Supplementary Material to The Conveyor Belt Umbrella Sampling (CBUS) Scheme: Principle and Application to the Calculation of the Absolute Binding Free Energies of Alkali Cations to Crown Ethers.

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S.1 Influence of the CBUS Parameters

The CBUS sampling scheme, inspired from the recently proposed CBTI approach for alchemical free-energy calculations,¹⁰⁶ is introduced here for the first time. For this reason, some preliminary investigations are necessary to assess the effect of its parameters on the results of the free-energy calculations, and to determine appropriate parameters combinations for its application. These test simulations exclusively consider the binding of K⁺ to 15C5 in CH₃OH. The parameter sensitivity of CBUS is tested by investigating the effect of changing the number of K replicas, the mass-parameter m_{Λ} , the thermostat coupling time τ_{Λ} , or the force constant c. All the parameter combinations tested are summarized in Tab. S.1 along with the corresponding results.

Table S.1: Relevant parameters and results of the CBUS simulations with different settings for the binding of K⁺ to 15C5 in CH₃OH. The successive entries are: the number K of replicas, the simulation time $t_{\rm sim}$ for the replica system, the mass-parameter m_{Λ} of the CB advance variable Λ , the thermostat coupling time τ_{Λ} of the CB, the harmonic biasing force constant c, the average temperature T_{Λ} of Λ , the standard deviation $\sigma_{\dot{\Lambda}}$ of the CB velocity $\dot{\Lambda}$, the autocorrelation time $\tau_{\dot{\Lambda}}$ of $\dot{\Lambda}$, the diffusion constant D_{Λ} along Λ and the highest free-energy barrier G^{\star}_{Λ} in the PMF along Λ . The value of D_{Λ} is half the slope of the mean-square displacement d_{Λ} as a function of time, based on the Einstein equation.¹⁶⁵ It was evaluated using a linear least-squares fit over the interval 0-0.25 ps. A dash ("-") for G^{\star}_{Λ} means that the value was not computable because the corresponding barrier was not crossed during the simulation, *i.e.* there was insufficient sampling of the $\tilde{\Lambda}$ range.

K	$t_{\rm sim}$	m_Λ	$ au_{\Lambda}$	c	T_{Λ}	$\sigma_{\dot{\Lambda}}$	$ au_{\dot{\Lambda}}$	D_{Λ}	G^{\star}_{Λ}
	[ns]	$[\mathbf{g} \cdot \mathbf{mol}^{-1} \cdot \mathbf{nm}^2]$	[ps]	$[kJ \cdot mol^{-1}]$	[K]	$[ps^{-1}]$	$[ps^{-1}]$	$[ns^{-1}]$	$[kJ \cdot mol^{-1}]$
4	20	100	0.50	2000	305.7	0.16	0.003	0.354	10.56
4	20	100	0.50	1000	307.5	0.16	0.002	0.423	8.19
4	20	100	0.50	4000	298.7	0.16	0.007	0.222	11.18
4	20	100	0.05	2000	289.4	0.16	0.006	0.291	11.62
4	20	100	0.05	1000	287.5	0.16	0.004	0.394	7.60
4	20	100	0.05	4000	292.0	0.16	0.018	0.258	10.24
4	20	100	5.00	2000	299.2	0.16	0.006	0.427	9.72
4	20	100	5.00	1000	304.7	0.16	0.002	0.524	7.22
4	20	100	5.00	4000	297.5	0.16	0.020	0.292	12.48
4	20	10	0.50	2000	293.7	0.49	0.131	0.327	8.43
4	20	10	0.50	1000	302.5	0.50	0.178	0.404	11.70
4	20	10	0.50	4000	300.2	0.50	0.005	0.212	18.26
4	20	10	0.05	2000	284.7	0.49	0.018	0.356	11.43
4	20	10	0.05	1000	283.8	0.49	0.118	0.554	5.63
4	20	10	0.05	4000	290.7	0.49	0.018	0.332	8.42
4	20	10	5.00	2000	300.5	0.50	0.015	0.355	9.42
4	20	10	5.00	1000	302.2	0.50	0.220	0.537	7.38
4	20	10	5.00	4000	299.9	0.50	0.002	0.238	12.25
4	20	1000	0.50	2000	314.6	0.05	0.327	0.290	9.82
4	20	1000	0.50	1000	318.2	0.05	0.418	0.415	9.22
4	20	1000	0.50	4000	313.6	0.05	0.257	0.101	-
4	20	1000	0.05	2000	286.1	0.05	0.347	0.282	11.14
4	20	1000	0.05	1000	280.9	0.05	0.454	0.498	7.77
4	20	1000	0.05	4000	289.6	0.05	0.279	0.144	10.52
4	20	1000	5.00	2000	318.9	0.05	0.506	0.359	10.69
4	20	1000	5.00	1000	313.7	0.05	0.632	0.490	6.56
4	20	1000	5.00	4000	310.9	0.05	0.391	0.240	10.48
10	8	100	0.50	2000	304.2	0.16	0.003	0.055	15.05
10	8	100	0.50	1000	295.3	0.16	0.015	0.153	6.07
10	8	100	0.50	4000	300.3	0.16	0.007	0.030	-
10	8	100	0.05	2000	293.6	0.16	0.006	0.034	15.13
10	8	100	0.05	1000	289.2	0.16	0.018	0.111	4.70

K	$t_{\rm sim}$	m_Λ	$ au_{\Lambda}$	c	T_{Λ}	$\sigma_{\dot{\Lambda}}$	$ au_{\dot{\Lambda}}$	D_{Λ}	G^{\star}_{Λ}
	[ns]	$[g \cdot mol^{-1} \cdot nm^2]$	[ps]	$[kJ \cdot mol^{-1}]$	[K]	$[ps^{-1}]$	$[ps^{-1}]$	$[ns^{-1}]$	$[kJ \cdot mol^{-1}]$
10	8	100	0.05	4000	288.5	0.16	0.016	0.050	-
10	8	100	5.00	2000	302.4	0.16	0.007	0.049	13.37
10	8	100	5.00	1000	300.6	0.16	0.002	0.161	4.90
10	8	100	5.00	4000	302.8	0.16	0.013	0.021	-
10	8	10	0.50	2000	292.0	0.49	0.096	0.068	11.07
10	8	10	0.50	1000	289.3	0.49	0.500	0.249	6.45
10	8	10	0.50	4000	299.4	0.50	0.017	0.043	-
10	8	10	0.05	2000	306.5	0.50	0.155	0.092	11.25
10	8	10	0.05	1000	293.0	0.49	0.016	0.186	4.51
10	8	10	0.05	4000	284.1	0.49	0.091	0.043	
10	8	10	5.00	2000	292.0	0.49	0.002	0.042	13.35
10	8	10	5.00	1000	295.6	0.50	0.628	0.230	5.50
10	8	10	5.00	4000	295.2	0.50	0.113	0.028	-
10	8	1000	0.50	2000	300.8	0.05	0.136	0.049	11.73
10	8	1000	0.50	1000	306.2	0.05	0.229	0.167	5.18
10	8	1000	0.50	4000	310.9	0.05	0.001	0.034	15.11
10	8	1000	0.05	2000	283.7	0.05	0.194	0.031	-
10	8	1000	0.05	1000	291.3	0.05	0.272	0.149	5.94
10	ð	1000	0.05	4000	287.7	0.05	0.017	0.025	-
10	ð	1000	5.00	2000	311.9	0.05	0.253	0.084	11.02
10	8	1000	5.00	1000	322.3	0.05	0.349 0.172	0.219	4.09
10	0	1000	0.50	4000	299.2	0.05	0.175	0.045	-
20	4	100	0.50	2000	291.4	0.10	0.014 0.245	0.089	4.07
20	4	100	0.50	4000	294.0	0.10	0.243 0.141	0.092	2.20
20	4	100	0.00	2000	206.6	0.10	0.141	0.004	1.20
20	4	100	0.05	2000	290.0	0.10	0.002	0.034 0.152	4.24 9.11
20	4	100	0.05	4000	281.5	0.15	0.001	0.152 0.117	5.67
20	4	100	5.00	2000	201.1	0.16	0.184	0.117	5.16
20	4	100	5.00	1000	298.0	0.16	0.104	0.000	2.08
$\frac{20}{20}$	4	100	5.00	4000	290.1	0.16	0.220 0.144	0.100	5.31
20	4	10	0.50	2000	292.2	0.49	0.205	0.112	4 53
$\overline{20}$	4	10	0.50	1000	306.4	0.50	0.019	0.083	1.92
$\overline{20}$	4	10	0.50	4000	291.0	0.49	0.130	0.047	2.87
20	4	10	0.05	2000	289.1	0.49	0.145	0.067	4.16
20	4	10	0.05	1000	296.6	0.50	0.166	0.058	2.86
20	4	10	0.05	4000	307.0	0.50	0.150	0.041	5.08
20	4	10	5.00	2000	294.6	0.50	0.229	0.080	4.72
20	4	10	5.00	1000	293.5	0.49	0.017	0.115	1.54
20	4	10	5.00	4000	282.9	0.49	0.017	0.086	6.83
20	4	1000	0.50	2000	304.6	0.05	0.020	0.080	6.22
20	4	1000	0.50	1000	311.2	0.05	0.018	0.058	2.07
20	4	1000	0.50	4000	312.4	0.05	0.004	0.070	5.32
20	4	1000	0.05	2000	281.5	0.05	0.010	0.097	5.11
20	4	1000	0.05	1000	288.3	0.05	0.171	0.119	2.78
20	4	1000	0.05	4000	288.3	0.05	0.018	0.076	3.86
20	4	1000	5.00	2000	298.0	0.05	0.004	0.082	4.36
20	4	1000	5.00	1000	312.5	0.05	0.193	0.081	2.01
20	4	1000	5.00	4000	301.8	0.05	0.018	0.038	6.25
40	2	100	0.50	2000	290.2	0.16	0.024	0.047	2.08
40	2	10	0.50	2000	274.4	0.48	0.009	0.020	2.47
40	2	1000	0.50	2000	299.6	0.05	0.001	0.032	1.54

The effect of the number K of replicas is illustrated in Fig. S.1, which compares simulations relying on 4, 10, 20 or 40 replicas (together with $m_{\Lambda} = 100 \text{ g}\cdot\text{mol}^{-1}\cdot\text{nm}^2$ and $\tau_{\Lambda} = 0.5$ ps). All simulations correspond to 80 ns total single-system sampling time (20, 8, 4 or 2 ns per replica for K = 4, 10, 20 and 40, respectively). The time evolution of Λ and the associated probability distribution $P(\Lambda)$ (Figs. S.1a-S.1d) shows that the CB rotates only a fraction of a full rotation (2π). However, since a shift of Λ by $\Delta\Lambda$ ($2\pi K^{-1}$) corresponds to an identical state of the CB up to a shift of all replicas by one position, the relevant variable to assess convergence¹⁰⁶ is actually $\tilde{\Lambda}$, which corresponds to Λ refolded to the interval [0, $\Delta\Lambda$). The time evolution of this variable along with the associated probability distribution $\tilde{P}(\tilde{\Lambda})$ (Figs. S.1e-S.1h) evidences numerous shifts in both cases. For K = 20 and 40, this results in a nearly homogeneous coverage, whereas a significant bias towards specific values of $\tilde{\Lambda}$ remains visible for K = 4 and 10 (towards $\tilde{\Lambda} \approx \pi/16$ and $\tilde{\Lambda} \approx 7\pi/16$ for K = 4, and towards $\tilde{\Lambda} \approx \pi/10$ for K = 10). Accordingly, the free-energy profiles $G_{\tilde{\Lambda}}(\tilde{\Lambda})$ calculated from the simulations (Figs. S.1i-S.1l) are flatter for K = 40, with variations on the order of 2 kJ·mol⁻¹, which become larger upon decreasing K. All production simulations of the Main Article were carried out with K = 20, which represents a good compromise between a free-energy surface with sufficiently low barriers $(3 - 4 \text{ kJ} \cdot \text{mol}^{-1})$ and a simulation time which can be longer at identical total single-system sampling time, *i.e.* computational cost.

The effect of the mass-parameter m_{Λ} of the CB is illustrated in Fig. S.2, where this parameter is changed from 10 to 100 and to 1000 g·mol⁻¹·nm² (together with K = 20 and $\tau_{\Lambda} = 0.5$ ps). The simulations last 4 ns for the replica system, which corresponds to 80 ns total single-system sampling time. Here again, the time evolution of Λ and the associated probability distribution $P(\Lambda)$ (Figs. S.2a-S.2c) shows only a fraction of a full rotation (at most about $\pi/4$). But the corresponding $\tilde{\Lambda}$ time series and probability distribution $\tilde{P}(\tilde{\Lambda})$ evidences again many shifts and an essentially homogeneous coverage in the three cases (data not shown). The time evolution of the velocity Λ along with the associated probability distribution $P_{\dot{\Lambda}}(\dot{\Lambda})$ is also shown (Figs. S.2d-S.2f). The distribution becomes narrower upon increasing the mass (lower square velocity at constant kinetic energy). The time series of the mean-square displacement d_{Λ} of $\dot{\Lambda}$ (Figs. S.2g-S.2i) shows that the diffusion along Λ is essentially independent of the mass. This is qualitatively in line with the Λ -range covered during the 4 ns simulations. As discussed previously,¹⁰⁶ this observation is not incompatible with the decrease of the average velocity upon increasing the mass-parameter (see above), considering that the diffusion rate depends not only on the average magnitude of the velocity, but also on its time-correlation function (Green-Kubo relation). Based on the above observations, a value $m_{\Lambda} = 1000 \,\mathrm{g \cdot mol^{-1} \cdot nm^2}$ was selected for all production simulations of the Main Article.



Figure S.1: Results of test simulations using CBUS with four different numbers of replicas. This figure considers the binding of K⁺ to 15C5 in CH₃OH, calculated using CBUS simulations with K = 4 replicas (a,e,i,m), K = 10 replicas (b,f,j,n), K = 20 replicas (c,g,k,o), or K = 40 replicas (d,h,l,p) along with $m_{\Lambda} = 100 \text{ g} \cdot \text{mol}^{-1} \cdot \text{nm}^2$ and $\tau_{\Lambda} = 0.5 \text{ ps}$. The time evolutions of the CB advance variable Λ and the associated probability distributions $\tilde{P}(\tilde{\Lambda})$ are shown (a-d). The time evolutions of the corresponding fractional advance variable $\tilde{\Lambda}$ and the associated probability distributions $\tilde{P}(\tilde{\Lambda})$ are also displayed (e-h). The variable $\tilde{\Lambda}$ corresponds to Λ refolded into the interval $[0, \Delta \Lambda)$ where $\Delta \Lambda = 2\pi K^{-1}$. The free-energy profiles $G_{\tilde{\Lambda}}(\tilde{\Lambda})$ calculated from the simulations are also shown (i-1). Finally, the time evolutions of the mean-square displacement d_{Λ} of Λ are also displayed (m-p), along with along with a linear least-squares fit over the interval 0-0.25 ps (brown dashed line). The slope of this line is equal to twice the diffusion constants D_{Λ} along Λ . All probability distributions are normalized to one.



Figure S.2: Results of test simulations using CBUS with three different values of the mass-parameter. This figure considers the binding of K⁺ to 15C5 in CH₃OH, calculated using CBUS simulations with K = 20 replicas and a mass-parameter m_{Λ} of 10 (a, d, g), 100 (b, e, h), or $1000 \text{ g} \cdot \text{mol}^{-1} \cdot \text{nm}^2$ (c, f, i) along with $\tau_{\Lambda} = 0.5 \text{ ps}$. The time evolutions of the CB advance variable Λ and the associated probability distributions $P(\Lambda)$ are shown (a-c). The time evolutions of the corresponding velocities $\dot{\Lambda}$ and the associated probability distributions $P_{\dot{\Lambda}}(\dot{\Lambda})$ are also shown (d-f), together with the the analytical one-dimensional Maxwell-Boltzmann velocity distribution (red line). Finally, the time evolutions of the mean-square displacement d_{Λ} of Λ are also displayed (g-i), along with a linear least-squares fit over the interval 0-0.25 ps (brown dashed line). The slope of this line is equal to twice the diffusion constants D_{Λ} along Λ .

S.2 PMFs of all Systems with Different Sampling Schemes and Free-Energy Estimators



Figure S.3: PMFs calculated for the 15 host-guest-solvent systems involving the host 12C4. The different systems are shown in Main Article Fig. 2. The PMFs $G(\xi)$ are calculated using various combinations of the sampling schemes DCNT, TRUS, REUS or CBUS along with the estimators DCAN, WHAM, MFIN or UINT (the latter two are discussed in Appendix B of the Main Article). The calculations involve a total single-system sampling time of 40 ns for DCNT and CBUS or 42 ns for TRUS and REUS. The rows correspond to the different alkali cations Li⁺ (a-c), Na⁺ (d-f), K⁺ (g-i), Rb⁺ (j-l) and Cs⁺ (m-o). The columns correspond to the different solvents H₂O (a,d,g,j,m), DMSO (b,e,h,k,n) and CH₃OH (c,f,i,l,o). The PMFs are anchored to zero at the positions ξ_o of their global minima. The vertical lines indicate the positions of the cutoff ξ_* selected to distinguish bound and free states (Main Article Tab. 2). The standard absolute binding free energies ΔG° calculated from these PMFs are reported in Main Article Tab. 4 and illustrated graphically in Fig. S.6. The positions ξ_o of the minima (based on TRUS-WHAM) are reported in Main Article Tab. 2.



Figure S.4: PMFs calculated for the 15 host-guest-solvent systems involving the host 15C5. The different systems are shown in Main Article Fig. 2. The PMFs $G(\xi)$ are calculated using various combinations of the sampling schemes DCNT, TRUS, REUS or CBUS along with the estimators DCAN, WHAM, MFIN or UINT (the latter two are discussed in Appendix B of the Main Article). The calculations involve a total single-system sampling time of 40 ns for DCNT and CBUS or 42 ns for TRUS and REUS. The rows correspond to the different alkali cations Li⁺ (a-c), Na⁺ (d-f), K⁺ (g-i), Rb⁺ (j-l) and Cs⁺ (m-o). The columns correspond to the different solvents H₂O (a,d,g,j,m), DMSO (b,e,h,k,n) and CH₃OH (c,f,i,l,o). The PMFs are anchored to zero at the positions ξ_o of their global minima. The vertical lines indicate the positions of the cutoff ξ_* selected to distinguish bound and free states (Main Article Tab. 2). The standard absolute binding free energies ΔG^{\oplus} calculated from these PMFs are reported in Main Article Tab. 4 and illustrated graphically in Fig. S.7. The positions ξ_o of the minima (based on TRUS-WHAM) are reported in Main Article Tab. 2.



Figure S.5: PMFs calculated for the 15 host-guest-solvent systems involving the host 18C6. The different systems are shown in Main Article Fig. 2. The PMFs $G(\xi)$ are calculated using various combinations of the sampling schemes DCNT, TRUS, REUS or CBUS along with the estimators DCAN, WHAM, MFIN or UINT (the latter two are discussed in Appendix B of the Main Article). The calculations involve a total single-system sampling time of 40 ns for DCNT and CBUS or 42 ns for TRUS and REUS. The rows correspond to the different alkali cations Li⁺ (a-c), Na⁺ (d-f), K⁺ (g-i), Rb⁺ (j-l) and Cs⁺ (m-o). The columns correspond to the different solvents H₂O (a,d,g,j,m), DMSO (b,e,h,k,n) and CH₃OH (c,f,i,l,o). The PMFs are anchored to zero at the positions ξ_o of their global minima. The vertical lines indicate the positions of the cutoff ξ_* selected to distinguish bound and free states (Main Article Tab. 2). The standard absolute binding free energies ΔG^{\oplus} calculated from these PMFs are reported in Main Article Tab. 4 and illustrated graphically in Fig. S.8. The positions ξ_o of the minima (based on TRUS-WHAM) are reported in Main Article Tab. 2.



S.3 Graphical Comparison of the Free-Energy Results

Figure S.6: Calculated and experimental standard absolute binding free energies for the 15 host-guestsolvent systems involving the host 12C4. The different systems are shown in Main Article Fig. 2. The standard absolute binding free energies ΔG° are calculated using various combinations of the sampling schemes DCNT, TRUS, REUS or CBUS along with the estimators DCAN, WHAM or MFIN (the latter discussed in Appendix B of the main article), based on the PMFs of Figs. S.3-S.5. Statistical error bars η are also provided, evaluated by bootstrapping using 100 bootstrap samples. Values obtained previously using alchemical calculations with the MS- λ -LEUS approach⁸⁴ as well as experimental data based on Refs.¹²⁶⁻¹²⁹ (EXP) are also displayed. The ions considered are Li⁺ (a), Na⁺ (b), K⁺ (c), Rb⁺ (d) and Cs⁺ (e). The solvents (three blocks of bars) are water (H₂O), dimethylsulfoxide (DMSO) and methanol (CH₃OH). Missing bars for DCNT-DCAN indicate that the PMF was insufficiently sampled to obtain a ΔG° estimate. Missing bars for EXP indicate that no experimental data is available or that complexation was too weak to be monitored. All values are assumed to pertain to a one molar reference concentration $m^{\circ} = 1 \mod dm^{-3}$. The ΔG° values and associated errors η are reported numerically in Main Article Tab. 4.



Figure S.7: Calculated and experimental standard absolute binding free energies for the 15 host-guestsolvent systems involving the host 15C5. The different systems are shown in Main Article Fig. 2. The standard absolute binding free energies ΔG° are calculated using various combinations of the sampling schemes DCNT, TRUS, REUS or CBUS along with the estimators DCAN, WHAM or MFIN (the latter discussed in Appendix B of the main article), based on the PMFs of Figs. S.3-S.5. Statistical error bars η are also provided, evaluated by bootstrapping using 100 bootstrap samples. Values obtained previously using alchemical calculations with the MS- λ -LEUS approach⁸⁴ as well as experimental data based on Refs.¹²⁶⁻¹²⁹ (EXP) are also displayed. The ions considered are Li⁺ (a), Na⁺ (b), K⁺ (c), Rb⁺ (d) and Cs⁺ (e). The solvents (three blocks of bars) are water (H₂O), dimethylsulfoxide (DMSO) and methanol (CH₃OH). Missing bars for DCNT-DCAN indicate that the PMF was insufficiently sampled to obtain a ΔG° estimate. Missing bars for EXP indicate that no experimental data is available or that complexation was too weak to be monitored. All values are assumed to pertain to a one molar reference concentration $m^{\circ} = 1 \mod \cdot dm^{-3}$. The ΔG° values and associated errors η are reported numerically in Main Article Tab. 4.



Figure S.8: Calculated and experimental standard absolute binding free energies for the 15 host-guestsolvent systems involving the host 18C6. The different systems are shown in Main Article Fig. 2. The standard absolute binding free energies ΔG° are calculated using various combinations of the sampling schemes DCNT, TRUS, REUS or CBUS along with the estimators DCAN, WHAM or MFIN (the latter discussed in Appendix B of the main article), based on the PMFs of Figs. S.3-S.5. Statistical error bars η are also provided, evaluated by bootstrapping using 100 bootstrap samples. Values obtained previously using alchemical calculations with the MS- λ -LEUS approach⁸⁴ as well as experimental data based on Refs.¹²⁶⁻¹²⁹ (EXP) are also displayed. The ions considered are Li⁺ (a), Na⁺ (b), K⁺ (c), Rb⁺ (d) and Cs⁺ (e). The solvents (three blocks of bars) are water (H₂O), dimethylsulfoxide (DMSO) and methanol (CH₃OH). Missing bars for DCNT-DCAN indicate that the PMF was insufficiently sampled to obtain a ΔG° estimate. Missing bars for EXP indicate that no experimental data is available or that complexation was too weak to be monitored. All values are assumed to pertain to a one molar reference concentration $m^{\circ} = 1 \mod \cdot dm^{-3}$. The ΔG° values and associated errors η are reported numerically in Main Article Tab. 4.



S.4 Influence of the Cutoff Distance ξ_*

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Figure S.9: Calculated PMFs (blue) and calculated ΔG^{\diamond} as a function of the cutoff distance ξ_* (orange) for the 15 host-guest-solvent systems involving the host 12C4. The different systems are shown in Main Article Fig. 2. The PMFs $G(\xi)$ are calculated using REUS (Main Article Fig. 5). All calculations involve a total single-system sampling time of 42 ns. The rows correspond to the different alkali cations Li⁺ (a-c), Na⁺ (d-f), K⁺ (g-i), Rb⁺ (j-l) and Cs⁺ (m-o). The columns correspond to the different solvents H₂O (a,d,g,j,m), DMSO (b,e,h,k,n) and CH₃OH (c,f,i,l,o). The PMFs are anchored to zero at the positions ξ_o of their global minima. The vertical lines indicate the cutoff ξ_* selected to distinguish bound and unbound states (Main Article Tab. 2). The standard absolute binding free energies ΔG^{\diamond} for different values of the cutoff ξ_* are shown as an orange line (left scale).



Figure S.10: Calculated PMFs (blue) and calculated ΔG^{\diamond} as a function of the cutoff distance ξ_* (orange) for the 15 host-guest-solvent systems involving the host 15C5. The different systems are shown in Main Article Fig. 2. The PMFs $G(\xi)$ are calculated using REUS (Main Article Fig. 5). All calculations involve a total single-system sampling time of 42 ns. The rows correspond to the different alkali cations Li⁺ (a-c), Na⁺ (d-f), K⁺ (g-i), Rb⁺ (j-l) and Cs⁺ (m-o). The columns correspond to the different solvents H₂O (a,d,g,j,m), DMSO (b,e,h,k,n) and CH₃OH (c,f,i,l,o). The PMFs are anchored to zero at the positions ξ_o of their global minima. The vertical lines indicate the cutoff ξ_* selected to distinguish bound and unbound states (Main Article Tab. 2). The standard absolute binding free energies ΔG^{\diamond} for different values of the cutoff ξ_* are shown as an orange line (left scale).



Figure S.11: Calculated PMFs (blue) and calculated ΔG^{\diamond} as a function of the cutoff distance ξ_* (orange) for the 15 host-guest-solvent systems involving the host 18C6. The different systems are shown in Main Article Fig. 2. The PMFs $G(\xi)$ are calculated using REUS (Main Article Fig. 5). All calculations involve a total single-system sampling time of 42 ns. The rows correspond to the different alkali cations Li⁺ (a-c), Na⁺ (d-f), K⁺ (g-i), Rb⁺ (j-l) and Cs⁺ (m-o). The columns correspond to the different solvents H₂O (a,d,g,j,m), DMSO (b,e,h,k,n) and CH₃OH (c,f,i,l,o). The PMFs are anchored to zero at the positions ξ_o of their global minima. The vertical lines indicate the cutoff ξ_* selected to distinguish bound and unbound states (Main Article Tab. 2). The standard absolute binding free energies ΔG^{\diamond} for different values of the cutoff ξ_* are shown as an orange line (left scale).

Table S.2: Influence of the cutoff distance ξ_* on the calculated binding free energy ΔG^{\diamond} . The estimates are calculated from the PMFs obtained by REUS (Main Article Fig. 5) for the cutoff distance ξ_* decreased by 5%, the cutoff distance as given in Main Article Tab. 2, and the cutoff distance increased by 5%.

Host	Guest	$\Delta G^{\circ}(0.95\xi_*)$	$\Delta G^{\bullet}(\xi_*)$	$\Delta G^{\diamond}(1.05\xi_*)$	
		[kJ·mol ⁻¹]	[kJ · mol ⁻¹]	[kJ·mol ⁻¹]	
			Li ⁺		
12C4	H_2O	3.6	3.4	3.3	
12C4	DMSO	-0.7	-0.7	-0.7	
12C4	CH_3OH	-9.3	-9.5	-9.8	
15C5	H_2O	2.1	1.8	1.4	
15C5	DMSO	3.7	3.7	3.7	
15C5	CH₃OH	-9.2	-9.5	-9.9	
18C6	H _a O	-2.4	-2.4	-2.4	
18C6	DMSO	-11.5	-11.5	-11.5	
18C6	CH ₃ OH	-19.9	-20.2	-20.8	
	- 0 -	<u>ן</u> ז	Va ⁺		
1004	цо	1.1	1.5	1.0	
12C4	H_2O	-1.4	-1.5	-1.0	
12C4	DMSO	-19.7	-19.7	-19.7	
12C4	CH ₃ OH	-12.2	-12.5	-12.7	
15C5	H_2O	-3.8	-3.8	-3.9	
15C5	DMSO	-16.1	-16.1	-16.1	
15C5	CH_3OH	-15.6	-15.9	-16.1	
18C6	H_2O	-10.8	-10.9	-10.9	
18C6	DMSO	-24.2	-24.6	-24.6	
18C6	CH_3OH	-30.2	-31.1	-31.6	
		-	K ⁺		
12C4	H ₂ O	-3.2	-3.3	-3.3	
12C4	DMSO	-8.9	-8.9	-8.9	
12C4	CH ₂ OH	-11.8	-12.0	-12.2	
15C5	H ₂ O	-6.7	-6.7	-6.8	
15C5	DMSO	-13.2	-13.2	-13.1	
15C5	CH ₂ OH	-19.1	-19.3	-19.5	
18C6	H ₂ O	-13.8	-13.9	-13.9	
18C6	DMSO	-17.6	-17.6	-17.5	
18C6	CH ₂ OH	-34.2	-34.5	-34 7	
	0113011		2h+		
1904	ПО		25	2.6	
1204 12C4	$\Pi_2 \cup$	-0.4	-0.0	-0.0	
1204 1904	CIL OIL	-11.0	-11.0	-10.9	
1204 1505		-14.5	-14.0	-10.1	
1505	$\Pi_2 O$	-0.5	-0.0	-0.0	
15C5	DM50	-10.7	-10.0	-10.0	
1900	И ОП	-20.7	-21.1	-21.0	
1800	H_2O	-13.1	-13.2	-13.2	
18C6	DMSO	-18.9	-18.9	-18.9	
1806	CH ₃ OH	-30.8	-31.1	-31.4	
		(Cs ⁺		
12C4	H_2O	-2.9	-3.0	-3.1	
12C4	DMSO	-12.6	-12.6	-12.6	
12C4	CH ₃ OH	-10.6	-10.7	-10.8	
15C5	H_2O	-6.9	-7.0	-7.0	
15C5	DMSO	-12.2	-12.1	-12.1	
15C5	CH ₂ OH	-18.3	-18.6	-18.7	
18C6	H ₂ O	-10.7	-10.7	-10.8	
18C6	DMSO	-21.2	-21.2	-21.2	
18C6	CH ₃ OH	-27.7	-28.1	-28.3	
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