## 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. 

 Document date: 27/01/20David F. Hahn, Rhiannon A. Zarotiadis, and Philippe H. Hünenberger*

Laboratory of Physical Chemistry, Department of Chemistry and Applied Biosciences, ETH
Zürich, Vladimir-Prelog-Weg 2, 8093 Zürich, Switzerland

E-mail: phil@igc.phys.chem.ethz.ch

## 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 $\mathrm{K}^{+}$to 15 C 5 in $\mathrm{CH}_{3} \mathrm{OH}$. The parameter sensitivity of CBUS is tested by investigating the effect of changing the number of $K$ replicas, the mass-parameter $m_{\Lambda}$, the thermostat coupling time $\tau_{\Lambda}$, 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 $\mathrm{K}^{+}$to 15 C 5 in $\mathrm{CH}_{3} \mathrm{OH}$. The successive entries are: the number $K$ of replicas, the simulation time $t_{\text {sim }}$ for the replica system, the mass-parameter $m_{\Lambda}$ of the CB advance variable $\Lambda$, the thermostat coupling time $\tau_{\Lambda}$ of the CB , the harmonic biasing force constant $c$, the average temperature $T_{\Lambda}$ of $\Lambda$, the standard deviation $\sigma_{\dot{\Lambda}}$ of the CB velocity $\dot{\Lambda}$, the autocorrelation time $\tau_{\dot{\Lambda}}$ of $\dot{\Lambda}$, the diffusion constant $D_{\Lambda}$ along $\Lambda$ and the highest free-energy barrier $G_{\Lambda}^{\star}$ in the PMF along $\Lambda$. The value of $D_{\Lambda}$ is half the slope of the mean-square displacement $d_{\Lambda}$ as a function of time, based on the Einstein equation. ${ }^{165}$ It was evaluated using a linear least-squares fit over the interval $0-0.25 \mathrm{ps}$. A dash ("-") for $G_{\Lambda}^{\star}$ 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.

| $K$ | $t_{\text {sim }}$ <br> $[\mathrm{ns}]$ | $m_{\Lambda}$ <br> $\left[\mathrm{g} \cdot \mathrm{mol}^{-1} \cdot \mathrm{~nm}^{2}\right]$ | $\tau_{\Lambda}$ <br> $[\mathrm{ps}]$ | $c$ <br> $\left[\mathrm{~kJ} \cdot \mathrm{~mol}^{-1}\right]$ | $T_{\Lambda}$ <br> $[\mathrm{K}]$ | $\sigma_{\dot{\dot{L}}}$ <br> $\left[\mathrm{ps}^{-1}\right]$ | $\tau_{\dot{\dot{L}}}$ <br> $\left[\mathrm{ps}^{-1}\right]$ | $D_{\Lambda}$ <br> $\left[\mathrm{ns}^{-1}\right]$ | $G_{\Lambda}^{\star}$ <br> $\left[\mathrm{kJ} \cdot \mathrm{mol}^{-1}\right]$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 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 | -10.13 |
| 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 | $\begin{gathered} t_{\mathrm{sim}} \\ {[\mathrm{~ns}]} \end{gathered}$ | $\begin{gathered} m_{\Lambda} \\ {\left[\mathrm{g} \cdot \mathrm{~mol}^{-1} \cdot \mathrm{~nm}^{2}\right]} \end{gathered}$ | $\begin{gathered} \tau_{\Lambda} \\ {[\mathrm{ps}]} \end{gathered}$ | $\left[\mathrm{kJ} \cdot \mathrm{~mol}^{-1}\right]$ | $\begin{gathered} T_{\Lambda} \\ {[\mathrm{K}]} \end{gathered}$ | $\begin{gathered} \sigma_{\dot{\Lambda}_{1}} \\ {\left[\mathrm{ps}^{-1}\right]} \end{gathered}$ | $\begin{gathered} \tau_{\dot{\Lambda}_{1}} \\ {\left[\mathrm{ps}^{-1}\right]} \end{gathered}$ | $\begin{gathered} D_{\Lambda} \\ {\left[\mathrm{ns}^{-1}\right]} \end{gathered}$ | $\begin{gathered} G_{\Lambda}^{\star} \\ {\left[\mathrm{kJ} \cdot \mathrm{~mol}^{-1}\right]} \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 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 | 15.11 |
| 10 | 8 | 1000 | 0.05 | 1000 | 291.3 | 0.05 | 0.272 | 0.149 | 5.94 |
| 10 | 8 | 1000 | 0.05 | 4000 | 287.7 | 0.05 | 0.017 | 0.025 | - |
| 10 | 8 | 1000 | 5.00 | 2000 | 311.9 | 0.05 | 0.253 | 0.084 | 11.62 |
| 10 | 8 | 1000 | 5.00 | 1000 | 322.3 | 0.05 | 0.349 | 0.219 | 4.09 |
| 10 | 8 | 1000 | 5.00 | 4000 | 299.2 | 0.05 | 0.173 | 0.043 | - |
| 20 | 4 | 100 | 0.50 | 2000 | 291.4 | 0.16 | 0.014 | 0.089 | 4.37 |
| 20 | 4 | 100 | 0.50 | 1000 | 294.5 | 0.16 | 0.245 | 0.092 | 2.26 |
| 20 | 4 | 100 | 0.50 | 4000 | 300.6 | 0.16 | 0.141 | 0.064 | 5.25 |
| 20 | 4 | 100 | 0.05 | 2000 | 296.6 | 0.16 | 0.002 | 0.084 | 4.24 |
| 20 | 4 | 100 | 0.05 | 1000 | 281.5 | 0.15 | 0.007 | 0.152 | 2.11 |
| 20 | 4 | 100 | 0.05 | 4000 | 287.7 | 0.16 | 0.001 | 0.117 | 5.67 |
| 20 | 4 | 100 | 5.00 | 2000 | 292.9 | 0.16 | 0.184 | 0.066 | 5.16 |
| 20 | 4 | 100 | 5.00 | 1000 | 298.0 | 0.16 | 0.223 | 0.108 | 2.08 |
| 20 | 4 | 100 | 5.00 | 4000 | 290.1 | 0.16 | 0.144 | 0.056 | 5.31 |
| 20 | 4 | 10 | 0.50 | 2000 | 292.2 | 0.49 | 0.205 | 0.112 | 4.53 |
| 20 | 4 | 10 | 0.50 | 1000 | 306.4 | 0.50 | 0.019 | 0.083 | 1.92 |
| 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 $m_{\Lambda}=100 \mathrm{~g} \cdot \mathrm{~mol}^{-1} \cdot \mathrm{~nm}^{2}$ and $\tau_{\Lambda}=0.5$ $\mathrm{ps})$. 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 $\Lambda$ and the associated probability distribution $P(\Lambda)$ (Figs. S.1a-S.1d) shows that the CB rotates only a fraction of a full rotation $(2 \pi)$. However, since a shift of $\Lambda$ by $\Delta \Lambda\left(2 \pi K^{-1}\right)$ corresponds to an identical state of the CB up to a shift of all replicas by one position, the relevant variable to assess convergence ${ }^{106}$ is actually $\tilde{\Lambda}$, which corresponds to $\Lambda$ 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 $2 \mathrm{~kJ} \cdot \mathrm{~mol}^{-1}$, 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 sufficently low barriers $\left(3-4 \mathrm{~kJ} \cdot \mathrm{~mol}^{-1}\right)$ 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 $m_{\Lambda}$ of the CB is illustrated in Fig. S.2, where this parameter is changed from 10 to 100 and to $1000 \mathrm{~g} \cdot \mathrm{~mol}^{-1} \cdot \mathrm{~nm}^{2}$ (together with $K=20$ and $\tau_{\Lambda}=0.5 \mathrm{ps}$ ). 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 $\Lambda$ 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 $\dot{\Lambda}$ 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 $d_{\Lambda}$ of $\dot{\Lambda}$ (Figs. S.2g-S.2i) shows that the diffusion along $\Lambda$ is essentially independent of the mass. This is qualitatively in line with the $\Lambda$-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 $m_{\Lambda}=1000 \mathrm{~g} \cdot \mathrm{~mol}^{-1} \cdot \mathrm{~nm}^{2}$ 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 $\mathrm{K}^{+}$to 15 C 5 in $\mathrm{CH}_{3} \mathrm{OH}$, 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 $m_{\Lambda}=100 \mathrm{~g} \cdot \mathrm{~mol}^{-1} \cdot \mathrm{~nm}^{2}$ and $\tau_{\Lambda}=0.5 \mathrm{ps}$. The time evolutions of the CB advance variable $\Lambda$ 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 $\Lambda$ refolded into the interval $\left[0, \Delta \Lambda\right.$ ) where $\Delta \Lambda=2 \pi K^{-1}$. The free-energy profiles $G_{\tilde{\Lambda}}(\tilde{\Lambda})$ calculated from the simulations are also shown (i-l). Finally, the time evolutions of the mean-square displacement $d_{\Lambda}$ of $\Lambda$ are also displayed (m-p), along with along with a linear least-squares fit over the interval $0-0.25 \mathrm{ps}$ (brown dashed line). The slope of this line is equal to twice the diffusion constants $D_{\Lambda}$ along $\Lambda$. 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 $\mathrm{K}^{+}$to 15 C 5 in $\mathrm{CH}_{3} \mathrm{OH}$, calculated using CBUS simulations with $K=20$ replicas and a mass-parameter $m_{\Lambda}$ of $10(\mathrm{a}, \mathrm{d}, \mathrm{g}), 100(\mathrm{~b}, \mathrm{e}, \mathrm{h})$, or $1000 \mathrm{~g} \cdot \mathrm{~mol}^{-1} \cdot \mathrm{~nm}^{2}(\mathrm{c}, \mathrm{f}, \mathrm{i})$ along with $\tau_{\Lambda}=0.5 \mathrm{ps}$. The time evolutions of the CB advance variable $\Lambda$ 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 MaxwellBoltzmann velocity distribution (red line). Finally, the time evolutions of the mean-square displacement $d_{\Lambda}$ of $\Lambda$ 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 $D_{\Lambda}$ along $\Lambda$.

## 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 12 C 4 . 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 $\mathrm{Li}^{+}(\mathrm{a}-\mathrm{c}), \mathrm{Na}^{+}(\mathrm{d}-\mathrm{f}), \mathrm{K}^{+}(\mathrm{g}-\mathrm{i}), \mathrm{Rb}^{+}(\mathrm{j}-\mathrm{l})$ and $\mathrm{Cs}^{+}(\mathrm{m}-\mathrm{o})$. The columns correspond to the different solvents $\mathrm{H}_{2} \mathrm{O}(\mathrm{a}, \mathrm{d}, \mathrm{g}, \mathrm{j}, \mathrm{m})$, DMSO (b,e,h,k,n) and $\mathrm{CH}_{3} \mathrm{OH}(\mathrm{c}, \mathrm{f}, \mathrm{i}, \mathrm{l}, \mathrm{o})$. The PMFs are anchored to zero at the positions $\xi_{o}$ of their global minima. The vertical lines indicate the positions of the cutoff $\xi_{*}$ selected to distinguish bound and free states (Main Article Tab. 2). The standard absolute binding free energies $\Delta G^{\ominus}$ calculated from these PMFs are reported in Main Article Tab. 4 and illustrated graphically in Fig. S.6. The positions $\xi_{o}$ 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 $\mathrm{Li}^{+}(\mathrm{a}-\mathrm{c}), \mathrm{Na}^{+}(\mathrm{d}-\mathrm{f}), \mathrm{K}^{+}(\mathrm{g}-\mathrm{i}), \mathrm{Rb}^{+}(\mathrm{j}-\mathrm{l})$ and $\mathrm{Cs}^{+}(\mathrm{m}-\mathrm{o})$. The columns correspond to the different solvents $\mathrm{H}_{2} \mathrm{O}(\mathrm{a}, \mathrm{d}, \mathrm{g}, \mathrm{j}, \mathrm{m})$, DMSO (b,e,h,k,n) and $\mathrm{CH}_{3} \mathrm{OH}(\mathrm{c}, \mathrm{f}, \mathrm{i}, \mathrm{l}, \mathrm{o})$. The PMFs are anchored to zero at the positions $\xi_{o}$ of their global minima. The vertical lines indicate the positions of the cutoff $\xi_{*}$ selected to distinguish bound and free states (Main Article Tab. 2). The standard absolute binding free energies $\Delta G^{\ominus}$ calculated from these PMFs are reported in Main Article Tab. 4 and illustrated graphically in Fig. S.7. The positions $\xi_{o}$ 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 $\mathrm{Li}^{+}(\mathrm{a}-\mathrm{c}), \mathrm{Na}^{+}(\mathrm{d}-\mathrm{f}), \mathrm{K}^{+}(\mathrm{g}-\mathrm{i}), \mathrm{Rb}^{+}(\mathrm{j}-\mathrm{l})$ and $\mathrm{Cs}^{+}(\mathrm{m}-\mathrm{o})$. The columns correspond to the different solvents $\mathrm{H}_{2} \mathrm{O}(\mathrm{a}, \mathrm{d}, \mathrm{g}, \mathrm{j}, \mathrm{m})$, DMSO (b,e,h,k,n) and $\mathrm{CH}_{3} \mathrm{OH}(\mathrm{c}, \mathrm{f}, \mathrm{i}, \mathrm{l}, \mathrm{o})$. The PMFs are anchored to zero at the positions $\xi_{o}$ of their global minima. The vertical lines indicate the positions of the cutoff $\xi_{*}$ selected to distinguish bound and free states (Main Article Tab. 2). The standard absolute binding free energies $\Delta G^{\ominus}$ calculated from these PMFs are reported in Main Article Tab. 4 and illustrated graphically in Fig. S.8. The positions $\xi_{o}$ 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 $\Delta G^{\ominus}$ 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 $\eta$ are also provided, evaluated by bootstrapping using 100 bootstrap samples. Values obtained previously using alchemical calculations with the MS- $\lambda$-LEUS approach ${ }^{84}$ as well as experimental data based on Refs. ${ }^{126-129}$ (EXP) are also displayed. The ions considered are $\mathrm{Li}^{+}$(a), $\mathrm{Na}^{+}(\mathrm{b}), \mathrm{K}^{+}$(c), $\mathrm{Rb}^{+}$(d) and $\mathrm{Cs}^{+}$(e). The solvents (three blocks of bars) are water $\left(\mathrm{H}_{2} \mathrm{O}\right)$, dimethylsulfoxide (DMSO) and methanol $\left(\mathrm{CH}_{3} \mathrm{OH}\right)$. Missing bars for DCNT-DCAN indicate that the PMF was insufficiently sampled to obtain a $\Delta G^{\ominus}$ 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 $m^{\circ}=1 \mathrm{~mol} \cdot \mathrm{dm}^{-3}$. The $\Delta G^{\ominus}$ values and associated errors $\eta$ 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 $\Delta G^{\ominus}$ 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 $\eta$ are also provided, evaluated by bootstrapping using 100 bootstrap samples. Values obtained previously using alchemical calculations with the MS- $\lambda$-LEUS approach ${ }^{84}$ as well as experimental data based on Refs. ${ }^{126-129}$ (EXP) are also displayed. The ions considered are $\mathrm{Li}^{+}$(a), $\mathrm{Na}^{+}(\mathrm{b}), \mathrm{K}^{+}(\mathrm{c}), \mathrm{Rb}^{+}$(d) and $\mathrm{Cs}^{+}$(e). The solvents (three blocks of bars) are water $\left(\mathrm{H}_{2} \mathrm{O}\right)$, dimethylsulfoxide (DMSO) and methanol $\left(\mathrm{CH}_{3} \mathrm{OH}\right)$. Missing bars for DCNT-DCAN indicate that the PMF was insufficiently sampled to obtain a $\Delta G^{\ominus}$ 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 $m^{\circ}=1 \mathrm{~mol} \cdot \mathrm{dm}^{-3}$. The $\Delta G^{\ominus}$ values and associated errors $\eta$ 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 $\Delta G^{\ominus}$ 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 $\eta$ are also provided, evaluated by bootstrapping using 100 bootstrap samples. Values obtained previously using alchemical calculations with the MS- $\lambda$-LEUS approach ${ }^{84}$ as well as experimental data based on Refs. ${ }^{126-129}$ (EXP) are also displayed. The ions considered are $\mathrm{Li}^{+}$(a), $\mathrm{Na}^{+}(\mathrm{b}), \mathrm{K}^{+}(\mathrm{c}), \mathrm{Rb}^{+}$(d) and $\mathrm{Cs}^{+}$(e). The solvents (three blocks of bars) are water $\left(\mathrm{H}_{2} \mathrm{O}\right)$, dimethylsulfoxide (DMSO) and methanol $\left(\mathrm{CH}_{3} \mathrm{OH}\right)$. Missing bars for DCNT-DCAN indicate that the PMF was insufficiently sampled to obtain a $\Delta G^{\ominus}$ 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 $m^{\circ}=1 \mathrm{~mol} \cdot \mathrm{dm}^{-3}$. The $\Delta G^{\ominus}$ values and associated errors $\eta$ are reported numerically in Main Article Tab. 4.

## S. 4 Influence of the Cutoff Distance $\xi_{*}$



Figure S.9: Calculated PMFs (blue) and calculated $\Delta G^{\ominus}$ as a function of the cutoff distance $\xi_{*}$ (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 $\mathrm{Li}^{+}(\mathrm{a}-\mathrm{c}), \mathrm{Na}^{+}$ (d-f), $\mathrm{K}^{+}(\mathrm{g}-\mathrm{i}), \mathrm{Rb}^{+}(\mathrm{j}-\mathrm{l})$ and $\mathrm{Cs}^{+}(\mathrm{m}-\mathrm{o})$. The columns correspond to the different solvents $\mathrm{H}_{2} \mathrm{O}(\mathrm{a}, \mathrm{d}, \mathrm{g}, \mathrm{j}, \mathrm{m})$, DMSO (b,e,h,k,n) and $\mathrm{CH}_{3} \mathrm{OH}\left(\mathrm{c}, \mathrm{f}, \mathrm{i}, \mathrm{l}, \mathrm{o}\right.$ ). The PMFs are anchored to zero at the positions $\xi_{o}$ of their global minima. The vertical lines indicate the cutoff $\xi_{*}$ selected to distinguish bound and unbound states (Main Article Tab. 2). The standard absolute binding free energies $\Delta G^{\ominus}$ for different values of the cutoff $\xi_{*}$ are shown as an orange line (left scale).


Figure S.10: Calculated PMFs (blue) and calculated $\Delta G^{\ominus}$ as a function of the cutoff distance $\xi_{*}$ (orange) for the 15 host-guest-solvent systems involving the host 15 C 5 . 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 $\mathrm{Li}^{+}(\mathrm{a}-\mathrm{c}), \mathrm{Na}^{+}$ (d-f), $\mathrm{K}^{+}(\mathrm{g}-\mathrm{i}), \mathrm{Rb}^{+}(\mathrm{j}-\mathrm{l})$ and $\mathrm{Cs}^{+}(\mathrm{m}-\mathrm{o})$. The columns correspond to the different solvents $\mathrm{H}_{2} \mathrm{O}(\mathrm{a}, \mathrm{d}, \mathrm{g}, \mathrm{j}, \mathrm{m})$, DMSO ( $\mathrm{b}, \mathrm{e}, \mathrm{h}, \mathrm{k}, \mathrm{n}$ ) and $\mathrm{CH}_{3} \mathrm{OH}(\mathrm{c}, \mathrm{f}, \mathrm{i}, \mathrm{l}, \mathrm{o})$. The PMFs are anchored to zero at the positions $\xi_{o}$ of their global minima. The vertical lines indicate the cutoff $\xi_{*}$ selected to distinguish bound and unbound states (Main Article Tab. 2). The standard absolute binding free energies $\Delta G^{\ominus}$ for different values of the cutoff $\xi_{*}$ are shown as an orange line (left scale).


Figure S.11: Calculated PMFs (blue) and calculated $\Delta G^{\ominus}$ as a function of the cutoff distance $\xi_{*}$ (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 $\mathrm{Li}^{+}(\mathrm{a}-\mathrm{c}), \mathrm{Na}^{+}$ (d-f), $\mathrm{K}^{+}(\mathrm{g}-\mathrm{i}), \mathrm{Rb}^{+}(\mathrm{j}-\mathrm{l})$ and $\mathrm{Cs}^{+}(\mathrm{m}-\mathrm{o})$. The columns correspond to the different solvents $\mathrm{H}_{2} \mathrm{O}(\mathrm{a}, \mathrm{d}, \mathrm{g}, \mathrm{j}, \mathrm{m})$, DMSO (b,e,h,k,n) and $\mathrm{CH}_{3} \mathrm{OH}$ (c,f,f,i,o). The PMFs are anchored to zero at the positions $\xi_{o}$ of their global minima. The vertical lines indicate the cutoff $\xi_{*}$ selected to distinguish bound and unbound states (Main Article Tab. 2). The standard absolute binding free energies $\Delta G^{\ominus}$ for different values of the cutoff $\xi_{*}$ are shown as an orange line (left scale).

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

| Host | Guest | $\begin{gathered} \Delta G^{\ominus}\left(0.95 \xi_{*}\right) \\ {\left[\mathrm{kJ} \cdot \mathrm{~mol}^{-1}\right]} \end{gathered}$ | $\begin{array}{r} \Delta G^{\ominus}\left(\xi_{*}\right) \\ {\left[\mathrm{kJ} \cdot \mathrm{~mol}^{-1}\right]} \end{array}$ | $\begin{gathered} \Delta G^{\ominus}\left(1.05 \xi_{*}\right) \\ {\left[\mathrm{kJ} \cdot \mathrm{~mol}^{-1}\right]} \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: |
| $\mathrm{Li}^{+}$ |  |  |  |  |
| 12 C 4 | $\mathrm{H}_{2} \mathrm{O}$ | 3.6 | 3.4 | 3.3 |
| 12 C 4 | DMSO | -0.7 | -0.7 | -0.7 |
| 12 C 4 | $\mathrm{CH}_{3} \mathrm{OH}$ | -9.3 | -9.5 | -9.8 |
| 15C5 | $\mathrm{H}_{2} \mathrm{O}$ | 2.1 | 1.8 | 1.4 |
| 15C5 | DMSO | 3.7 | 3.7 | 3.7 |
| 15 C 5 | $\mathrm{CH}_{3} \mathrm{OH}$ | -9.2 | -9.5 | -9.9 |
| 18C6 | $\mathrm{H}_{2} \mathrm{O}$ | -2.4 | -2.4 | -2.4 |
| 18C6 | DMSO | -11.5 | -11.5 | -11.5 |
| 18C6 | $\mathrm{CH}_{3} \mathrm{OH}$ | -19.9 | -20.2 | -20.8 |
| $\mathrm{Na}^{+}$ |  |  |  |  |
| 12C4 | $\mathrm{H}_{2} \mathrm{O}$ | -1.4 | -1.5 | -1.6 |
| 12 C 4 | DMSO | -19.7 | -19.7 | -19.7 |
| 12 C 4 | $\mathrm{CH}_{3} \mathrm{OH}$ | -12.2 | -12.5 | -12.7 |
| 15C5 | $\mathrm{H}_{2} \mathrm{O}$ | -3.8 | -3.8 | -3.9 |
| 15C5 | DMSO | -16.1 | -16.1 | -16.1 |
| 15C5 | $\mathrm{CH}_{3} \mathrm{OH}$ | -15.6 | -15.9 | -16.1 |
| 18C6 | $\mathrm{H}_{2} \mathrm{O}$ | -10.8 | -10.9 | -10.9 |
| 18C6 | DMSO | -24.2 | -24.6 | -24.6 |
| 18C6 | $\mathrm{CH}_{3} \mathrm{OH}$ | -30.2 | -31.1 | -31.6 |
| $\mathrm{K}^{+}$ |  |  |  |  |
| 12C4 | $\mathrm{H}_{2} \mathrm{O}$ | -3.2 | -3.3 | -3.3 |
| 12 C 4 | DMSO | -8.9 | -8.9 | -8.9 |
| 12 C 4 | $\mathrm{CH}_{3} \mathrm{OH}$ | -11.8 | -12.0 | -12.2 |
| 15C5 | $\mathrm{H}_{2} \mathrm{O}$ | -6.7 | -6.7 | -6.8 |
| 15C5 | DMSO | -13.2 | -13.2 | -13.1 |
| 15 C 5 | $\mathrm{CH}_{3} \mathrm{OH}$ | -19.1 | -19.3 | -19.5 |
| 18C6 | $\mathrm{H}_{2} \mathrm{O}$ | -13.8 | -13.9 | -13.9 |
| 18C6 | DMSO | -17.6 | -17.6 | -17.5 |
| 18C6 | $\mathrm{CH}_{3} \mathrm{OH}$ | -34.2 | -34.5 | -34.7 |
| $\mathrm{Rb}^{+}$ |  |  |  |  |
| 12C4 | $\mathrm{H}_{2} \mathrm{O}$ | -3.4 | -3.5 | -3.6 |
| 12 C 4 | DMSO | -11.0 | -11.0 | -10.9 |
| 12 C 4 | $\mathrm{CH}_{3} \mathrm{OH}$ | -14.3 | -14.8 | -15.1 |
| 15C5 | $\mathrm{H}_{2} \mathrm{O}$ | -6.5 | -6.6 | -6.6 |
| 15C5 | DMSO | -10.7 | -10.6 | -10.6 |
| 15C5 | $\mathrm{CH}_{3} \mathrm{OH}$ | -20.7 | -21.1 | -21.3 |
| 18C6 | $\mathrm{H}_{2} \mathrm{O}$ | -13.1 | -13.2 | -13.2 |
| 18C6 | DMSO | -18.9 | -18.9 | -18.9 |
| 18C6 | $\mathrm{CH}_{3} \mathrm{OH}$ | -30.8 | -31.1 | -31.4 |
| $\mathrm{Cs}^{+}$ |  |  |  |  |
| 12C4 | $\mathrm{H}_{2} \mathrm{O}$ | -2.9 | -3.0 | -3.1 |
| 12 C 4 | DMSO | -12.6 | -12.6 | -12.6 |
| 12 C 4 | $\mathrm{CH}_{3} \mathrm{OH}$ | -10.6 | -10.7 | -10.8 |
| 15C5 | $\mathrm{H}_{2} \mathrm{O}$ | -6.9 | -7.0 | -7.0 |
| 15C5 | DMSO | -12.2 | -12.1 | -12.1 |
| 15C5 | $\mathrm{CH}_{3} \mathrm{OH}$ | -18.3 | -18.6 | -18.7 |
| 18C6 | $\mathrm{H}_{2} \mathrm{O}$ | -10.7 | -10.7 | -10.8 |
| 18C6 | DMSO | -21.2 | -21.2 | -21.2 |
| 18C6 | $\mathrm{CH}_{3} \mathrm{OH}$ | -27.7 | -28.1 | -28.3 |

