# Supplemental Material

## Interactions of Amino Acid Side Chain Analogs within Membrane Environments

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# Tables

**Table S1**: Simulation time in nanoseconds for explicit solvent simulations of amino-acid analog pairs at different umbrella potentials. Sampling in forward and backward directions (see text) were simulated for the same time.

| | z | 3 | 3.5 | 4 | 4.5 | 5 | 5.5 | 6 | 6.5 | 7 | 7.5 | 8 | 8.5 | 9 | 9.5 | 10 | 10.5 | 11 | 11.5 | 12 | 12.5 | 13 | 13.5 | 14 | 14.5 | 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acetamide | 0 | 20 | 20 | 30 | 20 | 20 | 200 | 120 | 20 | 20 | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 20 | 20 | 30 | 20 | 20 | 200 | 120 | 20 | 20 |
| | 4 | 30 | 70 | 30 | 50 | 200 | 90 | 150 | 50 | 50 | 30 | 30 | 20 | 20 | 10 | 10 | 10 | 30 | 70 | 30 | 50 | 200 | 90 | 150 | 50 | 50 |
| | 8 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 10 | 20 | 10 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | 12 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | 16 | 20 | 20 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 40 | 14 | 10 | 20 | 20 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | 24 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Methanol | 0 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 50 | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 50 |
| | 4 | 20 | 20 | 20 | 200 | 30 | 30 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 20 | 20 | 20 | 200 | 30 | 30 | 20 | 20 | 20 |
| | 8 | 20 | 20 | 92 | 40 | 20 | 20 | 20 | 20 | 20 | 30 | 20 | 30 | 20 | 10 | 10 | 10 | 20 | 20 | 92 | 40 | 20 | 20 | 20 | 20 | 20 |
| | 12 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | 16 | 20 | 20 | 50 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 20 | 20 | 50 | 20 | 20 | 20 | 20 | 20 | 20 |
| | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| | 24 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 10 | 10 | 10 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Toluene | 0 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 10 | 10 | 10 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| | 4 | 12 | 12 | 12 | 20 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 10 | 10 | 10 | 12 | 12 | 12 | 20 | 12 | 12 | 12 | 12 | 12 |
| | 8 | 12 | 12 | 12 | 12 | 12 | 20 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 10 | 10 | 10 | 12 | 12 | 12 | 12 | 12 | 20 | 12 | 12 | 12 |
| | 12 | 12 | 12 | 12 | 12 | 40 | 40 | 40 | 40 | 20 | 20 | 30 | 20 | 20 | 10 | 62 | 10 | 12 | 12 | 12 | 12 | 40 | 40 | 40 | 40 | 20 |
| | 16 | 70 | 70 | 70 | 70 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 10 | 30 | 70 | 70 | 70 | 70 | 40 | 40 | 40 | 40 | 40 |
| | 20 | 12 | 12 | 12 | 12 | 12 | 12 | 20 | 12 | 12 | 12 | 12 | 12 | 12 | 10 | 10 | 10 | 12 | 12 | 12 | 12 | 12 | 12 | 20 | 12 | 12 |
| | 24 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 30 | 30 | 12 | 12 | 12 | 12 | 10 | 10 | 10 | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 30 | 30 |
| Propane | 0 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| | 4 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| | 8 | 6 | 6 | 6 | 6 | 6 | 20 | 6 | 6 | 6 | 6 | 6 | 20 | 6 | 6 | 20 | 6 | 6 | 6 | 6 | 6 | 6 | 20 | 6 | 6 | 6 |
| | 12 | 6 | 6 | 16 | 16 | 16 | 16 | 16 | 16 | 30 | 30 | 30 | 16 | 30 | 30 | 20 | 6 | 6 | 6 | 16 | 16 | 16 | 16 | 16 | 16 | 30 |
| | 16 | 6 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 40 | 100 | 40 | 60 | 30 | 20 | 20 | 6 | 6 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 40 |
| | 20 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 20 | 20 | 6 | 6 | 6 | 6 | 20 | 20 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 20 |
| | 24 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |

**Table S2**: Improved HDGB parameters, dielectric profile (ε) and non-polar profile (γ)

| z | ε(z) - old | ε(z) - new |
|---|---|---|
| 0.0 | 1.80 | 1.15 |
| 0.5 | 1.80 | 1.15 |
| 1.0 | 1.81 | 1.16 |
| 1.5 | 1.82 | 1.17 |
| 2.0 | 1.83 | 1.18 |
| 2.5 | 1.84 | 1.19 |
| 3.0 | 1.85 | 1.20 |
| 3.5 | 1.86 | 1.21 |
| 4.0 | 1.87 | 1.22 |
| 4.5 | 1.89 | 1.24 |
| 5.0 | 1.91 | 1.26 |
| 5.5 | 1.93 | 1.28 |
| 6.0 | 1.97 | 1.32 |
| 6.5 | 2.00 | 1.35 |
| 7.0 | 2.04 | 1.49 |
| 7.5 | 2.09 | 1.64 |
| 8.0 | 2.15 | 1.80 |
| 8.5 | 2.22 | 1.87 |
| 9.0 | 2.31 | 1.96 |
| 9.5 | 2.41 | 2.06 |
| 10.0 | 2.53 | 2.18 |
| 10.5 | 3.23 | 2.28 |
| 11.0 | 3.63 | 2.38 |
| 11.5 | 4.13 | 2.58 |
| 12.0 | 4.73 | 2.89 |
| 12.5 | 5.43 | 3.42 |
| 13.0 | 6.13 | 4.00 |
| 13.5 | 6.98 | 5.08 |
| 14.0 | 7.84 | 6.04 |
| 14.5 | 8.80 | 7.50 |
| 15.0 | 10.96 | 10.06 |
| 15.5 | 14.05 | 13.75 |
| 16.0 | 19.04 | 19.04 |
| 16.5 | 25.85 | 25.85 |
| 17.0 | 35.38 | 35.38 |
| 17.5 | 45.88 | 45.88 |
| 18.0 | 54.11 | 54.11 |
| 18.5 | 60.79 | 60.79 |
| 19.0 | 65.52 | 65.52 |
| 19.5 | 69.42 | 69.42 |
| 20.0 | 72.31 | 72.31 |
| 20.5 | 74.07 | 74.07 |
| 21.0 | 75.53 | 75.53 |
| 21.5 | 76.63 | 76.63 |
| 22.0 | 77.14 | 77.14 |
| 22.5 | 77.83 | 77.83 |
| 23.0 | 78.22 | 78.22 |
| 23.5 | 78.92 | 78.92 |
| 24.0 | 79.35 | 79.35 |
| 24.5 | 79.66 | 79.66 |
| 25.0 | 80.00 | 80.00 |

| z | γ(z) |
|---|---|
| 0.0 | 0.0000 |
| 0.6 | 0.0001 |
| 1.2 | 0.0002 |
| 1.8 | 0.0010 |
| 2.4 | 0.0050 |
| 3.0 | 0.0075 |
| 3.6 | 0.0100 |
| 4.2 | 0.0150 |
| 4.8 | 0.0200 |
| 5.4 | 0.0250 |
| 6.0 | 0.0300 |
| 6.6 | 0.0350 |
| 7.2 | 0.0410 |
| 7.8 | 0.0470 |
| 8.4 | 0.0520 |
| 9.0 | 0.0610 |
| 9.6 | 0.0720 |
| 10.2 | 0.0850 |
| 10.8 | 0.1000 |
| 11.4 | 0.1200 |
| 12.0 | 0.1500 |
| 12.6 | 0.1900 |
| 13.2 | 0.2500 |
| 13.8 | 0.3200 |
| 14.4 | 0.4000 |
| 15.0 | 0.5000 |
| 15.6 | 0.6200 |
| 16.2 | 0.7500 |
| 16.8 | 0.8753 |
| 17.4 | 0.9500 |
| 18.0 | 1.0308 |
| 18.6 | 1.0680 |
| 19.2 | 1.0921 |
| 19.8 | 1.1000 |
| 20.4 | 1.1000 |
| 21.0 | 1.0927 |
| 21.6 | 1.0690 |
| 22.2 | 1.0468 |
| 22.8 | 1.0328 |
| 23.4 | 1.0197 |
| 24.0 | 1.0130 |
| 24.6 | 1.0052 |
| 25.2 | 1.0005 |
| 25.8 | 1 |
| 26.4 | 1 |
| 27.0 | 1 |
| 27.6 | 1 |
| 28.2 | 1 |
| 28.8 | 1 |
| 29.4 | 1 |
| 30.0 | 1 |

# Figures

**Figure S1**: Amino acid analogs used in this study: acetamide (Asn), methanol (Ser), toluene (Phe) and propane (Val)

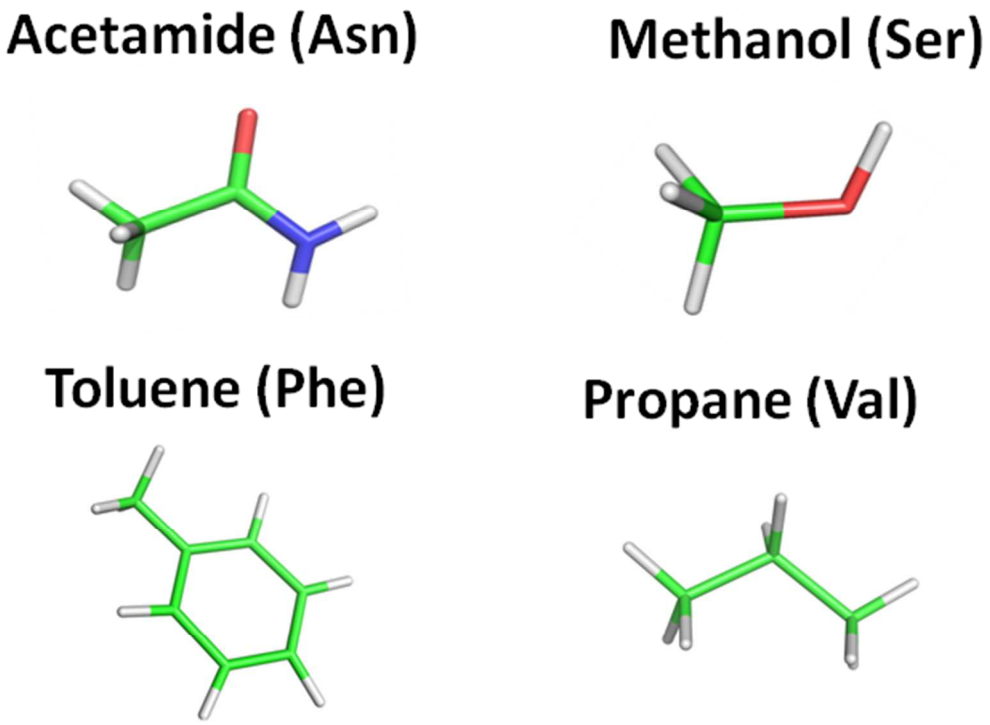


**Figure S2**: Root mean square deviation between the PMF profiles for each umbrella in forward and backward directions.

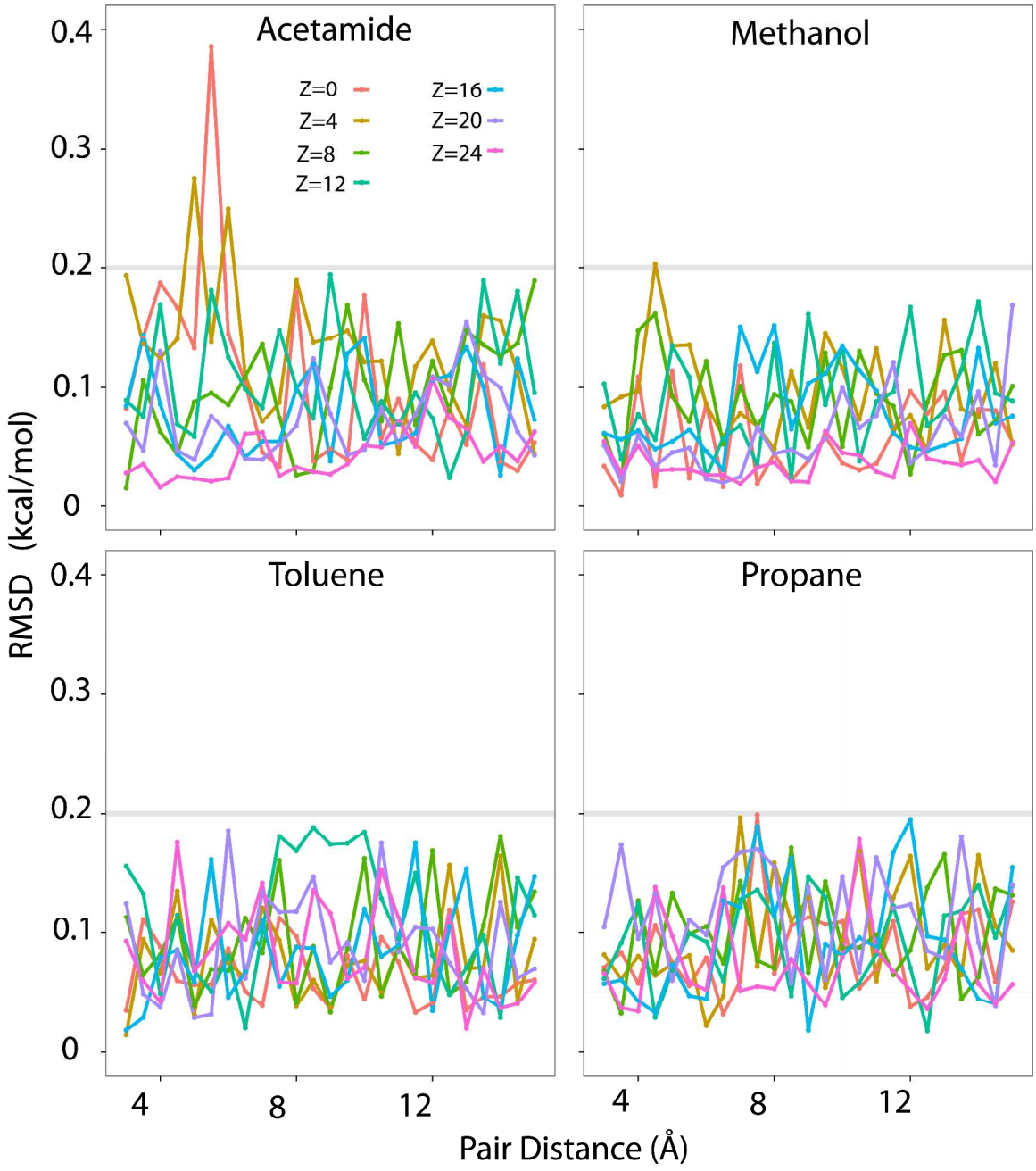


**Figure S3**. A: 2D PMF of acetamide pair association at z=0 and water density in biasing cylinder; B: Corrected 1D PMF as a function of pair distance after Boltzmann averaging along the water density reaction coordinate.

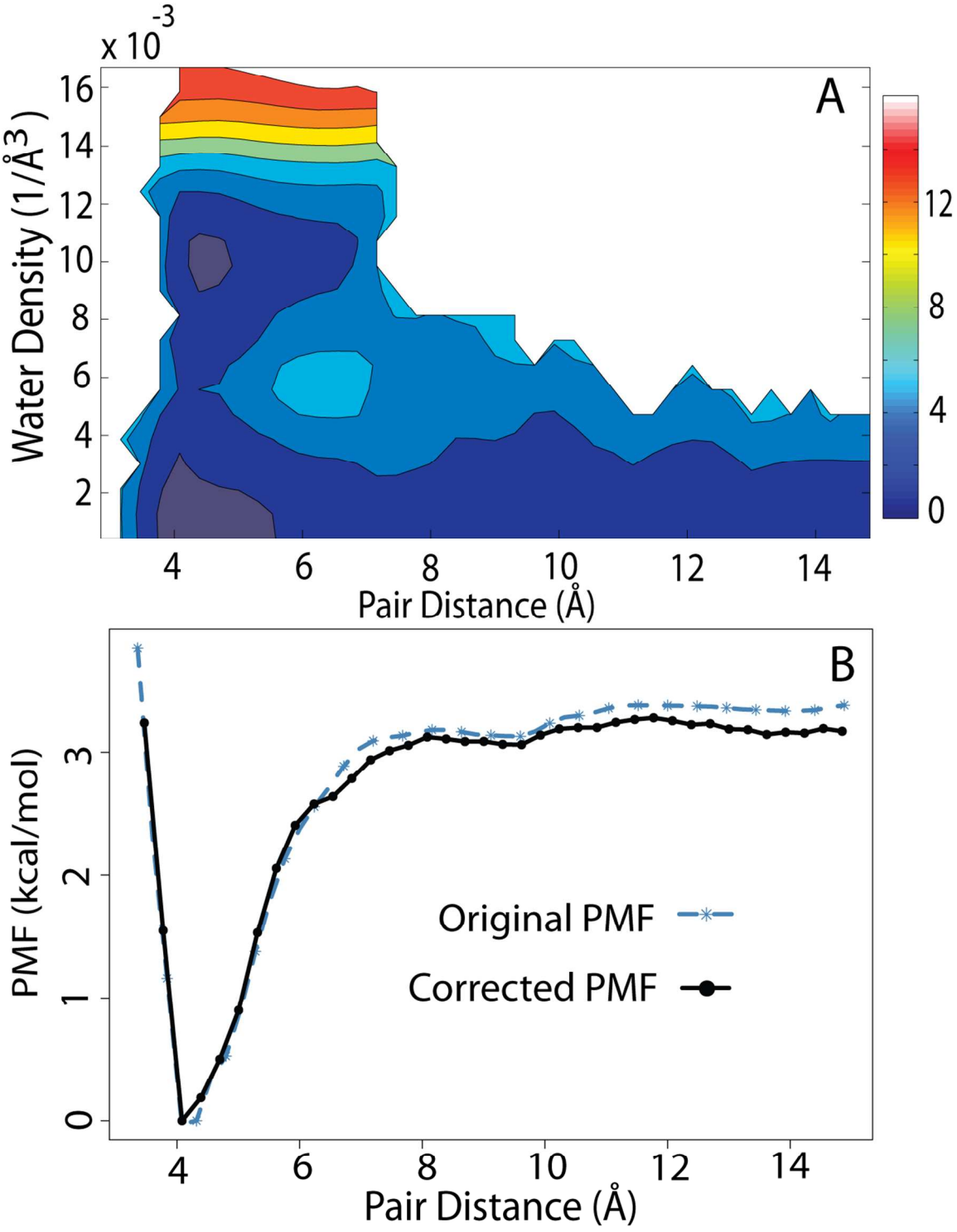


**Figure S4**. A: 2D PMF of methanol pair association at z=4 Å and water density in biasing cylinder; B: Corrected 1D PMF as a function of pair distance after Boltzmann averaging along the water density reaction coordinate.

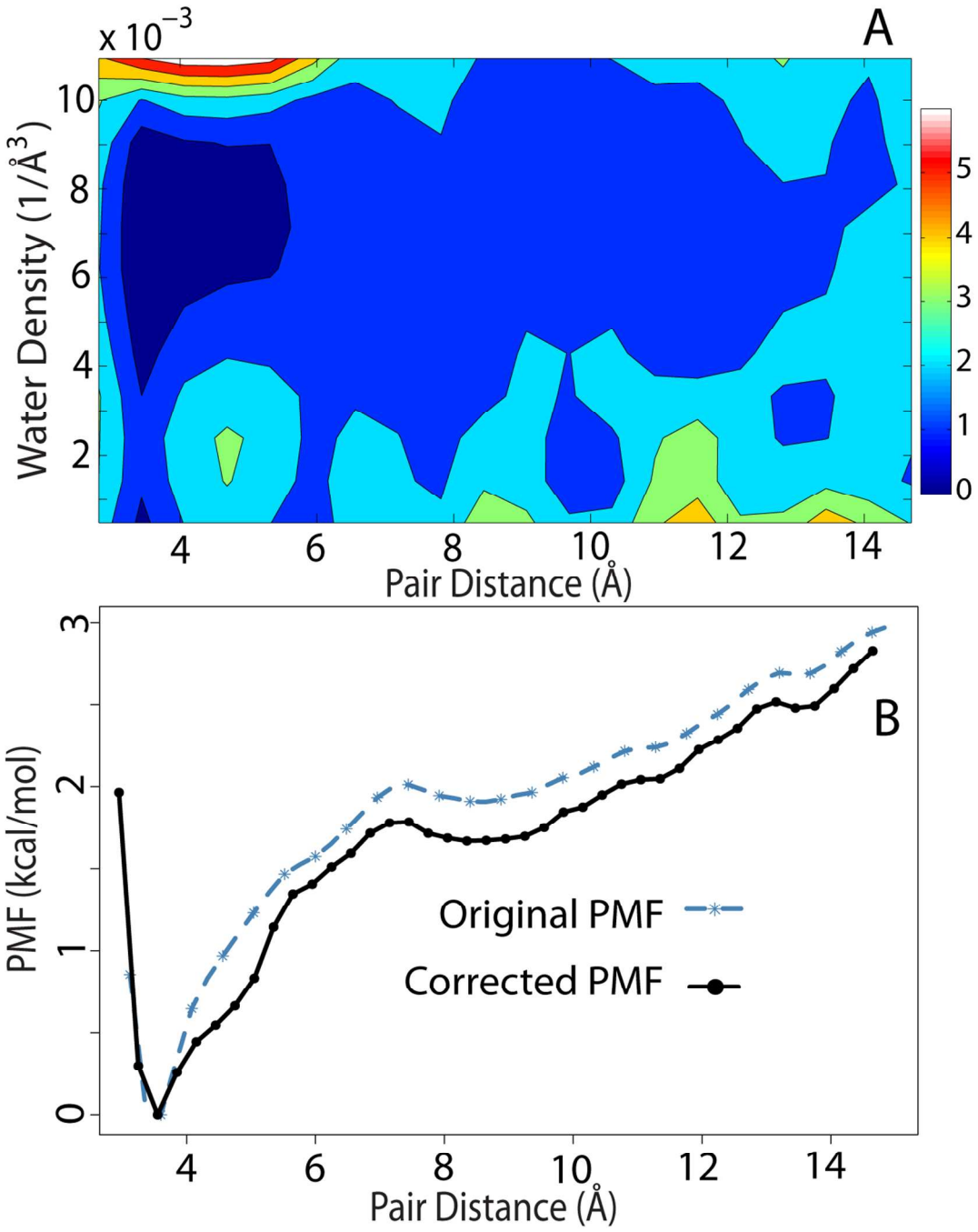
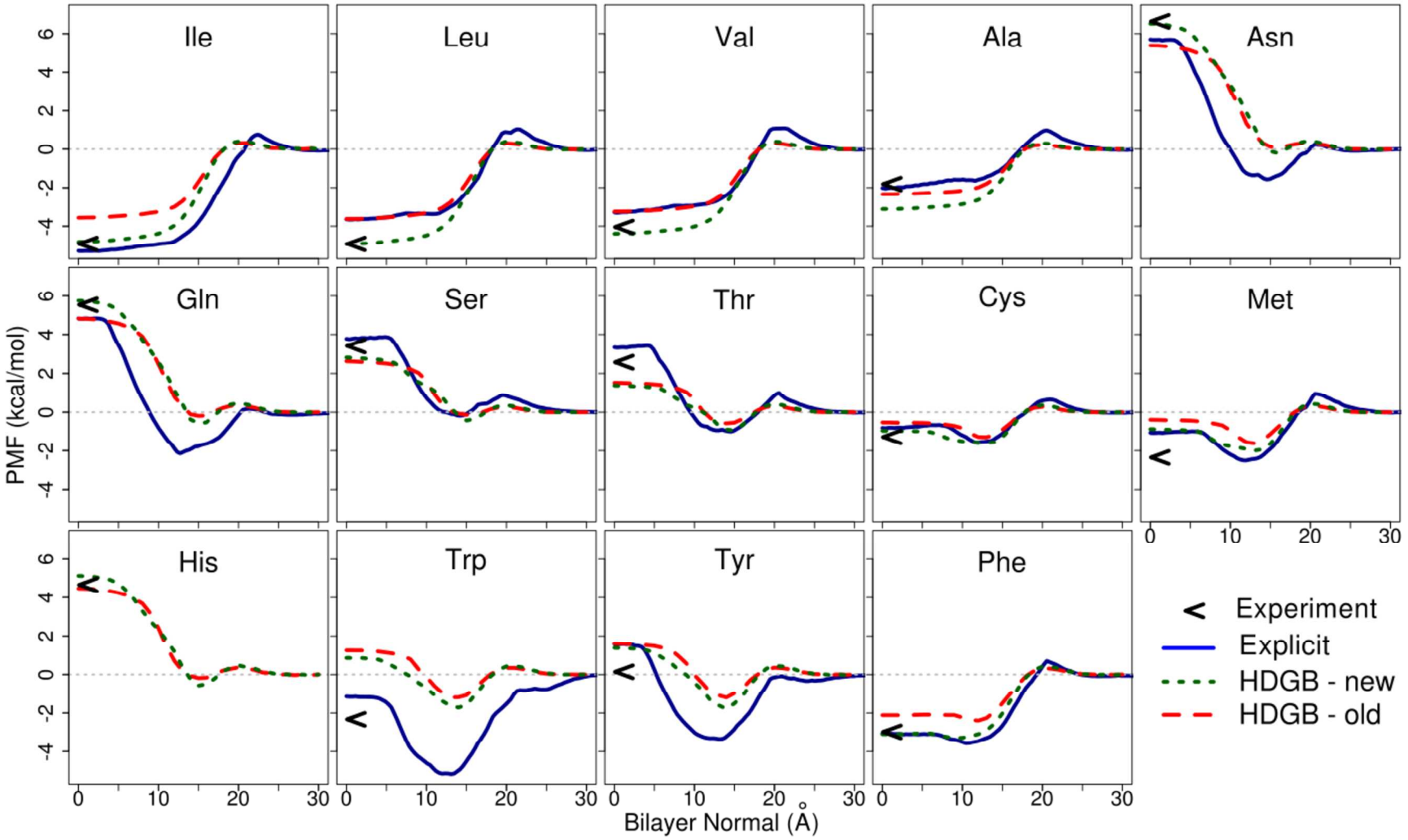


**Figure S5**: Free energy profiles of insertion of single amino acid side-chain analogs using HDGB simulations with old and improved parameters compared with results of explicit simulation[1] and experimental measurements[2]



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2. Radzicka A, Wolfenden R. Comparing the polarities of the amino acids: side-chain distribution coefficients between the vapor phase, cyclohexane, 1-octanol, and neutral aqueous solution. Biochemistry 1988;27:1664-1670.