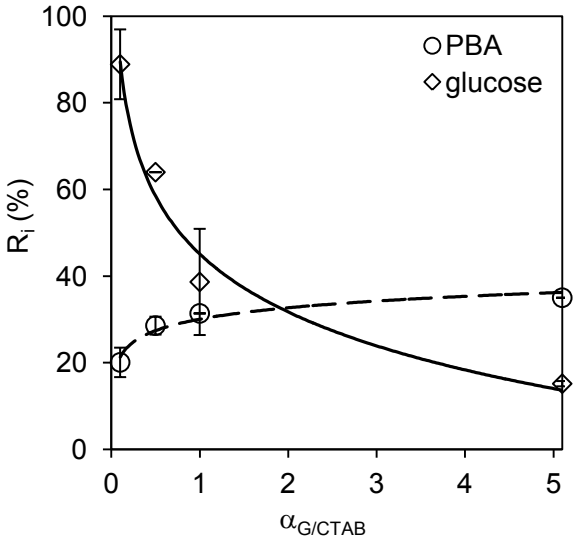


Figure 4.19: Influence of the molar sugar/ CTAB ratio $\alpha_{G/CTAB}$ on the rejection R_i of glucose and PBA; experimental conditions: 0.005-0.2 wt% glucose, 0.17 wt% PBA, 0.2 wt% CTAB, 2 h equilibration, 25°C, lines show trends.

The rejection of glucose decreases with increasing glucose/ CTAB ratio $\alpha_{G/CTAB}$ while the rejection of phenylboronic acid slightly increases.

With increasing sugar/ CTAB ratio $\alpha_{G/CTAB}$ the PBA rejection increases, since the ratio PBA/ sugar $\alpha_{PBA/G}$ is reduced (cf. Figure 4.18). At the same time the glucose rejection decreases significantly. As described before, the high rejection of the sugar/ carrier complex can be explained by the strong electrostatic interactions of the complex with the cationic micelle. Up to the sugar/ CTAB ratio $\alpha_{G/CTAB}$ of 1.3 the carrier PBA is available in excess for the 2:1 complex formation. As shown in Figure 4.18, the glucose rejection stays constant at constant glucose concentration for PBA/ sugar ratio $\alpha_{PBA/G} > 2$. Thus, the sharp decrease of the glucose rejection (for $\alpha_{G/CTAB} \leq 1.3$) cannot be attributed to limitations of the complex

formation, but is directly connected to the CTAB content. It is expected, that the glucose rejection is enhanced by an increase of the micelle concentration.

Influence of the Equilibration Time

Analogous to the sugar extraction with organic solvents,[369] an equilibration time of two hours prior to ultrafiltration was chosen for all the presented results. For industrial applications shorter equilibration times are favorable. Therefore, the influence of the equilibration time on the recovery of glucose was investigated as shown in Figure 4.20.

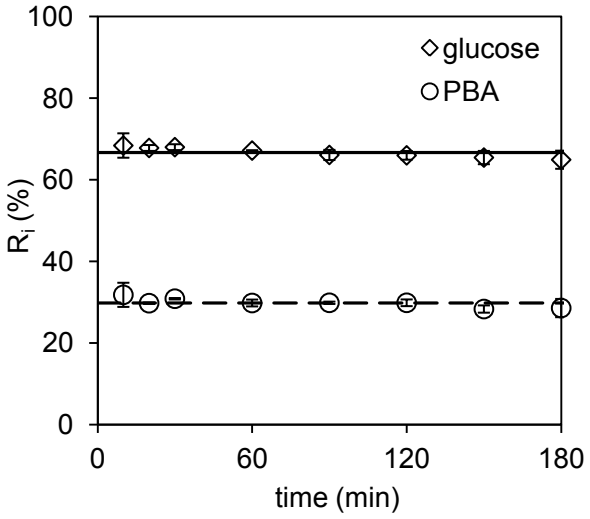


Figure 4.20: Influence of the equilibration time prior to ultrafiltration on the glucose and PBA rejection R_i; experimental conditions: 0.05 wt% glucose, 0.17 wt% PBA, 0.2 wt% CTAB, 25°C, lines represent the mean values of the corresponding measurements.

In the investigated range, the rejection of glucose and PBA are not affected by the equilibration time. Thus, the equilibration time can be decreased dramatically, making MEUF a promising technique for the recovery of sugars in a continuous process.

In contrast, a time dependent extraction efficiency of sugars based on organic solvents was observed for the extraction with the primary amine cyclooctylamine.[421] For the ion pair based process a detailed investigation of the influence of the equilibration time was not yet published. However, the results of this work suggest an improved reaction rate and solubilization in micellar systems compared to organic solvents, which can be ascribed to the larger interfacial areas, improving the mass transfer.[432]

In further studies, the recovery of sugars from the micellar solution needs to be investigated, to ensure an entire effective and efficient process. One possibility to recover the sugar is based on the change of the pH value resulting in the destabilization of the sugar/ carrier complex. Furthermore the substitution of KOH by fluoride-salts to promote the complex formation at neutral pH as proposed by Smith[423] can be promising.[369] Besides, the modification of the pK_a value of PBA by derivatisation and complexation was described in order to obtain stable complexes at physiological pH.[433] Although the solubilization of the

complex is mainly based on strong electrostatic interactions,[369,418,419,423] the influence of the hydrophobicity of the carrier can be significant. Furthermore, if the carrier and the surfactant can be combined within a single molecular structure as shown by Labeque et al.[434] a further improvement and innovation of the system can be achieved. Nevertheless, it was shown, that organic solvents can be replaced by surfactants, maintaining the efficiency of the process.

As was shown before, the COSMO-RS model can be applied for an enhanced process optimization. In the following paragraph, the utility for the sugar extraction will be evaluated.

4.7.4 Prediction of the Rejection in MEUF with COSMO-RS

The efficiency of the sugar recovery is influenced by the reaction kinetics and the affinity of the complex to the micelle. The COSMO-RS model cannot be applied for the description of dynamic processes, thus the reaction kinetics is not accounted for. Furthermore, the molecular characteristics of the formed complex need to be known in detail, to allow a reliable prediction of the sugar partitioning between the micelle and the aqueous bulk phase. However, if the partition coefficients are known, the rejection in MEUF can be derived, combining equations 2.8 and 3.4 for the calculation of the partition coefficient and the rejection, respectively. For the investigated sugars the thus predicted data in the carrier-free, single surfactant systems, is compared to the experimental rejection in Table 4.20.

Table 4.20: Comparison of the prediction (pred.) to experimental data (exp.) of the rejection (R_i in %) of sugars in MEUF, in different micellar solutions, no carrier was added in these experiments.

	TritonX-100		CTAB		SDS	
Sugar	$R_i^{pred.}$	$R_i^{exp.}$	$R_i^{pred.}$	$R_i^{exp.}$	$R_i^{pred.}$	$R_i^{exp.}$
arabinose	0.047	5.10 ± 0.52	0.136	1.28 ± 0.54	0.635	4.52 ± 0.53
cellobiose	0.002	9.84 ± 4.44	0.002	2.41 ± 2.38	0.149	6.30 ± 1.25
glucose	0.003	6.32 ± 1.29	0.001	1.87 ± 0.36	0.104	7.26 ± 2.19
sucrose	0.001	10.12 ± 4.95	0.009	2.59 ± 2.39	0.187	6.12 ± 1.08

For all the used surfactants, the predicted rejection of the sugars is very low, as expected due to their water solubility. However, the actual deviation to the experimental data is significant. On the one hand, the rejection was determined with a high experimental uncertainty. On the other hand the partition coefficient was predicted for infinite dilution, which does not exactly correspond to the experimental conditions. Besides the intermolecular interactions considered for infinite dilution, other effects attributed to the interactions between the sugar and the hydrophilic head groups might arise and enhance the rejection at higher sugar concentrations.

Based on the current knowledge, the rejection of sugars cannot be predicted with the COSMO-RS model. The issue of defining the actual molecular conditions is even more complex, considering the sugar-carrier complexes. From the results presented in the

previous paragraphs, the detailed structure and distribution of the different kinds of complexes remains unknown. For the reliable prediction of the partitioning and subsequent of the rejection, this information is absolutely essential. Currently, the COSMO-RS model can make only a minor contribution to optimizing the micellar extraction of sugars.

5 Conclusions

The application of surfactants in novel separation processes requires fundamental knowledge of the complex phase equilibria in aqueous surfactant solutions. Of particular importance are the liquid-liquid-equilibria as well as the partition coefficients of a target compound between the micelles and the surrounding water. Up to now, micellar systems are insufficiently investigated, especially regarding important parameters such as the influence of additives or the pH value. In this work, experimental and a predictive method for the determination of micelle/ water partition coefficients were evaluated, with special regard to multicomponent surfactant solutions.

For this purpose, micelle/ water partition coefficients for several solutes were measured in binary surfactant/ water solutions with the molar solubilization ratio (MSR) method, the cloud point extraction (CPE), micellar enhanced ultrafiltration (MEUF), and micellar liquid chromatography (MLC). The four experimental methods show very good reproducibility. Moreover, the results from the different methods are in good agreement, supplementing one another concerning the applicable temperature range. While the CPE is restricted to temperatures above the cloud point temperature (CPT), MLC, MSR, and MEUF are employed at temperatures below the CPT. Among the used techniques, the MLC stands out due to its automatism, robustness, and in particular its straightforward applicability for the analysis of multi component samples. In this work, partition coefficients in the range $\log P_i^{MW}$=1.2-4.0 were measured for ionic and nonionic surfactants with a small experimental error. The error rises with increasing affinity of the solutes to the micelle. As a consequence, partition coefficients for very hydrophobic solutes cannot be determined with MLC. In line with the characterization of analytes in MLC (non-binding, antibinding and binding) these molecules are defined as “overbinding” solutes.

The evaluation of partition equilibria can be supported by means of thermodynamic models. As was shown in recently published studies, the COSMO-RS model predicts micelle/ water partition coefficients in binary surfactant/ water systems reliably. In this work the predictability was proven for the investigated surfactants, the influence of the surfactant type and the temperature is reflected correctly. However, the deviation from the experimental data increases with the solutes’ hydrophobicity. Nevertheless, it was demonstrated, that based on these methods (experimental and predictive), partition coefficients can be determined successfully.

Further, the introduced methods were evaluated for the quantification of relevant process parameters. Special focus was set on the effect of the presence of alcohols, the pH value and surfactant mixtures on the LLE and the partition coefficients. The characteristic phase separation of nonionic surfactants upon increasing temperature is rarely affected by the pH value, whereas only small amounts of ionic surfactant show a pronounced effect: due to a drastic increase of the CPT, the phase split can even be repressed completely. In contrast, in presence of alcohols, a phase separation is observed over a wide concentration range. Depending on the kind of alcohol, a shift towards higher or lower temperatures takes place. This behavior is linked to the affinity of short-chain alcohols like ethanol for the water phase, while long-chain alcohols partition preferably into the micellar aggregates. Accordingly, the micelle/ water partition coefficient decreases (in the case of ethanol) or increases (in the case of butanol), although only a minor effect is observed. This is different in case of the pH value, considering dissociable components. While in nonionic surfactant solution, in analogy to the octanol/ water system, the partition coefficient decreases with increasing degree of dissociation, a contrary effect was observed in solutions containing ionic surfactants. In particular, the micelle/ water partition coefficients of acids in cationic and bases in anionic surfactant solutions increase dramatically for the dissociated solute species. This effect can be explained by the strong electrostatic interactions between the solute and surfactant head group. Accordingly, by mixing ionic and nonionic surfactants, micelle/ water partition coefficients can be adjusted in a wide range. In the case of dissociable components, log D_i^{MW} values, covering up to three magnitudes (a factor of 1000) were measured, depending on the surfactant composition. The lipophilicity profiles, determined for different compositions revealed that the partition coefficients do not increase linearly with the ionic surfactant content in the solution, but depend on the composition of the mixed micelle.

At known composition of the micelles, the partition coefficients can be predicted with COSMO-RS. This applies for the description of the alcohol content as well as in mixed surfactant solutions. Furthermore, it was demonstrated, that in reverse, based on the experimental partition coefficients the micellar composition can be predicted with the COSMO-RS model. Generally, the partitioning of the non-dissociated solute is predicted in good agreement with the experimental data, while the dissociated species is not yet described satisfactorily. Though, using the introduced methods, and based on the above findings, the applicability of surfactants can now be demonstrated for novel applications. Therefore, in this work selected processes were investigated for the first time regarding the implementation and optimization of micellar systems.

In order to evaluate the methods for pharmaceutical and food relevant systems, the lipid derived surfactant LPC was employed in the MLC for the first time. It was shown, that the partition coefficients between micelles and water can be determined in a wide hydrophobicity range. Moreover, the experimental data are compared to *a priori* predictions with the COSMO-RS model. The prediction assuming the pseudo phase approach is compared to the prediction using COSMOmic, thus taking into account the anisotropic structure of the micelles, obtained from molecular dynamics all-atom simulations. Both methods agree well

with the experimental data of the partition coefficients between LPC and water and between the anionic surfactant SDS and water. It was demonstrated, that combining reliable experimental methods and thermodynamic models results in an enhanced evaluation of different surfactant/ solute systems and thus will contribute to the extension of the application areas for micellar systems.

The MLC itself is readily applied for analytical purposes. To facilitate the optimization of the chromatographic parameters, the prediction of the retention data is desirable. Therefore, in this work, the predicted partition coefficients along with the retention data of a single measurement were combined with a common retention model. As a result, the description of the retention data based on a minimum of experimental data was realized successfully, with a level of quality comparable to the LSER approaches. The introduced method for the estimation of the retention in MLC is especially promising for highly retarding solutes and appears to be suitable for the flexible and qualitative prediction of the retention data.

Finally, the potential of micellar systems in reactive separation processes was evaluated for the first time for the recovery of sugars from aqueous streams. Based on the complex formation of the sugar with phenylboronic acid, sugars can be separated efficiently from aqueous streams with the MEUF method. The charge density of the micelle was assigned to as a crucial factor for the recovery. Compared to the state of the art extraction with organic solvents, the partition coefficients can be increased dramatically, while the carrier concentration and equilibration time are reduced at the same time. Thus, it was shown that the MEUF is a high potential method for the recovery of hydrophilic components from dilute aqueous streams.

The proposed applications demonstrate the versatility of surfactant systems. Based on the determination of the micelle/ water partition coefficients the suitability of surfactants for a given process and its optimization can be evaluated. The tools, provided in this work including different experimental methods and the prediction with COSMO-RS, allow for the efficient description of the partition coefficients considering the relevant process parameters. Complex surfactant systems are validated successfully with these methods, which represents the basis for an enhanced application range of surfactant systems.

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Directories

Symbols and Abbreviations

0	standard state
a	activity
a	solvent/ stationary phase specific regression coefficient (LSER)
a	empirical parameter
A	hydrogen bond acidity (LSER)
A^-	dissociated acid
ACN	acetonitrile
a_{eff}	effective thermodynamic contact area
AI	average information index
a_S^M	activity of surfactant monomer in the micelle
a_S^W	activity of surfactant monomer in the aqueous bulk phase
A^-X^+	ion pair (dissociated acid/ cation)
b	solvent/ stationary phase specific regression coefficient (LSER)
b	empirical parameter
B	hydrogen bond basicity (LSER)
BMC	biopartitioning micellar chromatography
Brij 35	polyoxyethylene (23) lauryl ether
c	concentration (mol/L)
c	solvent/ stationary phase specific regression coefficient (LSER)
c	empirical parameter
c_0	solvent specific constants for the calculation of the pK_a value
c_1	solvent specific constants for the calculation of the pK_a value
c_{hb}	empirical hydrogen bonding energy parameter (COSMO-RS)
c_i^F	solute concentration in the feed
c_i^{hexane}	solute concentration in the hexane phase (mol/L)
c_i^M	solute concentration in the micelles (mol/L)
c_i^P	solute concentration in the permeate
c_i^{tot}	total solute concentration in the overall solution (mol/L)
c_i^W	solute concentration in the aqueous bulk phase (mol/L)
CL	central analytical laboratory, Hamburg University of Technology
c_m	concentration of surfactant, aggregated to micelles
cmc	critical micelle concentration
cmc_1/ cmc_2	critical micelle concentration in single surfactant systems
cmc_{12}	critical micelle concentration in a surfactant mixture
cmc_i*	cmc of surfactant i at a given surfactant mixture
comb	combinatorial
COSMO	conductor-like screening model
COSMO-RS	conductor-like screening model for realistic solvation

CPE	cloud point extraction
CPT	cloud point temperature
c_S	surfactant concentration
C_S	electrolyte concentration
c_S^F	surfactant concentration in the feed
CTAB	cetyltrimethylammonium bromide
d	empirical parameter
D	pH dependent, concentration based partition coefficient
e	element (COSMO-RS)
e	solvent/ stationary phase specific regression coefficient (LSER)
e	empirical parameter
E	excess molar refraction (LSER)
e'	opponent element (COSMO-RS)
e_{hb}	hydrogen bonding contribution to the interaction energy (COSMO-RS)
E_i	separation efficiency
e_{int}	interaction energy between two contacting surface segments (COSMO-RS)
e_{misfit}	electrostatic contribution to the interaction energy (COSMO-RS)
EO	ethylene oxide unit
EoS	equations of state
e_{vdW}	van der Waals contribution to the interaction energy (COSMO-RS)
exp.	experimental
F	feed
FH	Flory-Huggins
f_m	fraction of mobile phase, inaccessible to the solute
f_S	fraction of stationary phase, inaccessible to the solute
$\Delta G^{(i)}_{diss.}$	Gibbs energy of the dissociated (ionized) solute
$\Delta G^{(i)}_{non\text{-}diss.}$	Gibbs energy of the non-dissociated solute
Δg^0_{mic}	standard Gibbs energy of micellization per mole of surfactant
ΔG^0_{mic}	standard Gibbs energy of micellization
g^E	molar excess free enthalpy
grad.	gradient mobile phase
ΔH^0_{mic}	standard enthalpy of micellization
H_1	hexagonal phase
HA	non-dissociated acid
HLB	hydrophilic-lipophilic balance
H_i^{diff}	different enthalpies
H_{ring}	enthalpy correction for ring size
i	component/ solute
isocr.	isocratic mobile phase
k	retention factor (chromatography)
K	mole fraction based partition coefficient
K	equilibrium constant
K	empirical parameter
k_0	retention factor in a micelle-free mobile phase (chromatography)
k_0	retention factor of the non-dissociated solute (chromatography)
k_1	retention factor of the dissociated solute (chromatography)
K_1	solute/ stationary phase association constant
K_2	solute/ micelle association constant (non-dissociated solute)
K_4	solute/ micelle association constant (dissociated solute)

K_a	dissociation constant
k_B	Boltzmann constant
KH	Kier & Hall index
K_i^{MW}	mole fraction based micelle/ water partition coefficient
L_1	normal micellar solution
L_1'	surfactant-lean phase
L_1''	surfactant-lean rich
L_2	reverse micellar solution
L_3	isotropic solution containing bilayers
L_α	lamellar liquid crystalline phase
$[L_S]$	concentration of stationary phase binding sites
LLE	liquid-liquid-equilibrium
LPC	(18:0) lysophosphatidycholine
LSER	linear solvation energy relationship
M	micelles
MAM	mass action model
MD	molecular dynamics
MECC	micellar electrokinetic capillary chromatography
MEEKC	microemulsion electrokinetic chromatography
MEKC	micellar electrokinetic chromatography
MELC	microemulsion liquid chromatography
MEUF	micellar enhanced ultrafiltration
MLC	micellar liquid chromatography
MP	micellar phase/ surfactant-rich phase
MSR	molar solubilization ratio
$m_{Surf.}$	mass of the surfactant
n	mole number
N	Avogadro's constant
N_{agg}	aggregation number
n_C	number of carbon atoms
n_i^F	mole of solute in the feed
NRTL	Non-Random-Two-Liquid model
n_S^F	mole of surfactant in the feed
n_W^F	mole of water in the feed
OF	objective function
P	concentration based partition coefficient
P	permeate
P	pressure
PAH	polycyclic aromatic hydrocarbon
P_I	partition coefficient of dissociated/ ionized solutes
$P_{I;IP}$	partition coefficient of dissociated solutes, combining ionized and ion pair species
$P_i^{\alpha\beta}$	partition coefficient between phase α and phase β
P_i^{HW}	hexane/ water partition coefficient
P_i^{MS}	micelle/ stationary phase partition coefficient
P_i^{MW}	micelle/ water partition coefficient
P_i^{OW}	octanol/ water partition coefficient
P_{IP}	partition coefficient of ion pair species
P_i^{SW}	stationary phase/ water partition coefficient

P_N	partition coefficient of non-dissociated species
pred.	predicted
$p'_s(\sigma')$	normalized σ-profile of the system
PSA	pseudo phase approximation
Q_{cmc}	amount of adsorbed surfactant on the stationary phase
QRAR	quantitative retention-activity relationships
QSAR	quantitative structure-activity relationships
QSPR	quantitative structure-property relationships
QSRR	quantitative structure-retention relationships
r	empirical parameter
R	gas constant
R	rejection (MEUF)
res	residual
RI	resolution of identity
r_m	molecular radius
RMSE	root mean square error
RNNO	relative number of N and O atoms
RPLC	reverse phase liquid chromatography
RST	real solution theory
s	solvent/ stationary phase specific regression coefficient (LSER)
s	empirical parameter
S	entropy
S	polarizability/ dipolarity (LSER)
S	solubility
S	stationary phase
S	surfactant monomer
$\hat{S}$	solvent accessible surface
S_{cmc}	apparent solubility of the solute at surfactant concentration according cmc
ΔS^0_{mic}	standard entropy of micellization
SDS	sodium dodecyl sulfate
SE	standard error
SPME	solid phase microextraction
surf	surfactant
T	temperature
TritonX-100	polyethylene glycol mono(octylphenyl) ether (n=9-10)
TritonX-114	polyethylene glycol mono(octylphenyl) ether (n=7-8)
TSA	total molecular surface area
TUHH	Hamburg University of Technology
TZVP	triple zeta valence polarized
U	internal energy
Δu^0_{mic}	contribution to the Gibbs energy of micellization according to Tanford[103]
UNIFAC	universal quasichemical functional group activity coefficients
v	molar volume
v	solvent/ stationary phase specific regression coefficient (LSER)
V	volume
V	molecular volume (LSER)
V_0	dead volume (chromatography)
V_1	cubic phase
V_{Aq}	volume of the aqueous (micellar) solution

V_e	elution volume (chromatography)
V_S	volume of stationary phase (chromatography)
w	weight fraction
W	water/ aqueous bulk phase
w_i^{Feed}	weight fraction of component i in the feed
$w_i^{Permeate}$	weight fraction of component i in the permeate
w_{mic}	contribution to the Gibbs energy of micellization according to Tanford[103]
WP	aqueous phase/ surfactant-lean phase
x	mole fraction
x_1	mole fraction of ionic surfactant
$x_1^{Solution}$/ $x_2^{Solution}$	mole fraction of component 1/ 2 in solution
x_2	mole fraction of nonionic surfactant
x_{cmc}	surfactant mole fraction at cmc
x_i^M	mole fraction of solute in the micelles
x_i^{MP}	mole fraction of solute in the surfactant-rich phase
x_i^W	mole fraction of solute in the aqueous bulk phase
x_i^{WP}	mole fraction of solute in the surfactant-lean phase
x_{Surf}^{MP}	mole fraction of surfactant in the surfactant-rich phase
x_{Surf}^{WP}	mole fraction of surfactant in the surfactant-lean phase

Greek Symbols

α	phase
α	surfactant bulk composition in mixed surfactant solutions
α'	empirical misfit energy factor
$\alpha_{G/CTAB}$	molar glucose/ CTAB ratio
$\alpha_{PBA/G}$	molar phenylboronic acid/ glucose ratio
β	binding of counterion
β	interaction parameter
β	phase
Φ	volume ratio of the stationary to the mobile phase
γ	activity coefficient
γ_i^{FH}	Flory-Huggins contribution to the activity coefficient
γ_i^{NRTL}	NRTL contribution to the activity coefficient
φ	phase
μ	chemical potential
μ_i^M	chemical potential of surfactant monomer in a single surfactant micelle
μ_i^{MM}	chemical potential of surfactant monomer in a mixed surfactant micelle
π	phase
π_{20}	surface tension reduction equal to 20 dyn/ cm
π_{cmc}	surface pressure at cmc
ρ_M	density of the micelles
σ	polarization charge density
σ'	polarization charge density of opponent surface segment
σ_{acc}	threshold polarization charge density of hydrogen bonding acceptor
σ_{don}	threshold polarization charge density of hydrogen bonding donor
τ_{vsW}	empirical, element specific van der Waals parameter

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Appendix

A 1 Derivation of the Relevant Equations

A 1.1 Derivation of the pH-Dependent Partition Coefficient (Equation 2.13)

$$D_i^{\alpha\beta} = \frac{c_{HA}^{\alpha} + c_{A^-}^{\alpha} + c_{A^-X^+}^{\alpha}}{c_{HA}^{\beta} + c_{A^-}^{\beta} + c_{A^-X^+}^{\beta}} \qquad 2.12$$

From the definition of the dissociation constant K_a in dilute aqueous solutions:

$$K_a = \frac{c_{H_3O^+} \cdot c_{A^-}}{c_{HA}} \qquad A.1$$

the relation between pK_a (pK_a=-log K_a) and the pH value can be derived:

$$pH = pK_a - \log \frac{c_{HA}}{c_{A^-}} \qquad A.2$$

Regarding the aqueous phase in a two phase system, the ratio of non dissociated to dissociated acid can be expressed as:

$$\frac{c_{HA}^{\beta}}{c_{A^-}^{\beta}} = 10^{pK_a - pH} \qquad A.3$$

Considering the ionized and ion pair form as a single species, inserting equation A.3 in the equation for the partition coefficient (2.12) and substituting the concentrations in the organic phase (α) with the corresponding equations in the aqueous phase (β) and the partition coefficients P_N and $P_{I;IP}$, the pH-dependent description of the partition coefficient is described:

$$D_{acid}^{\alpha\beta} = \frac{P_N^{\alpha\beta} \cdot 10^{(pK_a - pH)} + P_{I;IP}^{\alpha\beta}}{1 + 10^{(pK_a - pH)}} \qquad 2.13$$

A 1.2 Derivation of the Retention Models (Equations 2.57 to 2.63)

Retention Model of Armstrong and Nome (Equation 2.57)

Armstrong and Nome[310] developed a retention model, based on the division of the chromatographic column into equilibrium stages. On each plate, the mass balance of a component i is met according the following equation:

$$w_i^W + w_i^M + w_i^S = 1 \qquad \text{A.4}$$

with its mass fraction w_i in the bulk aqueous phase (W), the stationary (S) phase and the micelles (M). The partition coefficients P_i^{MW} and P_i^{SW} are defined as the ratio of the concentrations in the respective phases:

$$P_i^{SW} = \frac{[\text{solute on stationary phase}]}{[\text{solute in aqueous phase}]} = \frac{w_i^S}{hA_S} \cdot \frac{hA_{mob}(1-\beta)}{w_i^W} \qquad \text{A.5}$$

$$P_i^{MW} = \frac{[\text{solute in micelles}]}{[\text{solute in aqueous phase}]} = \frac{w_i^M}{\beta h A_{mob}} \cdot \frac{hA_{mob}(1-\beta)}{w_i^W} \qquad \text{A.6}$$

where h denotes the heights equivalent to a theoretical plate, A_{mob} and A_S are defined as the cross sectional area of the mobile and the stationary phase and β as the volume fraction occupied by micelles in the mobile phase. β is calculated from the molar volume v and the concentration c_m of the surfactant in the micelle:

$$\beta = v \cdot c_m \qquad \text{A.7}$$

Combing equations A.4 to A.6, it results:

$$w_i^W \cdot \left(\frac{hA_{mob}(1-\beta) + P_i^{SW} hA_S + \beta h A_{mob} P_i^{MW}}{hA_{mob}(1-\beta)} \right) = 1 \qquad \text{A.8}$$

Defining the effective volume V as

$$V = hA_{mob}(1-\beta) + P_i^{SW} hA_S + \beta h A_{mob} P_i^{MW} \qquad \text{A.9}$$

and W as

$$W = (1-\beta) + \beta \cdot P_i^{MW} \qquad \text{A.10}$$

the mass fraction of solute in the mobile phase is calculated as:

$$w_i^M + w_i^W = \frac{\beta h A_{mob} P_i^{MW}}{V} + \frac{h A_{mob}(1-\beta)}{V} = \frac{h A_{mob} W}{V} \qquad \text{A.11}$$

Considering an infinitesimally small volume of mobile phase δV passing through the column, the corresponding solute fraction is $W(\delta V/V)$. After the passage of n theoretical plates, the solute is eluted from the column, the elution volume V_e is calculated as:

$$V_e = n \cdot \delta V \qquad \text{A.12}$$

After the passage of the n successive volumes of mobile phase, the location of the band center of the solute on the column can be expressed as the serial number of the maximally occupied theoretical plate, so that:

$$\frac{n \cdot W \cdot \delta V}{V} = \frac{W \cdot V_e}{V} = 1 \qquad \text{A.13}$$

Combining equations A.9, A.10, and A.13 equation A.14 is derived:

$$\frac{W \cdot V_e}{h A_{mob}(1-\beta) + P_i^{SW} h A_S + \beta h A_{mob} P_i^{MW}} = \frac{W \cdot V_e}{P_i^{SW} V_S + W V_{mob}} = 1 \qquad \text{A.14}$$

From the definition of β (A.7) and W (A.10) it follows:

$$\frac{V_s}{V_e - V_0} = \frac{v(P_i^{MW}-1)}{P_i^{SW}} \cdot c_m + \frac{1}{P_i^{SW}} \qquad 2.57$$

Retention Model of Arunyanart and Cline-Love (Equation 2.58)

The retention model of Arunyanart and Cline-Love[317] is derived based on kinetic considerations. The partitioning according to the three phase model is expressed by the equilibrium reactions of the solute E. The partitioning between stationary (L_S), aqueous bulk phase (E_m) and micelles (M_m) is described as:

$$\begin{aligned} E_m + L_S &\overset{K_1}{\leftrightarrow} EL_S \\ E_m + M_m &\overset{K_2}{\leftrightarrow} EM_m \\ EM_m + L_S &\overset{K_3}{\leftrightarrow} EL_S + M_m \end{aligned} \qquad \text{A.15}$$

The equilibrium constants K_i are quantified as the binding constants for the stationary phase (K_1) and the micelles (K_2), K_3 is dependent on K_1 and K_2. The relation of the binding constant with the retention factor k in a chromatographic process is defined as:

$$k = \Phi \cdot K \qquad \text{A.16}$$

with Φ, the volume ratio of stationary to mobile phase. From experimental data k is derived as:

$$k=\frac{V_e - V_0}{V_0} \qquad \text{A.17}$$

Regarding micellar mobile phases, the binding constant can be expressed as:

$$K=\frac{[EL_S]}{[E_m]+[EM_m]} \qquad \text{A.18}$$

Considering the single equilibrium constants (equation A.15), the retention factor (equation A.16) can then be calculated as:

$$k=\Phi\cdot\frac{[EL_S]}{[E_m]+[EM_m]}=\frac{\Phi\cdot[L_S]\cdot K_1}{1+[M_m]\cdot K_2} \qquad \text{A.19}$$

With $[M_m]=c_m$, the linearized form of equation A.19 is given as:

$$\frac{1}{k}=\frac{K_2}{\Phi\,[L_s]\,K_1}\cdot c_m+\frac{1}{\Phi\,[L_s]\,K_1} \qquad 2.58$$

Retention Model of Foley (Equation 2.60)

Foley[318] considers the "complex formation" between solute (S) and micelle (M) in the mobile phase with the equilibrium constant K_{SM} as given in the following expression:

$$S+M \overset{K_{SM}}{\longleftrightarrow} SM \qquad \text{A.20}$$

The retention of the individual forms of the solute (S and SM), is described with the corresponding retention factors k_S and k_{SM}, the overall retention factor k is expressed according to the respective contributions:

$$k=\frac{[M]\cdot K_{SM}}{[M]\cdot K_{SM}+1}\cdot k_{SM}+\frac{1}{[M]\cdot K_{SM}+1}\cdot k_S \qquad \text{A.21}$$

Since the micelle is part of the mobile phase, the solute-micelle "complex" is unretained, and consequently $k_{SM}=0$. Adopting the designation of Arunyanart and Cline-Love (K_{SM} corresponds to K_2), and defining k_S as k_0 and [M] as c_m, the linearized form of the Foley equation is obtained:

$$\frac{1}{k}=\frac{K_2}{k_0}\cdot c_m+\frac{1}{k_0} \qquad 2.60$$

Retention of Very Hydrophobic Solutes (Equation 2.61)

Based on the model of Armstrong and Nome (equation 2.57), Borgerding et al.[320] derived a relation between k and c_m for very hydrophobic solutes. Originated from the retention factor as described by means of the Armstrong equation:

$$\frac{1}{k}=\frac{1}{\Phi}\cdot\left(\frac{v(P_i^{MW}-1)}{P_i^{SW}}\cdot c_m+\frac{1}{P_i^{SW}}\right) \quad \text{A.22}$$

and with the relation of the partition coefficients

$$P_i^{SM}=\frac{P_i^{SW}}{P_i^{MW}} \quad \text{A.23}$$

a simplified equation for hydrophobic solutes ($P_i^{MW}-1\approx P_i^{MW}$) can be derived:

$$\frac{1}{k}=\frac{v\cdot c_m}{\Phi P_i^{SM}}+\frac{1}{\Phi P_i^{SW}} \quad \text{A.24}$$

In the limit of very poor water solubility (P_i^{MW} and P_i^{SW} are very large), equation A.24 becomes (inverted):

$$k=\frac{\Phi\cdot P_i^{SM}}{v\cdot c_m} \quad \text{2.61}$$

Retention of Anti-Binding Solutes (Equation 2.62)

The approach from Jandera and Fischer[321] considers a reduced stationary and mobile phase volume for the description of the retention of anti-binding solutes. The inaccessible part of the volume of the stationary phase is directly proportional to the concentration of the adsorbed surfactant Q_{cmc} (due to electrostatic repulsion between solute and surfactant) as calculated with:

$$V_S=V_{S,0}-f_S\cdot Q_{cmc}\cdot V_{S,0}=V_{S,0}\cdot(1-f_S\cdot Q_{cmc}) \quad \text{A.25}$$

f_S is a proportionality constant which depends on both, the solute and the surfactant. Analogues, the inaccessible part of the mobile phase volume, due to repulsion between solute and micelles is accounted for:

$$V_M=V_{M,0}\cdot(1-f_m\cdot c_m) \quad \text{A.26}$$

with the corresponding proportionality constant f_m. From the definition of the retention factor in equation A.16, the retention for anti-binding solutes can thus be calculated:

$$k=\Phi\cdot K=\frac{V_S}{V_M}\cdot\frac{[S]_S}{[S]_M}=\frac{V_{S,0}\cdot(1-f_S\cdot Q_{cmc})}{V_{M,0}\cdot(1-f_m\cdot c_m)}\cdot\frac{[S]_S}{[S]_M} \quad \text{A.27}$$

where $[S]_\alpha$ is the solute concentration in the mobile (M) and stationary phase (S). In the micelle free system ($V_{S,0}$ and $V_{M,0}$), the retention factor k_0 is calculated from the equilibrium

constant between aqueous mobile phase and the stationary phase K_1 (compare equation A.15):

$$k_0=\Phi\cdot K_1 = = \frac{V_{S,0}}{V_{M,0}}\cdot\frac{[S]_S}{[S]_M} \qquad \text{A.28}$$

Combining equations A.27 and A.28 it follows:

$$k=k_0\cdot\frac{1-f_S\cdot Q_{cmc}}{1-f_m\cdot c_m}\cdot \qquad \text{A.29}$$

Inverting equation A.29, equation 2.62 is derived:

$$\frac{1}{k}=\frac{1-f_m\cdot c_m}{\Phi\cdot K_1-\Phi\cdot K_1\cdot f_S\cdot Q_{cmc}} \qquad 2.62$$

Retention of Dissociable Solutes (Equation 2.63)

Based on the model of Arunyanart and Cline-Love, the pH-dependent retention of dissociable solutes can be described.[323,324] Exemplarily this is shown for a monoprotic acid HA, dissociating according to its dissociation constant K_a:

$$HA \overset{K_a}{\leftrightarrow} H^+ + A^- \qquad \text{A.30}$$

Thus, besides the equilibria for the molecular form of the solute (equation A.15), the equilibria of the dissociated form need to be considered:

$$\begin{aligned} HA+L_S &\overset{K_1}{\leftrightarrow} HAL_S \\ HA+M_m &\overset{K_2}{\leftrightarrow} HAM_m \\ A^-+L_S &\overset{K_3}{\leftrightarrow} AL_S^- \\ A^-+M_m &\overset{K_4}{\leftrightarrow} AM_m^- \\ HAM_m+L_S &\overset{K_5}{\leftrightarrow} HAL_S+M_m \\ AM_m^-+L_S &\overset{K_6}{\leftrightarrow} AL_S^-+M_m \end{aligned} \qquad \text{A.31}$$

In analogy to equation A.19 the retention factor is calculated as:

$$k=\Phi\cdot\frac{[HAL_S]+[AL_S^-]}{[HA]+[HAM_m]+[A^-]+[AM_m^-]} \qquad \text{A.32}$$

Assuming that k_0 expresses the retention of the non-dissociated molecule, k_1 of the fully dissociated form:

$$k_0=\frac{\Phi\cdot[L_S]\cdot K_1}{1+[M_m]\cdot K_2} \qquad \text{A.33}$$

and

$$k_1 = \frac{\Phi \cdot [L_S] \cdot K_3}{1 + [M_m] \cdot K_4} \qquad \text{A.34}$$

equation A.32 is transformed to calculate the pH-dependent retention:

$$k = \frac{k_0(1 + K_2 \cdot c_m) + k_1(1 + K_4 \cdot c_m) \cdot \frac{K_a}{[H^+]}}{1 + K_2 \cdot c_m + (1 + K_4 \cdot c_m) \cdot \frac{K_a}{[H^+]}} + 1 \qquad 2.63$$

where c_m corresponds to the micellar concentration $[M_m]$.

A 2 Details for MLC Measurements

Partition coefficients were determined by MLC. Therefore the surfactant content in the mobile phase was increased from 0.05 wt% to 0.25 wt% in case of CTAB, and from 0.5 to 2.5 wt% in case of the CTAB/ Brij 35 mixture. Partition coefficients in Brij 35 solutions were determined at both mentioned concentration ranges. For TritonX-100 solutions, the retention was investigated in the range 0.05 – 0.5 wt%, for LPC in the range 0.05 – 0.20 wt%.
Injection volumes were 50 µL in case of the LPC measurements and 20 µL for Brij 35, CTAB and their mixtures. Using a TritonX-100 mobile phase, 2 µL were injected in case of vanillin and phenol, 20 µL in case of 3-methoxyphenol. The absorption maxima, at which the retention time of the solutes was measured, are summarized in Table A 1.

Table A 1: Detection wavelength for all solutes, measured by MLC.

Solute	Detection wavelength (nm)
2-vanillin	235, 262, 340, 380
3-methoxyphenol	244, 275
4-hydroxybenzaldehyde	275, 284, 323
4-hydroxybenzoic acid	246, 280
acetophenone	246
benzaldehyde	250
benzyl alcohol	214
coumarin	275, 310, 245
diclofenac sodium salt	220, 275
dopamine hydrochloride	220, 280, 295
ethyl vanillin	230, 275, 310, 347
ferulic acid	230, 320, 340
ibuprofen sodium salt	220, 265
isovanillin	245, 280, 310, 355
lidocaine hydrochloride	220, 265
p-coumaric acid	225, 295, 310, 325
phenol	220, 244, 270
propranolol hydrochloride	230, 290
retinol	313
salicylic acid	235, 295, 305
sodium salicylate	235, 295, 305
syringic acid	275, 310
vanillic acid	260, 280, 300
vanillin	275, 280, 310, 347

A 3 Rejection of Solute and Surfactant in MEUF

The evaluation of partition coefficients with MEUF is based on the measured rejection of surfactant and solute. To investigate the influence of the membrane on the rejection, solutes in surfactant free medium and surfactants in solute free medium were measured. Furthermore, for dissociating solutes, the influence of the pH value was investigated. The respective rejection needs to be considered, calculating the partition coefficient. The solute rejection in surfactant free medium is accounted for according to equation 3.3 and 3.4. The deviation of the surfactant mole fraction from the cmc in the permeate is accounted for according to equation A.35.

$$x_i^{Micelle} = \frac{x_i^{Feed} m^{Feed} - x_i^{Permeat}\left(1\text{-}x_i^{Feed} - x_S^{Feed}\right) m^{Feed}}{\left(x_S^{Feed} - x_{cmc}\right) m^{Feed} - \int_{t_1}^{t_2} \dot{m}(t)\left(x_S^{Permeat}(t) - x_{cmc}\right) dt} \qquad \text{A.35}$$

In Table A 2 the measured rejections for the surfactants, and the calculated rejections of the micelles is given for all investigated membranes.

Table A 2: Rejection R_i (%) of the surfactants (and corresponding micelles), as determined in this work; investigated membranes: regenerated cellulose (RC) and polysulfone (PS) with different molecular weight cut-off; (σ(TX-100) < 0,022%; σ(SDS) < 0,25%; σ(CTAB) < 0,33%).

Membrane	TX-100	SDS	CTAB
1 kDa, RC	99.31	81.36	82.39
	(100.74)	(106.07)	(99.32)
5 kDa, PS	90.73	90.99	97.45
	(91.63)	(115.72)	(114.38)
10 kDa, RC	97.77	75.55	82.85
	(99.02)	(100.28)	(100.04)

The rejection of the solutes in surfactant free medium is given in Table A 3, the dependence of the pH value is shown in Table A 4.

Table A 3: Rejection R_i (%) of the investigated solutes in surfactant free solution depending on the used membrane; RC: regenerated cellulose, PS: polysulfone.

Solute	1 kDa (RC)	5 kDa (PS)	10 kDa (RC)
acetone			2.00
arabinose			1.88
cellobiose			4.41
cycloocytamine			11.96
glucose			0.52
phenol	< 1.00	23.55	5.00
phenylboronic acid			1.74
sucrose			1.79
toluene			13.00
vanillin	3.85	23.96	

Table A 4: Rejection R_i (%) of the investigated dissociable solutes in surfactant free solution; used membrane YM-10 (Millipore, regenerated cellulose).

Solute	pH 2	pH 4.2	pH 6	pH 6.5	pH 8	pH 8.4	pH 10	pH 12
dopamine	1.63							
ephedrine	0.36							1.50
ferulic acid	1.58	3.24						14.31
lidocaine	0.63							2.36
propranolol	0.47		0.39		0.28		1.92	5.62
vanillic acid	0.00	3.74		10.67		11.94		18.49

A 4 Cmc_{12} Data for Surfactant Mixtures

Table A 5: Composition of CTAB/ Brij 35 and SDS/ Brij 35 mixed micelles, as determined based on the RST; data from [93,97,379].

α_{CTAB}	x_{CTAB}	α_{SDS}	x_{SDS}
0	0	0	0
0.25	0.06	0.20	0.1059
0.33	0.09	0.33	0.0890
0.50	0.15	0.40	0.0839
0.67	0.23	0.50	0.1220
0.80	0.34	0.60	0.2081
0.90	0.44	0.67	0.1460
0.95	0.52	0.80	0.1640
1	1	0.80	0.1691
		0.90	0.2300
		0.95	0.209
		0.95	0.300
		1	1

Table A 6: Cmc_{12} of ionic/ nonionic mixed surfactant systems for different surfactant compositions. Literature data[93,97,435] was used for the calculation of the micellar composition with COSMO-RS $x^{COSMO\text{-}RS}$ (Approach I, as described in section 3.3.2).

CTAB/ Brij 35			SDS/ Brij 35		
α_{CTAB}	cmc_{12} (mmol/ L)	$x_{CTAB}^{COSMO\text{-}RS}$	α_{SDS}	cmc_{12} (mmol/ L)	$x_{SDS}^{COSMO\text{-}RS}$
0	0.060	0.000	0	0.085 0.055	0
0.25	0.075	0.001	0.10	0.043	0.08
0.33	0.081	0.001	0.20	0.090	0.08
0.50	0.098	0.001	0.30	0.067	0.08
0.67	0.130	0.001	0.40	0.130	0.08
0.80	0.155	0.045	0.50	0.094	0.08
0.90	0.194	0.269	0.60	0.180	0.08
0.95	0.247	0.506	0.70	0.110	0.08
1	0.920	1.000	0.80	0.360	0.14
			0.90	0.580 0.240	0.14
			0.95	0.990	0.18
			1	8.000 5.500	1

A 5 MLC: Parameters Influencing the Evaluation

Partition coefficients determined with MLC were evaluated with both retention models (from Armstrong and Nome[310] and Arunyanart and Cline-Love[317]). The resulting partition coefficients are shown in Table A 7 for Brij 35 and in Table A 8 for CTAB.

Table A 7: Comparison of partition coefficients evaluated with the retention model of Armstrong and Nome[310] and Arunyanart Cline-Love[317] in Brij 35, determined by MLC.

Solute	Armstrong and Nome	Arunyanart and Cline-Love
2-vanillin	1.50 ± 0.02	1.54 ± 0.03
4-hydroxybenzaldehyde	1.58 ± 0.02	1.62 ± 0.02
4-hydroxybenzoic acid	1.98 ± 0.01	2.02 ± 0.01
coumarin	1.43 ± 0.02	1.48 ± 0.02
diclofenac sodium salt	3.42 ± 0.12	3.24 ± 0.15
dopamine hydrochloride	0.78 ± 0.03	0.78 ± 0.04
ethyl vanillin	1.67 ± 0.03	1.70 ± 0.03
ferulic acid	2.28 ± 0.08	2.33 ± 0.08
ibuprofen sodium salt	4.00 ± 0.15	3.53 ± 0.17
isovanillin	1.50 ± 0.01	1.54 ± 0.02
lidocaine hydrochloride	1.81 ± 0.02	1.84 ± 0.11
p-coumaric acid	2.35 ± 0.11	2.40 ± 0.11
phenol	1.68 ± 0.06	1.65 ± 0.08
salicylic acid	2.18 ± 0.01	2.22 ± 0.01
sodium salicylate	2.27 ± 0.08	2.24 ± 0.11
syringic acid	1.80 ± 0.01	1.84 ± 0.01
vanillic acid	1.86 ± 0.02	1.90 ± 0.02
vanillin	1.58 ± 0.01	1.62 ± 0.01

Table A 8: Comparison of partition coefficients evaluated with the retention model of Armstrong and Nome[310] and Arunyanart Cline-Love[317] in CTAB, determined by MLC.

Solute	Armstrong and Nome	Arunyanart and Cline-Love
2-vanillin	2.11 ± 0.08	2.12 ± 0.09
4-hydroxybenzaldehyde	2.12 ± 0.08	2.13 ± 0.09
4-hydroxybenzoic acid	2.59 ± 0.10	2.59 ± 0.11
coumarin	2.15 ± 0.03	2.17 ± 0.03
diclofenac sodium salt	3.34 ± 0.13	3.34 ± 0.14
dopamine hydrochloride	2.73 ± 0.10	2.70 ± 0.11
ethyl vanillin	2.35 ± 0.09	2.35 ± 0.10
ferulic acid	2.91 ± 0.04	2.92 ± 0.04
ibuprofen sodium salt	3.25 ± 0.12	3.25 ± 0.14
isovanillin	2.36 ± 0.07	2.37 ± 0.07
lidocaine hydrochloride	2.99 ± 0.11	3.00 ± 0.13
p-coumaric acid	2.99 ± 0.11	2.99 ± 0.13
phenol	2.39 ± 0.09	2.40 ± 0.10
propranolol hydrochloride	3.78 ± 0.14	3.79 ± 0.16
salicylic acid	3.77 ± 0.14	3.88 ± 0.16
sodium salicylate	3.78 ± 0.14	3.89 ± 0.16
syringic acid	2.33 ± 0.02	2.35 ± 0.01
vanillic acid	2.49 ± 0.01	2.50 ± 0.01
vanillin	2.28 ± 0.09	2.33 ± 0.10

In Table A 9 it is shown, that the used column has a negligible impact on the micelle/ water partition coefficient.

Table A 9: Comparison of partition coefficients evaluated using two different columns: Nucleodur and Nuclesosil in Brij 35; for details see methods section.

	Nucleodur	Nucleosil
acetophenone	1.32	1.29
benzaldehyde	0.82	0.85
benzyl alcohol	1.18	1.22

A 6 Influence of Alcohol on the Partition Coefficient

To evaluate the influence of the alkyl chain length of an alcohol on the patition coefficient, the effect of different alcohols was predicted for several solutes, as plotted in Figure A 1.

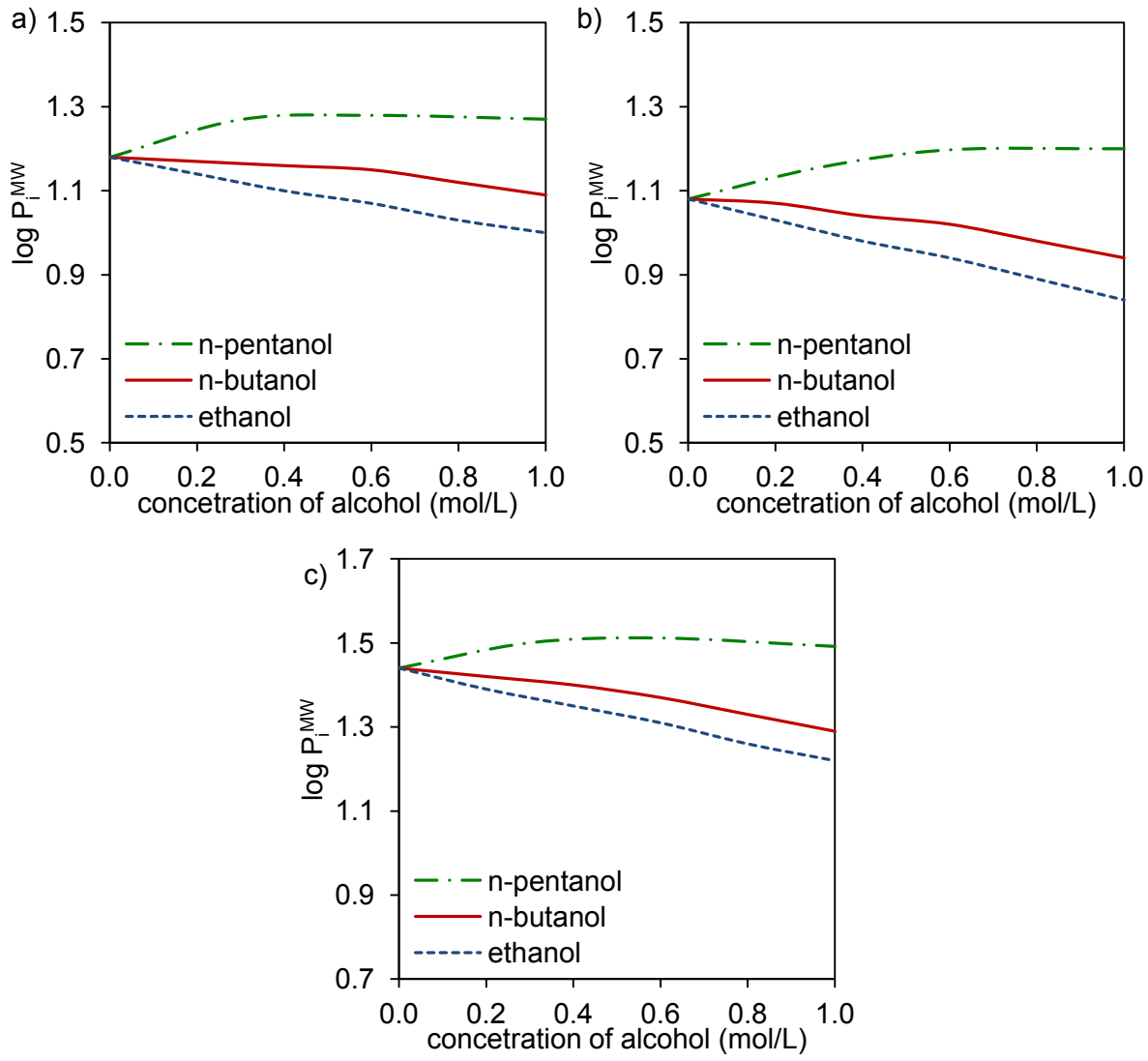

Figure A 1: Influence of different alcohols on the partition coefficient of a) phenol, b) vanillin and c) 3-methoxyphenol between TritonX-100 micelles and water at 85°C as predicted by the model COSMO-RS.

A 7 Prediction of the Lipophilicity Profile with COSMO-RS

In Figure A 2 an example for the prediction of the lipophilicity profile with COSMO-RS is given. Different approaches and assumptions are compared for the partitioning of isovanillin in an aqueous CTAB solution. However, significant deviations of the prediction of the ionized/ ion pair solute (log $P_{I;IP}^{MW}$) from the experimental data is observed for all the applied predictions.

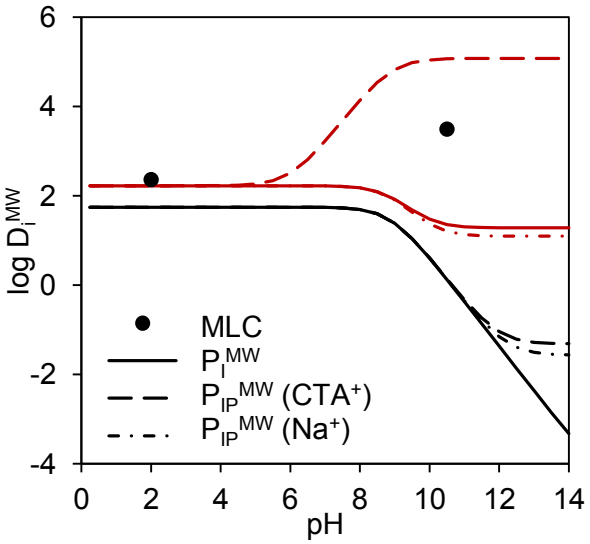

Figure A 2: pH-dependent partitioning of isovanillin in CTAB as determined by MLC and predicted with COSMO-RS. The prediction based on the pseudo phase approach (black lines) is compared to the predictions considering the anisotropy of the micelles (COSMOmic: red lines). Different assumptions for the prediction are compared: at elevated pH value, isovanillin is considered in the ionized (P_I^{MW}), or ion pair form (P_{IP}^{MW}) with the surfactant cations (CTA^+) or the sodium cations (Na^+).