Some Transport Properties of γ-Cyclodextrin Aqueous Solutions at (298.15 and 310.15) K

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Values of binary mutual diffusion (interdiffusion) coefficients, obtained by using the Taylor dispersion method, for aqueous solutions of γ-cyclodextrin in the concentration range from (0.002 to 0.010) mol·dm^{-3} and temperatures (298.15 and 310.15) K are reported. From these experimental results, the hydrodynamic radius values for the γ-cyclodextrin are estimated. Also, the measured diffusion coefficients are used with both Hartley's and Gordon's equations to estimate activity coefficients for aqueous γ-cyclodextrin. These studies are complemented by some density and viscosity measurements, carried out at the same range of concentrations and temperatures. The effect of both the viscosity of the medium and the formation of γ-cyclodextrin dimers on the estimated hydrodynamic radius is discussed.

Introduction

As it is well-known, cyclodextrins consist of various glucopyranose units (six, seven, and eight for α-, β-, and γ-cyclodextrin, respectively) condensed under the form of a truncated cone ring.[1,2] Because the primary and secondary groups of the glucose units point to the external part of the structure, cyclodextrin molecules have a hydrophilic external surface but a largely hydrophobic internal cavity which makes available the formation of inclusion complexes with a wide variety of organic and inorganic compounds in different solvents (including water).[3–7] This capability has been of assistance for different applications in food technology, pharmaceutical, and chemical industries as well as in agriculture and environmental engineering.[8–11]

Generally, the thermodynamic stability of inclusion compounds depends on three facts: the size of host and guest molecules (normally, the highest association constants are being found for host–guest complexes that fit in a tight way[5]), the dehydration of host molecules, and the removal of water molecules from the cyclodextrin cavity. Consequently, complex formation involving γ-cyclodextrin is not a favorable process because it has a large cavity volume (510 Å^3) when compared with those for α- and β-cyclodextrin [(176 and 346) Å^3, respectively]. Therefore, in the last years, the use of γ-cyclodextrin has grown for applications involving large guests like DNA,[12] surfactants,[13] and polymers [14,15] and, in general, in the pharmaceutical and biomedical fields.[16–18]

Diffusion coefficients for some aqueous cyclodextrin solutions at 298.15 K have been reported,[19–22] but as far as the authors know, no data on mutual diffusion coefficients of γ-cyclodextrin for the same concentrations at (298.15 and 310.15) K for in vivo pharmaceutical applications are available. We are particularly interested in data on the diffusion and on the viscosity of γ-cyclodextrin in aqueous solutions, especially at the physiological temperature and in a low concentration range, correspondingly to the therapeutic dosage.

In this study, we report values of mutual diffusion (interdiffusion) coefficients D, measured by the Taylor dispersion method, for γ-cyclodextrin aqueous solutions in the concentrations range from (0.002 to 0.010) mol·dm^{-3} and temperatures (298.15 and 310.15) K. From these experimental mutual diffusion coefficients, the hydrodynamic radii of this cyclodextrin were estimated, and the possible presence of γ-cyclodextrin association structures was evaluated. On the other hand, the measured diffusion coefficients were used with both Hartley's and Gordon's equations to estimate the activity coefficient values for these aqueous carbohydrate solutions.

Also we have measured densities and viscosities for aqueous solutions of γ-cyclodextrin at both the same concentrations (from (0.002 to 0.010) mol·dm^{-3}) and temperatures [(298.15 and 310.15) K]. These measurements intend to contribute to a better understanding of the diffusion behavior of this carbohydrate in aqueous solutions.

Experimental Section

Materials. γ-Cyclodextrin (Sigma, pro analysi > 98.5 %) was used as received. Conductivity-grade water ($\kappa_0 = 5 \cdot 10^{-7}$ Ω^{-1}·cm^{-1}) was used as solvent.

The solutions for the diffusion measurements were prepared in calibrated volumetric flasks. They were freshly prepared and deaerated for about 30 min before each set of runs. The uncertainty concerning their compositions was usually within ± 0.02 %.

The solutions for the density and viscosity measurements were made up by direct weighing, and correcting in vacuo, both the solute and water by using a Mettler AE240 balance with a resolution of ± 0.0001 g. The uncertainty concerning their composition was usually within ± 0.02 %.

Diffusion Measurements. The determination of diffusion properties, through the dispersion methods, involves injecting a small quantity of a given solution within the pale of laminar carrier streams of either solvent or solution flowing all along a

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10.1021/je700598v CCC: $40.75
Published on Web 02/06/2008

capillary tube.[23–27] In the present study, we used a Teflon tube whose length, 3.2799 (± 0.0001)·10^3 cm, was directly measured with the help of two high-quality theodolytes.[21] The radius of the tube, 0.05570 (± 0.00003) cm, was calculated by accurately weighing (resolution 0.1 mg) the tube empty and filled with distilled water.

For each run, 0.063 cm^3 of a given solution was introduced, through the six-port Teflon injection valve (Rheodyne, model 5020), into the laminar carrier stream of slightly different composition. The flow rate (0.17 cm^3·min^{-1}) was kept by using a metering pump (Gilson model Minipuls 3) to reach a retention time of about 1.1·10^4 s. The equipment was maintained at (298.15 and 310.15) K (± 0.1 K) with the assistance of an air thermostat.

The control of the samples injected by dispersion was done by using a differential refractometer (Waters model 2410) placed at the dispersion tube outlet. Voltages, $V(t)$, were accurately measured at 5 s intervals with a digital voltmeter (Agilent 34401 A) supplied with an IEEE interface. Binary diffusion coefficients were calculated by fitting the measured voltages to the dispersion equation

$$V(t)/(\mathrm{mV}) = V_0 + V_1 t + V_{\max}(t_R/t)^{1/2} \exp\{-12[D/(10^{-9}\ \mathrm{m^2 \cdot s^{-1}})] \cdot [(t - t_R)/(\mathrm{s})]^2/[r/(\mathrm{m})]^2 \cdot [t/(\mathrm{s})]\} \quad (1)$$

where t_R, V_{max}, V_0, and V_1 are the additional fitting parameters: mean sample retention time, peak height, baseline voltage, and baseline slope, respectively.

The difference in concentration between the injected solutions ($\bar{c} + \Delta c$) and the carrier solutions ($\bar{c}$) was always 0.010 mol·dm^{-3} or even less. To prove the independence, from the initial concentration difference, of the measured diffusion coefficients, various experiments were performed for each carrier solution by using different injected solution concentrations.

Density Measurements. The density of the γ-cyclodextrin solutions was determined by pycnometry. The volume of the pycnometer, approximately 20 mL, was previously calibrated with water.[28,29]

The pycnometer filled with the sample solution was kept in a transparent-walled circulating-water bath, furnished with a heating/cooling system, for at least 2 h to achieve thermal equilibrium. Afterward, a set of six weighing values was obtained for each sample solution. The elapsed time between two consecutive weighings was 30 min, approximately. At all the times, the temperature was controlled with an uncertainty of ± 0.01 °C by using both a mercurial and a digital thermometer.

The density for each solution studied was determined as the mean value of at least four weighings. The values thus obtained have an uncertainty less than 0.01 %.

Viscosity Measurements. The viscosity measurements were performed with an Ostwald-type viscometer, previously calibrated with water.[30–32] As occurred with the density measurements, after 2 h immersed in the same water-thermostat bath, a set of six replicate flow time measurements were carried out. The arithmetic mean value of at least four of these flow times was taken to calculate the viscosity of the solution sample. The efflux time was determined by using stopwatches with a resolution of 0.2 s. Viscosity values were reproducible within ± 0.1 %.

Results and Discussion

Table 1 gives the average diffusion coefficient values, D, measured by using the Taylor dispersion technique for aqueous solutions of γ-cyclodextrin at (298.15 and 310.15) K and concentrations from (0.002 to 0.010) mol·dm^{-3}. For each carrier solution, four profiles were generated by injecting samples that were more or less concentrated than the carrier solution (uncertainties of (1 to 2) %).

Table 1. Mutual Diffusion Coefficients for Aqueous γ-Cyclodextrin Solutions and the Respective Standard Deviations, $D \pm S_D$, at Different Concentrations, c, and Two Temperatures, T

	$D \pm S_D/(10^{-9}\ \mathrm{m^2 \cdot s^{-1}})$	
c/(mol·dm^{-3})	T/K = 298.15	T/K = 310.15
0.002	0.357 ± 0.003	0.480 ± 0.002
0.005	0.355 ± 0.001	0.470 ± 0.002
0.008	0.353 ± 0.003	0.461 ± 0.001
0.010	0.352 ± 0.003	0.453 ± 0.003

Table 2. Least-Squares Values for the Parameters D^0 and A of γ-Cyclodextrin Obtained from the Concentration Dependence of D

T/K	$D^0/(10^{-9}\ \mathrm{m^2 \cdot s^{-1}})$	A	$\sigma^c/(10^{-13}\ \mathrm{m^2 \cdot s^{-1}})$
298.15	0.358_2[a]	−0.633[a]	8.07[a]
	0.358_2[b]	−0.492[b]	7.06[b]
310.15	0.486_7[a]	−3.320[a]	1.64[a]
	0.486_7[b]	−3.135[b]	1.42[b]

[a] By using the Hartley equation. [b] By using the Gordon equation. [c] Standard deviation.

The concentration dependence of the measured diffusion coefficients is accurately represented (correlation coefficient deviations < 1 %) by the linear equation

$$D/(10^{-9}\mathrm{m^2 \cdot s^{-1}}) = D^0[1 + A(c/\mathrm{mol \cdot dm^{-3}})] \quad (2)$$

D^0 is the diffusion coefficient at infinitesimal concentration. The least-squares values of both D^0 and parameter A are listed in Table 2 together with the standard deviation of the fitting.

Concentration Dependence of D. As can be observed, these D values in Table 1 decrease with concentration, mainly at 310.15 K. This behavior is equal to that found for α- and β-cyclodextrin[22] with drifts, at 298.15 K, of the same order in all cases. This decrease is usually considered as a result of both the viscosity change of the medium and the appearance of solute–solute aggregates when the concentration increases.

For dilute solutions of nonionic and nonassociating solutes (for which changes in the viscosity with concentration as well as the solvent counterflow with respect to the solute could be disregarded), the concentration dependence of the mutual diffusion coefficient is usually analyzed through the Hartley equation[33]

$$D/(10^{-9}\ \mathrm{m^2 \cdot s^{-1}}) = D^0\left(1 + \frac{\mathrm{d}\ln\gamma}{\mathrm{d}\ln c}\right)_{T,P} \quad (3)$$

with γ being the solute thermodynamic activity coefficient. This equation has the same structure as eq 2 with: (d ln γ)/dc = A, so that the data of Table 2 are pertinent with this analysis.

However, the Hartley equation neglects the solution viscosity variation with concentration, which for these solutions becomes relatively important so that it would be taken into account. As a consequence, these mutual diffusion coefficient data were also analyzed through the Gordon equation[34]

$$D/(10^{-9}\ \mathrm{m^2 \cdot s^{-1}}) = D^0\left(1 + \frac{\mathrm{d}\ln\gamma}{\mathrm{d}\ln c}\right)_{T,P}(\eta^0/\eta) \quad (4)$$

in which the relative viscosity coefficient is introduced as a factor responsible of the changes observed, with concentration, in the D value. The values found for D^0 and parameter A (= (d ln γ)/dc), obtained by a least-squares method, are also collected

Table 3. Activity Coefficients for Aqueous Solutions of γ-Cyclodextrin Obtained from the Equation $\ln \gamma = B[c/(\text{mol}\cdot\text{dm}^{-3})]$ (where $B = A$ of Table 2)

c/(mol·dm^{-3})	T/K = 298.15	T/K = 310.15
0.002	0.9987[a]	0.9934[a]
	0.9990[b]	0.9937[b]
0.005	0.9968[a]	0.9835[a]
	0.9975[b]	0.9844[b]
0.008	0.9949[a]	0.9738[a]
	0.9961[b]	0.9752[b]
0.010	0.9937[a]	0.9673[a]
	0.9951[b]	0.9691[b]

[a] By using the Hartley equation. [b] By using the Gordon equation.

Table 4. Density Data for Aqueous γ-Cyclodextrin Solutions and the Respective Standard Deviations, $\rho \pm S_D$, at Different Concentrations, c, and Two Temperatures, T

	$\rho \pm S_D$/(g·cm^{-3})	
c/(mol·dm^{-3})	T/K = 298.15	T/K = 310.15
0.0018604	0.99748 ± 0.00002	0.99380 ± 0.00005
0.0049786	0.99897 ± 0.00001	0.99491 ± 0.00002
0.0079233	1.00059 ± 0.00003	0.99698 ± 0.00003
0.0099809	1.00248 ± 0.00001	0.99837 ± 0.00002

Table 5. Least-Squares Values Obtained for the Parameters ρ^0, b_1, and b_2 of γ-Cyclodextrin from the Concentration Dependence of ρ

T	ρ^0	b_1	b_2	σ^a
K	(g·cm^{-3})	(dm^3·mol^{-1})	(dm^6·mol^{-2})	(10^{-4} g·cm^{-3})
298.15	0.99704 ± 0.00043	0.1897 ± 0.1715	34.94 ± 14.30	2.03
310.15	0.99332 ± 0.00043	0.1745 ± 0.1742	33.85 ± 14.53	2.06

[a] Standard deviation.

in Table 2. As can be observed, the values of D^0 are coincident, but those for the parameter $A$are different.

For dilute solutions of α- and γ-cyclodextrin (for which the molarity c and molality m values are practically identical), Miyajima et al.[35] have shown that the activity coefficient data are accurately represented by the equation

$$\ln \gamma = B[c/(\text{mol}\cdot\text{dm}^{-3})] \quad (5)$$

with $B = -1.17$ at 298.15 K.

By combining either Hartley's or Gordon's equations with eq 5, activity coefficients can then be estimated from the concentration dependence of the ratio D/D^0. The values thus obtained for the activity coefficients of γ-cyclodextrin are shown in Table 3. As can be seen, nonsignificant differences are observed from the use of both the Hartley and Gordon equations. From the decrease observed in the values of this parameter, it can be followed that the solute–solute interactions are favored with respect to the solute–solvent ones in this range of concentrations.

Densities and Viscosities of γ-Cyclodextrin Solutions. Experimental density values, ρ, are reported in Table 4 for the different concentrations and temperatures studied. These values were adequately fitted (with R^2 values very close to 1), using a least-squares regression method, by the equation $\rho/(\text{g}\cdot\text{cm}^{-3}) = \rho^0\{1 + b_1[c/(\text{mol}\cdot\text{dm}^{-3})] + b_2[c^2/(\text{mol}^2\cdot\text{dm}^{-6})]\}$, where ρ^0 and c stand for the pure water density value and the molarity, respectively, and b_1 and b_2 are adjustable coefficients. The values found from the regression correlation are shown in Table 5, together with both the correlation coefficient value, R^2, and the standard deviation of the fitting, σ. As can be observed, the values obtained for the pure water density, at both temperatures studied, agree very well with those collected in the literature.[28,29]

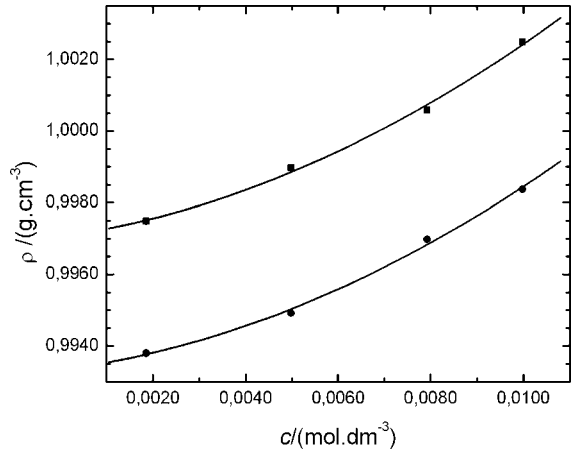

Figure 1. Density values for γ-cyclodextrin aqueous solutions at ■, 298.15 K and ●, 310.15 K as a function of the medium molar concentration.

Table 6. Viscosity Data for Aqueous γ-Cyclodextrin Solutions and the Respective Standard Deviations, $\eta \pm S_D$, at Different Concentrations, c, and Two Temperatures, T

	$\eta \pm S_D$/(mPa·s)	
c/(mol·dm^{-3})	T/K = 298.15	T/K = 310.15
0.0018604	0.8962 ± 0.00004	0.6970 ± 0.00002
0.0049786	0.9061 ± 0.00005	0.7082 ± 0.00006
0.0079233	0.9192 ± 0.00002	0.7172 ± 0.00008
0.0099809	0.9270 ± 0.00007	0.7234 ± 0.00006

Figure 1 shows the plot of the experimental density values against molarity. As can be clearly seen, the lines found exhibit a monotonous increase with concentration which is practically independent of the temperature studied (both lines are almost parallel). The positive values found for the b_2 coefficient can be mainly connected with the high structure-making capacity of γ-cyclodextrin, which would get to a larger packaging of the solution when the solute concentration increases.

Measured viscosity values, η, are collected in Table 6 for both the concentration and temperature ranges studied. These experimental values were fitted by using a least-squares regression method. For that purpose, two different relationships were used: the first one was derived from the Jones and Dole equation[36] ($\eta/cp = \eta^0\{1 + a[c/(\text{mol}\cdot\text{dm}^{-3})]^{1/2} + b[c/(\text{mol}\cdot\text{dm}^{-3})]\}$); η^0 and c being the viscosity value for pure water and the molarity, respectively, and the a and b coefficients are mainly related, in that order, to the solute–solute and solute–solvent interactions taking place in the solution. For a nonelectrolyte, Jenkins and Marcus[37] proved that the a coefficient is negligible and, consequently, that the square-root term can be disregarded. As a result, the ensuing linear equation for the fitting was $\eta/cp = \eta^0\{1 + b[c/(\text{mol}\cdot\text{dm}^{-3})]\}$. The second equation used was derived from the empirical extension proposed by Kaminsky,[38] after considering negligible the square-root term: $\eta/cp = \eta^0\{1 + b[c/(\text{mol}\cdot\text{dm}^{-3})] + d[c^2/(\text{mol}^2\cdot\text{dm}^{-6})]\}$, where the d coefficient can be correlated with the presence of solute–solute interactions. The optimized coefficients found for both temperatures studied are shown in Table 7 (together with both the values for σ) and plotted in Figure 2.

Let us first analyze Figure 2. As was expected, a monotonous rising with concentration is observed. Nevertheless, such rising is significantly much smaller than that for other (α- and β-) cyclodextrins. This different enhancement ought to be related to the larger size of the γ-cyclodextrin hydrophobic cavity and, as a consequence of it, to the greater structure-making capability of this most open cyclodextrin, on the water network, which facilitates the movement in the bulk solution. On the other hand, the lines obtained for both temperatures are almost parallel

Table 7. Least-Squares Values for the Parameters η^0, b, and d of γ-Cyclodextrin Obtained from the Concentration Dependence of η

T	η^0	b	d	σ^a
K	(mPa·s)	($dm^3 \cdot mol^{-1}$)	($dm^6 \cdot mol^{-2}$)	(10^{-4} mPa·s)
298.15	0.88828 ± 0.00128	3.850 ± 0.185	-	11.3
298.15	0.89043 ± 0.00220	2.846 ± 0.888	85.37 ± 74.03	10.5
310.15	0.69145 ± 0.00072	3.225 ± 0.104	-	6.4
310.15	0.68996 ± 0.00064	3.926 ± 0.256	−59.59 ± 21.34	3.0

[a] Standard deviation.

(although the slope is small when the temperature goes up), which indicates that the temperature effect on the viscosity change in the medium is similar in the considered temperature range.

Notwithstanding, looking at the results in Table 7, it can be seen that both equations fit quite well the viscosity experimental data. However, it is important to notice that while at 298.15 K the extrapolated η^0 value found by using the quadratic relation completely agrees with the literature, to reproduce the corresponding value at 310.15 K[30–32] it is necessary to use the linear correlation equation. Moreover, the value of the d parameter decreases with temperature (it appears positive at 298.15 K but negative at 310.15 K) which results in a negative value of $\partial d/\partial T$. Despite the large uncertainty that accompanies this d parameter (see Table 7), such a result would seem to indicate that the solute–solute interactions (which can result in the aggregate stabilization) are enhanced, in this low concentration range, despite the thermal motion.

Hydrodynamic Radius of γ-Cyclodextrin. As is well-known, the Stokes–Einstein equation[33]

$$D/(10^{-9}\ m^2 \cdot s^{-1}) = k_B T/6\pi(\eta/Pa \cdot s)(r_s/m) \qquad (6)$$

established a link between the diffusion process of a solute (through its D coefficient) in a solvent (which is considered as a continuum fluid characterized by its macroscopic viscosity value, η). k_B and T are the Boltzmann's constant and temperature, respectively, and r_s is the effective kinetic radius of the solute.

Although this relation can only be considered as an approximated one (mainly arising from the fact that questions concerning the structure of both the solute kinetic species and the solvent are disregarded), it can be used to derive some valuable information about changes occurring in the solvation of the solute and, therefore, in the radius of the moving species. Thus, eq 6 can be rearranged in the form

$$(D\eta/T)/(N \cdot K^{-1}) = k_B/6\pi(r_s/m) \qquad (7)$$

showing a reciprocal dependence between the grouping $(D\eta/T)$ and the effective hydrodynamic radius r_s. If this radius keeps constant when the medium viscosity changes, the right-hand side in eq 7 ought to be constant, which would mean that the diffusion process is solely controlled by the viscosity of the medium. In Table 8, the values of $(D\eta/T)$ as well as those for the corresponding r_s are collected. As can be seen, such constancy is not observed, with the discrepancies being greater for the highest temperature. Nevertheless, it is necessary to indicate that at infinitesimal concentration the variations observed in $D^0\eta^0/T$ and r_s with temperature are relatively small (less than 2 %, which is within the imprecision of the diffusion measurements). A similar situation occurs in the case of the values found for solutions of finite concentration at 298.15 K (approximately 1 %). On the contrary, at 310.15 K, such discrepancies are important (around 6 %).

By keeping caution, let us analyze these deviations from the relative values for the grouping $(D\eta/T)$ at the different concentrations, with respect to that present at infinitesimal concentration, a situation for which solute–solute interactions are not present (since the solute–solute interactions between nonelectrolytes are only of short range). That is, the ratio

$$(D\eta/T)_{rel} = (D\eta/T)/(D^0\eta^0/T) \qquad (8)$$

where η^0stands for the water viscosity value at temperature T. Under the supposition of constant r_s, the relative ratio in eq 8 would be equal to 1 in the case of viscosity control. On the contrary, a constant decrease of these values with concentration is observed (Table 8), especially at 310.15 K. This behavior indicates that the decrease in D with concentration is not adequately compensated by the viscosity increase of the medium, and hence, it would be necessary to take into account any other effect.

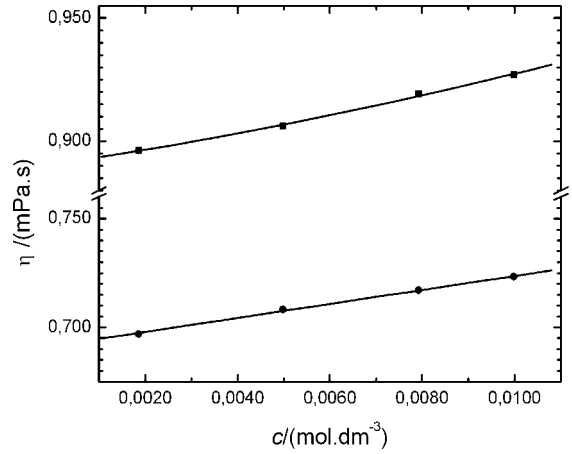

Figure 2. Viscosity values for γ-cyclodextrin aqueous solutions at ■, 298.15 K and ●, 310.15 K, as a function of the medium molar concentration.

Table 8. Hydrodynamic Radius, r_s, of γ-Cyclodextrin (from Equation 6) at (298.15 and 310.15) K

T	c	$\{10^{16} D\eta/T\}$	r_s	
K	($mol \cdot dm^{-3}$)	($m \cdot s^{-1} \cdot kg \cdot K^{-1}$)	nm	$(D\eta/T)_{rel}$
298.15	0	10.7	0.685	1
	0.0018604	10.7	0.677	0.998
	0.0049786	10.6	0.680	0.994
	0.0079233	10.6	0.684	0.989
	0.0099809	10.6	0.685	0.987
310.15	0	10.9	0.674	1
	0.0018604	10.7	0.675	0.986
	0.0049786	10.5	0.688	0.967
	0.0079233	10.3	0.701	0.950
	0.0099809	10.1	0.713	0.934

At this point, we have to bring attention to some approximations included in the Stokes–Einstein relation. On the one hand, the replaced viscosity value concerns the bulk solution instead of the local one in the neighborhood of the solute molecules, whose presence may affect the solvent structure and, consequently, its viscosity. Besides, the shape of the solute molecule is far from being spherical.

Despite these limitations, in the light of the deviations observed for $(D\eta/T)_{rel}$, it could be asserted that in all probability r_s, away from being constant, is influenced by the change in the solution concentration, this being a bigger influence at 310.15 K. The presence of any kind of associative phenomena has been pointed out for α-cyclodextrin and β-cyclodextrin.[22] Moreover, the same authors consider that a close behavior may be expected for γ-cyclodextrin dilute solutions since their structures are quite similar. In view of our results, it is possible to ensure, prudently, that dimer structures of γ-cyclodextrin are increasingly present in solution at this low concentration range. Such presence would

justify the effective rising in r_s and, correspondingly, the fall in the mobility, $(D\eta/T)_{rel}$.

Conclusions

(1) Diffusion coefficients measured for aqueous solutions of γ-cyclodextrin provide transport data necessary to model the diffusion in pharmaceutical and engineering applications.

(2) From the decrease in the values found for the different parameters reported here (the $(D\eta/T)_{rel}$ ratio, the estimated activity coefficients, density and viscosity of the solutions), the presence of γ-cyclodextrin dimers can be assumed.

(3) The change in the viscosity follows the increasing usual pattern with concentration, but is sensibly less pronounced than for the other (α- and β-) cyclodextrins for the same concentration range. This behavior can be attributed to a greater structure-making capability of the γ-cyclodextrin.

Literature Cited

(1) Li, S.; Purdy, W. C. Cyclodextrins and Their Applications in Analytical-Chemistry. *Chem. Rev.* **1992**, *92*, 1457–1470.

(2) Uekama, K.; Hirayama, F.; Irie, T. Cyclodextrin Drug Carrier Systems. *Chem. Rev.* **1998**, *98*, 2045–2076.

(3) Ortona, O.; Paduano, L.; Costantino, L.; Vitagliano, V. Physicochemical Characterization of Some Surfactants in Aqueous-Solution and Their Interaction with Alpha-Cyclodextrin. *J. Mol. Liq.* **1995**, *63*, 291–302.

(4) Nilsson, M.; Cabaleiro-Lago, C.; Valente, A. J. M.; Söderman, O. Interactions between Gemini Surfactants, *12-s-12*, and Beta-cyclodextrin as Investigated by NMR Diffusometry and Electrical Conductometry. *Langmuir* **2006**, *22*, 8663–8669.

(5) Valente, A. J. M.; Nilsson, M.; Söderman, O. Interactions between n-Octyl and n-Nonyl Beta-D-Glucosides and Alpha- and Beta-Cyclodextrins as Seen by Self-Diffusion NMR. *J. Colloid Interface Sci.* **2005**, *281*, 218–224.

(6) Ribeiro, A. C. F.; Esteso, M. A.; Lobo, V. M. M.; Valente, A. J. M.; Simões, S. M. N.; Sobral, A. J. F. N.; Ramos, M. L.; Burrows, H. D.; Amado, A. M.; Amorim da Costa, A. M. Interactions of Copper (II) Chloride with β-Cyclodextrin in Aqueous Solutions at 25 and 37 °C. *J. Carbohydr. Chem.* **2006**, *25*, 173–185.

(7) Ribeiro, A. C. F.; Lobo, V. M. M.; Valente, A. J. M.; Simões, S. M. N.; Sobral, A. J. F. N.; Ramos, M. L.; Burrows, H. D. Association between Ammonium Monovanadate and β-Cyclodextrin as seen by NMR and Transport Techniques. *Polyhedron* **2006**, *25*, 3581–3587.

(8) Stella, V. J.; Rao, V. M.; Zannou, E. A.; Zia, V. Mechanisms of Drug Release from Cyclodextrin Complexes. *Adv. Drug Delivery Rev.* **1999**, *36*, 3–16.

(9) Valle, E. M. M. Cyclodextrins and Their Uses: a Review. *Process Biochem.* **2004**, *39*, 1033–1046.

(10) Burckbuchler, V.; Kjoniksen, A. L.; Galant, C.; Lund, R.; Amiel, C.; Knudsen, K. D.; Nystrom, B. Rheological and Structural Characterization of the Interactions between Cyclodextrin Compounds and Hydrophobically Modified Alginate. *Biomacromolecules* **2006**, *7*, 1871–1878.

(11) Loftsson, T.; Duchêne, D. Cyclodextrins and Their Pharmaceutical Applications. *Int. J. Pharm.* **2007**, *329*, 1–11.

(12) Spies, M.; Schowen, R. L. The Trapping of a Spontaneously "Flipped-out" Base from Double Helical Nucleic Acids by Host-Guest Complexation with Beta-cyclodextrin: The Intrinsic Base-Flipping Rate Constant for DNA and RNA. *J. Am. Chem. Soc.* **2002**, *124*, 14049–14053.

(13) Guerrero-Martinez, A.; Palafox, M. A.; Tardajos, G. Unexpected Binding Mode of Gemini Surfactants and Gamma-Cyclodextrin: DOSY as a Tool for the Study of Complexation. *Chem. Phys. Lett.* **2006**, *432*, 486–490.

(14) Kawabata, R.; Katoono, R.; Yamaguchi, M.; Yui, N. Bundling two Polymeric Chains with Gamma-Cyclodextrin Cavity contributing to Supramolecular Network Formation. *Macromolecules* **2007**, *40*, 1011–1017.

(15) Kawazaki, J.; Satou, D.; Takagaki, T.; Nemoto, T.; Kawaguchi, A. Structural Features of Inclusion Complexes of Gamma-Cyclodextrin with Various Polymers. *Polymer* **2007**, *48*, 1127–1138.

(16) Bettinetti, G.; Sorrenti, M.; Catenacci, L.; Ferrari, F.; Rossi, S.; Salvadeo, I.; Carraro, P. Solid-state Interactions and Drug Release of Teicoplanin in Binary Combinations with Peracetylated Alpha-, Beta-, and Gamma-Cyclodextrins. *J. Inclusion Phenom. Macrocyclic Chem.* **2007**, *57*, 329–332.

(17) Chirio, D.; Cavalli, R.; Trotta, F.; Carlotti, M. E.; Trotta, M. Deformable Liposomes Containing Alkylcarbonates of Gamma-Cyclodextrins for Dermal Applications. *J. Inclusion Phenom. Macrocyclic Chem.* **2007**, *57*, 645–649.

(18) Heeringa, M.; Suy, K.; Morias, K.; Hans, P.; Demeyer, I. Encapsulation of Vecuronium by the Modified Gamma-Cyclodextrin Sugammadex: a New Concept in Clinical Pharmacology. *Br. J. Clin. Pharmacol.* **2006**, *62*, 723–723.

(19) Ribeiro, A. C. F.; Leaist, D. G.; Lobo, V. M. M.; Esteso, M. A.; Valente, A. J. M.; Santos, C. I. A. V.; Cabral, A. M. T. D. P. V.; Veiga, F. J. B. Binary mutual Diffusion Coefficients of Aqueous Solutions of β-cyclodextrin at Temperatures from 298.15 to 312.15 K. *J. Chem. Eng. Data* **2006**, *51*, 1368–1371.

(20) Ribeiro, A. C. F.; Santos, C. I. A. V.; Lobo, V. M. M.; Valente, A. J. M.; Prazeres, P. M. R. A.; Burrows, H. D. Diffusion Coefficients of Aqueous Solutions of Carbohydrates as Seen by Taylor Dispersion Technique at Physiological Temperature (37 °C). *Defect Diffusion Forum* **2006**, *305*, 258–260.

(21) Ribeiro, A. C. F.; Valente, A. J. M.; Santos, C. I. A. V.; Prazeres, P. M. R. A.; Lobo, V. M. M.; Burrows, H. D.; Esteso, M. A.; Cabral, A. M. T. D. P. V.; Veiga, F. J. B. Binary Mutual Diffusion Coefficients of Aqueous Solutions of α-Cyclodextrin, 2-Hydroxypropyl-α-cyclodextrin and 2-Hydroxypropyl-β-cyclodextrin at Temperatures from 298.15 to 312.15 K. *J. Chem. Eng. Data* **2007**, *52*, 586–590.

(22) Paduano, L.; Sartorio, R.; Vitagliano, V.; Costantino, L. Diffusion Properties of Cyclodextrins in Aqueous Solution at 25°C. *J. Solution Chem.* **1990**, *19*, 31–39.

(23) Tyrrell, H. J. V.; Harris, K. R. *Diffusion in Liquids*, 2nd ed.; Butterworths: London, 1984.

(24) Leaist, D. G. Relating Multicomponent Mutual Diffusion and Intradiffusion for Associating Solutes. Application to Coupled Diffusion in Water-in-oil Microemulsions. *Phys. Chem. Chem. Phys.* **2002**, *4*, 4732–4739.

(25) Callendar, R.; Leaist, D. G. Diffusion Coefficients for Binary, Ternary, and Polydisperse Solutions from Peak-Width Analysis of Taylor Dispersion Profiles. *J. Solution Chem.* **2006**, *35*, 353–379.

(26) Barthel, J.; Gores, H. J.; Lohr, C. M.; Seidl, J. J. Taylor Dispersion Measurements at Low Electrolyte Concentrations. 1. Tetraalkylammonium Perchlorate Aqueous Solutions. *J. Solution Chem.* **1996**, *25*, 921–935.

(27) Van de Ven-Lucassen, I. M. J. J.; Kemmere, M. F.; Kerkhof, P. J. A. M. Complications in the Use of the Taylor Dispersion Method for Ternary Diffusion Measurements: Methanol plus Acetone plus Water Mixtures. *J. Solution Chem.* **1997**, *26*, 1145–1167.

(28) *International Critical Tables of Numerical Data, Physics, Chemistry and Technology*; Washburn, E. W., Ed.; 1st Electronic ed.; Knovel Library, 2003; Vol. III, (1926), 25−26.

(29) Owen, B. B.; White, J. R.; Smith, J. S. An Evaluation of the Density of Water at 5° intervals between 45 and 85°. *J. Am. Chem. Soc.* **1956**, *78*, 3561–3564.

(30) Swindells, J. F.; Coe, J. R.; Godfrey, T. B. Absolute Viscosity of Water at 20 Degrees-C. *J. Res. Natl. Bur. Stand.* **1952**, *48*, 1–31.

(31) Coe, J. R.; Godfrey, T. B. Viscosity of Water. *J. Appl. Phys.* **1944**, *15*, 625–626.

(32) *CRC Handbook of Chemistry and Physics*; Lide, D. R., Ed. National Bureau of Standards; 64th ed.; C.R.C. Press: Boca Raton, FL, 1983.

(33) Erdey-Grúz, T. *Transport Phenomena in Aqueous Solutions*, 2nd ed.; Adam Hilger: London, 1974.

(34) Gordon, A. R. Diffusion coefficient of Sucrose in supersaturated solution. *J. Am. Chem. Soc.* **1950**, *72*, 4840–4840.

(35) Miyajima, K.; Sawada, M.; Nakagaki, M. Viscosity B-coefficients. Apparent Molar Volumes, and Activity Coefficients for Alpha-Cyclodextrin in Aqueous Solutions. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3556–3560.

(36) Jones, G.; Dole, M. The viscosity of aqueous solutions of strong electrolytes with special reference to barium chloride. *J. Chem. Soc.* **1929**, *51*, 2950–2964.

(37) Jenkins, H. D. B.; Marcus, Y. Viscosity B-coefficients of ions in solution. *Chem. Rev.* **1995**, *95*, 2695–2724.

(38) Kaminsky, M. Experimental investigation of the effect of concentration and temperature on the viscosity of strong electrolyte solutions. Part III. KCl, K_2SO_4, $MgCl_2$, $BeSO_4$, and $MgSO_4$ solutions. *Z. Phys. Chem. (Frankfurt)* **1957**, *12*, 206–231.

Received for review October 12, 2007. Accepted January 04, 2008. Financial support from POCTI/FCT/FEDER (MAT/2004/03827) is gratefully acknowledged. We are grateful to the University of Alcalá for a grant to C.I.A.V.S. and to the University of Coimbra for giving her leave of absence.

JE700598V