The SAMPL6 Host-Guest Challenge with the AMOEBA force field

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The approach

• **AMOEBA** = Atomic Multipole Optimized Energetics for Biomolecular Applications
  – Parameterization of guest molecules following the standard AMOEBA protocol\(^1\)
    •QM low-level to obtain initial guess multipoles
    •QM high-level to fit dipoles and quadrupoles
    •Valence via fitting to QM, MMFF, and existing AMOEBA parameters
  
• **TINKER** and **TINKER-OpenMM\(^2\)**
  – *bar* program on CPUs and *dynamic_omm* program on GPUs

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\(^1\) P. Ren, C. Wu, JW Ponder *JCTC* 7, 3143 (2011).
The approach

- **dynamic_omm**: 40 Å explicit water box, Respa integrator (2 fs time step), Bussi thermostat, Montecarlo barostat, 10 ns trajectories

- **bar**: Tossed out first ns as equilibration, monitored FEP forward and backward for hysteresis

- **Annihilation-Decoupling scheme**: Slowly annihilate electrostatics first and then decouple vdw (Further comments to come...)

- **Restraint for host-guest**: Harmonic,¹ restraint distance and restraint atoms defined via analysis of extended (>50 ns) simulation of unrestrained system

¹ D. Hamelberg, JA McCammon *JACS* 126, 7683 (2004).
SAMPL6 CB8 Binding Results

12a is 1:1 H:G and 12b is 1:2 H:G

Green region = 2 kcal/mol error margin
What we learned: Sampling

• “Equivalent sampling” in the solvation versus bound simulations for the 000-000 (elec-vdw) state
  – 2 trajectories locked in different guest conformations (e.g. CB8-G2)
  – Issue that could present itself with non-rigid guests
• **Two blues curves**: **Intramolecular vdw present** (G2 has two conformations that do not interconvert over 100 ps and never over 10 ns)

• **Green curve**: **Intramolecular vdw turned off** (G2 has only one main conformation from which it makes a number of excursions over 100 ps)

• **Red curve**: **No intramolecular vdw and zero torsion parameters for the key torsion** (Now structure undergoes many rotations about the key torsion and samples quite extensively)
What we learned: Sampling

- “Equivalent sampling” in the solvation versus bound simulations for the 000-000 (elec-vdw) state
- **RESOLUTION**: Annihilate electrostatics AND annihilate vdw AND zero-out key torsion parameters
What we learned: CB8

- Noticed indentations that resulted in a heart (single indentation) or an eight (double indentation)
  - Interactions between guest and carbonyl oxygens
  - Shifting of guest within the ring opening (e.g. G13, double indentation)
What we learned: CB8

<table>
<thead>
<tr>
<th>Molecule</th>
<th>ωB97X-D/6-311G(1d,1p)</th>
<th>AMOEBA Tors. at -0.25</th>
<th>AMOEBA Tors. at -1.50</th>
<th>AMOEBA Tors. at -1.70</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB7-CB7 Indentation</td>
<td>-20.89</td>
<td>-12.52</td>
<td>-19.91</td>
<td>-21.07</td>
</tr>
<tr>
<td>CB8-CB8 Indentation x 2</td>
<td>-23.35</td>
<td>-11.43</td>
<td>-22.04</td>
<td>-23.65</td>
</tr>
<tr>
<td>CB8 Indentation-CB8 Indentation x 2</td>
<td>-9.44</td>
<td>-4.47</td>
<td>-9.04</td>
<td>-9.67</td>
</tr>
</tbody>
</table>

Units: kcal/mol

- Comparing to QM
- Modify ONE torsion
  - Three-fold torsional parameters....modified (increased)
    - Testing values of -1.50, -1.70, -2.25 from original of -0.25
What we learned: CB8

- Modification to the CB8 torsional parameter = no more indentations
- Re-examining binding free energies

<table>
<thead>
<tr>
<th>Guest</th>
<th>Original</th>
<th>Post-mod</th>
<th>Expt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0</td>
<td>-8.51</td>
<td>-8.87(^a)</td>
<td>-6.69</td>
</tr>
<tr>
<td>G1</td>
<td>-8.88</td>
<td></td>
<td>-7.65</td>
</tr>
<tr>
<td>G2</td>
<td>-15.76</td>
<td>-11.18(^a), -10.57(^b)</td>
<td>-7.66</td>
</tr>
<tr>
<td>G3</td>
<td>-16.06</td>
<td></td>
<td>-6.45</td>
</tr>
<tr>
<td>G13</td>
<td>-3.61</td>
<td>-4.51(^a)</td>
<td>-7.11</td>
</tr>
</tbody>
</table>

\(^{a}\) Torsion parameter set to -1.50
\(^{b}\) Torsion parameter set to -2.25

Units: kcal/mol
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