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Topical Review

Thermophoresis of biological and biocompatible compounds in aqueous solution

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Abstract

With rising popularity of microscale thermophoresis for the characterisation of protein-ligand binding reactions and possible applications in microfluidic devices, there is a growing interest in considering thermodiffusion in the context of life sciences. But although the understanding of thermodiffusion in non-polar mixtures has grown rapidly in recent years, predictions for associated mixtures like aqueous solutions remain challenging. This review aims to give an overview of the literature on thermodiffusion in aqueous systems, show the difficulties in theoretical description that arise from the non-ideal behaviour of water-mixtures, and highlight the relevance of thermodiffusion in a biological context. We find that the thermodiffusion in aqueous systems is dominated by contributions from heat of transfer, hydrogen bond interactions and charge effects. However, the separation of these effects is often difficult, especially in case of biological systems where a systematic exclusion of contributions may not be feasible.

Keywords: thermodiffusion, thermophoresis, hydration, hydrophilicity, hydrophobicity

1. Introduction

Thermophoresis, or thermodiffusion, is the movement of a particle in a temperature gradient. Although the very first experiments investigating thermodiffusion were done in electrolyte solutions [1], the focus of the field shifted quickly towards organic mixtures. This was partly due to the complications in the description of solutions containing ions and polar solutes, partly due to applications which demanded a better understanding of non-polar mixtures. One of them is thermal field flow fractionation (th-FFF), a method to fractionate and characterize polymers. It was reported to fractionate polystyrene in 1967 [2] and has been successfully applied on colloids and synthetic polymers since [3]. Another main application is the investigation and modelling of hydrocarbon reservoirs, in which thermal gradients occur naturally. These thermal gradients lead to a separation of components so that modelling of the spacial composition of these deposits demands that thermodiffusion is considered when planning the extraction [4]. It has also been shown that thermodiffusion has to be considered in combustion processes [5].

In recent years, the interest in thermodiffusion in the context of life sciences and therefore in aqueous solutions has grown. There are two major new applications for the effect: (1) the monitoring of protein binding reactions through the sensitivity of thermodiffusion to complex formation and (2)
accumulation of a component in microfluidic devices through a combination of thermodiffusion and convection. The former application is realised in the commercially available microscale thermophoresis, where the sensitivity of the effect is used to determine precisely the dissociation constant $K_d$, which gives access to the change in Gibbs free energy $\Delta G^0$. The reasons for the change in thermophoretic behaviour of the biomolecules upon binding are not yet understood. It is assumed that an important contribution stems from changes in the hydration layer when conformation changes from free protein to complex as illustrated in figure 1(a). Readers interested in technological aspects of a commercially available instrument are referred to the review article by Jerabek-Willemsen et al [6]. For the second application, thermophoresis is combined with convection, similar to the operating principle of a thermogravitational column, and can be used to accumulate a component in a microfluidic setup. The flow behaviour of fluids in enclosed spaces and along surfaces [7, 8] is itself a complex field and relevant in the engineering of thermophoretic devices, but will not be a focus of this paper. To our best knowledge Gaeta et al [9] were the first, who made the connection between the prebiotic evolution and temperature gradients. Nowadays this is a very active field [10–13]. For instance it was possible to replicate DNA strands by a polymerase chain reaction (PCR) in a thermophoretic cell with convection [14].

As illustrated in figure 1(b) proteins are in the center of the magic triangle of soft matter showing the highest complexity. In the folded state proteins might be treated as charged colloids, in the unfolded state they show characteristics of polymers and additionally they consist of hydrophobic and hydrophilic units displaying features found for amphiphilic systems. Under these circumstances it can be useful to investigate simpler systems located at the corners or edges of the triangle in order to understand underlying principles. This review aims to give an overview of the literature on thermodiffusion or thermophoresis in aqueous systems with the focus on experimental studies and to illustrate the difficulties in theoretical description and simulations that arise from the non-ideal behaviour of water-mixtures. While the thermodiffusion behaviour of non-polar mixtures can be predicted with reasonable accuracy, aqueous and other associated mixtures often behave anomalously. Despite such difficulties, we want to highlight the relevance of thermodiffusion in a biological context. The focus will be on water soluble systems with the goal to understand the processes occurring in biotechnological application and devices. Experimental results and theoretical concepts of non-polar systems are discussed in a recent review by Köhler and Morozov [15]. For a detailed discussion of theoretical concepts of colloids we refer the interested reader to a review by Würger [16].

1.1. Applications

The two major new applications for the thermophoresis effect are presented in more detail below.

1.1.1. Microscale thermophoresis. Microscale thermophoresis has become the most important and most widely known application for thermophoresis. Although relatively new, it is already becoming a standard method for the quantitative characterization of biomolecular interactions [18] and is used as a high-throughput screening method for drug discovery [19]. It is based on the thermophoretic behaviour of biomolecules and its sensitivity to non-covalent binding [6].

The method is schematically described in figure 2. An infrared-laser (IR-laser) is pointed to an aqueous solution of fluorescently labelled protein and the fluorescence is detected. Before the laser is switched on, there is a constant fluorescence intensity $I_{fluor}$ according to the protein concentration in the solution. When the laser is switched on, light is absorbed by the water and the solution is heating up in the illuminated area. Typically, the protein vacates the heated zone more or less strongly, depending on its Soret coefficient. This leads to a lower concentration of protein in the observed area and a decrease in fluorescent intensity. Apart from some bleaching,
the initial fluorescent intensity is reached again after switching off the laser. This measurement is repeated at varying ligand concentrations and a titration curve of the fluorescence intensity in the heated zone is recorded, which can be used to calculate the dissociation constant $K_d$ and the Gibbs free energy $\Delta G^0$ of the ligand binding reaction.

The precision of this method is due to the high sensitivity of the Soret coefficient to any changes of the protein. The binding of a ligand alters the protein’s response to the thermal gradient so that the fluorescence intensity in the heated spot is shifted. While the effect is very successfully used as an indicator for ligand binding, the underlying mechanism that makes the thermodiffusion response so sensitive is not understood. The accepted explanation is that the addition of the ligand and any conformational changes the protein may undergo lead to a modification of the protein’s hydration shell, which affects thermophoresis. While the microscopic reasons for the altered thermodiffusion behaviour upon ligand binding may be highly specific to the observed system, a general understanding of the influence of hydration on thermophoresis would be desirable.

1.1.2. Thermogravitational column and microfluidic traps. Thermogravitational columns were one of the first instruments used to measure thermodiffusion and also the first application of the effect. A temperature gradient is applied horizontally across a column filled with a gas or liquid mixture. A circular convectional flow down the cold side and up the warm side occurs and combines with the thermodiffusion in horizontal direction. If the thermophobic component also has a higher mass density, the combination with convection enhances the de-mixing effect of thermodiffusion: the thermophobic component is carried down on the cold side and the thermophilic one up on the warm side of the column. After some time, a steady state is reached with a concentration gradient along the column from which the Soret coefficient can be calculated. Thermogravitational columns can also be used for isotope separation and were employed in the Manhattan project to enrich uranium [20], but it has since been replaced by less energy and cost intensive methods. Nowadays the strength of conventional thermogravitation columns lies in the investigation of ternary mixtures as this technique is superior to optical methods, because the extracted sample can be investigated using state of the art analytical methods and does not rely only on refractive index measurements [15].

Similar geometries are promising for microfluidic applications. It has been shown that the same combination of convection and thermodiffusion which is used in thermogravitational columns can also be used in capillaries and pores to trap and enrich one component of a mixture. One example is the optimisation of PCR in a capillary [14]. Here, the reaction is...
continually fed and the necessary temperature cycling provided by the convectional stream that circulates the molecules through hot and cold regions, while the convectional pattern allows the accumulation of replicated DNA fragments in the capillary.

A central issue concerning theories about the origin of life is the so-called concentration problem, posing that any organic matter in the primordial ocean would have been present only in very small concentrations. This would make effective polymerisation virtually impossible, since hydrolysis would be the dominating reaction pathway. From the viewpoint of thermodynamics a similar problem has been expressed: the formation of structure that is necessary for even the simplest building blocks of life is connected with a reduction of entropy and will therefore only occur spontaneously under non-equilibrium conditions [21]. One possible solution to this problem is an accumulation process driven by a non-equilibrium setting. In a mechanism similar to thermal columns, mineral pores near hydrothermal vents could have trapped and enriched prebiotic molecules, making polymerisation reactions possible [22]. The key difference is that these pores are not closed, like the thermal columns, but are open on the top to a reservoir with a fixed concentration of the thermophobic component, so that this component can diffuse into the pore and be accumulated at the bottom.

1.2. Contributions to the Soret effect

Experimental findings show that the thermodiffusion behaviour of a substance is dependent on a large number of factors. Figure 3 gives an overview of the main parameters influencing the Soret coefficient and the trends that have been identified.

Mass, size and moment of inertia are the contributions to the Soret effect that are independent of particle interactions. They contribute to the so-called isotope Soret effect or the mass contribution to the Soret effect \( \Delta S_{\text{chem}} \). The former name derives from the first experiments done to investigate this contribution, where isotope mixtures were used to observe species with identical chemical interactions, but different mass [23, 24]. Since then, it has been shown that in non-polar mixtures there is a contribution to the Soret effect that is only dependent on mass and moment of inertia [25, 26], and so the meaning has been widened.

Attractive or repulsive interactions (hydrogen bonds, cross interactions, hydrophobic interactions) between particles lead to another contribution to the Soret coefficient. Since these interactions are determined by the chemical nature of the mixture, this is called the chemical contribution to the Soret effect \( \Delta S_{\text{chem}} \) [25]. For non-polar mixtures the chemical contribution can be predicted with reasonable accuracy by the heat of transfer scale, which is described in detail in section 2.1. For aqueous systems and other associated mixtures, the anomalous temperature and concentration dependence of the interactions complicate the theoretical approach. The effective hydrogen bond strength decreases linearly between 273–373 K [27]. This leads to a weakening of the hydrogen bond network at higher temperatures leading to the typical temperature dependence found for many solutes in water [28, 29] (see sections 1.3.1 and 3). The strong cross interactions result in a sign change as function of concentration [30–32], as for energetic reasons the minority component enriches always on the cold side.

In charged systems, interactions between the particles are dominated by electrostatic forces and the Soret coefficient becomes a function of the Debye screening length, which is determined by particle charge and the ionic strength in solution. As charge interactions are important for aqueous solutions of biological and biocompatible molecules the different theoretical approaches and the physical picture behind it will be discussed in section 2.2.2. Also membranes and vesicles play an important role in the biological context. As a preliminary step we will look into micellar systems and microemulsion. For those larger systems the surrounding solvent can be treated as a continuum and \( \Delta S_{T} \) can be predicted using the interfacial tension difference due to the temperature gradient across the particle surface (see section 3.4.2).
1.3. Thermal and other relevant properties in aqueous mixtures

Although water has a deceptively simple structure and is one of the most closely investigated substances, its behaviour is notoriously difficult to describe. Water has numerous properties that are anomalous compared to other liquids. Its markedly non-ideal behaviour is caused by strong polarity which results in hydrogen bonds. It is important to note that these are directional interactions. Depending on the properties one would like to calculate, this can lead to difficulties in the theoretical treatment when spherical potentials are assumed [33]. The following paragraphs contain pertinent information on hydrogen bonds, discuss concepts to describe water-solute interactions and introduce some peculiarities of water properties that play a role in the following chapters.

1.3.1. Hydrogen bonds. Hydrogen bonds are electrostatic in nature with a small covalent contribution [34]. They are formed between atoms with opposite partial charge, most commonly between a positively charged hydrogen atom and a negatively charged oxygen or nitrogen atom. The strength of the hydrogen bond depends on the strength of the partial charges and is therefore not only dependent on the binding atom itself, but is influenced by the chemical context even for the same donor-acceptor couple. Note that the weak hydrogen bond HO—H...OH₂ in neutral water changes in an acidic or basic environment to a 6-times stronger bond [35]. In water the enthalpy of the hydrogen bond is \( \Delta H = 23.4 \text{ kJ mol}^{-1} \), which is about 5% the strength of the covalent bonds in water, and the entropy is \( \Delta S = 37 \text{ J K}^{-1} \text{ mol}^{-1} \) [36]. While hydrogen bond formation is common in polar solvents, its effects are strongest in water where each atom can have as many hydrogen bonds as covalent bonds. The tetrahedral structure of water allows for a far-reaching 3-dimensional network [37, 38], whereas other polar solvents form far smaller clusters, because they are less cohesive [39]. However, the hydrogen bond network in liquid water is also very dynamic. The average hydrogen bond lifetime is about 1 ps and the lifetime of ‘dangling’ OH-groups is shorter than 200 fs [37], so that hydrogen bonds are continually broken and reformed. This leads to a situation where the enthalpy gain by formation of a highly structured hydrogen bond network (narrow distribution of geometries and high average binding energy) is balanced against the entropy gain that results from the bending and breaking of hydrogen bonds (wide distribution of geometries and low average binding energy). The phenomenon of enthalpy-entropy compensation in biological systems, which is controversially discussed in literature [40–44], might be a result of such a balance.

1.3.2. Hydrophilicity. While hydrogen bonds in pure water are well characterized, the situation becomes more complicated when we consider the solvation of an additional compound (or the behaviour of water at surfaces). It is clear that the hydrogen bond network has to be in some way reorganized in order to accommodate the solute, but the microscopic picture on how this is achieved is unclear and might very well depend on the individual composition and geometry of the molecule. It is this mechanism that leads to the non-ideal behaviours of most aqueous solutions. Although there are very few facts about hydration that are not hotly debated in literature, there is a general agreement that three cases have to be distinguished [37]: first, the solvation of charged or polar solutes, where surrounding water molecules orient themselves to screen the charge or to form a hydrogen bond with the solute. Second, the solvation of non-polar molecules, where there is no favourable interaction with water, but the hydrogen bond network has to rearrange in order to accommodate the solute. And third, solvation of large molecules, which can be treated similarly to the hydration of surfaces. Macroscopically, the free energy changes caused by these rearrangements contribute to the chemical potential of the solute: an non-polar compound will cause predominantly unfavourable rearrangements and have a high chemical potential, while compounds that can engage in hydrogen bonding with the surrounding water can lower their chemical potential. The structural changes caused by such rearrangements influence the intermolecular distances, changing density and thermal properties of the mixtures. While the picture of distinct ice-like and liquid-like structures in water is probably inaccurate, there is evidence that the distribution of binding lengths and energies of water can shift when a solute is introduced, leading to modified heat conductivity and thermal expansion coefficient. Indeed, the Soret coefficient has been discussed in connection with many concepts that are directly or indirectly linked to the chemical potential of the solute, such as solubility [45, 46] or the Hofmeister series [47, 48], and to concepts related to the water structure like thermal conductivity and expansion [39].

An established empirical method to characterize the affinity of different chemical compounds towards water is to ascribe a property called hydrophilicity (or hydrophobicity, if the affinity is small). One of the most common parameters to describe hydrophilicity is the 1-octanol partition coefficient \( P \). In the original experiment a small amount of solute is put in a shaking flask containing water and 1-octanol (or another immiscible organic solvent). After shaking the mixture, the aqueous and organic phases are allowed to separate and the concentration of the solute in each phase is measured. The ratio of concentrations in the two phases \( (c_{\text{octanol}}/c_{\text{water}}) \) is \( P \) and the hydrophilicity of a compound commonly given as its logarithm \( \log P \). The concentration difference between the phases is caused by the different standard chemical potential the solute has in the two solvents. These days, \( \log P \) is usually not determined by experiment, but by algorithms that sum up incremental contributions from the chemical groups of the molecule in question, based on experimental data sets.

1.3.3. Salt effects. Beside hydrogen bonds, salt effects also play an important role in the context of protein stability and protein interactions. Conceptually, salts are often ordered in the Hofmeister series, which ranks the ions in order of their physical behaviour influencing the stability of colloidal or protein solutions [49]. The effects are generally more pronounced for anions than for cations. For a long time it was believed that stabilization and denaturation of the proteins is
an indirect result of the changes in the water structure caused by ions: the so-called kosmotropic ions (water structure makers) would lead to a less dense water structure and the chaotropic ions (water structure breakers) to a denser water structure. Only roughly 15 years ago spectroscopic and thermodynamic studies showed that ions do not influence the bulk water properties [50, 51]. Studies in thin layers showed that the anions influence the monolayers directly and not indirectly due to water structure changes [49]. These studies show, that the direct interactions between the ions and proteins or colloids are more important than structural changes in the bulk water. As we will see in sections 3.3.3 and 3.4.3 the thermophoretic behaviour of charged micelles and colloids is also substantially influenced by the nature of the ions and often the charge effects dominate the behaviour compared to non-ionic effects caused by hydrogen bonds.

1.3.4. Thermal expansion. The isobaric thermal expansion coefficient describes how the size of a gas or fluid element varies due to temperature changes at constant pressure. Note that we use \( \alpha \) as symbol for thermal expansion coefficient following the IUPAC recommendations, which differs from papers in the field [52, 53]. It measures deviations from ideal solution behaviour and it can be expressed either using the specific volume \( V \) or the density \( \rho \) as

\[
\alpha \equiv \frac{1}{V} \frac{\partial V}{\partial T} \bigg|_p = -\frac{1}{\rho} \frac{\partial \rho}{\partial T} \bigg|_p .
\]

(1)

Compared to non-polar liquids the isobaric thermal expansion coefficient of aqueous solutions is fairly small, which might be related to the stronger hydrogen bonds compared to van der Waals forces [54]. If the equation of state of the system is known, \( \alpha \) can be determined. Intuitively it can be understood that systems with a smaller isobaric thermal expansion coefficient should also be less sensitive to temperature gradients leading to smaller thermal diffusion coefficients. Indeed, as discussed in section 2.2, several theoretical approaches relate the thermophoretic mobility or the thermal diffusion coefficient with the isobaric thermal expansion coefficient \( \alpha \) [52, 53].

It turns out that the ability of the solute to form hydrogen bonds is also reflected in the thermal expansion coefficient. While for dimethylformamide/water mixtures \( \alpha \) shows a minimum as function of composition, the isobaric thermal expansion coefficient increases monotonously as function of the amide concentration in the case of more hydrophilic solutes such as formamide [55] and urea [56]. Since the compressibility is reflecting solute-water interactions [57], the physical reason for the monotonic behaviour is probably related to the stronger hydrophillicity of formamide and urea leading to a better compatibility with the water network. The compressibility minimum of DMF and other hydrophobic amides might be rationalized by a clathrate-like water structure surrounding the solute molecules at sufficiently high water content [58]. A similar observation has also been made for the isentropic compressibility. Papamatthaiakis et al [57] found a minimum of the isentropic compressibility in the case of the less hydrophilic compounds, while there was a monotonous decay for formamide. In conclusion we can state that the thermal expansion coefficient is very sensitive to interactions between solute and water.

1.3.5. Thermopolarization. It has been shown by simulations that thermal gradients can induce a preferred orientation in molecules, which gives rise to an electric field in dielectric materials [59]. The electric field depends linearly on the induced temperature gradient and also influences thermal conductivity, which is lowered at stronger polarization. The effect can be significant especially on the nanoscale and might have an impact on heat transport across biological membranes or medical applications like the heating of nanoparticles as cancer therapy [60, 61]. In water the thermal polarization shows a dependence on temperature and even an inversion of sign that has been explained by the interplay of two contributions: a contribution from the dipolar field, which is almost temperature independent, and the quadrupolar one, which shows a strong dependence on temperature and correlates with the thermal expansion of the fluid [62]. Simulations show that the electric field arising from thermopolarization also contributes to the observed Soret coefficient of electrolytes in aqueous solutions [63–65].

2. Theoretical description and computer simulations

2.1. Heuristic descriptions

The movement of molecules or particles in a temperature gradient can be described as a mass flux \( \vec{\jmath} \), which is the sum of two contributions [66]

\[
\vec{\jmath} = -\rho D_T \nabla c - \rho c (1 - c) D_T \nabla T .
\]

(2)

\( \rho \) is the mass density and \( c \) the mass fraction. Analogously, the molar density and mole fraction concentration can be used to calculate the particle flux. \(-\rho c (1 - c) D_T \nabla T \) is the flux along the temperature gradient characterized by the thermodiffusion coefficient \( D_T \), and \(-\rho D_T \nabla c \) the Fickian diffusion along the concentration gradient that necessarily arises from the thermodiffusion. Note that the latter term is assuming an ideal system where the activity gradient is equal to the concentration gradient. The activity of a substance in solution is an ‘effective concentration’, correcting for non-ideality so that the chemical potential in a non-ideal solution depends on activity like it would depend on concentration in an ideal solution. In a non-ideal systems, the chemical potential of a solute shows a stronger temperature dependence compared to ideal systems (e.g. due to hydrogen bonds) and diffusion can contribute to a concentration gradient (see partition experiment described in section 1.3.2). As a consequence the Fickian diffusion term in equation (2) likely deviates from the diffusion occurring in non-ideal solutions and the difference is then contained in \( D_T \) when it is experimentally determined. With a constant temperature gradient, Fickian and thermal diffusion cancel when a steady state is reached. Then \( \vec{\jmath} \) becomes zero.
and the ratio of Fickian and thermal diffusion coefficients is a constant proportional to the concentration gradient observed along the temperature gradient. This constant is called the Soret coefficient $S_T$:

$$
S_T \equiv \frac{D_T}{D} = -\frac{1}{c(1-c)} \frac{\Delta c}{\Delta T}.
$$

It is sometimes given as the dimensionless thermal diffusion factor $\alpha_T = S_T T$.

In section 1.2, we pointed out that the Soret coefficient is sensitive to a number of factors. There are several approaches to decompose the Soret coefficient into different contributions in order to gain a better understanding of the way in which each contribution changes $S_T$. In non-polar molecular mixtures, the observed Soret coefficient is the sum of a contribution that is dependent only on mass and moment of inertia, called the isotope effect or mass contribution $S_T^{Sm}$, and a contribution dependent on molecular interactions termed the chemical contribution $S_T^{chem}$:

$$
S_T = S_T^{Sm} + S_T^{chem}.
$$

There are slight variations in the equations characterizing $S_T^{Sm}$ [15, 67], most common is

$$
S_T^{Sm} = \frac{aM}{M_1 + M_2} \left( \frac{M_2 - M_1}{M_1} \right) + b_1 \frac{I_1 - I_2}{I_1 + I_2}.
$$

This equation is derived from descriptions of gaseous mixtures [68] and adjusted for liquids by the factors $aM$ and $b_1$. For non-polar solvents, it was found experimentally that the difference in $S_T$ for two isotopes does not change with solvent, however, there was a slight deviation when the more polar acetone was used as solvent [67]. Note that equation (5) predicts a positive Soret coefficient for component 1, if $M_1 > M_2$. This result is in accordance with the kinetic gas theory by Chapman and Enskog [69] and might be intuitively understood, that the heavier molecules get more easily trapped in the cold region. Furthermore, the non-equilibrium system tries to minimize its entropy production by redistributing the particles, so that the heat is conducted most efficiently through the system. This can be achieved by placing the light particles in the warm region, as they carry the larger part of the heat flux due to their higher mobility [70, 71].

The chemical contribution is caused by interactions between the particles in solution and can depend on concentration of the components and on temperature. An empirical equation to characterize the chemical contribution of different mixtures was proposed by Wittko and Köhler [72]:

$$
S_T(c, T) = \alpha_c(T) \beta_T(T) + S_T^{\infty},
$$

where $\alpha_c(T)$ and $\beta_T(T)$ are fitted by polynomial series expansions:

$$
\alpha_c(T) = a_0 + a_1 c + a_2 c^2 + a_3 c^3 + \ldots,
\beta_T(T) = 1 + b_1 (T - T_0) + b_2 (T - T_0)^2 + \ldots.
$$

The concentration and temperature dependence of molecular mixtures with water can also be described with these equations. Generally, the $b_1$-value found for aqueous systems is larger than that for non-polar mixtures and the isotopic contribution $S_T^{Sm}$ shows a correlation with $\ln P$, implying that it is not entirely independent from chemical interactions [73] (see section 3.3.1).

Another promising framework to describe the chemical contribution is the heat-of-transfer concept. These models are based on the works of Denbigh [74] and Rutherford and Drickamer [75] and strongly depend on the concept of activation energy in chemical processes. Similar to the thermodiffusion in solids, where the heat of transfer can be understood as the energy needed to jump from a neighbouring lattice position into a vacancy due to a crystal defect [76], the heat of transfer in liquids is an activation energy for the movement of particles.

For mixtures of organic solvents, Hartmann et al [77, 78] found that the heats of transport can be considered as a property of the pure components and that the Soret coefficient of a binary mixture calculated with

$$
S_T = \frac{Q_1 - Q_2}{RT^2 \left[ 1 + (\partial \ln \gamma_1 / \partial \ln x_1)_{p,T} \right]},
$$

where $R$ is the gas constant, $\gamma_1$ is the activity coefficient and $x_1$ the concentration of component 1. Note that the chemical potential of component 2 has been expressed with the chemical potential of component 1 using Gibbs–Duhem equations [79]. $Q_i$ are the molar absolute reduced heats of transport of the respective pure components. These values have been calculated from experimental data and can be interpreted as a thermophobicity scale with $Q_{\text{strain}} = 0$ as an arbitrary offset: in an equimolar mixture the component with the larger $Q$-value will move towards the cold side.

However, while equation (8) shows a very good agreement with experimental data on non-polar mixtures, the results for acetone, the only polar component investigated, deviate significantly [78]. The temperature dependence of $S_T \propto T^{-2}$ implied by equation (8) is not in good agreement with experimental data either [72, 73]. This might be due to the simplified term describing the molar chemical potential $\hat{\mu}_1, \left[ 1 + (\partial \ln \gamma_1 / \partial \ln x_1)_{p,T} \right] = x_1 (\partial \hat{\mu}_1 / \partial x_1)_{p,T}$, which does not include a possible temperature dependence.

2.1.1. Temperature and concentration dependence. It has been observed that in many aqueous systems the Soret coefficient shows an increase with rising temperature, often there is a sign change from a negative $S_T$ (thermophilic behaviour) to a positive value (thermophobic). The increase is steep at low temperatures and flattens out at high temperatures. Iacopini and Piazza describe this behaviour with the equation [28]

$$
S_T(T) = S_T^{\infty} \left[ 1 - \exp \left( \frac{T - T_0}{T_0} \right) \right],
$$

where $S_T^{\infty}$ is a constant value that is approached at high temperatures, $T^*$ is the temperature of the sign change and $T_0$ characterises the slope. This function holds for many aqueous mixtures [28, 45, 80–84], but has been shown to fail for some systems, like mixtures with a relatively low water concentration [12, 73, 85] or aqueous solutions of some alcohols.
accounts for the thermal properties for the number of hydrogen bonds and the parameter \( A_H \), suggesting a lower hydrophilicity of the solute.

Recently Niether et al [92] proposed a slightly modified form of equation (9) assuming that the temperature dependence of \( S_T \) in aqueous systems is mainly due to the temperature dependent formation and breaking of hydrogen bonds,

\[
S_T(T) = S_T^c - C_H \exp (-A_H T).
\]

(10)

As in equation (9) \( S_T^c \) accounts for the thermal properties of the core material, possible charges, etc. without the presence of hydrogen bonds. The second term \( C_H \) is a measure for the number of hydrogen bonds and the parameter \( A_H > 0 \) accounts for the temperature dependent strength of hydrogen bonds. Fitting the experimental data with equation (10) reveals a quite significant correlation between parameters \( C_H \) and \( A_H \), which makes it impossible to distinguish whether a stronger contribution is due to stronger interaction or a greater number of hydrogen bonds. Practically the linear correlation between \( \ln(C_H) \) and \( A_H \) was used to eliminate one parameter. The remaining parameter \( A_H \) was a measure for the temperature sensitivity of the strength of hydrogen bonds. This concept needs to be tested for a larger number of systems.

A sign change of \( S_T \) with temperature has been observed only rarely in non-aqueous systems [93], although the reason might not exclusively lie in a weaker \( T \)-dependence of non-polar systems, but also in the relatively small concentration ranges in which temperature dependent measurements have been conducted. A sign change in dependence of concentration has been observed for several non-polar systems [25, 72]. For some mixtures the concentration of sign change \( c^* \) is identical with the isothermal crossing point \( c^* \), i.e. the concentration where \( S_T \) is constant over a broad temperature range [89].

There is some controversy regarding the significance of the sign changes observed for \( S_T \) at \( T^* \) or \( c^* \). The concentration of sign change \( c^* \) has been connected with the heats of vaporization of the pure components [89] and the negative Soret coefficients at low temperatures is thought to be related to poor solvent conditions [83]. Others suggest that it is simply a consequence of the positive mass contribution and a negative concentration and temperature dependent chemical contribution [67].

2.2. Theory of aqueous systems

The theoretical description of the thermophoretic behaviour in aqueous systems is strongly influenced by the presence of hydrogen bonds. In contrast to non-polar interactions such as van der Waals forces these specific interactions show a stronger temperature dependence. The presence of directed interactions is crucial for the proper description of the thermophoretic behaviour of aqueous systems, because each water molecule has a preferred side with a stronger interaction compared to the non-preferred side [31]. Therefore, it is unlikely that it is possible to describe an aqueous system with one effective interaction parameter, as it is often done in the different theoretical approaches. Conceptually, we can also differentiate here between volume and surface forces as elucidated by Köhler and Morozov [15]. The majority of theoretical approaches for aqueous and non-aqueous systems focus on colloidal solutions, considering small solvent particles as a continuum [94–104]. The material included here is not meant to be exhaustive and focuses on approaches applicable for aqueous systems. There are different theoretical approaches for uncharged and for charged systems.

The dependence of \( S_T \) on the radius of the solute particles and its theoretical background are still controversially discussed. Würger [16] expects a linear size dependence for charged and uncharged solid colloids and only for soft colloids a quadratic dependence of \( S_T \), while others predicted also for charged solid colloids a quadratic dependence [80, 98]. Note that the linear radial dependence of \( S_T \) leads to a constant \( D_T \), which agrees with the molar mass independence of polymers [105–109]. As we will discuss later in section 3.4.3 most experimental studies confirm the radial independence of \( D_T \).

2.2.1. Uncharged solutes.

In the case of non-polar fluid mixtures it is quite common to use phenomenological equations [15, 110]. For associated liquid mixtures the agreement between predicted and experimental data is unsatisfactory using similar concepts. In recent years several attempts have been made to modify phenomenological equations to achieve a better description of the experimental data obtained for associated mixtures. Abbasi et al introduced an adjustable composition dependent interaction parameter [111] and Artola et al expanded Prigogine’s original approach by implementing a phenomenological parameter depending on the mass ratio of the two components [112], which was capable to predict the sign change of \( S_T \) with composition for the system ethanol/water reasonably well.

An important empirical approach relates the thermal diffusion coefficient with the thermal expansion coefficient, \( \alpha \), which has been introduced in section 1.3.4. Semenov and Schimpf [53] find for dilute solutions, that the thermal diffusion coefficient, \( D_T \), is proportional to the ratio between the isobaric thermal expansion coefficient and the dynamic viscosity as

\[
D_T = \frac{8}{27} \frac{A \cdot r_{\text{solute}}^2}{v_0 \cdot \eta} \alpha,
\]

(11)

with the solute radius, \( r_{\text{solute}} \), the Hamaker constant, \( A \) (describing interaction with the solvent), the volume occupied by one molecule, \( v_0 \), and the dynamic solvent viscosity, \( \eta \). The starting point of their approach is the independence of polymer thermophoresis on chain length and branching, so that they consider the interfacial surface potential around individual monomers using the Fowkes equation, which works for non-polar systems, but fails for aqueous solutions [113]. Likewise, Brenner’s [52] kinematic model of thermal diffusion for liquid and gases establishes that \( D_T \) is proportional to the isobaric thermal expansion coefficient \( \alpha \) times the solvent’s isothermal self diffusion coefficient \( D_s \), which is inversely proportional to the viscosity, \( \eta \).
are only important in the case of solvents with low is due to the solvent flow that is induced by electric body forces arising from the asymmetry of a sphere with radius $a$ of a sphere with radius $a$ with $Soret$ coefficient, which describes a steady state and correlates (theoretical models are expected: first, for small Debye lengths $\lambda_DH \leq 1$ nm) due to the presence of its double layer [99, 104]. Note that deviations between the experimental data and the particle due to the presence of its double layer [99, 104].

sider only the thermophoretic force on the charged colloidal Piazza and Parola [115]. Some of the theoretical approaches rger [16] and by $\ddot{u}$ colloids can be found in the review by W

are charged, so that the thermophoresis of salts and charged solutes has been studied extensively by theory [94, 98–104]. An overview of theoretical concepts especially for spherical colloids can be found in the review by Würg [16] and by Piazza and Parola [115]. Some of the theoretical approaches consider thermoelectric effects [101, 102], while others consider only the thermophoretic force on the charged colloidal particle due to the presence of its double layer [99, 104]. Note that deviations between the experimental data and the theoretical models are expected: first, for small Debye lengths ($\lambda_DH \leq 1$ nm) due to the high salinity leading to a violation of the Debye-Hückel approximation where the finite extent of ions is neglected. Secondly, for large Debye lengths ($\lambda_DH > 6$ nm), where the surface potential is high ($e\Psi_S/(k_B \cdot T) > 0.9$), so that the linearisation of the Poisson–Boltzmann equation is probably no longer valid.

The ionic contribution has been calculated in detail for highly dilute solutions of charged spheres [99] and rods [116]. Figure 4 illustrates the three forces acting on a charged colloidal sphere. The electric force $F_{el}$ and the solvent-friction force $F_{sol}$ are only important in the case of solvents with low dielectric constants. For a charged colloidal particle we find for the double layer contribution of the thermal diffusion coefficient $D_{T}^{DL}$ of a sphere with radius $a$ and $N = 1$ or of a rod with radius $a$, length $L$ and $N = L/(2a)$

$$D_{T} = \lambda D_{T} \alpha \quad (12)$$

with $\lambda$ an $\mathcal{O}(1)$ dimensionless parameter, probably equal to unity in the case of non-polar large solutes at high dilution. In the case of polar solutions a weak dependence of $\alpha$ upon the nature of the solute is expected [52]. For diluted aqueous solutions there is only very little evidence for possible chemically specific interactions leading to a reduction of the self diffusion of water [114]. Brenner’s approach implies that $D_{T}$ depends predominantly on the solvent, being-for a given solvent-insensitive to the physicochemical nature of the particular solute. Experimental results supporting equation (12) will be discussed in section 3.3.1. Note, that by dividing both sides of equation (12) by $D_{T}$ we obtain a quantity similar to the Soret coefficient, which describes a steady state and correlates with $\alpha$, a thermodynamic equilibrium property.

2.2.2. Charged solutes. Many of the water soluble solutes are charged, so that the thermophoresis of salts and charged colloids has been studied extensively by theory [94, 98–104].

$$D_{T}^{DL} = \frac{D_{0}}{T} \left\{ \frac{1}{4} N \left[ \frac{4\pi \lambda_{Bj}^{2}/a}{e} \right]^{2} \left( \frac{a}{\lambda_{Bj}} \right)^{3} \frac{\kappa a}{(1 + \kappa a)^{2}} \times \left[ 1 - \frac{d \ln \bar{\varepsilon}}{d \ln T} \left( 1 + \frac{2}{\kappa a} \right) \right] + \Lambda(T) \right\} \quad (13)$$

where $\sigma$ is the surface charge density, $\kappa^{-1}$ the Debye length, $\lambda_{Bj} = 3e^{2}/4\pi \varepsilon$ is the Bjerrum length (0.71 nm for water at room temperature), $\varepsilon$ is the permittivity of water at ambient temperature, and $\Lambda(T)$ is the additive contribution from the solvation layer and the core material of the colloid, which is treated as an adjustable parameter. The Stokes–Einstein translational diffusion coefficient $D_{0}$ can be measured at low concentrations. Equation (13) implies that charged rods can be...
described by constructing a rod as ‘shish-kebab’ model built by connected charged beads in a linear disposition.

Another contribution stems from thermoelectricity, which plays an important role in the development of liquid Seebeck cells [117]. Figure 4(d) shows the typical sketch used to illustrate thermoelectricity [16, 118]. The picture is similar to electrophoresis experiment and the basic idea results from differences in the heats of transport \( Q \), that the ions create, which lead to a non-uniform salt distribution along the thermal gradient. This leads to an electric field acting on charged solute particle with the surface potential \( \zeta \). The resulting thermoelectric contribution of the thermal diffusion coefficient is given by [16]

\[
D_1^{TE} = \frac{\varepsilon \zeta}{\eta T} \left( \frac{\zeta}{3} + \psi_0 \right),
\]

with \( \varepsilon \) the solvent permittivity, \( \eta \) the dynamic viscosity and for binary electrolytes \( \psi_0 = (Q_+ - Q_-)/2\varepsilon \) is related to the heat of transport of the ions.

The theoretical description of the thermophoretic behaviour of charged systems is still controversially discussed. As we will see in the experimental section some experiments can be fully described by taking into account only the thermophoretic force on a charged colloidal particle due to the presence of its double layer [98, 116, 119–121], while other experiments use a combination of double layer and thermoelectric effects to describe the experimental data [47, 48, 118, 122]. Due to electrostatic screening it might be difficult to design an experiment, which can clearly differentiate between the different contributions. Also performing computer simulations is not easy due to the long range character of the Coulomb interactions.

### 2.2.3. Polymers.

There is no special theory to describe the thermophoretic behaviour of water soluble polymers, so that we refer to the most recent review by Köhler and Morozov [15]. As in the case of low molecular weight mixtures water soluble polymers show sign changes with temperature or concentration, while non-polar polymers are in general accumulating on the cold side, implying a positive Soret coefficient. One of the most striking observations is the molar mass independence of thermophoretic velocity of a macromolecule with polymerization degree \( N \gtrsim 20 \) in a temperature gradient [108]. The thermophoretic velocity is characterized by an absence of long-range interactions e.g. hydrodynamic coupling between the monomers [123], which holds for non-polar as well as for polar polymers. It is also reasonable to expect that the recently derived concepts differentiating between non-draining versus draining coil hold also for water-soluble polymers [124].

### 2.3. Simulations of aqueous systems

In the following section we will highlight some simulations important for the understanding of aqueous systems. Readers interested in the physical basis, limits and applications of different simulation methodologies we refer to the reviews by Artola and Rousseau [125] and Bresme et al. [126]. Note that we are not going to discuss simulations and finite element calculations in hydrothermal pores [12, 22] and micro-pores [127–129] relevant for accumulation processes and characterization of petroleum reservoirs. There have also been numerous interesting simulations for colloidal systems [123, 130–134] with a special emphasis on a fundamental understanding of attractive and repulsive forces, solvent flow around particles, driving forces and possible applications as microscale machines and thermophoretic swimmers [135–139], which we will not discuss in detail as this would be beyond the scope of a single review article. The recent simulations of aqueous systems [62, 65, 85, 140–142] showed clearly the necessity of specific directed interactions for aqueous systems, which can only be neglected when introducing composition dependent interaction parameters [111]. In the following we will focus on molecular dynamic simulations of Lennard–Jones fluids [32, 143–145], aqueous solutions of small non-ionic molecules [146–149], and solution of alkali halides [59, 62, 65, 140–142].

#### 2.3.1. Lennard-Jones fluids.

Simulations of Lennard-Jones fluids have been extensively used to gain fundamental understanding of the different contributions such as mass, size, interactions and gravitational segregation [32, 71, 143–145, 150, 151]. Artola and Rousseau investigated the influence of the chemical contributions to the Soret coefficient in non-equilibrium molecular dynamics (NEMD) simulations [32]. It turned out that the thermophoretic behaviour depends strongly on cross interactions between unlike molecules [144] and these interactions are responsible for sign changes of the systems [31]. The systematic simulations [32] show that also the pronounced concentration dependence of those mixtures is strongly related to these cross interactions \( \kappa_{12} \). They used a modified Lorentz–Berthelot (LB) mixing rule with \( \kappa_{12} = k_{12} \sqrt{\epsilon_{11} \epsilon_{22}} \). The parameter \( k_{12} \) controls the strength of interactions between unlike species. Note that \( k_{12} = 1 \) holds for the classical LB mixing rule. They find for simple Lennard-Jones mixtures that the Soret coefficient decreases linearly with concentration and the slope gets larger, when \( k_{12} \) increases. On the other hand a larger ratio between like-like interactions does not significantly change the slope, but shifts \( S_T \) towards smaller values. This ratio might be related to \( S_T \) in equation (6) the so-called isotopic contribution, introduced by Wittko and Köhler [72] accounting for mass and inertia effects.

#### 2.3.2. Molecular aqueous mixtures.

In order to investigate the properties of experimentally relevant molecular aqueous mixtures, the simulations need to account for a more precise atomistic description than the one provided by the Lennard-Jones fluids. The first simulations were done for aqueous mixtures of methanol, ethanol, acetone and dimethyl sulfoxide (DMSO) [147, 152]. For the two mixtures acetone/water and DMSO/water a sign change was predicted, which was only afterwards observed experimentally [153]. Later the concentration dependence of \( S_T \) has been simulated for water/ethanol based on the approach by Prigogine, which describes thermal diffusion as an activated process and is independent.
from the mass ratio of the two components. Starting from the same picture Artola et al. [112] displace barycentrically the diffusion transition state to account for mass effects. The results reproduced well the concentration of sign change found in experiments, but underestimated the amplitude of the Soret coefficient, due to inaccuracies of the water force field.

Recently, for aqueous solutions of urea, concentration and temperature dependent NEMD simulations have been performed [85] showing qualitative agreement with experiments. It was found that the slope of the Soret coefficient as function of temperature changes from positive to negative with increasing urea concentration. The authors assumed that with increasing urea concentration the urea-water interactions are reduced leading to $S_T/dT < 0$. To test this hypothesis they increased the interaction strength by a factor of two $U_2 = 2U_1$ at a high concentration of 50wt% with $S_T/dT < 0$ at the normal interaction strength $U_1$. Confirming the hypothesis, the stronger interaction between urea and water lead to a positive $S_T/dT > 0$. The simulations showed further that with increasing urea concentration also the urea-water coordination number decreased. These studies demonstrate clearly the importance of the hydration shell for the thermophoretic properties of aqueous solutions.

### 2.3.3. Solution of alkali halides

Because of their importance for biological systems and as charge carrier in thermoelectric cells, solutions of alkali halides have been investigated in computer simulations to determine both the thermophoretic properties and the heat of transport of the ions [140, 142, 154]. The simulations of KCl and NaCl by Römer et al. reproduced the magnitude of the Soret coefficient, and the general dependence of $S_T$ on temperature and salt concentration.

Recent simulations [59, 62, 65, 141, 142] include the thermal polarization of water molecules, influencing the heat flux and the thermophoretic behaviour (see section 1.3.5). Lithium chloride (LiCl) showed the weakest temperature dependence compared to other alkali halides in water, which might be related to the small size of the ion supporting a stronger tetrahedral hydration shell. All salts showed a sign change from thermophilic to thermophobic behaviour with increasing temperature. While the sign change temperature of the various alkali halides does not really follow the Hofmeister series, temperature dependence of the Soret coefficient $\Delta S_T$ follows much better the Hofmeister Series [65]. The simulation of LiCl [154] confirmed the sharp minimum at 240 K, but could not reproduce the minimum at ambient temperature, where it had been observed experimentally [155, 156]. The microscopic understanding of the minimum and its location will require further investigation.

### 3. Experimental results

#### 3.1. Experimental methods

The currently used experimental methods are presented in recent reviews [15, 157], therefore we will only elucidate some special experimental problems one has to face when studying aqueous mixtures. In general all methods with boundary heating can be used for aqueous systems. Nevertheless, in the case of biological samples the affordability of the required sample volume might be an issue. Typically, much smaller sample volumes are required for the all-optical techniques, which use light not only for detection, but also for heating the sample by converting the light energy into thermal energy. This requires often the addition of a small amount of dye having an absorption band at the wavelength used. Ideally, this dye is inert, which means that there is no photobleaching and no dye contribution to the measurement signal. In the case of aqueous systems the spectroscopic properties of the dye often depend on pH, ionic strength and other parameters. Many of the water soluble dyes are charged, which change the ionic strength of the system and will also influence the thermophoretic behaviour (see section 3.3.3). In studies on aqueous surfactant systems [158–160] it was found that the dye changes the phase diagram and leads to a second slow thermophoretic mode, which could be explained by a feedback mechanism of the micelles containing the dye as co-surfactant [160].

In the literature we find three all-optical set-ups optimized for aqueous systems: a thermal lens [161] and TDFRS set-up [162] using laser light at $\lambda = 980$ nm and as third set-up a fluorescence microscopy method developed in the group of Braun [163], which uses a solid state laser with a center wavelength of $\lambda = 1480$ nm. According to the absorption spectrum of water the absorption at the longer wavelength is 40-times higher and therefore a laser with much less power is needed. Unfortunately, the longer wavelength is technically difficult to realize in a grating experiment [162] as it requires the optical rotation of the polarization direction. In general also more sophisticated IR-viewers for alignment are needed at $\lambda = 1480$ nm. Developing new instruments different factors need to be balanced for finding the optimal wavelength of the heating laser used.

#### 3.2. General empirical correlations

There are two main correlations which are important for aqueous systems in general regardless whether low or high molecular weight systems are examined. First we have the correlation between the thermal diffusion coefficient and the expansion coefficient (see section 1.3.4), which has also a theoretical basis. Second we have the empirical correlation between the temperature sensitivity of the Soret coefficient and the logarithm of the 1-octanol/water partition coefficient (see section 1.3.2). Additionally there are some concepts such as counting donor and acceptors sites, which are not so generally applicable. Interested readers find these concepts explained in some recent references [88, 164, 165].

#### 3.3. Molecular mixtures

**3.3.1. Uncharged systems.** Experimental results are available on a number of uncharged aqueous mixtures, from solvents like acetone [46, 153, 166], alcohols [86, 89, 167–170], and DMSO [89, 153], amides [12, 73, 85, 170], cyclodextrins [92, 165], ethylene glycols and crown ethers [88, 164], to biologically relevant systems like oligosaccharides [82, 83, 171]
and nucleotides [13, 22, 29]. Most of these investigations focus either on the concentration dependence of $S_T$ or on its temperature dependence, there are relatively few systems for which both are known. Many systems show interesting features like a sign change of $S_T$ at a certain concentration, $c^*$, or temperature, $T^*$, or an isothermal crossing point $c^*$, a concentration where the Soret coefficient is temperature independent.

While electrostatic interactions dominate the thermodiffusion behaviour in charged systems, the main contribution in uncharged aqueous solutions comes from the hydrogen bond network of water and hydrogen bonds between water and solute. Several approaches have been developed to quantify these interactions. Maeda et al. found that the difference of the number of hydrogen bond donor and acceptor sites on ethylene glycols and crown ethers is linearly correlated to the temperature dependence of their Soret coefficients [88]. However, the question if this linearity holds outside the homological group has not been conclusively answered. Polyakov et al. [89, 172] relate the concentration $c^*$, at which the sign change occurs, with microscopic structural changes in the mixture, suggesting that deformation of the tetrahedral network structure of water at high solute concentrations decreases the Soret coefficient. They find a linear correlation between $c^*$ and the ratio of the vaporization enthalpies of the pure components, corresponding to the ratio of the like-like interaction parameters as described by Artola and Rousseau [32]. The correlation holds for ethanol, methanol, propionaldehyde, acetone, and DMSO in H$_2$O and in D$_2$O, it fails, however, for propanol/water. This might be related to the tendency of propanol to form clusters [173].

Another correlation has been observed between the temperature dependence of the Soret effect and the hydrophilicity of the solute. Figure 5 shows $\Delta S_T$, the difference between the values at 20 and 50°C, against the partition coefficient $\log P$ for cyclodextrins (1%) [165], sugars (10%) [82, 83], alcohols (25%) [87], and glycols (1%) [88, 164]. The percentages in the brackets are the concentration in weight fractions.

The shaded areas mark the range of $\Delta S_T$ for nonpolar mixtures investigated by Wittko and Köhler [72].

Recenty obtained concentration and temperature dependent experimental values of $S_T$ of five different amides in water [73] could be described by an empirical equation developed for non-polar mixtures (see equations (6) and (7) in section 2.1). Figure 6 shows $b_1$ and $S_T$ as function of $\log P$ for the five investigated systems. The shaded areas mark the range of the values determined by Wittko and Köhler [72] for mainly non-polar mixtures. While $S_T$ of non-polar systems can be related to their differences in mass and moment of inertia this is not possible for aqueous systems. It is suspected that the decoupling of $\alpha_T(c)$ and $\beta_T(T)$ in equation (7) is not possible as the structure in the fluid mixture changes as function of temperature and concentration. One crucial point is also the temperature dependence of hydrogen bonds compared to temperature independent short range Van-der-Waals interactions in non-polar mixtures. This is also reflected by wider distribution of $b_1$ of the amides (indicated by the blue arrow in figure 6) compared to the non-polar mixtures.

Experimentally, a linear correlation between $D_T$ and $\alpha$ has been observed for non-polar mixtures [174], but also for aqueous solutions of sugars and amides [73, 82, 83]. This implies that the correlation with the isobaric thermal expansion coefficient (see equation (12)) holds also in the presence of hydrogen bonds, which influence the isobaric thermal expansion coefficient in a similar way as the thermal diffusion...
coefficient. Whether charges could change this relation still needs to be investigated.

3.3.2. Charged systems. Measurements of the concentration dependent thermodiffusion behaviour of various salts have been conducted by Tanner [175, 176]. Snowdon and Turner [177] have measured the Soret coefficient and calculated the heat of transfer for a large number of salts. They find that additivity of the ionic contributions holds for the heat of transfer of univalent salts, but not for the multivalent ones. The single-ion heats of transfer have also been calculated by Agar et al [178] for many commonly used ions from the standard ionic equivalent conductance. However, experimental results on cadmium sulfate [179] show that there is an appreciable concentration dependence of the heat of transport so that these values found for dilute solutions might be inaccurate when used at different concentrations and temperatures. The temperature and concentration dependence of the Soret coefficient has been measured for KCl and NaCl [140, 155, 180]. Longworth [180] found the concentration dependence to be almost linear at concentrations above 1 M, while Gaeta [155] found that the alkali halides show a sharp minimum of the Soret coefficient at \( c < 1 \text{ M} \) that becomes more pronounced and shifted to lower concentrations at higher temperatures.

It is worth noting that neither the absolute Soret coefficients of salts [175, 176], nor the concentration dependence of \( S_T \) or the single-ion heats of transfer [177] correlate to the Hofmeister series, although such ion-specific effects have been observed for polystyrene beads and DNA in electrolyte solutions [47, 48, 118]. This is an indicator that the thermodiffusive motion of the ions is influenced by the direct ion-water interaction and not by structural changes induced by the various ions [49, 181].

While charged colloids and multiple component systems composed of colloids in an electrolyte solution have been measured frequently due to their relevance for biological and technological applications, there are only very few systematic measurements of organic salts and small charged molecules. The investigation of tetramethylammonium and tetrabutylammonium hydroxides [182] poses questions about the interplay between charge effects and hydrogen bond effects of the organic side chains, which cannot be answered on the basis of the experimental data available. However, understanding this interplay might be necessary in order to understand thermodiffusion of proteins and other charged biomolecules.

3.3.3. Non-ionic and ionic micellar systems. There are only a few studies of micellar system [158–160, 183–186] by thermal lens experiments and by TDFRS. Typically, instruments like optical beam deflection technique and thermogravitational columns are not suitable since those experimental techniques require temperature differences of a couple of degrees so that, depending on the phase diagram, the shape and/or size of the micelles might be different at the warm and cold side. Some of the performed optical measurements were complicated by the addition of a dye converting the light energy into thermal energy [158, 159, 183]. As the dye often acts as co-surfactant in micellar systems, the phase behaviour changes and makes the interpretation of the data difficult [160].

Three studies investigated the thermophoretic behaviour in the vicinity of the critical micelle concentration (cmc) and temperature (cnt) [183, 184, 186]. In all studies it was observed that the thermophoretic behaviour shows a pronounced change at the cmc or cnt. The hypothesis is that the formation of micelles alters the interaction between solute and solvent as the hydrophobic part of the surfactant molecules is hidden in the inside of the micelles. Therefore, the direct interaction of this hydrophobic part and the solvent is screened, so that the solvent starts to interact mainly with the more hydrophilic parts of the surfactant molecule. At the time these experiments were performed, the correlation between the temperature dependence of the Soret coefficients and the partition coefficient was not known. We are therefore revisiting the study of the thermophoretic behaviour of the sugar surfactant \( n\)-Octyl \( \beta\)-D-glucopyranoside (C\(_8\)G\(_1\)) in regard to changes of hydrophilicity. In figure 7 we display the diffusion and Soret coefficients measured for three different concentrations of C\(_8\)G\(_1\) in water as function of temperature. In the entire temperature range the lowest concentration of 0.5 wt% is well below, and the two higher concentrations are well above the cmc. For the lowest concentration we observe a slight decay of the Soret coefficient with increasing temperature, which is typical for less hydrophilic solutes. With \( \log P = 0.1 \) the amphiphilic molecule C\(_8\)G\(_1\) belongs to the more hydrophobic solutes similar as 1-propanol, which also tends to form clusters in water and shows a similar temperature dependence of the Soret coefficient [87]. In contrast, the two higher concentrations show the typical temperature dependence of the Soret coefficient found for hydrophilic systems and can be described by equation (9). Although the partition coefficient of the micelle cannot be determined experimentally, we can estimate a \( \log P \) value from the hydrophilic head group multiplied by the aggregation number. Due to the large uncertainty of the aggregation number between 27–100 [187] and the ambiguity which of the chemical groups are in contact with water,
this can only be a rough estimate. Nevertheless, assuming the smallest aggregation number we can estimate \( \log P \leq -75 \), so that we expect a strong increase of the temperature dependence of the Soret coefficient, which we indeed observe. We therefore conclude that the thermophoretic behaviour of micelles also follows the empirical correlation with \( \log P \). In a very recent study Lattuada et al. [186] investigated an industrially used block copolymer, poloxamer P407, which shows a complex phase behaviour including multi phases. For this system they observed a double sign change behaviour at the cmt as it has also been observed for simple salts [155, 156]. For all investigated concentrations they found in a small temperature range of a few degrees above the cmt a negative temperature dependent slope of the Soret coefficient. The microscopic structure of the micelles formed by the block copolymers in this regime is not known. Below the cmt they behave like any other nonassociated neutral polymer, but above the cmt mixed micellar aggregates are formed [188]. In analogy to other systems we suspect that just above the cmt more hydrophobic units dominate the behaviour, while with increasing temperature the more hydrophilic groups are forming the interface to water.

The group of Piazza studied SDS micelles [185, 189]. The focus of these studies laid in the investigated of charge effects. They studied anionic surfactant sodium dodecyl sulfate (SDS) micelles in the presence of sodium chloride (NaCl) and sodium
hydroxide (NaOH). Initially, they described the $S_T$ of the SDS micelles by model of Ruckenstein predicting a quadratic dependence on the Debye length $\lambda_{OH}$ [189]. Later it turned out that for the large Debye length the surface potential was so high that the linearization of the Poisson–Boltzmann equation was probably not valid anymore [119] (see section 2.2.2). The two ionic compounds influenced the thermophoretic behaviour of the SDS micelles in a different way (see figure 8(a)). While the thermophobicity of the SDS micelles increased with increasing NaCl concentration the opposite effect was observed with NaOH. In the latter case the Soret coefficient even changed sign. Vigolo et al could only partially explain the measured $S_T$ in presence of NaCl and NaOH due to differences in the single ion heats of transport [178]. In figures 8(b) and (c) we display $S_T$ determined from a fit according to equation (9) and $\Delta S_T = S_T(50°C) - S_T(20°C)$, the calculated difference of $S_T$ for the various solutions. Comparing NaCl and NaOH, we observe with increasing NaCl concentration a reduction of $S_T$ and an increase of the temperature sensitivity of $\Delta S_T$. Both observations are a clear signature of the hydrogen bonds between the solute and the hydrating water. One possible explanation might be that NaOH acts as a base, transforming the weak HO–H...OH$_2$ bond in water into the very strong [HO...H...OH$_2$]-bond [35]. For particular ions, especially larger organic ions like in ionic liquids, it is necessary to consider also the chemical contributions to the thermophoretic behaviour.

These systematic studies of micellar systems are very important in biological context as membranes are typically formed by amphiphilic molecules and many biomolecules such as proteins have an amphiphilic character.

3.4. Polymers, microemulsions and colloids

In this section we summarize experimental results for aqueous polymers, microemulsions and water soluble colloids and discuss the results in terms of hydrogen bond strength and charge effects. Numerous publications have appeared in recent years investigating thermoelectric effects of ferromagnetic colloids [121, 190–193]. These systems are often rather complex as they tend to contain salt for electrostatic stabilization and exhibit a more or less pronounced polydispersity, which makes them effectively multi-component systems. It is expected that the diffusion of the salt anion and cation can lead to an additional electric field, which can be probed, if the cold and warm sides are also build as electrode [194]. In some cases organic salts are used, where the diffusion of anion and cation can be quite different leading to an additional electric field due to thermophoresis [191]. Note that in all those combined electrophoresis/thermophoresis experiments in the presence of salt special care needs to be taken that no electrochemical processes occur at the electrodes. The present literature is still quite diverse and a clear picture requires more careful experimental and theoretical studies. As we are focusing in this review on biological and biocompatible systems utilizing thermophoresis as sensor for changes in biological systems, we will not discuss ferromagnetic colloids in this review.

3.4.1. Synthetic and biopolymers

Conceptually, we can differentiate between thermophoretic studies of synthetic water soluble polymers [81, 171, 196–203] and charged biopolymers such as deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) [80, 163]. Note that no synthetic polyelectrolytes have been studied, all investigated synthetic polymers displayed in figure 9 are uncharged. While non-polar polymers have been investigated over a wide concentration and molecular weight range water soluble polymers have been investigated only at high dilution.

Figure 9 shows the chemical structures of the investigated non-ionic water soluble polymers in the sequence of decreasing hydrophilicity. In the case of the two polysaccharides pullulan and dextran the incremental change of the logarithm of the partition coefficient $\Delta \log P$ has been calculated for one sugar ring, while for polyvinylalcohol (PVA), polyethylene-lycol (PEG) and PNIPAM (Poly-N-isopropylacrylamide) it corresponds to the log $P$-value of one monomer unit. In the case of the polymers the estimated log $P$-values will deviate from the experimentally determined values as it is expected that due to the coiling of the polymer chain not all monomers are accessible to the solvent.

Figure 10 shows the temperature dependence of $S_T$ of four synthetic polymers displayed in figure 9. PVA is missing as it had been measured only at room temperature. As in the case of low molecular weight mixtures (see section 3.3) the reduced temperature dependence of the Soret coefficient with decreased hydrophilicity is also observed for polymers. Except for PNIPAM the temperature dependence of $S_T$ of all systems can be described by equation (9). The unusual temperature dependence of $S_T$ of PNIPAM is related to the coil-globule transition of the polymer close to $T = 31°C$ [201]. Additionally, we see an increase of $S_T$ with increasing hydrophilicity, which is also often observed, when the solute forms less hydrogen bonds with water due to addition of a hydrogen bond breaking compound [195] or with increasing temperature.

Figure 10. (a) Soret coefficient of the synthetic non-ionic water soluble polymers: PNIPAM (solid green squares) [201], PEO (solid blue triangles) [199], pullulan (open black circles) [81] and dextran (red bullets) [195]. (b) $S_T$ of charged bio-polymers as function of temperature: $\lambda$-DNA(10kbp)(solid orange triangle) [80], plasmid-DNA(6.7kbp)(open red square) [28], $\lambda$-DNA(50bp)(solid green diamond) [80] and lysozyme(400mM NaCL/H$_2$O, pH = 4.65)(black circle) [204]. The solid lines are fits according to equation (9) and the dashed line is a guide to the eye.
The temperature dependence of the Soret coefficient of all DNA and protein solutions displayed in figure 10(b) can be described by equation (9). While at low temperatures the thermophoretic behaviour is strongly influenced by hydrogen bonds, at higher temperatures $S_T$ is governed by the molar masses. As expected due to the slower diffusion for higher molar masses, the magnitude of the Soret coefficient at high temperatures, corresponding to $S_T \approx \gamma_a/\lambda T$ in equation (9), increases with molar mass of the solutes lysozyme ($M_w \approx 1.4 \times 10^4$ g/mol) [204], λ-DNA(50bp)($M_w \approx 3 \times 10^4$ g/mol) [80], plasmid-DNA(6.7kb)($M_w \approx 4 \times 10^6$ g/mol) [28] and λ-DNA(10kb) ($M_w \approx 6 \times 10^6$ g/mol) [80].

The charge contributions of polyelectrolytes have been solely investigated for biopolymers like DNA and RNA. As mentioned in section 2.2.2 we can differentiate conceptually between a local (see figures 4(a)–(c)) and a global electric field (see figure 4(d)). Reichl et al [118] investigated systematically DNA strands of different lengths in aqueous solutions of various salts as function of temperature. They were able to describe the Soret coefficient by four different contributions

\[ S_T = S_{DL}^{SE} + S_{SE} + S_{TD}^{SD} + 1/T, \]  

$S_{DL}^{SE}$ stemming from the electric double layer, $S_{SE}$ caused by a global electric field due to a salt gradient (Seebeck effect), $S_{TD}^{SD}$ a non-ionic contribution mainly determined by hydration effects influencing the temperature dependence (see equation (9)), and the ideal gas term $1/T$. Note, that in the mentioned work the double layer contribution is denoted as capacitor model. Further we would like to point out, that the last three terms in equation (15) show no Debye length dependence and can be identified with the intercept $A(T)$ in equation (13) divided by the Stokes–Einstein diffusion coefficient $D_0$. For salts with unknown Seebeck coefficient it will not be possible to separate the thermolectric contribution from the offset of the chemical contribution $S_E$ given in equation (9). Especially in the case of large organic salts it might

**3.4.2. Microemulsions.** Soft colloids such as microemulsions (MEs) formed by amphiphilic molecules are also of interest in biological context, as the amphiphilic molecules form membranes playing an essential role in many biological processes [205]. So far there is only a small number of ME studies [206–208]. Vigolo et al [206] studied water swollen reversed MEs in a water-poor phase, while we focus here on the non-ionic MEs studied in a water-rich phase [207, 208]. MEs are thermodynamically stable mixtures that are macroscopically isotropic but structured on the nano-scale. They consist of at least three components: (A) polar (e.g. water), (B) non-polar and amphiphilic (C). A and B are in general immiscible with each other. The amphiphile will preferentially adsorb at the interface between the polar (A) and non-polar (B) components which leads to the formation of an amphiphilic interfacial film.

Depending upon composition and temperature, aggregates of different size and shape, networks, bicontinuous or lamellar structures are formed [209]. The left hand side of figure 11 corresponds to the vertical section (see blue section in inset) through the phase prism at a constant mass fraction $\gamma_a = m_C/(m_A + m_C)$. As can be seen, a one-phase region is formed at intermediate temperatures, i.e. between the emulsification failure boundary (efb) above the 2 state (oil-in-water microemulsion + excess oil) and below the 2 state (water-in-oil microemulsion + excess water) at the near critical boundary (ncb). The one-phase region narrows with increasing mass fraction of oil $m_w = m_B/(m_A + m_B + m_C)$. Increasing the temperature away from the efb, the droplets change from spherical to elongated to network-like structures. Following the efb while increasing both temperature and the oil fraction $m_w$, the radius of the spherical droplets rises. Experimentally it was found that $S_T$ increased linearly with radius of the
droplets [207] (see discussion of the size dependence in section 3.4.3). Note that in this study not only the diameter, but also the temperature increased. By varying the chain length of the n-alkanes it is possible to study the thermodiffusion behaviour of droplets of different sizes at the same temperature, also this study confirmed the linear radial dependence of $S_T$ [208].

The concentration dependence of the Soret coefficient can be studied iso thermally along the straight binodal line, i.e. keeping the oil-to-surfactant ratio constant (see figure 11 right). It turned out that $D$ shows a slight increase due to the effect of stronger interactions with increasing volume fraction, $\phi$, $D_T$ remains almost constant and $S_T$ decreases slightly. A decay of $S_T$ with increasing concentration is also often observed for hard [210] and polymer solutions [211].

Piazza and Parola [97] calculated that the Soret coefficient of a soft colloid with radius $R$ should be proportional to the temperature derivative of the product of the interfacial tension $\sigma_{ab}$ and a characteristic length $l$ [97] in the following way

$$S_T = \frac{4\pi R}{k_B T} \frac{\partial (\ell \sigma_{ab})}{\partial T}. \quad (16)$$

The characteristic length $l$ had initially been related to the width of the attached fluid layer. Later it had been clarified to that width, where the pressure tensor is asymmetric [115]. In one systematic study of the interfacial tension and the Soret coefficient of five different ME systems using the same non-ionic surfactant pentaethylene glycol monododecyl ether (H$_2$O/n – alkane/C$_{12}$E$_5$) and varying the chain length of the n-alkanes, it was possible to determine the transition layer $l$ between 0.1 and 0.2 nm. The values correspond to typical van der Waals radii and are too small to be identified with a surfactant film. Further research and other experimental methods are required to elucidate the physical meaning and confirm the magnitude of $l$.

3.4.3. Colloids. As many aspects of the thermophoretic behaviour are still a puzzle, colloidal model systems have been used to test theoretical approaches [98, 116, 119, 210]. Synthetic as well as biological colloids such as proteins or viruses have been used as model systems. Especially for the investigation of charge effects biological systems are often superior as they are typically more monodisperse in size, shape and surface charge density. In the following we will summarize the studies investigating the size, charge and interfacial tension influence on the thermophoretic behaviour of hard and soft colloids.

Size dependence: The size dependence of the Soret coefficient has been investigated for hard and soft colloids in water by several groups [206–208, 212–215]. While Duhr and Braun [212] observed an unambiguous quadratic dependence of $S_T$ for carboxyl modified polystyrene (PS) beads in 1 mM Tris(hydroxymethyl)-aminomethan (TRIS) buffer on the radius in the range from 20 nm to 1000 nm using a microscopic fluorescence technique, studies by Putnam and Cahill of carboxyl functionalized PS spheres in a size range from 26 nm to 92 nm (PS) gave some indication that the behaviour could also be linear. Later Vigolo et al [206] obtained a linear dependence investigating bis(2-ethylhexyl)sulfosuccinate (AOT)/iso octane/water microemulsion droplets with a radius between 1.8 nm to 16 nm. Braibanti et al [214] repeated the experiment of Duhr and Braun [212] and studied the thermodiffusive behaviour of highly diluted carboxyl modified PS spheres under the same conditions except that they used a 1:1 mixture of H$_2$O + D$_2$O to minimize sedimentation effects which can occur for the larger colloids. In the investigated radial range between 11 nm and 253 nm they found a linear radial dependence for $S_T$. We know that the thermophoretic properties strongly depend on interfacial properties such as grafting or surface charge densities [215, 216], which are hard to control during the synthesis. Therefore it is difficult to compare the thermophoretic data of colloids with different radii stemming from distinct syntheses. Identical interfacial chemical groups can be realized for microemulsion systems. Recent studies of non-ionic microemulsions support the linear radial dependence of $S_T$ [207, 208]. From the linear dependence of $S_T$ follows that $D_T$ is independent of radius, which is in agreement with the molar mass independence of $D_T$ of polymers with sufficiently high molar masses [108].

Charge effects: As already discussed in sections 2.2.2 and 3.4.1 the influence of local and global electric fields have been investigated in theory and experiment. The first systematic experimental study of charged colloidal particles was done by Ning et al [119] for spherical Ludox particles at high dilution. The thermophoretic behaviour could be described by equation (13) shown in figure 12(a). It was also possible to describe $D_T$ of a bare charged fd-virus [116] (see figure 12(b)) and the calculated surface charge densities of both systems agreed within the errors with electrophoretic measurements. Recently, Wang et al [120] investigated the thermodiffusion behaviour of a colloidal rod with a polymer layer as function of Debye length, $\lambda_D$. The system consisted of an fd-virus grafted with polyethylene glycol (PEG) with a molecular mass of 5000 g mol$^{-1}$. The thermal diffusion coefficient, $D_T$ of the grafted fd-virus showed only a very weak increase. The Debye length dependence is described by equation (13). It turned out that the ratio of the determined surface charges compared to those of the bare virus is inverse to the ratio of the surfaces of the two systems, which means that the total charge remains almost constant. The determined offset of the grafted fd-virus describing the chemical contributions is the sum of $D_T$ of PEG and the offset of the bare fd-virus. The volume fraction of the grafted polymer layer is only 5%, which might imply that both the polymeric chains and the colloidal rod are in contact with the solvent so that the thermal diffusion coefficients are additive. At high $\lambda_D$, corresponding to low ionic strength, the $S_T$-values of both colloidal model systems approach each other. This implies a contribution from the polymer layer, which is strong at small $\lambda_D$ and fades away for the larger Debye lengths, when the electric double layer reaches further than the polymer chains and therefore dominates interactions with the surrounding water. Note that all experiments had been performed in a TRIS buffer without an additional salt. The ionic strength of all solutions was only changed by varying the buffer concentration. The authors did not account for a global electric field as observed by others [47, 48, 118, 122, 191] and discussed in section 3.4.1, but
the Seebeck contribution might be hidden in offset $A(T)$ in equation (13).

Eslahian et al [47, 48] studied PS particles in the presence of different salts as function of salt concentration and temperature. As in the case of other physical properties (see section 1.3.3), a change of the anion had a stronger effect on the thermophoretic behaviour than a change of the cation. They observed an increase of $S_T$ of the PS particles going from kosmotropic to chaotropic anions. In case of the PS particles they found a weaker temperature dependence by increasing the sodium chloride content, while $S_T$ of the PS particles in the presence of sodium hydroxide was almost constant. On the other hand, Blanco et al [84] found for all investigated fd-concentrations the strongest temperature dependence is in case of a high salt content.

Sehnem et al [191] investigated charge stabilized magnetic particles in the presence of two different organic salts, tetramethylammonium hydroxide (TMAOH) and tetrabutylammonium hydroxide (TBAOH), as function of temperature and salt concentration. The Soret coefficient of the charged nanoparticles increases with increasing salt concentration, approaching a constant value at high salt concentration. $\Delta S_T$, the difference between the values at 20 and at 50$^\circ$C (see section 3.3.1) decreases in the presence of TMAOH. If TBAOH is added $\Delta S_T$ changes sign from positive to negative, indicating an increasing hydrophobicity of the solutes. The attempt to describe the Soret coefficient of both systems by accounting for the double layer contribution around the particle and the electric field induced by the electrolytes underestimate the experimental $S_T$ by a temperature independent offset. The authors assume that the difference can be explained by a change of the surface properties of the nano particles caused by organic cations sticking to the surface. This could reduce the surface charge and decrease the hydrophilicity of the system leading to a chemical offset similar to $A(T)$ in equation (13).

Although protein-ligand binding reactions are frequently monitored by the so-called microscale thermophoresis [6], there is so far only one study relating the change of the hydration layer upon binding with a small ligand molecule to the hydration layer of a free protein. As model system the binding reaction between streptavidin (STV) and biotin (B) has been investigated [217]. The experiments showed that the temperature sensitivity of $S_T$ is reduced for the STV + B complex compared to free STV. This indicates that the complex is less hydrophilic, so that it is likely that the STV + B complex forms fewer hydrogen bonds with the hydrating water. Consequently, we expect a higher entropy of the water molecules in the hydration shell as they are less bound to the complex. This hypothesis is also confirmed by quasi elastic incoherent neutron scattering, which find that the flexibility of STV is greatly reduced upon biotin binding, while the entropy of the hydration layer increases [217].

In conclusion we can state that convincing theoretical concepts exist for charged systems. Typically, charge effects dominate those of other, more short range, interactions. If a series of salts with known Seebeck coefficients is investigated, it is possible to identify the Seebeck contribution of the solute, which is expressed as an additive term (equation (15)). In general, such an experimental study requires well characterized monodisperse colloids or polyelectrolytes like DNA. If only a single salt or buffer is used, the electric double layer contribution dominates the thermophoretic behaviour and analysis gives the surface charge density within experimental accuracy, but the Seebeck contribution can not be separated from the chemical contribution stemming from the core material. Whether the temperature dependence of $S_T$ becomes weaker or stronger with increasing salt content can not be answered at the present moment as both effects have been observed experimentally, but are not fully understood.
4. Concluding remarks

In recent years there have been numerous papers dealing with the thermophoretic behaviour of different solutes in water. With this review we collected a variety of publications and in some cases we revisited the studies looking at the temperature sensitivity of the Soret coefficient, which gives us information about the hydrophilicity of the solute. This connection had only been carved out recently [73]. Our goal is to shed some light on biological and biocompatible compounds in aqueous solutions to figure out to which extent the various parameters e.g. ionic strength, hydrogen bonds, specific interactions are contributing to the thermophoretic behaviour of the solute molecules to gain a better understanding of the thermophoretic changes, which occur when a protein binds to a small ligand molecule.

The situation is quite complex, which makes the theoretical description of thermophoresis and thermodiffusion difficult. Already Waldmann [218] pointed out that the thermodiffusion coefficient might be one of the strongest tests for interaction potentials. In contrast to non-polar mixtures interactions in aqueous mixtures are stronger and more directional, and might be coupled in large hydrogen bond networks, the accuracy, with which the interaction potentials are known, poses a considerable challenge. Even with a rigorous theoretical understanding of the mechanisms governing water structure around a solute, detailed microscopic knowledge of the molecule’s surface might be needed to make exact predictions of its thermophoretic behaviour. With proteins we have a compound consisting of hydrophobic, hydrophilic and charged chemical units, which can undergo conformational changes, so that the interface with the hydrating water depends on the status of the protein. Due to the complexity of the physical phenomena we separated different contributions stemming from heat of transfer, hydrogen bonds and charge effects and focused on each contribution separately.

We have seen that the heat of transfer concept derived for non-polar systems cannot fully predict the behaviour of aqueous solutions (see section 3.3.1), while empirical concepts tend to hold as long as they contain some parameters able to express the non-ideal nature of the aqueous mixtures due to hydrogen bonding. Experimental results for low molecular weight mixtures (see figure 5), polymer solutions (see figure 9) and micellar systems (see figure 7) follow the trend that the temperature sensitivity of the Soret coefficient is correlated with the logarithm of the partition coefficient \( \log P \). The studies on micellar systems confirm the interfacial character of the thermophoresis as already pointed out by several authors [16, 105, 115]. The hydrophilicity of the surface of the solute determines the temperature dependence of the Soret coefficient and makes it a powerful tool to quantify solute hydration in a similar way as hydrophillicity scales. For example, it might be possible to probe interactions between protein and surrounding water and how it is influenced by temperature, co-solvents and other parameters.

Besides hydrogen bonds also charges play an important role in aqueous solutions. The Debye length dependence of the Soret coefficient is determined by the electric double layer contribution, while the thermoelectric effect leads to a shift of \( S_T \), which is sometimes difficult to separate from the chemical contributions. If the charge contributions are dominating, the theoretical description is conclusive. More complicated scenarios arise when ions modify the hydrogen bond network as in the case OH\(^-\). In this case we observe a coupling between charge and hydrogen bond effects.

At the moment, experimental data on aqueous solutions are still relatively scarce and the interpretation of existing data on biologically relevant systems is often hard as the systems contain multiple compounds for stabilization. Experiments often require fluorescent labelling, if the system does not contain intrinsic fluorophore, which introduces charged chemical groups influencing the thermophoretic motion [219]. Therefore it is sometimes better to reduce the complexity by using simple systems to answer fundamental questions. One important objective is the development of new experimental methods combining the high sensitivity of fluorescent methods without modifying the systems by introducing dye. In the case of larger biomolecules, where dye might not influence the thermophoretic behaviour and methods like TDFRS reach their limits due to long diffusion times or low concentrations, it would be interesting to test, if the scope of MST measurements could be widened in order to use its superb sensitivity to obtain temperature and concentration dependent \( S_T \)-values.

In order to gain a better understanding of the microscopic process for protein-ligand binding it will certainly be useful to combine different methods such as isothermal titration calorimetry and quasi elastic incoherent neutron scattering in order to determine the enthalpic and entropic conformational changes and relate them to the hydration layer of free protein and complex. Certainly also more systematic measurements of inorganic and organic salts would be of high interest to separate charge effects from effects of the hydration. The outcome would not only be useful in the biological context but also for the development of thermoelectric cells. On a long term perspective it would be interesting to develop methods to study how temperature gradients can influence the transport across and through membranes in order to direct drug components into inflamed areas.

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