## Supplementary Material

## for

# Accurate Calculation of Hydration Free Energies using Pair-Specific Lennard-Jones Parameters in the CHARMM Drude Polarizable Force Field

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## Heterodimeric Interactions with Water Molecules

### 1. Methods

Calculations were performed to assess the impact of the inclusion of atom-pair-specific LJ parameters on the heterodimer interactions of each of the parametrization set solute molecules with a single water molecule, focusing particularly on hydrogen bonding interactions. As a reference, quantum mechanical (QM) calculations were performed by constraining the geometry of the solute to an MP2/6-31G* optimized geometry (extended, all trans monomer geometries were used in all cases, except for the ethers, where the conformations considered are noted in Table S3) and the geometry of the water molecule to that of the SWM4-NDP model.[1] The water molecule was then placed in a pre-determined position and orientation relative to the solute (Figure S1), and the solute-water separation was optimized at the MP2/6-31G* level of theory using the program Gaussian03.[2] Final interaction energies were then determined at the RIMP2/cc-pVQZ level of theory using the program QCHEM,[3] with the counterpoise correction[4] applied to account for basis set superposition error.[5]

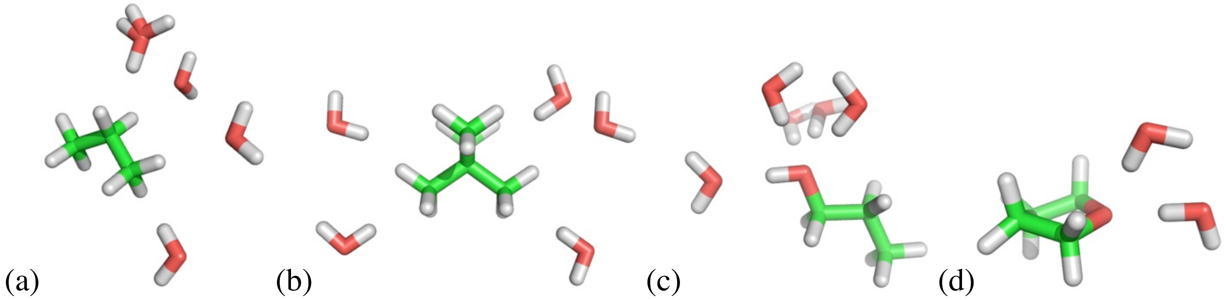

**Figure S1.** Water molecule orientations considered in the calculation of solute-water heterodimer interaction energies. (a) propane (b) neopentane (c) propan-1-ol (d) tetrahydrofuran.

## 2. Results and Discussion

In general, the inclusion of pair-specific LJ parameters had only a minor effect on the interaction energies and minimum interaction distances of the solute-water complexes considered (Tables S1-S3). For the alkanes, prior to the addition of pair-specific LJ parameters the difference in $E_{int}$ relative to the QM calculated values ranged from -1.56 kcal/mol to 0.43 kcal/mol, with an average difference of -0.08 kcal/mol. After the addition of pair-specific LJ parameters, the difference in $E_{int}$ relative to the QM calculated values ranged from -1.50 kcal/mol to 0.46 kcal/mol, with an average difference of -0.05 kcal/mol. Overall, it is clear that, for the alkanes, changes are very minor, although a slight shift towards less favorable interaction energies is observed, consistent with the pair-specific LJ parameters being introduced to make hydration free energies less favorable.

For MEOH, which has no atom types with atom-pair-specific LJ parameters, there are no changes in the interactions with water. For ETOH, PRO2 and BUO2, the changes in the water interaction energies are of a similar magnitude to those in the alkanes, as no pair-specific LJ parameters were applied to the hydroxyl atom types. For PRO1 and BUO1 the situation is somewhat different. Following the addition of alkane pair-specific LJ parameters the hydration free energies calculated for these molecules became not favorable enough, and pair-specific LJ parameters were applied to the O atom to make the hydration free energies more favorable. The result is that the interactions with water also become more favorable: considering only these two molecules, the average difference between the MM and QM calculated solute-water interaction energies is -0.66 kcal/mol without pair-specific LJ parameters, and -0.86 kcal/mol with pair-specific LJ parameters.

In the ethers, the O pair-specific LJ parameters always act to make the hydration free energy less favorable and, as a result, the interactions with water also become less favorable in their presence. The average difference between the MM and QM calculated interaction energies changes from 0.07 kcal/mol to 0.26 kcal/mol upon inclusion of the pair-specific LJ parameters. This is a significantly larger change than was observed in the alkanes, but similar in magnitude (but opposite in sign) to that obtained from PRO1 and BUO1.

| Molecule | Structure | QM | | MM – without pair-specific LJ parameters | | MM – with pair-specific LJ parameters | |
|---|---|---|---|---|---|---|---|
| | | $E_{int}$ | Rmin | $E_{int}$ | Rmin | $E_{int}$ | Rmin |
| ETHA | C1_out | -0.90 | 2.64 | -0.77 | 2.36 | -0.78 | 2.35 |
| | H11_out | -0.55 | 2.61 | -0.41 | 2.85 | -0.40 | 2.86 |
| PROP | C2_out | -0.85 | 2.68 | -0.73 | 2.50 | -0.73 | 2.45 |
| | C2_bis | -0.23 | 3.57 | -0.49 | 3.62 | -0.47 | 3.59 |
| | H21_out | -0.58 | 2.60 | -0.45 | 2.83 | -0.42 | 2.83 |
| | C1_out | -0.95 | 2.62 | -0.65 | 2.41 | -0.64 | 2.40 |
| | H11_out | -0.56 | 2.60 | -0.54 | 2.82 | -0.52 | 2.83 |
| BUTA | C2_out | -1.00 | 2.67 | -1.12 | 2.44 | -1.12 | 2.40 |
| | C2_bis | -0.30 | 3.55 | -0.44 | 3.62 | -0.40 | 3.60 |
| | H21_out | -0.69 | 2.55 | -0.44 | 2.83 | -0.40 | 2.83 |
| | C1_out | -0.96 | 2.62 | -0.58 | 2.42 | -0.56 | 2.42 |
| | H11_out | -0.57 | 2.60 | -0.58 | 2.81 | -0.56 | 2.82 |
| IBUT | C2_out | -0.96 | 2.61 | -0.53 | 2.44 | -0.50 | 2.43 |
| | C2_bis | -0.24 | 2.18 | -0.25 | 2.13 | -0.20 | 2.17 |
| | H21_out | -0.69 | 2.56 | -0.32 | 2.86 | -0.28 | 2.88 |
| | C1_out | -0.31 | 3.18 | -1.88 | 2.96 | -1.82 | 2.96 |
| | H11_out | -0.67 | 2.77 | -1.39 | 2.58 | -1.40 | 2.53 |
| NEOP | C1_CH3 | -0.99 | 2.60 | -0.57 | 2.44 | -0.54 | 2.44 |
| | HT_180 | -0.76 | 2.54 | -0.51 | 2.83 | -0.47 | 2.84 |
| | H13_180 | -0.26 | 3.22 | -1.53 | 3.02 | -1.45 | 3.03 |
| | CT_out | -0.11 | 4.17 | -0.42 | 3.71 | -0.37 | 3.72 |
| | CT_ang | -0.30 | 3.47 | -1.16 | 3.27 | -1.09 | 3.27 |
| CPEN | C1_out | -0.90 | 2.67 | -0.59 | 2.58 | -0.57 | 2.53 |
| | C1_bis | -0.23 | 3.55 | -0.56 | 3.60 | -0.57 | 3.54 |
| | H1_out | -0.60 | 2.57 | -0.49 | 2.82 | -0.44 | 2.84 |
| CHEX | C1_out | -0.95 | 2.67 | -0.60 | 2.54 | -0.57 | 2.57 |
| | C1_bis | -0.24 | 3.55 | -0.60 | 3.55 | -0.54 | 3.59 |
| | H1_out | -0.58 | 2.58 | -0.47 | 2.83 | -0.46 | 2.83 |
| | Average Difference | | | -0.08 | -0.02 | -0.05 | -0.02 |
| | RMSD | | | 0.50 | 0.22 | 0.48 | 0.22 |

**Table S1.** Gas phase heterodimer interactions between alkanes and water. Interaction energies ($E_{int}$) are in kcal/mol, minimum interaction distances (Rmin) in Å. QM data calculated at the RIMP2/cc-pVQZ//MP2/6-31G* level of theory including BSSE correction, geometries are as described in Figure S1.

| Molecule | Structure | QM | | MM – without pair-specific LJ parameters | | MM – with pair-specific LJ parameters | |
|---|---|---|---|---|---|---|---|
| | | $E_{int}$ | Rmin | $E_{int}$ | Rmin | $E_{int}$ | Rmin |
| MEOH | H1_rOH | -4.40 | 2.92 | -4.58 | 2.89 | -4.58 | 2.89 |
| | O1_120 | -4.80 | 1.97 | -5.39 | 1.81 | -5.39 | 1.81 |
| | O1_120ip | -3.96 | 2.02 | -4.62 | 1.82 | -4.62 | 1.82 |
| | O1_180 | -2.47 | 2.12 | -3.00 | 1.94 | -3.00 | 1.94 |
| | O1_bis | -4.57 | 1.98 | -4.91 | 1.86 | -4.91 | 1.86 |
| ETOH | H1_rOH | -4.36 | 2.92 | -4.83 | 2.88 | -4.81 | 2.88 |
| | O1_120 | -4.97 | 1.96 | -5.85 | 1.81 | -5.83 | 1.80 |
| | O1_120ip | -4.05 | 2.02 | -4.76 | 1.82 | -4.73 | 1.82 |
| | O1_180 | -2.51 | 2.12 | -2.93 | 1.95 | -2.91 | 1.95 |
| | O1_bis | -4.90 | 1.98 | -5.68 | 1.86 | -5.66 | 1.85 |
| PRO2 | H1_rOH | -4.29 | 2.94 | -4.54 | 2.90 | -4.52 | 2.89 |
| | O1_120 | -5.08 | 1.95 | -5.61 | 1.82 | -5.57 | 1.82 |
| | O1_120ip | -4.14 | 2.02 | -4.53 | 1.83 | -4.49 | 1.83 |
| | O1_180 | -2.65 | 2.11 | -3.05 | 1.94 | -3.00 | 1.95 |
| | O1_bis | -5.03 | 1.97 | -5.74 | 1.86 | -5.70 | 1.86 |
| BUO2 | H1_rOH | -4.34 | 2.93 | -4.54 | 2.90 | -4.51 | 2.89 |
| | O1_120 | -2.13 | 1.95 | -2.13 | 2.75 | -2.07 | 2.76 |
| | O1_120ip | -4.02 | 2.01 | -4.57 | 1.86 | -4.51 | 1.85 |
| | O1_180 | -2.61 | 2.12 | -3.22 | 1.93 | -3.17 | 1.93 |
| | O1_bis | -3.26 | 1.98 | -3.87 | 2.20 | -3.80 | 2.20 |
| PRO1 | H1_rOH | -4.38 | 2.92 | -4.96 | 2.86 | -5.10 | 2.83 |
| | O1_120 | -5.03 | 1.95 | -5.88 | 1.78 | -6.15 | 1.74 |
| | O1_120ip | -4.09 | 2.01 | -4.85 | 1.79 | -5.10 | 1.75 |
| | O1_180 | -2.52 | 2.12 | -3.04 | 1.91 | -3.16 | 1.87 |
| | O1_bis | -4.96 | 1.98 | -5.56 | 1.83 | -5.78 | 1.79 |
| BUO1 | H1_rOH | -4.37 | 2.92 | -5.11 | 2.85 | -5.25 | 2.83 |
| | O1_120 | -5.08 | 1.95 | -5.93 | 1.78 | -6.19 | 1.74 |
| | O1_120ip | -4.12 | 2.01 | -4.89 | 1.79 | -5.14 | 1.75 |
| | O1_180 | -2.55 | 2.12 | -2.99 | 1.92 | -3.12 | 1.88 |
| | O1_bis | -4.99 | 1.98 | -5.51 | 1.84 | -5.72 | 1.80 |
| | Average Difference | | | -0.55 | -0.11 | -0.60 | -0.13 |
| | RMSD | | | 0.59 | 0.17 | 0.66 | 0.18 |

**Table S2.** Gas phase heterodimer interactions between alcohols and water. Interaction energies ($E_{int}$) are in kcal/mol, minimum interaction distances (Rmin) in Å. QM data calculated at the RIMP2/cc-pVQZ//MP2/6-31G* level of theory including BSSE correction, geometries are as described in Figure S1.

| Molecule | Structure | QM | | MM – without pair-specific LJ parameters | | MM – with atom-specific LJ parameters | |
|---|---|---|---|---|---|---|---|
| | | $E_{int}$ | Rmin | $E_{int}$ | Rmin | $E_{int}$ | Rmin |
| THF | C2_O1_180 | -5.45 | 1.95 | -5.22 | 1.75 | -5.01 | 1.79 |
| | C2_O1_180 | -5.95 | 1.90 | -6.18 | 1.73 | -5.98 | 1.75 |
| | CS_O1_180 | -5.09 | 1.96 | -5.42 | 1.75 | -5.21 | 1.78 |
| | CS_O1_120 | -5.47 | 1.93 | -5.90 | 1.73 | -5.70 | 1.76 |
| THP | Chair_O1_180 | -5.23 | 1.94 | -5.23 | 1.78 | -5.01 | 1.81 |
| | Chair_O1_120 | -5.54 | 1.92 | -5.57 | 1.77 | -5.37 | 1.80 |
| DEET | tt_O3_180 | -5.41 | 1.94 | -5.71 | 1.71 | -5.51 | 1.73 |
| | tt_O3_120 | -6.00 | 1.91 | -6.14 | 1.70 | -6.00 | 1.71 |
| | gt_O3_180 | -5.60 | 1.93 | -5.11 | 1.72 | -4.92 | 1.74 |
| | gt_O3_120 | -5.99 | 1.92 | -5.62 | 1.77 | -5.52 | 1.77 |
| | gg_O3_180 | -5.49 | 1.94 | -4.69 | 1.72 | -4.50 | 1.74 |
| | gg_O3_120 | -5.44 | 1.96 | -4.59 | 1.84 | -4.51 | 1.85 |
| MEET | t_O3_180 | -5.24 | 1.94 | -5.31 | 1.70 | -4.99 | 1.76 |
| | t_O3_120 | -5.78 | 1.92 | -5.82 | 1.69 | -5.48 | 1.75 |
| | g_O3_180 | -5.56 | 1.94 | -4.70 | 1.71 | -4.40 | 1.77 |
| | g_O3_120 | -5.81 | 1.94 | -5.30 | 1.76 | -5.08 | 1.81 |
| DME | O2_180 | -5.01 | 1.95 | -4.91 | 1.70 | -4.75 | 1.72 |
| | O2_120 | -5.47 | 1.94 | -5.50 | 1.69 | -5.34 | 1.71 |
| DMOE | ttt_O2_180 | -5.22 | 1.93 | -5.56 | 1.69 | -5.05 | 1.71 |
| | ttt_O2_120 | -5.42 | 1.92 | -5.47 | 1.69 | -5.30 | 1.70 |
| | ttt_O2_240 | -5.27 | 1.94 | -5.11 | 1.70 | -4.95 | 1.72 |
| | ttt_O5_180 | -5.22 | 1.93 | -5.56 | 1.69 | -5.05 | 1.71 |
| | ttt_O5_120 | -5.42 | 1.92 | -5.47 | 1.69 | -5.30 | 1.70 |
| | ttt_O5_240 | -5.27 | 1.94 | -5.11 | 1.70 | -4.95 | 1.72 |
| | gtt_O2_180 | -5.04 | 1.95 | -4.61 | 1.71 | -4.42 | 1.73 |
| | gtt_O2_120 | -5.19 | 1.93 | -5.00 | 1.70 | -4.85 | 1.72 |
| | gtt_O2_240 | -4.01 | 2.01 | -3.56 | 1.86 | -3.51 | 1.86 |
| | gtt_O5_180 | -5.04 | 1.94 | -5.01 | 1.69 | -4.80 | 1.72 |
| | gtt_O5_120 | -5.14 | 1.93 | -5.21 | 1.70 | -5.05 | 1.71 |
| | gtt_O5_240 | -4.93 | 1.94 | -5.00 | 1.70 | -4.83 | 1.72 |
| | tgg_O2_180 | -4.28 | 2.03 | -4.51 | 1.74 | -4.32 | 1.74 |
| | tgg_O2_120 | -3.19 | 2.21 | -5.08 | 1.81 | -4.95 | 1.83 |
| | tgg_O2_240 | -4.81 | 1.95 | -5.03 | 1.70 | -4.86 | 1.71 |
| | tgg_O5_180 | -5.69 | 1.94 | -5.19 | 1.71 | -5.00 | 1.73 |
| | tgg_O5_120 | -5.57 | 1.92 | -5.73 | 1.68 | -5.56 | 1.69 |
| | tgg_O5_240 | -3.95 | 2.29 | -2.69 | 2.46 | -2.63 | 2.47 |
| Average Difference | | | | 0.07 | -0.21 | 0.26 | -0.19 |
| RMSD | | | | 0.51 | 0.23 | 0.56 | 0.21 |

**Table S3.** Gas phase heterodimer interactions between ethers and water. Interaction energies ($E_{int}$) are in kcal/mol, minimum interaction distances (Rmin) in Å. QM data calculated at the RIMP2/cc-pVQZ//MP2/6-31G* level of theory including BSSE correction, geometries are as described in Figure S1.

| Molecule | Without Pair-Specific LJ Parameters | | | With Pair-Specific LJ Parameters | | |
|---|---|---|---|---|---|---|
| | Repulsion | Dispersion | Electrostatic | Repulsion | Dispersion | Electrostatic |
| Alkanes | | | | | | |
| CPEN | 14.49 ± 0.06 | -13.63 ± 0.02 | -0.26 ± 0.00 | 14.33 ± 0.07 | -12.45 ± 0.01 | -0.27 ± 0.00 |
| CHEX | 15.95 ± 0.06 | -14.60 ± 0.02 | -0.28 ± 0.00 | 15.90 ± 0.11 | -13.82 ± 0.02 | -0.28 ± 0.00 |
| ETHA | 9.91 ± 0.07 | -7.79 ± 0.01 | -0.22 ± 0.00 | 9.81 ± 0.09 | -7.61 ± 0.01 | -0.24 ± 0.00 |
| PROP | 12.11 ± 0.05 | -10.05 ± 0.01 | -0.35 ± 0.00 | 12.17 ± 0.08 | -9.38 ± 0.01 | -0.42 ± 0.00 |
| BUTA | 14.23 ± 0.12 | -12.14 ± 0.02 | -0.43 ± 0.02 | 14.09 ± 0.10 | -11.14 ± 0.02 | -0.48 ± 0.02 |
| IBUT | 14.12 ± 0.09 | -11.75 ± 0.02 | -0.46 ± 0.01 | 14.11 ± 0.02 | -10.74 ± 0.01 | -0.73 ± 0.01 |
| NEOP | 15.49 ± 0.10 | -13.77 ± 0.01 | -0.48 ± 0.00 | 15.65 ± 0.12 | -12.52 ± 0.01 | -0.48 ± 0.00 |
| Alcohols | | | | | | |
| MEOH | 8.67 ± 0.06 | -7.40 ± 0.02 | -6.24 ± 0.05 | 8.67 ± 0.06 | -7.40 ± 0.02 | -6.24 ± 0.05 |
| ETOH | 11.08 ± 0.03 | -8.99 ± 0.02 | -6.93 ± 0.04 | 10.95 ± 0.05 | -8.41 ± 0.01 | -7.10 ± 0.04 |
| PRO2 | 13.24 ± 0.11 | -10.94 ± 0.12 | -7.55 ± 0.04 | 12.95 ± 0.04 | -9.96 ± 0.14 | -8.18 ± 0.04 |
| BUO2 | 15.05 ± 0.12 | -12.83 ± 0.01 | -7.30 ± 0.06 | 15.13 ± 0.12 | -11.52 ± 0.01 | -7.39 ± 0.07 |
| PRO1 | 13.25 ± 0.08 | -11.10 ± 0.01 | -6.96 ± 0.05 | 13.05 ± 0.08 | -10.07 ± 0.02 | -7.58 ± 0.04 |
| BUO1 | 15.18 ± 0.11 | -13.17 ± 0.02 | -7.11 ± 0.05 | 15.13 ± 0.10 | -11.78 ± 0.01 | -7.65 ± 0.05 |
| Ethers | | | | | | |
| THF | 13.66 ± 0.07 | -12.65 ± 0.01 | -5.39 ± 0.04 | 13.57 ± 0.08 | -11.46 ± 0.02 | -5.28 ± 0.05 |
| THP | 15.23 ± 0.05 | -14.49 ± 0.02 | -5.59 ± 0.03 | 15.49 ± 0.12 | -12.65 ± 0.02 | -5.45 ± 0.04 |
| DEE | 16.00 ± 0.14 | -13.56 ± 0.02 | -4.61 ± 0.05 | 15.90 ± 0.13 | -12.38 ± 0.01 | -4.90 ± 0.05 |
| DMOE | 16.82 ± 0.13 | -14.98 ± 0.01 | -6.93 ± 0.04 | 16.60 ± 0.14 | -13.73 ± 0.03 | -7.42 ± 0.06 |
| DME | 11.15 ± 0.04 | -9.36 ± 0.01 | -3.33 ± 0.03 | 11.20 ± 0.05 | -9.02 ± 0.01 | -3.73 ± 0.04 |
| MEET | 13.41 ± 0.10 | -11.49 ± 0.01 | -4.02 ± 0.02 | 13.41 ± 0.07 | -10.73 ± 0.01 | -4.09 ± 0.05 |

**Table S4.** Contributions to $\Delta G_{hyd}$ obtained from FEP calculations. Values are the mean energies obtained over 5 independent FEP calculations, with errors calculated as the standard deviation of the mean over 500 iterations of a bootstrap procedure. All values in kcal/mol.

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