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How does the dehydration change the host-guest association in homogeneous and heterogeneous conditions?

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In this study, the thermodynamic properties of association of some inorganic ions (ClO_4^-, SO_4^{2-}) with β-cyclodextrins (β-CD) in aqueous solution are determined with both free β-CD and surface confined β-CD conditions using atomistic simulations. The potential of mean force (PMF) is calculated as a function of the environment and the thermodynamic properties of association are deduced by integrating the free energy profiles. No inclusion complex between SO_4^{2-} and β-CD is detected. Nevertheless, the PMF curve obtained with gold-confined CD seems to evidence a small minimum at a larger separation distance that shows specific interactions such as hydrogen bonding outside the cavity. As concerns ClO_4^-, our simulations reveal the formation of an inclusion complex with free β-CD in perfect agreement with the available experimental results. Nevertheless, we do not detect any formation of host-guest inclusion complex in heterogeneous conditions. Finally, the differences observed as a function of the anions are interpreted through an atomistic description. The general trend to weaker complex stabilities with the increasing free energy of hydration of the anions is found in homogeneous system.

1 Introduction

Cyclodextrins (CD) are widely used in the field of supramolecular chemistry, in particular as molecular receptors in an aqueous environment. They have been used for studying weak molecular interactions and their functions as carriers for active substances have important applications in biochemistry, drug research, and food industry[1–7]. Because of the possibilities to create useful devices, such as analyte-sensitive sensors or reactant-selective catalysts[8–14], the immobilization of CD onto solid surface is an active field of reserach.

Since the surface leads to a different environment from the bulk solution for the host-guest association, the thermodynamic properties of association of surface-immobilized molecules often show significant differences from those in bulk solutions. Some studies in the literature have been already done regarding the association between CDs and various guests at the surface[8,10,12,15–19]. For all guests that can be totally inserted into the CD cavity, a higher association constant was generally reported at the surface than in the solution[15]. This trend was rather attributed to the entropic factor assuming that there is no significant difference in the enthalpy contribution[8,10,15].

We have recently reported the thermodynamic properties of association involving ferrocenemethanol and β-CD in homogeneous (free CD) and heterogeneous conditions (gold-confined CD)[20]. As expected, the association constant between the surface-confined CD and Fc derivatives was greater than the corresponding association constant in solution. However, molecular simulations[20] have shown a significant difference in the enthalpy whereas the comparison between the entropic values does not show significant differences between the two environments. Then, a larger negative enthalpy change for the surface confined-CD was found. This most favorable $\Delta_r H^0$ was associated with the largest number of inserted atoms due to the wider opening of the surface-confined CD[20]. To enable a better understanding of the role of liquid water and hydrogen bonds on the complexation thermodynamics of this model system[21], these supramolecular assemblies were also studied in both isolated and water phases.

While much is known about interactions between organic guests and cyclodextrins, interactions between inorganic ions and cyclodextrins have drawn much less attention. In fact, few works have been done on the thermodynamics of complexation of inorganic ions with CDs in aqueous solution. This is probably due to the fact that these anions have much lower association constants ($\log K < 1.0$) than those for organic compounds[2]. However, some inorganic anions such as perchlorate seems to display thermodynamic features with negative enthalpy reaction in aqueous solution[2]. In fact, few

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values of the surface association constants for the inclusion of inorganic anions are reported in the literature. To the best of our knowledge, there are only two reports on the surface association constants for the inclusion of inorganic anions. logK values from 0.5 to 1.2 for the inclusion of nitrate anion into a per-2,3-dimethyl 6-thioβ-CD SAM on a Hg electrode were reported[22]. From capacitance measurements, they have shown that the less well solvated anions Cl^-, NO_3^- and ClO_4^- are included in the cyclodextrin cavities of these monolayers whereas the more strongly solvated anions SO_4^{2-}, F^- and $H_2PO_4^-$ are excluded. More recently, the inclusion of inorganic anions such as SO_4^{2-}, NO_3^- and HPO_4^{2-} into the cavity of β-CD monolayers on Au have been studied by Domi et al.[23] using X-ray photoelectron spectroscopy (XPS), quartz crystal microbalance (QCM) and chronocoulometric measurements of the competitive inclusion with ferrocene. Surprisingly, they have obtained a stronger anion inclusion into the cavities of CD-SH immobilized on Au for the larger and more strongly solvated anions such as SO_4^{2-} and HPO_4^{2-} whereas the smaller and less well solvated ClO_4^- are excluded. They have found that the surface association constants for the inclusion of SO_4^{2-}, NO_3^- and HPO_4^{2-} are much larger than those of common organic guests such as ferrocene in aqueous solution. Despite the fact that several factors have been considered to explain this result (size, specific adsorption and hydrogen bonding), the origin of this effect remains unclear.

Molecular modeling should help to more fully explore the scope of present findings. Our purpose is to gain insights into the differences between the solution and surface association strengths. In this study, the free energy profiles of the association of two inorganic ions, ClO_4^- and SO_4^{2-} with β-CD monolayers on Au are determined from numerical experiments in aqueous solution in both homogeneous (free CD) and heterogeneous system (grafted CD). The differences observed as a function of the anions are interpreted through an atomistic description. We take the route of modeling the interactions with the atoms of the surface by using only effective Lennard-Jones potential though additional possible effects[24–26] can occur at the Au surface.

2 Simulation methodology

The free-CD system is composed by one β-CD and one inorganic anion (SO_4^{2-} or ClO_4^-). The aqueous phase is modeled by 3000 water molecules. Na^+ counterions are added in the water phase in order to neutralize the negative charge of the anion and maintain the electroneutrality of the simulation box. The grafted-CD system consists of one per-6-thio-β-cyclodextrin (β-CD) immobilized on a five layer Au(111) surface through the seven sulfur atoms. The Au atoms of the surface involved in the grafting are selected with an angle between the carbon, sulfur and gold atoms that is the closest to the equilibrium angle value defined in the forcefield. The gold surface is composed of five 13 × 16 hexagonal layers representing a fcc lattice, so that the dimensions of the simulation box along the x and y axis are 37.4 and 39.9 Å, respectively. Since the system is non periodic along the direction normal to the surface (z-axis), the simulation box is closed by an additional gold layer. The separation distance between the two surfaces is fixed to 50 Å. The aqueous phase is modeled by adding 2000 water molecules between the two surfaces to reach the correct bulk-water density. The simulation cell is then elongated along the z-direction with empty spaces, up to 280 Å, in order to apply a three-dimensional scheme for the calculation of the electrostatic interactions[27,28]. To observe the effect of the solvent in the association process, the same simulations were also performed in vacuum (without water phase).

The β-CD is described by the CHARMM forcefield[29,30]. The Au parameters for the grafting are taken form the work of Ayappa and coworkers[31]. SO_4^{2-} anion is modeled with parameters published by Cannon *et al*[32]. ClO_4^- is described by the model of Wu *et al*[33]. The Na^+ parameters are taken from Aqvist forcefield[34]. The water molecules are represented by a flexible SPC-based model[35]. The partial charges of the β-CD are calculated from the density functional theory (DFT)[36,37] with the B3LYP functional[38,39] with effective core potential (SD-DALL) Gaussian basis using the Gaussian 03 package and the CHELPG procedure as a grid-based method. The repulsion-dispersion interactions are described using the Lennard-Jones potential. The LJ potential parameters between unlike atoms are calculated with Lorentz-Berthelot mixing rules. The electrostatic interactions are calculated with a standard coulombic potential for isolated systems and with the three-dimensional Smooth Particle Mesh Ewald (SPME)[40] in aqueous phase systems.

The potential of mean force (PMF)[41] $W(\mathbf{r}_{12})$ represents the interaction between two particles 1 and 2 kept at a fixed distance $\mathbf{r}_{12}$ from each other when the $N-2$ particles are averaged over all the configurations. The potential of mean force is calculated by both the Thermodynamic Integration (TI) method[42–46] and the Constraint Force (FC) method[46]. The details of the calculation are given in Ref.[20,21]. The PMF profile provides a measure of the difference in free energy along a reaction coordinate. In our case, to study the association process between the host and guest molecules, the considered reaction coordinate is the distance d between the centers of mass of β-CD and anion along z-axis (Figure 1).

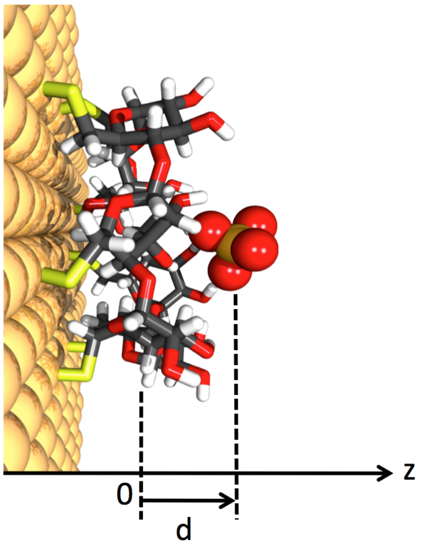

Fig. 1 Scheme of the reaction coordinate choosen for the PMF calculation.

We have shown that the TI and FC methodologies give the same results within the statistical fluctuations for the calculation of the PMFs. This is illustrated on Figure 2 that reports PMF profiles for association of both SO_4^{2-} and ClO_4^- with grafted-CD. This is an important result because these two types of calculation do not use the same strategy. The TI methodology use the energy and the FC formalism uses the constraint force. The equivalence of the two approaches shows the ability of these two methods to accurately describe the free energy profile in the case of heterogeneous systems.

The thermodynamic properties are then obtained by integrating the PMF profile along the separation distance between β-CD and the anion[47–49] considering a cylindrical approach[50,51].

$$K = \int dz\, \pi r_{cyl}^2 N_A \exp\left(-\frac{W(z)}{k_B T}\right) \tag{1}$$

where N_A is the Avogadro number, k_B the Boltzmann constant, T the temperature and r_{cyl} the radius of the cylinder in which the anion can move.

The thermodynamic properties of binding are calculated using the following expressions

$$\begin{aligned} \Delta rG^0 &= -k_B T \ln K && (2)\\ &= -k_B T \ln \int dh\, \pi r_{cyl}^2 N_A \exp\left(-\frac{W(z)}{k_B T}\right) && (3)\end{aligned}$$

$$\begin{aligned} \Delta rH^0 &= k_B T^2 \frac{d\ln K}{dT} && (4)\\ &= \frac{\int dz\, r_{cyl}^2 W(z) \exp\left(-\frac{W(z)}{k_B T}\right)}{\int dz\, r_{cyl}^2 \exp\left(-\frac{W(z)}{k_B T}\right)} && (5)\end{aligned}$$

$$\begin{aligned} T\Delta rS^0 &= \Delta rH^0 - \Delta rG^0 && (6)\\ &= \frac{\int dz\, r_{cyl}^2 W(z) \exp\left(-\frac{W(z)}{k_B T}\right)}{\int dz\, r_{cyl}^2 \exp\left(-\frac{W(z)}{k_B T}\right)} \\ &+ k_B T \ln \int dz\, \pi r_{cyl}^2 N_A \exp\left(-\frac{W(z)}{k_B T}\right) && (7)\end{aligned}$$

For the calculation of the potential of mean force, MD simulations were performed in the constant-NVE ensemble after equilibration of the system in the constant-NpT ensemble for free-CD system and in the constant-NVT ensemble for grafted-CD system at $T = 298$ K and $p = 1$ atm. The equations of motion were integrated using the Verlet Leapfrog algorithm scheme with a timestep equals to 2 fs. The C-H and O-H covalent bonds were kept of fixed length by using the SHAKE algorithm[52]. The cutoff radius for the LJ interactions and for the real part of the electrostatics was chosen to 12 Å. The convergence parameter for the SPME summation was fixed to 0.2650 $Å^{-1}$. The reciprocal space for the SPME method was developed on a number of k-vectors equal to 16 along the $x-$,$y-$ and $z-$ directions for the free-CD system. This number is extended up to 128 in the $z-$direction for the grafted-CD system due to the elongation of the simulation cell along the axis of heterogeneity. With these parameters, the calculation of the electrostatic interactions satisfies a relative error of 10^{-6}. Simulations were performed using the parallel version of the modified DL_POLY_MD package[53] using up to 12 processors at a time. Each separation distance between host and guest molecules corresponds to one simulation. The distance between the molecules was constrained with the SHAKE algorithm. One simulation was performed every 0.2 Å, and each typical simulation run of the system consisted of an equilibrium period of 200 ps and a production phase of 400 ps. In the case of the free-CD, the multiple hydrogen bonds that forms with the anion causes important deformations of the CD. As a consequence the acquisition phase was extended to 800 ps in order to get a better convergence of the energetic properties. To obtain the total PMF curve for free CD in aqueous phase the simulation time is 68 ns which would represent 1.3 CPU year on a single processor. For free-CD, seven harmonic external potentials (k = 30 kJ.mol.$Å^{-2}$)

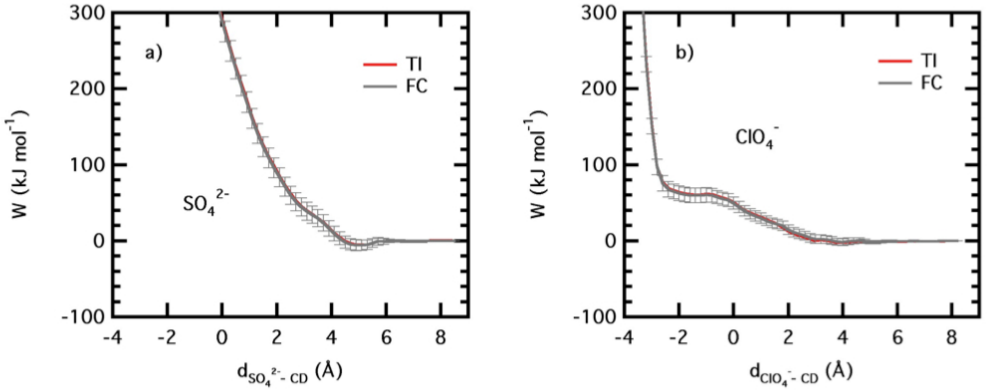

Fig. 2 Free energy profiles obtained for the inclusion of (a) SO_4^{2-} and (b) ClO_4^- with grafted-CD with the thermodynamic integration (TI) and force constraint (FC) methods.

are applied on each glucosidic oxygen site and centered at the corresponding initial positions. This external potential helped to preserve the initial orientation of the β-CD with its revolution axis along the *z*-axis with only minor modifications of its overall dynamics.

3 Results and discussions

The free energy profiles characterizing the association process of SO_4^{2-} into β-CD in various environments are shown in Figure 3.

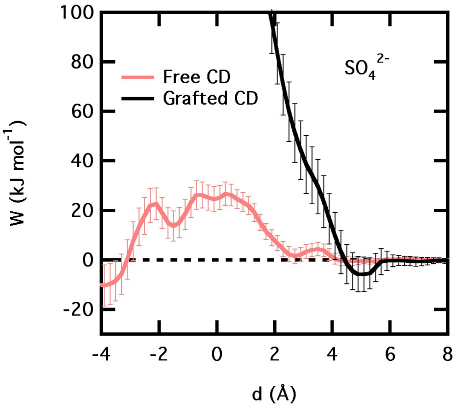

Fig. 3 Free energy profiles obtained for the inclusion of SO_4^{2-} into the free CD cavity and the surface-confined CD cavity in water.

For free CD, no local minimum is observed. The free energy increases progressively as sulfate anion approaches β-CD, leading to a maximum when the anion penetrates within the CD cavity. This indicates unambiguously no association between SO_4^{2-} and the β-CD in homogeneous system. As concerns the surface-confined CD, the PMF curve (Figure 3) also evidences the noninclusion of the SO_4^{2-}. However, a small negative minimum at a separation distance of 5 Å is observed in Figure 3. This larger separation distance cannot correspond to the formation of host-guest inclusion complex between SO_4^{2-} and β-CD since the inorganic anion starts to approach to the wider side of the β-CD at a distance of the center of mass of CD of 2 Å. Thus, at 5 Å the anion is inevitably located outside the cavity of the CD. By integrating this free energy profile along the host-guest separation distances, the association constant and the enthalpy change are obtained. The values of the thermodynamic properties of association are equal to $\Delta_r G^0$ = 0.4 kJ mol^{-1}, $\Delta_r H^0$ = -4.5 kJ mol^{-1} and $T\Delta_r S^0$ = -4.9 kJ mol^{-1}. According to literature, similar thermodynamic trend ($\Delta_r H^0 < 0$ and $T\Delta_r S^0 < 0$)[2,54,55] was obtained for guests that form complexes with CDs predominantly through hydrogen bonding. Indeed, at 5 Å, the SO_4^{2-} oxoanion forms 1.5 ± 0.6 hydrogen bonds upon complexation with CDs. The typical configuration of the system establishing the presence of the hydrogen bonding is shown in Figure 4a. In fact, there are strong requirements in distance and angle for optimal hydrogen-bonding interaction[13,56,57]. Stronger hydrogen bonds are obtained if both the angle θ_{HB} is 0° and the distance d_{HB} is close to 1.5 Å. As shown from the hydrogen bonds distribution represented in Figure 4b for this system, hydrogen bonds formed between the sulfate anion and β-CD are rather strong.

To understand why the sulfate anion is not included into the cavity of CD, the partionning of the free energy profile is performed. We report in Figure 5 the SO_4^{2-}-H_2O and

SO_4^{2-}-CD free energy contributions at different separation distances in both homogeneous and heterogeneous conditions.

In both cases, it can be noticed that the unfavorable SO_4^{2-}-H_2O free energy contributions are never compensated by the favorable SO_4^{2-}-CD contributions. As concerns the gold-confined CD, the more positive SO_4^{2-}-H_2O free energy contributions are attributed to the larger desolvation of the guest. Indeed, our simulations indicate releases of 13 and 8 water molecules from the first hydration shell of the anion upon complexation of surface-confined CD and free CD respectively. However, it can be observed that the SO_4^{2-}-H_2O free energy contribution becomes less unfavorable as the separation distance for free CD becomes negative along the z-axis. At this distance, the SO_4^{2-} anion leaves the narrower sites of the CD at this distance and consequently may recover its hydration shell.

The SO_4^{2-}-CD free energy contribution for the grafted CD becomes less favorable from 2 Å (Figure 5a) whereas it decreases continuously with free CD. By comparing the free energy (Figure 5a) and energy contributions (Figure 5b), we can estimate the entropy changes. For the surface-confined CD, the SO_4^{2-}-CD free energy and energy profiles show similar shapes. This is not the case for free CD. Indeed, from a distance of 1 Å the energy becomes less favorable whereas the corresponding free energy contribution decreases regularly. These differences can only be explained by entropic effects. When the sulfate anion returns to the bulk, it recovers some degrees of freedom and contributes positively to the entropy. This effect is partially counterbalanced by a less favorable SO_4^{2-}-CD enthalpy contribution. For the grafted CD, the sulfate anion is trapped near the surface and then the entropic term remains unfavorable. Actually, the energetic cost of the desolvation of SO_4^{2-} is 300 $\mathrm{kJ\,mol^{-1}}$ from 2 to 8 Å whereas the favorable energy change due to the interaction with β-CD is only equal to -200 $\mathrm{kJ\,mol^{-1}}$. In the case of grafted CD, the desolvation cost is 600 $\mathrm{kJ\,mol^{-1}}$ and the favorable energy change is -400 $\mathrm{kJ\,mol^{-1}}$. In conclusion, the insertion of the SO_4^{2-} into the cavity of the β-CD is never energetically favorable in both homogeneous and heterogeneous conditions. The thermodynamic cost to be paid for this insertion is a partial desolvation of SO_4^{2-} that is highly unfavorable considering its greater hydration energy. The calculated hydration energy for this anion in bulk water is found equal to -970 $\mathrm{kJ\,mol^{-1}}$. Both the first and second hydration shells are considered for the calculation. As a comparison, the experimental value is given equal to -1018 $\mathrm{kJ\,mol^{-1}}$[58] leading to a deviation between simulation and experiments less than 5 % .

We also investigated the role of water in the noninclusion of the sulfate. For this purpose, we specially focus on the comparison of the PMF in both gas and water phases (Figure 6). In the gas phase, the interaction between the host and the guest at larger separation distance is due to the formation of intermolecular hydrogen bonds. This effect is more pronounced in free CD because its conformation may change in order to favor hydrogen bonds formation. The study of the association process in the gas phase suggests a possible favorable interaction between SO_4^{2-} and CD. As a result, the non association in the water phase can only be explained by the unfavorable desolvation of the anion.

The fact that we did not detect any formation of host-guest inclusion complex with the surface-confined CD seems to be in conflict with the results of Domi et al.[23]. Indeed, they have found a stronger association of SO_4^{2-} with β-CD immobilized to gold electrode. In order to explain this phenomenon, the assumptions of multiple hydrogen bonding was discussed. To verify this hypothesis, we therefore decided to evaluate the number of hydrogen bonds. The number of hydrogen bonds and the energy contributions of SO_4^{2-}-CD have been reported in Figure 7 as a function of the separation distance. A number of 6 hydrogen bonds is obtained from our simulations at 2 Å. As shown in Figure 7, a correlation is observed between this number and the electrostatic part of the SO_4^{2-}-CD energy contributions. Figure 7 also highlights that the major contribution to the SO_4^{2-}-CD contribution energy comes from the electrostatic energy since the Lennard-Jones energy contributions do not contribute significantly.

However this favorable electrostatic part never compensates the unfavorable term due to the desolvation of the anion (Figure 5b). As shown previously, the desolvation cost is 600 $\mathrm{kJ\,mol^{-1}}$ and the favorable energy change is -400 $\mathrm{kJ\,mol^{-1}}$ in the case of the grafted CD. In conclusion, the insertion of the SO_4^{2-} into the cavity of the β-CD is never energetically favorable in both homogeneous and heterogeneous conditions.

To study how the nature of the anion impacts on the association process, we now focus on the PMF curves characterizing the association process of ClO_4^- into β-CD (Figure 8).

Unlike sulfate anion, ClO_4^- is rather a hydrophobic anion that can be transported with almost no associated water molecules. With free CD, the free energy profile presents a minimum with a free energy of -5 $\mathrm{kJ\,mol^{-1}}$ when the perchlorate anion penetrates deeper into the cavity of β-CD. This evidences the formation of inclusion complex. In Figure 9 is reported a snapshot of the inclusion complex between free CD and ClO_4^- in aqueous solution.

From the integration of this free energy profile along the host-guest separation distances we have obtained K = 0.3,

$\Delta_r H^0$ = -2,2 kJ mol^{-1} and $T\Delta_r S^0$ = -5,1 kJ mol^{-1}. This can be compared with the available literature values that are equal to K = 12, $\Delta_r H^0$ = -16,5 kJ mol^{-1} and $T\Delta_r S^0$ = -10,3 kJ mol^{-1} [23]. The MD simulations are consistent with the experimental thermodynamic properties showing that the very weak association between ClO_4^- into free β-CD is enthalpy driven ($\Delta_r H^0$ <0). More precise comparison is difficult due to the low affinity of ClO_4^- towards β-CD that leads to large uncertainties. In bulk (Figure 10a), the dehydration of the anion (+150 kJ mol^{-1}) is partially compensated by the favorable anion-CD interaction (-100 kJ mol^{-1}). It also means that other contributions such as favorable entropic terms mainly due to the release of water molecules in the bulk must occur to explain the association. As concerns the surface-confined CD, the PMF curve highlights that the association process is not favorable. Figure 10a shows that in this case the interaction anion-CD is weaker than for free CD and the cost of the desolvation is more important. The energy balance is clearly unfavorable for this system. The ClO_4^-/ CD energy contribution is negative in bulk condition and remains close to zero for the grafted CD due to the fact that the grafting modifies the CD conformation.

Finally, to compare the effect of the anion on the association process of free CD, we now focus in Figure 10b on the calculated energy of the SO_4^{2-}-H_2O, SO_4^{2-}-CD, ClO_4^--H_2O and ClO_4^--CD contributions in homogeneous system. A global look at these contributions immediately leads to a general conclusion that the hydration energy of the anion plays a crucial role upon inclusion into the CD cavity. SO_4^{2-}, considered as an hydrophilic anion, has a greater hydration energy that leads to a strong energy change due to the dehydration. This effect can not be compensated by the favorable energy change due to the anion-CD interaction. Hydrophobic anion such as ClO_4^- gives a contribution for the desolvation that is partially compensated by favorable anion-CD energetic contributions.

4 Conclusions

Throughout this paper, we report computational investigations of the association of some inorganic ions (ClO_4^-, SO_4^{2-}) with β-CD monolayers in aqueous solution in both homogeneous (free CD) and heterogeneous system (gold-confined CD). For each system, we have calculated the free energy profile in water as a function of the separation distance to give an answer to the possible association between the macrocycle and the inorganic ions.

The simulations did not detect any inclusion of SO_4^{2-} into the cavity of β-CD in both homogeneous and heterogeneous systems. The PMF curve only shows a small minimum at a separation distance of 5 Å with gold-confined CD. In fact, at this larger distance the SO_4^{2-} oxoanion that is located outside the cavity of the macrocycle forms 1.5 hydrogen bonds upon complexation with CDs. From the analysis of the different energy contributions, it has been shown that the major part of the SO_4^{2-}-CD energy comes from the electrostatic interaction since the Lennard-Jones part do not contribute significantly. However this favorable electrostatic part never compensates the unfavorable term due to the desolvation of the anion considering the greater hydration energy of SO_4^{2-}.

The PMF curves characterizing the association process of ClO_4^- into β-CD are also calculated to study how the nature of the anion impacts on the association process. As expected, the formation of inclusion complex is evidenced with free CD in agreement with the available experimental results. Despite the fact that the association of ClO_4^- with β-CD is very weak, the thermodynamic properties deduced from the PMF curve indicate that the process is enthalpy driven. This is consistent with the experimental enthalpies of complexation.

In conclusion, the fundamental issue of the formation of inclusion complex have been thoroughly studied in this work from the change of the free energy as a function of the separation distance between the host and guest. This type of calculation is time-consuming but allows to definitively conclude on the factors that may favor the association between two species for a given force field. Since the parameters of the force fields have been developed from experimental properties, they implicitly consider polarizability and quantum effects. Nevertheless, it would be very interesting in the future to check the impact of explicit polarization on the association process for the SO_4^{2-} anion, for example.

5 Acknowledgment

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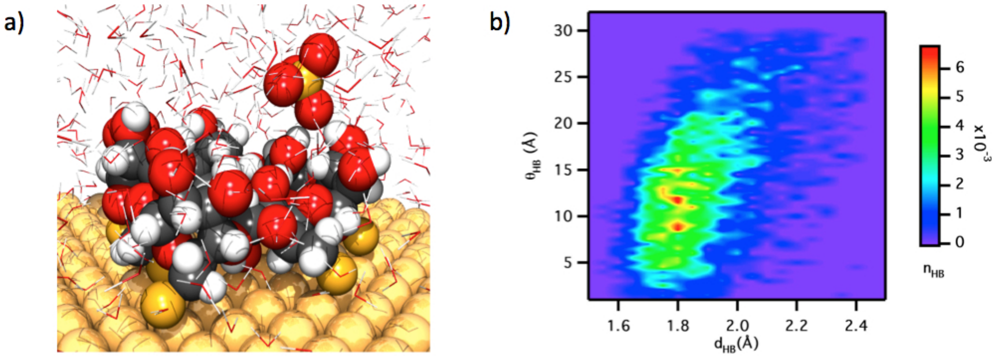

Fig. 4 (a) Scheme of the approach of SO_4^{2-} towards the surface-confined β-CD showing the presence of the hydrogen bonding (b) Distribution of both distances and angles of hydrogen bonds towards the surface-confined β-CD.

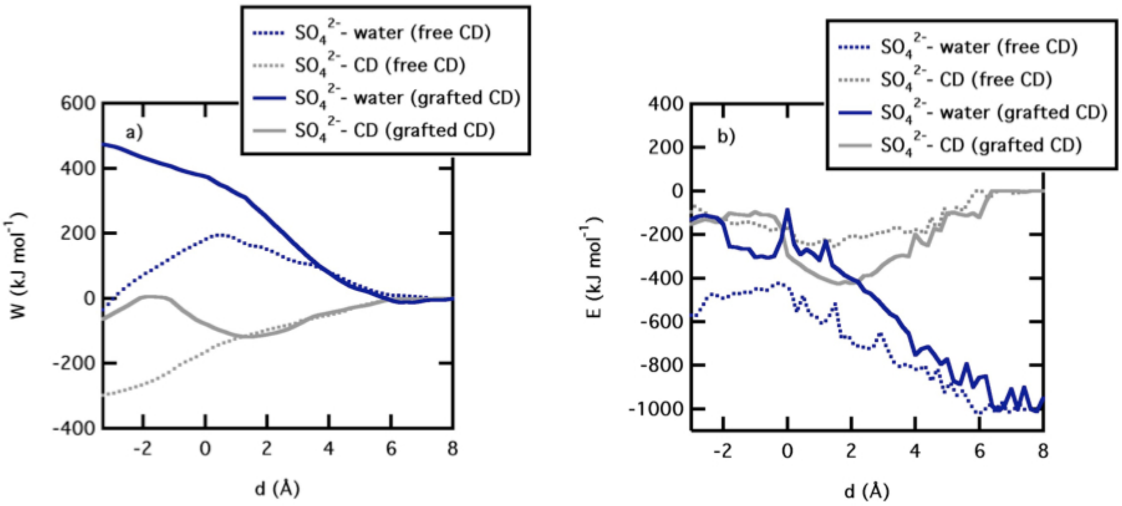

Fig. 5 (a) Partitioning of the PMF into the SO_4^{2-}-H_2O and SO_4^{2-}-CD free energy contributions at different separation distances in both homogeneous and heterogeneous conditions (b) SO_4^{2-}-H_2O and SO_4^{2-}-CD energy contributions at different separation distances in both homogeneous and heterogeneous conditions.

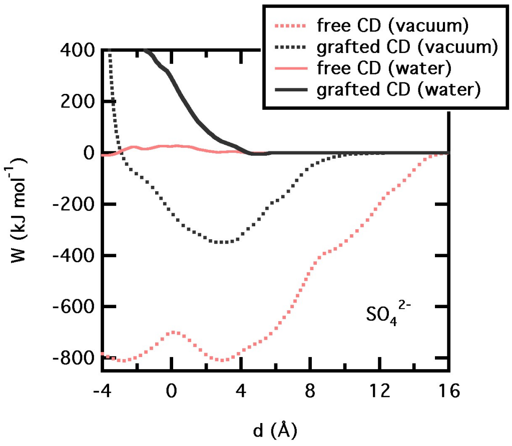

Fig. 6 Comparison of the free energy profiles obtained for the inclusion of SO_4^{2-} into the free CD cavity and the surface-confined CD cavity in both isolated and water phases.

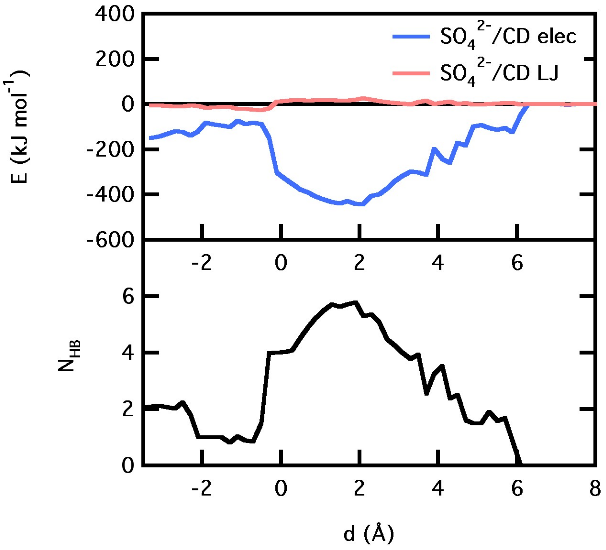

Fig. 7 Correlation between the number of the hydrogen bonds and both the calculated Lennard-Jones and electrostatic energy contributions between SO_4^{2-} and CD along the host-guest separation distances for the grafted CD in water.

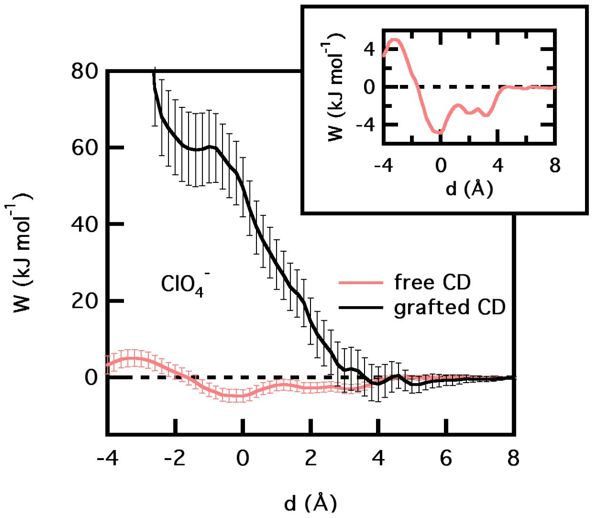

Fig. 8 Free energy profiles obtained for the inclusion of ClO_4^- into (a) the free CD cavity and (b) the surface-confined CD cavity in water.

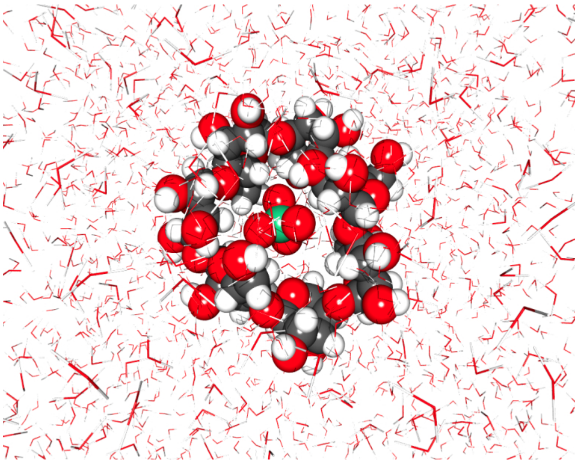

Fig. 9 Structure of inclusion complexes between free CD and ClO_4^- in aqueous solution.

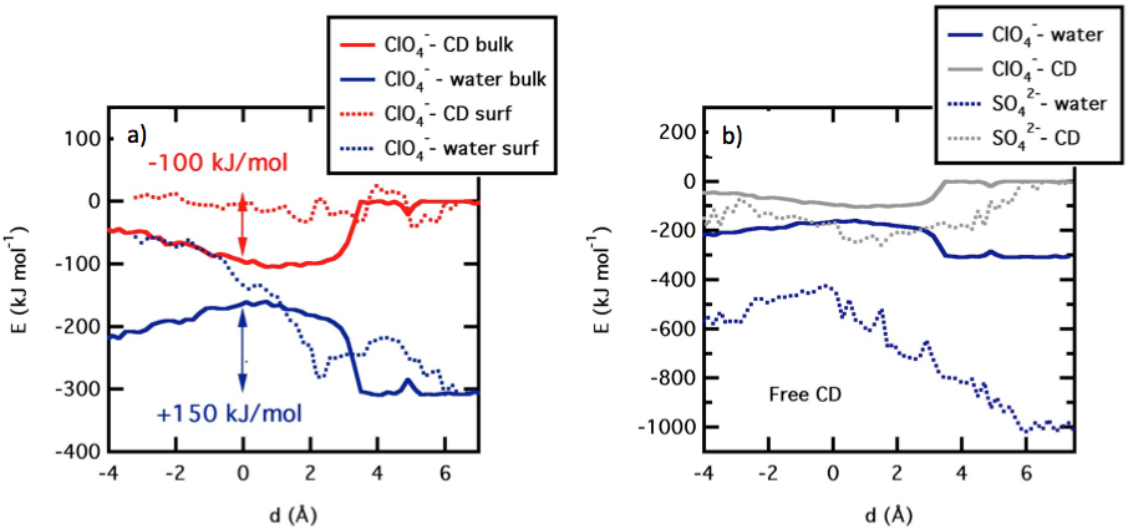

Fig. 10 (a) ClO_4^--H_2O and ClO_4^--CD energy contributions at different separation distances in both homogeneous and heterogeneous conditions and (b) ClO_4^--H_2O, ClO_4^--CD and also SO_4^{2-}-H_2O, SO_4^{2-}-CD energy contributions at function of separation distance in homogeneous system.

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