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Thermophoresis of cyclic oligosaccharides in polar solvents

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Abstract. Cyclodextrins are cyclic oligosaccharides which are interesting as drug delivery systems, because they can be used as containers for pharmaceutical substances. We studied the Ludwig-Soret effect of α-, β-, γ- and methyl-β-cyclodextrin in water and formamide by infrared thermal diffusion forced Rayleigh scattering (IR-TDFRS). In water the Soret coefficient, S_T, of α-, β- and γ-cyclodextrin increases with increasing temperature and shows a sign change from negative to positive around $T = 35°C$, while S_T of methyl-β-cyclodextrin is positive in the entire investigated temperature. In formamide S_T-values of all cyclodextrins coincide and show a slight decrease with temperature. We discuss the obtained results and relate the S_T-values to the different hydrogen bonding capabilities of the cyclodextrins and the used solvents. It turns out that the change of S_T with temperature correlates with the partition coefficient, log P, which indicates that more hydrophilic substances show a more pronounced temperature sensitivity of S_T. Additionally we obtained a surprising result measuring the refractive index contrast factor with temperature, $(\partial n/\partial T)_{c,p}$ of cyclodextrins in formamide, which might be explained by a complex formation between cyclodextrins and formamide.

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1 Introduction

Thermodiffusion is the migration of molecules under a temperature gradient. For binary fluid mixtures the flux, $\boldsymbol{J}$, of the solute can be described as [1]

$$\boldsymbol{J} = -\rho D \nabla c - \rho c(1-c) D_T \nabla T \qquad (1)$$

where ρ is the density. The second term expresses the thermal diffusion along the temperature gradient, ∇T, with the thermal diffusion constant, D_T, and the first term describes the Fickian diffusion along the resulting concentration gradient of the solute, ∇c, with the diffusion constant, D. In a stable temperature gradient a steady state with $\boldsymbol{J} = 0$ is reached. The resulting concentration difference, Δc, at an applied temperature difference, ΔT, is proportional to the ratio of D_T and D, which defines the Soret coefficient of the solute

$$S_T \equiv \frac{D_T}{D} = -\frac{1}{c(1-c)} \frac{\Delta c}{\Delta T} \; . \qquad (2)$$

A larger S_T implies a larger concentration gradient for a given temperature gradient. Note also that S_T is larger for slow diffusing compounds such as colloids or small molecules in porous media due to the slower diffusion. There are many practical applications which are influenced by thermodiffusion in different areas such as petroleum reservoirs [2], solar ponds [3], polymer fractionation [4], biopolymers [5] and prebiotic evolution [6]. An extended discussion about the various application areas can be found in the recent review by Köhler and Morozov [7].

Cyclodextrins (CDs) are cyclic oligosaccharides. The glycopyranose units (6, 7 or 8 in α-, β- and γ-cyclodextrin respectively) are linked by α-(1,4) glycosidic bonds. The molecules arrange in a torus-like shape with the hydroxyl

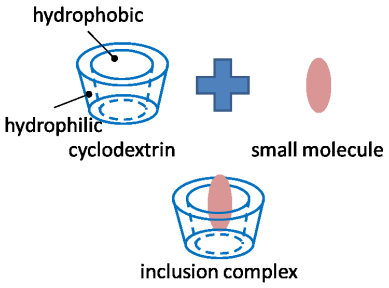

Fig. 1. Schematic drawing of the formation of an inclusion complex formed by cyclodextrins.

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Table 1. Properties of α-, β-, γ and methyl-β-cyclodextrin. M_W is the molecular mass. The octanol/water partition coefficient log P given in this table is the average of two incremental calculation methods, Consensus and ChemAxon. Details about the calculation of $N_{don} - N_{acc}$ can be found in the text.

cyclo-dextrin	number of glucose units	M_W / g/mol	log P	$N_{don} - N_{acc}$
α	6	973	-11.65	6
β	7	1135	-13.61	7
γ	8	1297	-15.82	8
methyl-β	7	1303	-6.28	-11.9

groups at the outer edges to form a hydrophilic exterior while the cavity is lined with apolar parts of the molecule to form a hydrophobic interior [8]. Due to the formation of this 'sub-micron heterogeneous environment' small compounds can enter the cavity and form inclusion complexes with the CD (fig. 1). The cavity diameter varies depending on ring size which leads to differences in the complex formation for the various CDs [9].

The propensity for complex formation is used in pharmaceutical industry to enhance solubility and controlling speed of uptake of drugs [8]. In this context a better understanding of the thermodiffusion behaviour of CDs and their drug-complexes would be advantageous. It is unclear if or how thermodiffusion contributes to the transport processes in the human body. The idea of controlled movement of drugs into certain, e.g. inflamed, areas of the bodies is attractive, but maybe not realistic. A more feasible application would be to tune the complexes so that they show no thermophobic behaviour which might lead to a depletion of the drug complexes in areas of inflammation. Another interesting aspect of CDs is the possibility that the interior of the ring and the CD or the attached side groups can be varied independently. This makes it possible to do systematic experiments to differentiate draining and non-draining effects in aqueous systems, which makes it possible to validate, whether concepts derived for non-polar systems are applicable for aqueous mixtures [10].

The theoretical understanding of the thermophoretic behavior of non-polar systems [7] is much more comprehensive than for aqueous mixtures. For non-polar substances systematic studies of isotopic and other mixtures identified three contributions to the Soret coefficient stemming from differences in the molecular masses and moments of inertia and an additional *chemical contribution*. Due to the specific interactions, e.g. hydrogen bonds, the *chemical contribution* is the dominant factor for aqueous systems, which changes with temperature and influences the thermodiffusion of aqueous mixtures. To describe this temperature dependence Iacopini and Piazza [11] proposed an empirical equation

$$S_{\mathrm{T}}(T) = S_{\mathrm{T}}^{\infty}\left[1 - \exp\left(\frac{T^* - T}{T_0}\right)\right], \qquad (3)$$

with fitting parameters S_{T}^{∞}, T^* and T_0. In principle T_0 is a measure of the temperature dependence, if S_{T}^{∞} and T^* are fixed. Note that only under these circumstances T_0-values can be compared. At very high temperature the enthalpic *chemical contributions* are negligible and the entropic contribution dominates the behavior, so that we expect that S_{T}^{∞} is determined by differences in physical parameters e.g. moment of inertia and mass.

Lately, it has been shown, that this empirical correlation breaks down, if the solute concentration becomes too high [6]. For diluted aqueous solutions the empirical behavior might be understood by a free energy concept as suggested by Wang *et al.* [12]. The basic idea is that at low temperatures the system forms hydrogen bonds to minimize its free energy, so that the water molecules enrich at the cold side, while at higher temperature the entropy is maximized by breaking up the hydrogen bond networks, which leads to an enrichment of water on the warm side. As a consequence the Soret coefficient S_{T} of the solute molecules increases when hydrogen bonds break [13]. Another possibility is to add an ingredient with a strong affinity to water, so that the bonds open [14]. The strength of a hydrogen bond network in a mixtures is influenced by the donor and acceptor sites. Recently, it has been shown that S_{T} depends linearly on the difference of donor and acceptor sites of the solute molecule belonging to a homologous series [15]. Hydrogen bonding certainly plays an important role in aqueous CD solutions.
Cyclodextrins can form hydrogen bonds (HB) with water via their hydroxyl groups which act as HB donor sites or as acceptor via the oxygens (see fig. 2, left). The donor and acceptor sites are indicated by red and blue arrows, respectively. There are different ways of counting donor and acceptor sites, we follow in our analysis the work by Maeda

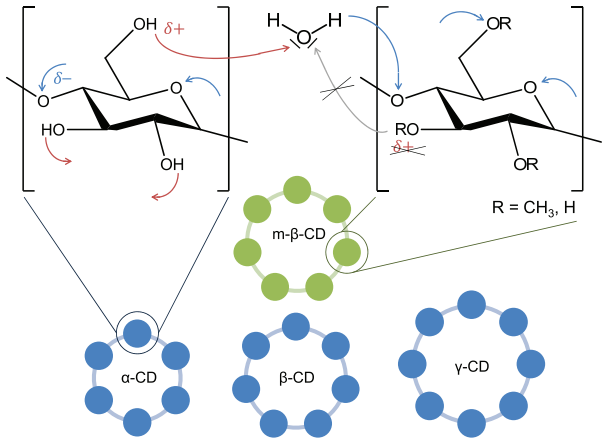

Fig. 2. Sketch of the investigated cyclodextrins and chemical structure of unmethylated (left) and methylated (right) glycopyranose units. Red and blue arrows show hydrogen bond donor and acceptor sites, respectively. In methyl-β-CD 55% of the hydroxyl-H are substituted with methyl group. These sites will not form hydrogen bonds (grey arrow). Further explanations are in the text.

et al. [15]. So that we count the hydroxyl groups only as a donor cite and ignore that the oxygen atom might serve as an acceptor. The free electron pairs of the ether oxygens can act as HB acceptors, but due to the low polarity the bonding is weak in the order of 20 kJ/mol (corresponding to 5 kcal/mol) [16,17]. We count the oxygen ether only as one acceptor, because due to steric hindrance it is unlikely that it can bind two water molecules. In the used methyl-β-cyclodextrin 55% of the hydroxyl groups are methylated and hence unable to form hydrogen bonds with the solvent (fig. 2, right). The difference $N_{don} - N_{acc}$ is listed in table 1. Note that a different way of counting donor and acceptor sites will not change the sequence of the compounds.

In this work we studied the Ludwig-Soret effect of α-, β-, γ-, and methyl-β-cyclodextrin in water and in formamide by infrared thermal diffusion forced Rayleigh scattering (IR-TDFRS). The un-methylated CDs α-, β-, and γ-cyclodextrin are chemically very similar and differ only in the number of their glycopyranose units and accordingly in their molecular weight and partition coefficient log P, which is a measure for the hydrophilicity (see Table 1). In methyl-β-CD 55% of the hydroxyl-H are substituted with methyl, which results in a similar molecular weight to γ-CD, but drastically changes the interaction with the surrounding solvent.

2 Experimental section

2.1 Thermal diffusion forced Rayleigh Scattering

We used infra-red thermal diffusion forced Rayleigh scattering (IR-TDFRS), a laser-induced transient grating technique [18]. Two laser beams create a holographic grating within the sample. The inherent absorption of water in that range converts the laser light into a temperature grating [19]. Due to thermodiffusion eventually a superimposed concentration grating is created. Both the temperature and the concentration grating result in a refractive index grating that is read out by Bragg diffraction of a third laser beam. The IR-TDFRS has been especially developed for aqueous systems, because the water soluble dyes often change the behavior as function of pH, so that it is not possible to use a suitable dye as it is done in the classical TDFRS, which has been developed to its present status in the group of Köhler [20]. Also the investigation of surfactant systems is altered by the addition of the dye, which can act as co-surfactant and then leads to changes of the phase behavior [21,22]. A detailed description of the used IR-TDFRS can be found in the paper by Blanco *et al.* [23].

The total heterodyne scattering intensity $\zeta_{\mathrm{het}}(t)$, assuming an ideal excitation with a step function, is given by

$$\zeta_{\mathrm{het}}(t) = 1 - \exp\left(-\frac{t}{\tau_{\mathrm{th}}}\right) - A\left(\tau - \tau_{\mathrm{th}}\right)^{-1} \quad (4)$$
$$\times \left\{\tau\left[1 - \exp\left(-\frac{t}{\tau}\right)\right] - \tau_{\mathrm{th}}\left[1 - \exp\left(-\frac{t}{\tau_{\mathrm{th}}}\right)\right]\right\}$$

with the steady state amplitude A

$$A = \left(\frac{\partial n}{\partial c}\right)_{p,T}\left(\frac{\partial n}{\partial T}\right)_{p,c}^{-1} S_{\mathrm{T}} c\,(1-c) \quad (5)$$

where c is the mass concentration of the solute, τ_{th} the heat diffusion time, $(\partial n/\partial c)_{p,T}$ and $(\partial n/\partial T)_{p,c}$ are refractive index contrast factors with respect to mass concentration at constant pressure and temperature, and referring to temperature at constant pressure and mass concentration, respectively. The Soret coefficient, $S_{\mathrm{T}} = D_{\mathrm{T}}/D$, can be expressed as ratio of the thermal diffusion coefficient, D_{T}, and the collective diffusion coefficient, D. Whereas the diffusion coefficient $D = 1/(q^2\tau)$ can be calculated from the diffusion time, τ (cf. eq. 5), using the magnitude of the grating vector q, which is given by $q = (4\pi/\lambda_w)\cdot\sin(\theta/2)$. Here θ is the angle between the two writing beams and λ_w is the wavelength of the laser beam. The transport coefficients are determined by fitting eq. 5 to the measured heterodyne signal and deconvoluting the excitation function [24,25].

2.2 Sample preparation

Investigated substance were α-cyclodextrin (α-CD, Tokyo chemical industry, $> 98.0\%$), β-cyclodextrin (β-CD, Tokyo chemical industry, 99.0%), γ-cyclodextrin (γ-CD, Tokyo chemical industry, $> 98.0\%$), and methyl-β-cyclodextrin (methyl-β-CD, Tokyo chemical industry). All of them were dissolved in distilled and deionized water (Millpore) and formamide (Sigma-Aldrich, $\geq$99.5) with a concentration of (1.00 ± 0.01)wt%. To ensure homogeneity of the mixture all CD solutions have been stirred for one hour at room temperature. Approximately 2 mL of the prepared solutions were filtered through a 0.2 μm filter (Whatman Anotop 10) before filling them into an optical quartz cell (Hellma) with an optical path length of 0.2 mm. At least two measurements with different cells and freshly prepared samples were done for each system.

2.3 Contrast factor measurements

The refractive index increments with the mass concentration $(\partial n/\partial c)_{p,T}$ was measured by an Anton Paar RXA 156 refractometer, with an accuracy of 0.00002 nD and a temperature control of ΔT = $\pm$0.03K. The refractometer uses the sodium line with a wavelength of 589.3 nm, which is roughly 40 nm shorter than the HeNe-laser of 632.8 nm used as read-out beam in the IR-TDFRS. This causes a small systematic error in the refractive index increment in the order of 0.5-1% [26,27]. For each CD in water and formamide, the refractive index has been measured for at least six concentrations around 1 wt%. The refractive index increments with temperature $(\partial n/\partial T)_{p,c}$ was measured interferometrically [28]. Measurements were either performed around the desired temperature or continuously in the entire temperature range between 10-60°C. We measured the contrast factors by heating and cooling the solutions with a typical rate of 1 mK/sec.

3 Results

3.1 Contrast factors

In figure 3 $(\partial n/\partial c)_{p,T}$ is shown, which corresponds to the slope of the linear interpolated refractive index as function of concentration. For both solvents the refractive index contrast factors with concentration show only a weak temperature dependence. For evaluation of the IR-TDFRS measurements the measured $(\partial n/\partial c)_{p,T}$ and $(\partial n/\partial T)_{p,c}$ values at the respective temperatures were taken or the value was interpolated from the neighboring values. The error bars represent the standard deviation of multiple measurements. The optical contrast for the aqueous systems is two to three times higher than for the formamide solution. The error bars correspond to less than 0.5% and up to 17% for water and formamide solutions, respectively.

For the aqueous CD solutions $(\partial n/\partial T)_{p,c}$ shows a strong linear decrease with temperature, while the variation of the refractive index with temperature in formamide is much weaker (see fig. 4). In the investigated temperature range $(\partial n/\partial T)_{p,c}$ of the aqueous solution changes by a factor four and we find identical values for cooling and heating the sample. In contrast to the aqueous solution we observe an unusual behavior of $(\partial n/\partial T)_{p,c}$ for freshly prepared CD/formamide solutions (see inset of fig. 4). For all four solutions we find a minimum between 16 and 20°C shifting to higher temperatures with increasing number of glycopyranose units. The absolute variation between the local minimum and maximum of $(\partial n/\partial T)_{c,p}$ lies between $2.7 \cdot 10^{-6}\mathrm{K}^{-1}$ and $4.2 \cdot 10^{-6}\mathrm{K}^{-1}$ and the relative change of $(\partial n/\partial T)_{c,p}$ is between 0.7 and 2.3%. It turns out that the minimum becomes weaker when the sample ages or is preheated overnight. There are differences between the different CDs. In the case of the γ-CD the minimum disappears completely with time or temperature, while for both β-CDs a shallow minimum remains. The very shallow noisy minimum can be observed around 30°C and is within the typical measurement uncertainty of 0.5%. According to these temperature- and time-dependent changes in the solutions, measurement results for the fresh solutions differ between cooling and heating cycles.

3.2 IR-TDFRS experiments

The thermal diffusion of (1.00 ± 0.01) wt% α-, β-, γ-, and methyl-β-cyclodextrin in water and in formamide was measured in a temperature range from 10 to 55°C. The results are shown in fig. 5. In water, the Soret coefficients of α-, β-, and γ-cyclodextrin show a temperature dependence as described by eq. 3. There is a sign change around 35°C and they reach the same S_T^∞ value at high temperatures. In comparison, methyl-β-cyclodextrin is much more thermophobic with a predicted sign change outside the measured range and a much higher S_T^∞. The fitting parameters are summarized in Table 2. In formamide, the behaviour does not follow eq. 3, but shows a decline of the Soret coefficient with increasing temperature. The error bars are

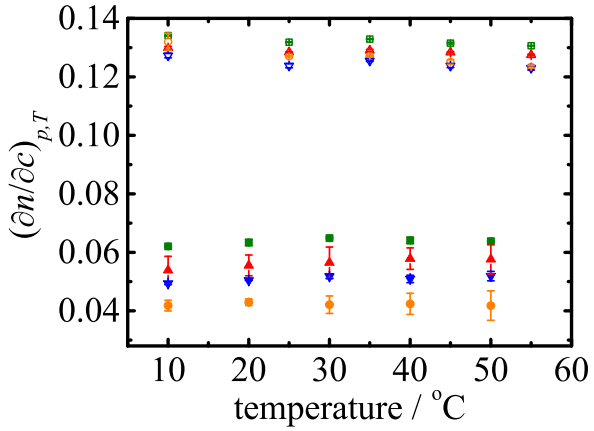

Fig. 3. Contrast factor $(\partial n/\partial c)_{T,p}$ as function of temperature in water and in formamide. Open and solid symbols refer to the aqueous and formamide solutions, respectively (α-CD (red triangle up), β-CD (blue triangle down), γ-CD (green square) and methyl-β-CD (orange circle)).

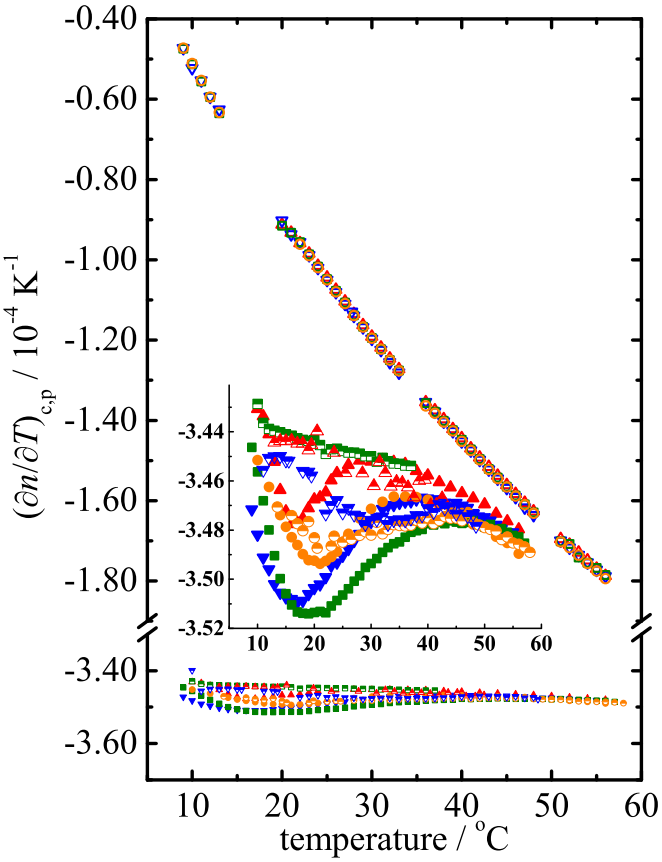

Fig. 4. Contrast factor $(\partial n/\partial T)_{c,p}$ as function of temperature in water and in formamide. We used the same symbols as in fig. 3. The inset magnifies the measurement results in formamide. The additional half filled symbols mark the corresponding systems, which have been preheated over night at 50°C.

Table 2. Fitting parameters and their uncertainties according to Eq. 3 shown as solid lines in fig. 5.

cyclo-dextrin	S_T^∞ / $10^{-3}K^{-1}$	T^* / °C	T_0 / K
α	6.50 ± 0.41	32.4 ± 0.3	29.7 ± 1.7
β	6.42 ± 1.83	35.5 ± 0.9	30.0 ± 6.7
γ	6.95 ± 0.59	34.6 ± 0.3	29.8 ± 2.2
methyl-β	11.8 ± 0.3	-3.33 ± 3.18	12.5 ± 2.8

much larger than for aqueous solutions. The uncertainties are typically 8% in water and 13% in formamide. The larger uncertainties for formamide solutions might be understood by the lower optical contrast with concentration and the weaker absorption of the laser light by formamide. Additionally we have a variation of $(\partial n/\partial T)_{p,c}$ in the order of 2.3%.

4 Discussion

4.1 Contrast factor $(\partial n/\partial T)_{p,c}$

While the aqueous solutions show the typical decay of $(\partial n/\partial T)_{p,c}$ with temperature, which is related to the lower density at high temperature, the temperature dependence of $(\partial n/\partial T)_{p,c}$ in formamide solutions is unusual and has to our best knowledge never been observed. Note that the effect is small with a relative amplitude in the order of 2.3%. The inset in fig. 4 shows a decrease of $(\partial n/\partial T)_{p,c}$ in the temperature range between 16 and 20°C, which would suggest the formation of cavities leading to a more pronounced temperature decrease than caused by the temperature raise. From X-ray diffraction studies it is known that CDs form inclusion complexes with small molecules such as dimethylformamide [29] and formic acid [30], but to our best knowledge the kinetics of such inclusions has not been investigated. From the size of the molecules one would expect very fast kinetics, but our measurements suggest that the process takes several days if the solution is stored at room temperature or it can be accelerated by heating the sample. An explanation might be another, slower, complex formation that blocks the CD cavities from the formamide. A stacking of two or more CDs at temperatures around 20°C might lead to blocked empty CD-cavities that can only be filled up when the stacks break at higher temperatures or over time. To clarify the involved processes further quantitative studies are necessary, which are beyond the scope of this work. Due to the small relative error (2.3%), which is smaller than the uncertainty of the steady state amplitude A (ca. 14%), it will not influence the evaluation of our IR-TDFRS results. Nevertheless it would be interesting to understand the mechanism, which leads to this unusual behavior of $(\partial n/\partial T)_{p,c}$.

4.2 IR-TDFRS measurements

The upper graph of figure 5 shows the Soret coefficient of the CDs in water and in formamide. While all aqueous solutions show the typical temperature dependence for systems dominated by hydrogen bonds (see eq.3), this is not the case for solutions in formamide.

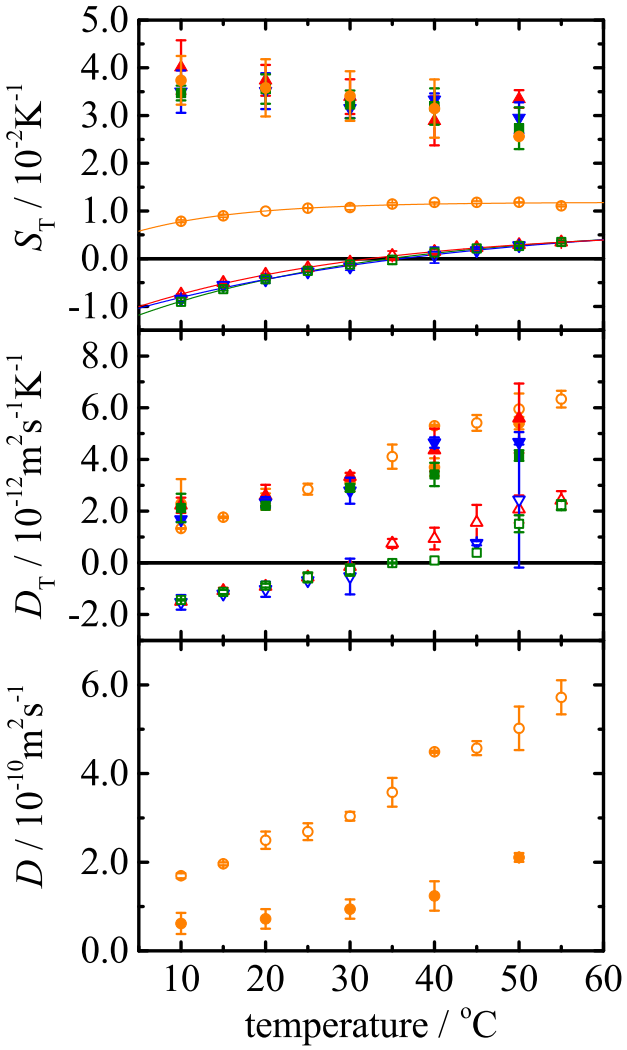

Fig. 5. The Soret coefficient S_T and the thermal diffusion coefficient D_T of α- (red triangle up), β- (blue triangle down), γ- (green square), and methyl-β- (orange circle) cyclodextrin in water and formamide as function of temperature. For better readability the bottom plot shows only a comparison of the diffusion coefficient of D for methyl-β-cyclodextrin in water and formamide as function of temperature. Open and solid symbols refer to the aqueous and formamide solution.

For aqueous systems the Soret coefficient of methyl-β-CD deviates strongly from that of the un-methylated CDs. This change in behaviour is caused by reduced hydrogen bond interactions between the methyl-β-cyclodextrin and the water due to the partial methylation, which reduces number of potential hydrogen bonds more than a factor two. The observed increase of S_T is comparable to observations made by Sugaya *et al.* where the addition of urea to an aqueous solution led to a similar increase of the

measured S_T [14]. Also Kishikawa *et al.* observed a similar behavior of S_T for pullulan in water and DMSO[13]. In that experiment the addition of urea (up to 5M, which corresponds to a 28 wt% urea solution) lead to a replacement of water as solvent and the observed shift in S_T due to the weaker solute solvent interaction of urea.

In the case of cyclodextrins in formamide we also measure higher Soret coefficients than in water and the temperature dependent S_T of methyl-β-CD in formamide is equal to those of the other CDs in formamide . The strength of interactions is already weak in comparison to that with water, so that the methylation does not lead to such a pronounced change. Despite the fact that the number of hydrogen bonds formed by formamide is comparable to water [31], the water hydrogen bonds are expected to be stronger due to the larger polarity of water compared to formamide.

Additionally to the already mentioned uncertainties we also observe instabilities of the measured signal of IR-TDFRS at long times (0.5 sec). These instabilities in the intensity of the refracted beam points towards fluctuations in the concentration grating that overlays the laser-induced temperature grating, but the cause is unclear, but might be related to the minimum observed for $(\partial n/\partial T)_{p,c}$. One explanation might be the formation of complexes mentioned before that leads to this atypical behaviour. The scattering of the measurements in formamide prevents an analysis of subtle changes in the behaviour between different cyclodextrins.

The center graph in fig. 5 shows the temperature dependence of the thermal diffusion coefficient D_T. As in the case of S_T we observe an increase of D_T by using formamide as solvent instead of water. Surprisingly D_T and its temperature dependence for methyl-β-CD is very similar in water and formamide. The difference of the Soret coefficients of methyl-β-CD evident in the upper graph of fig. 5 is due to the Fickian diffusion (bottom fig. 5) which is slower in formamide than in water and consistent with the higher viscosity of formamide. Compared to β-CD in water the hydrogen bonds interactions in the two other systems β-CD/formamide and methyl-β-CD/water are weakened. It is expected that the two last named systems show the same trend, but at the present stage it is unclear why this leads to identical D_T-values. Note that D_T increases for methyl-β-CD in water and formamide, although S_T of methyl-β-CD in water increases, while S_T of methyl-β-CD decreases slightly in formamide.

4.3 Solute-solvent interactions in water

It is evident that interactions with the solvent have a strong impact on the thermodiffusion behaviour of the solute, especially in water, which can strongly interact due to hydrogen bonds. Unfortunately, solute-solvent interactions in liquids are difficult to predict on a microscopic level. In the following discussion we will look for correlations between the thermodiffusion behaviour measured for the four cyclodextrins and two parameters describing the solute-solvent interaction: the difference between donor and acceptor sites in the solute molecule N_{don}-N_{acc} and the octanol/water partition coefficient log P, which are a measure for the hydrophilicity of a compound. Both values are listed in table 1 and will be explained in the following paragraphs.

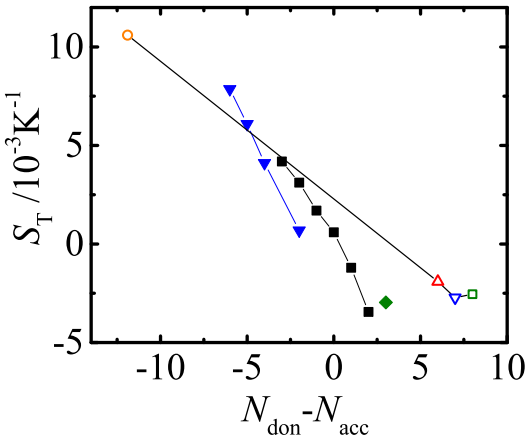

Fig. 6. S_T at 20°C (concentration (1.00 ± 0.01) wt%) versus the difference of donor and acceptor sites of the substances. Cyclodextrins (α- (red triangle up), β- (blue triangle down), γ- (green square), and methyl-β- (orange circle) CD) were measured for this work, crown ethers (blue triangles), ethylene glycol oligomers (black squares) and glycerol (green diamond) are reproduced from ref. [15].

A direct way to estimate the capability of a substance to interact with water is to count potential donor and acceptor sites in the molecule. A hydroxyl group, for example, would count as a hydrogen bond donor, because a hydrogen bond can be formed by the partially positive hydrogen, an ether oxygen with its free electron pairs and partial negative charge would be counted as hydrogen bond acceptor (see fig. 2). This method does not take into account the polarization strength and hence the relative strengths of the hydrogen bonds. Nevertheless, Maeda *et al.* [15] followed this approach and found for homologous groups a linear correlation between measured Soret coefficient of a solute dissolved in water and the difference between its HB donor and HB acceptor sites. The values for the investigated cyclodextrins fit reasonably well with their findings (see fig. 6). Why the Soret coefficient should dependent on N_{don}-N_{acc} is not obvious, because the surrounding water should be equally capable of forming hydrogen bonds with donor as well as acceptor sites of the solute molecule. A possible explanation is the formation of intramolecular hydrogen bonds, so that one donor and one acceptor site block each other against hydrogen bond formation with the surrounding solvent. The difference between donor and acceptor sites would therefore give a better estimate of the potential HB sites open to the solvent than the sum of them. This could be tested by investigation of substances where intramolecular hydrogen bonds are impossible due to sterical hindrance.

The partition coefficient P or, more commonly, its logarithm, log P, are a measure for the relative difference

of solubility for a solute in two different solvents. Most commonly used is the octanol/water partition coefficient, because it is a good measure for hydrophilicity/hydrophobicity of a chemical substance and therefore an important parameter for drug compounds [32]. In a system where a solute can diffuse freely between two phases, P is the ratio of its equilibrium concentration in octanol over that in water, so a smaller (or negative) log P signifies stronger hydrophilicity. The hydrophilicity decreases from γ-, β-, α- to methyl-β-CD. In figure 7 the log P values of the CDs are plotted versus ΔS_T, the difference of the Soret coefficients at 10 and 50°C (*cf.* fig. 5). We have chosen the S_T-values at these two reference temperatures as a measure for the temperature sensitivity of the systems in the investigated range. ΔS_T increases from methyl-β-, α-, β- to γ-CD in the same way as the hydrophilicity. So the compound with the lowest hydrophilicity shows the weakest temperature dependence.

The isotopic contribution to the Soret coefficient is temperature independent and the cyclodextrins are not charged, the measured temperature dependence of S_T is due to the chemical contribution [33], that is to say the interactions between solute and solvent. In water, these interactions are dominated by hydrogen bonds, which are sensitive to temperature changes. We can assume that at 50°C the hydrogen bonds in the system, those between solute and solvent as well as the HB network of the water, are significantly weakened. This reduces the chemical contribution of S_T leading, in the case of the investigated cyclodextrins, to a rise in the Soret coefficient with rising temperature. So for these substances, as well as all substances for which the temperature dependence of S_T can be described by eq. 3, the chemical contribution to S_T due to the formation of hydrogen bonds is negative. As explained in the introduction this temperature dependence can be understood under the assumption that the formation of hydrogen bonds minimizes the free energy of the system at low temperatures. This should certainly be the case for the formation of hydrogen bonds between solute and solvent. So it seems reasonable that in our investigation the systems which show the highest compatibility with water (lowest log P-value) reacts most strongly to temperature changes (high ΔS_T).

In conclusion this study confirms that hydrogen bonds play an essential role in the thermophoretic behaviour of aqueous systems. The systematic study of cyclodextrins give a clear correlation between the change of the Soret coefficient with temperature and the logarithm of the partition coefficient.

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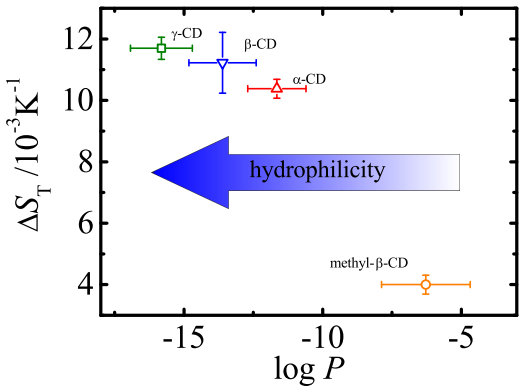

Fig. 7. Correlation of the S_T-difference across the measured range, $\Delta S_\mathrm{T} = S_\mathrm{T}(50^\circ\mathrm{C}) - S_\mathrm{T}(10^\circ\mathrm{C})$, with the partition coefficient log P. Substances with weaker hydrophilicity show smaller S_T-change with temperature.

References

1. S.R. de Groot and P. Mazur. *Non-equilib. Thermodyn.* New York: Dover, 1984.
2. F. Montel, J. Bickert, A. Lagisquet, and G. Galliero. Initial state of petroleum reservoirs: A comprehensive approach. *J. Pet. Sci. Eng.*, 58:391–402, 2007.
3. C. Angeli and E. Leonardi. The effect of thermodiffusion on the stability of a salinity gradient solar pond. *Int. J. Heat Mass Transfer*, 48:4633–4639, 2005.
4. M. E. Schimpf and J. C. Giddings. Characterization of thermal-diffusion in polymer-solutions by thermal field-flow fractionation - dependence on polymer and solvent parameters. *J Polym. Sci. Pol. Phys.*, 27:1317–1332, 1989.
5. C. B. Mast and D. Braun. Thermal trap for dna replication. *Phys. Rev. Lett.*, 104:188102–1–188102–4, 2010.
6. D. Niether, D. Afanasenkau, J.K.G. Dhont, and S. Wiegand. Accumulation of formamide in hydrothermal pores to form prebiotic nucleobases. *Proc. Natl. Acad. Sci. U.S.A.*, 113:4272–4277, 2016.
7. W. Köhler and K. I. Morozov. The soret effect in liquid mixtures - a review. *J. Non-Equil. Thermody.*, 2016.
8. E. M. Martin Del Valle. Cyclodextrins and their uses: A review. *Process Biochem.*, 39:1033–1046, 2004.
9. Sunil S. Jambhekar and Philip Breen. Cyclodextrins in pharmaceutical formulations i: Structure and physicochemical properties, formation of complexes, and types of complex. *Drug Discov. Today*, 21(2):356–362, 2015.
10. K.I. Morozov and W. Köhler. Thermophoresis of polymers: Nondraining vs draining coil. *Langmuir*, 30:6571–6576, 2014.
11. S. Iacopini, R. Rusconi, and R. Piazza. The "macromolecular tourist": Universal temperature dependence of thermal diffusion in aqueous colloidal suspensions. *Eur. Phys. J. E*, 19:59–67, 2006.

12. Z. Wang, H. Kriegs, and S. Wiegand. *J. Phys. Chem. B*, 116:7463–7469, 2012.
13. Y. Kishikawa, S. Wiegand, and R. Kita. Temperature dependence of soret coefficient in aqueous and nonaqueous solutions of pullulan. *Biomacromolecules*, 11:740–747, 2010.
14. R. Sugaya, B.A. Wolf, and R. Kita. *Biomacromolecules*, 7:435–440, 2006.
15. K. Maeda, N. Shinyashiki, S. Yagihara, S. Wiegand, and R. Kita. Ludwig-soret effect of aqueous solutions of ethylene glycol oligomers, crown ethers, and glycerol: Temperature, molecular weight, and hydrogen bond effect. *J. Chem. Phys.*, 143:124504, 2015.
16. P. R. Rablen, J. W. Lockman, and W. L. Jorgensen. Ab initio study of hydrogen-bonded complexes of small organic molecules with water. *J. Phys. Chem. A*, 102:3782–3797, 1998.
17. J. P. M. Lommerse, S. L. Price, and R. Taylor. Hydrogen bonding of carbonyl, ether, and ester oxygen atoms with alkanol hydroxyl groups. *J. Comput. Chem.*, 18:757–774, 1997.
18. Simone Wiegand and Werner Köhler. Measurement of transport coefficients by an optical grating technique. *LNP Vol. 584: Thermal Nonequilibrium Phenomena in Fluid Mixtures*, 584:189–210, 2002.
19. S. Wiegand, H. Ning, and H. Kriegs. *J. Phys. Chem. B*, 111:14169–14174, 2007.
20. W. Khler and P. Rossmanith. Aspects of thermal-diffusion forced rayleigh-scattering - heterodyne-detection, active phase tracking, and experimental constraints. *J. Phys. Chem.*, 99(16):5838–5847, 1995.
21. H. Ning, S. Datta, T. Sottmann, and S. Wiegand. Soret effect of nonionic surfactants in water studied by different transient grating setups. *J. Phys. Chem. B*, 112:10927–10934, 2008.
22. B. Arlt, S. Datta, T. Sottmann, and S. Wiegand. Soret effect of n-octyl beta-d-glucopyranoside (c(8)g(1)) in water around the critical micelle concentration. *J. Phys. Chem. B*, 114:2118–2123, 2010.
23. P. Blanco, H. Kriegs, M. P. Lettinga, P. Holmqvist, and S. Wiegand. Thermal diffusion of a stiff rod-like mutant y21m fd-virus. *Biomacromolecules*, 12:1602–1609, 2011.
24. G. Wittko and W. Köhler. *Philos. Mag.*, 83:1973–1987, 2003.
25. H. Ning, R. Kita, H. Kriegs, J. Luettmer-Strathmann, and S. Wiegand. Thermal diffusion behavior of nonionic surfactants in water. *J. Phys. Chem. B*, 110:10746–10756, 2006.
26. R.D. Camerini-Otero, R.M. Franklin, and L.A. Day. Molecular weights, dispersion of refractive index increments, and dimensions from transmittance spectrophotometry. bacteriophages r17, t7, and pm2, and tobacco mosaic virus. *Biochemistry*, 13(18):3763–3773, 1974.
27. V. V. Sechenyh, J. Legros, and V. Shevtsova. Experimental and predicted refractive index properties in ternary mixtures of associated liquids. *J. Chem. Thermodynamics*, 43:1700–1707, 2011.
28. A. Becker, W. Köhler, and B. Müller. A scanning michelson interferometer for the measurement of the concentration and temperature derivative of the refractive- index of liquids. *Ber. Bunsen. Phys. Chem.*, 99(4):600–608, 1995.
29. K. Harata. Structure of the cyclodextrin complex .8. crystal-structures of alpha-cyclodextrin complexes with 2-pyrrolidone and n,n-dimethylformamide. *Bull. Chem. Soc. Jpn.*, 52:2451–2459, 1979.
30. T. Aree, B. Schulz, and G. Reck. Crystal structures of beta-cyclodextrin complexes with formic acid and acetic acid. *J. Inclusion Phenom.Macrocyclic Chem.*, 47:39–45, 2003.
31. M. D. Elola and B. M. Ladanyi. Computational study of structural and dynamical properties of formamide-water mixtures. *J. Chem. Phys.*, 125:184506–1–184506–14, 2006.
32. C. A. Lipinski, F. Lombardo, B. W. Dominy, and P. J. Feeney. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev.*, 64:4–17, 2012.
33. S. Hartmann, W. Köhler, and K. I. Morozov. The isotope soret effect in molecular liquids: A quantum effect at room temperatures. *Soft Matter*, 8:1355–1360, 2012.