

Supporting Information for

Cooperative Binding of Cyclodextrin Dimers to Isoflavone Analogs Elucidated by Free Energy Calculations

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1. Thermodynamic analysis.

After removing the first 2 ns for system equilibration, a periodic version of the weighted histogram analysis method (WHAM)¹⁻² was implemented to construct the PMFs. Statistical errors of the PMFs were estimated by the Bayesian bootstrapping of complete histograms.² All the PMFs were defined to zero at $\xi = -2.5$ and $\xi = 2.5$ where there exists no host-guest interactions such that we can directly quantify the free energy difference (ΔG) with respect to the separated state of the [host:guest] complexes.

From the free energy landscapes (i.e., PMF profiles), standard thermodynamic parameters of the entire binding reactions for [β -CD₂:guest] associations are derived using a cylinder approximation.³⁻⁶ The sampled volume for the guest penetrating into the β -CD cavity will be constrained to a small cylinder that is defined by the accessible area of guest movements in the X - Y plane. The average radius of that cylinder, $r(\xi)$, was determined from COM positions of the guest at a given window. The association equilibrium constant K_a can be written as

$$K_a = \pi N_A \int r(\xi)^2 \exp[-\Delta G(\xi)/RT] d\xi \quad (\text{S1})$$

where N_A is Avogadro constant and R the ideal gas constant.⁴⁻⁵ The thermodynamics of binding can therefore be calculated using

$$\Delta G^0 = -RT \ln(K_a C^0) \quad (\text{S2})$$

$$\Delta H^0 = RT^2 \frac{d}{dT} \ln(K_a C^0) = \frac{\int r(\xi)^2 \Delta G(\xi) \exp[-\Delta G(\xi)/RT] d\xi}{\int r(\xi)^2 \exp[-\Delta G(\xi)/RT] d\xi} \quad (\text{S3})$$

$$-T\Delta S^0 = \Delta G^0 - \Delta H^0 \quad (\text{S4})$$

where C^0 is the standard concentration of 1 mol/L.⁷ Note that ΔG^0 here is the standard free energy of the binding process, while $\Delta G(\xi)$ denotes free energy profiles obtained from PMF calculations. The integration in eqs. S1-S3 is computed from each side of the PMF to the central maximum

(roughly in-between the two CD monomers) and these two reaction pathways are then averaged to obtain the thermodynamic properties.^{6, 8} If no obvious central maximum exists, the integral is performed over the entire PMF.

For actual binding reactions, the enthalpy change (ΔH) was estimated as the potential energy difference with respect to a completely separated state between the dimer and its guest.⁸⁻⁹ The entropy change (ΔS) of the system was then computed by subtracting ΔH from ΔG (eq. S5):

$$-T\Delta S(\xi) = \Delta G(\xi) - \Delta H(\xi) \quad (\text{S5})$$

The functional dependence of ξ for all thermodynamic variables are omitted hereafter for simplicity.

ΔH and ΔS can be further decomposed into individual contributions from the binding partners and solvent environment (see eqs. S6 and S7, respectively). In eq. S6 the first two items refer to

$$\begin{aligned} \Delta H = & \Delta H_{\text{host}} + \Delta H_{\text{guest}} + \Delta H_{\text{host-host}} + \Delta H_{\text{guest-guest}} \\ & + \Delta H_{\text{sol-sol}} + \Delta H_{\text{host-guest}} + \Delta H_{\text{host-sol}} + \Delta H_{\text{guest-sol}} \end{aligned} \quad (\text{S6})$$

$$\Delta S_{\text{sol}} = \Delta S - \Delta S_{\text{host}} - \Delta S_{\text{guest}} \quad (\text{S7})$$

the bonded interactions (bond angle and dihedral angle) and the rest of the terms describe intra- and inter-molecular non-bonded energies (electrostatic and van der Waals interactions). In eq. S7 configurational entropies of host and guest molecules were separately calculated from the covariance matrices of atomic fluctuations using the quasi-harmonic approximation.¹⁰ Standard errors in the enthalpy were estimated using a binning analysis.¹¹ All entropy items were given the same errors as ΔH because the error in ΔH propagates to ΔS and the error in ΔH is significantly larger than that in ΔG . Further details on these equations have been given in the ref.⁸

2. Convergence of entropy calculations

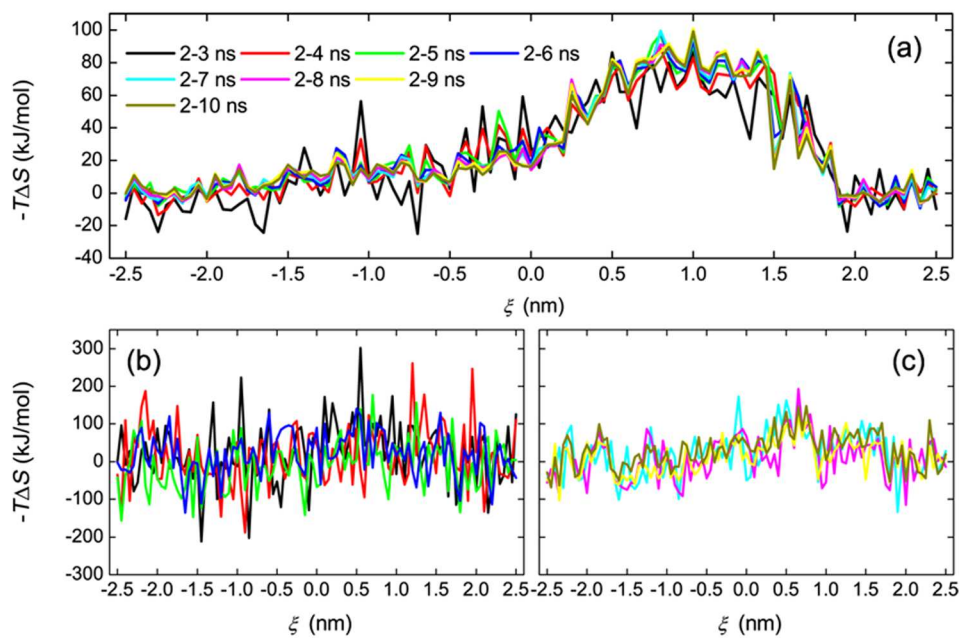


Figure S1. Convergence of entropy contributions to the free energy for daidzin (a) and β -CD (b and c) in the BHHP binding mode.

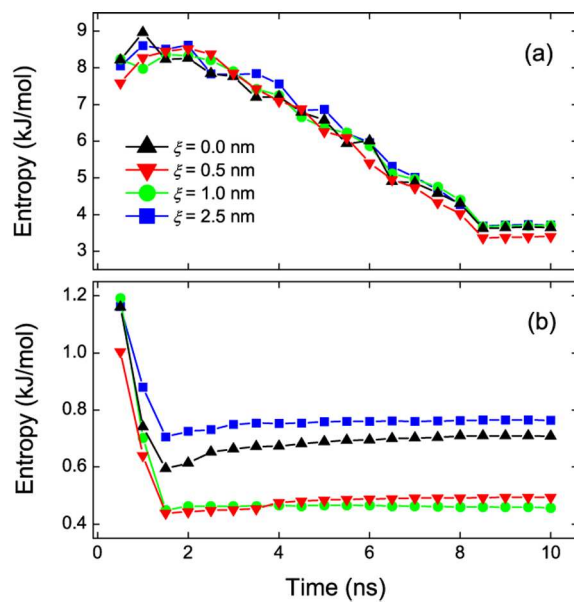


Figure S2. Convergence for estimated configurational entropy of β -CD (a) and daidzin (b) as a function of simulation time in the BHHP binding mode.

The simulations with a length of at least 4 ns for daidzin were required for convergence of entropy calculations (Figures S1a and S2b). For β -CD, however, at least 8 ns is needed (Figures S1b, S1c, and S2a). In this work, we simulated 10 ns for each window, ensuring the convergence of all entropy calculations.

3. Correlation between ΔG and ΔS

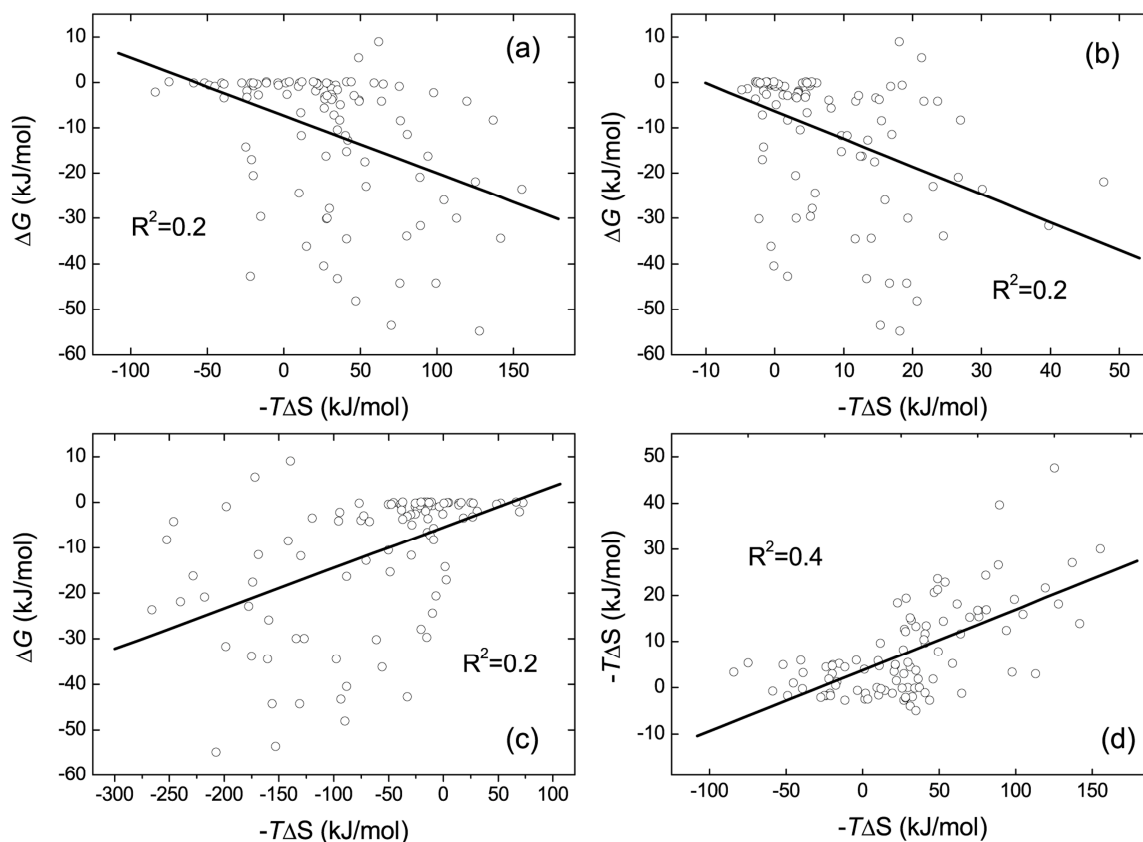


Figure S3. (a) ΔG vs $-T\Delta S_{\text{host}}$, (b) ΔG vs $-T\Delta S_{\text{guest}}$, (c) ΔG vs $-T\Delta S_{\text{sol}}$, and (d) $-T\Delta S_{\text{guest}}$ vs $-T\Delta S_{\text{host}}$ for $[\beta\text{-CD}_2\text{:daidzin}]$ in the BHHP mode. A linear fit to data points is shown as a solid line and R^2 the correlation coefficient.

References

- (1) Kumar, S.; Rosenberg, J. M.; Bouzida, D.; Swendsen, R. H.; Kollman, P. A. The Weighted Histogram Analysis Method for Free-Energy Calculations on Biomolecules. I. The Method. *J. Comput. Chem.* **1992**, *13*, 1011-1021.
- (2) Hub, J. S.; de Groot, B. L.; van der Spoel, D. g_wham—A Free Weighted Histogram Analysis Implementation Including Robust Error and Autocorrelation Estimates. *J. Chem. Theory Comput.* **2010**, *6*, 3713-3720.
- (3) Cai, W.; Sun, T.; Liu, P.; Chipot, C.; Shao, X. Inclusion Mechanism of Steroid Drugs into Beta-Cyclodextrins. Insights from Free Energy Calculations. *J. Phys. Chem. B* **2009**, *113*, 7836-7843.
- (4) 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. β -Cyclodextrin Host-Guest Complexes Probed under Thermodynamic Equilibrium: Thermodynamics and Afm Force Spectroscopy. *J. Am. Chem. Soc.* **2004**, *126*, 1577-1584.
- (5) Yu, Y.; Chipot, C.; Cai, W.; Shao, X. Molecular Dynamics Study of the Inclusion of Cholesterol into Cyclodextrins. *J. Phys. Chem. B* **2006**, *110*, 6372-6378.
- (6) Filippini, G.; Goujon, F.; Bonal, C.; Malfreyt, P. Energetic Competition Effects on Thermodynamic Properties of Association between β -CD and Fc Group: A Potential of Mean Force Approach. *J. Phys. Chem. C* **2012**, *116*, 22350-22358.
- (7) Deng, Y.; Roux, B. Calculation of Standard Binding Free Energies: Aromatic Molecules in the T4 Lysozyme L99a Mutant. *J. Chem. Theory Comput.* **2006**, *2*, 1255-1273.
- (8) Zhang, H.; Tan, T.; Hetényi, C.; van der Spoel, D. Quantification of Solvent Contribution to the Stability of Noncovalent Complexes. *J. Chem. Theory Comput.* **2013**, *9*, 4542-4551.
- (9) Hub, J. S.; Caleman, C.; van der Spoel, D. Organic Molecules on the Surface of Water Droplets - an Energetic Perspective. *Phys. Chem. Chem. Phys.* **2012**, *14*, 9537-9545.
- (10) Andricioaei, I.; Karplus, M. On the Calculation of Entropy from Covariance Matrices of the Atomic Fluctuations. *J. Chem. Phys.* **2001**, *115*, 6289-6292.
- (11) Hess, B. Determining the Shear Viscosity of Model Liquids from Molecular Dynamics Simulations. *J. Chem. Phys.* **2002**, *116*, 209-217.