# Supporting Information

# Effect of Electrostatic Polarization and Bridging Water on CDK2-ligand Binding Affinities Calculated with the Highly Efficient Interaction Entropy Method

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Four simulations: 1) simulation without the bridging Wat145 using AMBER force field ($MD_A$), 2) simulation with the bridging Wat145 using AMBER force field ($MD_{WA}$), 3) simulation without the bridging Wat145 using PPC force field ($MD_P$), 4) simulation with the bridging Wat145 using PPC force field ($MD_{WP}$).

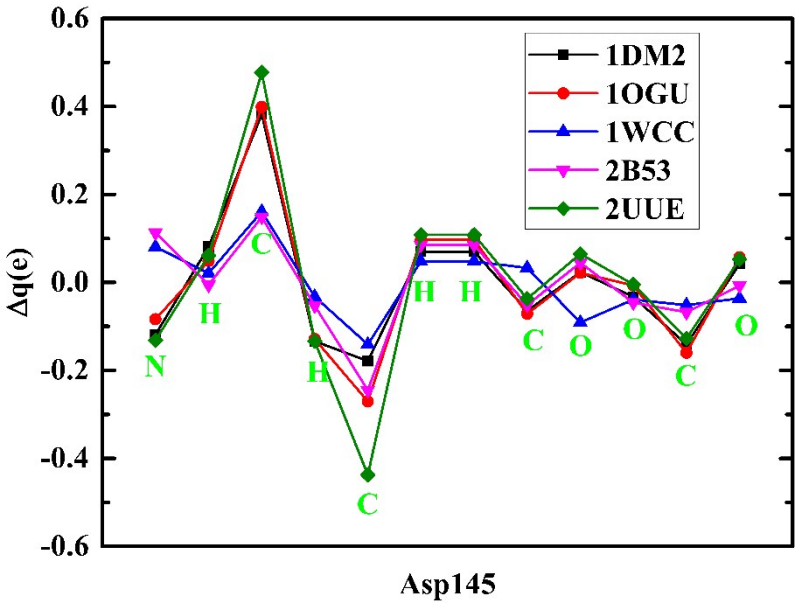


**Figure S1.** The difference in the partial charges of Asp145 residue in all systems calculated using the PPC scheme and Amber force field, respectively ($\Delta q$ is the deviation between PPC scheme and Amber force field).

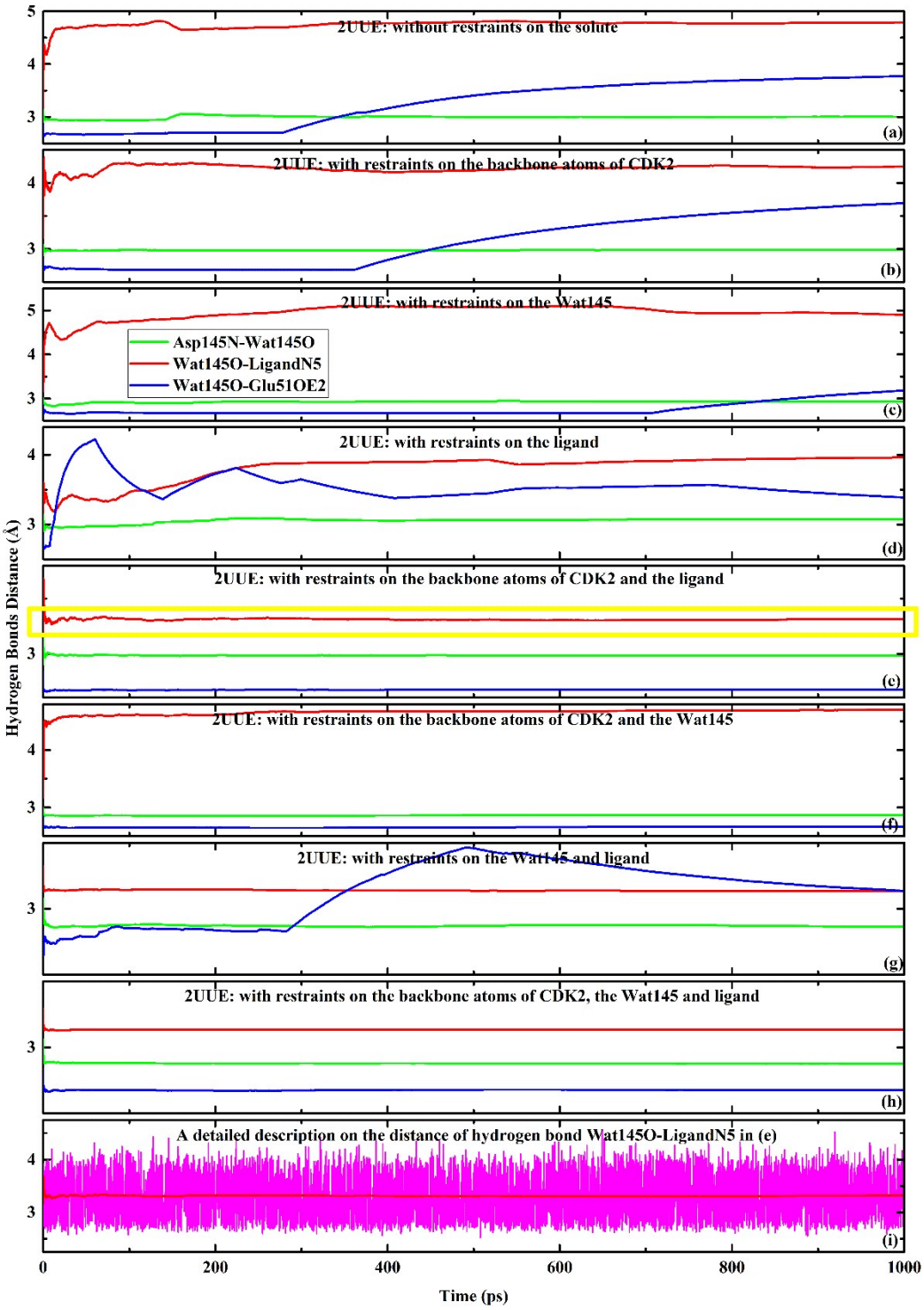


**Figure S2.** The effect of constraining partial solute on hydrogen bonds distance of Wat145-CDK2, Wat145-ligand in a series of 1ns $MD_{WA}$ simulations with a 10kcal/(mol·Å²) harmonic constraint. (a) without any constrain on the solute, (b) constrain on the backbone atoms of CDK2, (c) constrain on the Wat145, (d) constrain on the ligand, (e) constrain on the backbone atoms of CDK2 and ligand, (f) constrain on the backbone atoms of CDK2 and Wat145, (g) constrain on the Wat145 and ligand, (h) constrain on the backbone atoms of CDK2, Wat145 and ligand, (i) the distance of hydrogen bond Wat145O-ligandN5 shown in (e).

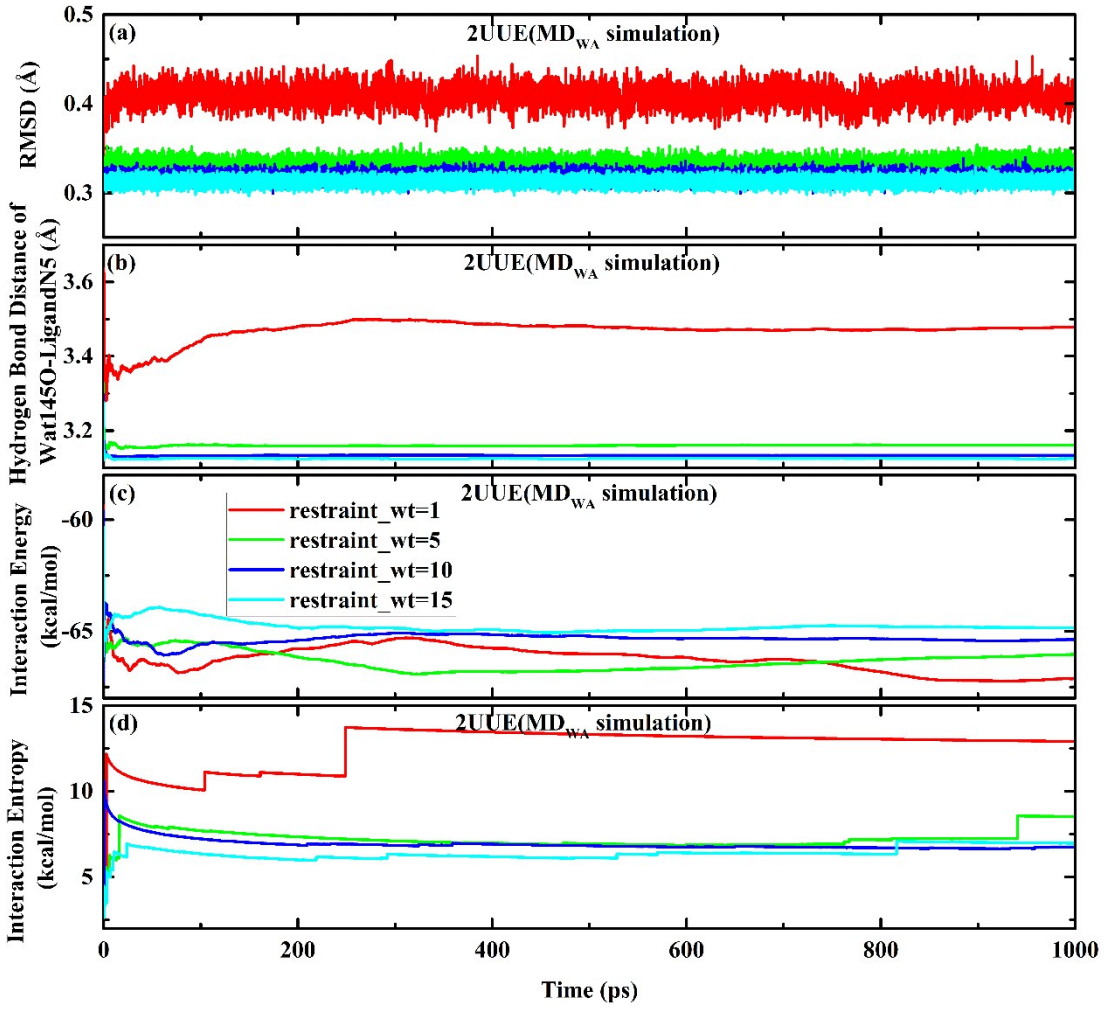


**Figure S3.** Effect of restraint force constant on RMSD of backbone CDK2, hydrogen bonds distance, calculated interaction energy and interaction entropy. The computational processes are employed with different restraint force constants (1, 5, 10, 15 kcal/(mol·Å²)) on the backbone atoms of CDK2, the Wat145 and ligand in a series of $MD_{WA}$ simulations.

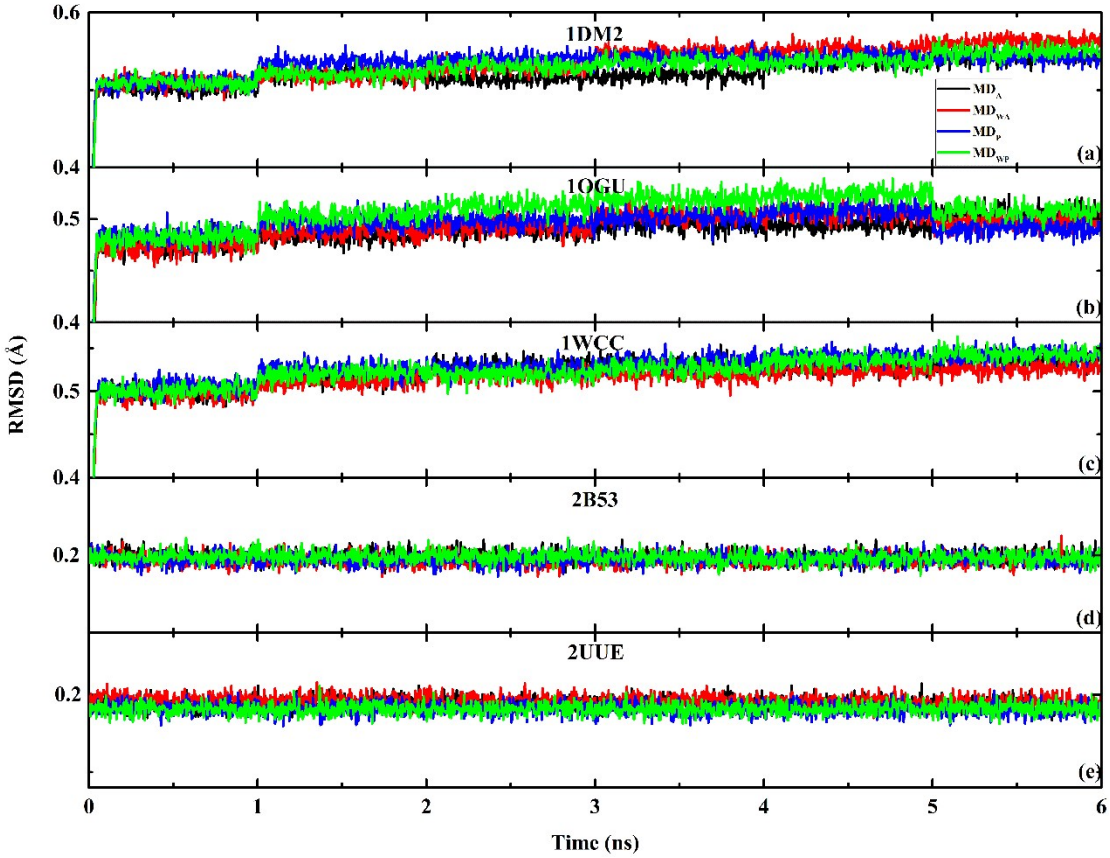


**Figure S4.** The RMSDs of the CDK2 backbone in all system with four MD simulations.

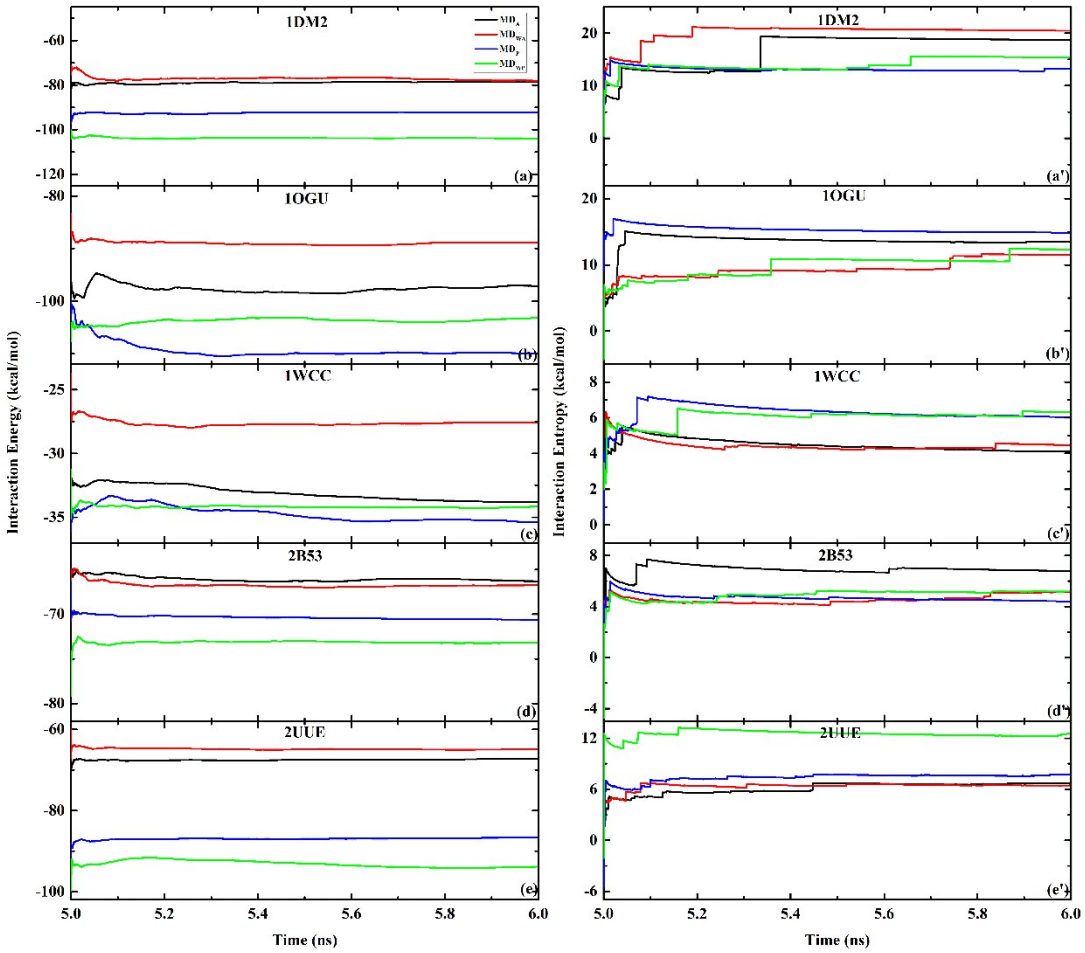


**Figure S5.** The average interaction energy and interaction entropy of all system with four MD simulations. The last 1ns MD simulations are used to computing the interaction energy and interaction entropy with 100,000 snapshots.

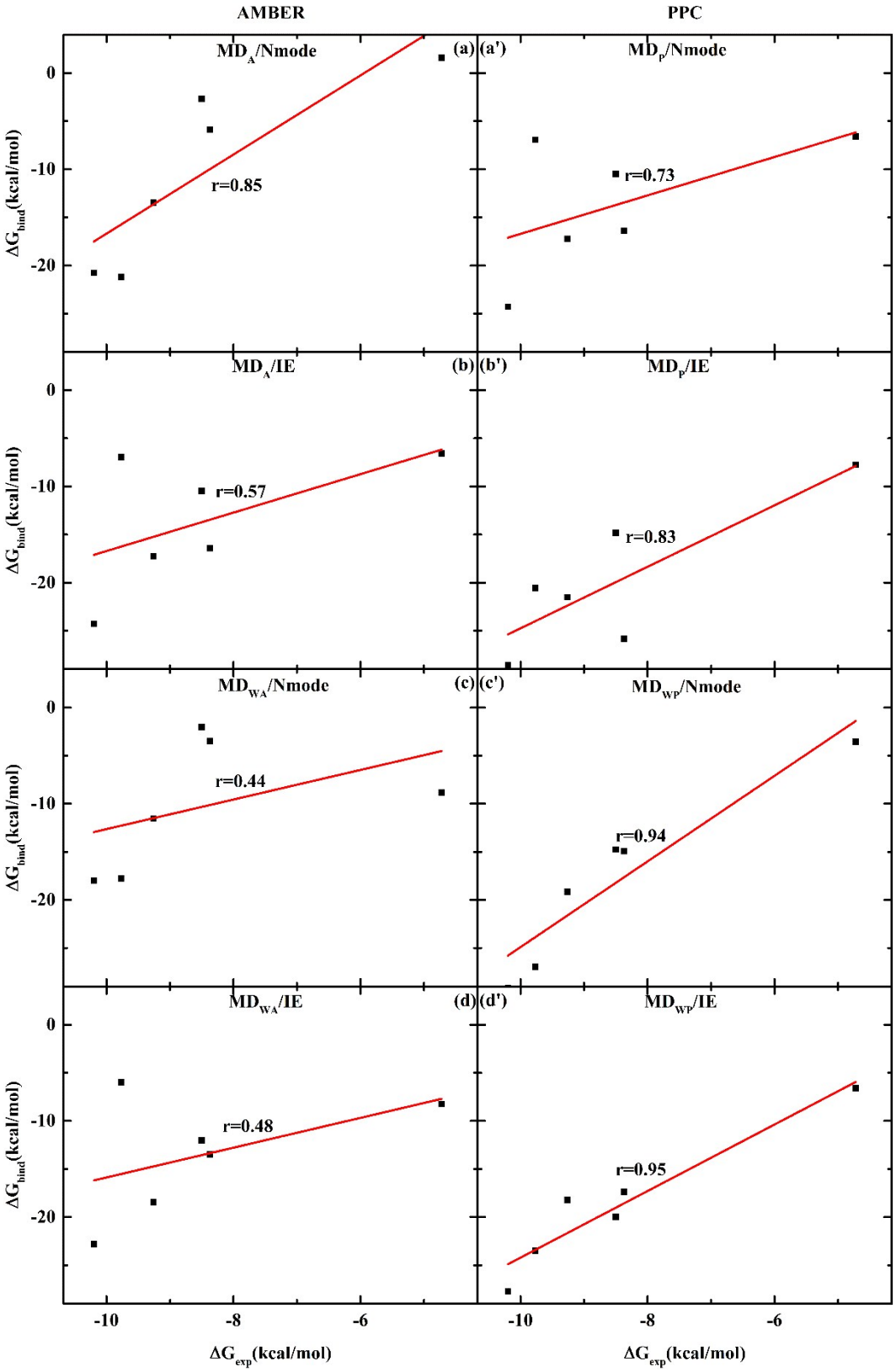


**Figure S6.** The correlation between experimentally measured and calculated data. Four MD simulations and two methods are employed.

**Table S1.** Effect of restraint force constant on calculated interaction energy and interaction entropy. The computational processes are employed with restraints on the backbone atoms of CDK2, the Wat145 and ligand in a series of 1ns $MD_{WA}$ simulations. $\langle E_{pl}^{\text{int}} \rangle$ is the ensemble averaged CDK2-ligand interaction energy, $-T\Delta S$ is calculated by IE method.

**Table S1**

| PDB code | Restraint force constant (kcal/(mol·Å²)) | $\langle E_{pl}^{\text{int}} \rangle$ | $-T\Delta S$ |
|---|---|---|---|
| 2UUE | 1 | -67.13 | 12.91 |
| | 5 | -66.03 | 8.52 |
| | 10 | -65.36 | 6.76 |
| | 15 | -64.84 | 6.97 |

**Table S2 to Table S5.** Different energy terms of binding free energy in all systems under four version MD simulations. $\Delta G_{sol}$ is calculated by MM/PBSA method and $-T\Delta S$ is calculated by normal mode analysis and IE method. And errors labeled by the signs ± represent the standard deviation (STD).

**Table S2: $MD_A$.**

| PDB code | $\langle E_{pl}^{\text{int}} \rangle$ | $\Delta G_{sol}$ | $-T\Delta S$ | | $\Delta G_{bind}$ | | $\Delta G_{\text{exp}}$ |
|---|---|---|---|---|---|---|---|
| | | | Nmode | IE | Nmode | IE | |
| 1DM2 | -78.50±4.62 | 52.85±2.69 | 4.44±8.41 | 18.71±3.88 | -21.21 | -6.94 | -9.77 |
| 1OGU | -97.16±5.11 | 59.37±4.89 | 17.02±6.71 | 13.49±1.54 | -20.77 | -24.30 | -10.20 |
| 1WCC | -33.79±1.99 | 23.13±2.39 | 12.28±9.79 | 4.09±0.51 | 1.62 | -6.57 | -4.72 |
| 2B53 | -66.32±2.47 | 49.06±2.92 | 14.60±5.69 | 6.78±0.42 | -2.66 | -10.48 | -8.50 |
| 2UUE | -67.27±2.93 | 44.16±2.38 | 17.23±4.99 | 6.70±0.89 | -5.88 | -16.41 | -8.37 |

**Table S3: $MD_{WA}$.**

| PDB code | $\langle E_{pl}^{\text{int}} \rangle$ | $\Delta G_{sol}$ | $-T\Delta S$ | | $\Delta G_{bind}$ | | $\Delta G_{\text{exp}}$ |
|---|---|---|---|---|---|---|---|
| | | | Nmode | IE | Nmode | IE | |
| 1DM2 | -77.99±6.40 | 51.53±4.32 | 8.70±7.38 | 20.46±1.77 | -17.76 | -6.00 | -9.77 |
| 1OGU | -88.89±3.47 | 54.55±3.48 | 16.36±5.22 | 11.50±2.42 | -17.98 | -22.84 | -10.20 |
| 1WCC | -27.58±1.99 | 14.87±1.37 | 3.85±5.47 | 4.47±0.30 | -8.86 | -8.24 | -4.72 |
| 2B53 | -66.76±2.23 | 49.57±3.09 | 15.14±7.16 | 5.16±0.69 | -2.05 | -12.03 | -8.50 |
| 2UUE | -64.91±2.72 | 44.95±2.93 | 16.47±7.88 | 6.49±0.42 | -3.49 | -13.47 | -8.37 |

**Table S4: $MD_P$.**

| PDB code | $\langle E_{pl}^{\text{int}} \rangle$ | $\Delta G_{sol}$ | $-T\Delta S$ | | $\Delta G_{bind}$ | | $\Delta G_{\text{exp}}$ |
|---|---|---|---|---|---|---|---|
| | | | Nmode | IE | Nmode | IE | |
| 1DM2 | -92.20±4.22 | 58.41±2.94 | 10.23±7.28 | 13.24±0.59 | -23.56 | -20.55 | -9.77 |
| 1OGU | -110.00±4.72 | 66.56±4.19 | 15.71±4.98 | 14.86±0.69 | -27.73 | -28.58 | -10.20 |
| 1WCC | -35.39±2.50 | 21.60±2.49 | 9.05±8.12 | 6.03±0.55 | -4.74 | -7.76 | -4.72 |
| 2B53 | -70.66±2.09 | 51.41±2.63 | 16.73±7.71 | 4.40±0.37 | -2.52 | -14.85 | -8.50 |
| 2UUE | -86.67±3.17 | 53.11±2.68 | 13.90±4.20 | 7.70±0.63 | -19.66 | -25.86 | -8.37 |

**Table S5: $MD_{WP}$.**

| PDB code | $\langle E_{pl}^{\text{int}} \rangle$ | $\Delta G_{sol}$ | $-T\Delta S$ | | $\Delta G_{bind}$ | | $\Delta G_{\text{exp}}$ |
|---|---|---|---|---|---|---|---|
| | | | Nmode | IE | Nmode | IE | |
| 1DM2 | -103.92±4.18 | 65.01±2.72 | 11.94±8.40 | 15.39±1.83 | -26.97 | -23.52 | -9.77 |
| 1OGU | -103.21±4.03 | 63.13±4.25 | 10.90±8.23 | 12.34±2.99 | -29.18 | -27.74 | -10.20 |
| 1WCC | -34.17±2.40 | 21.24±1.66 | 9.38±11.80 | 6.32±0.53 | -3.55 | -6.61 | -4.72 |
| 2B53 | -73.21±2.39 | 48.03±2.54 | 10.41±6.58 | 5.20±0.48 | -14.77 | -19.98 | -8.50 |
| 2UUE | -93.81±4.41 | 63.88±3.18 | 15.00±5.83 | 12.52±0.50 | -14.93 | -17.41 | -8.37 |

**Table S6 to Table S7.** Simple tests of binding free energy in all systems under 1ns $MD_A$ and $MD_P$ simulations without any constraint, respectively. $\Delta G_{sol}$ is calculated by MM/PBSA method and $-T\Delta S$ is calculated by IE method.

**Table S6: $MD_A$/IE.**

| PDB code | Restraint force constant (kcal/(mol·Å²)) | $\langle E_{pl}^{\text{int}} \rangle$ | $\Delta G_{sol}$ | $-T\Delta S$ | $\Delta G_{bind}$ | $\Delta G_{\text{exp}}$ |
|---|---|---|---|---|---|---|
| 1DM2 | | -52.02 | 28.59 | 17.88 | -5.55 | -9.77 |
| 1OGU | | -94.33 | 55.57 | 18.91 | -19.85 | -10.20 |
| 1WCC | 0 | -30.13 | 19.95 | 6.38 | -3.80 | -4.72 |
| 2B53 | | -72.84 | 51.31 | 16.47 | -5.06 | -8.50 |
| 2UUE | | -78.24 | 50.53 | 18.21 | -9.50 | -8.37 |

**Table S7: $MD_P$/IE.**

| PDB code | Restraint force constant (kcal/(mol·Å²)) | $\langle E_{pl}^{\text{int}} \rangle$ | $\Delta G_{sol}$ | $-T\Delta S$ | $\Delta G_{bind}$ | $\Delta G_{\text{exp}}$ |
|---|---|---|---|---|---|---|
| 1DM2 | | -81.57 | 52.62 | 17.42 | -11.53 | -9.77 |
| 1OGU | | -105.86 | 65.78 | 23.08 | -17.00 | -10.20 |
| 1WCC | 0 | -31.29 | 19.13 | 8.23 | -3.93 | -4.72 |
| 2B53 | | -70.23 | 45.57 | 17.43 | -7.23 | -8.50 |
| 2UUE | | -89.31 | 60.74 | 18.46 | -10.11 | -8.37 |