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

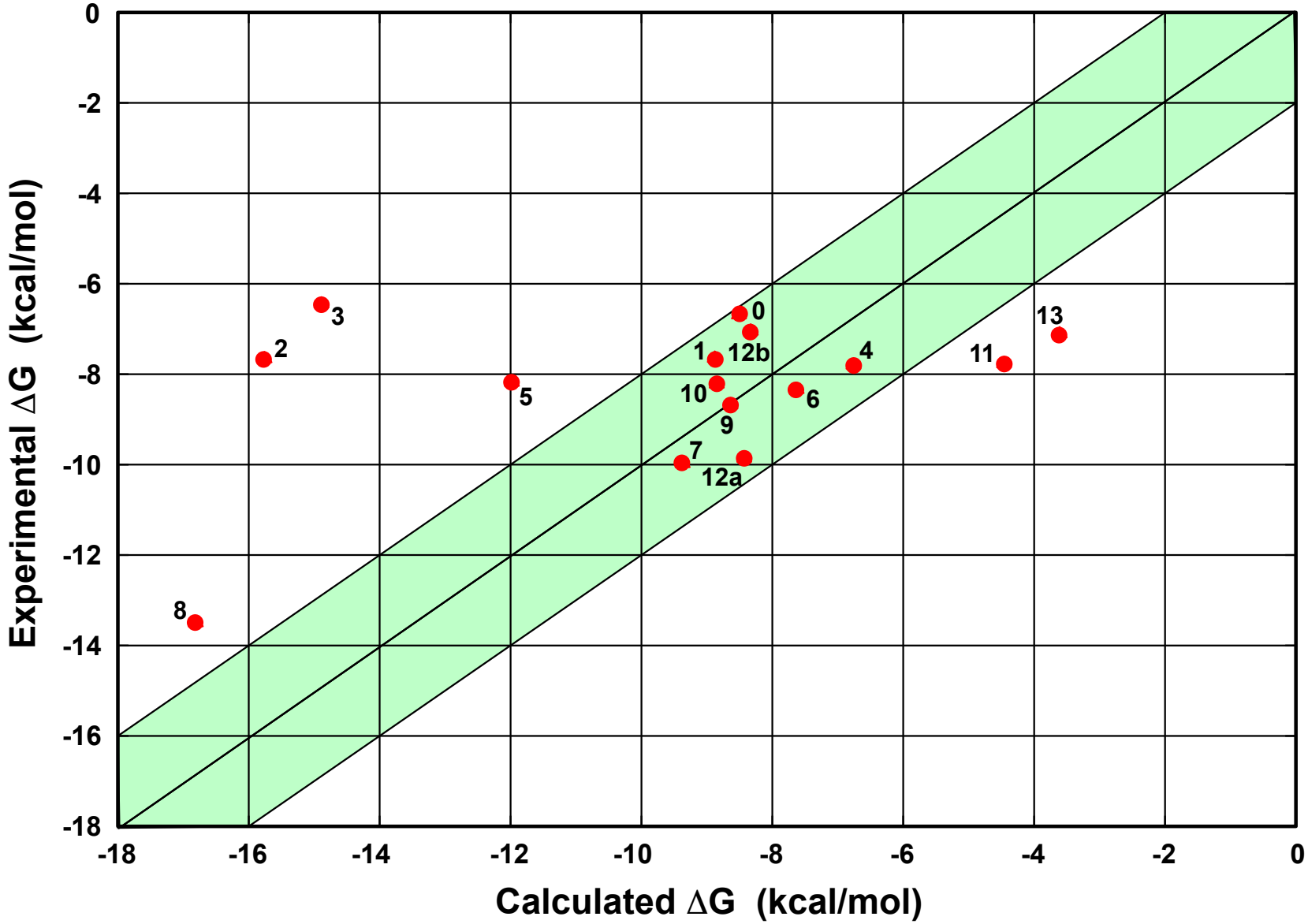
[1] P. Ren, C. Wu, JW Ponder *JCTC* 7, 3143 (2011).
[2] M. Harger, D. Li, Z. Wang, K. Dalby, L. Lagardere, J.-P. Piquemal, J. Ponder, P. Ren *JCC* 38, 2047 (2017).

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

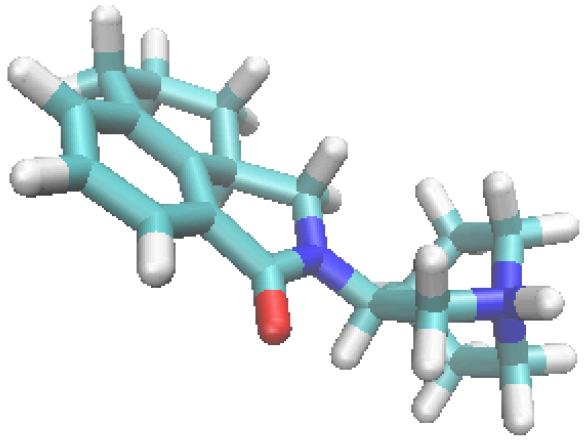


12a is 1:1 H:G and 12b is 1:2 H:G

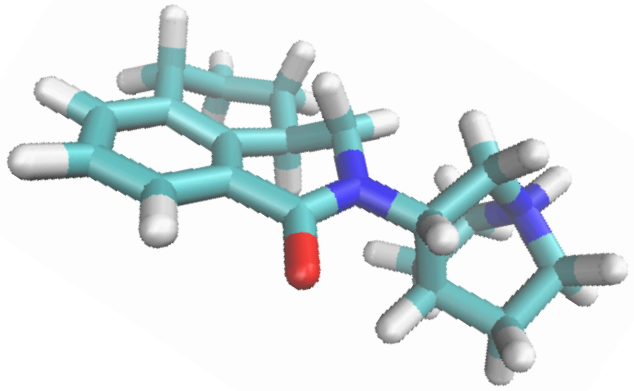
Green region = 2 kcal/mol error margin

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

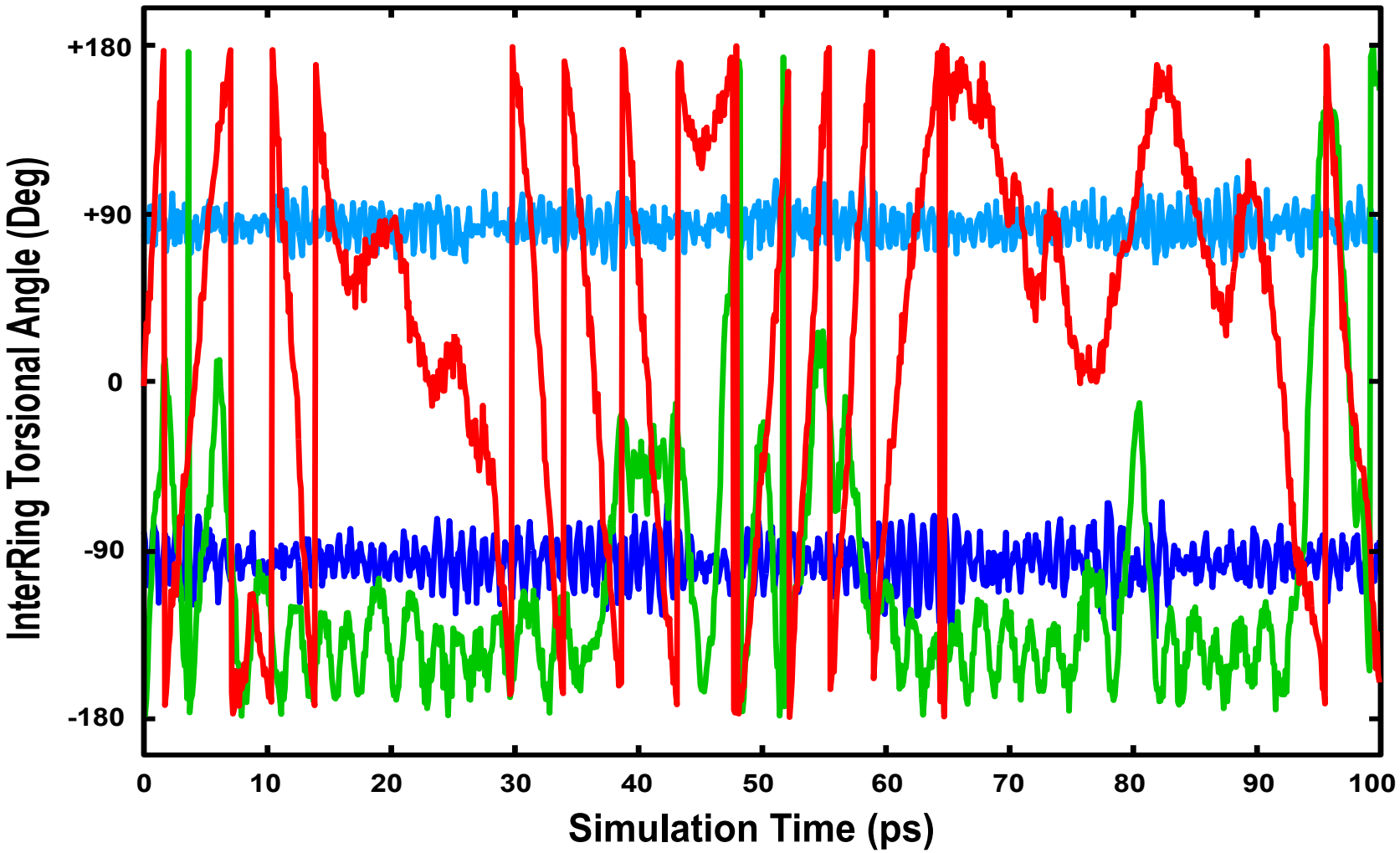


CB8 G2 Solvation 000-000



CB8 G2 Host-Guest 000-000

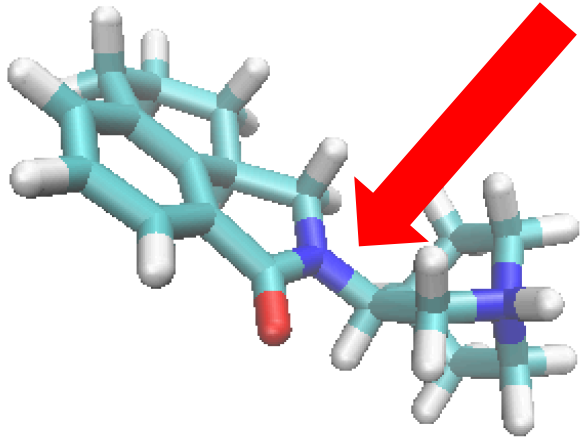
Palonosetron (CB8-G2): VDW Decoupling vs. Annihilation



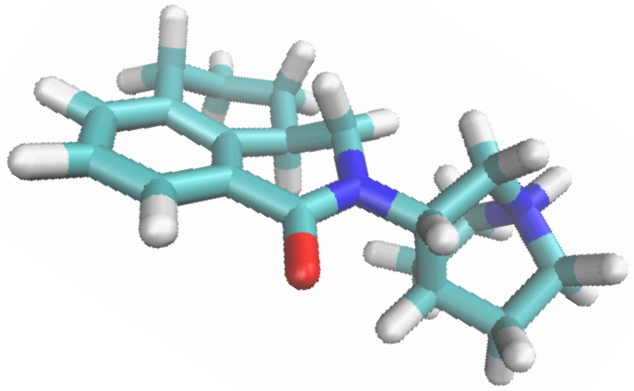
- **Two blues curves**: **Intramolecular vdw present** (G2 has two conformations that do not interconvert over 100 ps and never over 10 ns)
- **Green curve**: **Intramolecular vdw turned off** (G2 has only one main conformation from which it makes a number of excursions over 100 ps)
- **Red curve**: **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



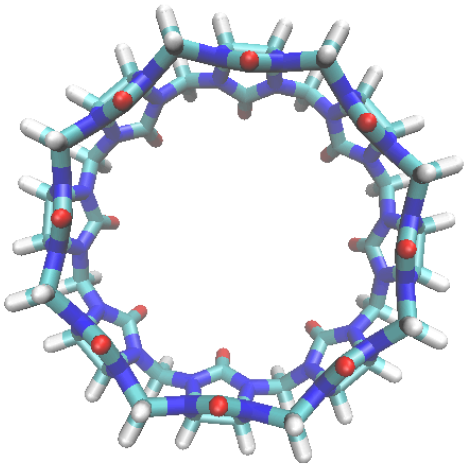
CB8 G2 Solvation 000-000

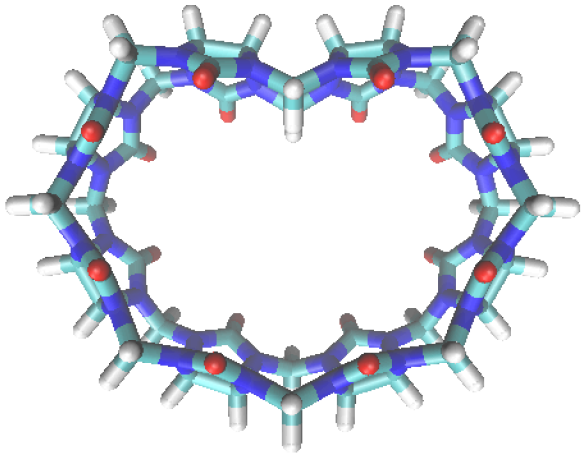


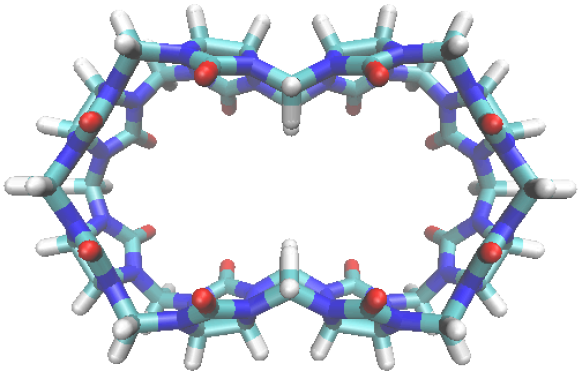
CB8 G2 Host-Guest 000-000

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)





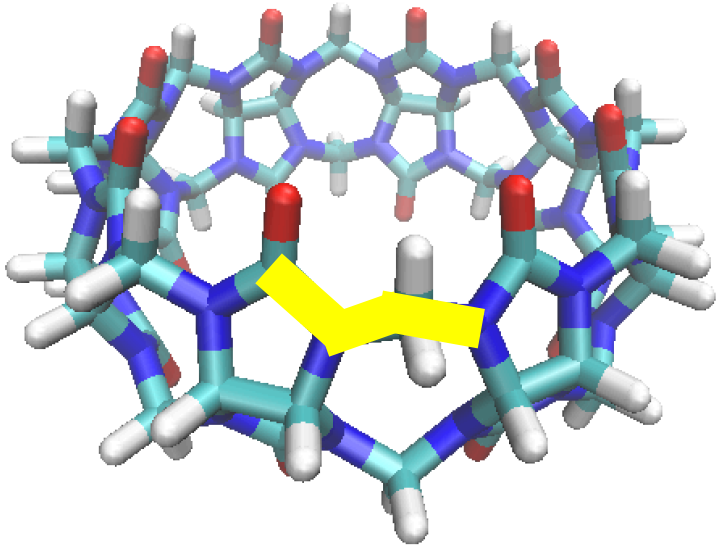


What we learned: CB8

Molecule	ωB97X-D/6-311G(1d,1p)	AMOEBA Tors. at -0.25	AMOEBA Tors. at -1.50	AMOEBA Tors. at -1.70
CB7-CB7 Indentation	-20.89	-12.52	-19.91	-21.07
CB8-CB8 Indentation	-13.91	-6.96	-12.99	-13.98
CB8-CB8 Indentation x 2	-23.35	-11.43	-22.04	-23.65
CB8 Indentation-CB8 Indentation x 2	-9.44	-4.47	-9.04	-9.67

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

Guest	Original	Post-mod	Expt.
G0	-8.51	-8.87[a]	-6.69
G1	-8.88		-7.65
G2	-15.76	-11.18[a] -10.57[b]	-7.66
G3	-16.06		-6.45
G13	-3.61	-4.51[a]	-7.11

[A] Torsion parameter set to -1.50
[B] Torsion parameter set to -2.25

Units: kcal/mol

Acknowledgements

- D3R/SAMPL6 Organizers
- Jay W. Ponder and Lab
  - Zhi Wang (Graduate student)
  - Aaron Gordon (Undergrad)

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