

Supporting Information

Binding Thermodynamics and Kinetics Calculations Using Chemical Host and Guest: A Comprehensive Picture of Molecular Recognition

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1. Lengths of MD Simulations

Force Field	System	Total (μ s)	Length Used (μ s)	# of Bound State Conformations
GAFF	1-Propanol	1.00	1.00	100000
	1-Butanol	2.56	2.56	256000
	Methyl Butyrate	1.00	1.00	100000
	t-Butanol	1.00	1.00	100000
	1-Naphthyl Ethanol	2.00	2.00	200000
	Aspirin	1.00	1.00	100000
	2-Naphthyl Ethanol	2.50	2.50	250000
TIP3P	Water	2.50	2.50	250000
GAFF-CD	β -CD-1-Propanol	6.50	6.50	23256
	β -CD-1-Butanol	6.50	6.50	48869
	β -CD-Methyl Butyrate	7.50	7.50	111496
	β -CD-t-Butanol	8.00	8.00	86200
	β -CD-1-Naphthyl Ethanol	11.00	4.00	369283
	β -CD-Aspirin	9.50	5.50	453449
	β -CD-2-Naphthyl Ethanol	11.00	4.50	319300
	β -CD	2.50	2.50	250000
q4MD-CD	β -CD-1-Propanol	4.50	2.50	60225
	β -CD-1-Butanol	5.00	2.50	152864
	β -CD-Methyl Butyrate	4.50	2.50	214756
	β -CD-t-Butanol	4.50	2.50	214310
	β -CD-1-Naphthyl Ethanol	6.00	2.50	236130
	β -CD-Aspirin	6.00	2.50	241138
	β -CD-2-Naphthyl Ethanol	6.00	4.50	442508
	β -CD	2.60	2.60	260000

Table SI 1. The lengths of MD simulations of β -cyclodextrin (β -CD) complexes and numbers of frames used in calculations of thermodynamic properties. We used GAFF-CD and q4MD-CD for free β -CD and the complexes. We used GAFF for the free ligands and TIP3P for water in all simulations. All trajectories are resaved every 10 ps for thermodynamics calculations. The lengths used in calculations of thermodynamic properties are shown in column 4. Column 5 shows the total numbers of frames in free β -CD, free ligands, and water trajectories, and the numbers of bound state conformations in complex trajectories corresponding to the length indicated in column 4. Only bound state complex conformations were used in thermodynamics calculations. All full lengths of trajectories were used in association and dissociation rate constant calculations.

2. Conformations of β -CD in Vacuum MD Simulations in GAFF-CD and q4MD-CD

We performed MD simulations of free β -CD in vacuum for 50 ns using GAFF-CD and q4MD-CD respectively. Periodic condition was not considered. The trajectories were saved every 10 ps and totally 5000 frames were saved for the two MD runs. The RMSDs were computed against the crystal structures and plotted in Figure SI 1.

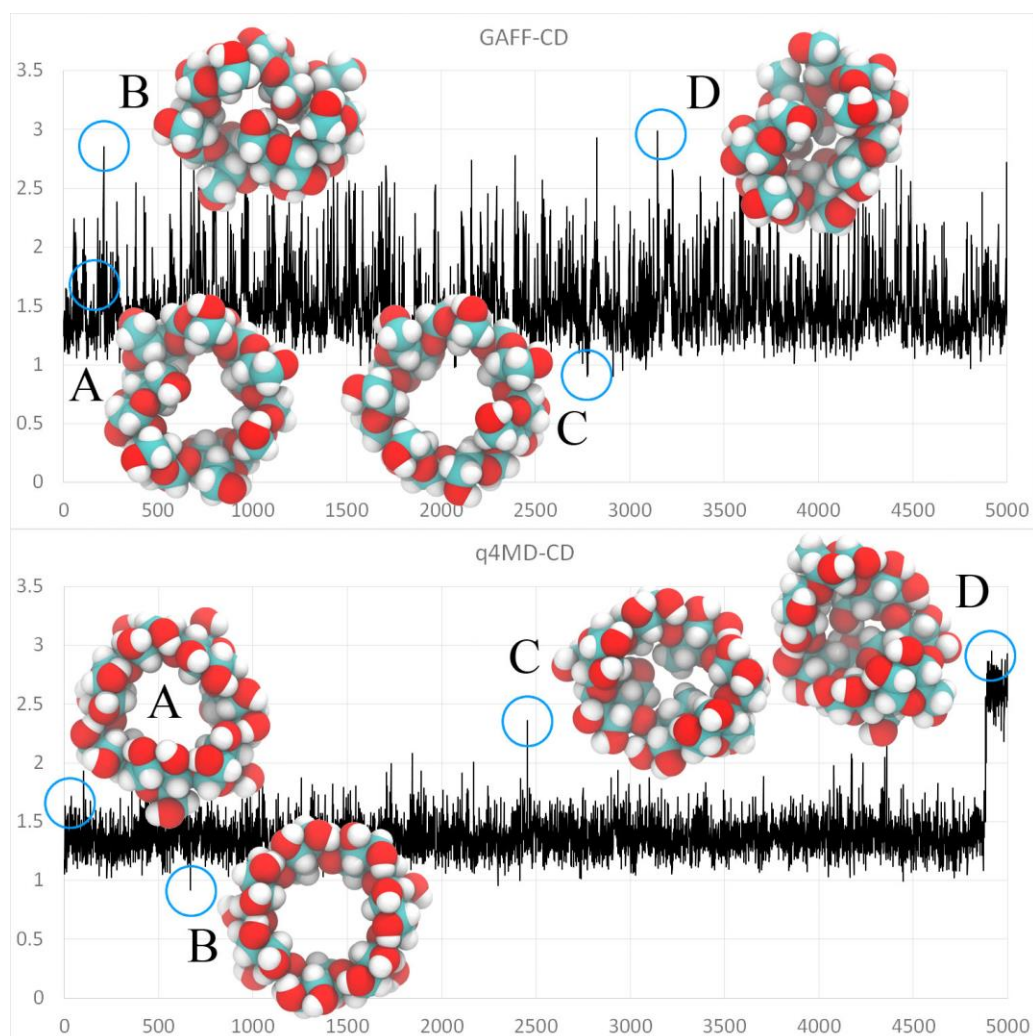


Figure SI 1. The RMSD plots and representative conformations of β -CD from MD simulations in vacuum in GAFF-CD and q4MD-CD. X-axes of RMSD plots are numbers of frames, and y-axes are RMSD against crystal structures in \AA . Representative conformations are circled on the RMSD plots. Conformations A on the two plots have RMSD roughly equal to 1.7 \AA . For GAFF-CD simulation, 80.5% conformations have RMSD smaller than 1.7 \AA . For q4MD-CD simulations, the percentage is 95.12%.

3. Details of Enthalpy Decomposition Calculations

The total enthalpy change (ΔH) is decomposed into changes of solute-solute interaction ($\Delta H_{\text{Host-Guest}}$) and desolvation energy ($\Delta H_{\text{desolvation}}$), where $\Delta H_{\text{desolvation}}$ includes interaction changes of host-water ($\Delta H_{\text{Host-Water}}$), guest-water ($\Delta H_{\text{Guest-Water}}$), and water-water ($\Delta H_{\text{Water-Water}}$). Because both conformational changes and intermolecular interactions contribute to $\Delta H_{\text{Host-Guest}}$, we further provide decomposition analysis of $\Delta H_{\text{Host-Guest}}$ into changes of host and guest conformational enthalpy $\Delta H_{\text{Host Conf}}$ and $\Delta H_{\text{Guest Conf}}$, respectively, and their interaction energy change ($\Delta H_{\text{Solute Inter}}$). To compute these decomposed energy terms, we also calculated average potential energies of water ($\langle E_{\text{Water}} \rangle_{\text{Complex}}$), water+host ($\langle E_{\text{Water+Host}} \rangle_{\text{Complex}}$), water+guest ($\langle E_{\text{Water+Guest}} \rangle_{\text{Complex}}$), host+guest ($\langle E_{\text{Host+Guest}} \rangle_{\text{Complex}}$), host ($\langle E_{\text{Host}} \rangle_{\text{Complex}}$) and guest ($\langle E_{\text{Guest}} \rangle_{\text{Complex}}$) in the complex trajectories, water ($\langle E_{\text{Water}} \rangle_{\text{Host}}$), water+host ($\langle E_{\text{Water+Host}} \rangle_{\text{Host}}$) and host ($\langle E_{\text{Host}} \rangle_{\text{Host}}$) in the free β -CD trajectory, water ($\langle E_{\text{Water}} \rangle_{\text{Guest}}$), water+guest ($\langle E_{\text{Water+Guest}} \rangle_{\text{Guest}}$) and guest ($\langle E_{\text{Guest}} \rangle_{\text{Guest}}$) in the free ligand trajectories, in addition to $\langle E \rangle_{\text{Complex}}$, $\langle E \rangle_{\text{Water}}$, $\langle E \rangle_{\text{Host}}$ and $\langle E \rangle_{\text{Guest}}$. Then we used eqs. 3.1 to 3.8 to calculate the decomposed energy terms.

$$\Delta H_{\text{Host-Guest}} = \langle E_{\text{Host+Guest}} \rangle_{\text{Complex}} - \langle E_{\text{Host}} \rangle_{\text{Host}} - \langle E_{\text{Guest}} \rangle_{\text{Guest}} \quad \text{eq. 3.1}$$

$$\Delta H_{\text{Host Conf}} = \langle E_{\text{Host}} \rangle_{\text{Complex}} - \langle E_{\text{Host}} \rangle_{\text{Host}} \quad \text{eq. 3.2}$$

$$\Delta H_{\text{Guest Conf}} = \langle E_{\text{Guest}} \rangle_{\text{Complex}} - \langle E_{\text{Guest}} \rangle_{\text{Guest}} \quad \text{eq. 3.3}$$

$$\Delta H_{\text{Solute Inter}} = \langle E_{\text{Host+Guest}} \rangle_{\text{Complex}} - \langle E_{\text{Host}} \rangle_{\text{Complex}} - \langle E_{\text{Guest}} \rangle_{\text{Complex}} \quad \text{eq. 3.4}$$

$$\begin{aligned} \Delta H_{\text{Host-Water}} = & (\langle E_{\text{Water+Host}} \rangle_{\text{Complex}} - \langle E_{\text{Water}} \rangle_{\text{Complex}} - \langle E_{\text{Host}} \rangle_{\text{Complex}}) - \\ & (\langle E_{\text{Water+Host}} \rangle_{\text{Host}} - \langle E_{\text{Water}} \rangle_{\text{Host}} - \langle E_{\text{Host}} \rangle_{\text{Host}}) \end{aligned} \quad \text{eq. 3.5}$$

$$\begin{aligned} \Delta H_{\text{Guest-Water}} = & (\langle E_{\text{Water+Guest}} \rangle_{\text{Complex}} - \langle E_{\text{Water}} \rangle_{\text{Complex}} - \langle E_{\text{Guest}} \rangle_{\text{Complex}}) - \\ & (\langle E_{\text{Water+Guest}} \rangle_{\text{Guest}} - \langle E_{\text{Water}} \rangle_{\text{Guest}} - \langle E_{\text{Guest}} \rangle_{\text{Guest}}) \end{aligned} \quad \text{eq. 3.6}$$

$$\Delta H_{\text{Water-Water}} = \langle E_{\text{Water}} \rangle_{\text{Complex}} + \langle E \rangle_{\text{Water}} - \langle E_{\text{Water}} \rangle_{\text{Host}} - \langle E_{\text{Water}} \rangle_{\text{Guest}} \quad \text{eq. 3.7}$$

$$\Delta H_{\text{Desolvation}} = \Delta H_{\text{Host-Water}} + \Delta H_{\text{Guest-Water}} + \Delta H_{\text{Water-Water}} \quad \text{eq. 3.8}$$

4. Surface Area, Hydrogen Bond and Solvation Water

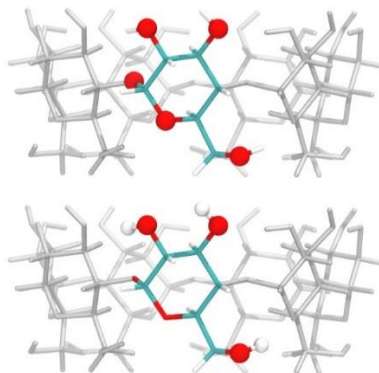


Figure SI 2. The hydrogen-bonding (H-bond) sites on β -CD. β -CD has totally 56 H-bonding sites, and on each of the seven glucopyranose units there are five H-bond acceptors (top) and three H-bond donors (bottom). The H-bonding sites are shown in spheres.

We evaluated the total solvent accessible surface area (SA_{Total}), polar solvent accessible surface area (SA_{Polar}) and non-polar solvent accessible surface area ($SA_{\text{Non Polar}}$) of β -CD. The solvent accessible surface area was evaluated by generating spherical meshes with radius set to the van der Waals radii of atoms plus 1.4 Å on the atoms and counting the exposed surface areas of the meshes. SA_{Total} , SA_{Polar} and $SA_{\text{Non Polar}}$ are evaluated by summing up the surface areas of all atoms, of oxygen atoms, and of carbon and hydrogen atoms, respectively. Values are averaged from all conformations of free β -CD and bound state conformations of complex trajectories.

To estimate the H-bonds with water molecules, we computed the average occupancy percentages of the 56 H-bonding sites (Figure SI 2) on β -CD. We only counted the H-bonds formed with water molecules on these H-bonding sites. For each H-bonding site, the number of conformations with water molecules forming H-bond to the H-bonding site was divided by the total number of conformations to compute the percentage of water H-bond occupancy percentage. The percentages of each H-bonding site were then averaged to compute the percentage of the conformation. Finally, the percentage of conformations were then average for all conformations of free β -CD or bound state conformations of complexes to compute the average H-bond occupancy percentage ($\Delta\%_{\text{H-Bond}}$).

The changes of total surface area (ΔSA_{Total}), polar surface area (ΔSA_{Polar}), non-polar surface area ($\Delta SA_{\text{Non Polar}}$), and average percentage of H-bond occupancy ($\Delta\%_{\text{H-Bond}}$) are calculated by subtracting values of free β -CD from values of complexes. The results are summarized in Table SI 2.

GAFF-CD								
Guest	SA _{Total}	SA _{Polar}	SA _{Non Polar}	% _{H-Bond}	ΔSA _{Total}	ΔSA _{Polar}	ΔSA _{Non Polar}	Δ% _{H-Bond}
β-CD-1-Propanol	1019	216	803	34.25%	-37	-6	-31	-3.58%
β-CD-1-Butanol	1024	217	807	32.17%	-32	-5	-27	-5.66%
β-CD-Methyl Butyrate	998	209	789	32.31%	-58	-13	-45	-5.52%
β-CD-t-Butanol	1038	221	817	32.78%	-18	-1	-17	-5.04%
β-CD-1-Naphthyl Ethanol	994	211	783	29.64%	-62	-11	-52	-8.18%
β-CD-Aspirin	1002	212	790	29.86%	-54	-10	-44	-7.97%
β-CD-2-Naphthyl Ethanol	986	210	776	29.86%	-70	-12	-58	-7.97%
β-CD	1056	222	834	37.83%				
q4MD-CD								
Guest	SA _{Total}	SA _{Polar}	SA _{Non Polar}	% _{H-Bond}	ΔSA _{Total}	ΔSA _{Polar}	ΔSA _{Non Polar}	Δ% _{H-Bond}
β-CD-1-Propanol	1058	228	829	28.74%	-66	-5	-61	-2.41%
β-CD-1-Butanol	1045	226	819	28.64%	-78	-7	-71	-2.51%
β-CD-Methyl Butyrate	1030	222	808	28.09%	-94	-12	-82	-3.05%
β-CD-t-Butanol	1055	231	824	28.44%	-68	-2	-66	-2.70%
β-CD-1-Naphthyl Ethanol	995	213	782	26.61%	-129	-21	-108	-4.54%
β-CD-Aspirin	1005	216	789	27.31%	-118	-17	-101	-3.83%
β-CD-2-Naphthyl Ethanol	993	212	781	27.18%	-130	-21	-109	-3.96%
β-CD	1123	234	890	31.14%				

Table SI 2. The solvent accessible surface area and H-bonds with water of β-CD in complexes and free state in GAFF-CD and q4MD-CD. The total surface area (SA_{Total}), polar surface area (SA_{Polar}) and non-polar surface area (SA_{Non Polar}) are in Å². The average H-bond occupancy percentage of 56 H-bond sites on β-CD (%_{H-Bond}) are in %. The corresponding changes (Δ) are calculated by subtracting values of free β-CD from values of complexes.

5. Definition of Probability Distribution of Conformations of Solutes

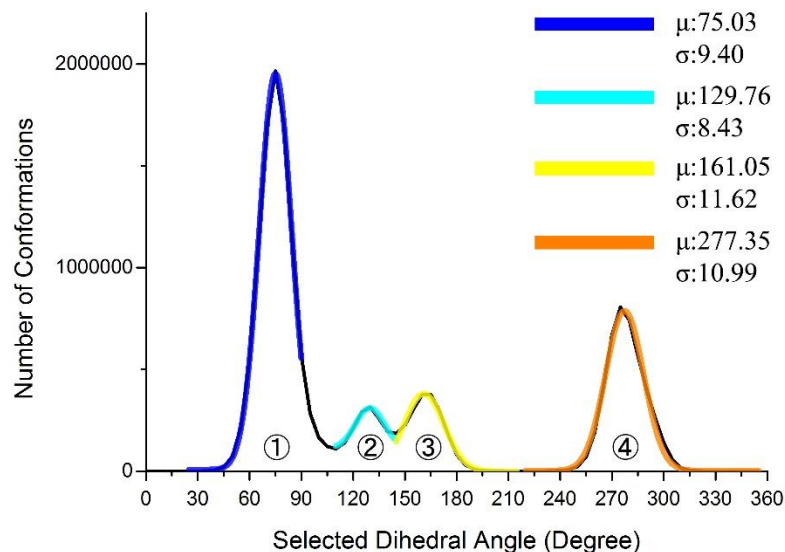


Figure SI 3. A representative dihedral population histogram used to define the conformation of individual dihedral angles. The population distribution is in black. Four Gaussian functions (1 in Blue, 2 in cyan, 3 in yellow and 4 in orange) were fitted onto the four population peaks and the averages (μ) and standard deviations (σ) are labeled.

We used the combinations of dihedral angles to define the conformations of β -CD and guest molecules, and used the probability distribution of conformations in the Gibbs entropy formula (eq. 1 in main text) to compute the internal entropy of β -CD and guest molecules. 14 dihedrals defined in Figure 1 were selected for β -CD while every dihedral except methyl and hydroxyl rotations were selected for the ligands. We obtained the population histograms of the dihedral angles from MD simulation. We defined the conformation of selected dihedral angles use the Gaussian functions illustrated in Figure SI 3. Given any dihedral angle, α , we define it in dihedral conformation i if,

$$\text{abs}\left(\frac{\text{Subtract}[\alpha, \mu(i)]}{\sigma(i)}\right) = \min\left\{\text{abs}\left(\frac{\text{Subtract}[\alpha, \mu(1)]}{\sigma(1)}\right), \text{abs}\left(\frac{\text{Subtract}[\alpha, \mu(2)]}{\sigma(2)}\right), \dots, \text{abs}\left(\frac{\text{Subtract}[\alpha, \mu(n)]}{\sigma(n)}\right)\right\} \quad \text{eq. 5.1}$$

where $\text{abs}(x)$ is to take the absolute value of x , $\mu(i)$ and $\sigma(i)$ indicate the average and standard deviation of Gaussian function i , $\min(\dots)$ is to take the minimum value of given values, the n denotes the total number

of peaks of the selected dihedral, and *Subtract* is an operator defined as eq. 5.2 used to subtract two dihedral angles,

$$\text{Subtract}[a, b] = \text{atan2}[\sin(a) \cos(b) - \sin(b) \cos(a), \cos(a) \cos(b) + \sin(a) \sin(b)] \quad \text{eq. 5.2}$$

where *atan2* is the standard arctangent function that convert from values of $\sin(\theta)$ and $\cos(\theta)$ to θ . We treated conformations that fall into each peak as one identical conformation of the corresponding dihedral angle, and neglected the width of the peaks shown in Figure SI 3.

With the definition of individual dihedral angles, we used the different combinations of individual dihedral conformations to define conformations of β -CD and ligands. Distinct combinations of dihedral angle conformations are considered as distinct conformations of β -CD and ligands. In β -CD case, its seven-fold symmetry was considered. The population distributions of β -CD and ligands were then calculated from the distinct conformations.

We tested the internal entropy calculation using β -CD-1-butanol complex by including all 21 rotatable dihedral angles and excluding the dihedral angles on the six-member rings of β -CD. By using 14 key dihedral angles, the computed internal entropy change ($-\Delta S_{\text{Host}}$) of β -CD is $-2.81 - (-1.61) = -1.20$ kcal/mol. By using all 21 rotatable dihedral angles, the computed internal entropy change ($-\Delta S_{\text{Host}}$) of β -CD is $-5.27 - (-3.96) = -1.32$ kcal/mol. By including more dihedral angles, the absolute value of internal entropy increases, but the internal entropy changes ($-\Delta S_{\text{Host}}$) differ by only 0.12 kcal/mol. Therefore, we believe that the approximation by using 14 key dihedral angles is appropriate.

6. Solvation Entropy Calculation Using Water Molar Entropy

Using grid cell method¹⁻³, the water molar entropy was evaluated by separating it into vibrational entropy ($S_{\text{Water Vib}}$) and conformational entropy ($S_{\text{Water Conf}}$), as in eq. 6.1,

$$S_{\text{Water}} = S_{\text{Water Vib}} + S_{\text{Water Conf}} \quad \text{eq. 6.1}$$

$S_{\text{Water Vib}}$ is further separated into translational entropy ($S_{\text{Water Trans}}$) and rotational entropy ($S_{\text{Water Rot}}$) as in eq. 6.2,

$$S_{\text{Water Vib}} = S_{\text{Water Trans}} + S_{\text{Water Rot}} \quad \text{eq. 6.2}$$

$S_{\text{Water Trans}}$ and $S_{\text{Water Rot}}$ are computed from forces and torques on the three principal axes of the target water molecule as in eqs. 6.3 and 6.4,

$$S_{\text{Water Trans}} \text{ or } S_{\text{Water Rot}} = R \sum_{i=1}^6 \left(\frac{\alpha_i}{\alpha_i - 1} - \ln(1 - e^{-\alpha_i}) \right) \quad \text{eq. 6.3}$$

$$\alpha_i = \begin{cases} \frac{F_i}{2k_B T} \frac{h}{(2\pi m k_B T)^{1/2}} & (i = 1, 2, 3, \text{ for trans}) \\ \frac{\tau_i}{2k_B T} \frac{h}{(2\pi I_i k_B T)^{1/2}} & (i = 4, 5, 6, \text{ for rot}) \end{cases} \quad \text{eq. 6.4}$$

where, R is the gas constant, k_B is the Boltzmann constant, h is the Planck constant, T is the temperature, m is the mass of a water molecule, F_i are the force and τ_i are the torques on the three principal axes. The gas phase values of moments of inertia I_i about x, y, and z axes are used.

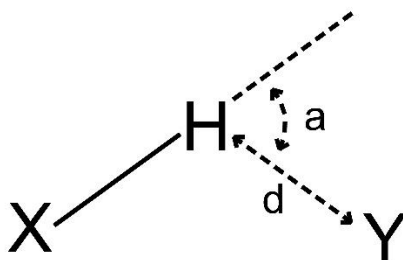


Figure SI 4. The definition of a loose H-bond. It is based on normal H-bond definition except that the complementary angle of X-H...Y (a) is less than 80° and the distance between H and Y (d) is less than 2.65\AA .

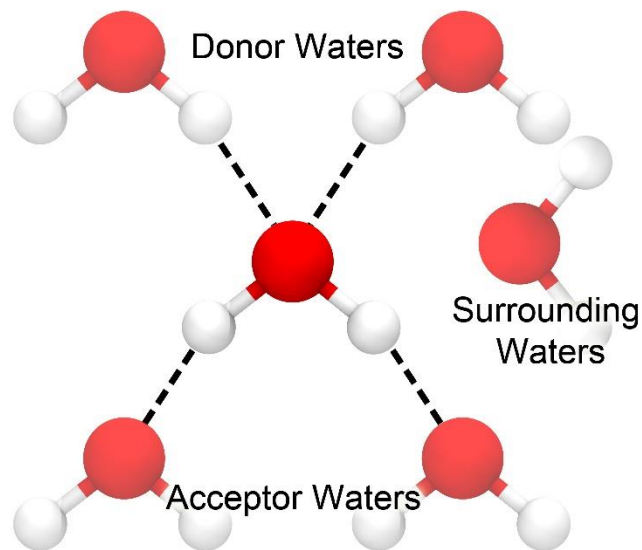


Figure SI 5. The water conformational entropy definition. It is based on the Pauling’s model. Around the target water molecule, the donor waters (DW) and acceptor waters (AW) are defined with the loose H-bond definition and any water molecule that is within 3.2 Å from the oxygen atom of the target water molecule but cannot form a loose H-bond is considered as a surrounding water (SW).

We derived model to evaluate water conformational entropy ($S_{\text{Water conf}}$) based on Pauling’s model²⁻⁴. First a loose H-bond is defined as shown in Figure SI 4, where the complementary angle of X-H...Y (α) must be less than 80° and the H...Y distance (d) must be less than 2.65 Å. The purpose of the loose definition is to capture the forming and breaking H-bonds due to thermal fluctuation. Based on that, the conformational entropy is defined according to Figure SI 5. The water molecules around the target water molecule are classified into three groups, 1) acceptor waters (AW), which are the loose H-bond acceptors from the target water, 2) donor waters (DW), which are the loose H-bond donors to the target water, and 3) surrounding waters (SW), whose oxygen atoms are within 3.2 Å of the oxygen atom of the target water molecule but form no H-bond with it. The number of conformations (Ω_{Water}) of the target water is calculated using eq. 6.5,

$$\Omega_{\text{Water}} = C_{2+\# \text{ of DW}+\# \text{ of SW}}^2 \cdot C_{\# \text{ of DW}+\# \text{ of SW}}^{\# \text{ of SW}} \cdot \left(\frac{1}{2}\right)^{\# \text{ of DW}+\# \text{ of SW}} \quad \text{eq. 6.5}$$

In the first term, both “2”s mean the two AW sites, regardless of the existence of water molecules there. This term can be interpreted as choosing two sites of the water molecules around as the acceptor sites. The second term means in the rest of the water around to choose # of SW of waters as the SW. The appearance of the last term is to compensate the double counting of water molecules around. For example, when there are exactly two AWs and two DWs, $\Omega_{\text{Water}} = C_4^2 \cdot C_2^0 \cdot \left(\frac{1}{2}\right)^2 = 6 \times \frac{1}{4} = 1.5$, which obeys the Pauling’s model. When there are two AWs, two DWs and one SW, $\Omega_{\text{Water}} = C_5^2 \cdot C_3^1 \cdot \left(\frac{1}{2}\right)^3 = 6 \times \frac{1}{4} = 3.75$, which means an additional water molecule around increases the number of conformations of the target water. Finally, the conformational entropy of the water is calculated as eq. 6.6,

$$S_{\text{Water Conf}} = R \ln(\Omega_{\text{Water}}) \quad \text{eq. 6.6}$$

The solvation entropy can be calculated using water molar entropy. The solvation energy of species *X* can be computed using eq. 6.7,

$$\Delta S_{\text{Solv.}} = N(\text{water}) \times (S_{\text{Water}(X)} - S_{\text{Water}(0)}) \quad \text{eq. 6.7}$$

where $N(\text{water})$ is given as # of Water in Tables SI 3 to 5, $S_{\text{Water}(X)}$ is the molar water entropy with species *X*, and $S_{\text{Water}(0)}$ is the molar water entropy of bulk water. The computed water molar entropy and solvation entropy are summarized in Tables SI 3 to 5.

System	S_{Water} (J/mol/K)					$-T\Delta S_{\text{Solv.}}$ (kcal/mol)					# of Water
	Trans	Rot	Vib	Conf	Total	Trans	Rot	Vib	Conf	Total	
β -CD-1-Propanol	47.69	20.83	68.52	5.01	73.53	4.62	0.59	5.21	2.48	7.69	403.01
β -CD-1-Butanol	47.7	20.85	68.54	5.01	73.55	4.44	0.23	4.66	2.53	7.19	401.58
β -CD-Methyl Butyrate	47.7	20.84	68.54	5.01	73.55	4.19	0.45	4.64	2.48	7.12	400.41
β -CD-t-Butanol	47.71	20.84	68.55	5.01	73.56	4.03	0.43	4.45	2.48	6.93	401.74
β -CD-1-Naphthyl Ethanol	47.72	20.85	68.56	5.01	73.57	3.74	0.21	3.95	2.46	6.41	397.53
β -CD-Aspirin	47.71	20.85	68.56	5.01	73.57	3.91	0.24	4.15	2.45	6.59	398.39
β -CD-2-Naphthyl Ethanol	47.72	20.85	68.57	5.01	73.58	3.69	0.13	3.82	2.47	6.29	397.49
β -CD	47.67	20.83	68.5	5.02	73.52	5.1	0.78	5.88	2.19	8.07	407.14

Table SI 3. The molar water entropy and solvation entropy of free β -CD and β -CD complexes in GAFF-CD. The molar water entropy (S_{Water}) is separated into vibrational ($S_{\text{Water Vib}}$), and conformational ($S_{\text{Water Conf}}$) terms. The vibrational ($S_{\text{Water Vib}}$) term is further separated into translational ($S_{\text{Water Trans}}$) and rotational ($S_{\text{Water Rot}}$) terms. The molar water entropy terms are in J/mol/K. The solvation entropy ($-T\Delta S_{\text{Solv.}}$) is separated into vibrational ($-T\Delta S_{\text{Solv. Vib}}$), and conformational ($-T\Delta S_{\text{Solv. Conf}}$) terms. The vibrational ($-T\Delta S_{\text{Solv. Vib}}$) term is further separated into translational ($-T\Delta S_{\text{Solv. Trans}}$) and rotational ($-T\Delta S_{\text{Solv. Rot}}$) terms. The solvation energy terms at 298K are in kcal/mol. The numbers of water molecules are corresponding to a volume of 13520 \AA^3 .

System	S_{Water} (J/mol/K)					$-T\Delta S_{\text{Solv.}}$ (kcal/mol)					# of Water
	Trans	Rot	Vib	Conf	Total	Trans	Rot	Vib	Conf	Total	
β -CD-1-Propanol	47.71	20.85	68.56	5.01	73.57	4.11	0.09	4.20	2.35	6.55	401.93
β -CD-1-Butanol	47.71	20.85	68.57	5.01	73.58	3.89	-0.02	3.86	2.30	6.16	400.86
β -CD-Methyl Butyrate	47.72	20.86	68.58	5.01	73.59	3.71	-0.16	3.55	2.35	5.90	400.01
β -CD-t-Butanol	47.72	20.85	68.57	5.01	73.58	3.82	0.05	3.88	2.34	6.22	401.15
β -CD-1-Naphthyl Ethanol	47.72	20.87	68.59	5.01	73.60	3.57	-0.49	3.08	2.34	5.43	397.77
β -CD-Aspirin	47.72	20.86	68.58	5.01	73.59	3.68	-0.22	3.46	2.32	5.77	398.05
β -CD-2-Naphthyl Ethanol	47.73	20.87	68.60	5.01	73.61	3.44	-0.60	2.83	2.38	5.22	397.45
β -CD	47.69	20.84	68.54	5.02	73.56	4.50	0.27	4.77	2.20	6.98	406.33

Table SI 4. The molar water entropy and solvation entropy of free β -CD and β -CD complexes in q4MD-CD. Refer to Table SI 3 for meanings of symbols.

System	S_{Water} (J/mol/K)					$-T\Delta S_{\text{Solv.}}$ (kcal/mol)					# of Water
	Trans	Rot	Vib	Conf	Total	Trans	Rot	Vib	Conf	Total	
1-Propanol	47.80	20.83	68.63	5.07	73.71	1.54	0.71	2.26	0.68	2.93	441.36
1-Butanol	47.83	20.85	68.68	5.07	73.75	0.52	0.17	0.69	0.80	1.49	440.41
Methyl Butyrate	47.82	20.82	68.64	5.06	73.70	1.01	1.03	2.04	1.00	3.04	439.02
t-Butanol	47.85	20.85	68.70	5.07	73.76	0.09	0.11	0.20	0.87	1.08	440.53
1-Naphthyl Ethanol	47.86	20.86	68.72	5.05	73.77	-0.23	-0.39	-0.62	1.24	0.62	436.48
Aspirin	47.81	20.84	68.65	5.06	73.71	1.17	0.36	1.53	1.07	2.61	437.33
2-Naphthyl Ethanol	47.86	20.86	68.72	5.05	73.78	-0.26	-0.41	-0.67	1.22	0.55	436.41
Water	47.85	20.85	68.70	5.09	73.80	0.00	0.00	0.00	0.00	0.00	565.84

Table SI 5. The molar water entropy and solvation entropy of free ligands and water. Refer to Table SI 3 for meanings of symbols.

Alternatively, the solvation water entropy can be computed using forces ($F_{i,s}$), torques ($\tau_{i,s}$), and number of water conformation (Ω_S) directly using eqs. 6.8 to 6.11, instead of computing the water molar entropy first,

$$\Delta S_{\text{Solv.Trans}} = NR \ln \left(\prod_{i=1}^3 \frac{F_{i,W}}{F_{i,S}} \right) \quad \text{eq. 6.8}$$

$$\Delta S_{\text{Solv.Rot}} = NR \ln \left(\prod_{i=1}^3 \frac{\tau_{i,W}}{\tau_{i,S}} \right) \quad \text{eq. 6.9}$$

$$\Delta S_{\text{Solv.Vib}} = \Delta S_{\text{Solv.Trans}} + \Delta S_{\text{Solv.Rot}} \quad \text{eq. 6.10}$$

$$\Delta S_{\text{Solv.Conf}} = NR \ln \left(\frac{\Omega_S}{\Omega_W} \right) \quad \text{eq. 6.11}$$

where, R is the gas constant, $F_{i,w}$ and $F_{i,s}$ are the averages of forces on three principal axes without solute and with solute, $\tau_{i,w}$ and $\tau_{i,s}$ are the averages of torques on three principal axes without and with solute, Ω_W and Ω_S are the average of number of conformations of water molecules without and with solute, and N is the number of water molecules in the sub water box defined in Figure SI 6.

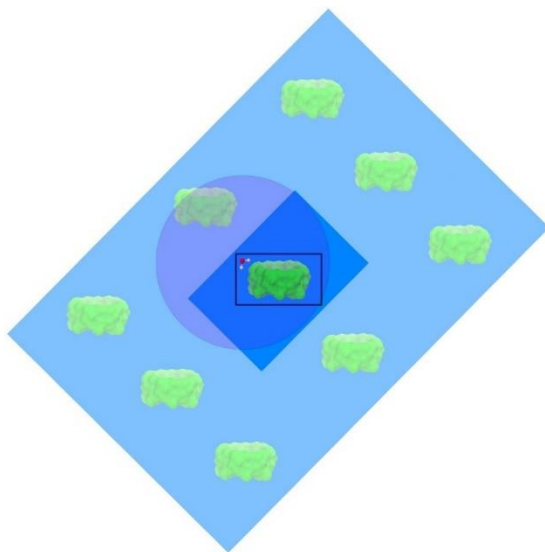


Figure SI 6. Illustration of water entropy calculation using free β -CD as representation. The original water box (deep blue) is align to the crystal structure of β -CD (deep green). One representative water molecule under calculation is shown in the sub water box (black lined box). Any periodic instances of atoms within the cutoff (purple circle) generated from original water box and periodic images of the original water box (light blue and light green) are used to calculate the forces and torques on the water molecule under calculation.

Practically, the complex and β -CD trajectories were aligned against the crystal structure of free β -CD. The ligand trajectories were aligned against the initial conformation of the ligand. Water molecules in a sub water box centered on the β -CD (in the case of free β -CD and complexes) and guest (in the case of free guests) with a size of $20\text{\AA} \times 26\text{\AA} \times 26\text{\AA}$ were considered in the water entropy calculation. For the empty water box, a sub water box with size $22\text{\AA} \times 22\text{\AA} \times 22\text{\AA}$ was used. A cutoff 50.0\AA was used for force and torque calculation in the vibrational term, and periodical atom instances generated from the full water box within this cutoff were used to calculate the forces and torques on the water molecules in the sub water box. The grid bin size was set to 1\AA in the grid cell method. The illustration of the water box for water entropy calculation is in Figure SI 6.

7. Solvation Water

We also counted the numbers of water molecules in the first solvation shells of free guest ($\#_{\text{Guest}}$), free β -CD ($\#_{\text{Host}}$) and the complex ($\#_{\text{Complex}}$) from the MD trajectory. We counted the number oxygen atoms in the water molecules within 3.5 Å of all atoms in the corresponding solute and took the average of the number of waters over the entire trajectory for free guest and free host and over the bound state conformations in trajectories for complexes. The changes of the numbers of water molecules in the first solvation shells upon ligand binding ($\Delta\#$) are calculated by $\#_{\text{Guest}} + \#_{\text{Host}} - \#_{\text{Complex}}$. The results are summarized in Table SI 6.

Guest	GAFF-CD				q4MD-CD			
	$\#_{\text{Guest}}$	$\#_{\text{Host}}$	$\#_{\text{Complex}}$	$\Delta\#$	$\#_{\text{Guest}}$	$\#_{\text{Host}}$	$\#_{\text{Complex}}$	$\Delta\#$
1-Propanol	15.21	77.92	80.46	12.67	15.21	81.43	80.21	16.43
1-Butanol	17.28	77.92	79.62	15.58	17.28	81.43	79.26	19.45
Methyl Butyrate	19.67	77.92	78.99	18.6	19.67	81.43	79.12	21.98
t-Butanol	16.66	77.92	79.75	14.83	16.66	81.43	79.5	18.59
1-Naphthyl Ethanol	23.53	77.92	78.47	22.98	23.53	81.43	78.53	26.43
Aspirin	22.02	77.92	78.83	21.11	22.02	81.43	78.92	24.53
2-Naphthyl Ethanol	24.02	77.92	79.5	22.43	24.02	81.43	79.18	26.27

Table SI 6. The number of water molecules in the first solvation shells of free guest ($\#_{\text{Guest}}$), free host ($\#_{\text{Host}}$), complex ($\#_{\text{Complex}}$) and number of water molecules released from the first solvation shell to the bulk ($\Delta\#$). Values are obtained by averaging the numbers of water molecules within 3.5 Å of atoms in the solute over the corresponding trajectories. The change is computed by $\#_{\text{Guest}} + \#_{\text{Host}} - \#_{\text{Complex}}$.

8. Solute Concentrations Used in Association Rate Constant Calculations

We used this protocol to calculate the concentration used in association rate constant (k_{on}) calculation and the concentrations are summarized in Table SI 7. We obtained the cell sizes of free state conformations in the complex trajectories saved in original trajectories, and used eq. 8.1 to calculate the volume of the water box,

$$\text{Volume} = \frac{1}{N} \sum_{i=1}^N (\text{Cell Size X}(i) \times \text{Cell Size Y}(i) \times \text{Cell Size Z}(i)) \quad \text{eq. 8.1}$$

where N is the number of free state conformations in the complex trajectory, and Cell Size X, Y, Z are the cell sizes of the water box in three dimensions.

Then we used eq. 8.2 to calculate the solute concentration ($[\text{solute}]$) of the free state in the complex trajectories,

$$[\text{Solute}] = \frac{1/N_A}{\text{Volume}} \quad \text{eq. 8.2}$$

where N_A is the Avogadro constant, and “1” is the number of complex particles in the trajectory.

Guest	GAFF-CD	q4MD-CD
1-Propanol	0.03079	0.03079
1-Butanol	0.03078	0.03078
Methyl butyrate	0.03076	0.03076
t-Butanol	0.03078	0.03077
1-Naphthyl Ethanol	0.03070	0.03072
Aspirin	0.03072	0.03072
2-Naphthyl Ethanol	0.03070	0.03071
Unit: M		

Table SI 7. The solute concentrations of β -CD and guest molecules used in association rate constant (k_{on}) calculation in GAFF-CD and q4MD-CD. The concentrations correspond to free state conformations in the complex trajectories. All values are in mol/L (M).

9. Diffusion Controlled Association Rate Constants Estimated from Diffusion Coefficient

System	D_{Expt} (m ² /s)	D_{TIP3P} (m ² /s)	D_{MD} (m ² /s)	$k_{\text{on_diffuse}}$ (1/s·M)
1-Butanol	8.7×10^{-10}	2.4×10^{-9}	5.9×10^{-9}	4.45×10^{10}
Methyl Butyrate	8.1×10^{-10}	2.3×10^{-9}	5.2×10^{-9}	4.07×10^{10}
t-Butanol	8.7×10^{-10}	2.4×10^{-9}	5.7×10^{-9}	4.33×10^{10}
1-Propanol	9.4×10^{-10}	2.6×10^{-9}	6.6×10^{-9}	4.76×10^{10}
1-Naphthyl Ethanol	7.1×10^{-10}	2.0×10^{-9}	3.8×10^{-9}	3.26×10^{10}
Aspirin	7.3×10^{-10}	2.0×10^{-9}	3.7×10^{-9}	3.14×10^{10}
2-Naphthyl Ethanol	7.0×10^{-10}	2.0×10^{-9}	3.8×10^{-9}	3.28×10^{10}
β -CD	4.1×10^{-10}	1.1×10^{-9}	7.2×10^{-10}	/

Table SI 8. Diffusion coefficients of ligands and β -CD and diffusion controlled association rate constants ($k_{\text{on_diffuse}}$) estimated from the diffusion coefficients. Diffusion coefficients (in m²/s) are estimated by eq. 9.1 using water viscosities from experiments (D_{Expt}) and TIP3P water model (D_{TIP3P}), and directly measured from MD trajectories (D_{MD}). $k_{\text{on_diffuse}}$ values are estimated using D_{MD} in eq. 9.2 for each β -CD-guest complex.

$$D = kT/6\pi\eta a \quad \text{eq. 9.1}$$

where k is the Boltzmann constant, T is the temperature (298K), η is the viscosity of water, and a is the radius of solute.

$$k_{\text{on_diffuse}} = 4\pi N_A D R \quad \text{eq. 9.2}$$

where N_A is the Avogadro constant, D is the sum of the diffusion coefficient of β -CD and guest, and R is the sum of radii of β -CD and guest.

10. Uncertainty Evaluation of Computed Properties

We evaluated the uncertainty of all computed properties. For potential energy terms ($\langle E \rangle_{\text{Complex}}$, $\langle E \rangle_{\text{Water}}$, $\langle E \rangle_{\text{Host}}$, and $\langle E \rangle_{\text{Guest}}$), we used standard deviation of mean to evaluate the uncertainty in the potential energy and it was calculated by using block analysis⁵ with 2 ns in a block. The uncertainties of $\langle E \rangle_{\text{Complex}}$, $\langle E \rangle_{\text{Water}}$, $\langle E \rangle_{\text{Host}}$, and $\langle E \rangle_{\text{Guest}}$ were added in quadrature to get the uncertainty of binding enthalpy (ΔH). For properties A other than total binding enthalpy, we used bootstrap error analysis to get the uncertainties. We generated random subsets of the data, and calculated values of A from the random subsets, and finally calculated the standard deviations of the values of A from the random subsets, as the uncertainty of A . In principle, roughly 80% of the data were used to generate the random subsets. The number of random subsets is 100000 if non-repeated random subsets can be generated or otherwise the maximum number of possible subsets was used.

We computed the conformational population distribution of β -CD and used the Gibbs entropy formula (eq. 1) to evaluate $S_{\text{Host Complex}}$, $S_{\text{Host Free}}$, $S_{\text{Guest Int Complex}}$ and $S_{\text{Guest Int Free}}$. For $S_{\text{Host Complex}}$, we generated the random subsets of the conformations, and reconstructed the conformational population distributions for each subset, and calculated the standard deviation of $S_{\text{Host Complex}}$ obtained from each subset as the uncertainty of $S_{\text{Host Complex}}$. We did identical evaluations for uncertainty of $S_{\text{Host Free}}$, $S_{\text{Guest Int Complex}}$ and $S_{\text{Guest Int Free}}$. For example, for the free β -CD in GAFF-CD, we generated 100000 subsets with 200000 random conformations from the total 250000 conformations, and evaluated $S_{\text{Host Free}}$ using the strategy above. The uncertainty of ΔS_{Host} and $\Delta S_{\text{Guest Int}}$ were evaluated by summing uncertainties of $S_{\text{Host Complex}}$ and $S_{\text{Host Free}}$ and by summing uncertainties of $S_{\text{Guest Int Complex}}$ and $S_{\text{Guest Int Free}}$, respectively. We evaluated $S_{\text{Guest Ext Complex}}$ using eq. 2. Therefore, we used similar strategy as in internal entropy uncertainty evaluation to create the random subsets of conformations, and reconstructed the spatial and angular distribution histogram for evaluation of $S_{\text{Guest Ext Complex}}$ in each subset using eq. 2. The uncertainty was computed, again, as the standard deviation of $S_{\text{Guest Ext Complex}}$ obtained from the subsets. The uncertainty of solute entropy change (ΔS_{Solute}) was evaluated by summing uncertainties of ΔS_{Host} , $\Delta S_{\text{Guest Int}}$, and $S_{\text{Guest Ext Complex}}$. Note that $S_{\text{Guest Ext Free}}$ was computed using exact analytical equations so this term does not have uncertainty. For uncertainties of $S_{\text{Water Complex}}$, $S_{\text{Water Host}}$ and $S_{\text{Water Guest}}$, the calculation is slightly different in the way the random subsets were created. We saved the water entropy values for every 10-ps-block (1000 frames) along the trajectories and obtained N water entropy values from each block. Then we generated subsets that contain random collections of roughly $0.8N$ water entropy values from the N values. The percentage

$P\%$ is changed for a suitable combination number $C_{N, P\%N}$ so that $C_{N, P\%N}$ is within 100000 to 4294967296 (the greatest number in unsigned integer or 2^{32}). The standard deviations of water entropy values averaged from the random subsets were reported as the uncertainties of the water entropy terms. For example, for β -CD-1-butanol complex in GAFF, we used 45 blocks from the total 49 blocks to generate 211876 ($C_{49, 45}$) subsets, and evaluated the uncertainty using first 100000 subsets. The uncertainties of water entropy change (ΔS_{Water}) were evaluated by summing up the uncertainties of $S_{\text{Water Complex}}$, $S_{\text{Water Host}}$ and $S_{\text{Water Guest}}$.

The uncertainty of binding entropy (ΔS) was evaluated by summing up the uncertainties of ΔS_{Solute} and ΔS_{Water} . The uncertainty of binding free energy from eq. 5 (ΔG_{Comp1}) was evaluated by summing up the uncertainties of ΔH and ΔS .

For association (k_{on}) and dissociation (k_{off}) rate constants, we created the random subsets of the time lengths of bound/free periods, and calculated the rate constants from these subsets, and finally computed the standard deviations of the rate constants from these subsets, as the uncertainties of k_{on} and k_{off} . The uncertainty of K_{eq} are evaluated based on subsets of random combinations of k_{on} and k_{off} values obtained from the random subsets used to evaluate uncertainty of k_{on} and k_{off} . For example, for β -CD-1-propanol complex in GAFF-CD, we used 34 bound state period lengths out of total 39 to generate 575757 ($C_{39, 34}$) random subsets, computed the uncertainty of k_{on} using the standard deviation of the k_{on} values from the first 100000 subsets.

11. Experimental Data of ΔG , ΔH and $-\Delta S$ of β -CD-Alcohol Complexes Using ITC and UV

Ligand	Expt. Method	ΔG (kcal/mol)	ΔH (kcal/mol)	$-\Delta S$ (kcal/mol)
cyclohexanol	cal	-5.95	-1.67	-4.28
1,3-butanediol	cal	-5.57	-0.33	-5.23
1-pentanol	cal	-5.40	0.53	-5.93
1-hexanol	cal	-5.14	0.14	-5.28
phenol	cal	-4.54	-2.63	-2.15
trans-4-methylcyclohexanol	cal	-4.54	-2.17	-2.37
cis-4-methylcyclohexanol	cal	-4.33	-2.29	-2.03
1-methylcyclohexanol	cal	-4.18	-2.29	-1.89
(+)-cis-2-methylcyclohexanol	cal	-4.08	-2.37	-1.72
4-iodophenol	cal	-4.06	-3.85	-0.22
3-methylcyclohexanol	cal	-3.98	-2.09	-1.90
(+)-trans-2-methylcyclohexanol	cal	-3.91	-2.07	-1.85
2,2-dimethyl-1-propanol	uv	-3.70	-2.10	-1.51
cyclohexanol	uv	-3.66	-2.39	-1.22
3-nitrophenol	cal	-3.32	-2.89	-0.43
4-chlorophenol	uv	-3.27	-3.82	0.48
1-hexanol	uv	-3.18	0.10	-3.27
2-chlorophenol	uv	-3.13	-4.54	1.43
3-chlorophenol	uv	-3.13	-4.54	1.20
resorcinol	cal	-2.77	-4.35	1.55
1-pentanol	uv	-2.46	1.10	-3.56
5-methylresorcinol	cal	-2.34	-5.07	2.68
(R)-(-)-2-pentanol	cal	-2.08	0.88	-2.99
(S)-(+)-2-pentanol	cal	-2.06	0.98	-3.06
1-butanol	uv	-1.67	0.69	-2.34
2-propanol	cal	-0.57	2.65	-3.20

Table SI 9. Experimental data of ΔG , ΔH and $-\Delta S$ of β -CD-alcohol complexes using calorimetry (cal) and spectrophotometry (uv). The data are taken from ref ⁶.

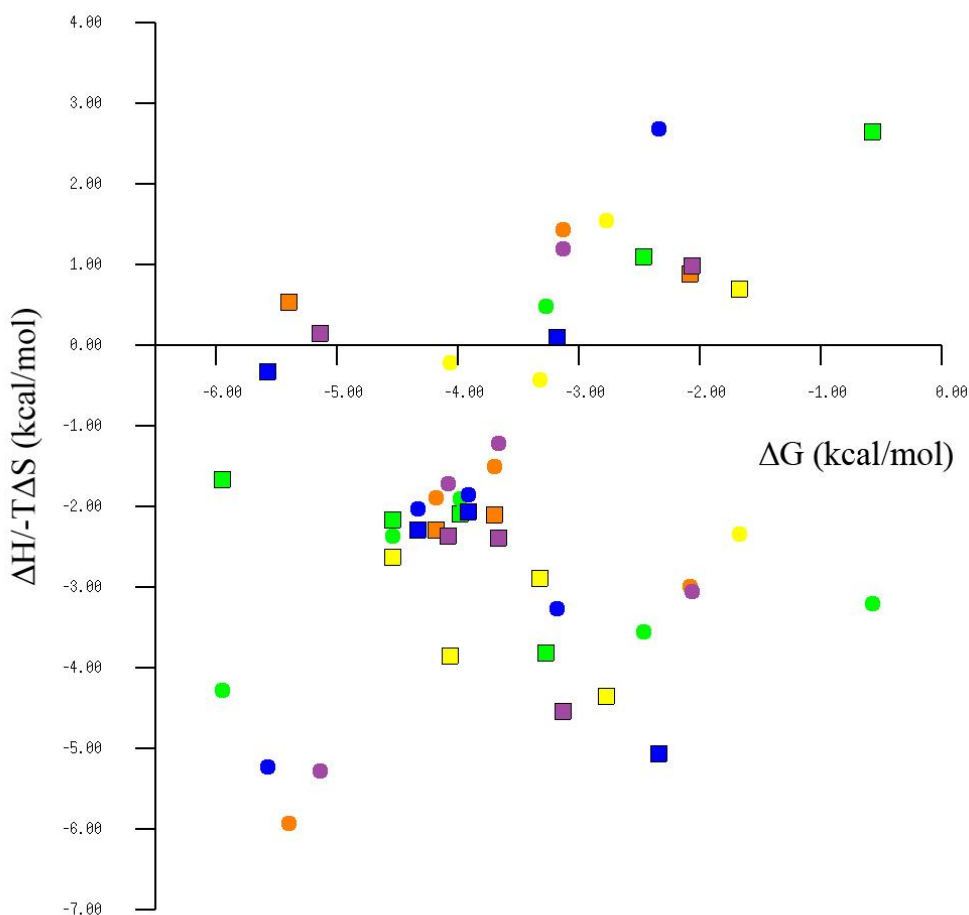


Figure SI 7. Plot of experimental ΔH and $-T\Delta S$ against experimental ΔG of β -CD-alcohol complexes using calorimetry and spectrophotometry. The plot uses values from Table SI 9. Enthalpy values are indicated by bordered rectangle, and entropy values are indicated by circles. The enthalpy and entropy of the same ligand are rendered in the same color. For ligands with ΔG ranging from 0 to -3 and -5 to -6 kcal/mol, $-T\Delta S$ is the major contribution to ΔG ; for ligands with ΔG ranging from -3 to -5 kcal/mol, both ΔH and $-T\Delta S$ contributes to ΔG .

12. Convergence of Enthalpy Calculations ($\langle E \rangle$)

We investigated the convergence of enthalpy calculation by plotting average potential energy ($\langle E \rangle$ in kcal/mol) against number of frames used in the average in Figures SI 8 to 10. We calculate the standard deviation (SD) of the last region of the average potential energy to estimate the fluctuation in the calculated enthalpy. The regions used in the SD calculation are indicated on the figures. Note that the SD is different from the uncertainty reported in the manuscript.

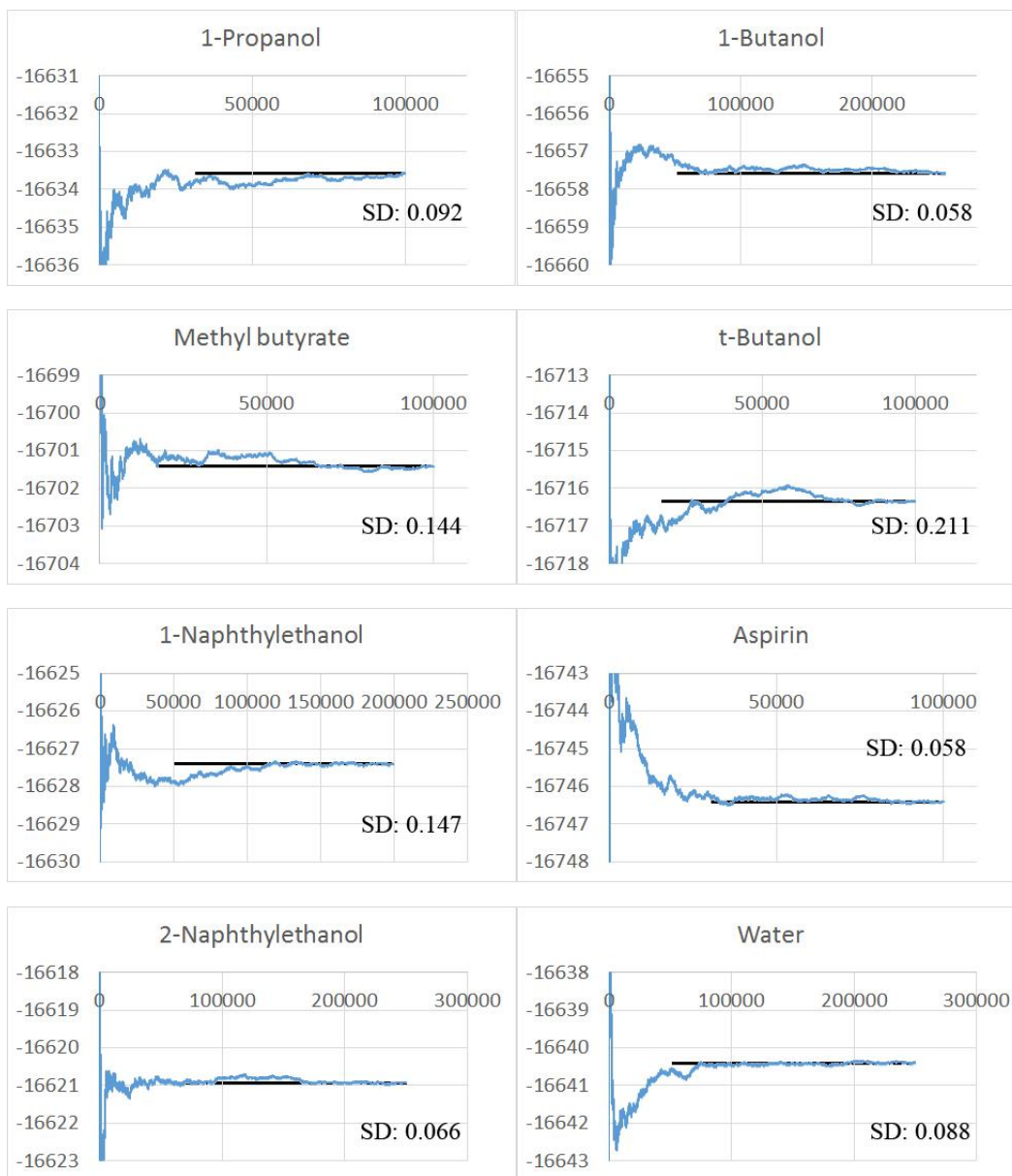


Figure SI 8. The enthalpy convergence of ligand and water trajectories. The convergence is represented by average potential energy ($\langle E \rangle$) plotted against the number of frames. X-axes are numbers of frames used in the average. Y-axes are average potential energies in kcal/mol. The Y value of the black line indicates the value used in reported enthalpy. The X range of the black line indicates the region used to calculate standard deviation (SD) of the averaged potential energy, and the SD (kcal/mol) is labeled on the figures.

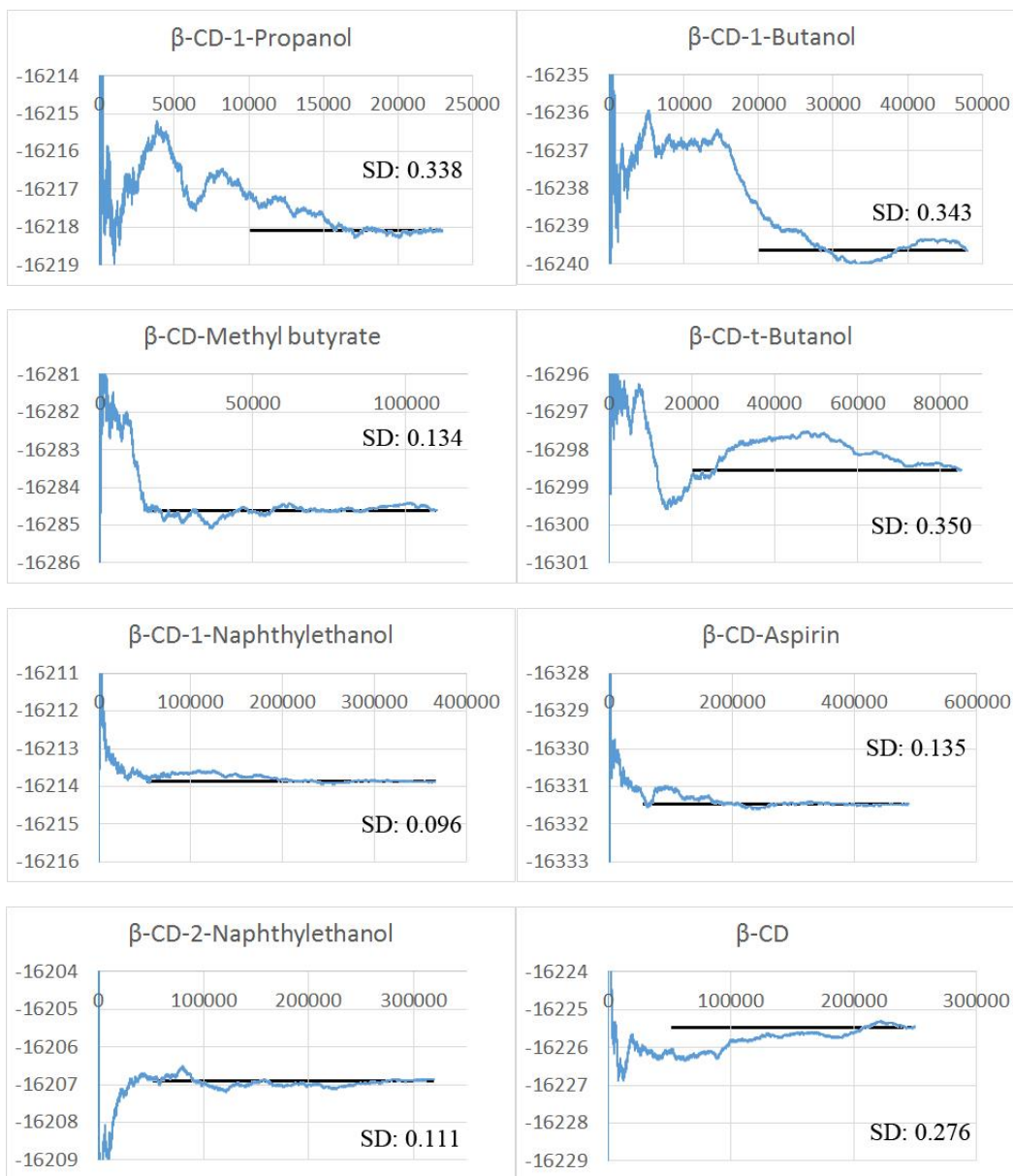


Figure SI 9. The enthalpy convergence of free β -CD and β -CD complexes using GAFF-CD force field. Refer to Figure SI 8 for the interpretation of the figures.

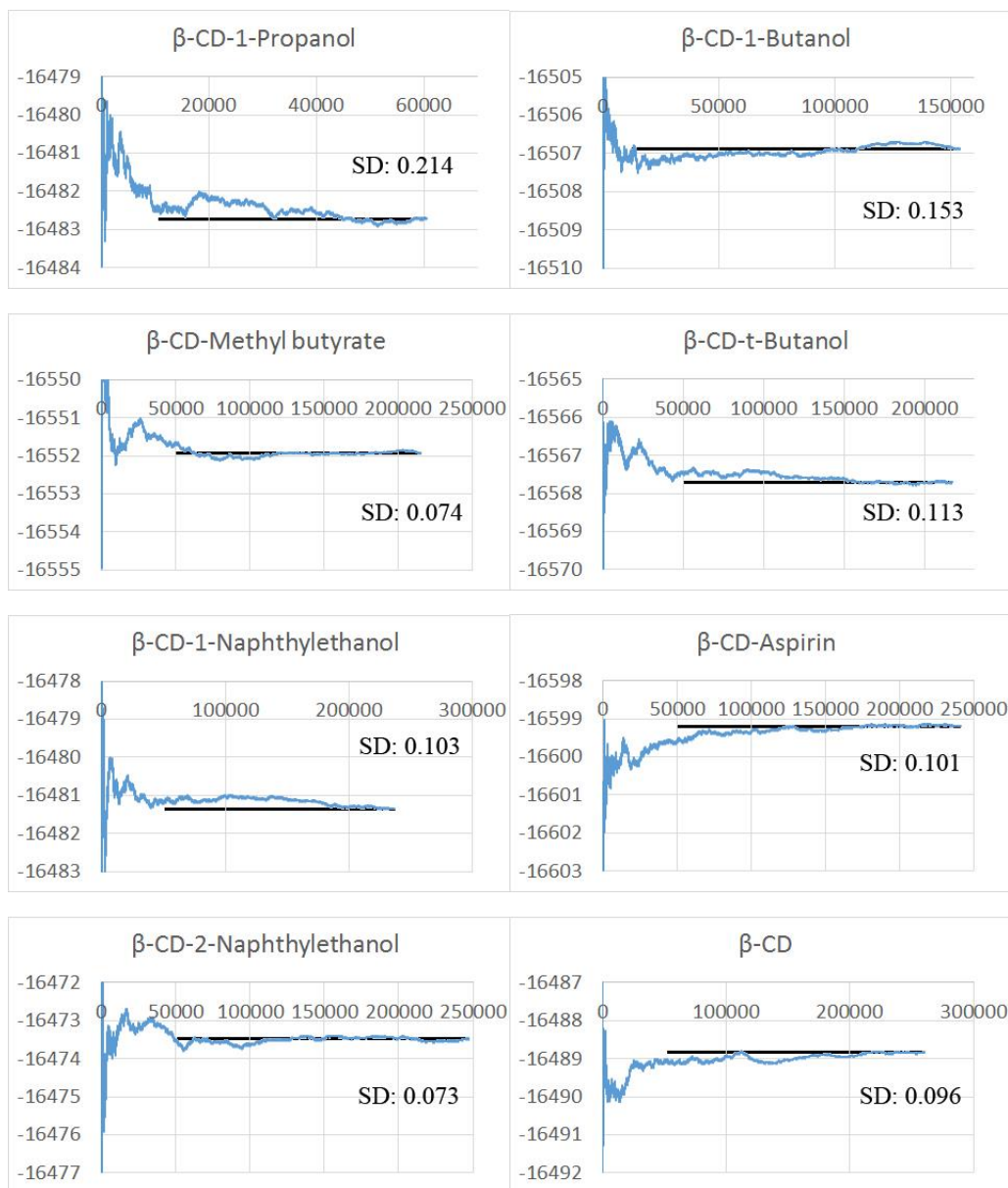


Figure SI 10. The enthalpy convergence of free β -CD and β -CD complexes using q4MD-CD force field. Refer to Figure SI 8 for the interpretation of the figures.

13. Movies of Association and Dissociation Pathways

In the movies, carbon atoms are in cyan and oxygen atoms are in red on β -CD. The ligands are rendered in green. Hydrogen atoms are omitted. Movies are listed as below.

From GAFF-CD force field:

1 β -CD-aspirin direct association: GAFF-CD-b-CD-aspirin_direct_association.swf

2 β -CD-aspirin direct dissociation: GAFF-CD-b-CD-aspirin_direct_dissociation.swf

3 β -CD-aspirin sticky association: GAFF-CD-b-CD-aspirin_sticky_association.swf

4 β -CD-aspirin sticky dissociation: GAFF-CD-b-CD-aspirin_sticky_dissociation.swf

5 β -CD-t-butanol direct association: GAFF-CD-b-CD-t-butanol_direct_association.swf

6 β -CD-t-butanol direct dissociation: GAFF-CD-b-CD-t-butanol_direct_dissociation.swf

From q4MD-CD force field:

7 β -CD-aspirin direct association: q4MD-CD-b-CD-aspirin_direct_association.swf

8 β -CD-aspirin direct dissociation: q4MD-CD-b-CD-aspirin_direct_dissociation.swf

9 β -CD-aspirin sticky association: q4MD-CD-b-CD-aspirin_sticky_association.swf

10 β -CD-aspirin sticky dissociation: q4MD-CD-b-CD-aspirin_sticky_dissociation.swf

11 β -CD-t-butanol direct association: q4MD-CD-b-CD-t-butanol_direct_association.swf

12 β -CD-t-butanol direct dissociation: q4MD-CD-b-CD-t-butanol_direct_dissociation.swf

14. Ligand External Degrees of Freedom

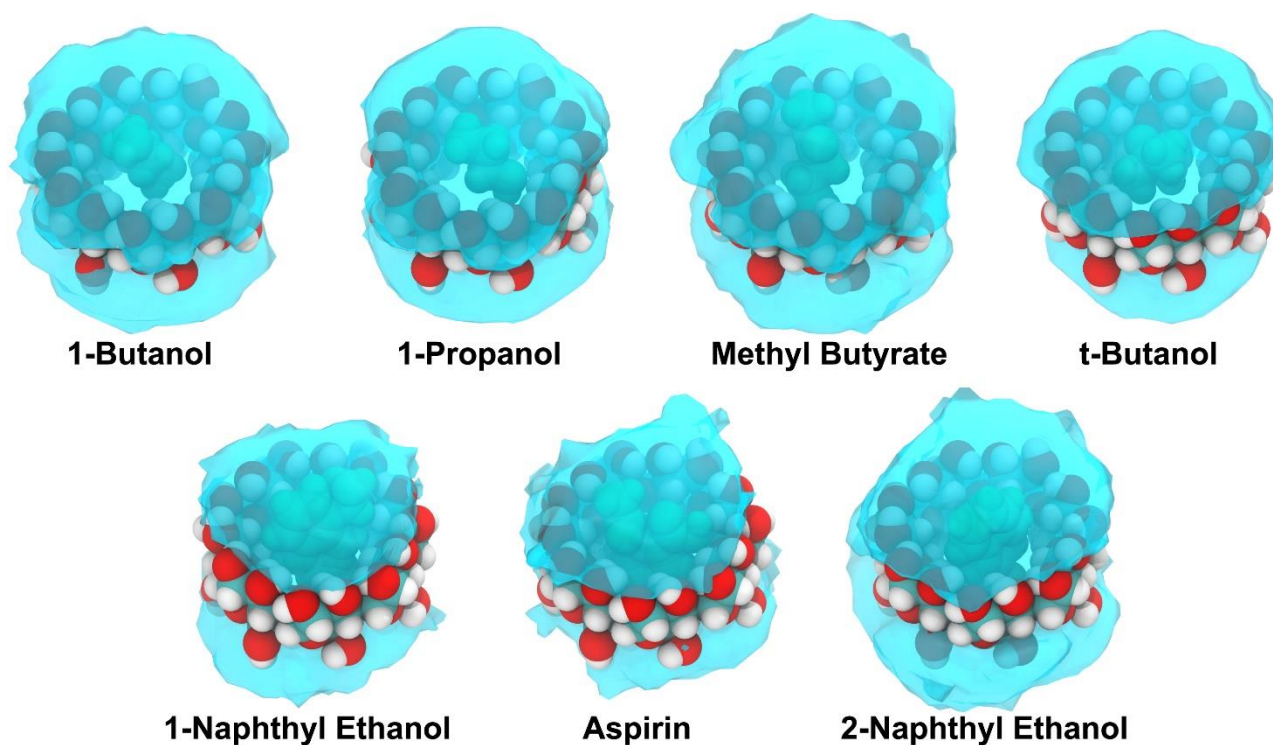


Figure SI 11. The binding poses of β -CD and ligand complex in GAFF-CD. For simplicity, the crystal structure of β -CD is shown in *VDW* representation. One representative conformation of ligands is rendered in green *VDW* representation. The volumes occupied by the bound state conformations are shown in cyan transparent *Surface* representation. The ligand conformations are obtained by superimposing β -CD coordinates in the trajectories to the crystal structure of β -CD. Similar binding volumes can be observed in q4MD-CD.

15. Bound and Free Period Lengths of the Complexes

	1-Propanol		1-Butanol		Methyl butyrate				t-Butanol			
	Bound	Free	Bound	Free	Bound		Free		Bound		Free	
1	1801	5834	9769	899	5287	189	639	8354	8381	119	594	20517
2	167	1521	6455	8840	885	298	2516	2143	171	119	17392	7004
3	1090	482	353	77243	2931	111	1730	23327	418	704	28343	6095
4	731	241	105	33202	342	394	14352	41390	109	108	1257	1631
5	153	57826	218	2025	302	1305	2672	1141	179	6601	54931	8604
6	107	26676	104	10408	101	14187	11150	13848	181	347	5509	42418
7	102	31381	318	32669	203	103	13537	37917	104	364	345	1985
8	268	23494	129	1050	152	150	6029	9514	156	137	4972	220
9	199	2233	136	20238	153	152	34568	5714	105	153	8409	7350
10	184	17913	205	7329	252	17996	26941	4260	111	482	57093	512
11	741	13660	161	15286	198	506	13582	1550	103	193	20737	885
12	113	42695	156	9173	151	217	7508	6697	290	1669	25645	18557
13	145	28855	141	5079	109	183	722	348	118	146	2032	30213
14	103	4623	104	4886	205	102	163	16516	178		10998	
15	100	16875	404	27418	1604	112	8441	32830	19253		3640	
16	106	5690	737	27469	1044	153	1339	2681	164		4157	
17	148	2049	320	10703	1296	449	1372	188	18665		18096	
18	108	18646	132	4843	130	175	6512	128	141		241	
19	142	23696	105	4345	1719	282	5651	1263	546		22927	
20	226	26882	116	3582	111	1116	16376	3612	156		4234	
21	239	128	182	1894	420	228	5834	6019	2234		4107	
22	364	48217	121	38219	102	138	3798	3953	120		345	
23	159	18383	264	1773	2658	103	5771	1967	114		5678	
24	103	43352	201	24159	299	171	1467	119	130		8925	
25	128	12708	315	2688	695	134	8344	20276	172		2267	
26	401	13298	102	16344	465	189	18912	14028	128		5984	
27	153	23600	142	38714	104	109	2265	6755	133		3860	
28	201	787	110	1534	390	184	5454	2378	323		3144	
29	108	720	178	894	4840	324	1586	1427	108		214	
30	119	16617	130	1318	112	1490	11015	12289	431		12414	
31	105	23846	115	4496	123		2417		152		2287	
32	127	5159	282	1977	397		708		112		6350	
33	111	10813	113	16631	126		1523		147		3421	
34	162	1775	100	23787	238		1279		263		12449	
35	253	37611	196	25623	151		387		477		2439	
36	151	11333	7042	3528	196		16738		3728		3933	
37	174	2753	418	6781	600		3703		176		5920	
38	101	16619	5800	13087	224		21087		143		14056	
39	123	993	461	1300	266		9822		177		17870	
40			199	758	156		34084		117		8000	
41			188	62738	152		4415		640		458	
42			133	18110	100		5236		236		17375	
43					9922		1564		233		9313	
44					4159		635		108		21409	
45					12086		3829		120		878	
46					101		2604		101		46032	
47					252		337		135		10473	
48					826		13528		209		31839	
49					195		4446		771		28408	
Avg.	256.8	16409.8	880.0	14596.2	1250.4		8243.3		1171.1		11732.1	
# of Periods	39	39	42	42	79		79		52		52	

Continued.

	1-Naphthyl Ethanol		Aspirin						2-Naphthyl Ethanol	
	Bound	Free	Bound			Free			Bound	Free
1	60007	2437	14310	419	228	1315	1955	8016	79434	1094
2	292	2171	3850	122	368	673	2497	2020	15270	2190
3	181	767	29400	2178	269	3586	3234	3849	4633	1380
4	6478	3866	407	169	275	3655	675	3969	411	1117
5	7108	4005	1002	255	115	148	10442	2624	156	4645
6	287	853	1042	120	146	3279	1057	2389	10619	534
7	487	3852	126	104	266	155	11040	487	609	338
8	146	11887	119	153	376	1959	3667	4619	154	227
9	293800	9182	10190	247	176	1752	1603	2014	1785	1130
10	206	4737	264	312	370	1539	586	1991	363	1250
11	512	8456	1271	115	199	2940	6580	1221	125	1230
12	259	344	1315	254	105	1103	825	5897	288	1452
13	599630	206	46697	130	3301	2840	870	6453	4976	10239
14	111	1850	2729	417	238	293	1002	4969	823	5208
15	705	2377	5417	17434	125	4436	3449	10530	223	1495
16	72801		232	5570	343	1375	1431	4637	432	1638
17			14907	848	4538	799	430	4674	150	1935
18			247	217	474	210	640	736	771	8741
19			849	119	478	650	12050	7552	35439	5824
20			8436	119	118	5095	8876	5736	125	3210
21			233	150	289	391	1931	3842	489	722
22			448	271	112	1437	1344	189	165	776
23			1096	114	9699	2252	1266	1835	717	7637
24			197	117	7116	3407	2658	680	153	4746
25			362	130	204	1072	2082	1488	192	1610
26			16445	109	764	3851	8874	1440	198	3272
27			276	218	178	1648	229	2132	8415	3760
28			124	152	274	2465	640	432	3003	4103
29			167	483	149	1415	16437	1535	180	13227
30			243	109	184	2052	1347	6401	138	1061
31			829	108	105	2467	2244	3062	101	15234
32			360	247	205	6322	6913	4841	193	3048
33			103	143	148	2129	2248	2453	147	2372
34			395	713	5682	2254	7830	347	191	2997
35			141	140	208	1480	251	1220	154	7530
36			172	175		1441	11777		20316	1138
37			387	111		11984	1962		8508	737
38			530	246		1669	331		5201	199
39			346	165		820	8042		12334	3273
40			2540	207		1290	339		188001	537
41			199	234		1169	1093		214790	1692
42			152	118		703	3593		1340	1333
43			206	122		4479	2950		3312	4452
44			37326	124		215	236		217	2548
45			2111	288		1714	3461		95640	8830
46			1585	164		549	3077		9632	7124
47			270594	155		203	239		250	1809
48			2878	318		1078	6615		277	3692
49			121	245		1708	2957		204624	
Avg.	65188.1	3799.3	4183.3			2959.6			19095.2	3423.7
# of Periods	16	15	133			133			49	48

Table SI 10. The bound and free period lengths of the complexes in GAFF-CD. All lengths of periods are in 10 ps.

	1-Propanol						1-Butanol				Methyl Butyrate		t-Butanol	
	Bound			Free			Bound		Free		Bound	Free	Bound	Free
1	1066	101	1337	927	3992	3705	1669	311	5868	2015	4075	254	2079	4536
2	726	751	155	1994	3029	356	4436	1216	2529	1686	7411	560	200	2727
3	110	2499	247	3265	157	1527	3418	1606	691	1731	2199	1595	4888	2110
4	388	1001	815	9801	107	1917	675	4533	4797	415	4978	715	1518	581
5	909	463	4468	1944	1384	7095	839	1397	403	610	7610	10426	40660	3023
6	211	1323	581	5500	5008	3284	3525	219	4471	4280	7614	1374	17924	996
7	328	105	476	10021	292	2142	3339	721	1554	3039	2318	3102	19064	4732
8	642	1930	538	1772	4243	1017	1718	4044	1887	803	59426	1601	225	2162
9	3051	104	404	798	357	268	8429	2363	1076	1430	1513	2075	42030	5703
10	321	1181	455	4932	3457	4589	7477	2014	1874	2083	19404	1543	162	1199
11	823	1104	366	962	3717	4783	1597	1987	4394	898	21044	1334	109	1899
12	1468	613	2245	1553	2755	3235	123	12994	793	4889	22974	765	12323	1948
13	644	554	111	2321	10977	2270	130	3018	337	1162	6295	852	84946	8435
14	418	1459	295	986	3376	545	3550	2099	1987	101	5330	2041	11078	728
15	749	104	216	488	6438	2996	8262	4062	1588	428	9781	1596	9311	4121
16	1158	728	105	258	794	2695	12898	6707	220	2743	45096	3450	1798	5267
17	271	642	1766	1840	100	5162	5868	1271	711	171	16006	569	5173	332
18	411	156	2064	147	8925	5071	276	1564	3439	7825	1751	5507	7726	6462
19	2034	493	151	5741	1848	4353	375	4661	2854	759	15608	701	1875	3918
20	1274	1126	257	8362	2226	660	1082	553	2271	219	796	1086	2130	5128
21	227	1512	589	4757	2646	686	1014	679	810	3644	7949	1607	27334	1724
22	1112	1126	490	416	710	4381	211	7893	1368	321	22236	1400	16820	1317
23	1830	440	340	1205	1098	597	6426	911	1790	175	2675	1938	32273	2846
24	1121	571	633	826	2727	634	3235	2964	1530	1253	10181	487	22784	1384
25	921	1376	1172	4051	1468	1811	1562	371	4497	2381	2960	3447	141	458
26	2138	1502	154	4796	3993	1605	10609	156	2045	2131	5905	2755	558	839
27	634	413	323	1928	1560	768	670	175	990	4592	12412	1043	10296	
28	118	127	1134	1078	6956	687	5644	480	2284	2993	1748	370		
29	519	884	793	1290	1075	1204	4651	663	346	422	4834	4757		
30	1167	194	995	566	1807	519	240	8417	1629	1100	5901	262		
31	688	1792		575	3608		1358	6132	1072	1528	5626	466		
32	460	1625		1589	453		2035	111	5150	4204	1066	1872		
33	365	900		2779	6987		1284	416	7472	701	134	3888		
34	666	257		3514	1546		9153	4337	479	2745	4463	3745		
35	108	129		5846	7895		161	1744	317	1528	117	4174		
36	2889	183		5320	845		4359	2431	844	6045	2955	1884		
37	2551	379		196	5664		6786	440	2917	957	8285	1671		
38	510	900		1777	4104		8748	3703	2521	595	196	3873		
39	509	910		926	844		5470	4059	3535	6623	5821	1554		
40	909	115		2147	3121		208	2320	861	4446		968		
41	513	260		3317	6226		3263		485					
42	2092	600		608	1280		1238		2300					
43	251	715		6986	877		1517		4515					
44	199	664		209	1552		629		1418					
45	2411	604		955	3575		2902		720					
46	813	238		261	140		2728		1749					
47	777	1167		3399	5357		667		3268					
48	494	3235		4399	1890		1279		198					
Avg.	848.6			2722.8			2994.0		2119.6		9402.4	2082.7	13904.6	2868.3
# of Periods	128			128			89		89		39	40	27	26

Continued.

	1-Naphthyl Ethanol		Aspirin		2-Naphthyl Ethanol	
	Bound	Free	Bound	Free	Bound	Free
1	19239	890	29988	737	388957	1465
2	138	2805	3198	593	103585	203
3	77015	5636	9970	2614	105790	
4	167	1597	11443	400		
5	280005	996	94979	1252		
6	88794	4855	13411	436		
7	12888	2118	44896	672		
8	102857		46931	521		
9			4055	320		
10			112077	1570		
11			626	661		
12			31966	1974		
13			40488	1767		
14			64727	535		
15			14034	1247		
16			1007	1287		
17			426	717		
18			58475			
Avg.	17360.1	1184.2	22624.7	1831.1	23275.2	949.3
# of Periods	8	7	18	17	3	2

Table SI 11. The bound and free period lengths of the complexes in q4MD-CD. All lengths of periods are in 10 ps.

16. Comparison of ΔG_{Comp1} and ΔG_{Comp2}

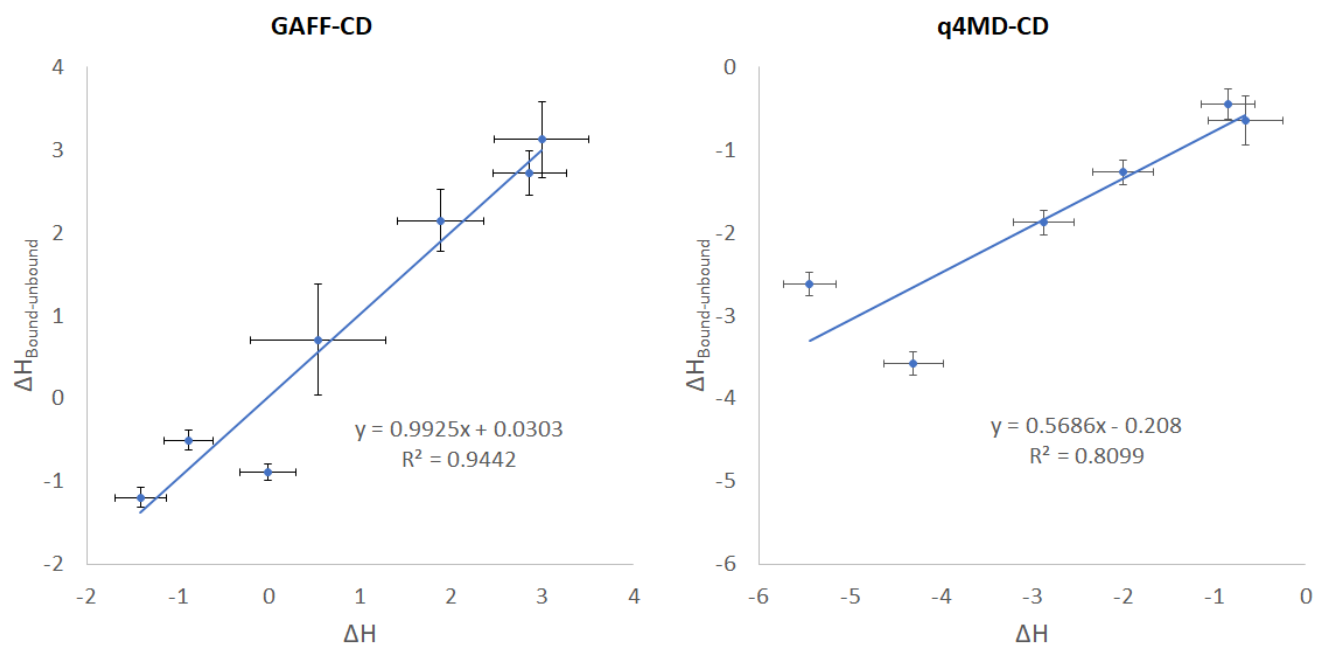


Figure SI 12. The correlations between ΔH , $\Delta H_{\text{Bound-unbound}}$ and experimental values. $\Delta H_{\text{Bound-unbound}}$ was computed by using average potential energy of bound and unbound conformations in the trajectories of the complexes. The correlations are label correspondingly. Error bars indicate the uncertainties.

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