

The Curious World of Polypseudorotaxanes: Cyclodextrins As Probes of Water Structure

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Polymeric chains and cyclodextrins in water produce supramolecular host–guest assemblies called *polypseudorotaxanes* (PPR). The guest polymers thread the host cyclodextrin molecules such as beads on a string. Once formed, these molecular necklaces aggregate into larger assemblies that reveal themselves in a significant increase of turbidity. This astonishing phenomenon is enthalpically driven and its kinetics depends strongly on choice of reactants, concentration, solvent nature, addition of cosolutes, and temperature. We have studied the effects on PPR assembly induced by temperature, surface nature, and solute. These studies provide some insights into the cooperative mechanisms behind the formation of these organized structures. Hydrophilic surfaces (e.g., glass), low temperatures, and high concentrations of host molecules all favor the threading process. The addition of sugars to the solution promotes the assembly process in a way that provides strong hints on the nature of aqueous solution structure. The highly specific effects induced by sugars and electrolytes mimic precisely those seen in bubble–bubble coalescence phenomena. They reflect the capacity of solutes to modify bulk solvent and solution structure. In agreement with previous observations, the experimental results can be explained by invoking the formation of pre-assembled, wormlike aggregates of cyclodextrins in aqueous solutions. Once formed, these worms instantly swallow the polymer chain.

Introduction

Weak noncovalent interactions, supposed to be the driving forces in the formation of supramolecular aggregates, are subsumed under the words hydrogen and ionic bonding, hydrophobic and van der Waals interactions, and molecular shape and recognition. To their combined operation are attributed the spontaneous self-assembly of a plenitude of structures.^{1,2} The study of such structures, embraced by the term supramolecular chemistry, finds potentially interesting application in the search for artificial “smart” nanomaterials. It is the hope, the wish, and an article of faith that such materials will exhibit useful physicochemical changes in response to weak perturbations (e.g., light, pH, polarity, and temperature). Ultimately, they should mimic some of the properties of natural self-organized supramolecular structures, be they ribosomes, nucleic acids or protein complexes, and antigen–antibody complexes.^{3–8} However, the main aim can hardly be achieved unless we can better quantify and understand the driving forces and solvent structures that dictate events. From that point of view, the present system is ideal, in its own right as a phenomenon, and as a probe of what we mean by water structure.

When a concentrated aqueous solution of cyclodextrin (CD) is mixed with a polymer like polyethylene-glycol (PEG) or polypropylene-glycol (PPG), the mixture rapidly becomes turbid. Subsequently, a white precipitate forms. The first reports of such effects were from the group of Harada.^{9,10} The phenomenon involves the cooperative threading of a number of CD molecules

along a single polymeric chain. The aggregation of such structures into larger objects follows and results in intense Rayleigh scattering. The threading, aggregation and precipitation of inclusion products has been studied by XRD,¹¹ AFM,^{12,13} STM,¹⁴ DSC,¹¹ TGA,¹⁵ FTIR,¹¹ NMR,^{16–19} molecular dynamics,²⁰ and other techniques. The assembly is called a “*polypseudorotaxane*” (from the Latin words for “wheel” and “axle”). It is in equilibrium with the solution from which it emerges, so that dethreading of cyclodextrins from the assembly can occur.¹ When the two ends of the polymeric chains are linked to two hindering stoppers, such as dinitrobenzene or anthracene derivatives, the synthesis results in the formation of a so-called “*polyrotaxane*”.⁴ The cyclodextrins can no longer escape. The molecular wheels remain on their axles. If CDs are in excess with respect to their polymeric guest molecules, they will cover the whole stretched polymeric chain fully. Further chemical treatments can lead to “*molecular necklaces*” and “*molecular tubes*”. These last are then available as channels that can act as hosts for ionic or nonionic guests (e.g., I_3^- and caffeine, respectively).²¹ Cross-linking of sparsely covered polypseudorotaxanes by cyanuric chloride results in the formation of a topological gel that can entrap enormous amounts of water.²²

α -, β -, and γ -cyclodextrin are able to form these supramolecular nano-objects in water with almost any sort of polymer (alkanes,²³ ethers,²⁴ amines,²⁵ esters,^{18,26} siloxanes,^{27,28} and so on).²⁹ The kinetics and the yield of the process depend on the structure of the CDs, on the polymer, polymer molecular weight, temperature, solvent, and presence of other solutes in the solution. The reason for such intriguing phenomena has to reside in the basic interactions that occur between the reactants and between reactants and solution. It is well-known that cyclodex-

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trins, made up of glucose moieties linked through α -1,4 glycosidic bonds, possess an internal hydrophobic cavity and two hydrophilic rims. The larger rim is occupied by secondary -OH groups (linked to C₂ and C₃), whereas the narrower ring bears the primary hydroxyl groups in position 6 of the glucose ring. The presence of the hydrophobic cavity has always been considered as an appealing refuge for rather lipophilic molecules dissolved in aqueous media. Therefore, the driving force for the formation of host-guest inclusion compounds between cyclodextrins and (overall) hydrophobic entities is thought to be enthalpically not entropically driven. This is because, although the penetration of a long polymer into the host cavities should lead to a significant lowering in entropy, the large number of water molecules that are released in the external environment during the threading process largely compensates the entropic loss. More recent studies have confirmed that a "hydrophobic" effect is involved in the phenomenon, with a resulting negative change of heat capacity. A further stabilizing effect occurs because of hydrogen bonding between neighboring cyclodextrin rings. The optimal configuration is one that results in an orientation in a "head-to-head/tail-to-tail" fashion. A calculation of the energy for such an arrangement provides a value that is about 3.8 kJ/mol lower than the "head-to-tail" array.²⁰

Generally speaking, the threading of cyclic molecules onto a linear chain is a reversible process for which the equilibrium constant is the result of an enthalpy/entropy interplay:¹

$$\Delta G = \Delta H - T\Delta S = -RT \ln K_{\text{eq}}$$

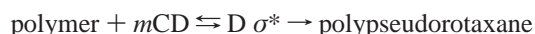
The host-guest formation process can then be envisaged as one of two extreme cases:

1. Statistical threading (typical of crown-ethers), in which a random collision and association of two cyclodextrins leads to the formation of the product, with an almost zero or positive enthalpy. It would then be an entropically driven process.¹

2. Template-directed threading. Here the association is energetically favored, due to specific, noncovalent interactions between the reactants. It has a negative enthalpic term. This kind of mechanism is typical of cyclodextrin-based threaded structures.¹

Kinetics of Threading. The time evolution of turbidity during the formation of the threaded structures, and their eventual precipitation, can be used to study the kinetics of threading. Typically, a plot of turbidity vs time can be divided into three regions (see Figure 1a). In the first region, absorbance does not change. Then it increases almost linearly. Finally, it approaches a more or less constant, asymptotic value. Some years ago, we developed a simple model that attempts to capture the kinetics of the process, an initial threading of CD molecules around the unfolding polymer ("threading time"), the growth of the such assembled structures (increment in turbidity), and final precipitation of the aggregates.^{30,31}

We depict the reaction as a pseudo-first-order process:



here σ^* represents the transition state of the process (rate step), which is not the same entity as the final polypseudorotaxane (abbreviated PPR), but it is rather the unstable intermediate structure that corresponds to the activation energy and evolves into the final product. Using a derivation borrowed from transition-state theory,³² we are able to calculate " m " and the Gibbs free energy of activation involved, ΔG^\ddagger , as fitting parameters of the measured threading time as a function of temperature. From " m " and ΔG^\ddagger , the enthalpic, entropic, and

TABLE 1: PEG₃₃₅₀ (1.094 mM) + α -CD (61.62 mM) in H₂O^a

<i>T</i> (K)	<i>t</i> _{th}	ΔG^\ddagger ($\pm 11\%$)	ΔH^\ddagger ($\pm 11\%$)	ΔS^\ddagger ($\pm 12\%$)	ΔC_p^\ddagger ($\pm 11\%$)	<i>m</i>
283.2	60	-54.0	-56.2	-7.8	-417.2	20
288.6	90	-54.0	-58.3	-15.1		
294.2	130	-54.1	-60.6	-22.2		
298.0	200	-53.7	-62.2	-28.6		
302.0	350	-53.0	-63.9	-36.1		
307.6	450	-53.3	-66.3	-42.3		
313.0	583	-53.5	-68.6	-48.4		

^a *T* in K, *t*_{th} in s, ΔG^\ddagger and ΔH^\ddagger in kJ/mol, ΔS^\ddagger and ΔC_p^\ddagger in J/(mol K).

ΔC_p^\ddagger parameters can then be extracted. The equations describing the processes are³¹

$$\frac{1}{t_{\text{th}}} = \frac{3k_{\text{B}}T}{2h} [\text{CD}]^m \exp\left(-\frac{\Delta G^\ddagger}{RT}\right)$$

$$\left[\frac{\partial(\Delta G^\ddagger/T)}{\partial T}\right] = -\frac{\Delta H^\ddagger}{T^2}$$

$$\Delta S^\ddagger = \frac{\Delta H^\ddagger - \Delta G^\ddagger}{T}$$

$$\Delta C_p^\ddagger = \left(\frac{\partial \Delta H^\ddagger}{\partial T}\right)_p$$

$$\ln K^\ddagger(T) = -\frac{\Delta G^\ddagger(T_0)}{RT_0} + \frac{\Delta H^\ddagger}{R} \left(\frac{1}{T_0} - \frac{1}{T}\right) - \frac{\Delta C_p^\ddagger}{R} \left[\left(1 - \frac{T}{T_0}\right) - \ln\left(\frac{T}{T_0}\right)\right]$$

Here *t*_{th}, *k*_B, *h*, [CD], and *K*[‡] are respectively the threading time at temperature *T*, the Boltzmann constant, the Planck constant, the concentration of CD, and the equilibrium constant, as defined in ref 33. *T*₀ is an arbitrarily chosen reference temperature, usually 298 K.³¹ The main assumption of the model is that the region of the turbidity plot with no change in absorbance is strictly related to the threading time. This means that no change in turbidity will be detected until aggregates reach the average size of $\lambda/20$ (λ being the incident wavelength at which the measurement is carried out), because of Rayleigh scattering. At the moment, we have no other experimental evidence to support this hypothesis. However, the agreement between the results obtained and other literature reports suggests the assumption is on firm ground. We have studied the PEG (MW = 3350)/ α -CD, the PPG(NH₂)₂ (MW = 2000)/ β -CD systems, and the PLURONIC₁₀₅ (MW = 6500)/ γ -CD and found the values for "*m*" and ΔG^\ddagger reported in Tables 1–9. This shows that the number of cyclodextrins threaded per single polymer chain, "*m*", depends mainly on the length of the polymer chain and only weakly on the solvent composition. The free energy of formation ΔG^\ddagger depends on the solvent in which the reaction is carried out.

Many questions are still open. For example, since the beginning of the study of PPR formation, a correct matching ratio between the internal cavity of CD and the cross-section of the polymer was indicated as the major determining parameter that allows the threading process to occur. However, this is not always the case.³⁴ Some kind of flexibility of the cyclodextrin rings has to be invoked. This seems reasonable. Molecular

TABLE 2: PEG₃₃₅₀ (1.094 mM) + α -CD (61.62 mM) in H₂O/D₂O 50%^a

T q(K)	<i>t</i> _{th}	ΔG^\ddagger ($\pm 8\%$)	ΔH^\ddagger ($\pm 8\%$)	ΔS^\ddagger ($\pm 10\%$)	ΔC_p^\ddagger ($\pm 8\%$)	<i>m</i>
284.8	60	-58.9	-50.8	28.4	-372.0	21
289.5	80	-59.1	-52.5	23.0		
294.2	110	-59.3	-54.2	17.4		
303.0	190	-59.6	-57.5	6.9		
305.6	280	-59.1	-58.5	2.0		
309.5	350	-59.2	-60.0	-2.4		

^a *T* in K, *t*_{th} in s, ΔG^\ddagger and ΔH^\ddagger in kJ/mol, ΔS^\ddagger and ΔC_p^\ddagger in J/(mol K).

TABLE 3: PEG₃₃₅₀ (1.094 mM) + α -CD (61.62 mM) in D₂O^a

<i>T</i> (K)	<i>t</i> _{th}	ΔG^\ddagger ($\pm 4\%$)	ΔH^\ddagger ($\pm 4\%$)	ΔS^\ddagger ($\pm 6\%$)	ΔC_p^\ddagger ($\pm 4\%$)	<i>m</i>
289.2	30	-70.8	-62.0	30.5	-444.8	22
294.1	50	-70.7	-64.1	22.4		
300.5	80	-71.0	-66.9	13.6		
305.5	120	-71.1	-69.2	6.4		
312.3	230	-71.0	-72.3	-4.2		

^a *T* in K, *t*_{th} in s, ΔG^\ddagger and ΔH^\ddagger in kJ/mol, ΔS^\ddagger and ΔC_p^\ddagger in J/(mol K).

TABLE 4: PEG₃₃₅₀ (1.094 mM) + α -CD (61.62 mM) in Urea 0.1 M^a

<i>T</i> (K)	<i>t</i> _{th}	ΔG^\ddagger ($\pm 7\%$)	ΔH^\ddagger ($\pm 7\%$)	ΔS^\ddagger ($\pm 8\%$)	ΔC_p^\ddagger ($\pm 7\%$)	<i>m</i>
282.8	740	-38.8	-35.7	11.1	-264.4	19
288.9	1030	-38.8	-37.2	5.5		
294.1	1350	-38.8	-38.6	0.8		
303.8	2180	-38.8	-41.2	-7.8		
309.2	2810	-38.8	-42.7	-12.5		

^a *T* in K, *t*_{th} in s, ΔG^\ddagger and ΔH^\ddagger in kJ/mol, ΔS^\ddagger and ΔC_p^\ddagger in J/(mol K).

TABLE 5: PPG₂₀₀₀(NH₂)₂ (0.075 mM) + β -CD (8.37 mM) in H₂O^a

<i>T</i> (K)	<i>t</i> _{th}	ΔG^\ddagger ($\pm 2\%$)	ΔH^\ddagger ($\pm 2\%$)	ΔS^\ddagger ($\pm 4\%$)	ΔC_p^\ddagger ($\pm 2\%$)	<i>m</i>
293.0	103	-104.4	-104.9	-1.6	-730.0	16
295.0	137	-104.4	-106.3	-6.4		
298.0	209	-104.4	-108.5	-13.8		
300.0	257	-104.3	-109.9	-18.7		
303.0	450	-104.3	-112.2	-26.0		

^a *T* in K, *t*_{th} in s, ΔG^\ddagger and ΔH^\ddagger in kJ/mol, ΔS^\ddagger and ΔC_p^\ddagger in J/(mol K).

TABLE 6: PPG₂₀₀₀(NH₂)₂ (0.075 mM) + β -CD (8.37 mM) in H₂O/D₂O 50%^a

<i>T</i> (K)	<i>t</i> _{th}	ΔG^\ddagger ($\pm 2\%$)	ΔH^\ddagger ($\pm 2\%$)	ΔS^\ddagger ($\pm 4\%$)	ΔC_p^\ddagger ($\pm 2\%$)	<i>m</i>
293.0	64	-93.7	-92.0	5.8	-640.0	15
295.0	88	-93.7	-93.2	1.5		
298.0	122	-93.7	-95.1	-4.9		
300.0	160	-93.7	-96.4	-9.2		
303.0	230	-93.6	-98.4	-15.7		

^a *T* in K, *t*_{th} in s, ΔG^\ddagger and ΔH^\ddagger in kJ/mol, ΔS^\ddagger and ΔC_p^\ddagger in J/(mol K).

dynamics simulation has shown that CD rings are quite flexible, even in the case of the supposedly rigid α -cyclodextrin.³⁵ If so, that evidence suggests that, once the polymer penetrates the hosting cavities, it may induce some kind of distortion in order to optimize interactions between hosts and guest. Moreover, it is known that cyclodextrins thread the polymer chain with a head-to-head/tail-to-tail arrangement. The mechanism through

TABLE 7: PPG₂₀₀₀(NH₂)₂ (0.075 mM) + β -CD (8.37 mM) in D₂O^a

<i>T</i> (K)	<i>t</i> _{th}	ΔG^\ddagger ($\pm 2\%$)	ΔH^\ddagger ($\pm 2\%$)	ΔS^\ddagger ($\pm 4\%$)	ΔC_p^\ddagger ($\pm 2\%$)	<i>m</i>
295.0	35	-131.5	-128.4	10.4	-880.0	18
298.0	50	-131.9	-131.1	2.9		
300.0	90	-131.3	-132.8	-4.9		
303.0	130	-131.7	-135.5	-12.5		

^a *T* in K, *t*_{th} in s, ΔG^\ddagger and ΔH^\ddagger in kJ/mol, ΔS^\ddagger and ΔC_p^\ddagger in J/(mol K).

TABLE 8: PPG₂₀₀₀(NH₂)₂ (0.075 mM) + β -CD (8.37 mM) in Urea 0.1 M^a

<i>T</i> (K)	<i>t</i> _{th}	ΔG^\ddagger ($\pm 2\%$)	ΔH^\ddagger ($\pm 2\%$)	ΔS^\ddagger ($\pm 4\%$)	ΔC_p^\ddagger ($\pm 2\%$)	<i>m</i>
293.0	1180	-98.5	-91.7	23.1	-640.0	16
295.0	1600	-98.5	-93.0	18.8		
298.0	2179	-98.5	-95.0	12.4		
300.0	2910	-98.6	-96.1	8.1		
303.0	4200	-98.6	-98.1	1.7		

^a *T* in K, *t*_{th} in s, ΔG^\ddagger and ΔH^\ddagger in kJ/mol, ΔS^\ddagger and ΔC_p^\ddagger in J/(mol K).

TABLE 9: PLU₁₀₅ (0.146 mM) + γ -CD (19.4) in H₂O^a

<i>T</i> (K)	<i>t</i> _{th}	ΔG^\ddagger ($\pm 2\%$)	ΔH^\ddagger ($\pm 2\%$)	ΔS^\ddagger ($\pm 4\%$)	ΔC_p^\ddagger ($\pm 2\%$)	<i>m</i>
293.0	38	-101.8	-108.5	-22.8	-770.0	19
298.0	60	-101.7	-112.2	-35.4		
303.0	112	-101.4	-116.0	-48.1		
308.0	240	-101.2	-119.9	-60.7		
313.0	498	-100.8	-123.8	-73.4		

^a *T* in K, *t*_{th} in s, ΔG^\ddagger and ΔH^\ddagger in kJ/mol, ΔS^\ddagger and ΔC_p^\ddagger in J/(mol K).

which this highly ordered structure gets organized is still obscure and requires further investigation.

Salts and Solutes Effects. The effects of salts on the threading phenomenon have recently been studied.³⁶ These showed that the ion pairs strongly affect the kinetics of such process: for example, the presence of Na₂SO₄ and NaCl in the solvent medium results in slower threading, whereas NaI or NaSCN work in the opposite way, following a Hofmeister series.^{37–39} The result indicates that solvent structure has a strong influence on the phenomenon.^{40,41} In fact, different ion pairs interact with the solutes and experience different adsorption potentials because of dispersion forces.^{42–47} Furthermore, they change the properties of the solvent itself. This is confirmed by the correlation between the threading time and some other physicochemical parameters, such as the molal surface tension increment, the Gibbs free energy of hydration, polarizability, and molar refractivity.³⁶

Similar effects on the threading action are induced by nonionic solutes. In previous papers, we have checked the effect of heavy water and urea on the solvent^{30,31} and, in this work, that of sugars. These solutes modify the structure of water significantly. In conventional language, they do so either by “strengthening” (D₂O or sugars) or “softening” (urea) the hydrogen bonding network that links the solvent molecules.⁴⁸

In the conventional characterization of the Hofmeister series, salts are classified into two categories as “kosmotropic” versus “chaotropic”.⁴⁹ Recent theoretical progress confirmed by experiments casts the whole Hofmeister series phenomena in a new light. The mechanism that drives it can be traced to a basic flaw in the theory of molecular forces. It is related to the previously neglected dispersion forces acting between ions and solutes that the ions experience and their effect on bulk solution

structure. These ultimately depend on the polarizability and, therefore, on the electronic structure of the charged (ions) or uncharged entities.^{39,42,43}

From this perspective, the study of PPRs becomes an interesting tool for a better understanding of solute induced solvent properties.

When the formation of the PPRs was performed in pure deuterium oxide rather than in water, a sharp decrease in the threading time was observed. By contrast, the addition of urea (0.1 M in water) leads to much longer threading times and inhibits the formation of the inclusion compounds, as expected for urea molecules that directly interact with cyclodextrins and polymer.^{50,51} This effect was tested with both PEG₃₃₅₀ and α -CD or with PPG₂₀₀₀(NH₂)₂ and β -CD.

The temperature effect shows that a temperature lowering enhances formation rates, whereas the process slows down when the reactants are heated. Again this observation indicates that the hydrogen bonding network is directly involved in the kinetics of threading.³¹

Diffusion of the reactants in the solvent is not a major factor. If that were so, the opposite trend should be recorded (higher temperature, lower viscosity, faster diffusion).

Sugars and Urea. We have rehearsed the situation in some detail before coming to and making sense of new results. In what follows, we report a study of PPR formation by α -CD and either PEG8000 or DMPG2000.

We have evaluated (1) the effect of the molecular weight and of the polar end groups (protic –OH in PEG, and aprotic –OCH₃ in DMPG); (2) the effect of different sugars (D-sucrose, D-glucose, D-fructose, D-ribose, D-deoxy-ribose, L-glucose) and urea, as well as some salts; (3) the effect of α -CD concentration and that of surfaces on formation.

The results seem to confirm the kinetic model outlined above. They support the hypothesis of a preassembled, wormlike, linear set of CDs in solution that can be threaded by the polymer. The cooperative threading phenomenon can then be envisaged as an “all at once” process rather than one composed from a sequential mechanism where CD molecules interact with the guest chain one at the time.

Materials and Methods

α -CD, D-sucrose, D-glucose, D-fructose, D-ribose, D-deoxy-ribose, L-glucose, urea, sodium thiocyanate, sodium chloride, sodium acetate, PEG₈₀₀₀, and DMPG₂₀₀₀ were purchased from Fluka (Milan, Italy). All chemicals were used as received.

For all experiments, we used bidistilled water purified with a MilliQ system (Millipore) to remove colloidal impurities.

UV spectra were recorded with a Lambda 5 spectrophotometer (Perkin-Elmer), using a thermostated bath to control the temperature of a Hellma quartz cell ($\pm 0.1^\circ$ C). The temperature effect was investigated in the 15–40° C range.

Fixed volumes of the guest and of the host water solutions were gently mixed in the cell, and the absorbance measurement (at $\lambda = 400$ nm) was started immediately after, until a thick solid, white gel was formed. The reference sample was pure water.

Results and Discussion

Kinetics Calculations. Figure 1a shows a typical turbidity plot that accompanies the formation of a polypseudorotaxane. The arrow in the inset (time axis in logarithmic scale) indicates the “threading time”. The measured threading times (t_{th}), the thermodynamic parameters (ΔG^\ddagger , ΔH^\ddagger , ΔS^\ddagger , ΔC_p^\ddagger), and the

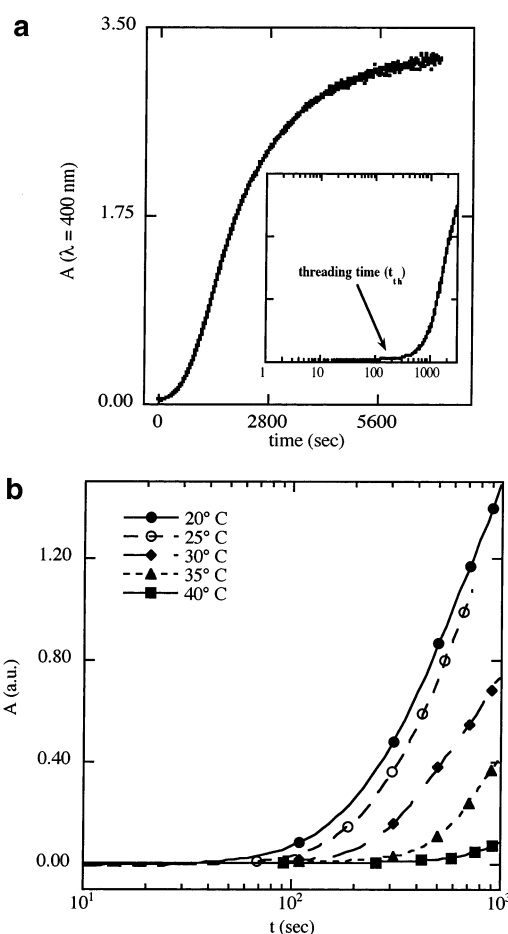


Figure 1. a: Turbidity plot at $\lambda = 400$ nm during the formation and precipitation of a PPR. The inset shows the time axis in logarithmic scale to show the extent of the threading time (t_{th}) indicated by the arrow. b: Turbidity plots as a function of temperature.

TABLE 10: PEG₈₀₀₀ (0.79 mM) + α -CD (88.2 mM) in H₂O^a

<i>T</i> (K)	<i>t</i> _{th}	ΔG^\ddagger ($\pm 8\%$)	ΔH^\ddagger ($\pm 8\%$)	ΔS^\ddagger ($\pm 8\%$)	ΔC_p^\ddagger ($\pm 8\%$)	<i>m</i>
288.0	6	−101.5	−94.7	23.6	−686.1	31
293.0	11	−101.8	−98.0	13.0		
298.0	24	−101.5	−101.4	0.5		
303.0	48	−101.5	−104.8	−11.0		
308.0	89	−101.5	−108.3	−21.9		
313.0	167	−101.5	−111.8	−33.0		

^a *T* in K, *t*_{th} in s, ΔG^\ddagger and ΔH^\ddagger in kJ/mol, ΔS^\ddagger and ΔC_p^\ddagger in J/(mol K).

TABLE 11: DMPG₂₀₀₀ (1.67 mM) + α -CD (49 mM) in H₂O^a

<i>T</i> (K)	<i>t</i> _{th}	ΔG^\ddagger ($\pm 4\%$)	ΔH^\ddagger ($\pm 4\%$)	ΔS^\ddagger ($\pm 5\%$)	ΔC_p^\ddagger ($\pm 4\%$)	<i>m</i>
288.0	30	−45.9	−41.9	14.1	−303.3	15
293.0	39	−46.0	−43.3	9.2		
298.0	53	−46.0	−44.8	4.0		
303.0	70	−46.0	−46.3	−0.97		
308.0	96	−45.9	−47.9	−6.3		
313.0	123	−46.0	−49.4	−11.0		

^a *T* in K, *t*_{th} in s, ΔG^\ddagger and ΔH^\ddagger in kJ/mol, ΔS^\ddagger and ΔC_p^\ddagger in J/(mol K).

fit parameter “*m*” for the number of beads extracted from experiments on PEG8000/ α -CD and DMPG2000/ α -CD are listed in Tables 10 and 11 as a function of temperature. Figure 1b shows the temperature dependence, with an increment in *t*_{th}

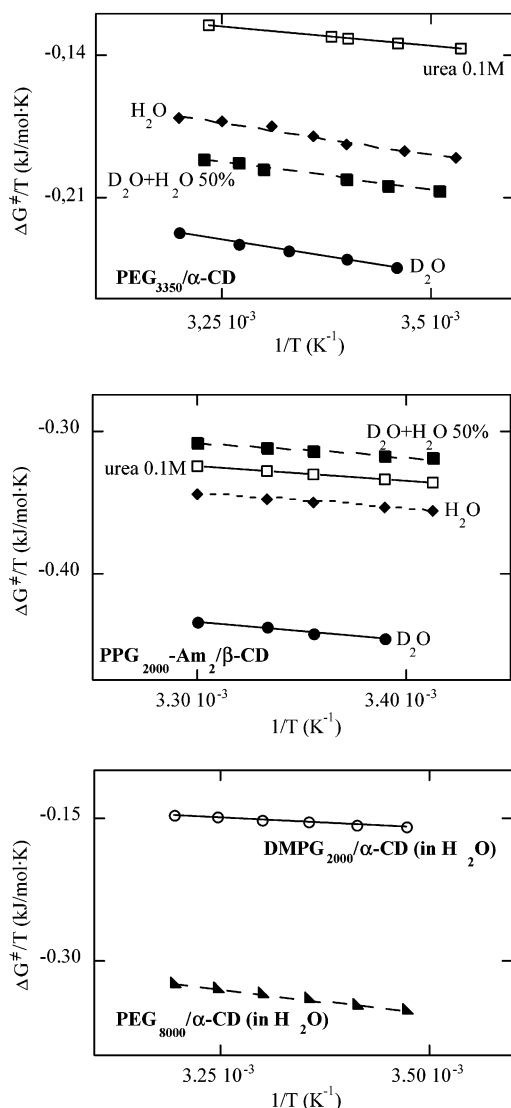


Figure 2. Arrhenius plots ($\Delta G^\ddagger/T$ vs. $1/T$) for PEG₃₃₅₀/α-CD in H₂O (●), D₂O (○), H₂O+D₂O 50% (■), and urea 0.1 M (□) (a); PPG₂₀₀₀-(NH₂)₂/β-CD in H₂O (●), D₂O (○), H₂O+D₂O 50% (■), and urea 0.1 M (□) (b); DMPG₂₀₀₀/α-CD (○) and PEG₈₀₀₀/α-CD (solid slanted triangle) in water (c).

as T increases. Figure 2, parts a–c, shows an Arrhenius plot of $\Delta G^\ddagger/T$ vs $1/T$ for the formation of polypseudorotaxanes from PEG₃₃₅₀/α-CD, PPG₂₀₀₀/β-CD, DMPG₂₀₀₀/α-CD, and PEG₈₀₀₀/α-CD in different solvents. Comparison with previously obtained data on similar systems (Tables 1–9)^{21,30,31} shows the following:

1. The threading process is indeed driven by enthalpic terms. The entropy change of formation, ΔS^\ddagger , is small for all cases and usually negative. The bead number “ m ” changes with molecular weight of the polymer, between 15 and 31, and only slightly with a change in solvent (higher for D₂O, lower for urea).

2. The heat capacity change related to the threading reaction is always negative, as is to be expected for events where hydrophobic effects are involved.³³

3. As the process is driven by hydrophobic interactions, ΔG^\ddagger reaches its maximum for the shorter and more hydrophilic polymers, whereas it reaches its minimum for the longer (PEG₈₀₀₀) and more hydrophobic (PPG₂₀₀₀ and PLU₁₀₅) guests. The same trend is shown by ΔH^\ddagger , ΔS^\ddagger , and ΔC_p^\ddagger .

4. In all cases, ΔH^\ddagger and ΔS^\ddagger decrease with T . Although these two thermodynamic quantities balance and produce little change

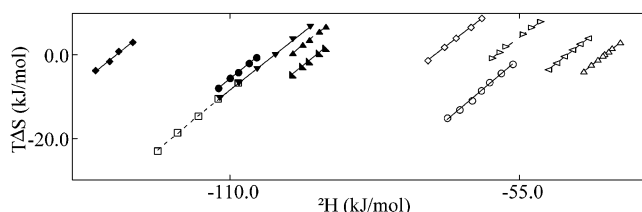


Figure 3. $T\Delta S$ vs ΔH plots for PPG₂₀₀₀/β-CD in H₂O (●); PPG₂₀₀₀/β-CD in D₂O+H₂O 50% (solid slanted triangle); PPG₂₀₀₀/β-CD in D₂O (◆); PPG₂₀₀₀/β-CD in urea 0.1M (▲); PLU₁₀₅/γ-CD in H₂O (□); PEG₃₃₅₀/α-CD in H₂O (○); PEG₃₃₅₀/α-CD in D₂O+H₂O 50% (triangle pointing right); PEG₃₃₅₀/α-CD in D₂O (◇); PEG₃₃₅₀/α-CD in urea 0.1M (Δ); DMPG₂₀₀₀/α-CD in H₂O (triangle pointing left); and PEG₈₀₀₀/α-CD in H₂O (▼).

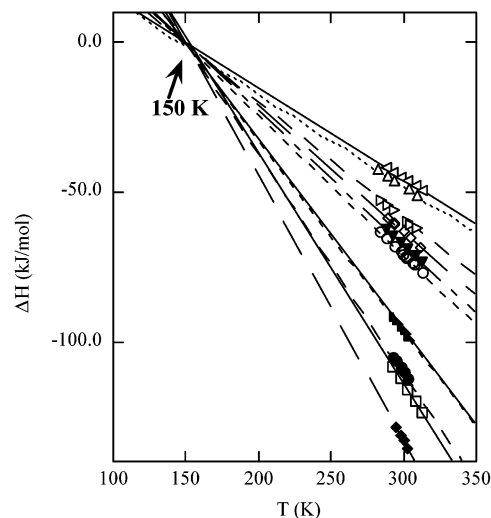


Figure 4. ΔH vs T plot for PPG₂₀₀₀/β-CD in H₂O (●); PPG₂₀₀₀/β-CD in D₂O+H₂O 50% (solid slanted triangle); PPG₂₀₀₀/β-CD in D₂O (◆); PPG₂₀₀₀/β-CD in urea 0.1M (▲); PLU₁₀₅/γ-CD in H₂O (□); PEG₃₃₅₀/α-CD in H₂O (○); PEG₃₃₅₀/α-CD in D₂O+H₂O 50% (triangle pointing right); PEG₃₃₅₀/α-CD in D₂O (◇); PEG₃₃₅₀/α-CD in urea 0.1M (Δ); DMPG₂₀₀₀/α-CD in H₂O (triangle pointing left); and PEG₈₀₀₀/α-CD in H₂O (▼).

in ΔG^\ddagger , the negative ΔC_p^\ddagger values indicate an enthalpy/entropy compensation, as the plot shown in Figure 3 confirms. The graph of $T\Delta S^\ddagger$ versus ΔH^\ddagger shows straight lines that have a slope between 0.96 and 1.06.⁵²

5. It is of interest to note that in a plot of ΔH^\ddagger versus T all points fall on straight lines that intersect at about 150 K (see Figure 4). This is typical behavior that confirms earlier observations of Ross and Rekharsky.³³

Surface Effects. A curious observation is the following. When the threading reaction is carried out in a plastic cuvette (polycarbonate), we observed a slight but significant increase in the threading time. There is also a lowering in the slope of the turbidity/time linear region of the plot (see Figure 5). This means that the threading phenomenon and the aggregation and growth of polyrotaxane assemblies are influenced by the solution–cuvette interface. This finding makes sense. It appears to indicate that the segment of the plot in which no change in absorbance occurs is indeed related to the threading process. This occurs between the aggregating moieties dissolved in the solution. However, the aggregation and precipitation of the PPRs (with hydrophilic external surface) should be inhibited by the presence of a more hydrophobic surface. This is consistent with some seemingly strange results of Tait and Davies. They reported that scratching the cuvette surface with a glass rod or seeding the solution with some previously produced crystals of

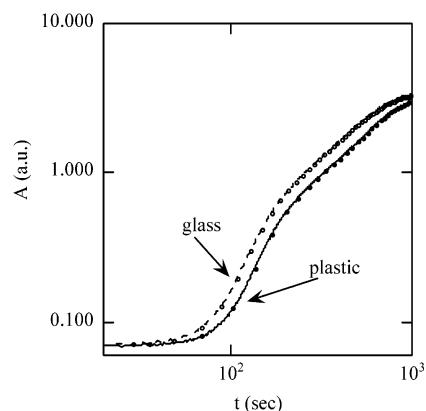
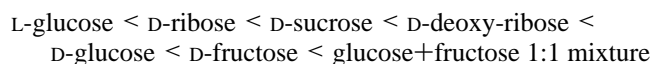


Figure 5. Turbidity plot for the formation of DMPG₂₀₀₀/α-CD PPRs in a glass and in a plastic cuvette; [DMPG₂₀₀₀] = 4.76 μM, [α-CD] = 40 mM.

PPRs resulted in a much faster precipitation of assemblies of PPRs.⁵³ Taken together these findings support the notion that the nucleation, growth, and separation of the large adducts are mediated by surface adsorption.

Solvent Structure. *Effects of Sugars and Urea.* We have further explored the effect of a variety of sugars and of urea. Sugars are known to act as “structure makers”, whereas urea is a “structure breaker” for water and it is known to interact directly at the surface of dispersed system as micelles.^{50,51} The effect of hydrotropic molecules, i.e., species that modify the structure of water, on the inclusion properties of cyclodextrins has been studied previously.⁵⁴ We used D-sucrose, D-glucose, D-fructose, D-ribose, D-deoxyribose, L-glucose, and urea as added solutes to the aqueous medium, and performed the same experiment at constant temperature. Sugar and urea concentrations range between 10⁻⁴ and 2.5 M. Figure 6 shows the dependence of the threading time of DMPG₂₀₀₀/α-CD on sugar structure and concentration.

The more concentrated the sugar solution, above 30 mM, the faster is the threading process. For $c > 1$ M, the threading time does not decrease any more. Quantitatively, the different solutes behave differently, with the threading time decreasing in the order



The same specificity occurs with bubble–bubble interactions, cloud point phenomena, and surfactant self-assembly. The same behavior and trends mimic the same specific ion effects of salts. For our case, the phenomena can be ascribed to the different bulk solvent structure induced by the solutes, be they sugars or salts.^{55–59} At 1 M concentration, the distance between two sugar molecules is about 11 Å so that it would be surprising if there were not some dramatic effects on water structure as a result.

It is of much interest to note that the two optical isomers of glucose produce different data. The results suggest that the threading time is a sensitive parameter that reflects the global structure of solution hydrogen bonding network and chirality, in the sense that chiral discrimination seems to be active during the threading process. The hydrogen bonding network is apparently strengthened by sugars or D₂O, softened by urea, and different ion pairs produce opposing or reinforcing effects. The sugar effects parallel those obtained previously on the effect of heavy water and urea on the kinetics of formation of PPRs.^{21,30,31} In those earlier studies, we found that ΔG^\ddagger reaches its minimum and maximum with D₂O and urea (see parts a and

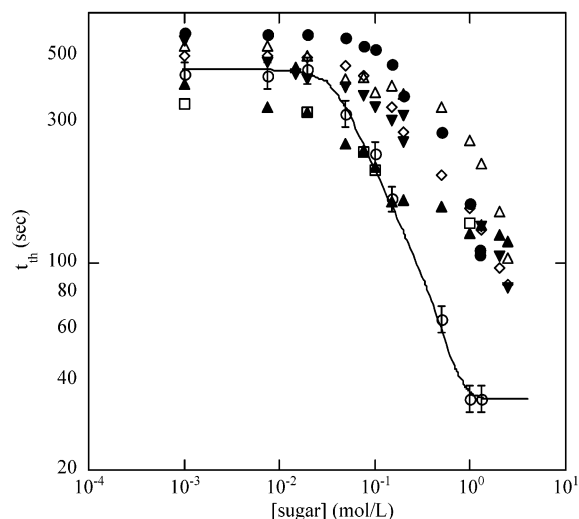


Figure 6. t_{th} as a function of sugar concentration at 25 °C for DMPG₂₀₀₀/α-CD; [DMPG₂₀₀₀] = 4.76 μM, [α-CD] = 40 mM. D-sucrose (○); D-glucose (◇); L-glucose (□); D-fructose (△); D-glucose/D-fructose 1:1 mixture (●); D-ribose (▲); D-deoxy-ribose (▼).

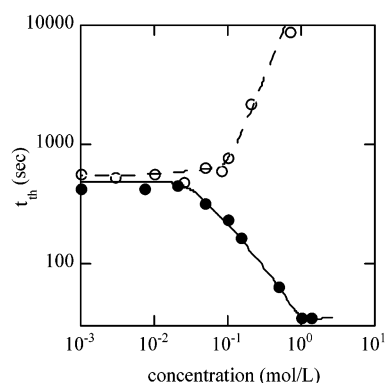


Figure 7. t_{th} at 25 °C for DMPG₂₀₀₀/α-CD in the presence of D-sucrose (●), and urea (○). [DMPG₂₀₀₀] = 4.76 μM, [α-CD] = 40 mM.

b of Figure 2, respectively). This feature reflects the water structure change induced by these solutes.^{60,61} It is interesting to note at this point that sucrose, made up of glucose and fructose moieties bound through a glycosidic linkage, has a larger effect than the two separated parent molecules, as for bubble–bubble interactions. Presumably, this is because sucrose produces a stronger ordering effect on water structure.⁵⁹

We note that the threading time decreases as the concentration of the sugar increases. This is strong evidence that (1) the threading phenomenon is not connected with the increase in viscosity of the medium and (2) the threading process is clearly strongly related to the hydrogen bonding network of the solution, which depends dramatically on the specific sugar isomer and on specific chiral discrimination with cyclodextrins as highlighted by the different behavior of L-glucose and D-glucose.

Figure 7 shows that urea greatly increases the threading time. The opposite behavior of urea with respect to sugars confirms that these solutes operate on the threading process by interacting directly with cyclodextrin/polymer and by destroying the hydrogen bonding network.^{50,51}

Salts and Hofmeister Effects. Although not the main focus of this study, we report some preliminary results on salt dependence of the threading time. Figure 8 shows the threading time as a function of aqueous salt concentration for thiocyanate, chloride, and acetate at room temperature. The differences induced by the different anions differ by a factor of 100 over

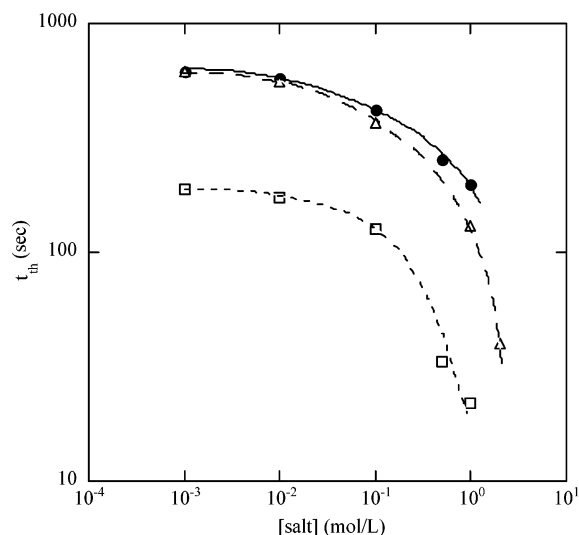


Figure 8. t_{th} at 25° C for DMPG₂₀₀₀/α-CD as a function of salt concentration for thiocyanate (●), chloride (□), and acetate (Δ).

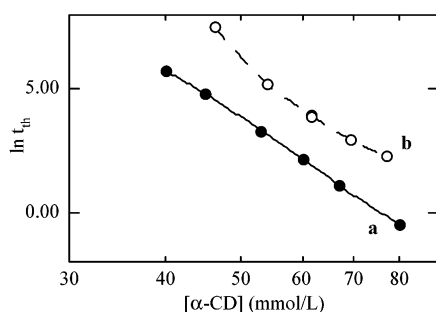


Figure 9. t_{th} as a function of α-cyclodextrin concentration at 25 °C. a: [DMPG₂₀₀₀] = 4.76 mM; b: [PEG₃₃₅₀] = 0.11 mM.

the range 10^{-3} to 0.1 M with effectiveness of $\text{CH}_3\text{COO}^- > \text{Cl}^- > \text{SCN}^-$. Note that this is the reverse of the sequence we obtained in a previous study with a less hydrophobic polymer.³⁶ This fact implicates specific anion adsorption by the polymer as the adsorption potential depends strongly and delicately on the frequency dependent dielectric properties of the polymer substrate. It is consistent with expectations from other recent works on Hofmeister effect.^{43–47,62}

Concentration Effect. The concentration of α-CD seems to be a crucial parameter for the threading process. Figure 9 shows t_{th} as a function of [α-CD] at 25° C for DMPG₂₀₀₀/α-CD (curve a) and PEG₃₃₅₀/α-CD (curve b). PPRs form instantly when [α-CD] is between 90 and 140 mM (saturation at about 150 mM). The threading time t_{th} increases at lower concentrations, and below 40 mM, we were not able to detect any turbidity increment within 3 h. This result probably indicates that below 40 mM the PPRs formed do not precipitate but are in equilibrium with free polymer and α-cyclodextrin.

Summary. In this paper, we have reported studies on the formation of polypseudorotaxanes (PPRs) from aqueous solutions of α-cyclodextrin (α-CD) and of polymers. These include effects induced by temperature, surface nature, and solution composition. We have compared them with previous measurements carried out on different host/guest pairs, in different solvents, and in the presence of various salts.

A kinetic model allows calculation of the number of participating CD hosts per polymer chain in the formation of the activated complex that precedes the formation and precipitation of the PPR. Further, it allows estimates of the activation

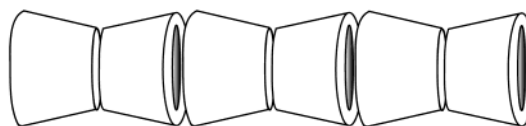


Figure 10. Schematic picture of a wormlike self-assembled aggregate of cyclodextrin (“poly-CD”).

parameters such as ΔG^\ddagger , HS^\ddagger , ΔS^\ddagger , and ΔC_p^\ddagger that are related to the formation process.

What emerges is the following:

(a) The threading phenomenon is driven by enthalpic interactions between the participating species.

(b) The process is significantly affected by subtle change induced in the solvent (solution) composition by the addition of either neutral (D_2O , urea, and sugars) or ionic species that modify the hydrogen bonding network and probably by adsorption of solutes at the polymer and/or cyclodextrin surface.

(c) The surface hydrophobicity of the reactant vessel affects the kinetics and precipitation of the supramolecular aggregates, again apparently through adsorption of solutes. This role for the surface is yet to be elucidated. A role for the surface seems implied to in the work of Antonietti on cyclodextrin self-assembly in polymer/water mixtures.⁶³

(d) A crucial factor in the formation of polypseudorotaxanes is the initial available concentration of host rings.

Taking all of the experimental evidence together, we can suppose that during the formation of the threaded polypseudorotaxane the linear polymer chain reacts with a preassembled, wormlike aggregate made up of several aligned cyclodextrins (see Figure 10), which we might call “poly-CD”. These are held together by intermolecular hydrogen bonds and by intermediate, bridging water molecules.

With such a hypothesis, the effect of sugars, urea, heavy water, salts, α-CD concentration, and temperature all fit together. In conventional language, sugars, D_2O , low temperatures, and kosmotropic salts increase the order of water structure, by “strengthening” the hydrogen bonding network, and therefore stabilize the supposed “poly-CD” structure. This can interact more readily with the polymer to produce the PPR. On the other hand, urea “softens” hydrogen bonds and directly interacts with solute molecules making the threading phenomenon more difficult. Moreover, in kinetic studies, we always detect a value for the number “ m ” of associated molecules of CD of around 15–22 molecules. These participate with a single polymeric chain in the transition state that leads to the formation of the PPR. This finding supports the presence of poly-CD “trains” and provides a reasonable number for its aggregation number, about 15–30 monomers, corresponding to about 12–24 nm length. The time ranges in which the phenomenon occurs and the strictly ordered “head-to-head/tail-to-tail” arrangement of the threaded CD rings cannot reasonably be expected if cyclodextrins were to thread the polymer one at the time and under random statistical control.

The existence of a poly-CD linear structure has already been proposed in previous work, since 1992. Coleman et al. found evidence for the aggregation of cyclodextrins in water from light-scattering and solubility measurements and concluded that α-, β-, and γ-CD form rodlike aggregates held together by intermolecular hydrogen bonding and bridging water.⁶⁴ Tchoreloff et al. suggested that the different symmetry of cyclodextrins is the key factor in determining their interactions with water and, therefore, their solubility.⁶⁵ Häusler and Müller-Goymann found that concentrated solutions of hydroxypropyl-β-CD in water have large viscosity values, have a decrease in freezable

water, and show the presence of micellar-like aggregates of about 15–25 nm through freeze fracture experiments. Furthermore, the addition of “structure-breakers” such as urea and potassium thiocyanate, result in the loss of these features and, more significantly, in failure to form inclusion compounds.⁶⁶ Some years ago, Polarz et al. found that cyclodextrins can act as templates for the production of mesoscopic silica gels. They supposed that to do so CDs alone must aggregate in solution and form wormlike objects by arranging the rings in the “head-to-head/tail-to-tail” configuration.⁶³ The reason for such behavior could be found in the hydrogen bonds between the rims in adjacent rings and in a sort of bridging architecture provided by water molecules, that would ensure stabilization for such assemblies in aqueous solutions.

If this likely scenario is so, it provides important features that account for the formation of polypseudorotaxanes, i.e., the presence of micellar-like linear assemblies of cyclodextrins in water. In fact, if the cyclodextrin rings preaggregate in solution (above a certain critical aggregation concentration) by virtue of their hydrogen bonding interactions and form what we might call a noncovalently bound “poly-CD”, then this structure would be a perfect ideal host for the linear polymer.

Conclusions

We have studied the formation and properties of polypseudorotaxanes (PPRs) formed through the inclusion process of polyethylene-glycols (PEG₈₀₀₀ and DMPG₂₀₀₀) in the free hydrophobic cavities of α -cyclodextrin (α -CD). The threading process was studied as a function of temperature, α -CD concentration, cosolutes, and surface effects induced by the cell walls. To find a reasonable explanation for all our findings, we suggest that α -CD rings form wormlike aggregates (“poly-CD”) in water solutions. This hypothesis, also supported by some previous experimental evidence, is consistent with the following observations:

1. The threading phenomenon is relatively fast at least below 25 °C (less than 3 min in water).
2. For dimethylpoly(ethylene glycol) (DMPG₂₀₀₀) and α -CD, the PPR precipitation does not occur at room temperature if the concentration of the host is equal to or lower than 40 mM. This would indicate the existence of a concentration threshold for preaggregate formation before threading can occur, much like a critical aggregation concentration.
3. The threading phenomenon does not depend on solvent viscosity (i.e., it is not driven by brownian diffusion rates) as the effects of sugars and temperature show.
4. The threading phenomenon depends strongly on the solvent hydrogen bonding network (as shown by effects of sugars, heavy water, urea, salts, and temperature)
5. This “poly-CD” template would present already setup cyclodextrin rings in the correct “head-to-head/tail-to-tail” arrangement that is found in the final polypseudorotaxanes.
6. In the kinetic model for characterization of polypseudorotaxanes formation from different polymers and cyclodextrins, the number of CDs that take part in the formation of the transition state is in the range 15–30 monomers. Considering that the depth of a single cyclodextrin is about 7.8 Å, we can calculate that the length of this self-assembled poly-CD is about 12–24 nm. That is close to the value of 15–25 nm already reported in the literature.⁶⁶

If this hypothesis is invalid, we would have to find other reasons to explain all these observations, especially the last. It is unlikely that the correct “head-to-head/tail-to-tail” arrange-

ment is created in a random statistical way, considering the effective relatively short threading times.

Perhaps the most interesting observation germane to our thesis that emerges is this. We are used to words, anthropomorphic in origin, like hydrophobic, lipophilic, hydrophilic, and others like hydrogen or ionic or van der Waals bonds. Any notions we have of water structure are ill defined and generally supposed to be very short ranged interactions. However, cooperativity is apparent in PPR formation as a function of solution and solution conditions. It is hard to see cooperativity emerging from short ranged weak interactions. The words to describe the weak noncovalent driving forces are inadequate and reflect our ignorance of aqueous solutions and water. Nor do we make any apology for using such words. However, the emerging intuition from these experiments and those parallel on bubble interactions and all those others cited in the text on other phenomena that bear on “water structure”, like laser cavitation, cloud points, etc. point to something else involved. Thus, much more cooperative and long ranged. It may be that a better way to think on these things is via the solid state. The transition from martensite to austenite in steel takes place at the speed of sound. Negligible energy is involved. All atoms of the lattice move together a very small amount by the so-called Bonnet transformation.⁶⁷ Then again, if such a harmonic lattice of vibrating atoms contains even isotopic impurities of different mass, it is well-known that the impurities attract each other and undergo a microphase separation. If then we imagine water as a random connected average harmonic lattice, cyclodextrins with their –OH bonds behave like impurities and must attract each other and microphase separate by a similar mechanism. Likewise a solution of sugar molecules, compatible with water, behaves like an alloy. In such a system, the collective modes of the solution are different to those of pure water. We can then expect that the microphase separation leading to assembled poly-CD precursors will have different strength and intensity. So too for salts which induce defects in the “lattice”, urea, and other solutes. The evidence for D₂O already confirms such a proposition. The point then is that one ought properly to view the processes of self-assembly differently, for they are weak but long ranged. That may be important for progress in understanding supra-self-assembly generally. Thus, at least cyclodextrins seem an interesting tool to explore such matters further.

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