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

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Binary mutual diffusion coefficients measured by the Taylor dispersion method are reported for aqueous solutions of α-cyclodextrin (α-CD), 2-hydroxypropyl-α-cyclodextrin (HP-α-CD), and 2-hydroxypropyl-*β*-cyclodextrin (HP-*β*-CD) at concentrations from (0.002 to 0.010) mol·dm^{-3} at temperatures from (298.15 to 312.15) K. The hydrodynamic radius and activation energy for the diffusion of aqueous α-CD, HP-α-CD, and HP-*β*-CD are calculated from the experimental results. In addition, the Hartley equation and the measured diffusion coefficients are used to estimate activity coefficients for aqueous α-CD, HP-α-CD, and HP-*β*-CD.

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides,[1,2] where the primary and secondary groups of the glucose unities are turn to the exterior ends of the molecule, making them hydrophilic as a whole. However, the interior surface of the truncated cone structure (i.e., the cavity), normally considered as the site of the guest molecules, is largely hydrophobic. These hydrophobic cavities provide a favorable host potential to form inclusion complexes with a large variety of organic and inorganic compounds in different solvents (including water).[3−7] These binding interactions have been used in a wide range of applications as in food, pharmaceutical and chemical industries as well as agriculture and environmental engineering.[8−10]

We are particularly interested in data on the diffusion of 2-hydroxypropyl cyclodextrin derivatives in aqueous solutions. This stems from the most common pharmaceutical application of cyclodextrins, that is, to enhance the solubility and stability of poorly soluble drugs and to engineer slow-release delivery systems for drug molecules.[11,12] Diffusion coefficients for some aqueous CD solutions at 298.15 K have been reported,[13,14] but we are unaware of relevant data in the literature for the same concentrations at other temperatures.

In the present study, mutual diffusion (interdiffusion) coefficients *D*, measured by the Taylor dispersion method, are reported for aqueous solutions of α-CD, HP-α-CD, and HP-*β*-CD at concentrations from (0.002 to 0.010) mol·dm^{-3} and temperatures from (298.15 to 312.15) K. These values are compared with those obtained at the same conditions for *β*-CD and reported elsewhere.[15] In addition, the accuracy of the Taylor diffusion measurements is assessed by measuring binary mutual diffusion coefficients for aqueous solutions of potassium chloride and sucrose at 298.15 K for comparison with previously reported *D* values measured by accurate optical interferometric and conductometric techniques.[16,17] Experimental mutual diffusion coefficients were used to estimate various parameters such as the hydrodynamic radii and activation energy for the diffusion of those aqueous cyclodextrins. In addition, the measured diffusion coefficients are used with the Hartley equation to estimate activity coefficients for aqueous carbohydrate solutions. The effect of CDs molar mass on mutual differential diffusion coefficients at infinite dilution will be discussed on the basis of an empirical equation.

Experimental Section

Materials. α-CD, HP-α-CD, and HP-*β*-CD supplied by Sigma had water contents of 10.5 %, 1.0 %, and 1.0 %, respectively. The solutions for the diffusion measurements were prepared in calibrated volumetric flasks using bi-distilled water. The solutions were freshly prepared and de-aerated for about 30 min before each set of runs. The uncertainty on their compositions was usually within ± 0.1 %.

Procedure. Dispersion methods for diffusion measurements are based on the dispersion of small amounts of solution injected into laminar carrier streams of solvent or solution of different composition, flowing through a long capillary tube.[18−22] The length of the Teflon dispersion tube used in the present study was measured directly by stretching the tube in a large room, using two high-quality theodolytes and appropriate mirrors to accurately focus on the tube ends. This technique gave a tube length of 3.2799 (± 0.0001) × 10^3 cm, in agreement with less-precise check measurements using a good-quality measuring tape. The radius of the tube, 0.05570 (± 0.00003) cm, was calculated from the tube volume obtained by accurately weighing (resolution 0.1 mg) the tube when empty and when filled with distilled water of known density.

At the start of each run, a six-port Teflon injection valve (Rheodyne, model 5020) was used to introduce 0.063 cm^3 of solution into the laminar carrier stream of slightly different composition. A flow rate of 0.17 cm^3·min^{-1} was maintained by a metering pump (Gilson model Minipuls 3) to give retention times of about 8 × 10^3 s. The dispersion tube and the injection

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

$T = 298.15$ K

c	Δc^a	$D \pm S_D$	$100(D - D_{lit})$
$mol \cdot dm^{-3}$	$mol \cdot dm^{-3}$	$10^{-9}\ m^2 \cdot s^{-1}$	$D_{lit}{}^b$
0.002	0.002	0.352 ± 0.003	0.3
0.004	0.004	0.350 ± 0.001	0.0
0.006	0.004	0.349 ± 0.003	0.0
0.008	0.004	0.347 ± 0.002	0.0
0.010	0.005	0.346 ± 0.001	0.3

$D \pm S_D/10^{-9}\ m^2.s^{-1}$

$T = 303.15$ K	$T = 308.15$ K	$T = 312.15$ K
0.407 ± 0.005	0.438 ± 0.006	0.502 ± 0.005
0.404 ± 0.004	0.436 ± 0.006	0.498 ± 0.006
0.403 ± 0.004	0.435 ± 0.006	0.488 ± 0.002
0.401 ± 0.004	0.434 ± 0.005	0.478 ± 0.002
0.398 ± 0.003	0.431 ± 0.004	0.472 ± 0.003

[a] Δc represents the difference between the flow and injection solutions, respectively. [b] $100(D - D_{lit})/D_{lit}$ is the relative difference in percent between our Taylor D values and the D_{lit} values reported by Paduano et al.[14]

Table 2. Mutual Diffusion Coefficients of Aqueous HP-α-CD Solutions and the Respective Standard Deviations, $D \pm S_D$, at Different Temperatures, T, and Concentrations, c

c	Δc^a	$D \pm S_D/10^{-9}\ m^2 \cdot s^{-1}$		
$mol \cdot dm^{-3}$	$mol \cdot dm^{-3}$	$T = 298.15$ K	$T = 310.15$ K	$T = 312.15$ K
0.002	0.002	0.342 ± 0.007	0.460 ± 0.006	0.479 ± 0.005
0.004	0.004	0.330 ± 0.002	0.450 ± 0.003	0.467 ± 0.002
0.008	0.004	0.327 ± 0.001	0.441 ± 0.002	0.455 ± 0.002
0.010	0.008	0.321 ± 0.005	0.433 ± 0.001	0.453 ± 0.005

[a] See Table 1.

Table 3. Mutual Diffusion Coefficients of Aqueous HP-β-CD Solutions and the Respective Standard Deviations, $D \pm S_D$, at Different Temperatures, T, and Concentrations, c

c	Δc^a	$D \pm S_D/10^{-9}\ m^2 \cdot s^{-1}$		
$mol \cdot dm^{-3}$	$mol \cdot dm^{-3}$	$T = 298.15$ K	$T = 310.15$ K	$T = 312.15$ K
0.002	0.002	0.319 ± 0.005	0.408 ± 0.006	0.433 ± 0.002
0.004	0.004	0.316 ± 0.002	0.407 ± 0.003	0.426 ± 0.002
0.008	0.004	0.310 ± 0.001	0.406 ± 0.002	0.425 ± 0.002
0.010	0.008	0.307 ± 0.003	0.406 ± 0.004	0.421 ± 0.001

[a] See Table 1.

Table 4. Least-Squares Values of Parameters D^0 and A for the Concentration Dependence of D (eq 2)

system	T/K	D^0	A	σ^a
α-CD	298.15	0.353	−0.75	3.16×10^{-4}
	298.15	0.353^b	-0.77^b	$6.90 \times 10^{-4\ b}$
	303.15	0.409	−1.05	6.06×10^{-4}
	308.15	0.440	−0.80	6.32×10^{-4}
	312.15	0.512	−4.00	1.93×10^{-3}
HP-α-CD	298.15	0.344	−2.25	3.97×10^{-3}
	310.15	0.465	−3.15	2.13×10^{-3}
	312.15	0.483	−3.20	3.56×10^{-3}
HP-β-CD	298.15	0.322	−1.50	1.00×10^{-6}
	310.15	0.408	−0.25	3.54×10^{-4}
	312.15	0.434	−1.25	2.47×10^{-3}

[a] Standard deviations. [b] From the D_{lit} values reported by Paduano et al.[14]

valve were kept at (298.15 and 303.15) K (± 0.1 K) in an air thermostat.

Dispersion of the injected samples was monitored using a differential refractometer (Waters model 2410) at the outlet of the dispersion tube. Detector voltages, $V(t)$, were measured at accurately timed 5-s intervals with a digital voltmeter (Agilent 34401 A) with an IEEE interface. Binary diffusion coefficients were evaluated by fitting the dispersion equation

$$V(t) = V_0 + V_1 t + V_{max}(t_R/t)^{1/2} \exp[-12D(t - t_R)^2/r^2 t] \quad (1)$$

to the detector voltages. The additional fitting parameters were the mean sample retention time t_R, peak height V_{max}, baseline voltage V_0, and baseline slope V_1.

The concentrations of the injected solutions ($\bar{c} + \Delta c$) and the carrier solutions ($\bar{c}$) differed by 0.004 $mol \cdot dm^{-3}$ or less. Solutions of different composition were injected into each carrier solution to confirm that the measured diffusion coefficients were independent of the initial concentration difference and therefore represented the differential value of D at the carrier-stream composition.

Results and Discussion

The Taylor dispersion equipment was used to measure diffusion coefficients for aqueous solutions of α-CD at (298.15, 303.15, 308.15, and 312.15) K and for HP-α-CD and HP-β-CD at (298.15, 310.15, and 312.15) K, and concentrations from (0.002 to 0.010) $mol \cdot dm^{-3}$. Tables 1 to 3 give the average D value for each carrier solution determined from four profiles generated by injecting samples that were more or less concentrated than the carrier solution (uncertainties of (1 to 2) %). Comparison of our results at 298.15 K with the interferometric D values for aqueous α-CD reported by Paduano et al.[14] (Table 1) suggests an acceptable uncertainty of (1 to 2) % for the Taylor D values.

The concentration dependence of the measured diffusion coefficients is accurately represented (standard deviation < 1 %) by the linear equation

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

D^0 is the diffusion coefficient at infinite dilution. The least-squares values of D^0 and parameter A are listed in Table 4.

Concentration Dependence of D. The concentration dependence of the mutual diffusion coefficient for dilute solutions of non-ionic, non-associating solutes is given by Hartley's equation:[23]

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

where γ is the thermodynamic activity coefficient of the solute. The Hartley equation, although very useful, is limited to the analysis of diffusion in dilute solutions because variations in the viscosity with concentration and the counterflow of solvent relative to the solute are neglected.

Miyajima et al.[24] have shown that for dilute solutions of α-cyclodextrin and γ-cyclodextrin, the molarity c and molality m composition scales are nearly identical numerically. The activity coefficients data are accurately represented by the equation

$$\ln \gamma = B(c/mol \cdot dm^{-3}) \quad (4)$$

with $B = -1.17$ at 298.15 K. Combining Hartley's equation and eq 4 gives

$$D/10^{-9}\ m^2 \cdot s^{-1} = D^0(1 + B(c/mol \cdot dm^{-3})) \quad (5)$$

for the predicted concentration dependence of the mutual diffusion coefficient of dilute aqueous solutions of α-CD.

Table 5. Comparison of the Thermodynamic *B* Coefficients Evaluated from the Taylor and Gouy Diffusion Data and from the Osmotic Data Reported by Ref 24

T	B	
K	α-CD	β-CD[d]
298.15	−0.75[a]	−1.00[a]
298.15	−0.77[b]	−0.69[b]
298.15	−1.17[c]	−1.17[c]
303.15	−1.05[a]	−2.00[a]
308.15	−0.80[a]	−1.10[a]
312.15	−4.00[a]	−0.45[a]

T	B	
K	HP-β-CD[a]	HP-α-CD[a]
298.15	−1.50	−2.25
310.15	−0.25	−3.15
312.15	−1.25	−3.20

[a] From our D values and eq 5 (i.e., $A = B$). [b] From the D_{lit} values reported by Paduano et al.[14] (Table 4) and eq 5 (i.e., $A = B$). [c] From the osmotic data values reported by Miyajima et al.[24] [d] See ref 15.

Table 6. Activity Coefficients of α-CD, HP-α-CD, and HP-*β*-CD from Equation 4 Using the Thermodynamic *B* Coefficients Indicated in Table 4

α-CD + Water

c	$T = 298.15$ K			$T = 303.15$ K	$T = 308.15$ K	$T = 312.15$ K
mol·dm^{-3}	γ	γ^a	γ^b	γ	γ	γ
0.002	0.9985	0.9985	0.9977	0.9979	0.9984	0.9920
0.004	0.9970	0.9969	0.9953	0.9958	0.9968	0.9841
0.006	0.9955	0.9954	0.9930	0.9937	0.9952	0.9763
0.008	0.9940	0.9938	0.9907	0.9916	0.9936	0.9685
0.010	0.9925	0.9923	0.9884	0.9896	0.9920	0.9608

HP-α-CD + Water

c/mol·dm^{-3}	$T = 298.15$ K	$T = 310.15$ K	$T = 312.15$ K
0.002	0.9955	0.9937	0.9936
0.004	0.9910	0.9875	0.9873
0.008	0.9822	0.9751	0.9747
0.010	0.9778	0.9690	0.9685

HP-β-CD + Water

c/mol·dm^{-3}	$T = 298.15$ K	$T = 310.15$ K	$T = 312.15$ K
0.002	0.9970	0.9995	0.9975
0.004	0.9940	0.9990	0.9950
0.008	0.9881	0.9980	0.9900
0.010	0.9851	0.9975	0.9876

[a,b] Values evaluated from the Gouy diffusion data[14] and from the osmotic data reported by Miyajima,[23] respectively.

If activity data are available for the evaluation of d ln γ/dc = B, then eq 5 can be used to calculate the concentration dependence of D. By inverting this procedure, activity coefficients can be estimated from the concentration dependence of D using d(D/D^0)/dc = B and eq 4 (Tables 5 and 6). To check the reliability of this procedure, which rests on several assumptions, we estimated B values from our diffusion coefficients and those obtained by Paduano et al.[14] and from the activity data reported by Miyajima et al.[24] As shown in Table 6, the agreement between different sets of B values for β -CD and α-CD is acceptable. The increase in the magnitude of B with increasing of temperature for α-CD, HP-α-CD, and HP-β-CD from (298.15 to 312.15) K may reflect increasing solute−solute interactions, contrary to the behavior of β-CD (Table 5).[15] In this latter case, no experimental evidence of this kind of interaction is seen, in agreement with observations by Paduano et al.[14] In fact, from thermodynamic data[14,24] it is possible to consider the presence of the highly favored solute−solute−solvent interactions for α-CD, HP-α-CD, and HP-β-CD systems. In our study, this is also supported by the large decrease in activity coefficients in low concentration observed at 312.15 K (Table 6). As shown in Table 6, the activity coefficients calculated from our diffusion coefficients, from the Gouy diffusion data, and from the osmotic data are in good agreement (± 0.1 %).

Table 7. Hydrodynamic Radius, *a*, of α-CD, HP-α-CD, and HP-*β*-CD (from eq 6) at Temperatures, *T*, from (298.15 to 312.15) K

	T	$10^{16}\,D^0\eta^0/T$	a
system	K	m·s^{-1}·kg·K^{-1}	nm
α-CD + water	298.15	10.5	0.70
	303.15	10.8	0.68
	308.15	10.3	0.71
	312.15	10.9	0.67
β-CD + water[a]	298.15	9.74	0.75
	303.15	10.3	0.71
	308.15	10.1	0.73
	312.15	9.72	0.75
HP-α-CD + water	298.15	10.3	0.71
	310.15	10.3	0.71
	312.15	10.3	0.71
HP-β-CD + water	298.15	9.62	0.76
	310.15	9.10	0.80
	312.15	9.24	0.79

[a] See ref 15.

Temperature Dependence of D. A study was made to see if the changes in D with temperature for aqueous α-CD, HP-α-CD, and HP-β-CD follow the Stokes−Einstein equation:[23]

$$D^0 = k_B T/6\pi\eta^0 a \qquad (6)$$

The values of $D^0\eta^0/T$ and the effective hydrodynamic radius a for infinitely dilute α-CD, HP-α-CD, and HP-β-CD solutions are given in Table 7. Similar results were obtained for β-CD solutions.[15] k_B and η^0 are Boltzmann's constant and the viscosity of pure water at temperature T.[25] The variations in $D^0\eta^0/T$ and a with temperature are, in general, relatively small, < 3 %, which is within the precision of the diffusion measurements. The Stokes−Einstein equation therefore gives a reliable account of the variation in D^0 over the temperature range used in the present study. Hydrodynamic radius of different cyclodextrins follow the order a(HP-β-CD) > a(β -CD) > a(HP-α-CD) > a(α-CD). Having in mind that the hydrodynamic radius follows in general the same order than those obtained by the molar mass and that the behavior of diffusion coefficient follows the opposite order, we may conclude that the hydration shells do not affect and change, in a significant way, these different carbohydrates.

Another interesting point is to know if there is any relationship between differential diffusion coefficients at infinite dilution of different CDs, at different temperatures, and the CD molar mass. In fact, from eq 6 it is possible to establish a relationship between the hydrodynamic radius (a) and the molar volume of the diffusing species. This parameter can also be related with the ratio between molar mass (M) and the density of those species (d). Assuming a constant density of CDs, equal to the density of glucose (1560 kg·m^{-3}), eq 6 can be rewritten as[26]

$$D^0 = \mathrm{T}/(\eta^0 M(9.5 \times 10^{13})) \qquad (7)$$

Comparing the diffusion coefficients at infinite dilution obtained using experimental data, described in this work (D^0_{obs}), and those calculated using eq 7 (D^0_{cal}) (Figure 1), it is possible to conclude that it is possible to estimate D^0 of CDs using eq 7, within an error of ca. 10 %. These results also show

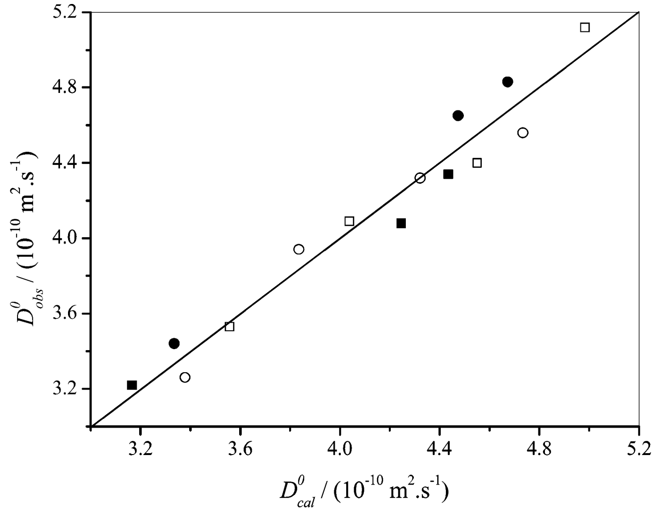

Figure 1. Relationship between differential diffusion coefficients at infinite dilution obtained from our experimental results (D^0_{obs}) and those obtained using eq 7, D^0_{cal}: □, α-CD, $M = 972.84$ g·mol^{-1}; ○, β-CD,[15] $M = 1135$ g·mol^{-1}; ■, HP-α-CD, $M = 1180$ g·mol^{-1}; ●, HP-β-CD, $M = 1380$ g·mol^{-1}. Solid line represents the fitting of data to a straight line with a standard deviation of 1.26×10^{-11} and a correlation coefficient of 0.98.

Table 8. Activation Energies, E_a, of the Diffusion Process at Temperatures from (298.15 to 328.15) K for α-CD, HP-α-CD, and HP-β-CD in Aqueous Solutions

system	E_a/kJ·mol^{-1}	σ^c
α-CD + water	17.11[a]	2.832×10^{-2}
	18.64[b]	1.307×10^{-2}
β-CD + water[d]	18.72[a]	2.000×10^{-2}
	18.64[b]	1.307×10^{-2}
HP-α-CD+ water	17.02[a]	1.543×10^{-2}
	19.40[b]	2.160×10^{-2}
HP-β-CD + water	13.66[a]	0.770×10^{-2}
	19.40[b]	2.160×10^{-2}

[a] Calculated values using Eyring relation. [b] Calculated values using Stokes−Einstein relation. [c] Standard deviations. [d] See ref 15.

that the hydrated shell does not change too much when functionalization of CD occurs.

D values measured at different temperatures can be used to evaluate activation energies E_D for diffusion by using the Eyring equation:

$$E_{\text{D}} = -R \text{ d} \ln (D^0/T)/\text{d}(1/T) \tag{8}$$

where *R* is the gas constant. Table 8 shows the expected linear relation between the logarithm of the limiting D^0 values and $1/T$. The activation energies calculated from the slope of the limiting in α-CD, HP-α-CD, and HP-β-CD are (17.11, 17.02, and 13.66) kJ·mol^{-1}, respectively. In general, these values are only slightly different from the values suggested by the Stokes−Einstein relation (that is, (18.64, 19.40, and 19.40) kJ·mol^{-1}, respectively, obtained by $-R[\text{d} \ln(T/\eta^0)/\text{d}(1/T)]$) (Table 8). These last values for HP-β-CD and HP-α-CD do appear to be very slightly upper than those measured for β-CD and α-CD in water[15] by the same method (that is, 18.64 kJ·mol^{-1} from the Stokes−Einstein relation). This behavior can be also explained by their upper molecular weights.

Conclusion

Diffusion coefficients measured for aqueous solutions of α-CD, HP-α-CD, and HP-β-CD provide transport data necessary to model the diffusion in pharmaceutical and engineering applications.

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