



Selective assembly of cyclodextrins on poly(ethylene oxide)–poly(propylene oxide) block copolymers

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Summary

This paper presents a computational study on the formation of a molecular necklace formed by specific threading of cyclodextrins (CDs) on block copolymers. Structural as well as energetic principles for the selective complexation of α - and β -cyclodextrin with poly(ethylene oxide)–poly(propylene oxide) block copolymers (PEO–PPO) are elucidated considering a diblock copolymer of equimolecular composition (PEO)₄–(PPO)₄ as guest. A non-statistical distribution of CDs, i.e. α -CDs primarily located on the PEO chain and β -CDs on PPO blocks of the polymer, is based on a variety of structural features and energetic preferences considering both potential as well as solvation energies. This selectivity becomes already obvious considering 1:1 complexes between PEO and PPO monomers and the two CDs, but is increasingly evident when calculating higher order ensembles. Besides the host–guest interaction, docking between CDs themselves is an important, also non-statistical, prerequisite for the self-assembly of highly ordered tubes. The formation of intermolecular hydrogen bonds between adjacent CDs in a tubular aggregate gives an important contribution to the overall stability of the molecular necklace. The net effect, based on the preferential interaction between host and guest as well as between the host molecules themselves, results in the formation of a stable, highly ordered macromolecular, multicomponent aggregate.

Introduction

Molecular self-assembly is a fundamental concept for the spontaneous formation of a supramolecular architecture with well-defined structure and functionality [1,2]. Most prominent examples like protein aggregates or membranes are found in biochemistry, but a variety of artificial macromolecular self-assembled structures have been reported recently [3–7].

Complexes of organic compounds with cyclodextrins (CDs) are well-suited models to study general questions in the process of molecular self-assembly. CDs are cyclic oligosaccharides consisting of 6 (α -), 7 (β -) or 8 (γ -CD) D-(+)-glucopyranose units linked by α -(1,4) bonds [8]. This configuration relaxes in

a truncated cone-like structure with a hydrophobic inner cavity of 4–8 Å diameter. The overall conformation is stabilized by intramolecular hydrogen bonds formed between adjacent hydroxyl groups located mainly on the secondary hydroxylic rim of the macrocycle [9,10].

A variety of hydrophobic molecules can be complexed by the CD cavity, leading to widespread applications in basic [11,12] as well as applied research [8,13,14]. Although 1:1 complexes of guest and host molecule have long been proposed as the most common type of cyclodextrin inclusion complexes, the formation of higher order structures (e.g. possessing a 1:2 stoichiometry between dimethoxy-phenols and α -CD [15] or between C₆₀ fullerene and γ -CD [16], as well as 2:2 complexes of α -tertiophene and γ -CD [17]) has been reported. Even higher order, tubular assemblies

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are described, for example by Harada et al. [18,19], who report the formation of CD nanotubes, where the individual CD molecules are threaded on polyethylene glycol (PEG) forming a ‘molecular necklace’.

The study of molecular complexation by cyclodextrins facilitates insight into the basic physicochemical mechanisms underlying the process of molecular recognition and self-assembly. Questions addressing the nature of the driving forces of aggregate formation, the specific molecular recognition sites on the substrate molecules, and the structural and dynamic properties of the resulting aggregates can be raised. A recent review [20] gives an overview of theoretical studies on the structure and energetics of various CD complexes, and a summary on experimental data is given in References 8 and 12.

In the light of these issues, we present a computational study on the site-selective threading of α - and β -CD on poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) chains. Recent experimental investigations by IR spectroscopy and X-ray diffraction on the complexation of α - and β -CDs with PEO–PPO diblock copolymers, compared to the complexation reaction on the respective homopolymers, indicate that non-statistical complexation yields α -CDs threaded preferentially on PEO and β -CDs on PPO subunits of the polymer [21,22]. This site-specific threading of the macrocycles results in the formation of molecular necklaces with several CD molecules selectively arranged on the two different polymer chains. Novel structures built up of rigid blocks of molecular necklaces as well as flexible chains of uncomplexed polymer are obtained.

We present structural and energetic causes for this non-statistical distribution of the CDs on the PEO–PPO block copolymer. We show how the highly ordered necklace emerges from intermolecular interactions between CDs and PEO/PPO polymers, which are mainly diffuse, electrostatic interactions and van der Waals forces, and the contributions from solvation. Individual energetic contributions arising from the interaction between CD host and polymeric guest molecules are analysed and the sensitive dependence of the self-assembling of an ordered CD tube on the steric properties of the polymer segment, on which it is threaded, is shown.

Method of calculation

All calculations are based on Allinger’s MM3-92 force field applying a block diagonal matrix minimization method [23]. The fully minimized reference structures of α -CD and β -CD, derived from crystallographic data [9,10], have energies of 257.1 kJ/mol and 298.0 kJ/mol, respectively. The potential energies of the monomeric guest units PEO and PPO result as 24.7 kJ/mol and 39.0 kJ/mol. All calculations are started from these reference structures.

Low-energy complex geometries are located by a dynamic Monte Carlo (DMC) routine [24,25] within the program package MultiMize [26]. Both potential energies (calculated by the force field) and solvation effects (calculated by a continuum approximation assigning atomic solvation parameters σ_j to the solvent-accessible molecular surface area A_j) are considered in a modified Metropolis criterion. Details on the algorithm are presented in Reference 27. This method, combining potential energies and free energies of solvation in a cominimization, proved to provide valuable structural results for cyclodextrin complexes in aqueous environment [15,16,27] as well as for structural properties of peptides [28]. It has been demonstrated that a good description of the contributions arising from solvation interactions and from hydrophobic effects in aqueous environment is an important prerequisite to obtain correct complex geometries [27].

In our approximation for a polar solvent, the total free energy of solvation, ΔG_{solv} , is calculated as the sum over solvating hydrophilic surface areas, ΔG^{philic} , characterized by atomic solvation parameters $\sigma_j < 0$, and hydrophobic surface areas with the respective solvation parameters $\sigma_j > 0$, leading to ΔG^{phobic} . The atomic solvation parameter set σ_j of Wesson and Eisenberg in the adjustment of Sharp et al. [29] is used in our calculations.

$$\begin{aligned}\Delta G_{\text{solv}} &= \Delta G^{\text{philic}} + \Delta G^{\text{phobic}} \\ &= \left(\sum_j \Delta \sigma_j A_j \right)_{\sigma_j < 0} + \\ &\quad \left(\sum_j \Delta \sigma_j A_j \right)_{\sigma_j > 0}\end{aligned}\quad (1)$$

‘Minimizing’ the hydrophobic contact area, in our case the solvent-accessible carbon surfaces, and consequently the corresponding contributions to the

solvation energy ΔG^{phobic} resembles the hydrophobic effect, and this is one of the most important contributions to CD complex formation [15,16,27].

Start geometries for DMC runs are defined by a randomly selected relative orientation of host and guest molecule within a distance of 5 Å. In each DMC step, the x , y and z coordinates of the relative position of host and guest are stochastically altered by a maximum step size of 0.5 Å, the guest is rotated by maximal 5°, and the individual glucose units within the host molecules are also twisted by maximal 5°. Each stochastically generated structure is fully minimized within the force field and accepted according to the modified Metropolis criterion [27], i.e. considering potential as well as solvation energies. The simulation temperature is kept constant at 300 K and all low-energy complex structures are obtained within 1000 DMC steps. This number of DMC steps proved to be sufficient to locate structurally as well as energetically equivalent low-energy CD complex structures independent of the initial relative position of host and guest [16,27]. This fact is mainly based on the full energy minimization of all generated structures at each DMC step.

The inclusion complexes are characterized by the potential energy E_P coming from the force field and dE_P giving the complexation energy as the difference between the potential energy of the complex and the potential energies of the individual, free molecules. Further characterization gives the differences of free energies of solvation after complexation compared to the isolated molecules, namely defined by the difference of solvating hydrophilic surfaces, dE_S^{philic} , hydrophobic surfaces, dE_S^{phobic} , and the sum of solvating hydrophilic and hydrophobic surfaces giving the difference of the total solvation energy dE_S^{total} , again comparing the complex and the free molecules.

Finally, the complexation energy dE is calculated as the energy difference between the sum of E_P and E_S^{total} of a complex and the summed potential and total solvation energies of the n isolated molecules:

$$dE = \left[E_P + E_S^{\text{total}} \right]_{\text{complex}} - \sum_{i=1}^n \left[E_{P,i} + E_{S,i}^{\text{total}} \right]_{\text{free}} \quad (2)$$

Furthermore, the host to guest distance d describes the complex geometries, and is defined as the distance

between the centre of mass of the guest and the centre of mass of the glycosidic oxygens of CD.

Results

Complexes of α - and β -CD with PEO and PPO moieties

Figure 1 shows typical low-energy structures of complexes between one α - or β -CD and one PEO (A, C) or PPO (B, D) monomer of the form $\text{CH}_3\text{-OCH}_2\text{CH}_2\text{-OCH}_3$ and $\text{CH}_3\text{-OCH}_2\text{CH}(\text{CH}_3)\text{-OCH}_3$. The respective potential energies E_P are 231.7 kJ/mol (A) and 245.0 kJ/mol (B) for the α -CD complexes, 221.4 kJ/mol (C) and 238.6 kJ/mol (D) for the β -CD complexes.

The gain in potential energy dE_P by forming complexes between PEO or PPO and α -CD is found in a comparable range of -50 kJ/mol for both guests. No discrimination of one type is thus found from the viewpoint of potential energy, but the total solvation energy difference dE_S^{total} gives -2.4 kJ/mol in the α -CD-PEO case and $+7.8$ kJ/mol in the α -CD-PPO case, resulting in a total complexation energy dE of -52.4 kJ/mol for α -CD-PEO complexes compared to -43.3 kJ/mol for α -CD-PPO. This contribution from solvation clearly favours the α -CD-PEO complex type compared to the α -CD-PPO complex. This difference in solvation energies is mainly based on shielding the hydroxyl groups on the secondary CD rims (dE_S^{philic} is 12.9 kJ/mol and 23.4 kJ/mol in the PEO and PPO case, respectively), which prevents those sites from effectively forming hydrogen bonds to either the solvent or, as will be discussed later, to other CD molecules.

The complexes for the two guests differ furthermore in a variety of geometrical characteristics. Most importantly, the host to guest distance d , which is found at $+0.9$ Å for the PEO complex, is much smaller than $+2.4$ Å obtained for the PPO complex. PEO is well embedded in the centre of the CD cavity and the complex is structurally well defined. PPO is located near a plane defined by the secondary OH groups of α -CD. A variety of different complex structures, especially concerning the relative tilt of the guest versus the plane defined by the glycosidic oxygens of CD, are realized in this case, although these complexes show comparable potential as well as solvation energies. A deeper penetration of PPO into the α -CD cavity to host the central methyl group results in better defined structures, and also in an energy increase of around 15 kJ/mol and a considerable deformation of the α -

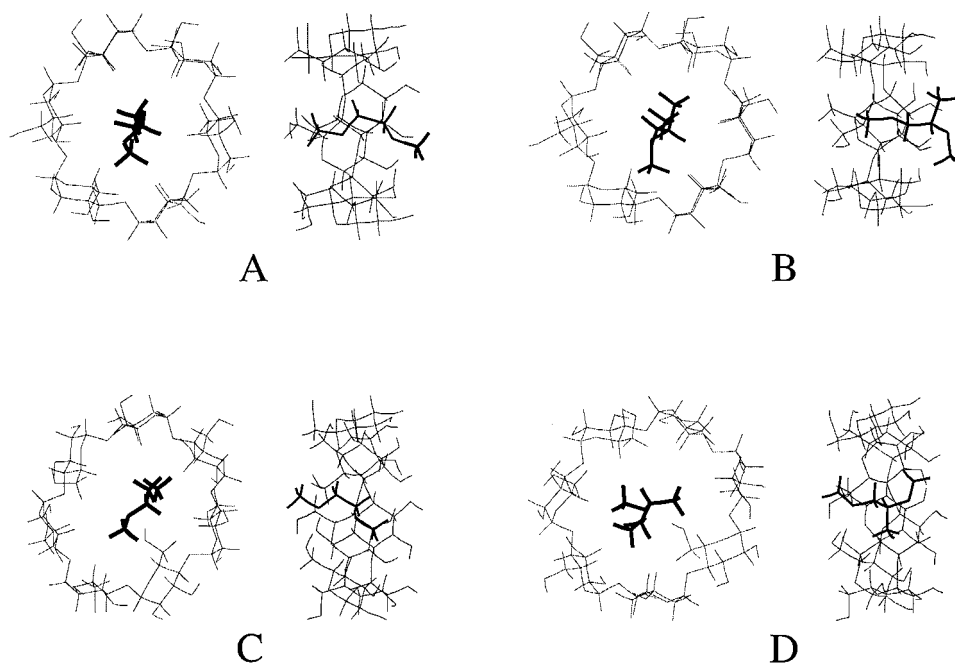


Figure 1. Low energy complexes of (A) α -CD and PEO, (B) α -CD and PPO, (C) β -CD and PEO and (D) β -CD and PPO. The drawings show a front view of the secondary OH rim as well as a side view after 90° rotation. The potential energies E_P , the gain in potential energy dE_P , the changes in solvation energies attributed to solvating hydrophilic (dE_S^{philic}) and hydrophobic (dE_S^{phobic}) surfaces, the change in total solvation energies dE_S^{total} , the overall complexation energies dE , and finally the host–guest distances d are respectively: (A) 231.7 kJ/mol, -50.0 kJ/mol, 12.9 kJ/mol, -15.4 kJ/mol, -2.4 kJ/mol, -52.4 kJ/mol, 1.0 Å; (B) 245.0 kJ/mol, -51.1 kJ/mol, 23.4 kJ/mol, -13.4 kJ/mol, 7.8 kJ/mol, -43.3 kJ/mol, 2.4 Å; (C) 221.4 kJ/mol, -101.3 kJ/mol, 21.3 kJ/mol, -15.7 kJ/mol, 5.6 kJ/mol, -95.7 kJ/mol, -2.9 Å; (D) 238.6 kJ/mol, -98.4 kJ/mol, 16.3 kJ/mol, -17.6 kJ/mol, -1.3 kJ/mol, -99.7 kJ/mol, -2.1 Å.

CD macrocycle. Such a deformation is energetically unfavourable, as the structure of the six-membered ring is highly constrained [30]. Comparable results are also found for α -CD complexing methyl-substituted phenols [27].

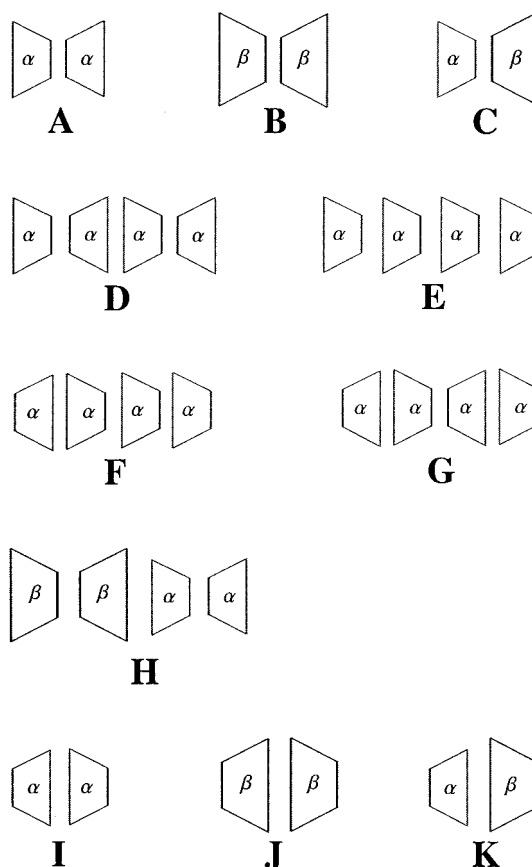
In the case of β -CD, the gain in potential energy dE_P for complexing PEO and PPO is also found in a comparable range for both guests, but the value of around -100 kJ/mol is approximately twice compared to the smaller macrocycle. This larger value is based on the higher flexibility of the β -CD ring [30], which can adopt its shape much better than α -CD to fit to the surface of the guest. However, in the β -CD case the total solvation energy difference dE_S^{total} gives $+5.6$ kJ/mol in the PEO case compared to -1.3 kJ/mol in the PPO situation. CD rim hydroxyl groups are not shielded in both the PEO and the PPO complexation, and the encapsulation of PPO gives therefore a beneficial solvation situation.

PEO-based complexes are, however, much less sterically constrained compared to PPO complexes, and energetically comparable structures are found in

a broad structural range in between host to guest distances of $+2$ Å and -3 Å. Furthermore, PEO is considerably tilted within the β -CD cavity, which improves the fit between the guest and one part of the host's cavity. PPO, on the other hand, gives an overall tight fit within the CD cavity which results in a well-defined low-energy structure where the guest is fully complexed by the host molecule. In general, the values for the total complexation energies shown in this and the next sections appear overestimated compared to experimental data [31]. This might be mainly based on neglecting entropic effects arising in the complex formation within our energy calculation described in the 'Methods of calculation' section.

Assembly of two CDs

Interactions between individual CD molecules give an important contribution to CD tube formation and the stabilization is mainly due to intermolecular hydrogen bond formation [9,10,16]. Table 1 summarizes the energetic parameters of various CD–CD complexes. Prim- α and prim- β denote the primary hydroxylic rim,



Scheme 1. Relative orientation of α - and β -CD in tubular ensembles considering the primary as well as the secondary OH rims as interaction sites.

and sec- α and sec- β denote the secondary hydroxylic rim of α - and β -CD as the interaction site, respectively.

1:1 CD-CD complexes are, considering only the potential energy gain dE_P , most stable when the interaction occurs between the two secondary hydroxylic rims [13,16], i.e. for the sec- α -sec- α , sec- β -sec- β and sec- α -sec- β orientations (Scheme 1 A-C). Complexation energies dE_P are found at around -155 kJ/mol and the α -CD- α -CD dimer is the most stable structure, followed by the α -CD- β -CD mixed complex and the β -CD- β -CD complex. The minimum energy of such configurations results mainly from a perfect geometrical arrangement of intermolecular hydrogen bonds between the secondary hydroxyl functionalities, which on the other hand is counteracted by unfeasible deformation of the macrocycle.

The preferential orientation of the individual macrocycles within CD-CD complexes solely based on dE_P suggests their defined ordering within CD tubes. Considering four α -CDs forming a tube gives

the following ordering as the most probable with highest interaction energy (Scheme 1D): sec- α -sec- α -prim- α -prim- α -sec- α -sec- α and a complexation energy $dE_P = -355.4$ kJ/mol is found for such tubes. This type of ordering is furthermore suggested by experiments on rotaxanes as well as on PEG containing threaded α -CDs [18,22]. Other configurations have considerably higher energies, e.g. sec- α -prim- α -sec- α -prim- α -sec- α -prim- α has $dE_P = -330.1$ kJ/mol (Scheme 1E), prim- α -prim- α -sec- α -prim- α -sec- α -prim- α has $dE_P = -250.9$ kJ/mol (Scheme 1F), and prim- α -prim- α -sec- α -sec- α -prim- α -prim- α has $dE_P = -230.2$ kJ/mol (Scheme 1G).

For β -CD, an equivalent situation is derived (the relative orientation of the CDs in the tubes given below is the same as in the α -CD situation shown in Scheme 1D-G): the highest gain in complexation energy $dE_P = -420.3$ kJ/mol is again found for the configuration sec- β -sec- β -prim- β -prim- β -sec- β -sec- β . No experimental data are available on the relative

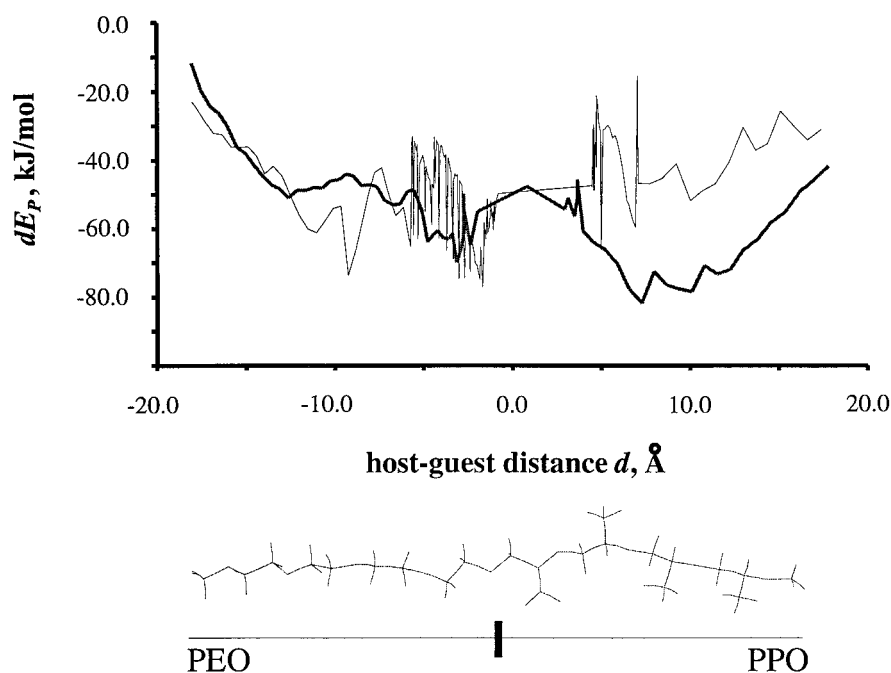


Figure 2. Complexation energies dE_P derived by moving α -CD (thin line) and β -CD (bold line) stochastically along the $(\text{PEO})_4$ – $(\text{PPO})_4$ block copolymer shown schematically at the bottom. A negative host–guest distance denotes the PEO part and positive values denote the PPO part of the polymer.

Table 1. Potential, solvation and complexation energies (in kJ/mol) of various CD–CD complexes

Interaction site	E_P	dE_P	dE_S^{philic}	dE_S^{phobic}	dE_S^{total}	dE
sec- α –sec- α	354.0	–160.1	159.5	–5.0	154.4	–5.7
sec- α –prim- α	410.9	–103.2	109.0	–12.8	96.0	–7.2
prim- α –prim- α	480.9	–33.2	34.0	–15.1	18.8	–14.4
sec- β –sec- β	444.8	–151.2	186.1	–4.0	182.7	31.5
sec- β –prim- β	481.3	–114.7	131.4	–13.0	118.4	3.7
prim- β –prim- β	473.8	–122.2	93.8	–21.9	72.0	–48.8
sec- β –sec- α	398.8	–156.3	165.1	–4.9	160.2	3.9
sec- β –prim- α	467.8	–87.3	112.6	–9.5	103.1	15.8
prim- β –sec- α	451.0	–104.1	112.8	–10.6	102.1	–2.0
prim- β –prim- α	492.2	–62.9	61.0	–19.4	41.6	–21.3

The *interaction site* defines the face-to-face positioning of the two CD molecules (prim denotes the primary and sec denotes the secondary OH CD rim). E_P gives the potential energy of the complex and dE_P gives the complexation energy based solely on the potential energy. dE_S^{philic} and dE_S^{phobic} give the changes of solvation energies arising from complexation considering hydrophilic and hydrophobic surfaces, respectively; both contributions result in dE_S^{total} . dE finally gives the total complexation energy, considering both the potential and solvation energies (see Equation 2).

positioning of β -CD in tubes, but results on the γ -CD tubes also suggest this type of arrangement [19]. Other ordering, as sec- β –prim- β –sec- β –prim- β –sec- β –prim- β with $dE_P = -350.3$ kJ/mol, prim- β –prim- β –sec- β –prim- β –sec- β –prim- β with $dE_P = -340.1$ kJ/mol,

and prim- β –prim- β –sec- β –sec- β –prim- β –prim- β with $dE_P = -400.5$ kJ/mol, again shows higher potential energies.

The energy differences of dE_P for the β -CD– β -CD arrays given above are smaller compared to those

of the respective α -CD assemblies. β -CD molecules can more easily adopt conformations suitable for optimal hydrogen bonding to the neighbouring CD [30]. α -CD is more rigid and deformation of the cone to adopt a geometry optimal for hydrogen bonding at the secondary as well as primary hydroxyl rims is counteracted by steric constraints within the macrocycle. This is the reason why the energy difference dE_P between the best and worst configuration is 125 kJ/mol for tubular arranged α -CDs, but only 80 kJ/mol for β -CDs.

Variation of α -CD and β -CD in mixed tubes gives as the most probable configuration (again considering solely the potential energy) sec- β -sec- β -prim- β -prim- α -sec- α -sec- α with a gain in potential energy of $dE_P = -380.9$ kJ/mol (Scheme 1H).

However, solvation counteracts the preferential tube formation driven by dE_P . This fact is not given by the contribution resulting from solvation of hydrophobic surfaces (all values of dE_S^{phobic} are negative, see Table 1), but from dE_S^{philic} . Considering this solvation of hydrophilic surfaces results in prim- α -prim- α , prim- β -prim- β and prim- α -prim- β as the most stable structures of CD dimers (Scheme 1I–K). These contributions from solvation even overwhelm the gain in potential energy dE_P (at least for this solvation parameter setting) as reflected by the total complexation energy dE (see the last column of Table 1), giving even positive values of dE for sec- β -sec- β and sec- β -sec- α .

These data suggest that CD–CD complex formation is guided by a balance between gain in potential energy and concomitant loss in solvation energy. This fact has a major impact on the necklace formation as discussed in the ‘CD nanotubes on PEO–PPO block copolymers’ section. However, X-ray data on α -CDs threaded on PEG showed that sec- α -sec- α interactions are preferentially realized [22]. Furthermore, data on the induced circular dichroism of 1:2 guest:host complexes indicate that the interaction between secondary hydroxyl rims of two cyclodextrins are the dominant form [15,16,27].

CD assembly on PEO–PPO block copolymers

Threading of α -CD and β -CD on a block copolymer of the form $\text{CH}_3-(\text{OCH}_2\text{CH}_2)_4-(\text{OCH}_2\text{CHCH}_3)_4-\text{OCH}_3$ is studied in dependence on the steric properties of the polymeric chain, i.e. if PEO or PPO units are the underlying segments.

Calculations are performed by stochastically moving CD molecules along the polymer chain (schemat-

ically shown at the bottom of Figure 2) within the DMC runs at a temperature of 300 K [11,13]. Eight runs are performed for α -CD and β -CD, respectively, starting with different initial conditions with respect to the relative orientation of host and guest (primary or secondary rim facing the polymer, as well as starting at the PEO or the PPO unit of the block copolymer). The complexation energies dE_P of accepted structures as well as the host–guest distances d of a typical run are sampled and graphically presented in Figure 2.

All calculated reaction pathways show qualitatively the same behaviour independent of the initial conditions of the DMC runs. The results given in Figure 2 clearly indicate that PPO units (located at the positive x -axis) are the favoured complexation sites for β -CD (bold line). β -CD complexing on PPO results in potential energies up to 20 kJ/mol below the respective complexes based on PEO units.

The situation is in reverse order when considering α -CD, where complexation on PEO units is slightly preferred on comparing PEO– and PPO– α -CD structures, and also with respect to β -CD complexes on PEO units. However, the energetic difference between α -CD and β -CD complexing PEO units is much smaller compared to the PPO situation.

Furthermore, the reaction pathway of α -CD is considerably rugged compared to that of β -CD, especially near the PEO–PPO intersection at -5 to 0 Å, and also at the PPO site. The low-energy regions for α -CD on the PPO units are separated by high-energy barriers, resulting in an improbable free movement of α -CD on this polymer site. The energy barriers around 0 Å also indicate a low probability for α -CD to traverse from the PEO to the PPO units of the polymer. The ruggedness of the α -CD pathway shown in Figure 2 is in part also given by the stochastics-based method used, as averaging over different DMC runs smoothens the reaction pathway. However, the ruggedness at certain host–guest distances still indicates a change in the overall properties of the underlying potential energy surface, i.e. traversing from a smooth (α -CD on PEO) to a rugged (α -CD on PPO) landscape.

Figure 3 gives the corresponding free energies of solvation (see Equation 1) in kJ/mol of the random walk across the polymer as discussed in the last paragraph.

Figures 3A and B give the free energies ΔG of solvating hydrophilic (ΔG^{philic}) and hydrophobic (ΔG^{phobic}) surfaces when moving α -CD (black, thin line) and β -CD (grey, thick line) across the model polymer, respectively. The negative x -axis

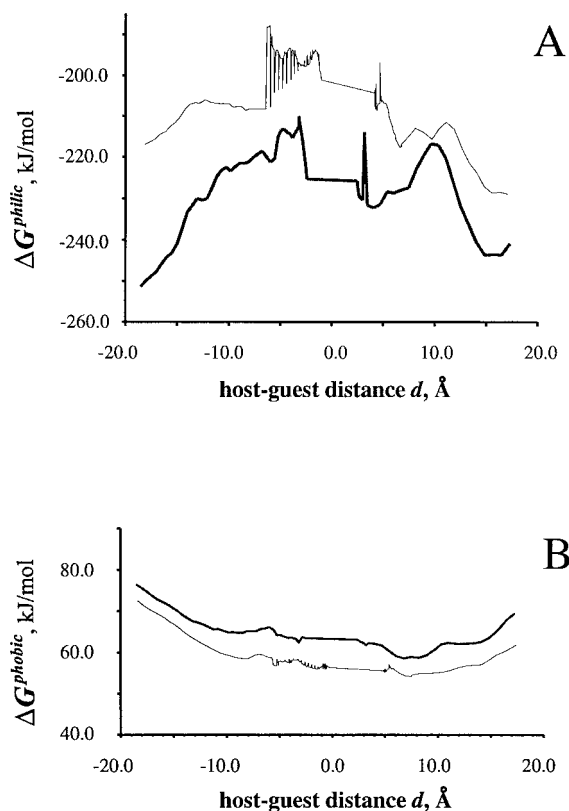


Figure 3. Free energies of solvation (kJ/mol) derived by moving α -CD (thin line) and β -CD (bold line) stochastically along the $(\text{PEO})_4$ – $(\text{PPO})_4$ block copolymer. ΔG^{philic} and ΔG^{phobic} denote free energies based on solvating hydrophilic and hydrophobic surfaces (see Equation 1). A negative host–guest distance denotes the PEO part and positive values denote the PPO part of the polymer.

again shows the PEO part of the polymer and the positive x -axis shows the PPO part of the polymer. Qualitatively, solvation does not discriminate the complexation of both CDs on either the PEO or the PPO site as both curves in Figures 3A and B are basically symmetric around a host–guest distance $d = 0$ Å.

Site-specific docking of CDs on PEO or PPO monomers of the polymer is therefore mainly determined by the enthalpic contributions shown in Figure 2. The negative correlation between ΔG^{philic} and dE_{P} is again reflected (see the ‘Complexes of α - and β -CD with PEO and PPO moieties’ and ‘Assembly of two CDs’ sections), for example by comparing the curves for β -CD in Figures 2 and 3A (grey line). Minima of dE_{P} are characterized by maxima of ΔG^{philic} . On the contrary, ΔG^{phobic} is lowest at full complexation at the minimum of dE_{P} around 7 Å for β -CD.

Figure 4 shows the geometry of different 2:1 complexes between CDs and the block copolymer relaxing α - and β -CD on PEO and PPO units of the polymer, respectively. The structure with the highest gain in potential energy is shown in Figure 4C, where β -CD relaxes on PPO units and α -CD relaxes on the PEO part of the block copolymer. This situation also gives the best complexation energy of all four arrangements with $dE = -120.1$ kJ/mol. Changes in solvation energy for hydrophilic and hydrophobic surfaces show qualitatively the same picture with a negative $dE_{\text{S}}^{\text{phobic}}$ in the range of -37 kJ/mol and a positive $dE_{\text{S}}^{\text{philic}}$ in the range of 50 kJ/mol.

One important geometrical characteristic is the strong deformation and relative tilt of β -CD with respect to the polymer axis (see the β -CDs in Figures 4B–D). In this way, the electrostatic interactions between β -CD and the polymer are maximized. On the contrary, the position of α -CD is constrained on both monomer types. We again note the high flexibility of β -CD located on the PEO units.

CD nanotubes on PEO–PPO block copolymers

The block copolymer used to study the assembly of four CDs is the same as in the ‘CD assembly on PEO–PPO block copolymers’ section, i.e. $(\text{PEO})_4$ – $(\text{PPO})_4$. Figure 5 shows the block copolymer complexed by two α - and two β -CD molecules. The arrangements of Figures 5A and B differ in the way in which primary and secondary hydroxyl rim sites interact, and Figure 5C shows a typical random arrangement of CD molecules on the polymer.

The configuration shown in Figure 5A (sec- β –sec- β –prim- β –prim- α –sec- α –sec- α) has the lowest potential energy of all tested combinations with 728.1 kJ/mol and a gain in potential energy $dE_{\text{P}} = -613.1$ kJ/mol. The enthalpic intermolecular stabilization between CD and polymer, but especially between individual CD molecules (see also Table 1), clearly exceeds the positive contribution from $dE_{\text{S}}^{\text{philic}}$. $dE_{\text{S}}^{\text{phobic}}$ is negative in all three CD arrangements presented, although the absolute value is smallest in the situation of Figure 5A. The type of configuration shown in Figure 5A, where sec-CD–sec-CD interactions are realized, is furthermore supported by experimental data [15,16,18,22].

Considering the results presented in the ‘Complexes of α - and β -CD with PEO and PPO moieties’ section on CD–monomer and in the ‘Assembly of two CDs’ section on CD–CD complexes, the situation pre-

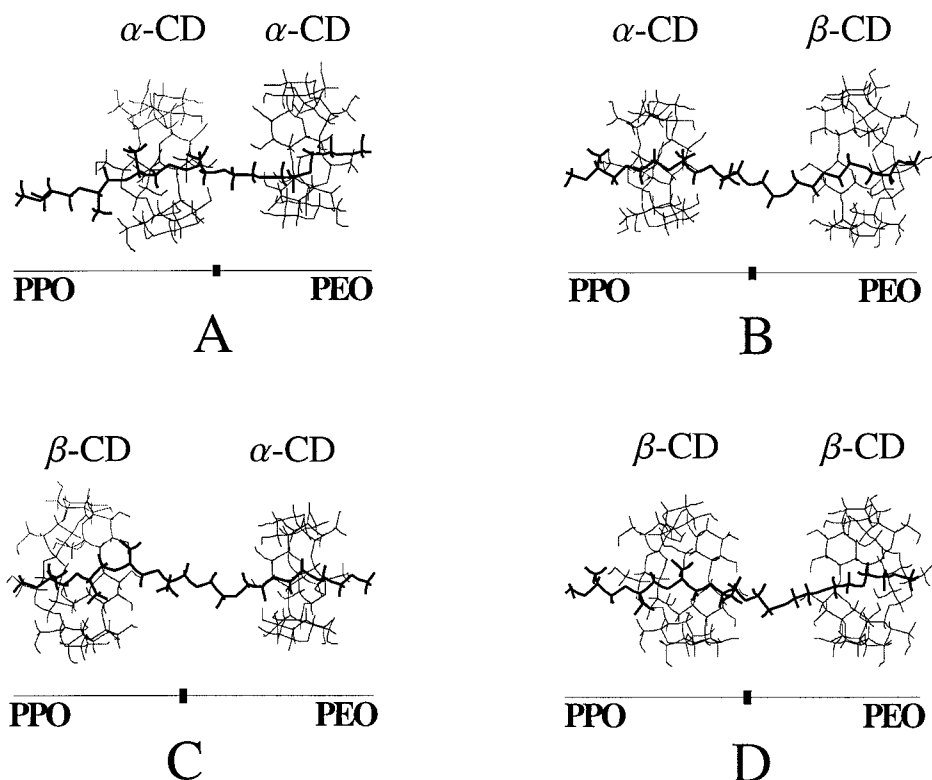


Figure 4. Low-energy complexes formed between the block copolymer $(\text{PPO})_4-(\text{PEO})_4$ and two CD molecules. The bars indicate the PPO and the PEO part of the block copolymer in the complex. The potential energies E_p , the gain in potential energy dE_p , the changes in solvation energies attributed to solvating hydrophilic (dE_S^{philic}) and hydrophobic (dE_S^{phobic}) surfaces, the change in total solvation energies dE_S^{total} , and the overall complexation energies dE are respectively: (A) 650.8 kJ/mol, -94.4 kJ/mol, 44.8 kJ/mol, -35.5 kJ/mol, 9.3 kJ/mol, -85.1 kJ/mol; (B) 678.0 kJ/mol, -108.1 kJ/mol, 50.7 kJ/mol, -38.7 kJ/mol, 11.9 kJ/mol, -96.2 kJ/mol; (C) 649.3 kJ/mol, -136.8 kJ/mol, 55.7 kJ/mol, -38.9 kJ/mol, 16.7 kJ/mol, -120.1 kJ/mol; (D) 696.3 kJ/mol, -130.7 kJ/mol, 57.5 kJ/mol, -39.6 kJ/mol, 18.2 kJ/mol, -112.5 kJ/mol.

sented in Figure 5A resembles the best solution from the enthalpic viewpoint, but is not optimal considering solvation, where prim-CD–prim-CD interaction gives the best values for dE_S^{total} . prim- β -CD–prim- β -CD as well as prim- α -CD–prim- α -CD are realized in Figure 5B, but in this tube situation enthalpic gains as well as contributions from solvation are worse compared to the situation given in Figure 5A and this results in an even positive complexation energy $dE = 135.5$ kJ/mol.

The most interesting fact is the high order of the tube shown in Figure 5A. The cyclodextrins are perfectly aligned to form a maximum number of intermolecular hydrogen bonds, mainly between CDs of the same type, but also between α - and β -CD. The high order is a characteristic feature of this multicomponent complex and is maintained also during long DMC runs, which give little variation in energetic as well as structural parameters.

However, other configurations of the four CD molecules on the block copolymer do not give such stable structures: Figure 5C shows exemplarily (out of eight tested configurations) the arrangement sec- α –prim- β –sec- β –sec- α –prim- α –sec- β . The assembly shown in Figure 5C gives a potential energy of 873.2 kJ/mol and a complexation energy $dE = -114.5$ kJ/mol. This third example, characteristic for a random distribution of CDs on the polymer, clearly indicates the misalignment of the individual CD molecules. The assembly is structurally highly flexible, and intermolecular hydrogen bonds are only partially formed as the individual CDs are strongly tilted. As a consequence, the overall stability of such random configurations is highly decreased compared to the stability of the structure given in Figure 5A.

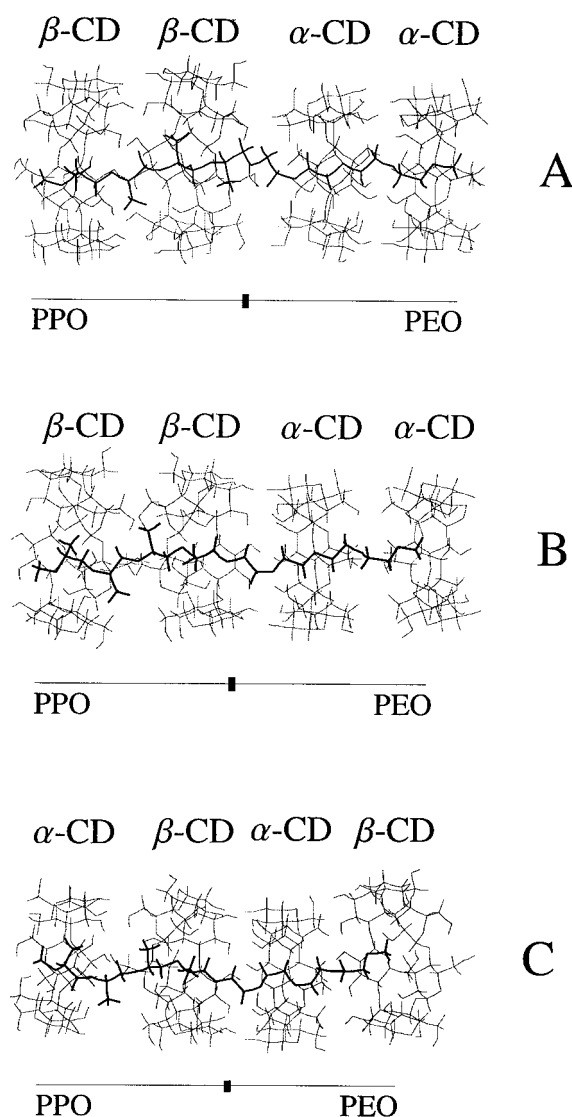


Figure 5. Low-energy structures of assembled CD tubes on a $(\text{PPO})_4-(\text{PEO})_4$ block copolymer derived by DMC simulations. The bars indicate the PPO and the PEO part of the block copolymer in the complex. The potential energies E_p , the gain in potential energy dE_p , the changes in solvation energies attributed to solvating hydrophilic (dE_S^{philic}) and hydrophobic (dE_S^{phobic}) surfaces, the change in total solvation energies dE_S^{total} , and the overall complexation energies dE are respectively: (A) 728.1 kJ/mol, -613.1 kJ/mol, 440.9 kJ/mol, -75.5 kJ/mol, 365.4 kJ/mol, -247.7 kJ/mol; (B) 911.65 kJ/mol, -429.5 kJ/mol, 705.8 kJ/mol, -140.9 kJ/mol, 565.0 kJ/mol, 135.5 kJ/mol; (C) 873.2 kJ/mol, -468.0 kJ/mol, 438.6 kJ/mol, -85.2 kJ/mol, 353.5 kJ/mol, -114.5 kJ/mol.

Discussion and conclusions

The selective, non-statistical threading of α - and β -CD on PEO and PPO results from various individual contributions:

(i) PPO monomers are preferentially complexed by β -CD, mainly due to the tight fit between host and guest. The respective complex geometries represent a defined minimum well below the respective α -CD-PPO complex and remain stable also during long simulation runs (Figure 1D). PPO is furthermore fully included in the β -CD cavity. PEO does not give structurally defined low-energy complexes with β -CD, as the lack of a tight fit permits the formation of stable complex geometries (Figure 1C). A tight fit is indicated for PEO- α -CD complexes (Figure 1A), whereas PPO cannot be fully complexed by α -CD due to steric hindrance (Figure 1B).

(ii) The interaction between CD molecules themselves is non-statistical (see Table 1). To favour a maximum number of intermolecular hydrogen bonds, especially the secondary OH rim sides are aligned, ensuring an optimal geometry for hydrogen bonding.

(iii) Complexing α - and β -CD on the model block copolymer $(\text{PPO})_4-(\text{PEO})_4$ clearly indicates the behaviour also found for the monomeric complexes. β -CD is situated preferentially on the PPO part of the polymer, whereas α -CD is located on the PEO branch of the polymer. β -CD fits tightly on the PPO sites, whereas the highly constrained α -CD rim is deformed when placed on PPO parts. Comparably free movement along the polymer chain is given for β -CD, and the respective reaction pathway for α -CD is characterized by large energy barriers.

The reason for the highly selective threading of α -CD on PEO and β -CD on PPO parts of the block copolymer results from the relative stability as well as the structural characteristics of the different individual bonded complexes between cyclodextrins of the same type.

The first non-statistical event is the energetic preference to form stable and structurally well-defined β -CD complexes on the PPO chain. This site preference as well as the preference of CDs to interact with other CDs of the same type results in the complexation of another β -CD unit on the same PPO branch of the polymer. The gain in binding energy of β -CD to PEO subunits is much smaller as no tight fit between the macrocycle and the polymer chain can be formed. Therefore, also a proper geometrical arrange-

ment for optimal hydrogen-bond formation between the CD units cannot be maintained over a long time scale. Similar cooperative effects are operative for the threading of α -CD on PEO chains.

Large individual contributions to the total enthalpy yield a negative free energy which makes the entropically unfavourable non-statistical distribution of the CDs on the polymer the optimum structure for these cyclodextrin nanotubes.

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