

# Supporting Information

## **Energetic competition effects on thermodynamic properties of association between $\beta$ -CD and Fc group: a potential of mean force approach**

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## Perturbation methods

### Reversibility of the calculation

The potential of mean force (PMF) was calculated by Thermodynamic Integration (TI), Finite Difference Thermodynamic Integration (FDTI) and Free Energy Perturbation (FEP) methods. The perturbation corresponds to a displacement of the ferrocenemethanol along the axis that connects the centers of mass of  $\beta$ -CD and FcOH. The amplitude of the displacement is  $10^{-4}$  Å for both TI and FDTI methods and 0.05 Å for FEP. Figure S1 shows PMF curves for free CD in aqueous phase calculated in forward and backward directions. TI and FDTI methodologies (panels a and b) are more reversible than FEP (panel c). Calculations performed in the forward, backward and the resulting centered values are perfectly overlapped for both TI and FDTI whereas they are slightly shifted for FEP (shift of about  $2.5 \text{ kJ.mol}^{-1}$  between forward and backward directions at the end of the integration). However, the centered values are similar for the different methods as shown in panel d) of Figure S1.

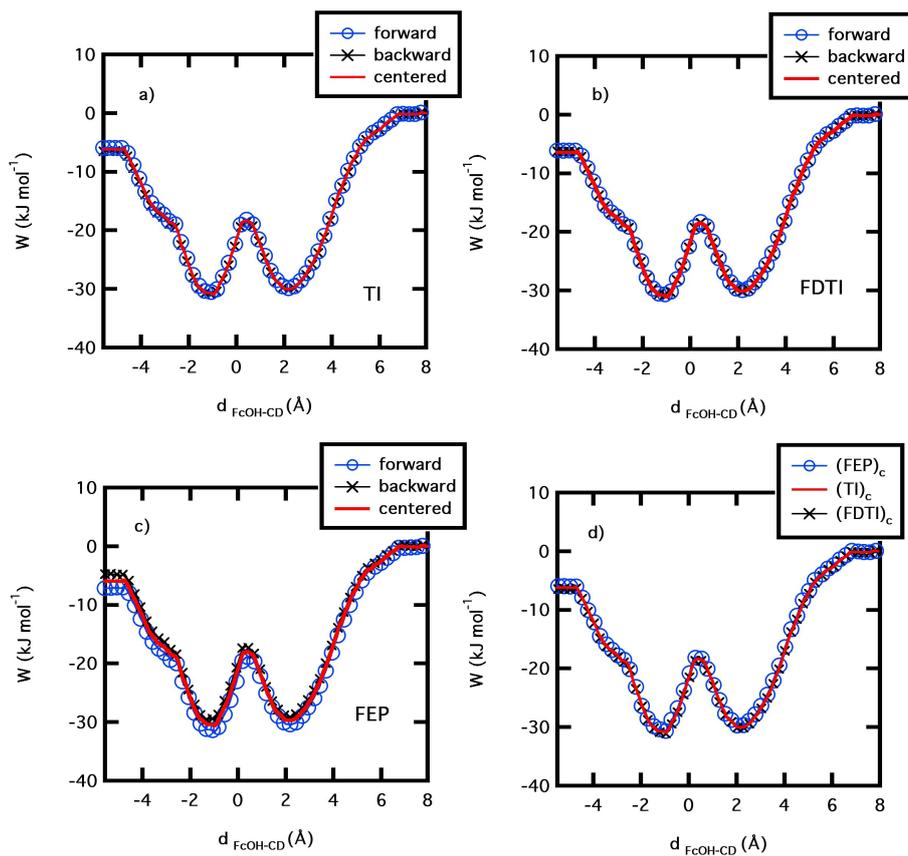


Figure S1: Potential of mean force along the separation distance between the centers of mass of free  $\beta$ -CD and FcOH in water obtained with TI (panel a), FDTI (panel b) and FEP (panel c) in both the forward and backward directions. The resulting centered value is also calculated. Panel d) compares the centered PMF curve for the different perturbation methods.

## Correlation of free energy contributions

The total PMF curve is decomposed into FcOH-CD and FcOH-H<sub>2</sub>O contributions in Figure S2. We can notice that for TI and FDTI (panels a and b) the sum of all the contributions is equal to the total PMF curve calculated using the total energy. By contrast, with FEP (panel c), the sum of all the contributions is different from the total PMF curve. This indicates that the different contributions are correlated and that the decomposition into specific contributions is no longer valid with FEP. In fact, the following approximation cannot be applied because of the exponential term.

$$\begin{aligned}
 W_{\text{FEP}}(d(\lambda_i)) &= k_B T \sum_{j=1}^{i-1} \ln \left\langle \exp \left[ -\frac{\Delta U_{\text{tot}}(\mathbf{r}^N, \lambda_j)}{k_B T} \right] \right\rangle_{\lambda_j} = k_B T \sum_{j=1}^{i-1} \ln \left\langle \exp \left[ -\frac{\sum_n \Delta U_n(\mathbf{r}^N, \lambda_j)}{k_B T} \right] \right\rangle_{\lambda_j} \\
 &\approx k_B T \sum_n \sum_{j=1}^{i-1} \ln \left\langle \exp \left[ -\frac{\Delta U_n(\mathbf{r}^N, \lambda_j)}{k_B T} \right] \right\rangle_{\lambda_j}
 \end{aligned} \tag{1}$$

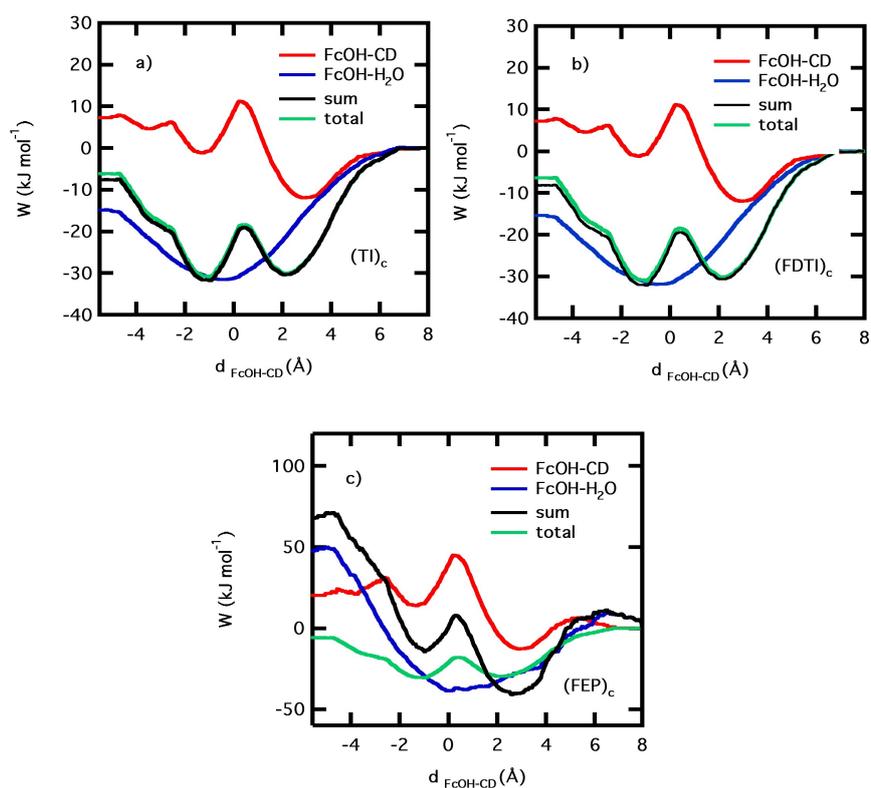


Figure S2: Decomposition of the total PMF curve for free  $\beta$ -CD system in solution into FcOH-CD, FcOH-H<sub>2</sub>O contributions calculated with TI (panel a), FDTI (panel b) and FEP (panel c). The sum of the contributions (black curve) is compared with the PMF curve obtained from the total energy (green curve).

## Potential of mean force convergence

With TI method, the convergence of the PMF is checked by the convergence of the  $\left\langle \frac{\partial U(\mathbf{r}^N, \lambda)}{\partial \lambda} \right\rangle$  term. Figure S3 represents this term as a function of the number of saved simulation configurations for each system (free CD and grafted CD) in both gas and water phases.

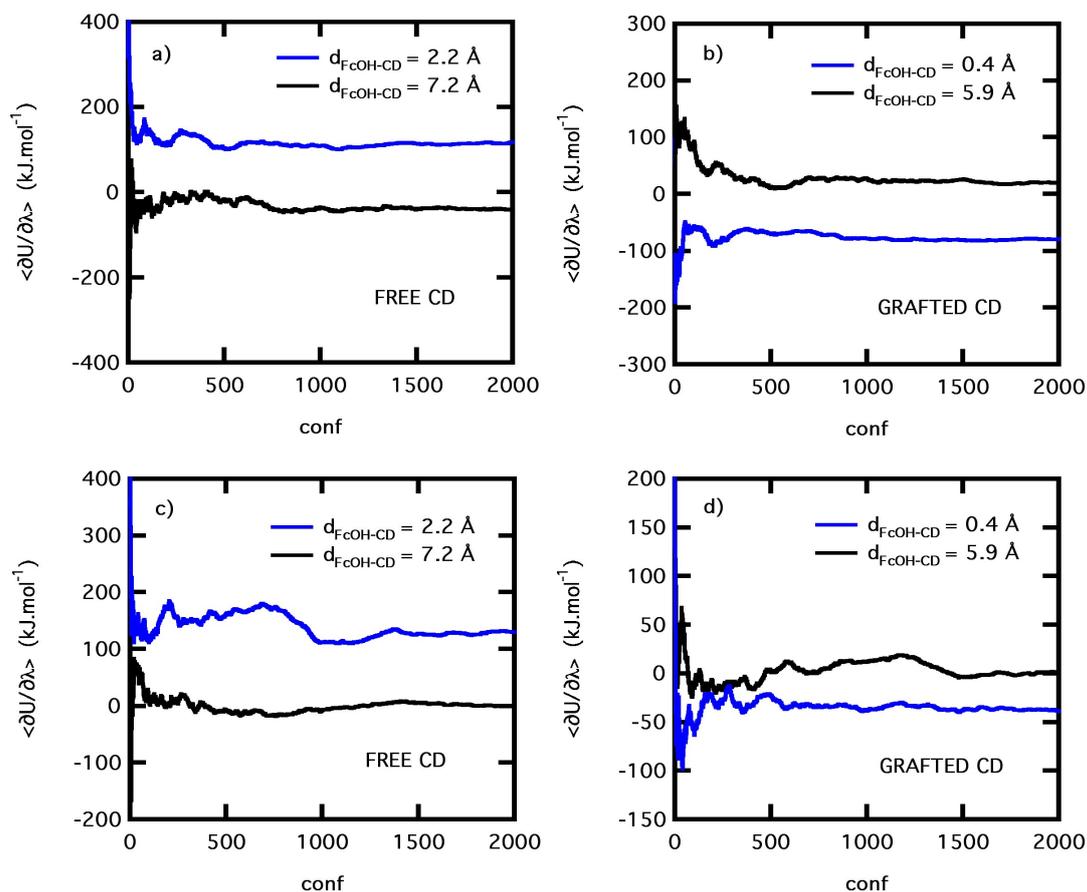


Figure S3: Cumulated average value of the  $\frac{\partial U(\mathbf{r}^N, \lambda)}{\partial \lambda}$  term as a function of the number of saved configurations for both free CD and grafted CD in gas phase (panels a and b) and in water phase (panels c and d). The blue curve corresponds to a separation distance for which the FcOH is inside the CD and the black curve to a configuration for which it is outside.

# Structural and energetic characterization of minimal energy conformations in water

We performed additional unconstrained MD simulations to obtain structural characteristics of the most stable structures. The results of these simulations are presented below and indicate quite small difference in comparison with the constrained ones (we obtained a maximum difference of 5% on the number of hydrogen bonds and of 3% on the energy values).

## Free CD

We analyze structural and energetic properties for the conformations corresponding to the first minimum ( $d_{\text{FcOH-CD}} = 2.2 \text{ \AA}$ ) and the second minimum ( $d_{\text{FcOH-CD}} = -1.0 \text{ \AA}$ ) of the PMF curve.

### - Structural parameters

**Table S1: Number of FcOH atoms inserted into the CD, values of the angle ( $^{\circ}$ ) between FcOH and CD axis and values of the radius ( $\text{\AA}$ ) of the large and small rings of the CD for the complex structures at the first and second minimum of the PMF profile.**

	first minimum	second minimum
FcOH atoms inserted	$18.4 \pm 2.3$	$18.1 \pm 3.8$
FcOH/CD angle	$43 \pm 12$	$10 \pm 5$
CD large ring radius	$7.4 \pm 0.1$	$7.3 \pm 0.1$
CD small ring radius	$6.0 \pm 0.1$	$6.1 \pm 0.1$

The angle between FcOH and CD axis is represented on Figure S4.

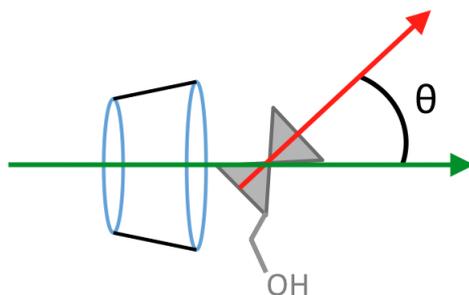


Figure S4: Scheme of the angle between FcOH and CD axis.

### - Hydrogen bonds

**Table S2: Number of different types of hydrogen bond in the system at the first and second minimum of the PMF profile for the free CD complex in water phase.**

h-bond type	first minimum	second minimum
CD intramolecular	$6.0 \pm 1.0$	$6.4 \pm 0.8$
CD/FcOH	0.0	0.0
CD/H <sub>2</sub> O	$23.3 \pm 2.0$	$23.1 \pm 2.0$
FcOH/H <sub>2</sub> O	$1.1 \pm 0.4$	$1.1 \pm 0.5$

### - Energy contributions

**Table S3: Energy contributions (kJ.mol<sup>-1</sup>) of the system at the first and second minimum of the PMF profile for the free CD complex in water phase.**

contribution	LJ disp	first minimum			second minimum			
		LJ rep	elec	tot	LJ disp	LJ rep	elec	tot
CD/FcOH	-118.6	54.6	-10.8	-74.8	-125.6	59.0	-7.2	-73.8
CD/H <sub>2</sub> O	-762.6	707.1	-1327.0	-1382.4	-752.7	697.7	-1339.4	-1394.4
FcOH/H <sub>2</sub> O	-79.1	52.3	-64.8	-91.6	-78.7	54.0	-72.5	-97.3

## Surface-confined CD

For the surface-confined CD in water, the minimum of the PMF profile corresponds to a separation distance  $d_{\text{FcOH-CD}}$  of 1.0 Å.

### - Structural parameters

**Table S4: Number of FcOH atoms inserted into the CD, values of the angle (°) between FcOH and CD axis and values of the radius (Å) of the large and small rings of the grafted CD for the complex structure at the minimum of the PMF profile.**

FcOH atoms inserted	$23.1 \pm 0.7$
FcOH/CD angle	$167 \pm 4$
CD large ring radius	$7.2 \pm 0.1$
CD small ring radius	$6.3 \pm 0.1$

### - Hydrogen bonds

**Table S5: Number of different types of hydrogen bond in the system at the first and second minimum of the PMF profile for the free CD complex in water phase.**

CD intramolecular	$5.0 \pm 0.8$
CD/FcOH	0.0
CD/H <sub>2</sub> O	$15.6 \pm 1.8$
FcOH/H <sub>2</sub> O	$1.4 \pm 0.6$

**- Energy contributions**

**Table S6: Energy contributions (kJ.mol<sup>-1</sup>) of the system at the first and second minimum of the PMF profile for the free CD complex in water phase.**

contribution	LJ disp	LJ rep	elec	tot
CD/FcOH	-149.9	78.7	-13.4	-84.5
CD/H <sub>2</sub> O	-532.6	459.0	-820.3	-893.9
FcOH/H <sub>2</sub> O	-58.4	49.0	-78.2	-87.6

## Calculation of thermodynamic properties

The thermodynamic properties of binding were calculated by integrating the PMF profile along the separation distance between  $\beta$ -CD and FcOH. This integration is made considering a cylindrical approach of the FcOH. We can assume that the trajectory of FcOH is confined into a cylinder of constant radius. We can also calculate the average radius of the cylinder,  $r_{\text{cyl}}$ , at each separation distance taking into account the movement of the center of mass of the FcOH into the  $\beta$ -CD. Auletta *et al*<sup>1</sup> made the assumption that taking  $r_{\text{cyl}}$  constant and equals to 2 Å was suitable for all the guests. The thermodynamic properties of binding calculated by both integration methods in water are given in Table S7. Changing the integration method does not induce significant effect : the thermodynamic values are identical.

**Table S7: Thermodynamic properties of binding (kJ mol<sup>-1</sup>) calculated from the PMF profile obtained by TI method for free and grafted CD in water. The integration is made along a cylinder of constant radius of 2 Å and also considering an average radius calculated at each separation distance and resulting from the in-plane movement of the FcOH.**

	$r_{\text{cyl}} = 2 \text{ \AA}$		$\langle r_{\text{cyl}} \rangle$	
	free CD	grafted CD	free CD	grafted CD
$\log K$	3.3	5.0	3.4	5.1
$\Delta_r G^0$	-19	-28	-20	-29
$\Delta_r H^0$	-29	-39	-29	-39
$T\Delta_r S^0$	-10	-11	-9	-10

## References

- (1) Auletta, T.; de Jong, M. R.; Mulder, A.; van Veggel, F. C. J. M.; Huskens, J.; Reinhoudt, D. N.; Zou, S.; Zapotoczny, S.; Schönherr, H.; Vancso, G. J.; Kuipers, L. *J. Am. Chem. Soc.* **2004**, *126*, 1577–1584.