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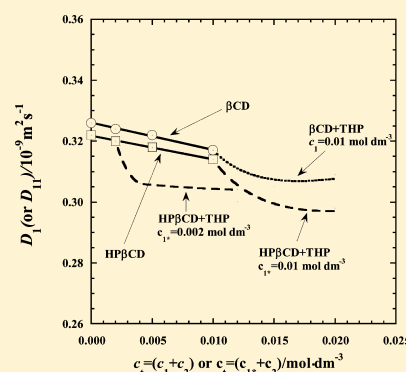
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ABSTRACT: Ternary mutual diffusion coefficients (D_{11} , D_{22} , D_{12} , and D_{21}) measured by the Taylor dispersion method at $T = 298.15$ K in two different laboratories (University of Naples, Federico II, Italy, and University of Coimbra, Portugal) are reported for aqueous systems, involving as components 2-hydroxypropyl- β -cyclodextrin (HP- β -CD) or β -cyclodextrin (β -CD) and theophylline. The aim of the paper was to determine the transport properties of these systems as well as the presence of an inclusion mechanism. On the basis of the diffusion coefficient data it can be argued that theophylline is included neither into β -cyclodextrin nor into 2-hydroxypropyl β -cyclodextrin. The variations of the main diffusion coefficients with composition are ascribable to nonspecific solute–solute interactions such as the viscosity increase induced by the presence of the drug or to an obstruction effect of which the bulky cyclodextrin is responsible.



INTRODUCTION

Cyclodextrins^{1–3} (CDs, or cyclic oligosaccharides) are relevant carriers used in drug release systems, with applications in the pharmaceuticals due to their ability to solubilize poorly soluble drugs, resulting in a striking increase in their water solubility and rate of diffusion. However, their interior surface is largely hydrophobic, providing an enormous host potential for molecular ability to form inclusion complexes with a large variety of guest entities (e.g., xantines^{4–6} and surfactants)^{7–9} in different solvents, permitting a wide range of applications, such as in food, chemical, and pharmaceutical industries.^{1–9}

While numerous studies have been dedicated to the structural aspects of systems involving CDs and different drugs in aqueous solutions,^{10,11} few studies have taken into account the multicomponent diffusion work on aqueous CD solutions and the alteration of their transport properties as a result of the presence of different components in these solutions.^{12–27} Among these systems, we have been focused on aqueous CD solutions with theophylline (THP, 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione),^{28,29} this substrate being a poorly water-soluble alkaloid with important functions, used in main actions (e.g., in pharmaceutical industry as mild stimulants and bronchodilators).^{28,29}

In fact, diffusion coefficients for some aqueous binary and ternary CD systems,^{12–14,30–33} at 298.15 K have been reported, but as far as the authors know, no data on mutual diffusion coefficients of ternary system 2-hydroxypropyl- β -cyclodextrin (HP- β -CD)-THP and β -cyclodextrin (β -CD)-THP for the same concentrations at 298.15 K have been published. This

paper reports experimental data for the systems (HP- β -CD)/THP and (β -CD)/THP in water, measured by the Taylor dispersion method installed in the laboratories of the University of Coimbra, Portugal, and University of Naples, Italy, at concentrations from (0.00 to 0.010) mol·dm^{−3} of each component, at 298.15 K.

EXPERIMENTAL SECTION

Theophylline (THP) (molecular weight $M = 180.164$ g·mol^{−1}) was purchased from Sigma, Germany, with a nominal purity higher than 99.0 %. 2-Hydroxypropyl- β -cyclodextrin (HP- β -CD) (molecular weight $M = 1541.54$ g·mol^{−1}) and β -cyclodextrin (β -CD) (molecular weight $M = 1135.00$ g·mol^{−1}) were purchased from Sigma, Germany, with water mass fraction of 1.0 % and 13.1 %, respectively. They were used as received. The solutions for the diffusion measurements were prepared in calibrated volumetric flasks using double distilled water. The solutions were freshly prepared and deaerated for about 30 min before each set of runs.

The theory of the Taylor dispersion technique is well-described in the literature,^{12–27,34–42} and consequently the authors only indicate some relevant points concerning this method on the experimental determination of binary and ternary diffusion coefficients.

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Table 1. Diffusion Coefficients for Aqueous HP- β -CD (1), β -CD (1*), and THP (2) Solutions at 298.15 K

c_1	D_1^a	η_1^0	c_{1*}	D_{1*}^b	η_{1*}^0	c_2	D_2^c	η_2^0
mol·dm ⁻³	10 ⁻⁹ m ² ·s ⁻¹	cp	mol·dm ⁻³	10 ⁻⁹ m ² ·s ⁻¹	cp	mol·dm ⁻³	10 ⁻⁹ m ² ·s ⁻¹	cp
0.000	0.322	0.8904	0.000	0.326	0.8904	0.000	0.796	0.8904
0.002	0.319	0.8945	0.002	0.324	0.8937	0.002	0.785	0.8913
0.005	0.314	0.9006	0.005	0.322	0.8987	0.005	0.762	0.8925
0.010	0.307	0.9109	0.010	0.316	0.9070	0.010	0.734	0.8945
$D_1^\infty/10^{-9} \text{ m}^2\cdot\text{s}^{-1} = 0.322 \pm 0.001$			$D_{1*}^\infty/10^{-9} \text{ m}^2\cdot\text{s}^{-1} = 0.326 \pm 0.002$			$D_2^\infty/10^{-9} \text{ m}^2\cdot\text{s}^{-1} = 0.796 \pm 0.003$		
$V_1^\infty/\text{mL} = 1062 \pm 20$			$V_{1*}^\infty/\text{mL} = 1100 \pm 10$			$V_2^\infty/\text{mL} = 73 \pm 15$		

^aSee ref 13. ^bSee ref 12. ^cSee ref 31.

The method is based on the dispersion of small amounts of solution injected into a laminar carrier stream of solvent or solution of different composition, flowing through a long capillary tube with the coil radius of 1.6 dm.¹² For the research carried out in Coimbra, this tube length is $(3.2799 \pm 0.0001) \cdot 10^4$ mm, and its radius is $0.5570 (\pm 0.0003)$ mm. At the start of each experiment performed in this laboratory (Coimbra), a flow rate of $0.17 \text{ mL}\cdot\text{min}^{-1}$ was maintained by a metering pump (Gilson model Minipuls 3) giving retention times of about $1.1 \cdot 10^4$ s, and a six-port Teflon injection valve (Rheodyne, model 5020) is used to introduce 0.063 mL of solution into the laminar carrier stream of a slightly different composition. This valve and the dispersion tube are inside an air thermostat at 298.15 K (± 0.01 K). At the outlet of this tube, the dispersion of the injected samples is monitored using a differential refractometer, and the detector voltages, $V(t)$, are measured at accurately 5 s intervals by using a digital voltmeter (Agilent 34401 A) with an IEEE interface.

For the measurements carried out at Federico II University of Naples the apparatus is formed by a 20 m capillary tube with an inner radius of $0.4020 (\pm 0.0001)$ mm connected to a metering pump Watson Marlow 403U/VM2 set at the flowing rate of $0.5 \text{ mL}\cdot\text{min}^{-1}$, the differential refractometer being a Knauer K2301. The inner radius of the tube is determined by calibration of the apparatus with a KCl 0.2 *m* solution at 298.15 K, the diffusion coefficient of this system being well-known, which corresponds to a minimum of the *D* versus composition trend.

The capillary tube was inserted into a thermostatted water bath, while the entire apparatus is once more thermostatted by an air bath at 298.15 K (± 0.01 K).

In the case of binary systems, the diffusion coefficients were evaluated by fitting the dispersion equation as described in refs 27 and 30.

The diffusion in a ternary solution is described by the diffusion equations

$$-(J_i) = (D_{ii})_v \frac{\partial c_i}{\partial x} + (D_{ij})_v \frac{\partial c_j}{\partial x} \quad (1)$$

$$-(J_j) = (D_{ji})_v \frac{\partial c_i}{\partial x} + (D_{jj})_v \frac{\partial c_j}{\partial x} \quad (2)$$

where J_i , J_j , $\partial c_i/\partial x$, and $\partial c_j/\partial x$ are the molar fluxes and the concentration gradients of solute *i* and *j*, respectively. The index *v* highlights that D_{ii} , D_{jj} , D_{ij} , and D_{ji} are expressed in the volume-fixed reference frame. The main diffusion coefficients, D_{ii} and D_{jj} , are concerned with the flux of each solute produced by its own concentration gradient, while the cross diffusion coefficients D_{ij} and D_{ji} give the coupled flux of each solute driven by a concentration gradient in the other solute. A

positive D_{ij} cross-coefficient ($i \neq j$) indicates cocurrent coupled transport of solute *i* from regions of higher to lower concentration of solute *j*. However, a negative D_{ij} coefficient indicates counter-current coupled transport of solute *i* from regions of lower to higher concentration of solute *j*.

These parameters have been evaluated by fitting the ternary dispersion equation, as published in ref 27.

In these experiments, small volumes, ΔV , of the solution, of composition $\bar{c}_i + \Delta\bar{c}_i$, $\bar{c}_j + \Delta\bar{c}_j$ are injected into carrier solutions of composition, \bar{c}_i and \bar{c}_j , at time $t = 0$.

RESULTS AND DISCUSSION

Binary Systems: β -CD(1)–Water, HP- β -CD(1*)–Water, and THP(2)–Water. The diffusion binary data are reported in Table 1 with the corresponding viscosity. These results are the average of six experiments. Good reproducibilities for main diffusion coefficients, D_{11} and D_{22} , were observed, as seen by the small standard deviations, S_D . The error limits of these results are close to the imprecision, therefore giving an experimental uncertainty of (1 to 3) %.

In the hypothesis that the solvent is a continuum medium, it is possible to evaluate the hydrodynamic radius of the migrating species through the use of the Stokes–Einstein equation

$$D_i^\infty = \frac{k_B T}{6\pi r_i \eta^0} \quad (3)$$

D_i^∞ limiting values are shown in Table 1.

In eq 3 r_i is the hydrodynamic radius of the diffusing particles, η^0 the viscosity of the solvent, k_B is the Boltzmann constant, and D_i^∞ is representative of $\lim_{c_i \rightarrow 0} D_i$.

By the knowledge of the hydrodynamic radius, it is straightforward to obtain the limiting hydrodynamic volume of each molecule, V_i^∞ . The data are also reported in Table 1.

As it can be observed, the volumes of β -CD and HP- β -CD are very similar, indicating that the hydroxypropyl group is well inserted in the hydration cosphere of the hydroxyl ones. Theophylline has a smaller volume but probably not so small to consider the system THP-water as a “mixed” solvent in respect to the β -CD and HP- β -CD molecules. This aspect will be discussed below for the ternary systems.

The attempt to foresee the D_i values at finite concentration by using the extended Stokes–Einstein equation, valid in the hypothesis that only a viscosity effect is responsible of the diffusivity reduction,

$$D_i = \frac{k_B T}{6\pi r_i \eta} = D_i^\infty \frac{\eta^0}{\eta} \quad (4)$$

does not give good results for any of the systems under consideration. In eq 4 the solvent viscosity η^0 has been

Table 2. Ternary Diffusion Coefficients, D_{11} , D_{12} , D_{21} , and D_{22} , for Aqueous β -CD (1) + Theophylline (2) Solutions and the Respective Standard Deviations, S_D , at 298.15 K

c_1^a	c_2^a	$D_{11} \pm S_D$	$D_{12} \pm S_D$	$D_{21} \pm S_D$	$D_{22} \pm S_D$
		$10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$	$10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$	$10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$	$10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$
0.002	0.002	0.321 ± 0.009 (−0.9 %) ^b	-0.003 ± 0.017	0.004 ± 0.005	0.721 ± 0.032 (−8.2 %) ^c
0.002	0.005	0.322 ± 0.007 (−0.3 %) ^b	-0.006 ± 0.017	0.003 ± 0.017	0.709 ± 0.030 (−7.0 %) ^c
0.002	0.010	0.319 ± 0.009 (−1.2 %) ^b	-0.005 ± 0.019	0.006 ± 0.008	0.680 ± 0.027 (−7.4 %) ^c
0.005	0.005	0.316 ± 0.005 (−1.9 %) ^b	0.005 ± 0.023	-0.024 ± 0.040	0.683 ± 0.034 (−10.4 %) ^c
0.010	0.002	0.310 ± 0.005 (−1.9 %) ^b	-0.011 ± 0.016	-0.029 ± 0.040	0.709 ± 0.021 (−3.4 %) ^c
0.010	0.005	0.305 ± 0.048 (−3.5 %) ^b	-0.033 ± 0.110	-0.053 ± 0.052	0.640 ± 0.077 (−12.8 %) ^c
0.010	0.010	0.309 ± 0.006 (−2.2 %) ^b	-0.016 ± 0.030	-0.063 ± 0.022	0.628 ± 0.017 (−14.4 %) ^c

^a c_1 and c_2 in units of $\text{mol} \cdot \text{dm}^{-3}$. ^bThe values indicated in parentheses represent the relative deviations between the experimental values of D_{11} and the binary values for the same concentration, D_{12} . ^cThe values indicated in parentheses represent the relative deviations between the experimental values of D_{22} and the binary values for the same concentration, D_{31} .

Table 3. Ternary Diffusion Coefficients, D_{11} , D_{12} , D_{21} , and D_{22} , for Aqueous HP- β -CD (1*) + Theophylline (2) Solutions and the Respective Standard Deviations, S_D , at 298.15 K

c_1^a	c_2^a	$D_{11} \pm S_D$	$D_{12} \pm S_D$	$D_{21} \pm S_D$	$D_{22} \pm S_D$
		$10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$	$10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$	$10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$	$10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$
0.002	0.002	0.306 ± 0.002 (−4.1 %) ^b	0.002 ± 0.001	0.068 ± 0.020	0.756 ± 0.017 (−3.7 %) ^c
0.002	0.005	0.305 ± 0.003 (−4.4 %) ^b	0.002 ± 0.003	0.070 ± 0.022	0.736 ± 0.009 (−3.4 %) ^c
0.002	0.010	0.304 ± 0.008 (−4.7 %) ^b	-0.002 ± 0.001	0.042 ± 0.016	0.713 ± 0.005 (−2.9 %) ^c
0.005	0.002	0.303 ± 0.007 (−3.8 %) ^b	0.008 ± 0.008	0.054 ± 0.019	0.719 ± 0.008 (−8.4 %) ^c
0.005	0.005	0.301 ± 0.006 (−4.4 %) ^b	0.024 ± 0.001	0.063 ± 0.024	0.682 ± 0.026 (−10.5 %) ^c
0.005	0.010	0.300 ± 0.007 (−4.8 %) ^b	-0.010 ± 0.002	0.020 ± 0.028	0.641 ± 0.020 (−12.7 %) ^c
0.010	0.002	0.300 ± 0.007 (−2.2 %) ^b	0.014 ± 0.0005	0.042 ± 0.002	0.597 ± 0.026 (−23.9 %) ^c
0.010	0.005	0.299 ± 0.008 (−2.6 %) ^b	0.023 ± 0.004	0.056 ± 0.053	0.570 ± 0.034 (−25.2 %) ^c
0.010	0.010	0.298 ± 0.005 (−2.9 %) ^b	-0.029 ± 0.029	-0.009 ± 0.090	0.548 ± 0.038 (−25.3 %) ^c

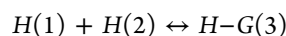
^a c_1 and c_2 in units of $\text{mol} \cdot \text{dm}^{-3}$. ^bThe values indicated in parentheses represent the relative deviations between the experimental values of D_{11} (or D_{11}^*) and the binary values for the same concentration, D_{12} . ^cThe values indicated in parentheses represent the relative deviations between the experimental values of D_{22} and the binary values for the same concentration, D_{31} .

substituted by the solution viscosity η . Probably the reason stays in the fact that the “thermodynamic factor”¹⁷ is not unitary.

Ternary Systems: β -CD(1)–THP(2)–Water and HP- β -CD(1*)–THP(2)–Water. The diffusion ternary data are reported in Tables 2 and 3. The results are the average of four independent experiments. Good reproducibility was observed, as seen by the small standard deviations, S_D . Also, the error limits of our results are close to the imprecision, therefore giving an experimental uncertainty of (1 to 3) %.

The diffusion properties of ternary systems containing a host (H)/guest (G) system are well-described in the literature. Their interest is connected with the possibility to obtain, under

some reasonable assumptions, the equilibrium constant of the inclusion process from the four experimental diffusion coefficients.^{18–23} Considering the inclusion equilibrium and the relative constant:



$$K = \frac{c_3^*}{c_1^* \cdot c_2^*} \quad (5)$$

where c_i^* are the equilibrium concentrations, it is possible to obtain the following relations between the experimental diffusion coefficients, D_{ij} with $i, j = 1, 2$, and the diffusivity of the species effectively present in solution, D_k^* with $k = 1, 2, 3$:

$$D_{11} = D_3^* + (D_1^* - D_3^*) \left(\frac{\partial c_1^*}{\partial c_1} \right) \quad (6)$$

$$D_{12} = (D_1^* - D_3^*) \left(\frac{\partial c_1^*}{\partial c_2} \right) \quad (7)$$

$$D_{21} = (D_2^* - D_3^*) \left(\frac{\partial c_2^*}{\partial c_1} \right) \quad (8)$$

$$D_{22} = D_3^* + (D_2^* - D_3^*) \left(\frac{\partial c_2^*}{\partial c_2} \right) \quad (9)$$

where c_i are the stoichiometric concentrations. The first derivatives depend on the stoichiometric concentrations as well as on the inclusion equilibrium constant. $(\partial c_i^*/\partial c_i)$ is always positive varying in the range $0 \leq (\partial c_i^*/\partial c_i) \leq 1$ while $(\partial c_i^*/\partial c_j)$ is always negative varying in the range $-1 \leq (\partial c_i^*/\partial c_j) \leq 0$. Consequently if $D_3^* < D_1^* < D_2^*$, which is the most common situation for neutral host molecules, we have:

$$D_3^* < D_{11} < D_1^* = D_1$$

$$D_{12} < 0$$

$$D_{21} < 0$$

$$D_3^* < D_{22} < D_2^* = D_2$$

Therefore, if the theophylline inclusion were effective, the experimental diffusion coefficients should respect the above prediction. Our experimental data do not respect this expectation and must be interpreted in a different way.

In Tables 2 and 3, the main coefficients D_{11} and D_{22} , giving the molar fluxes of β -CD or HP- β -CD and THP components driven by their own concentration gradients, are compared with those obtained for binary systems, respectively (β -CD/water,¹² HP- β -CD/water,¹³ and THP/water³¹) at the same temperature. In general, D_{11} and D_{22} are lower than those of the related binary aqueous systems, D_1 and D_2 , respectively, with deviations ranging between 0.3 % and 25 %, while the cross terms are almost zero in the error. As said before, this evidence excludes the possibility of admitting an inclusion of theophylline inside the CD cavity.

The trends of the two main diffusion coefficients are reported in Figures 1 and 2, as a function of the total concentration. The binary diffusion coefficients are also plotted. The best description of how concentration of solute i affects the motion of solute j , and vice versa, is obtained looking at the trend of D_{ij} as a function of c_i at $c_j = \text{constant}$ and $c_j = \text{variable}$.

From a perusal of Figure 1, where for simplicity only the fitting trends of the experimental data are reported, it appears that the effect of adding THP to CD solution is very small. In our opinion it is simply imputable to a viscosity effect, in the rough approximation that considers THP and H₂O as a mixed solvent.

A larger effect is observed for D_{22} as shown in Figure 2 where the trends for systems at $c_2 = \text{constant}$ are reported. It is to observe that the D_{22} decrease for THP is almost the same independently from adding β -CD and HP- β -CD. This large D_{22} decrease, in the absence of any inclusion process, can be attributed to an obstruction effect of the large CD molecules on the motion of the small THP. This effect is always present in solution of particles with large differences in size. The absence

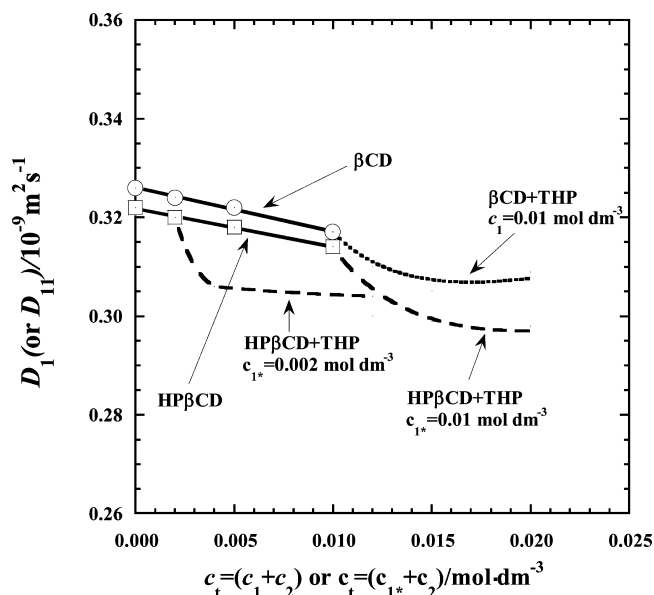


Figure 1. Binary diffusion coefficient of -O-, β -CD(1) in the system β -CD(c_1)-water; -□-, HP- β -CD(c_1^*) in the system HP- β -CD(c_1^*)-water. Interpolated trend of the experimental ternary diffusion coefficients of •••, β -CD(1) in the system β -CD($c_1 = 0.01$ M)-THP(c_2)-water; - - -, HP- β -CD($c_1^* = 0.002$ M)-THP(c_2)-water and HP- β -CD($c_1^* = 0.01$ M)-THP(c_2)-water.

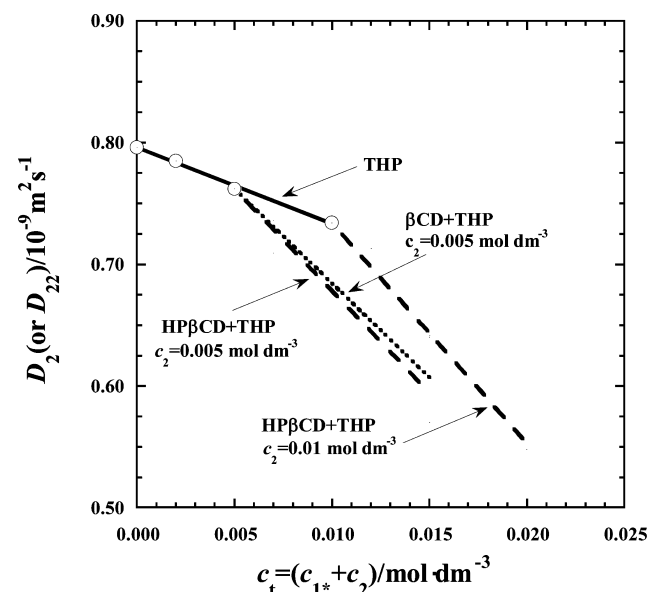


Figure 2. Binary diffusion coefficient of -O-, THP(2) in the system THP(c_2)-water. Interpolated trend of the experimental ternary diffusion coefficients of •••, THP(2) in the system β -CD(c_1)-THP($c_2 = 0.005$ M)-water; - - -, THP(2) in the system HP- β -CD(c_1^*)-THP($c_2 = 0.005$ M)-water and in the system HP- β -CD(c_1^*)-THP($c_2 = 0.01$ M)-water.

of any significant difference between β -CD and HP- β -CD behavior is a confirmation that the two hydrodynamic volumes of the CDs are practically coincident.

CONCLUSIONS

The diffusion data determined at several compositions of the aqueous ternary systems theophylline/ β -CD and theophylline/

2-hydroxypropyl β CD have shown that there is no inclusion of the theophylline molecule in the cavity of β -CD and HP- β -CD as well. For these systems the variations of the main diffusion coefficients with composition can be interpreted simply on the basis of a nonspecific solute–solute interaction. In fact, the effect of theophylline on the motion of β -CD and HP- β -CD can be interpreted as due to the increase of the medium viscosity consequent to the addition of THP to water, while the effect β -CD and HP- β -CD on the motion of THP is imputable to the obstruction that these large molecules exert on the motion of the small one.

Experimental data do not highlight any difference in the obstruction effect due to the two CD molecules, confirming their very similar hydrodynamic volumes.

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Notes

The authors declare no competing financial interest.

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