Correlation between thermophoretic behavior and hydrophilicity for various alcohols

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Recent experiments for various amides and sugars showed a clear correlation of the temperature dependence of the Soret coefficient with the hydrophilicity, quantitatively described by the logarithm of the 1-octanol/water partition coefficient $\log P$. This coefficient is a measure for the hydrophilicity/hydrophobicity balance of a solute and is often used to model the transport of a compound in the environment or to screen for potential pharmaceutical compounds. In order to validate whether this concept works also for other water soluble molecules we investigated systematically the thermophoresis of mono- and poly hydric alcohols. As experimental method we use a holographic grating technique called infrared Thermal Diffusion Forced Rayleigh Scattering (IR-TDFRS). Experiments showed that the temperature dependence of the Soret coefficient of polyhydric alcohols also correlates with $\log P$ and lies on the same master plot as amides and sugars.

I. INTRODUCTION

In the last decade Microscale Thermophoresis (MST) gained a lot of interest as analytical approach to monitor protein-ligand binding reactions in biological molecules that are relevant in pharmaceutical applications[1]. The success of this technique is due to the small sample amount compared to calorimetric methods. It relies on the sensitive changes in the thermodiffusion response when the hydration layer around a solute is modified, for example due to binding of a ligand. Although MST uses the observed change in thermodiffusion as an indicator of such modification, little is known about their causes or mechanisms.

Thermophoresis, or thermodiffusion, is the movement of molecules in a temperature gradient. The thermodiffusive response of a solute is quantified by the thermal diffusion coefficient D_T describing the mass flux $c(1-c)D_\mathrm{T}\nabla T$ caused by a temperature gradient, which is opposed to the Fickian mass flux $-\rho D\nabla c$ along the concentration gradient ∇c with diffusion coefficient D. The resulting mass flux of the solute $\vec{j}$ is

$$\vec{j} = -c(1-c)D_\mathrm{T}\nabla T - \rho D\nabla c. \tag{1}$$

When the temperature gradient is constant and a steady state is reached, both contributions become equal and the total flux becomes $\vec{j} = 0$. Then, the ratio D_T over D is proportional to the concentration gradient that builds up over the temperature gradient and defines the Soret coefficient S_T. A positive Soret coefficient indicates that the solute accumulates on the cold side (thermophobic), while a negative sign denotes accumulation on the warm side (thermophilic). Even for simple molecules the underlying microscopic processes are not well understood, and systems are even more complicated in the case of proteins: they can carry charges, show amphiphilic character, and vary between a colloidal and polymeric shape.

In recent years the thermophoresis of many aqueous solutions of biomolecules such as proteins [2–5] and other water soluble molecules [6–15] have been investigated experimentally. A key factor in the investigation of aqueous systems is the formation and the breaking of hydrogen bonds. This influences the temperature dependence and typically leads to an increase of the Soret coefficient with increasing temperature, which can be described by an empirical law [4]

$$S_\mathrm{T}(T) = S_\mathrm{T}^{\infty}\left[1 - \exp\left(\frac{T^{*} - T}{T_0}\right)\right] , \tag{2}$$

with the adjustable parameters S_T^{∞}, T^{*} and T_0. S_T^{∞} corresponds to the extrapolated Soret coefficient at high temperatures, T^{*} is the temperature at which S_T changes sign and T_0 describes its temperature sensitivity. It has been shown to hold for a number of diluted aqueous systems [16], but fails for less hydrophilic solvents such as ethanol [17], dimethyl sulfoxide [18] or ethylene glycol oligomers [10], which cause micro heterogeneities in water. Sugaya *et al.* [19] were the first emphasizing that the addition of a component, which easily forms hydrogen bonds like urea leads to breaking of hydrogen bonds similar to that induced by an increasing temperature. Previous works by Niether et al. on the hydrophilic solutes formamide and urea [13, 20] showed the typical temperature dependence of S_T for diluted solutions, while at higher concentrations the temperature dependence follows the trend typically found for hydrophobic solutes. A comparison with simulations of urea in water elucidated that the change in slope of the Soret coefficient with temperature can be explained by the strength of interaction between urea and water [13].

In the past, two approaches have been used to describe the hydrophilicity of a solute component and to relate it to its thermophoretic behavior in water. One concept is to consider donor and acceptor sites. For solute molecules belonging to a homologous series it has been shown that S_T depends linearly on the difference of donor and acceptor sites [10, 11]. Another good measure for hydrophilicity/hydrophobicity of a chemical substance is the partition coefficient P or, more commonly, its log-

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arithm, log P. Recent experiments for various amides show a clear correlation of the temperature dependence of the Soret coefficient with hydrophilicity [14]. Furthermore it has been shown that the concept works also for sugars, nonsteroidal anti-inflammatory drugs and cyclodextrins [21]. Note that this concept considers the temperature sensitivity of the Soret coefficient and not S_{T} itself. According to Eq. 2 aqueous systems show a stronger temperature dependence at low temperatures, while at higher temperatures, corresponding to a decreasing number of hydrogen bonds, S_{T}^{∞} is approached. Comparing systems with different hydrophilicities it seems reasonable to assume that those with the highest compatibility with water (lowest log P-value) react most strongly to temperature changes.

There are only a few simulation studies and theoretical considerations dealing with the thermophoresis of aqueous mixtures [13, 22–25]. Already Prigogine *et al.* [22] stressed the importance of strong cross interactions between unlike molecules as reason for observed sign changes in associated mixtures. Based on these early considerations recent systematic simulations of Lennard-Jones fluids [24, 25] confirm that the pronounced concentration dependence of such mixtures is strongly related to those cross interactions leading to an increase of the concentration dependent slope of S_{T}. Only recently in the group of Fernando Bresme, the influence of interactions on the slope of the Soret coefficient with temperature has been investigated in simulations [13]. It was demonstrated that stronger interactions between urea and water favour positive slopes, while weaker solute-solvent interactions and aggregation of the components was observed in connection with negative slopes.

As the Soret coefficient is the ratio of the two transport coefficients D_{T} and D it would be desirable to get some information about each transport coefficient. This is only to some extent possible for the diffusion coefficient. While the prediction of D is well established for large spherical particles or molecules by the Stokes-Einstein equation $D = k_B T/6\pi\eta R_h$, with k_B the Boltzmann constant, the dynamic viscosity η and the hydrodynamic radius R_h, the situation for small molecules is less developed [26]. The understanding of liquid diffusion depends primarily on rather crude hydrodynamic models and on activated-state models. Typically one relys on empirical expressions [26–30], for example the Wilke and Chang equation [27], which gives the diffusion coefficient in cm^2/s for small concentrations of the solute as

$$D = 7.4 \times 10^{-8} \frac{\sqrt{\psi_{\mathrm{sol}} M_{\mathrm{sol}}} T}{\eta \tilde{V}^{0.6}} \tag{3}$$

Here $\tilde{V}$ is the molar volume of the solute in cm^{3}g^{-1}, η is the viscosity of the solution in centipoises, ψ is an "association parameter", which is 2.6 in the case of water and T is the absolute temperature in Kelvin.

Recently Evans *et al.* [30] suggested an empirical expression for the diffusion coefficient of small solute molecules at high dilution,

$$D = \frac{k_{\mathrm{B}} T}{6\pi\eta f R_{\mathrm{H}}}, \tag{4}$$

which introduces a micro-viscosity friction factor f into the Stokes-Einstein equation. While f is equal to 1 under *no-slip* conditions valid for large colloidal particles it reaches 1.5 in the case of *slip* [26]. Evans *et al.* calculated $f = 1/(1.5 \cdot \alpha + 1/(1+\alpha))$ with $\alpha = \sqrt[3]{M_{\mathrm{solvent}}/M_{\mathrm{solute}}}$ and the hydrodynamic solute radius they estimated as $R_{\mathrm{H}} = \sqrt[3]{3M_{\mathrm{solute}}/4\pi\rho_{\mathrm{eff}} N_{\mathrm{A}}}$ with an effective density ρ_{eff}. The expression for the micro-viscosity friction factor goes back to an old work by Gierer and Wirtz [31]. Note that in the case of $\alpha = 1$ the micro-viscosity friction factor $f = 2$ and is larger than in *slip* case so that the expression probably breaks down in the case of $M_{\mathrm{solvent}} = M_{\mathrm{solute}}$.

Due to the fact that proteins are rather complex systems, which can undergo structural changes and carry charges it is rather difficult to separate the different effects and relate them to their thermophoretic behavior. Therefore, we investigate the thermodiffusion of simple uncharged water soluble molecules as a first step towards understanding the underlying effects. Encouraged by the clear correlation of the temperature dependence of the Soret coefficient with the hydrophilicity in amides and sugars, the idea was to expand the log$P$ range towards both positive (more hydrophobic) and negative (more hydrophilic) values using water soluble solutes, which can be varied systematically in their chemical structure. For that purpose we investigated systematically various aqueous solutions of alcohols with varying hydrophobicity and polarity by infra-red thermal diffusion forced Rayleigh scattering (IR-TDFRS). The first approach was to use monohydric alcohols, but due to some experimental difficulties explained later in the result section, we moved towards dihydric and polyhydric alcohols. It turned out that the investigation of solute with larger positive log P-values is complicated due to the formation of clusters in solution. Figure 1 shows the chemical structure and log$P$ values of the investigated alcohols mannitol, arabitol, glycerol, ethylene glycol, propane-1,3-diol, butane-1,4-diol and 1-propanol.

II. METHODS AND MATERIAL

A. Sample preparation

The investigated substances, 1-propanol (∼ 99%), methanol (∼99%), ethanol (∼99%), propane-1,2,3-triol (glycerol) (∼99%), ethane-1,2-diol (ethylene glycol) (∼99%), propane-1,3-diol (∼98%), butane-1,4-diol (∼99%), pentane-1,2,3,4,5-pentol (arabitol) (∼98%), hexane-1,2,3,4,5,6-hexol (mannitol) (∼96%) were purchased from Merck and Sigma-Aldrich and were used without further purification. The solutions were prepared with distilled and deionized water (Millipore), then

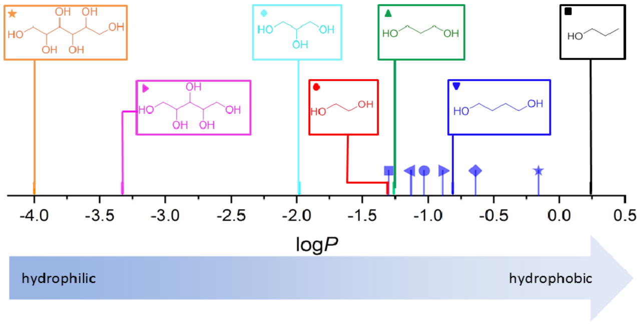

FIG. 1. Chemical structure of the investigated alcohols mannitol (orange), arabitol (magenta), glycerol (light blue), ethylene glycol (red), propane-1,3-diol (green), butane-1,4-diol (dark blue), 1-propanol (black) and the corresponding log$P$ values in comparison with previously investigated solutes (indicated by dark blue symbols): ethanol (★), DMF (♦), NMF (▶), acetamide (●), formamide (◀), urea (■).

filtrated through a 0.2 μm filter (Corning) before filling them into an optical quartz cell (Hellma) with an optical path length of 0.2 mm. The change of refractive index with temperature and concentration, the so-called contrast factors, were measured separately. Refractive indices were measured for seven concentrations for each system in the same temperature range as the IR-TDFRS measurments have been performed. Measurements of $(\partial n/\partial T)_{p,c}$ were performed interferometrically [32] for the same concentrations and in the same temperature range as TDFRS-measurements. The refractive index increments are listed in the supporting information.

B. Thermal diffusion forced Rayleigh scattering

To investigate the thermodiffusion behavior, we used infra-red thermal diffusion forced Rayleigh scattering (IR-TDFRS), a transient grating technique, which is described in detail elsewhere [33]. Two infra-red laser beams are crossed inside the sample and create a holographic grating that generates a temperature grating due to the inherent absorption of water at 980 nm. Thermodiffusion leads to migration of the particles in that temperature gradient and a superimposed concentration grating is formed. Both, temperature and concentration changes, give rise to changes in the refractive index of the sample. The refractive index grating is probed by measuring the intensity of a diffracted beam (633 nm). Assuming ideal excitation with a step function, the normalized heterodyne scattering intensity $\zeta_{\rm het}(t)$ of this diffracted beam is given by

$$\begin{aligned}\zeta_{\rm het}(t) = {} & \left(1-e^{-\frac{t}{\tau_{\rm th}}}\right) \\ & - A\left[\tau\left(1-e^{-\frac{t}{\tau}}\right) - \tau_{\rm th}\left(1-e^{-\frac{t}{\tau_{\rm th}}}\right)\right] \end{aligned} \qquad (5)$$

with the steady-state amplitude A

$$A = \frac{(\partial n/\partial c)_{\rm p,T}}{(\partial n/\partial T)_{\rm p,c}}\frac{D_{\rm T}}{D}c(1-c), \qquad (6)$$

where c is the mass fraction of the solute, $\tau_{\rm th}$ the heat diffusion time, τ the concentration diffusion time, $(\partial {\rm n}/\partial {\rm c})_{\rm p,T}$ and $(\partial {\rm n}/\partial {\rm T})_{\rm p,c}$ are refractive index contrast factors with respect to mass fraction at constant pressure and temperature, and to temperature at constant pressure and mass fraction, respectively. Heat diffusion time $\tau_{\rm th}$ is even for low molecular weight mixtures three orders of magnitude smaller than the concentration diffusion time τ, so that equation 5 might be approximated by a double exponential

$$\zeta_{\rm het} \approx \left(1-e^{-\frac{t}{\tau_{\rm th}}}\right) - A\left(1-e^{-\frac{t}{\tau}}\right) \qquad (7)$$

Note, that for the analysis of the data we used the numerical algorithm described by Wittko and Köhler [34].

III. RESULTS

A. Diffusion coefficient measurements

1. *Monohydric alcohol/water mixtures*

The thermophoretic behavior of aqueous solutions of some monohydric alcohols has been studied before [17, 36–38]. While there are comprehensive studies for ethanol/water [17, 37, 38], the system methanol/water has only been investigated at 40°C [36]. Unfortunately, our measurements of methanol/water mixtures with IR-TDFRS are not reliable, because for mass fractions between 0.3 to 0.7 the system is refractive index-matched and the contrast factor $(\partial n/\partial c)_{p,T}$ is close to zero leading to an amplitude A (c.f. Eq. 6) of the concentration

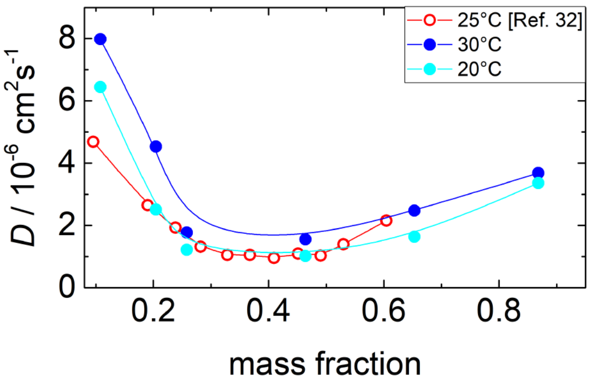

FIG. 2. Comparison of 1-propanol diffusion coefficients measured at 20°C (light blue bullet) and 30°C (dark blue bullet) with literature results by Großmann and Ebert at 25°C (red circle) [35]. The lines are guide to the eyes.

signal below 1%. The measurements at low methanol mass fractions also gave a low amplitude because A is proportional to c and at low water content heating with the infra-red writing laser is not effective. In order to obtain reliable data for methanol/water, thermogravitional column measurements are more promising as has been demonstrated recently for ethanol/water mixtures with low water content [12].

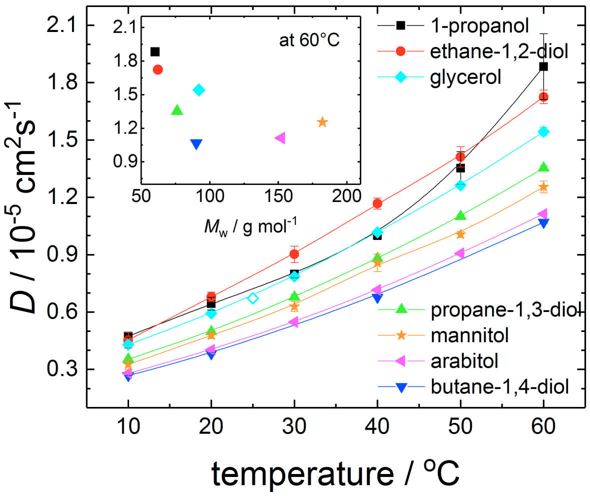

FIG. 3. Diffusion coefficient of 1-propanol, ethylene glycol, glycerol, propane-1,3-diol, mannitol, arabitol and butane-1,4-diol as function of temperature. Except for 1-propanol with a weight fraction of 0.1 the weight fraction of the alcohols was 0.25. The inset shows the diffusion coefficients at 60°C as function of the molar mass of the alcohols. A data point for glycerol (open diamond light blue) has been interpolated from concentration dependent measurements at 25°C [39]. The same symbols as in figure 1 are used.

The next monohydric alcohol is 1-propanol, which has a positive log$P$, indicating hydrophobic behaviour. Figure 2 shows the diffusion coefficient at 20 and 30°C determined from the time constant of the concentration part of the TDFRS signal as function of concentration in comparison with data obtained by Großmann and Ebert[35] at 25°C using dynamic light scattering (DLS). Note, that the slightly higher diffusion coefficients determined by TDFRS results from the differences in the statistical weighting of the two experimental methods [40]. Using van der Waals volumes we estimate $D \approx 8.7 \times 10^{-6}\mathrm{cm}^2\mathrm{s}^{-1}$ for 1-propanol at 30°C [41], which is roughly 8% faster than D measured by TDFRS. Typical uncertainties of diffusion coefficient measurements and the estimate using van der Waals volumes are of the order of 10%, so that both values agree within the error bars at the low mass fraction of 0.1. The low measured diffusion coefficients and the minimum around a mass fraction of 0.4 are a clear signature for cluster formation. Großmann and Ebert estimated clusters with eight 1-propanol molecules and 40 water molecules in the hydration layer of the cluster. Based on the results for 1-propanol we expect for 1-butanol an even stronger tendency to form clusters which makes it difficult to correlate the results with log$P$, as we expect that the partition coefficient is determined by the groups that are in contact with water. Therefore, it will be rather difficult to get a quantitative estimate and, since it is expected that cluster sizes change with temperature, the situation gets even more complicated, therefore we continued with the systematic investigation of dihydric and polyhydric alcohols.

2. *Dihydric and polyhydric alcohol/water mixtures*

Figure 3 shows the diffusion coefficient of various alcohols as a function of temperature. Except for 1-propanol, which was measured at a weight fraction of 0.1, the weight fraction of the alcohols was $c = 0.25$. As expected the diffusion becomes faster with increasing temperature due to decreasing viscosity. The disproportionate increase of the diffusion for 1-propanol with temperature is probably related to a breakup of clusters at higher temperatures. The inset of Fig. 3 shows the molecular weight dependence of D at 60°, which is not monotonous with increasing M_w.

Comparing the diffusion of propane-1,3-diol and glycerol (c.f. Fig.3), we observe over the entire temperature range a faster diffusion for glycerol although the mass of glycerol is roughly 20% larger compared to propane-1,3-diol. Our data agree well with the diffusion coefficient interpolated from concentration dependent measurements at 25°C using the Gouy interferometric technique [39]. Su *et al.* observed that the diffusion of water in n-alcohols slows down compared to n-alkanes taking into account the different viscosities [42]. The authors assumed that the hydrogen bonding between water and alcohols lead to a longer residence time. Here we observe that glycerol, which can form three hydrogen bonds with water, diffuses faster compared to propane-1,3-diol, which can form only two hydrogen bonds. According to Su *et al.* we would expect the opposite trend, because glycerol has three OH groups, while propane-1,3-diol has only two (c.f. Fig. 1). The reason for the observed behavior might be related to intramolecular hydrogen bonds, leading to a more compact form of glycerol with a smaller van der Waals volume and higher density compared to propane-1,3-diol (c.f. see supporting information Tab. S1).

B. Soret coefficient measurements

1. *Alcohol/water mixtures*

The temperature dependence of the Soret coefficient of the dihydric and polyhydric alcohol at a weight fraction of $c = 0.25$ follows the empirical Eq. 2. None of the systems shows a sign change in the investigated temperature

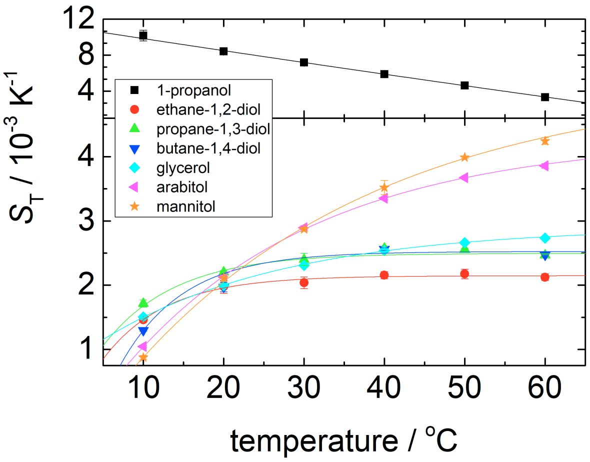

FIG. 4. Soret coefficient of 1-propanol, ethylene glycol, propane-1,3-diol, butane-1,4-diol, glycerol, arabitol and mannitol as a function of temperature. For the different alcohols we used the same colours as in figure 1.

range and the two largest alcohols, arabitol and mannitol, show the largest variation with temperature. S_T of 1-propanol decays with increasing temperature. To describe the temperature dependence we use the following exponential decay, which had been used before to describe hydrophobic systems [14] or hydrophilic systems at higher concentration [20]

$$S_\mathrm{T}(T) = S_\mathrm{T}^{\infty} + S_\mathrm{T}^{0} exp\left(-\frac{T}{T_0}\right) \tag{8}$$

Note that 1-propanol might still form some clusters, which have a different hydrophilicity compared to the single molecule.

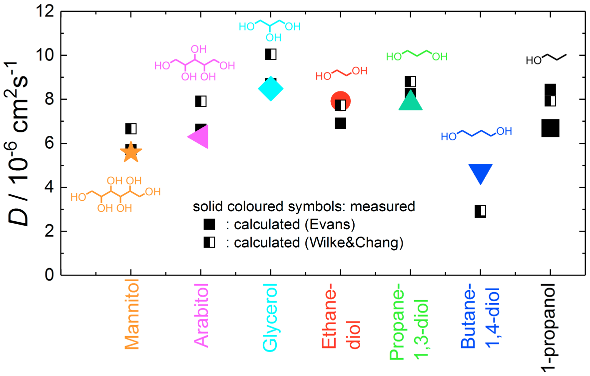

FIG. 5. Comparison of measured and calculated diffusion coefficient using Eq.9 and the Eq.3 by Wilke and Chang of 1-propanol, ethylene glycol, propane-1,3-diol, butane-1,4-diol, glycerol and arabitol. Except for 1-propanol with a weight fraction of 0.1 the weight fraction of the alcohols was 0.25.

IV. DISCUSSION AND CONCLUSION

A. Diffusion coefficient calculations

As mentioned in the introduction the prediction of diffusion coefficients for small molecules is empirical and not well understood [26]. We use the empirical approach by Wilke and Chang [27] and a modified approach following Evans [30]. While Evans *et al.* estimated the solute radius using the hard sphere approximation with a single effective density, ρ_eff, for all solute molecules, we used the density, ρ_mix, and viscosity, η_mix, of the mixture at the investigated weight fraction to calculate the diffusion coefficient with the following expression

$$D = \frac{k_B T\left(\frac{3\sqrt[3]{\frac{M_\mathrm{solvent}}{M_\mathrm{solute}}}}{2} + \frac{1}{1+\sqrt[3]{\frac{M_\mathrm{solvent}}{M_\mathrm{solute}}}}\right)}{6\pi\eta_\mathrm{mix}\sqrt[3]{\frac{3M_\mathrm{solute}}{4\pi\rho_\mathrm{mix}N_A}}} \tag{9}$$

The viscosity and density values have been taken from literature ([43–45]) and are listed in the supporting information (c.f. section S3).

In figure 5 we compare the calculated diffusion coefficients at 25°C according to Eq.3 and Eq. 9 with the interpolation to 25°C of our measured diffusion coefficients. The best agreement within a few percent we find for the larger polyhydric alcohols with Eq. 9. This is not surprising because for larger molecules the Stokes-Einstein equation should become valid. Butane-1,4-diol shows the largest deviation for both empirical equation in the order of 50%. This is larger than the deviations of 5-15% found for the other dihidric alcohols ethane-diol and propane-1,3-diol. Here we can only speculate that the larger deviation observed for butane-1,4-diol might be related to its asymmetric shape. The deviations in the order of 25% for 1-propanol and the overestimate of the diffusion coefficient can be explained by the cluster formation of the system. So we can conclude that there is still an urgent need for better theories to describe the diffusion of small water soluble molecules and small molecules in general.

B. Correlation with log P

One concept often used for drug compounds [46] is the partition coefficient, P, which is defined as the ratio of concentrations of a compound dissolved in the two phases of a mixture of water and organic solvent at equilibrium. The most commonly used organic solvent is 1-octanol. The partition coefficient consists of the concentrations of the solute and can be calculated by adding the contributions of the different chemical groups present in the molecule [47–49]. Depending on the database used the obtained log-p values differ considerably, but the relative scale within one database provides reasonable values. We used the calculator Plugins of Marvin 16.5.2.0

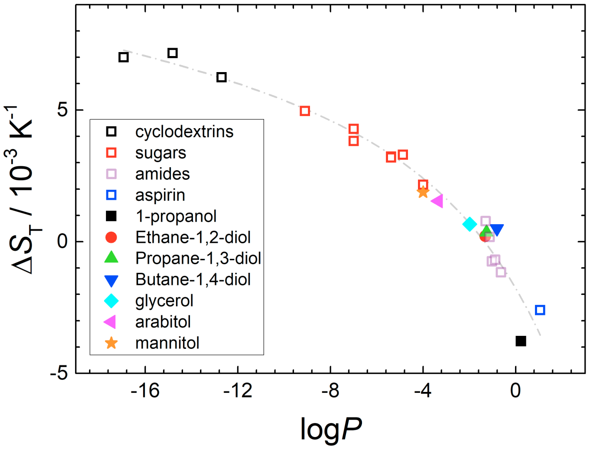

FIG. 6. Change of the Soret coefficient with temperature $\Delta S_{\mathrm{T}} = S_{\mathrm{T}}(50°\mathrm{C}) - S_{\mathrm{T}}(20°\mathrm{C})$ plotted versus log$P$. The line is a guide to the eyes.

to calculate the log$P$ (see SI Sec. S5). As mentioned in the introduction the temperature dependence of the Soret coefficient, $\Delta S_{\mathrm{T}}(\Delta\mathrm{T}) = S_{\mathrm{T}}(50°\mathrm{C})$-$S_{\mathrm{T}}(20°\mathrm{C})$, and the partition coefficients, log$P$, of the solute molecules are correlated. Figure 6 shows $\Delta S_{\mathrm{T}}(\Delta\mathrm{T})$ for the investigated alcohols together with the previously investigated water soluble molecules. It turns out that the alcohols fall on the same curve as the previously measured systems, so that the partition coefficient log P could potentially be used to make predictions about the thermodiffusion behaviour of hydrophilic solutes. Unfortunately, we can not expand the range towards more hydrophobic log P values as those systems, e.g. 1-propanol, tend to form clusters in water. Under these circumstances we do not have a good measure for log P. Most likely the hydrophilicity of the cluster is determined by the chemical units in contact with water and this will certainly change with temperature and concentration. So we can conclude that the correlation between the temperature dependence of the Soret coefficient and log P works only for rather hydrophilic substances. For more hydrophobic substance it would be interesting to perform experiments in 1-octanol, which is not possible with the IR-TDFRS setup due to the weak absorption of 1-octanol at the wavelength of the writing laser.

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AUTHOR CONTRIBUTION STATEMENT

DN and SW designed the research, MB and DN performed measurements, all authors contributed to the interpretation of the data and the writing of the manuscript.

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