Binding free energy: What did you learn?

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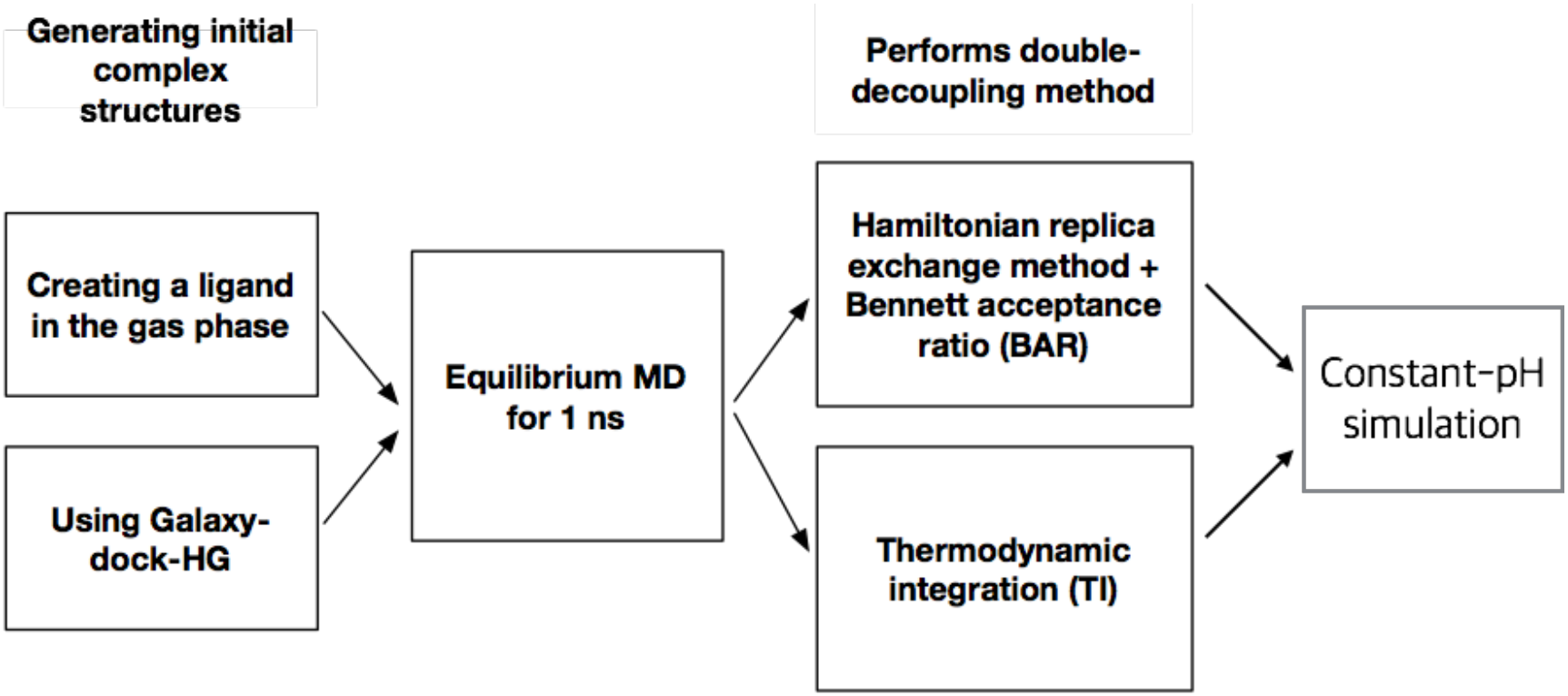
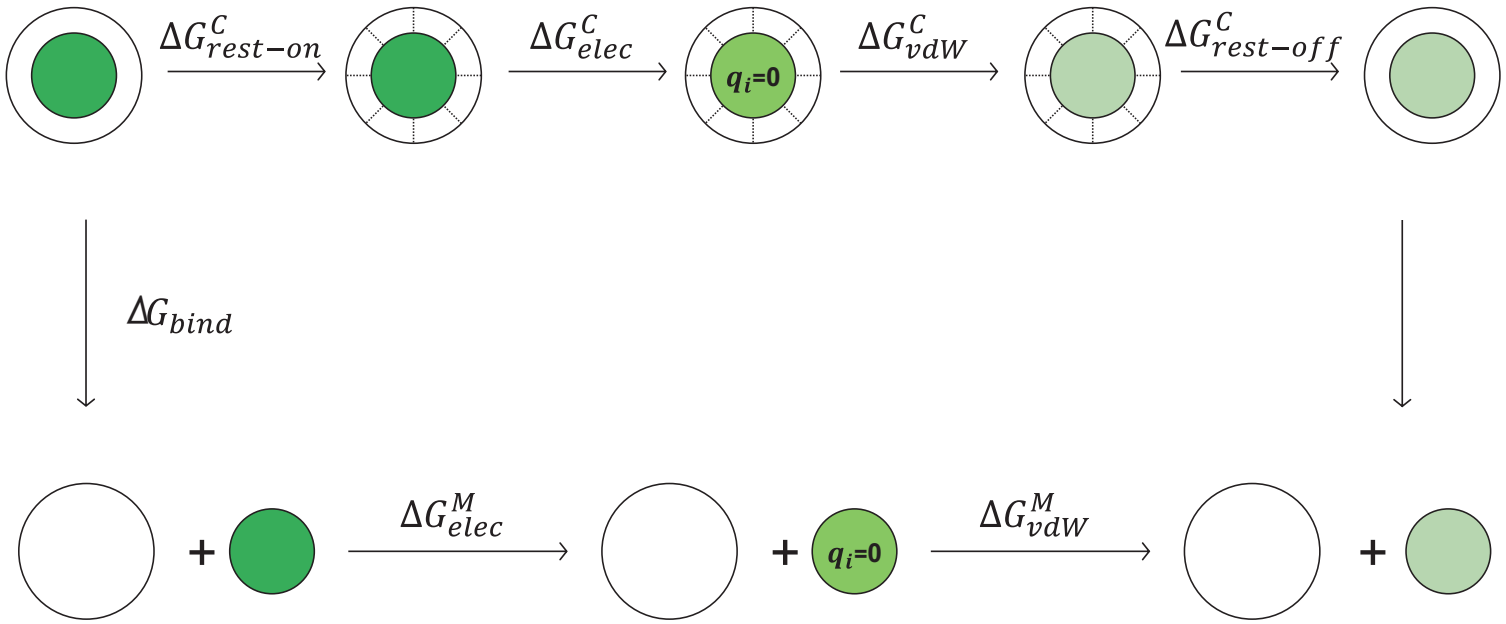
Free energy calculation procedure



We iterated the binding free energy calculation step:

- 3 times for CBClip systems
- 3-12 times for OAH/OAMe systems

The Double-Decoupling Method (DDM)



$$\Delta G_{bind} = \Delta G^{C}_{rest-on} + \Delta G^{C}_{elec} + \Delta G^{C}_{vdW} + \Delta G^{C}_{rest-off} - \Delta G^{M}_{vdW} - G^{M}_{elec}$$

Gilson, M. K., Given, J. A, Bush, B. L. & McCammon, J. A. Biophys. J. 72, 1047–1069 (1997)

Boresch, S. et al., J. Phys. Chem. B. 9535–9551 (2003)

Ionic concentration

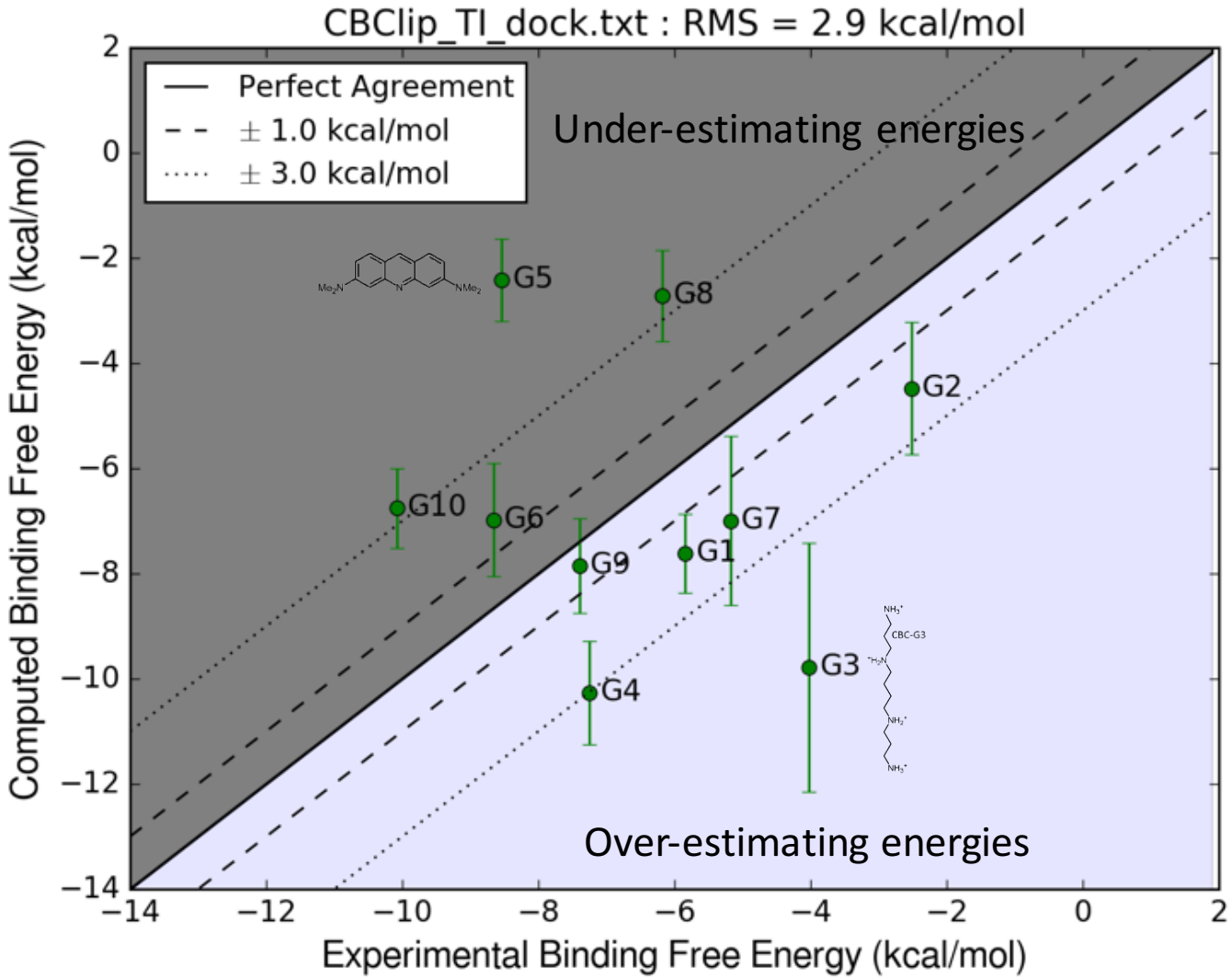
Na_3PO_4 ionic concentrations used experimentally:

- 20 mM @ pH 7.4 for CBClip
- 10 mM @ pH 11.5 for G1-G5 in OAH/OAMe G1-G5
- 50 mM @ pH 11.5 for G6 in OAH/OAMe

By using the ionic strength, we translated them into NaCl solutions:

- 50 mM NaCl
- 25 mM NaCl
- 165 mM NaCl

TI + Docking*



CBClip calculations performed by Dr. Juyong Lee, NIH/NHLBI.

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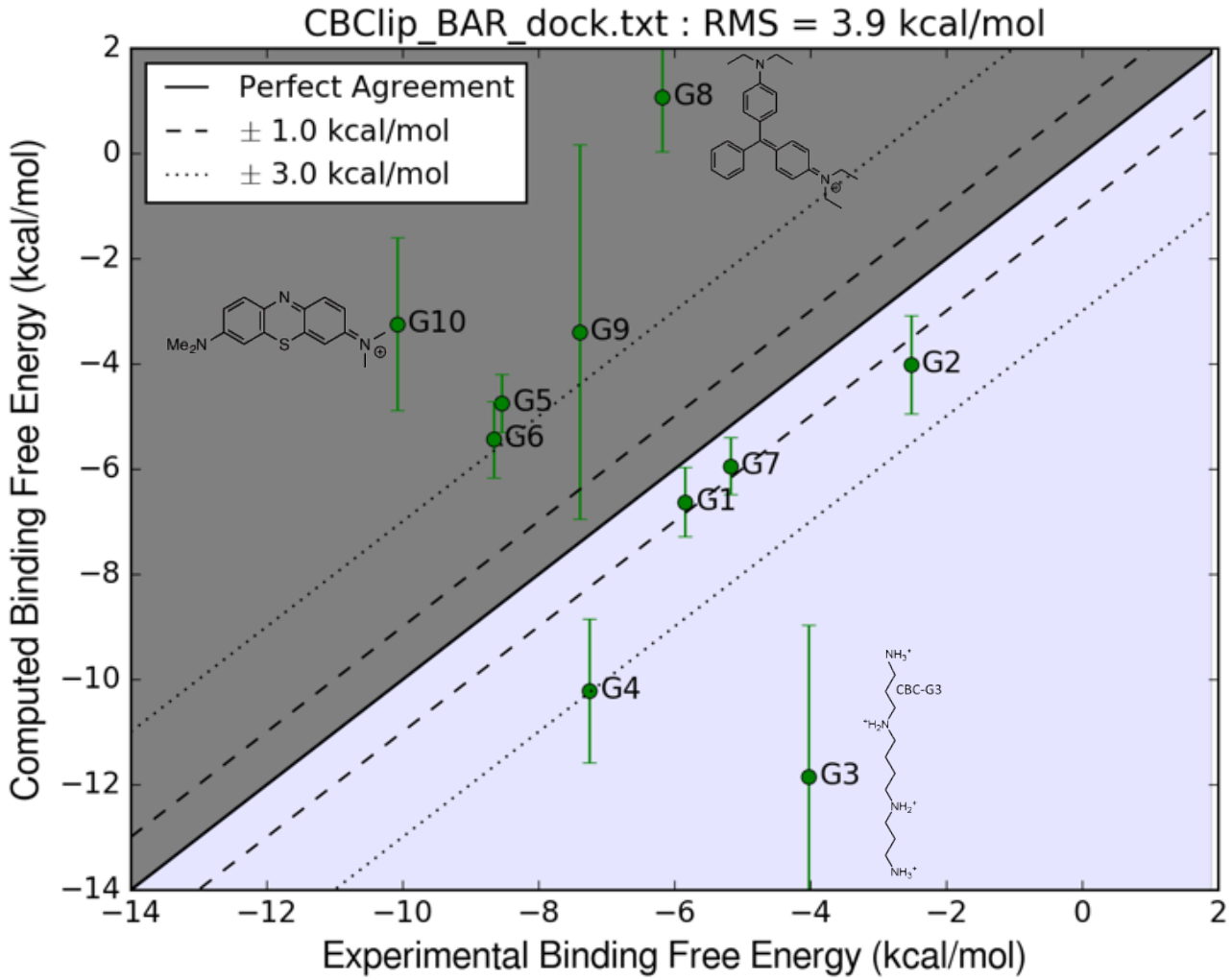
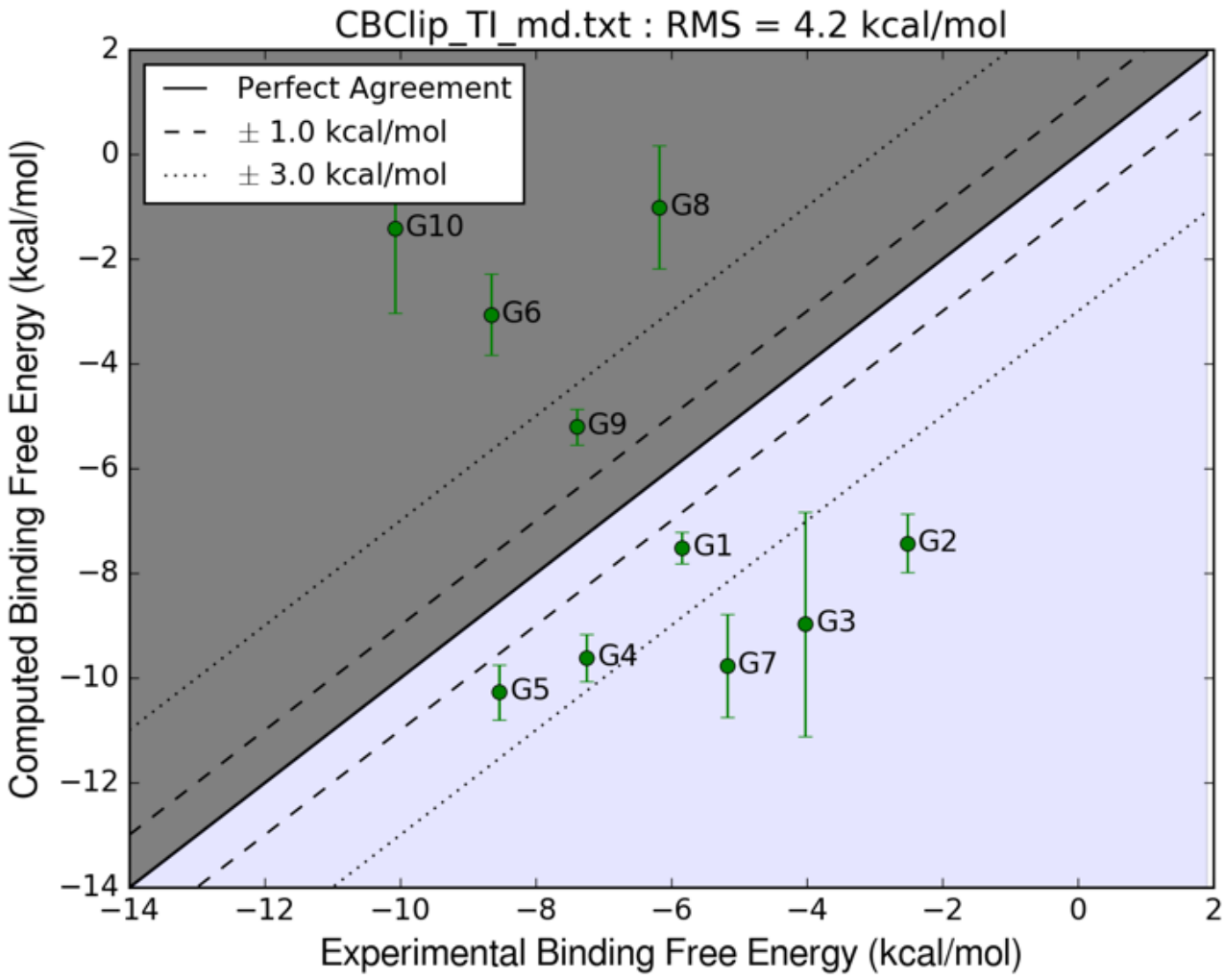
*Submission with the lowest RMS

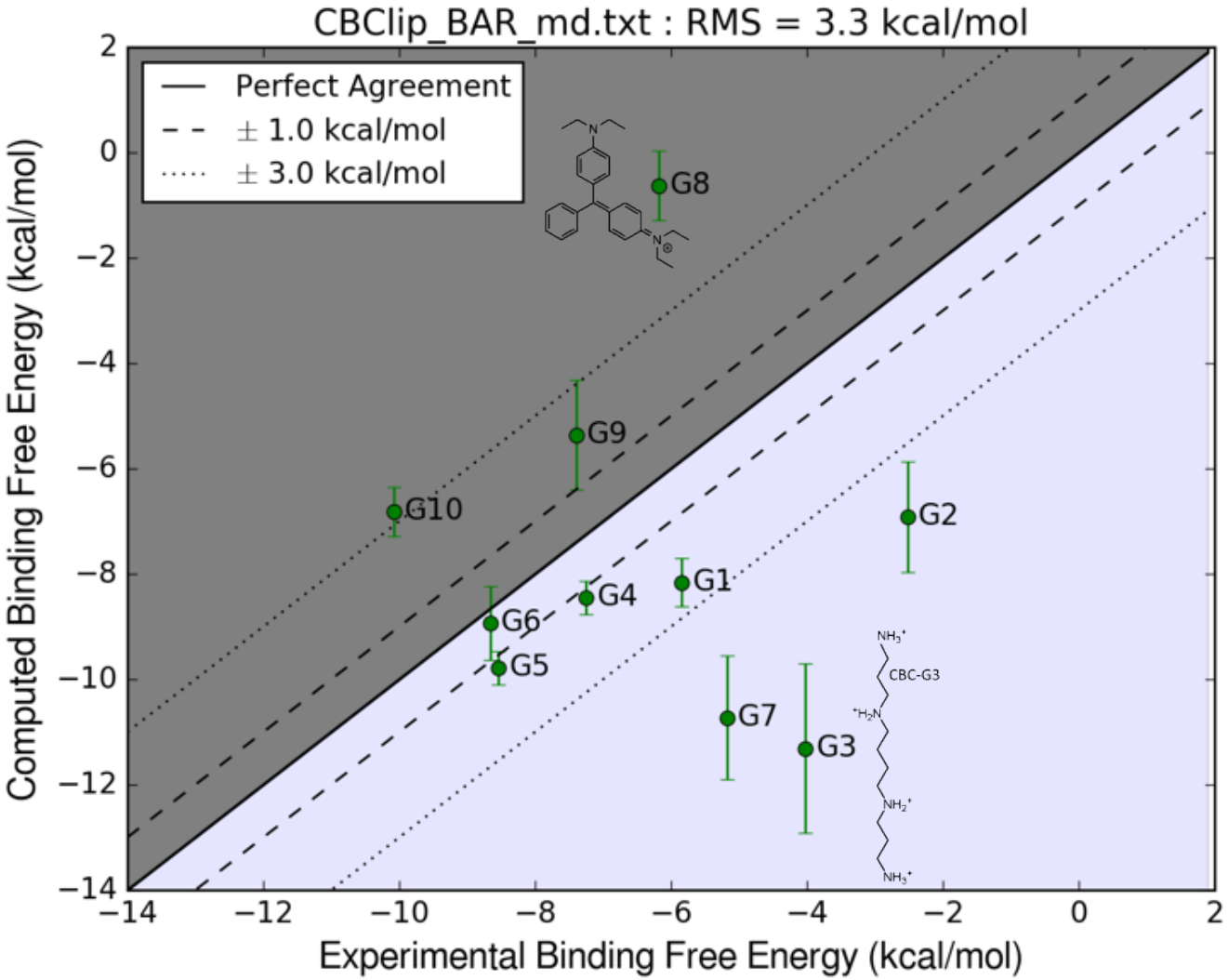
BAR + Docking


CBClip_BAR_dock.txt : RMS = 3.9 kcal/mol
Perfect Agreement
± 1.0 kcal/mol
± 3.0 kcal/mol
G8
G10
G9
G2
G5
G6
G7
G1
G4
G3
CBC-G3
Computed Binding Free Energy (kcal/mol)
Experimental Binding Free Energy (kcal/mol)
2
0
−2
−4
−6
−8
−10
−12
−14

TI + MD

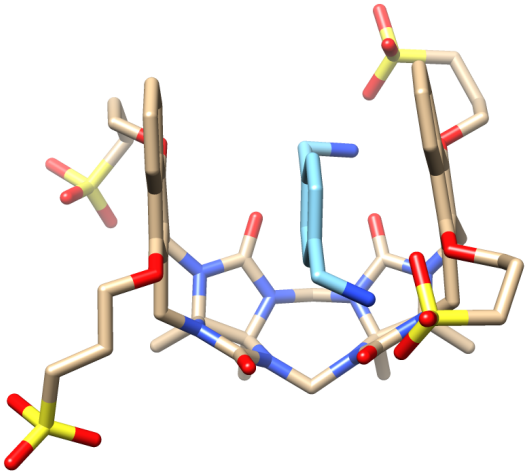

CBClip_TI_md.txt : RMS = 4.2 kcal/mol
Perfect Agreement
± 1.0 kcal/mol
± 3.0 kcal/mol
G10
G8
G6
G9
G1
G2
G3
G4
G7
G5
Computed Binding Free Energy (kcal/mol)
Experimental Binding Free Energy (kcal/mol)
2
0
−2
−4
−6
−8
−10
−12
−14

BAR + MD



G3: consistently over-estimating the binding energy

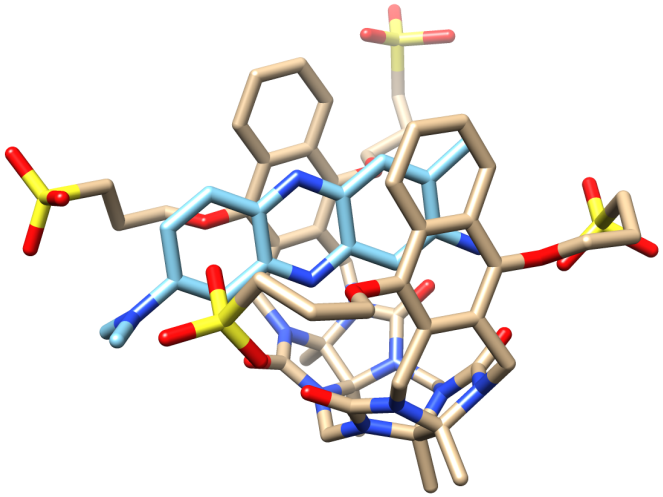
What went right: G1



Predicted binding pose

	Binding affinity (kcal/mol)
Experiment	-5.84
Calculation (TI + DOCK)	-7.61 (0.75)

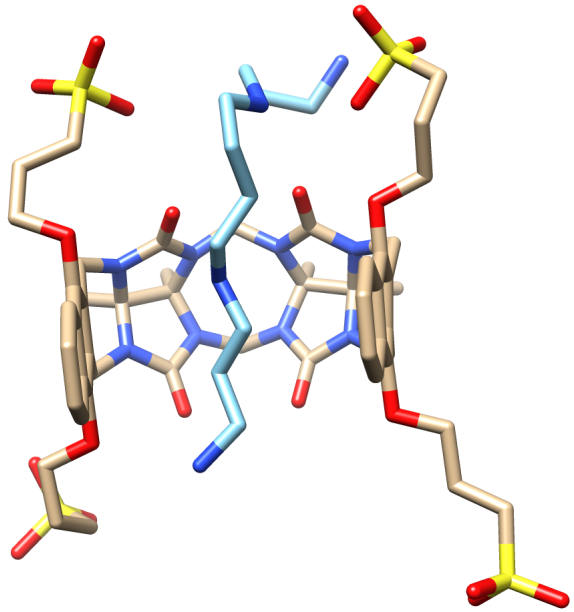
What went right: G9



Predicted binding pose

	Binding affinity (kcal/mol)
Experiment	-7.40
Calculation (TI + DOCK)	-7.85 (0.90)

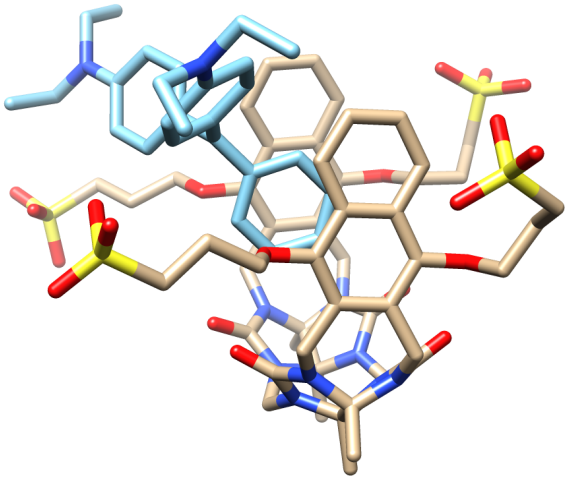
What went wrong: G3



Predicted binding pose

	Binding affinity (kcal/mol)
Experiment	-4.02
Calculation (TI + DOCK)	-9.78 (2.36)

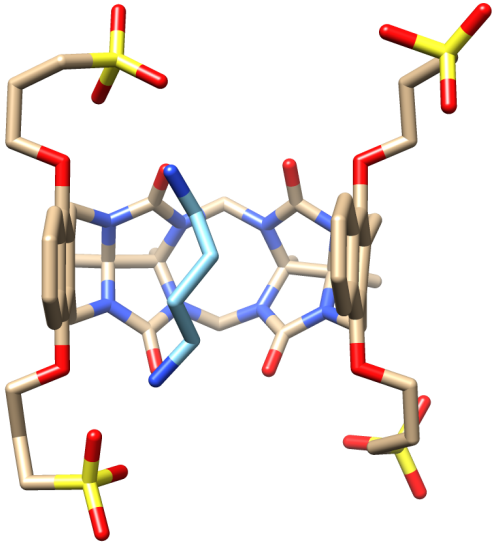
What went wrong: G8



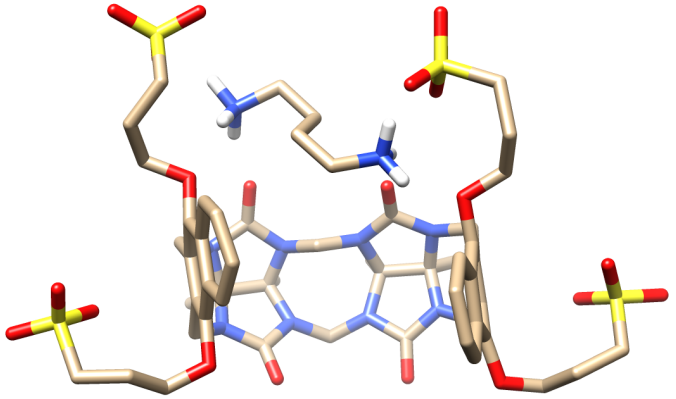
Predicted binding pose

	Binding affinity (kcal/mol)
Experiment	-6.18
Calculation (TI + DOCK)	-2.71 (0.87)

G2

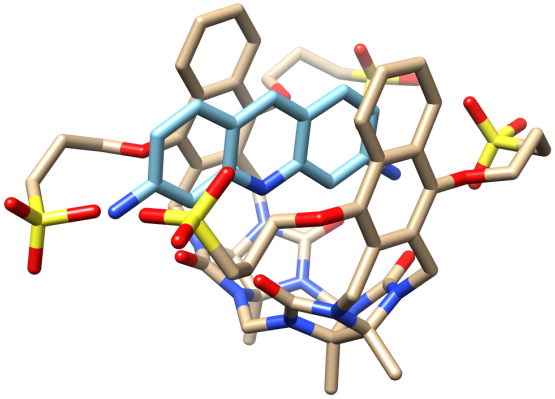


Docking result

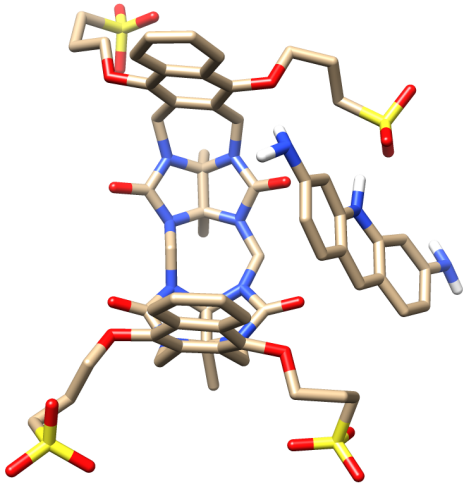


Gas phase simulation result

G4

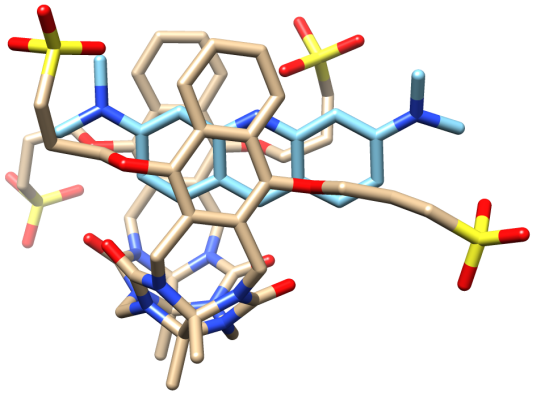


Docking result

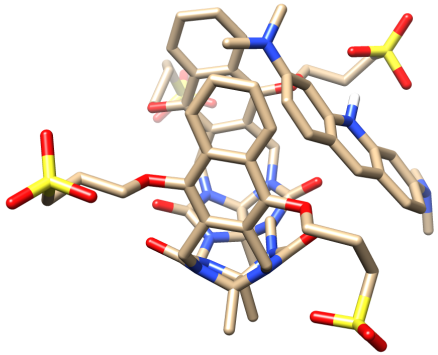


Gas phase simulation result

G5

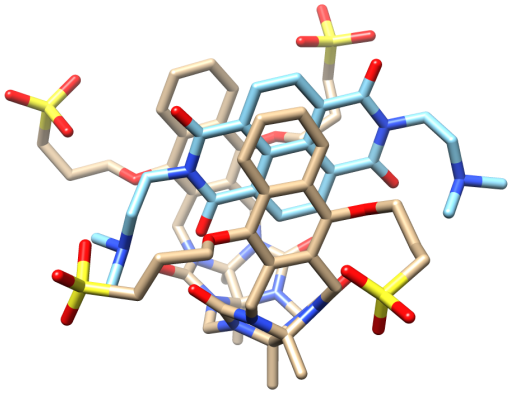


Docking result

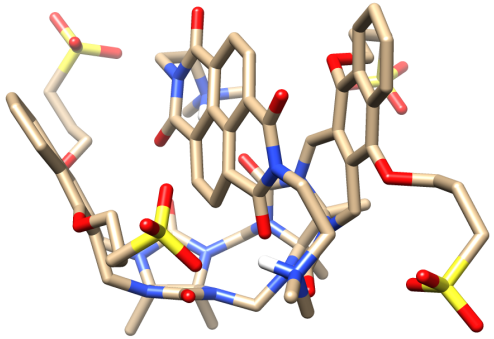


Gas phase simulation result

G6



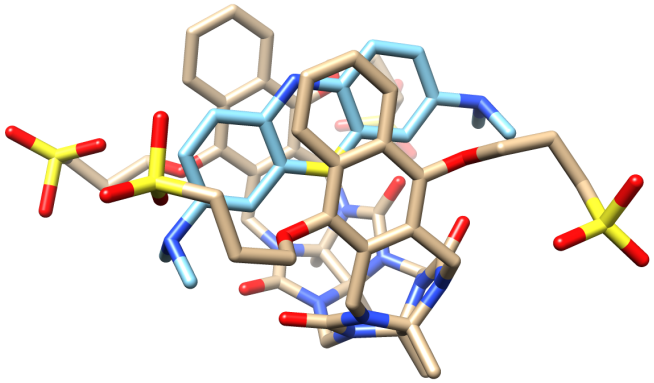
Docking result



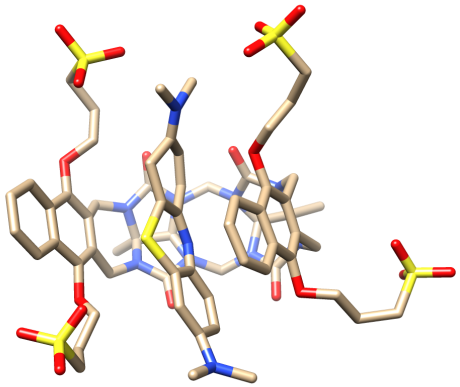
Gas phase simulation result

CBClip has an open conformation.

G10



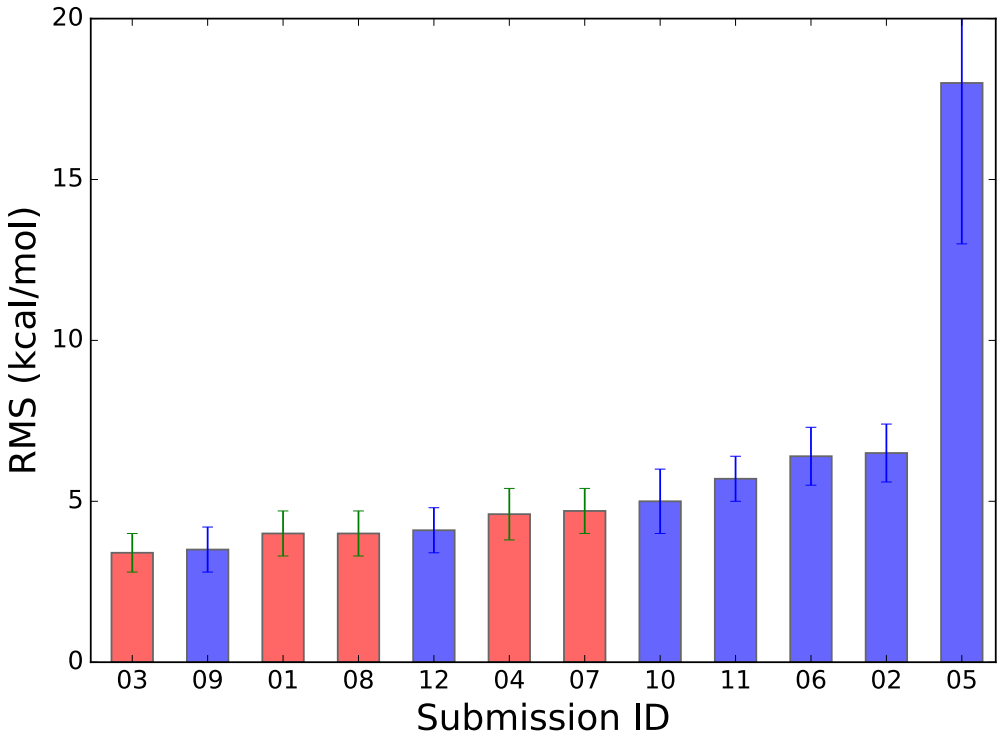
Docking result



Gas phase simulation result

CBClip has a semi-open conformation.

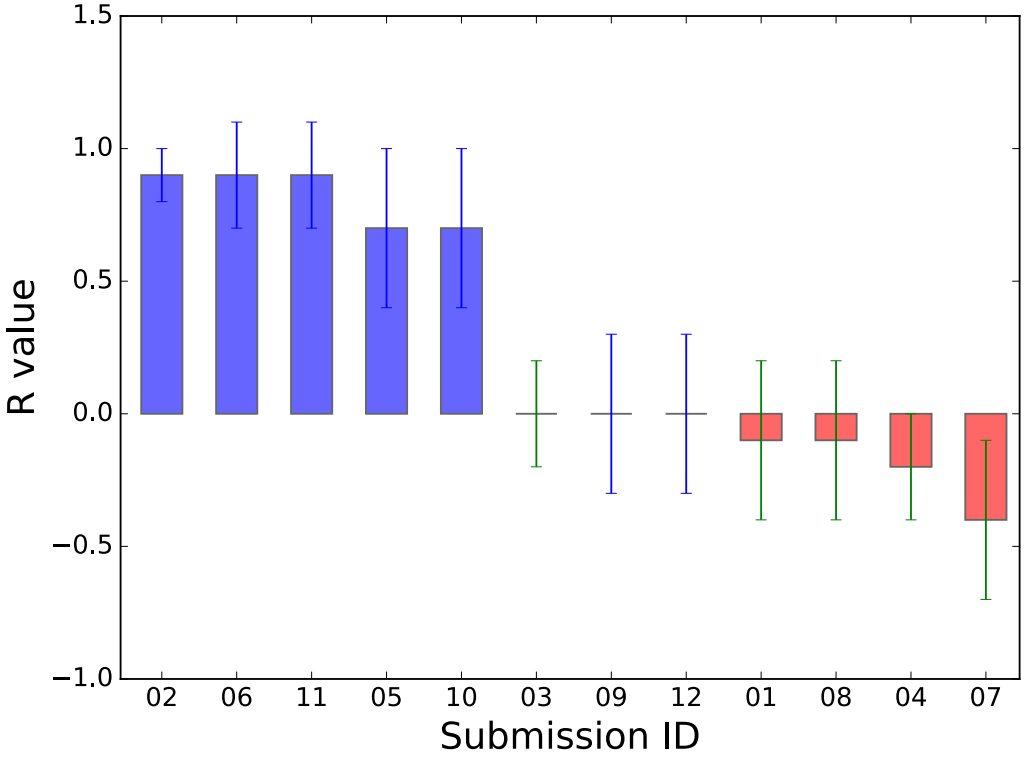
RMS errors of all CBClip submissions



Submission #	Method Name
1	CHARMM/CGENFF/BAR/TI/TIP3P/GALAXY-DOCK/DOCKING
2	SOMD/AM1BCC-GAFF-TIP3P/MBAR/A
3	CHARMM/CGENFF/TI/TIP3P/GALAXY-DOCK/DOCKING
4	CHARMM/CGENFF/BAR/TIP3P/GALAXY-DOCK/DOCKING
5	SOMD/AM1BCC-GAFF-TIP3P/MBAR/D
6	SOMD/AM1BCC-GAFF-TIP3P/MBAR/B
7	CHARMM/CGENFF/TI/TIP3P
8	CHARMM/CGENFF/BAR/TIP3P
9	MT-1 binding free energy
10	HSA/BEDAM/OPLS2005/AGBNP2
11	SOMD/AM1BCC-GAFF-TIP3P/MBAR/C
12	MT-2 binding free energy

CBClip calculations performed by Dr. Juyong Lee, NIH/NHLBI.

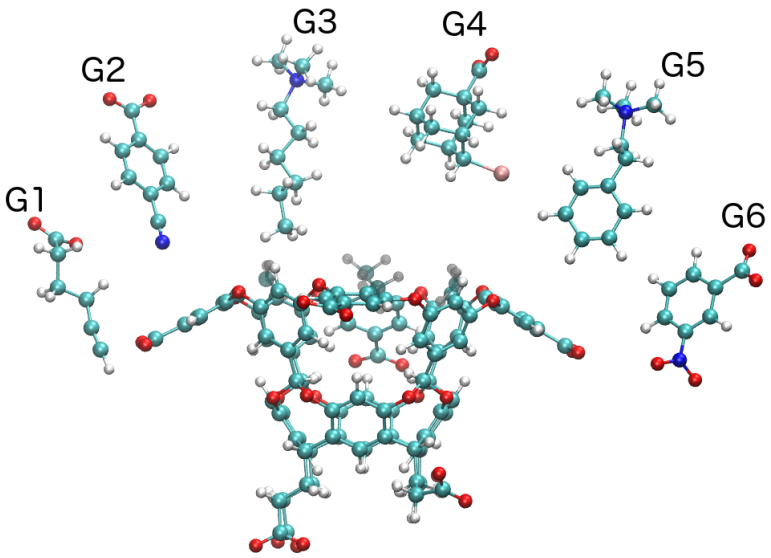
Correlations for CBClip submissions



Submission #	Method Name
1	CHARMM/CGENFF/BAR/TI/TIP3P/GALAXY-DOCK/DOCKING
2	SOMD/AM1BCC-GAFF-TIP3P/MBAR/A
3	CHARMM/CGENFF/TI/TIP3P/GALAXY-DOCK/DOCKING
4	CHARMM/CGENFF/BAR/TIP3P/GALAXY-DOCK/DOCKING
5	SOMD/AM1BCC-GAFF-TIP3P/MBAR/D
6	SOMD/AM1BCC-GAFF-TIP3P/MBAR/B
7	CHARMM/CGENFF/TI/TIP3P
8	CHARMM/CGENFF/BAR/TIP3P
9	MT-1 binding free energy
10	HSA/BEDAM/OPLS2005/AGBNP2
11	SOMD/AM1BCC-GAFF-TIP3P/MBAR/C
12	MT-2 binding free energy

OAH&OAMe Binding energies

OAH/OAMe and guests



Host: charge -8
Guests: charged & neutral

Ions: neutralized & ionic concentration ~ Na_3PO_4

Parameters: ParamChem CGENFF

Explicit solvent

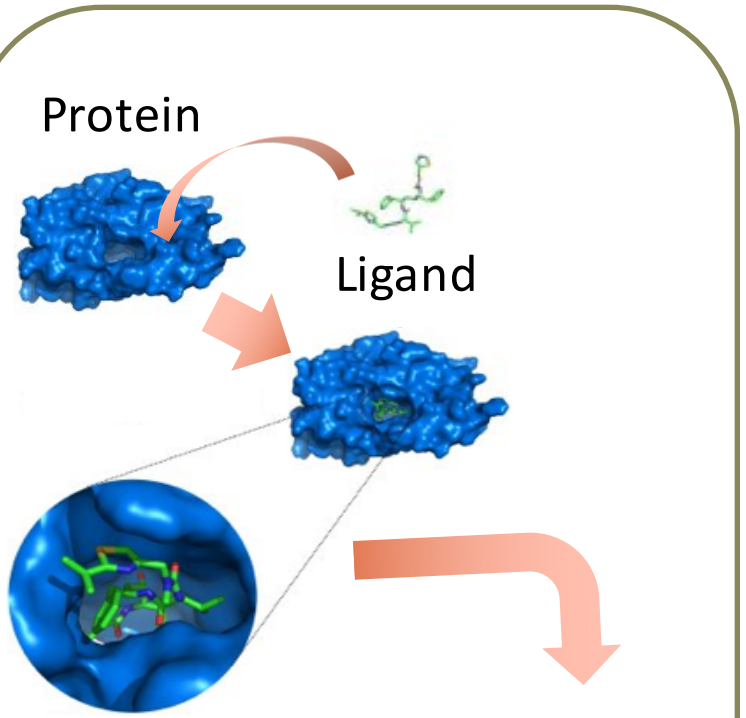
Dry cavity (no water molecules within)

3-12 calculations for each system

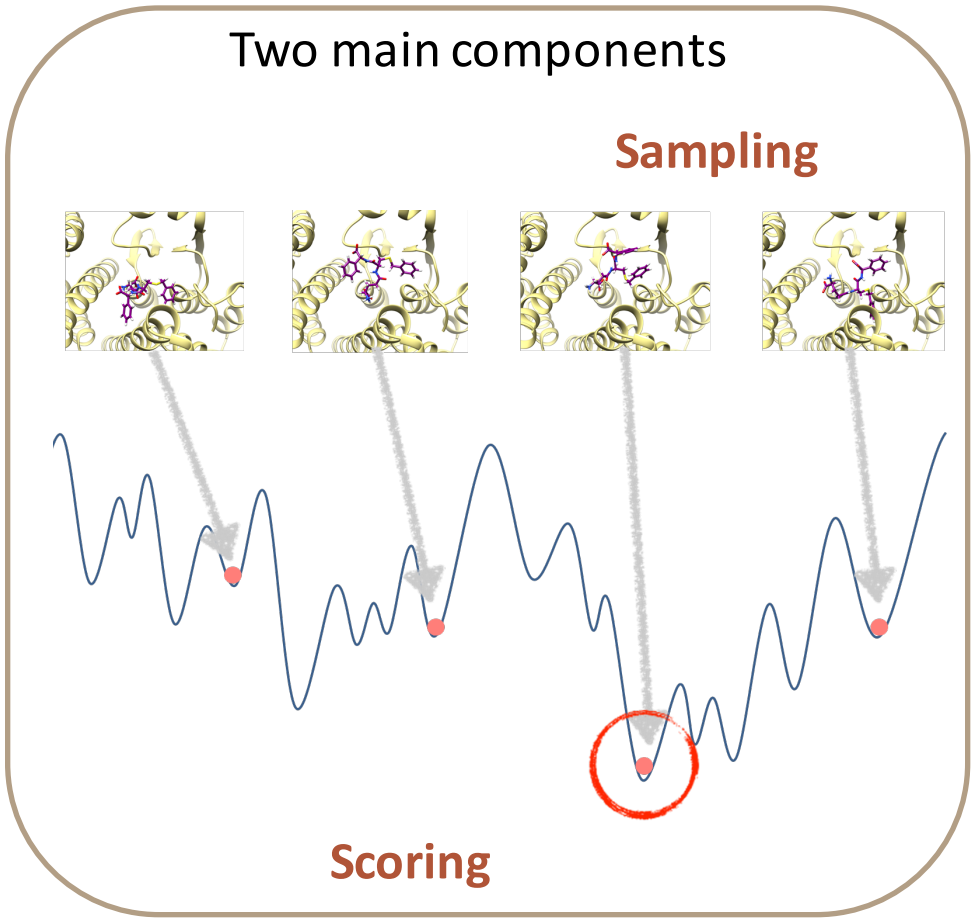
K. Vanommeslaeghe, E. Hatcher, C. Acharya, S. Kundu, S. Zhong, J. Shim, E. Darian, O. Guvench, P. Lopes, I. Vorobyov, A. D. MacKerell Jr.,, *J. Comput. Chem.* 2010, **31**, 671-690

GalaxyDock: Protein-Ligand Docking Program

Goal: predict the binding pose of a given ligand when it is bound to a given protein



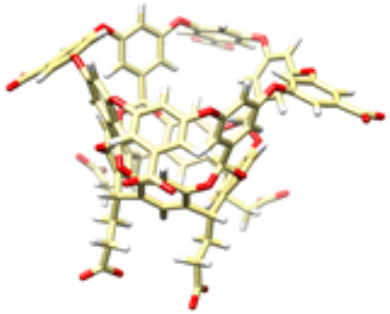
- Important for binding
- Clues to improving affinity



NIH National Heart, Lung, and Blood Institute

W. -H. Shin, J. K. Kim, D. S. Kim, C. Seok, *J. Comput. Chem.* 2013, **34**, 2647

GalaxyDock-HG: Host-Guest Docking



Host

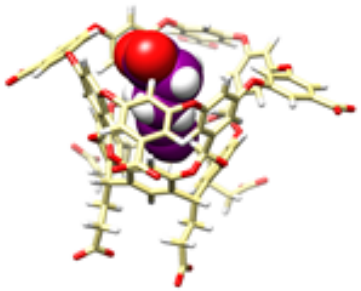
Guest

Randomly generate 50 initial binding poses

Optimize 50 binding poses using CSA with AutoDock4 scoring function

$$E_{\text{AutoDock}} = w_{\text{vdW}} \sum_{i,j} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} \right) + w_{\text{hbond}} \sum_{i,j} h(t_{ij}) \left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}} \right) + w_{\text{elec}} \sum_{i,j} \frac{q_i q_j}{\varepsilon(r_{ij}) r_{ij}} + w_{\text{sol}} \sum_{i,j} (S_i V_j + S_j V_i) \exp\left(-\frac{r_{ij}}{2\sigma^2} \right)$$

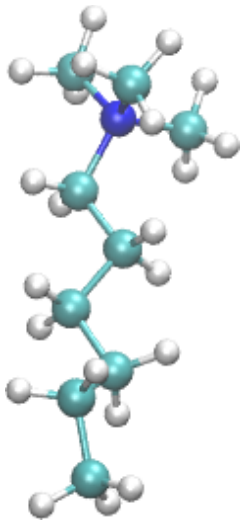
Select final binding pose

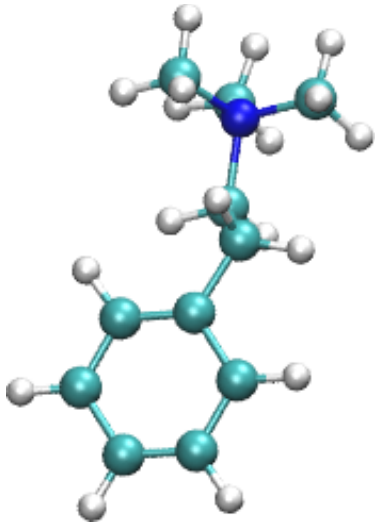


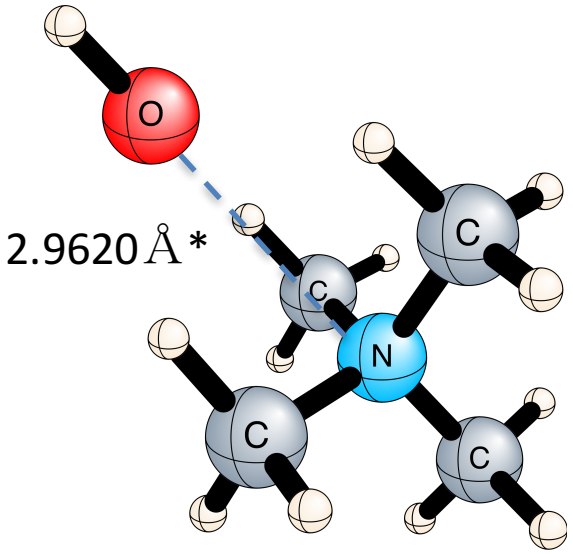
Final result

Select three binding poses for each system -> simulate the lowest

Neutral G3 &G5



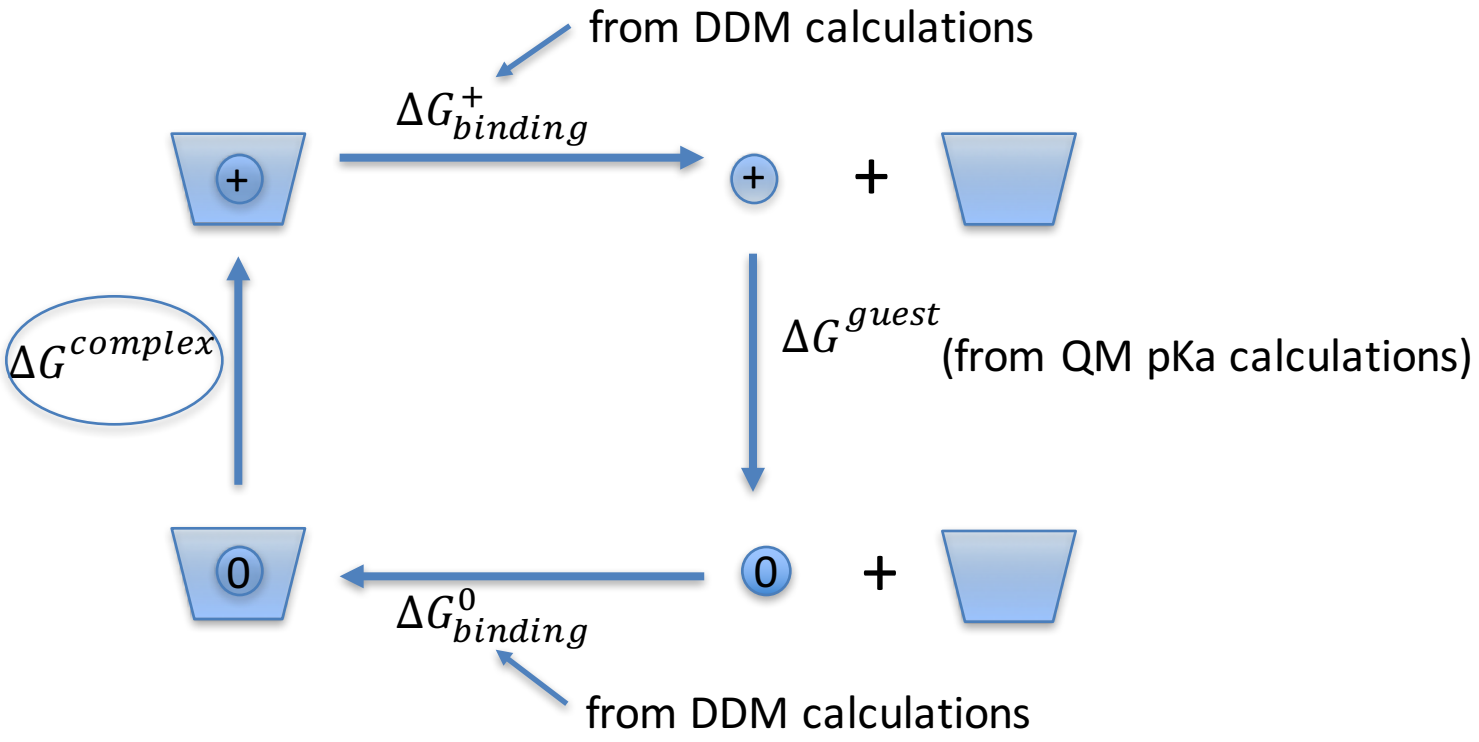




Tetramethyl-ammonium-hydroxide

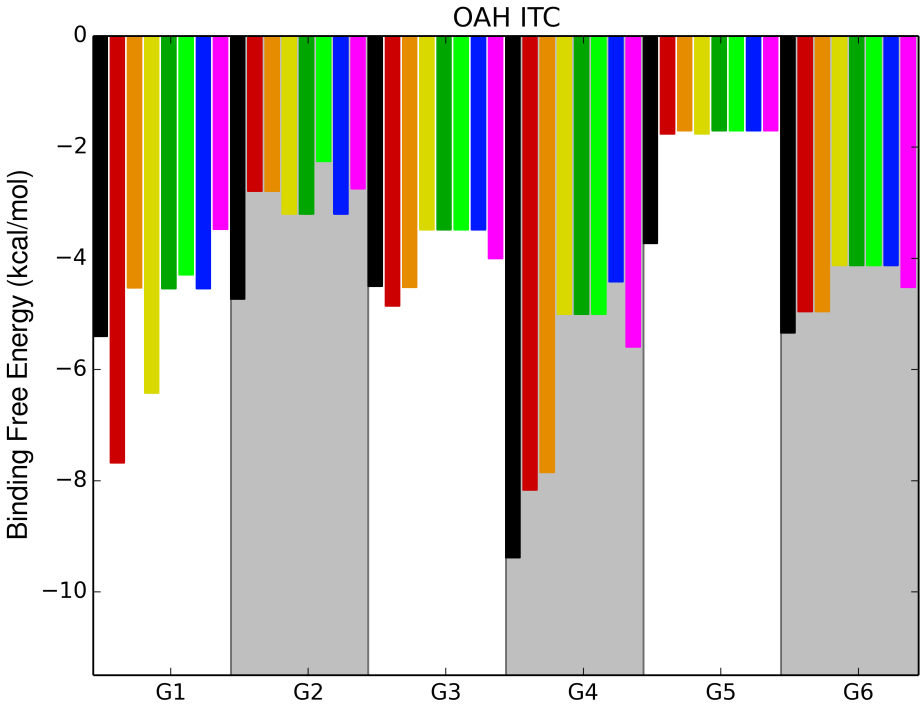
Distance from QM calculations; courtesy of Frank Pickard

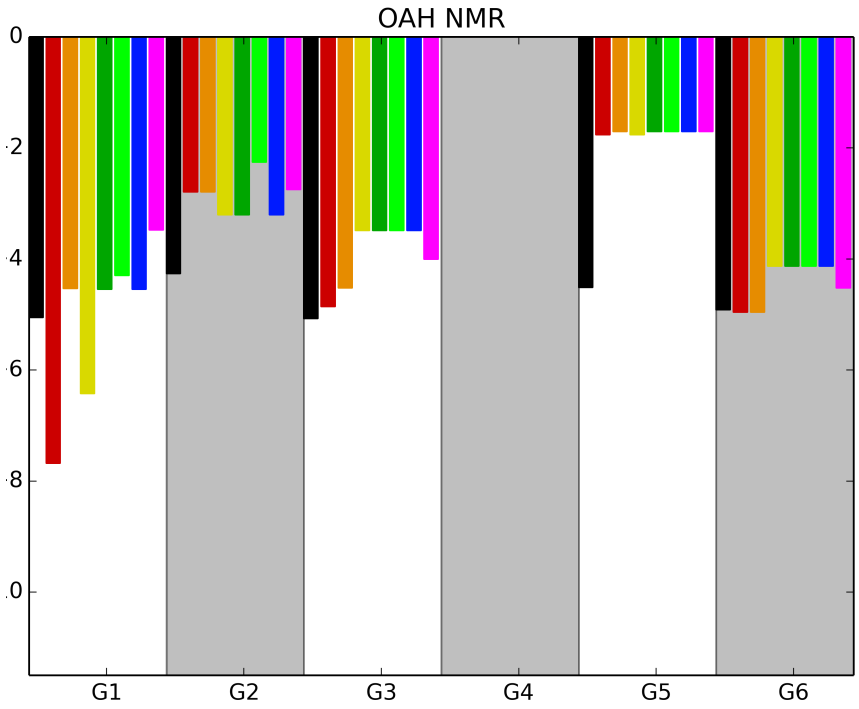
Assessing the guest protonation state in the complex

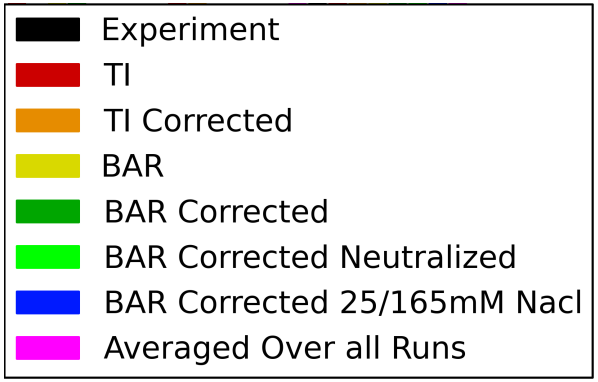


G1, G2, G4, G6 = negatively charged
G3, G5 = neutral

Binding free energy submissions for OAH



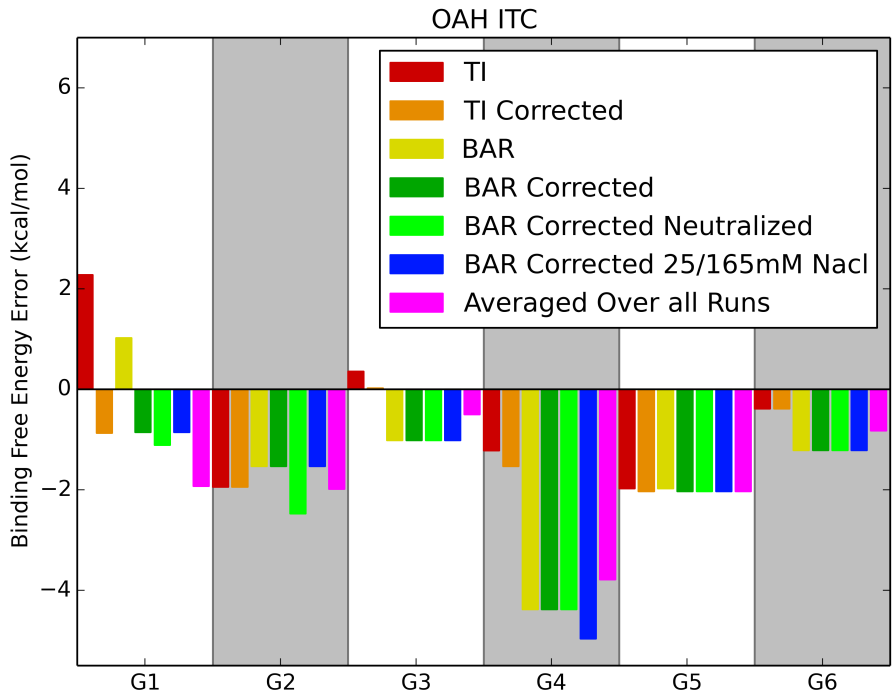


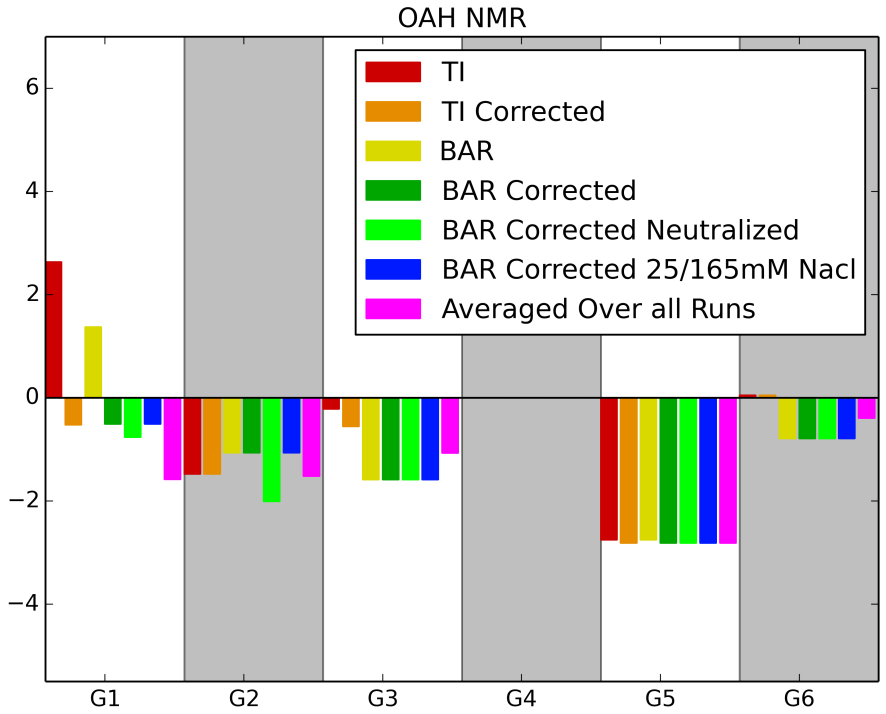


Binding free energies were under-estimated.

No NMR data for G4.

Errors for Binding free energy for OAH



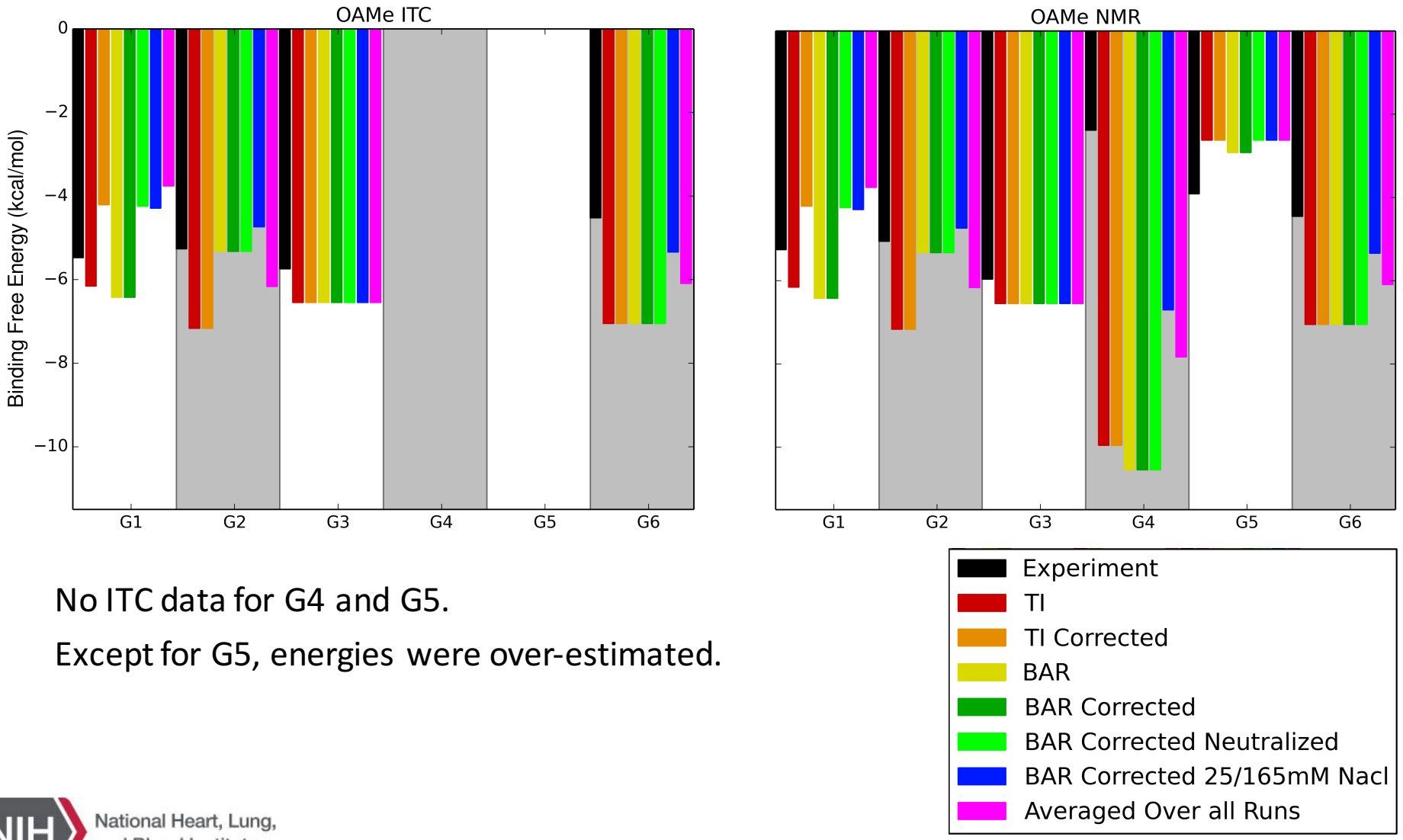


Difference between experimental and each computed value.

Binding free energies were under-estimated.
Highest errors for G4.

Best submission: TI, RMS values= 1.36/1.46

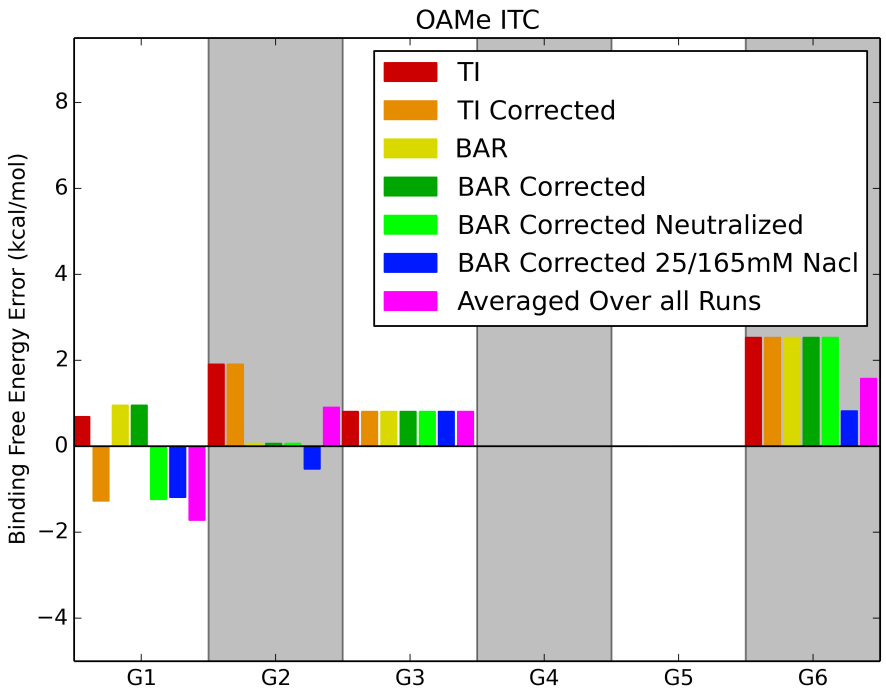
Binding free energy submissions for OAMe

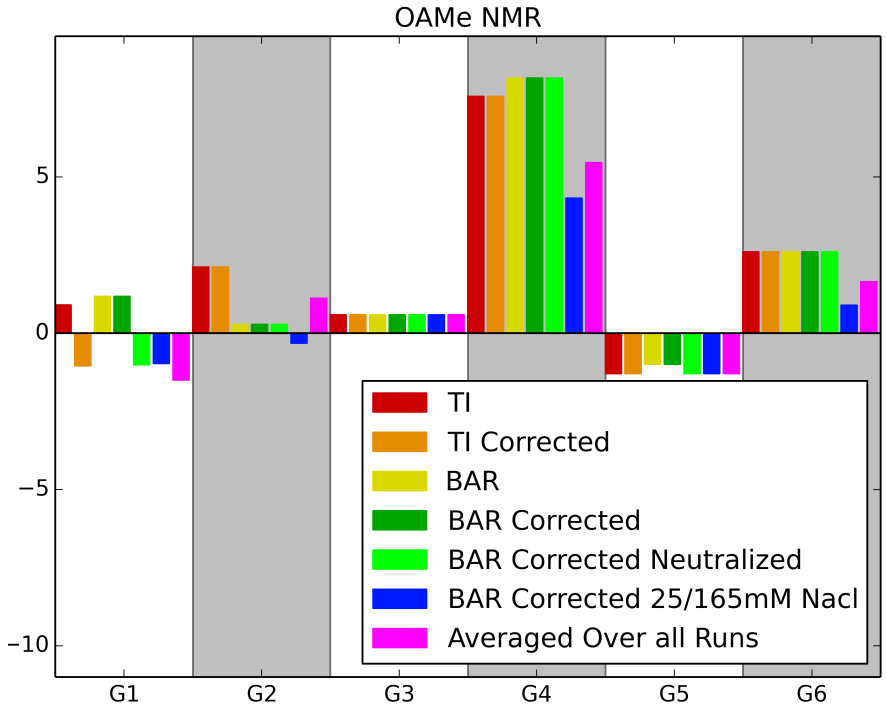


No ITC data for G4 and G5.

Except for G5, energies were over-estimated.

Errors for Binding free energy for OAMe





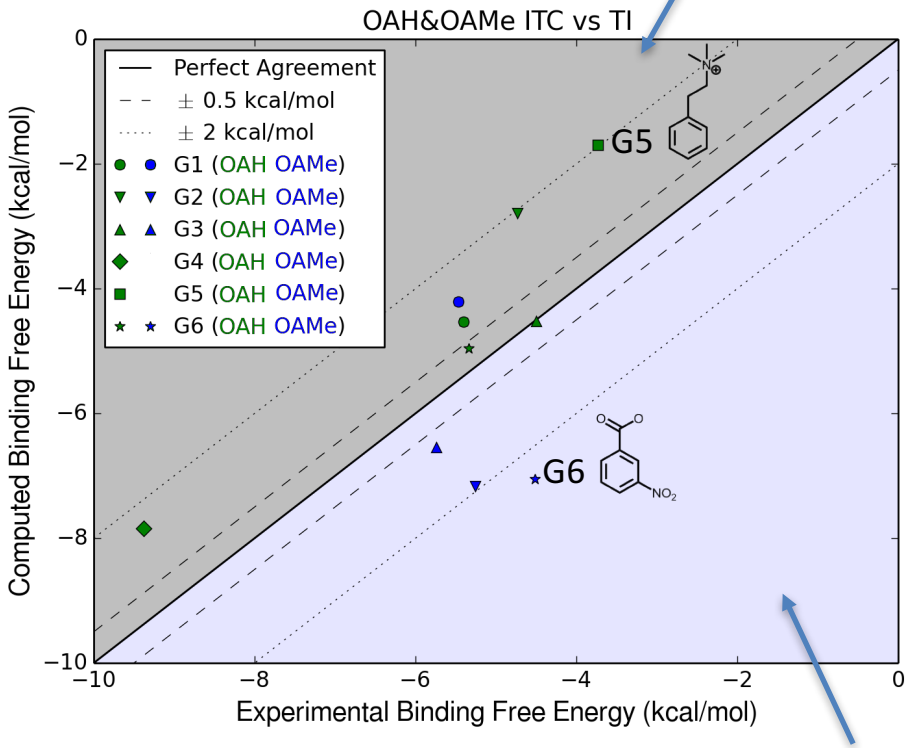
Difference between experimental and each computed value.

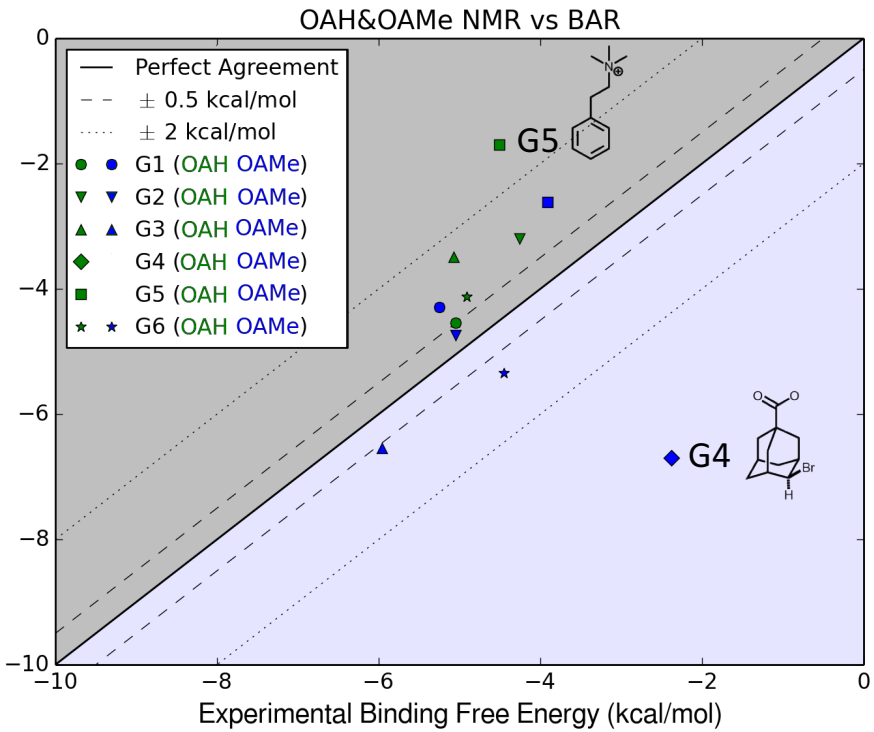
Binding free energies were over-estimated.
Highest errors for G4.

Best submission: BAR, RMS= 0.87, 1.94 kcal/mol

Experimental vs Computational Data

Under-estimating energies



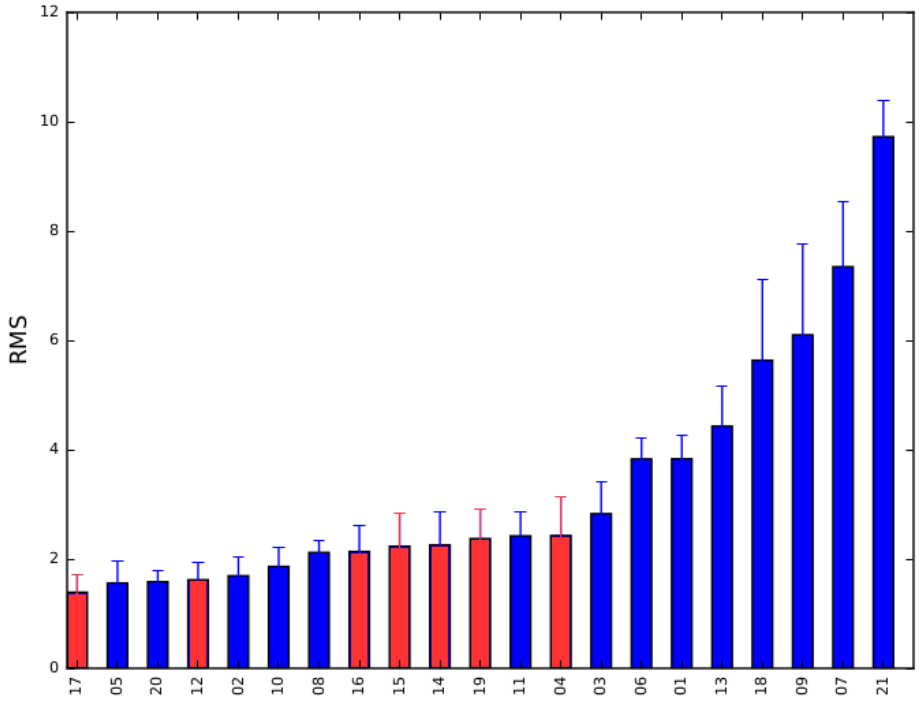


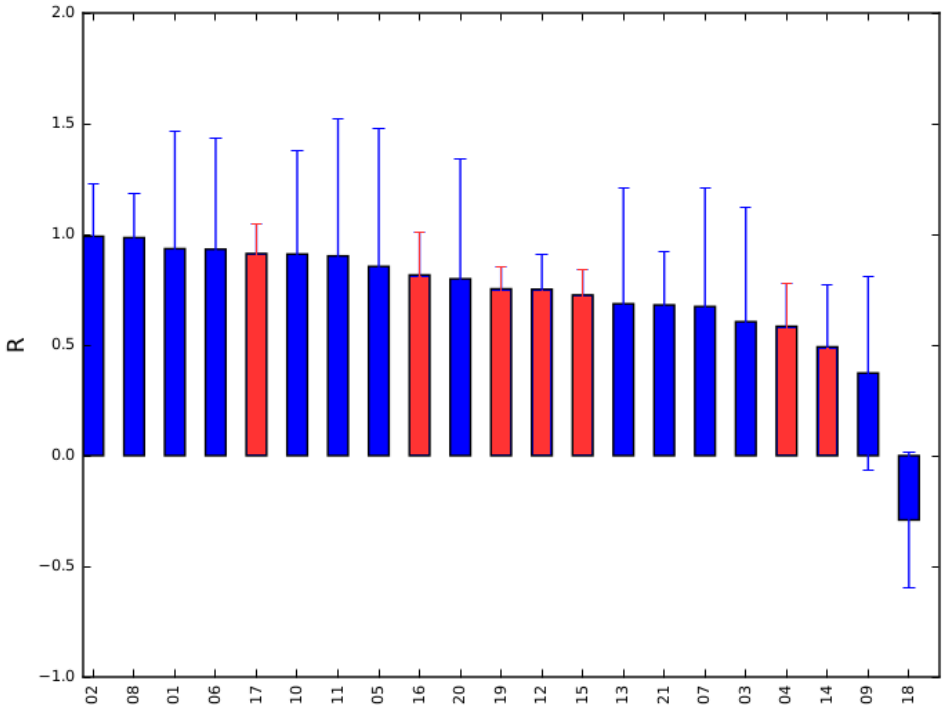
Over-estimating energies

Binding energies were mostly under-estimated.

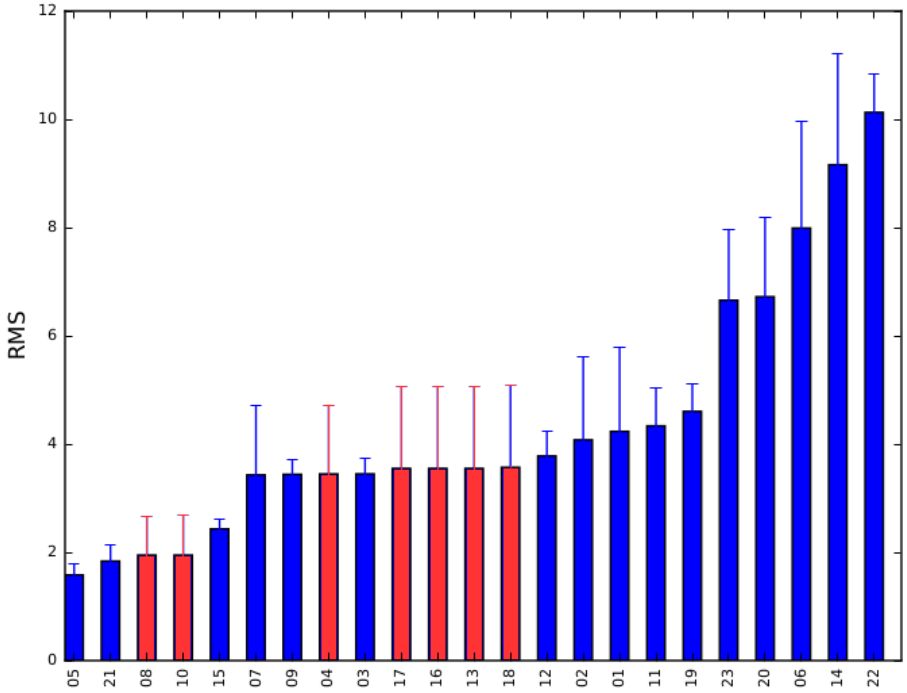
G4 had consistently high errors with respect to experiment. We suspect that either the Br ion needs re-parametrization, or the system is neutral (unlikely).

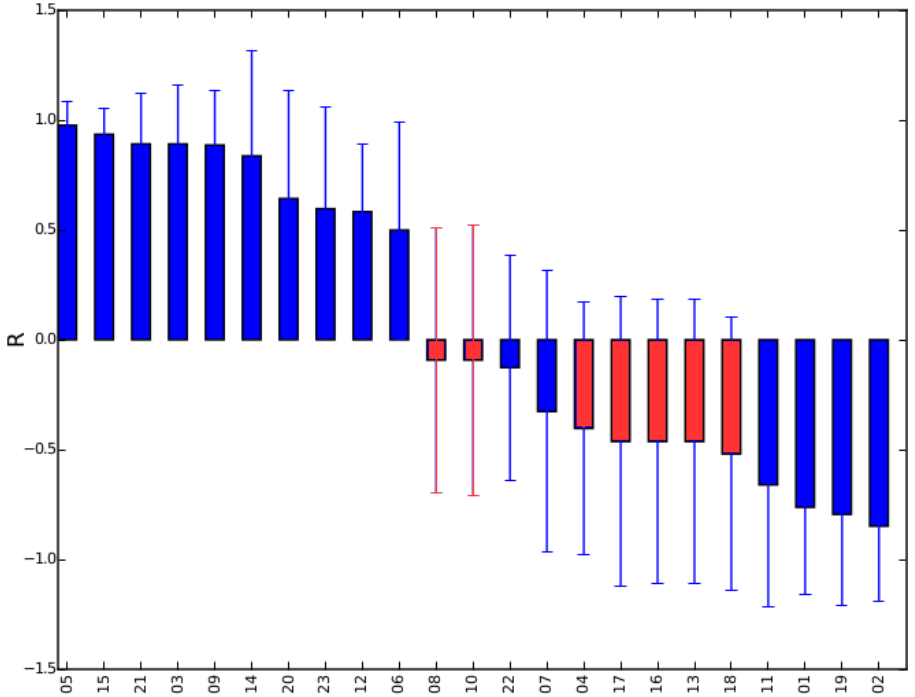
Comparison with others: OAH





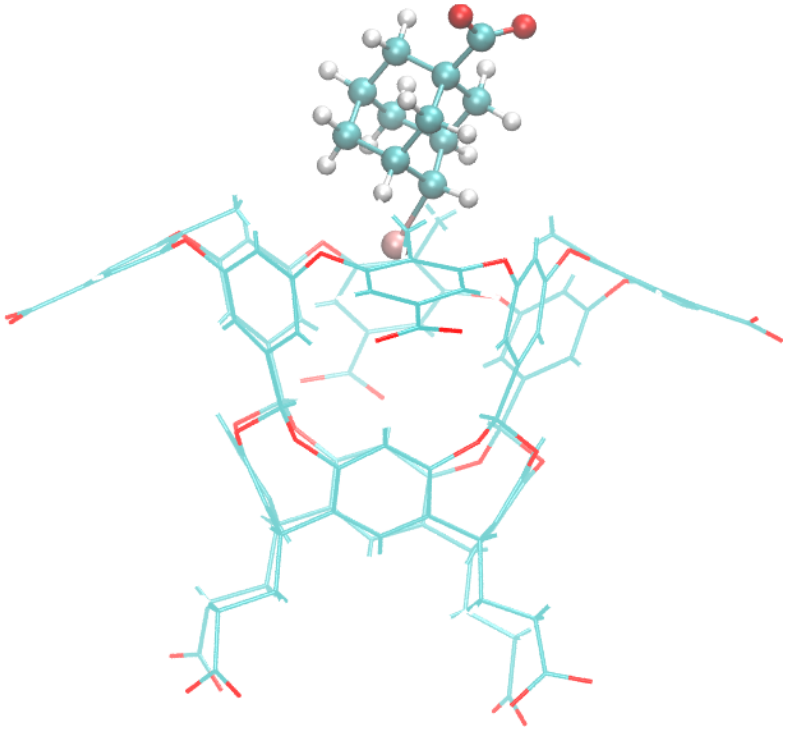
Comparison with others: OAMe



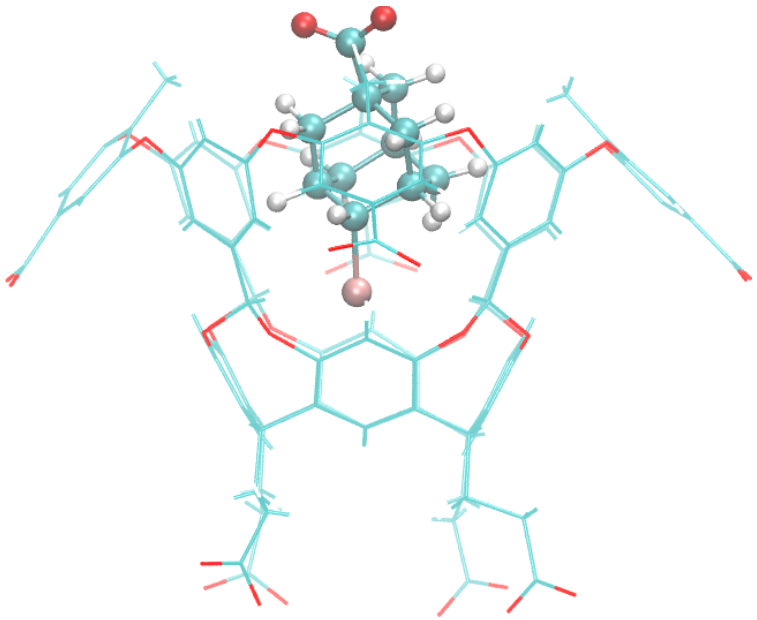


In cavity vs Atop the cavity

OAH

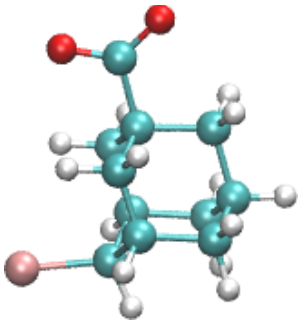


ΔG = -10.541 kcal/mol

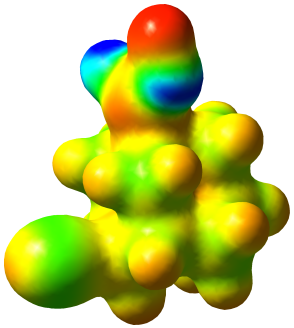


ΔG = -6.4 kcal/mol

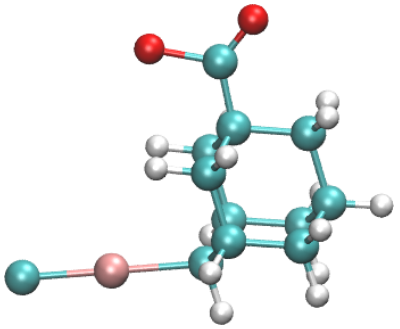
Why did we get the worst results for G4?



Initial parametrization



QM calculation



Lonepair addition*

Analyzing only the charged species

OAH

TI: -7.84 -> -4.30 (kcal/mol)
BAR: -4.89 -> -3.84 (kcal/mol)

Experimental value: -9.38 kcal/mol

OAMe

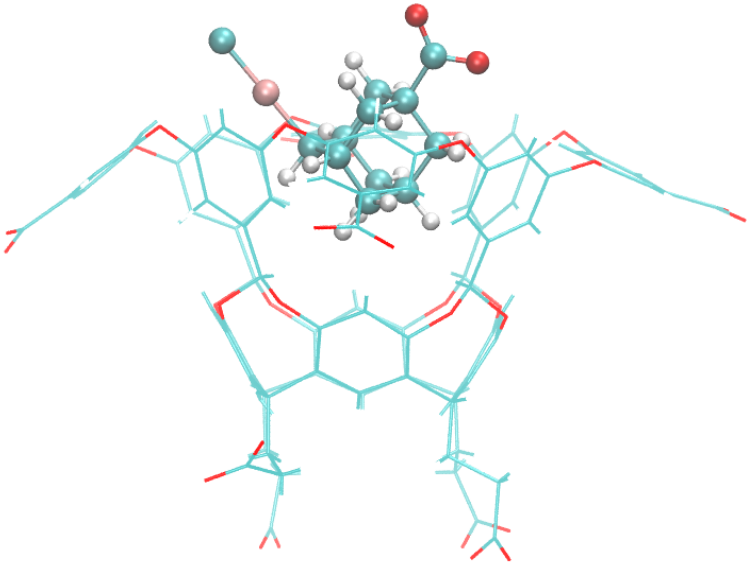
TI: -9.95 -> -0.08 (kcal/mol)
BAR: -10.54 -> 1.55 (kcal/mol)

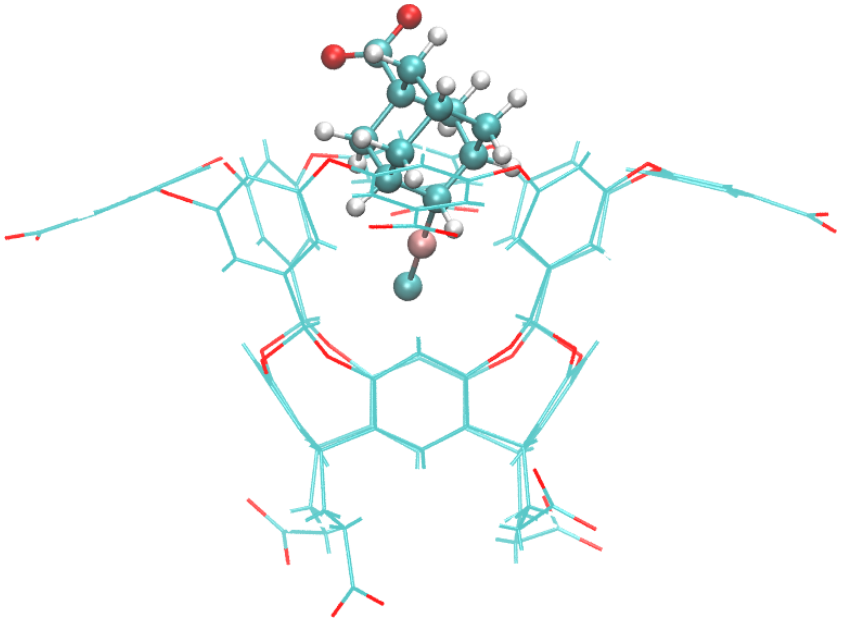
Experimental value: -2.38 kcal/mol

*Parameters from Alex MacKerell's group

Br is inside the cavity -> ΔG is more positive

OAH,
G4+lonepair

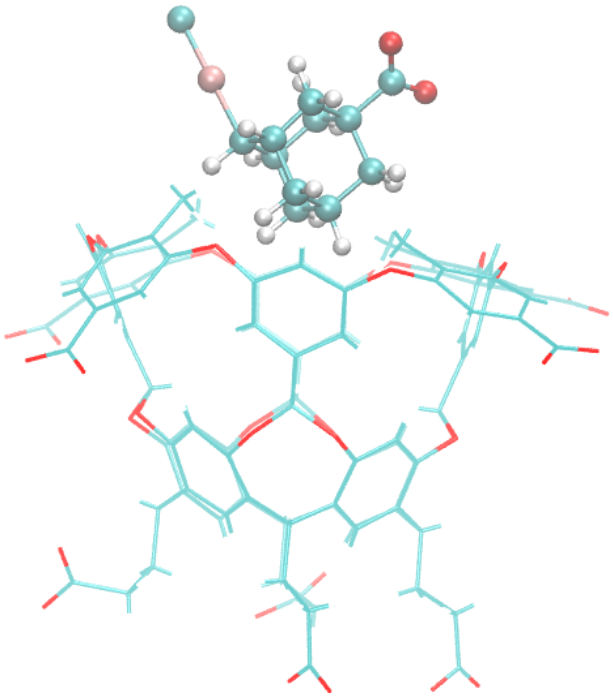


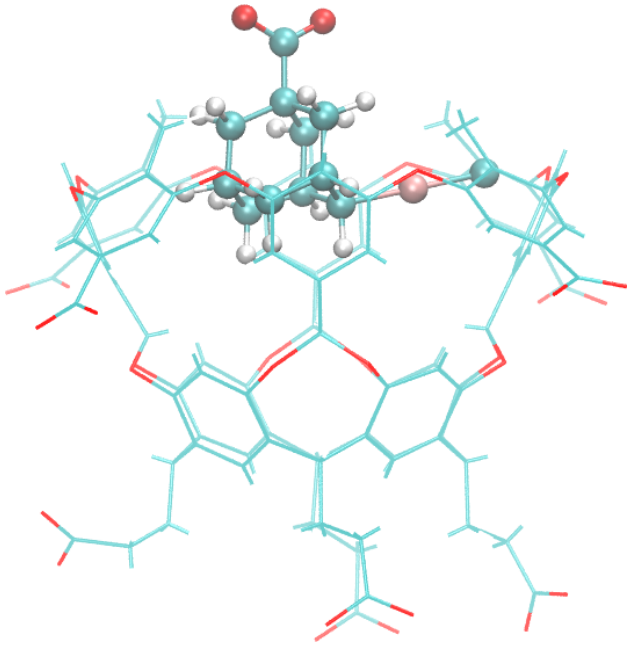


TI	-4.30 kcal/mol	-3.97 kcal/mol
BAR	-3.84 kcal/mol	-2.64 kcal/mol

Br is inside the cavity -> ΔG is more positive

OAMe
G4+lonepair





TI	-0.08 kcal/mol	+2.10 kcal/mol
BAR	+1.55 kcal/mol	+1.96 kcal/mol

Take-home messages

- CBClip: lowest errors for **small/rigid guests**
- Parametrization dictated the **open/close state** of CBClip
- **Ionic concentration** is important
- Treatment of **halogens** is important
- Further analysis of **hydration**

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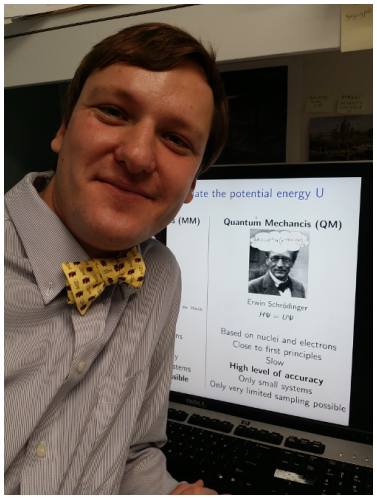
- Bernard Brooks



NIH National Heart, Lung, and Blood Institute