

# Effect of dimethyl sulfoxide on the binding of 1-adamantane carboxylic acid to $\beta$ and $\gamma$ -cyclodextrins

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# 1. Correction to the free energy of binding

The evaluation of the binding free energy of a charged species, such as carboxylic ADA (net charge of  $-1$ ), using explicit-solvent simulations and lattice-sum methods (PME) induces some artefacts that need to be corrected. We used the analytical scheme suggested by Rocklin et al.<sup>1</sup> for correcting the free energy evaluated from our simulations:

$$\Delta G_{MD,NBC} = \Delta G_{MD,PBC}(L) + \Delta\Delta G_{ANA}(L) + \Delta\Delta G_{DSC}(L) \quad (1)$$

where  $\Delta G_{MD,PBC}(L)$  is the raw value calculated from our simulations using periodic boundary conditions,  $\Delta G_{MD,PBC}(L)$  is the raw value calculated from our simulations using periodic boundary conditions,  $\Delta\Delta G_{ANA}(L)$  is a correction term for finite-size effects,  $\Delta\Delta G_{DSC}(L)$  is a correction term for discrete solvent effects, and  $\Delta G_{MD,NBC}$  is the binding free energy corrected for all these effects. All reported values in the main manuscript and in Table 1 are the corrected free energies  $\Delta G_{MD,NBC}$ . We explain hereafter how  $\Delta\Delta G_{ANA}(L)$  and  $\Delta\Delta G_{DSC}(L)$  were calculated. According to Rocklin et al.,  $\Delta\Delta G_{ANA}(L)$  is decomposed into four different terms, namely:

$$\Delta\Delta G_{ANA}(L) = \Delta\Delta G_{NET}(L) + \Delta\Delta G_{USV}(L) + \Delta\Delta G_{RIP}(L) + \Delta\Delta G_{EMP}(L) \quad (2)$$

where  $\Delta\Delta G_{NET}(L)$  and  $\Delta\Delta G_{USV}(L)$  are terms depending on the inverse of the box dimension  $L$  for which we have analytical expressions (equations (15) and (16) of Rocklin’s paper). These expressions also require the dielectric constant of the solvent  $\epsilon_S$  of the model used in the simulations. We used the values 66.7 for SPC water and 39.5 for the DMSO model present in GROMOS 54A7.<sup>2</sup> For simulations in the water/DMSO mixture, we used a linear interpolation between the value of water and DMSO based on a 95%/5% mixture. For all the other terms involving the dielectric constants, we used the same values as previously described.  $\Delta\Delta G_{RIP}(L)$  represents the residual integrated potential (RIP) and involves the evaluation

of the electrostatic potential. This latter was calculated using the program APBS (Adaptive Poisson-Boltzmann Solver, version 1.4.1).<sup>3</sup> The final RIPs ( $I_P$  and  $I_L$ ) were computed using the python scripts supplied by Rocklin et al..  $\Delta G_{EMP}(L)$  is an empirical correction term which also requires a Poisson-Boltzmann calculation (solvation contribution to the RIP), it was thus computed in the same way. Finally, we computed the discrete solvent correction term  $\Delta\Delta G_{DSC}(L)$ . For the simulations in water, we used equation (35) of Rocklin et al.:

$$\Delta\Delta G_{DSC}(L) = -\frac{\gamma_S Q_L N_S}{6\varepsilon_0 L^3} \quad (3)$$

where  $\gamma_S$  is the quadrupole-moment trace of the SPC model (we used a value of  $8.2 \times 10^3$  e nm<sup>2</sup> taken from Reif’s article<sup>2</sup> and  $Q_L$  is the ligand charge ( $-1$  in our case),  $N_S$  is the number of solvent molecules, and  $L$  is the edge length of the box. For the simulations in the water/DMSO mixture we could not use equation 3 since it assumes a homogenous solvent. Instead we used equation (30) of Rocklin et al.:

$$\Delta\Delta G_{DSC}(L) = -\frac{\gamma_S \rho_S Q_L}{6\varepsilon_0 M_S} \left(1 - \frac{V_C}{L^3}\right) \quad (4)$$

where  $\rho_S$  is the effective solvent density and  $V_C$  is the excluded volume of the complex (CD-ADA) or the ADA alone (for the simulations that do not involve the CDs).  $\rho_S$  was computed from a pure water/DMSO mixture (95%/5%) in the NPT ensemble after proper convergence.  $V_C$  was obtained by comparing the volume of a pure water/DMSO mixture, and another simulation with either the CD-ADA complex or the ADA alone within the same mixture of solvents. For  $\gamma_S$  and  $M_S$ , we used the same reasoning as for  $\varepsilon_S$ , that is, a linear interpolation between the value for water ( $\gamma_S = 8.20 \times 10^{-3}$  e nm<sup>2</sup> and  $M_S = 18$  g mol<sup>-1</sup>) and that for DMSO ( $\gamma_S = 1.45 \times 10^{-3}$  e nm<sup>2</sup> taken from Reif’s article<sup>2</sup> and  $M_S = 78$  g mol<sup>-1</sup>) based on a 95%/5% water /DMSO ratio.

All correction values are presented in Table S1. All these corrections have to be applied when we decouple the ligand from the complex (within the solvent), or when we decouple

the ligand alone from the solvent. In the end, the large terms tend to cancel out in the two legs of the thermodynamic cycle (especially  $\Delta\Delta G_{DSC}$ ) leading to an effective correction to the final free energy of binding that does not exceed 1 kJ/mol. Note that only the values of  $\Delta\Delta G_{RIP}$  and  $\Delta\Delta G_{EMP}$  can fluctuate, the others being constant whatever the MD frame. For each system, we thus took 10 different snapshots and computed these corrections. The standard deviations were systematically very small (below 0.1 kJ/mol), we thus do not report any error in Table S1 for  $\Delta\Delta G_{RIP}$  and  $\Delta\Delta G_{EMP}$ .

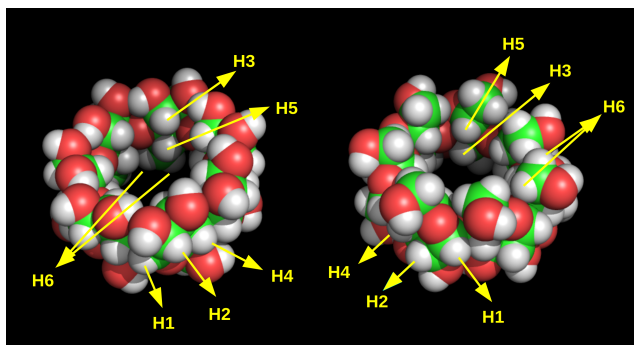
**Table S1**

(all values in kJ/mol)	$\Delta\Delta G_{NET}$	$\Delta\Delta G_{USV}$	$\Delta\Delta G_{RIP}$	$\Delta\Delta G_{EMP}$	$\Delta\Delta G_{ANA}$	$\Delta\Delta G_{DSC}$
water						
$\beta$ -CD/ADA	48.5	-47.8	-0.4	-0.1	0.2	-75.6
$\gamma$ -CD/ADA	42.9	-42.2	-0.5	0.0	0.2	-76.3
ADA	61.4	-60.5	0	0.0	0.9	-76.7
water/DMSO						
$\beta$ -CD/ADA	48.5	-47.8	-0.5	-0.1	0.2	-62.7
$\gamma$ -CD/ADA	42.2	-41.6	-0.5	0.0	0.1	-63.1
ADA	60.4	-59.5	0	0.0	0.9	-62.8

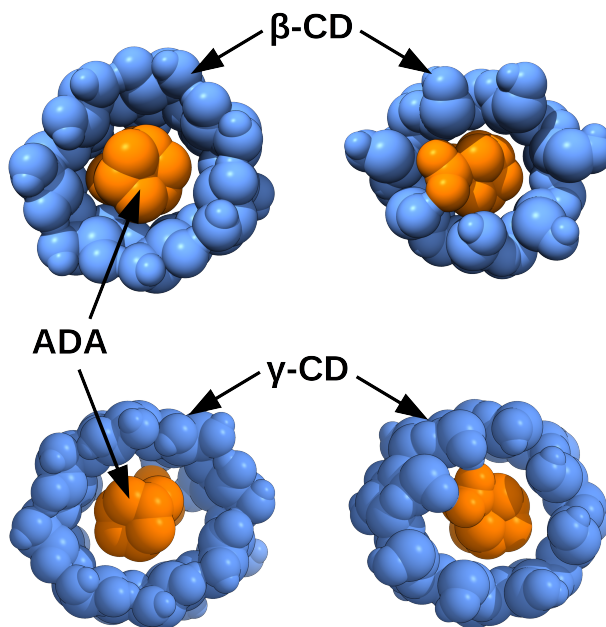
## 2. Supplementary figures

**Figure S1.** The figure shows the structure of  $\beta$ -cyclodextrin, viewed from above the larger (left panels) and narrower (right panels) cavity opening. The labels indicate the locations of H-atoms (white balls) that can be monitored by NMR. These labels are similar for  $\gamma$ -cyclodextrin. Green and red balls represent carbon and oxygen atoms respectively.





**Figure S2.** The figure displays the simulated complexes ADA –  $\beta$ -CD and ADA –  $\gamma$ -CD. The solvent molecules are not displayed for a better clarity. The left panels represent a top view of the larger cyclodextrin cavity opening, while the right panels show a view from the narrower CD cavity opening.



## References

- (1) Rocklin, G. J.; Mobley, D. L.; Dill, K. A.; Hünenberger, P. H. *J. Chem. Phys.* **2013**, *139*, 184103.
- (2) Reif, M. M.; Hünenberger, P. H. *J. Phys. Chem. B* **2016**, *120*, 8485–8517.

- (3) Baker, N. A.; Sept, D.; Joseph, S.; Holst, M. J.; McCammon, J. A. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 10037–10041.