Supplementary Information

Energy-Entropy Method Using Multiscale Cell Correlation to Calculate Binding Free Energies in the SAMPL8 Host-Guest Challenge

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Figure S1. Potential energy versus time for the host-guest systems G1 to G7.
**Figure S2.** Numbering of the flexible dihedrals in guests: G1, G2, G5, G6 and G7.

**Figure S3.** Dihedral distributions for all flexible dihedrals in guest G1 in the three unbound simulations (blue) and three bound simulations (red).
Figure S4. Dihedral distributions for all flexible dihedrals in G2 as in Figure S3.

Figure S5. Dihedral distributions for all flexible dihedrals in G5 as in Figure S3.

Figure S6. Dihedral distributions for all flexible dihedrals in G6 as in Figure S3.
Figure S7. Dihedral distributions for all flexible dihedrals in G7 as in Figure S3.

Table S1. Slopes of the Lines of Best Fit (kJ mol\(^{-1}\) ns\(^{-1}\)) for the Potential Energy versus Simulation Time in Figure S1

| Set of Calculations | G1   | G2     | G3    | G4    | G5    | G6    | G7    |
|---------------------|------|--------|-------|-------|-------|-------|-------|
| 1\(^{st}\)          | 0.003| 0.139  | -0.398| 0.389 | -0.138| 0.111 | 0.142 |
| 2\(^{nd}\)          | 0.026| -0.019 | -0.025| 0.019 | -0.013| 0.182 | -0.243|
| 3\(^{rd}\)          | 0.501| -0.165 | -0.408| 0.328 | 0.014 | -0.308| 0.328 |

Table S2. Standard Error of the Mean (SEM) for the Components of the Entropy Differences (J K\(^{-1}\) mol\(^{-1}\)) in Figures 4 and 5

| System      | G1  | G2  | G3  | G4  | G5  | G6  | G7  |
|-------------|-----|-----|-----|-----|-----|-----|-----|
| \(\Delta S_{\text{H,UA}}\) | 1.8 | 0.4 | 3.4 | 1.0 | 1.0 | 1.2 | 1.7 |
| \(\Delta S_{\text{H,M}}\)    | 0.5 | 0.6 | 0.4 | 0.8 | 0.2 | 0.6 | 0.7 |
| \(\Delta S_{\text{G,UA}}\)   | 0.6 | 0.9 | 1.6 | 0.8 | 0.8 | 5.2 | 0.7 |
| \(\Delta S_{\text{G,M}}\)    | 0.2 | 0.9 | 0.8 | 0.5 | 0.5 | 0.5 | 0.5 |
| \(\Delta S_{\text{H,WS}}\)   | 15.0| 4.3 | 12.2| 7.2 | 7.8 | 10.3| 6.4 |
| \(\Delta S_{\text{H,WB}}\)   | 5.5 | 2.0 | 0.9 | 0.4 | 1.0 | 0.6 | 1.4 |
| \(\Delta S_{\text{G,WS}}\)   | 3.1 | 4.5 | 1.0 | 4.2 | 2.2 | 3.3 | 1.0 |
| \(\Delta S_{\text{G,WB}}\)   | 1.1 | 7.7 | 6.4 | 5.6 | 2.9 | 5.0 | 2.4 |