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Peptide Binding to β-Cyclodextrins: Structure, Dynamics, Energetics, and Electronic Effects

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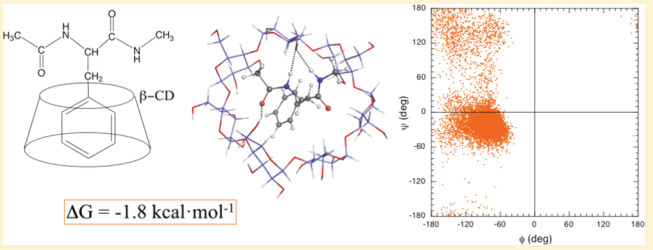
Supporting Information

ABSTRACT: Peptide−cyclodextrin and protein−cyclodextrin host−guest complexes are becoming more and more important for industrial applications, in particular in the fields of pharmaceutical and food chemistry. They have already deserved many experimental investigations although the effect of complex formation in terms of peptide (or protein) structure is not well-known yet. Theoretical calculations represent a unique tool to analyze such effects, and with this aim we have carried out in the present investigation molecular dynamics simulations and combined quantum mechanics−molecular mechanics calculations. We have studied complexes formed between the model Ace-Phe-Nme peptide and the β-cyclodextrin (β-CD) macromolecule, and our analysis focuses on the following points: (1) how is the peptide structure modified in going from bulk water to CD environment (backbone torsion angles), (2) which are the main peptide−CD interactions, in particular in terms of hydrogen bonds, (3) which relative peptide−CD orientation is preferred and which are the structural and energetic differences between them, and (4) how the electronic properties of the peptide changes under complex formation. Overall, our calculations show that in the most stable configuration, the backbone chain lies in the narrow rim of the CD. Strong hydrogen bonds form between the H atoms of the peptidic NH groups and oxygen atoms of the secondary OH groups in the CD. These and other (weaker) hydrogen bonds formed by the carbonyl groups reduce considerably the flexibility of the peptide structure, compared to bulk water, and produce a marked increase of the local dipole moment by favoring configurations in which the two C═O bonds point toward the same direction. This effect might have important consequences in terms of the peptide secondary structure, although this hypothesis needs to be tested using larger peptide models.



1. INTRODUCTION

Cyclodextrins (CDs) are molecular receptors of major importance in supramolecular chemistry.[1] They are cyclic nonreducing oligosaccharides composed of several glucopyranose units linked together via α-(1−4) glycoside bonds. The members composed of six (α-CD), seven (β-CD), and eight (γ-CD) units are the most common ones. They have the form of a truncated cone with a hydrophobic cavity and a hydrophilic outer surface resulting from the presence of hydroxyl groups in both the narrow (primary OH groups) and wide side of the cavity (secondary OH groups) (Figure 1).

CDs are capable of including a variety of hydrophobic guests, and thus they are specially well suited for practical applications in many industrial areas,[2−8] in particular in food and pharmaceutical chemistry. In these two specific cases, the formation of inclusion complexes with peptides and proteins has attracted much attention.[9] One reason is linked to the bitter or unpleasant taste inhibition under encapsulation of amino acids or peptides in a CD cavity,[10−14] as this property may have obvious interest in biotechnologies and drug formulation (note that cyclodextrins do also display low toxicity).[15] Besides, there is a wide range of effects of CDs on chemical properties of proteins such as aggregation suppression and protection against degradation or alteration of function; the investigations of Aachmann et al.[9] on noncarbohydrate-binding proteins suggested an explanation for such effects.

The role of CDs on peptide and protein drugs delivery was reviewed by Irie and Uekama,[16] and more recently by Challa et al.[17] and Pandey et al.[18] On the one hand, the complexation with CDs may improve the bioavailability of the drug through a modification of its solubility/permeability. On the other hand, CDs may protect the therapeutic agent against hydrolysis or degradation in the digestive tract.

The structures of complexes with amino acids, peptides, and proteins have been investigated by several authors using a variety of physical−chemical techniques.[14,19−24] The main interaction mode has been shown to be the inclusion of aromatic side chains into the CD cavity. Thus, using both UV and NMR spectroscopy, Matsubara et al.[25] showed that the aromatic side chains of

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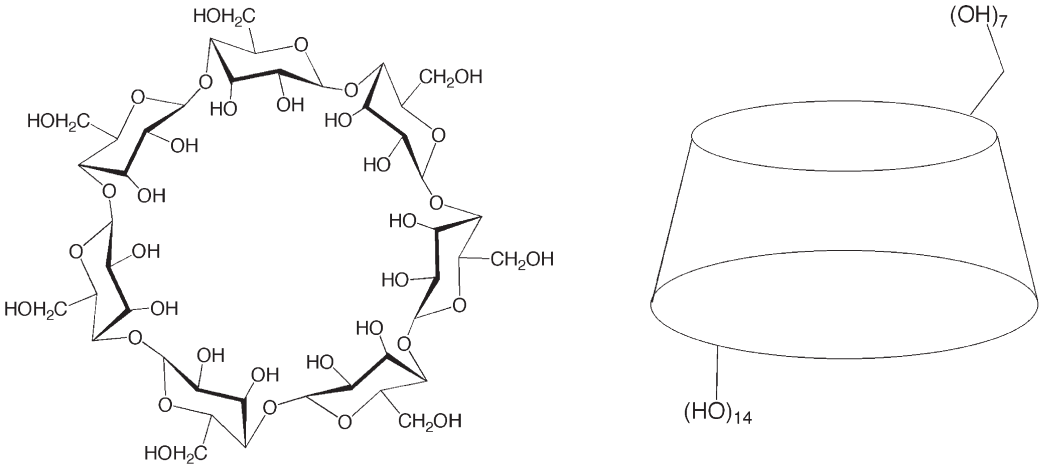

Figure 1. Schematic representation of a β-cyclodextrin. The truncated cone structure is illustrated in the right part with primary and secondary hydroxyl groups in the narrow and wide rims, respectively.

L-tryptophan and L-tyrosine of buserelin acetate (a peptide drug) enter the cavity of dimethyl-β-cyclodextrin. Similar conclusions were reached by Nishijo and Tsuchitani[26] for the interaction of L-tryptophan with α-cyclodextrins and Aachmann et al.[9] for the interaction of β-CD with several proteins. Depending on CD and peptide, both stabilization and destabilization against proteolytic and chemical degradation might happen.[9,27−30]

There are other reasons explaining the interest for investigating CD−peptide interactions, and in particular the fact that CDs have often been considered as appropriate models of enzymes[3,31,32] and are therefore promising systems for the development of new catalysts in green chemistry.[30−36] Hence, many other experimental studies have been devoted to the study of inclusion complexes formed by amino acids and peptides with CDs.[13,20,23,24,37−44]

Many theoretical works have been devoted to the study of CD inclusion complexes, but surprisingly very few concern amino acids and peptides.[45] Miertus et al.[46,47] reported a molecular mechanics and molecular dynamics study to investigate the ability of β-CD to form stable complexes with α-interferon; host−guest inclusion with L-α-aminoacids and pentapeptides were considered by these authors. Ahn et al.[48] reported a molecular modeling and experimental study that suggested that interaction of the amino acid with the CD rims favor the formation of zwitterionic species in gas phase. More recently, Lula et al.[23] studied the complex between angiotensin-(1−7) and β-CD using a self-consistent charge method coupled to a molecular mechanics approach.

In spite of these studies, the peptide−CD interaction mechanism is still poorly known. In particular, a comparison of the two possible orientations of the peptide with respect to the hydrophobic cavity has not been performed yet. Structural details in terms of hydrogen-bonds network, association free energies, and peptide properties changes induced by complex formation are also open questions. This work addresses some of these points by discussing the results of molecular dynamics simulations and combined quantum mechanics and molecular mechanics (QM/MM) calculations at the density functional theory level. The study has been done for β-CD and a simple peptide model involving two amide bonds. The choice of β-CD has been done because of its current importance in terms of industrial application in food, pharmaceutical, and cosmetics industries.

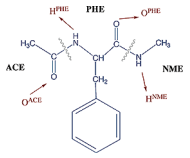

Figure 2. Model Ace-Phe-Nme peptide used in this work.

2. COMPUTATIONAL METHODOLOGY

Model. We have considered the interaction of β-CD with a model peptide Ace-Phe-Nme (Figure 2). In spite of its simplicity, this model is appropriate to study peptide−CD interactions since it includes a central Phe side chain, which is a typical site for CD binding, together with the two associated amide bonds. Addition of further residues would be interesting to analyze long-range effects (peptide secondary structure), and this indeed will be considered in future work. Here, however, we focus our attention on the effect of the interactions on the proximate backbone structure, torsions, mobility, and electronic properties of the amide bonds. Quantum mechanical calculations of the peptide have to be carried out for a number of snapshots in order to analyze electronic effects and to compute explicit polarization contributions to the interaction energy. Therefore, the Ace-Phe-Nme model represents a good compromise between peptide size and computational cost.

Molecular Dynamics Setup. Initial geometry for the tripeptide Ace-Phe-Nme was obtained with the TLEAP utility implemented in AMBER 9.0.[49] The system was then placed in the center of the β-CD cavity on two possible orientations, narrow-head (nh) and wide-head (wh) schematized in Figure 3. Molecular dynamics (MD) simulations were performed for the peptide and its two complexes with β-CD (nh and wh) in aqueous solution. The systems were hydrated with explicit TIP3P water molecules. For the peptide alone a box dimension of 50 × 52 × 56 Å^3 (3794 water molecules) was assumed in the calculations. For the wh complex, the dimension was 60 × 59 × 58 Å^3 (5531 water molecules), while for the nh conformation we used a slightly different value 60 × 56 × 61 Å^3 (5414 water molecules).

The AMBER03 force field of Duan et al.[50] was used to model the solvated systems. Energy minimizations and MD simulations

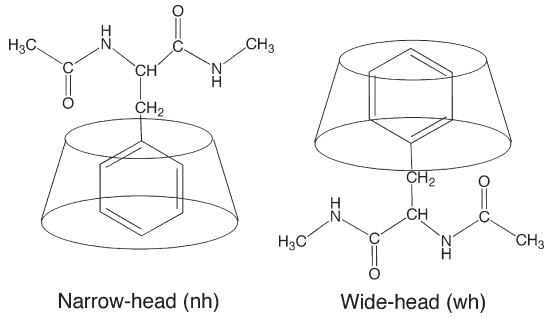

Figure 3. Possible orientations of the peptide−cyclodextrin complex.

were carried out using the SANDER and PMEMD routines included in the AMBER 9.0 suite of programs.[49] To eliminate bad contacts in the initial geometries, we carried out the following procedure: (1) relaxation of the solvent molecules by means of energy minimizations, (2) energy minimization of the chemical system (peptide or complex), (3) energy minimization of the solvent molecules, (4) 100 ps of MD simulation for relaxing the solvent molecules, and (5) energy minimization of the full system. The SHAKE algorithm[51] was employed to constrain all the R−H bonds, in which R is any atom linked to the H atom, and periodic boundary conditions were applied to simulate a continuous system. A cutoff of 10.0 Å was defined for the nonbonded interactions, and the particle-mesh Ewald (PME) method was used to include the long-range contributions.[52] Berendsen's method[53] was used to control the pressure (1 atm) and the temperature (300 K) of the system during the MD simulations. A 10 ns trajectory was computed for each model with a time step of 2 fs, but only the last 8.0 ns of each trajectory were analyzed (500 snapshots were saved for further analysis). Structural analyses were done using the PTRAJ module of AMBER 9.0.

Combined QM/MM Calculations Setup. After MD simulations, a combined QM/MM calculation was carried out for the 500 saved snapshots. In our QM/MM method, the peptide is described quantum mechanically (B3LYP method[54−56]) while its environment (that is the β-CD and the water solvent) is described classically (MM force field). In these calculations, all water molecules within 10 Å from the center of mass of the peptide were considered. A QM calculation is carried out for the peptide using a Hamiltonian that includes the electrostatic potential created by the point charges of the environment. Nonelectrostatic interactions between the QM and MM subsystems are calculated through a Lennard-Jones potential using parameters from the classical force field. Further details can be found in the original references.[57−59] QM calculations have been done at the B3LYP[54−56] level using the 6-311+G(d,p) basis set, but in order to check the suitability of this basis set, we also carried out a limited number of calculations at the B3LYP/6-311+G(2df,2p) level which include better polarization function. For interpretation purposes, a natural bond orbital (NBO) analysis was performed.[60,61] The Gaussian 03 program[62] was used for the QM calculations.

Calculation of free energies. Free energies of host−guest complex formation were estimated using a QM/MM variant of the molecular mechanics Poisson−Boltzmann surface area (MM/PBSA) method[63] implemented in AMBER. Snapshots from the MD trajectories of the nh and wh complexes were utilized to estimate the free energies in each case. The free energies of binding were computed as follows

$$\Delta G_{\text{bind}} = \Delta E_{\text{int}} + \Delta E_{\text{solv}} - T\Delta S \quad (1)$$

where ΔE_{int} represents the peptide−CD interaction energy at the QM/MM level, ΔE_{solv} is the difference in solvation energy between the separated peptide and CD and the complex (computed with the PBSA method), and $T\Delta S$ is the entropy for complex formation (computed after a geometry optimization + vibrational analysis of the snapshots using the NMODE module of AMBER).[49] Other details can be found in original references.[64−68]

3. RESULTS AND DISCUSSION

Structures. We first compare the peptide structures in bulk water and in the CD cavity (nh and wh complexes). The analysis focuses on the internal structure of the peptide in terms of usual backbone ψ and ϕ angles, as well as on the hydrogen-bond interactions, either intramolecular or intermolecular (peptide−water, peptide−CD). This discussion is relevant as a preliminary step toward the understanding of how complex formation of peptides (or proteins) with β-CD can potentially modify their secondary structure.

The variation of the ψ and ϕ angles for the Phe residue in different media is shown in Figure 4. In bulk water, the structure of the model peptide exhibits maximum probabilities for angles ψ of $-20°$ and $145°$, while angle ϕ spreads between $-40°$ and $-180°$ with a maximum at about $-70°$. The results for the wh complex are similar, but in the case of the nh complex, the largest proportion of structures falls around $\psi = -20°$ and $\phi = -80°$. These angles correspond to those usually found in α-helices meaning that this type of structure might be favored when the peptide−CD complex is formed according to nh orientation. For a better understanding, a clustering analysis[69] has been carried out. The main conformation types and associated percentages are illustrated by snapshots in Figure 5 and are consistent with the angular distributions in Figure 4. For the peptide in water and the wh complex, the same four main structures (**a**, **b**, **c**, **d**) are found though the probability of the structures changes slightly. Again, the nh complex behaves differently, and only one main structure has been identified. It may be noticed that there are not net intramolecular hydrogen bonds in these structures, although for some of them (**a**, **c**) stabilizing interactions between the NH and CO groups in the Phe residue are likely to occur.

Let us now focus on the radial distribution functions (RDFs) describing peptide−water and peptide−CD hydrogen-bond interactions. The corresponding curves are plotted in Figures 6 and 7, respectively. The number of hydrogen bonds obtained from integration of the RDF peaks is summarized in Table 1. As expected for this model peptide, the CO and NH groups form some hydrogen bonds with water. In going from bulk water to the CD complexes, there are however noticeable changes, peaks associated with these hydrogen bonds being significantly less intense. Thus, in the case of the nh complex, N−H···O_w bonds are very weak and there is only one C═O···H_w hydrogen bond (instead of almost two in bulk water). The situation is similar in the case of the wh complex although the two N−H···O_w hydrogen bonds are a little more pronounced.

The effect of relative host−guest orientation on hydrogen-bonds network is much bigger in the case of the interactions between the peptide and the hydroxyl groups on the CD cavity (see Figure 7). In particular, there are clearly net $N-H^{NME}\cdots O_{CD}$ and $N-H^{PHE}\cdots O_{CD}$ hydrogen bonds in the case of the

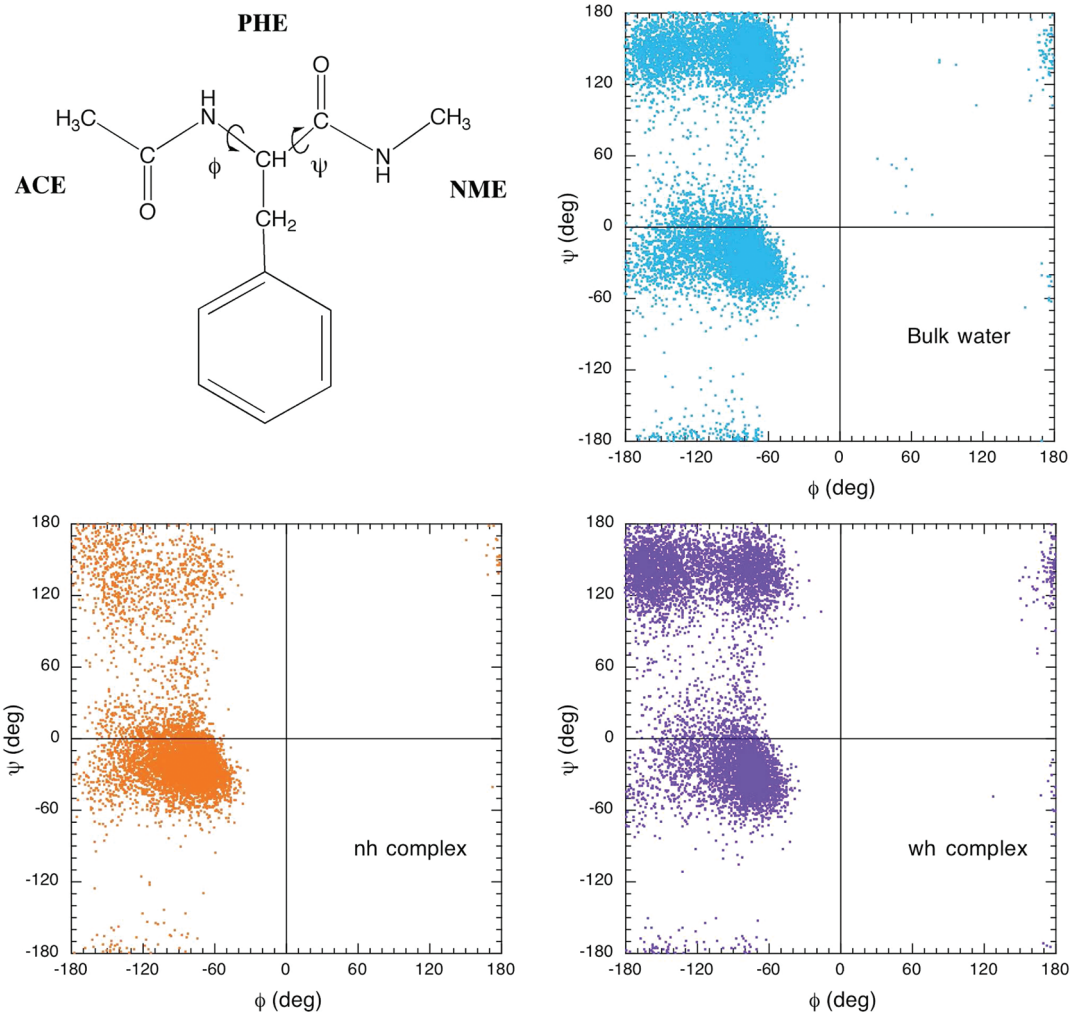

Figure 4. Distribution of the usual ψ and ϕ angles for the model peptide in bulk water and CD complexes along the MD simulation.

nh complex but not in the wh one. The analysis of the data shows that these hydrogen bonds in the nh complex involve the same OH unit of the CD. Besides, a net $C{=}O^{PHE}\cdots H_{CD}$ hydrogen bond exists in the wh complex which is absent in the nh one, while a net $C{=}O^{ACE}\cdots H_{CD}$ hydrogen bond occurs in both cases. There are other minor interactions, but the previous ones represent the most important ones. Overall, we can conclude that the hydrogen-bond networks in the nh and wh peptide−CD complexes are quite different and correspond to the situation schematized in Figure 8. This figure suggests that in nh and wh complexes the model peptide exhibits both different degree of hydration and different macrocycle binding properties. It is worth emphasizing, however, that the scheme in Figure 8 corresponds to average hydrogen bonds and that, accordingly, all the bonds are not necessarily formed simultaneously. In particular, in the case of the wh complex, in which the peptide can display four main configurations (Figure 5), the hydrogen-bond network can undergo large reorganization.

Energetics. The peptide−environment interaction energy computed at the QM/MM level is summarized in Table 2. The QM calculations have been done using the B3LYP/6-311+G(d,p) method. We have tested the suitability of the basis set by carrying out a limited number of computations with a more extended basis set 6-311+G(2df,2p) (18 structures for either nh or wh complex). The comparison shows that the differences in total peptide−environment interaction energy are small, below 0.3 kcal/mol, and therefore the 6-311+G(d,p) basis was considered as appropriate for this study.

In Table 2, QM/MM calculations are compared to the corresponding MM quantities. As shown, in going from bulk water to the aqueous CD environment, the total peptide−environment interaction energy substantially increases in absolute value. This trend is mainly due to the strong augmentation of the nonelectrostatic Lennard-Jones contribution, as expected from the hydrophobic nature of the interactions inside the CD cavity. But interestingly, the electrostatic interaction energy is also greater in the CD environment, therefore highlighting the important role of peptide−CD hydrogen bonds. Qualitatively, MM and QM/MM calculations for the electrostatic terms lead to similar results, but one should note the systematic underestimation of this property in MM calculations by roughly 6−9 kcal/mol, which can be ascribed to the lack of explicit polarization effects. Overall, the total interaction energy in the peptide−CD complexes is slightly larger for the nh one (by approximately 1 kcal/mol at the MM level and 0.2 kcal/mol at the QM/MM level). The preference for the nh interaction mode resembles that obtained in β-CD inclusion complexes for aryl-containing esters using MM and MD calculations.[70,71]

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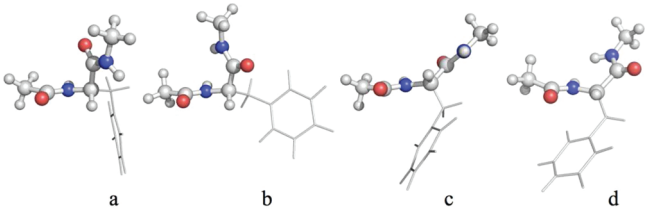
The calculation of free energy of complexation in water has been estimated here using the QM/MM/PBSA method, and the results are summarized in Table 3. The binding free energies are negative and small in absolute value. The values cannot be regarded as very accurate, taking into account the approximations made in the method and the fact that they are obtained as the difference of relatively large numbers. Nevertheless, their order of magnitude agrees very well with experimental measurements for the association of β-CD with L-phenylalanine or L-phenylalanineamide, for instance.[14,19,39] On the other hand, one expects some error cancelation in the comparison of the



		a	b	c	d
Bulk water	%	33.1	29.8	19.1	15.8
	φ	-75.1	-75.3	-144.4	-127.1
	ψ	142.6	-26.2	148.7	-13.5
nh complex	%		89.6		
	φ		-88.4		
	ψ		-20.4		
wh complex	%	21.8	31.2	31.8	8.2
	φ	-75.7	-75.4	-151.6	-106.2
	ψ	137.7	-30.9	141.5	14.6

Figure 5. Most populated representative structures derived from the clustering analyses of the MD simulations. The drawn structures (**a**, **b**, **c**, **d**) correspond to the analysis in bulk water. Similar structures are found in the peptide−CD complexes although their probabilities change; they are not drawn for simplicity. Main percentages of total population in each case are indicated in the table, together with average angles (in degrees).

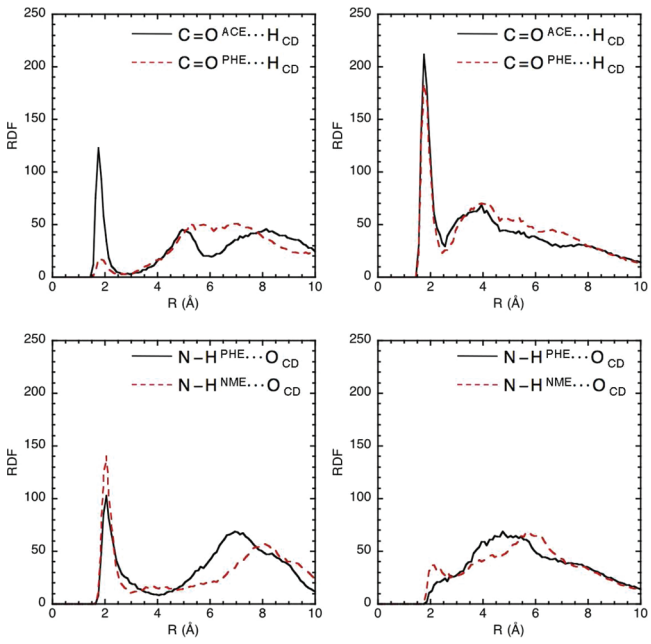


Figure 7. Radial distribution functions from MD simulations. Hydrogen bonds between the model peptide and the CD cavity. Left: nh complex. Right: wh complex.

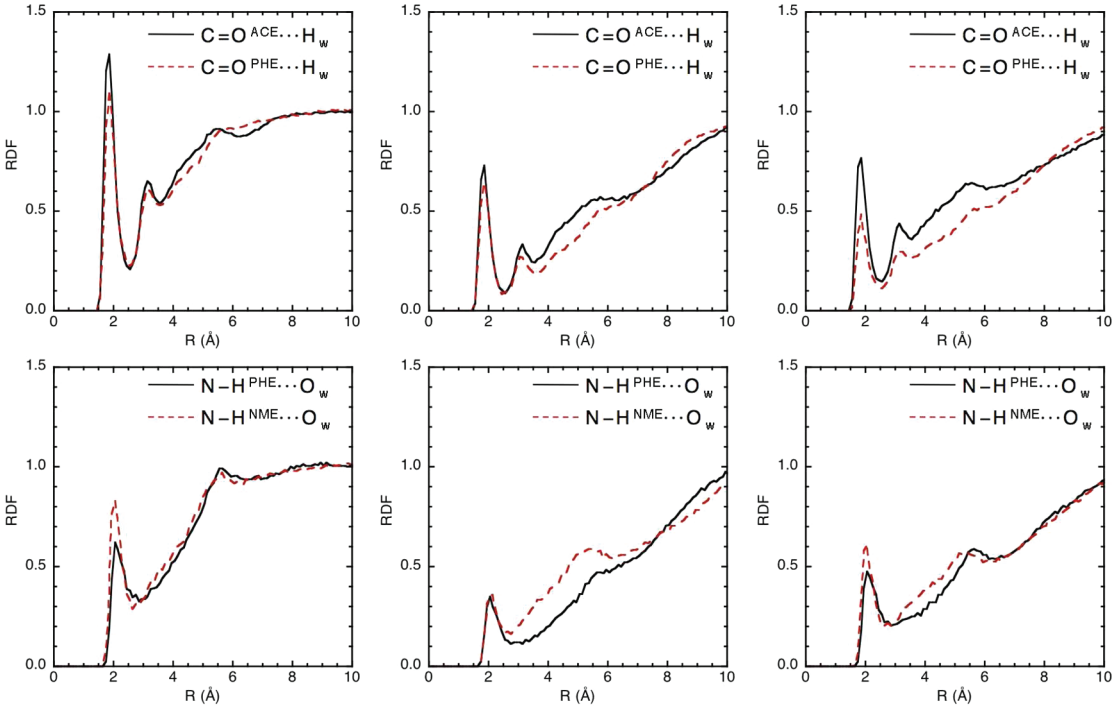


Figure 6. Radial distribution functions from MD simulations. Hydrogen bonds between the model peptide and water molecules. From left to right: bulk water, nh complex, wh complex.

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two coordination modes, and hence we can conclude that the nh complex is approximately 1.0 kcal/mol more stable than the wh complex.

Interestingly, unbinding events have not been observed at the time scale of the simulations in spite of the small QM/MM binding energy. This fact can be explained by noticing that in the simulations, the MM force field is employed, and in that case the peptide guest is more tightly bind to the CD host (compare MM and QM/MM energies for peptide−water and peptide−CD interactions in Table 2). Another possible explanation would be the existence of an unbinding energy barrier, which has not been searched in the present study.

Electronic Properties. Finally, let us analyze medium effects on the peptide electronic properties. The computed averages of the dipole moment in bulk water solution and CD environment are summarized in Table 4. The CD cavity environment is in principle less polar than water that has sometimes been described as a medium of low to medium dielectric constant. One would then expect lower polarization in the host−guest complex than in bulk water, and indeed this has been confirmed with simple substrates.[72] The values in Table 4 for the model considered here do not show such a trend: the dipole moment of the peptide in the wh complex is close (though slightly larger) than the dipole moment in bulk water, and that of the nh complex is much higher. To explain this finding, it is necessary to take into account the specific host−guest interactions and their impact on peptide conformation, rather than considering the electronic polarization alone. As seen in Figure 5, the main configuration in the nh CD complex (**b**) has the two carbonyl groups pointing toward the same direction leading to an additive contribution of C═O

Table 1. Hydrogen Bond Lengths with Water and Number of Solvent Molecules in the First Solvation Shell for the Model Peptide[a]

	distance (Å)			solvation number		
	water	CD nh	CD wh	water	CD nh	CD wh
$C{=}O^{ACE}\cdots H_w$	1.868	1.850	1.850	1.7	0.8	0.9
$C{=}O^{PHE}\cdots H_w$	1.868	1.850	1.850	1.6	0.7	0.6
$N{-}H^{PHE}\cdots O_w$	2.050	2.050	2.050	0.9	0.3	0.6
$N{-}H^{NME}\cdots O_w$	2.050	2.050	2.050	0.8	0.3	0.6

[a] See Figure 2 for atom labeling.

Table 2. Average Electrostatic (E_{elec}), van der Waals (E_{vdw}), and Total (E_{int}) Interaction Energy (kcal/mol) between the Model Peptide and Its Environment, Bulk Water Solution or Aqueous β-Cyclodextrin (nh and wh Complexes)[a]

		E_{elec}	E_{vdw}	E_{int}
water	QM/MM	−24.47 (±0.49)	−9.54 (±0.15)	−34.02 (±0.55)
	MM	−15.69 (±0.40)	−9.54 (±0.15)	−25.23 (±0.43)
CD (nh)	QM/MM	−28.60 (±0.42)	−31.32 (±0.15)	−59.92 (±0.46)
	MM	−22.53 (±0.35)	−31.32 (±0.15)	−53.85 (±0.38)
CD (wh)	QM/MM	−29.39 (±0.45)	−30.30 (±0.16)	−59.69 (±0.47)
	MM	−22.53 (±0.36)	−30.30 (±0.16)	−52.83 (±0.39)

[a] QM/MM averages have been computed over 500 structures extracted from the last 8 ns of MD simulations in water solution. QM calculations have been done at the B3LYP/6-311+G(d,p) level of theory. Standard deviations are given in parentheses.

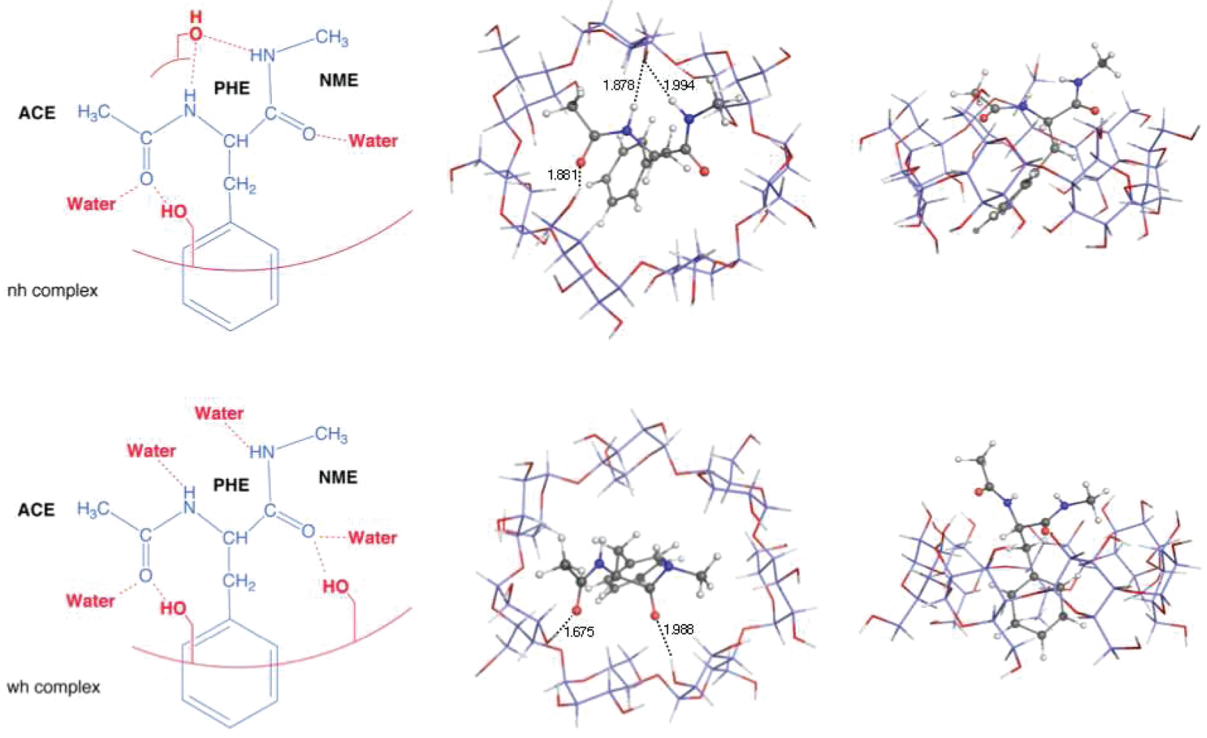

Figure 8. Schematic representation (left) of the average hydrogen-bond network in the nh and wh complexes of our model peptide with β-CD. The formation of peptide−CD hydrogen bonds are illustrated from two particular snapshots (right) corresponding to peptide configurations of type **b** in Figure 5; top and side views are drawn, water is not represented for simplicity, and hydrogen-bond distances are given in Å. Note the different CD anchoring modes for the two complexes.

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Table 3. Free Energy Contributions (kcal/mol) for the Peptide−CD Binding in Water Computed with a QM/MM Variant of the Molecular Mechanics Poisson−Boltzmann Surface Area (MM/PBSA) Method,[63] As Explained in Section 2 Computational Methodology[a]

	CD (nh)	CD (wh)
$\Delta E_{int,elec}$	−10.91 (±0.25)	−12.82 (±0.35)
$\Delta E_{int,vdW}$	−25.50 (±0.01)	−25.03 (±0.04)
ΔE_{int}	−36.41 (±0.25)	−37.85 (±0.35)
$\Delta E_{solv,nonelec}$	−3.79 (±0.00)	−3.65 (±0.00)
$\Delta E_{solv,elec}$	20.39 (±0.02)	23.50 (±0.03)
ΔE_{solv}	16.60 (±0.02)	19.85 (±0.03)
$T\Delta S$	−18.04 (±0.01)	−17.22 (±0.02)
ΔG_{bind}	−1.77 (±0.25)	−0.78 (±0.35)

[a] Averages energies have been computed over 500 structures extracted from the last 8 ns of the MD simulations. Standard deviations are given in parentheses.

Table 4. Average Dipole Moments and Standard Deviations (Debye) of the Model Peptide in Bulk Water and CD Environment from Sequential MD + QM/MM Calculations

	$\langle\mu\rangle$	σ
water	5.98	2.02
CD (nh)	7.63	1.81
CD (wh)	6.01	2.46

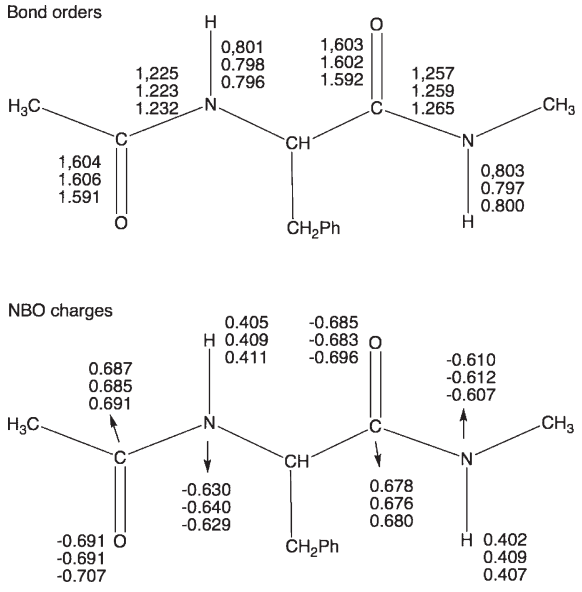

Figure 9. Average bond order and NBO atomic charges for the model peptide from the MD simulations (QM/MM calculations). From top to bottom, bulk water, nh complex, and wh complex.

bond dipole moments. The opposite happens, however, for the main conformation in water (**a**). Obviously the time average of the dipole moment takes into account other conformations too, but a qualitative interpretation of the $\langle\mu\rangle$ values shown in Table 4 can be limited to those structures. It is noteworthy to say, however, that the role of other conformations is not negligible, as illustrated by looking at the magnitude of the standard deviations. It appears, for instance, that the peptide dipole moment in the nh complex has a smaller standard deviation compared to the wh complex, which is of course a direct consequence of the reduced conformational mobility of the guest molecule in the former case.

For completeness, we summarize other quantities connected to electronic polarization effects in Figure 9. One can note the following points: (1) there is not a general trend in going from bulk water to CD complexes, in contrast with what would be expected in terms of dielectric properties of the media; (2) the most significant changes with respect to bulk water are found for the $N-H^{NME}$ bond, both in terms of bond order and H atomic charge.

4. CONCLUSIONS

The effect of peptide encapsulation in a β-CD cavity on the peptide properties has been analyzed in this paper using a simple peptide model. The results emphasize the preference for a nh complexation mode, where the peptide lies on the narrow rim of the CD cavity. According to this mode, the average backbone angles in water are considerably modified, values consistent with an α-helix being favored. The flexibility of the model peptide structure is lowered as a result of the formation of a hydrogen-bond network. These structural changes might have implications on the structure of peptides and proteins linked to CDs macromolecules although further computations with larger models are clearly required. It will be also interesting to check whether or not this type of interaction is capable of discriminating between peptide stereoisomers, and work in this direction is being done too. The free energy of CD encapsulation in water has been estimated to be slightly less than −2 kcal/mol, which is consistent with measurements for the association of β-CD with L-phenylalanine or L-phenylalanineamide reported before.[14,19,39]

■ ASSOCIATED CONTENT

Supporting Information. Full references, refs 49, 50, 62, and 63 This material is available free of charge via the Internet at http://pubs.acs.org.

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