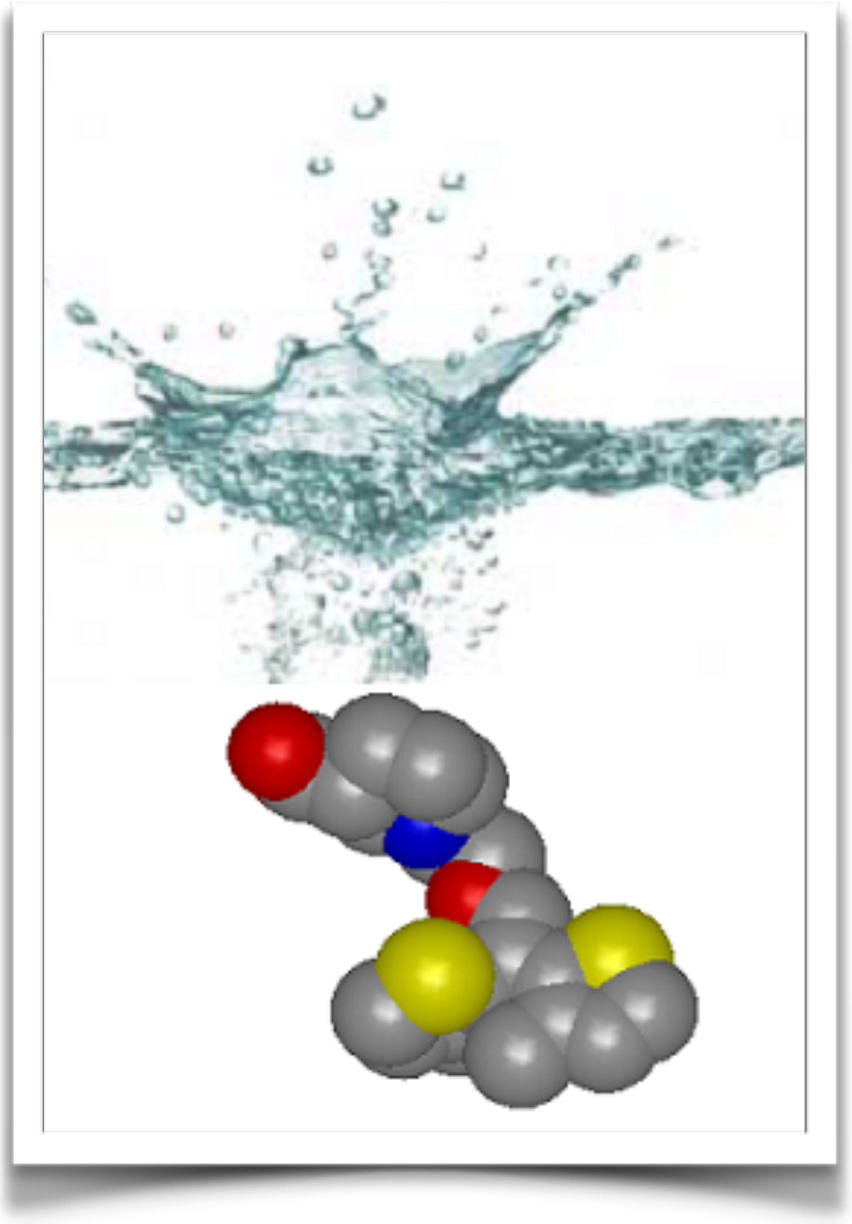
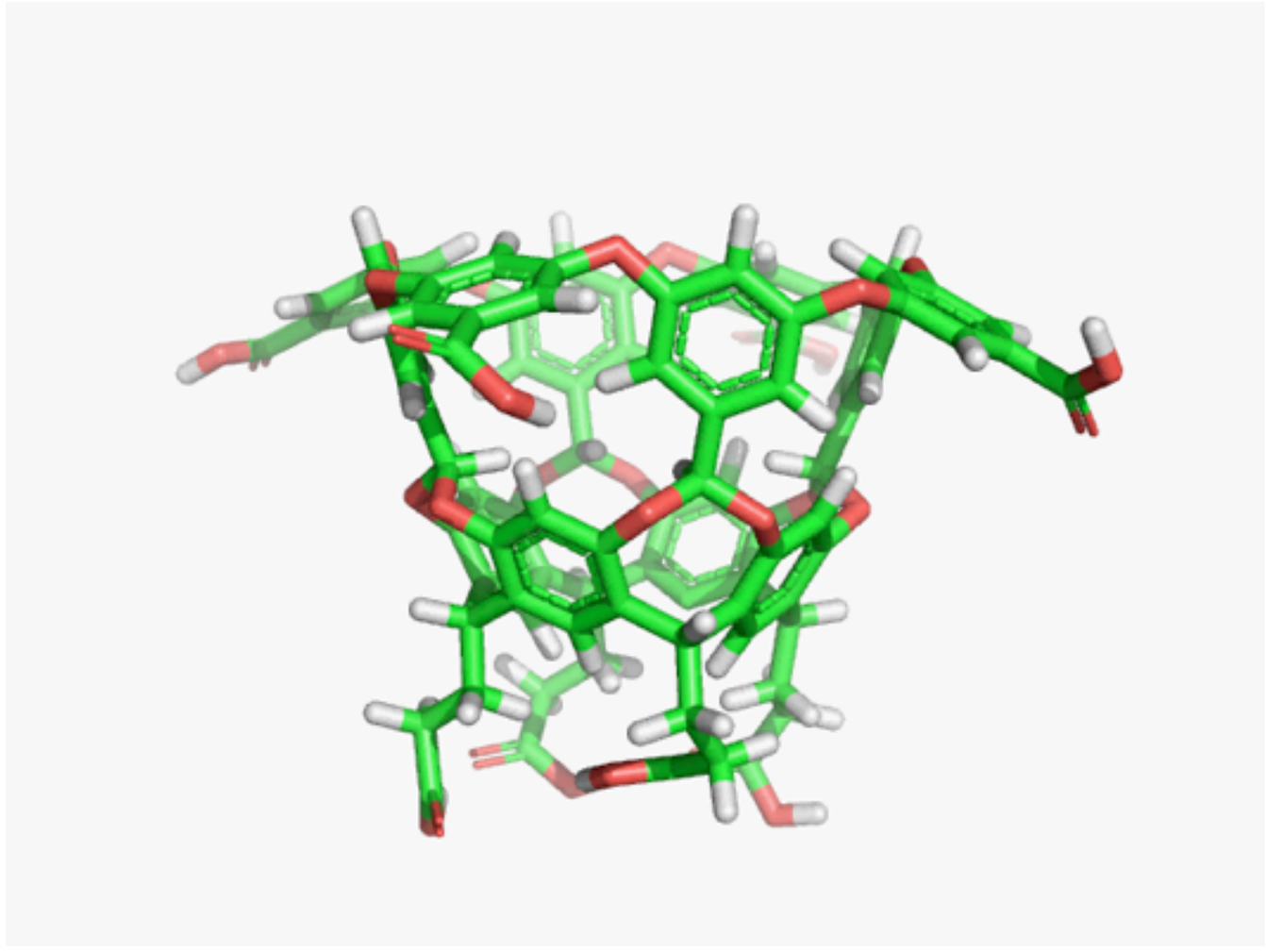
SAMPL5: Distribution coefficients and host-guest binding

David Mobley

SAMPL challenges often involve solvation, host-guest binding





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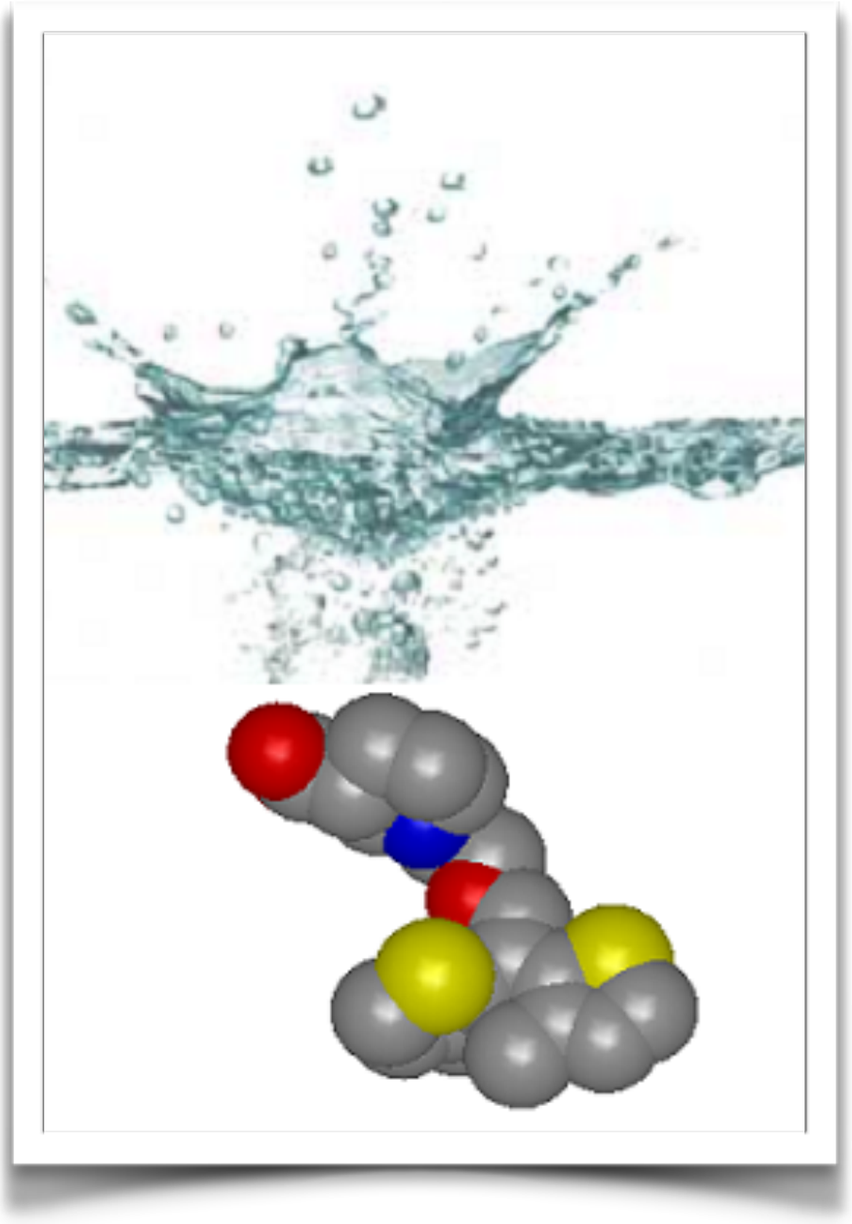
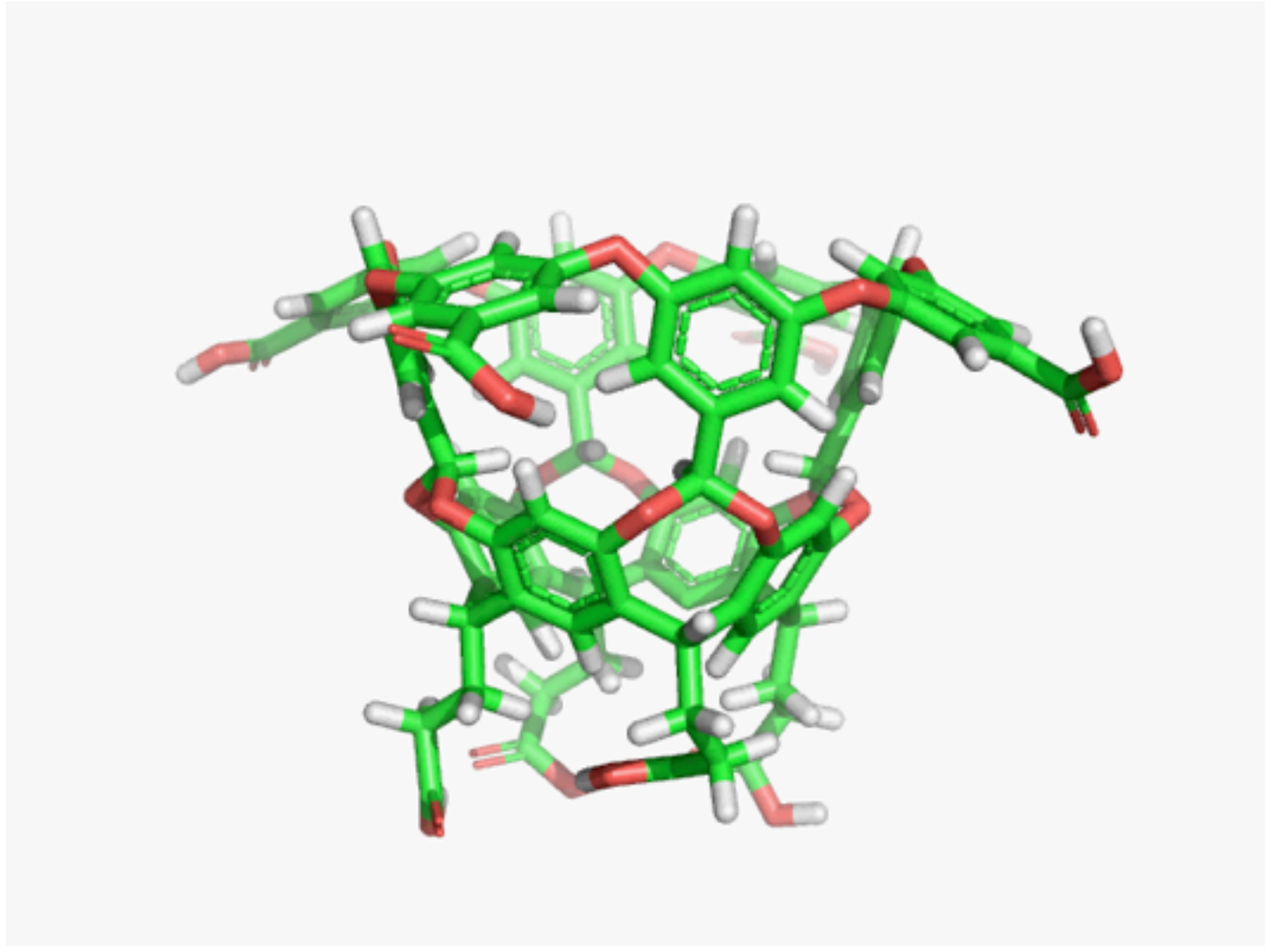
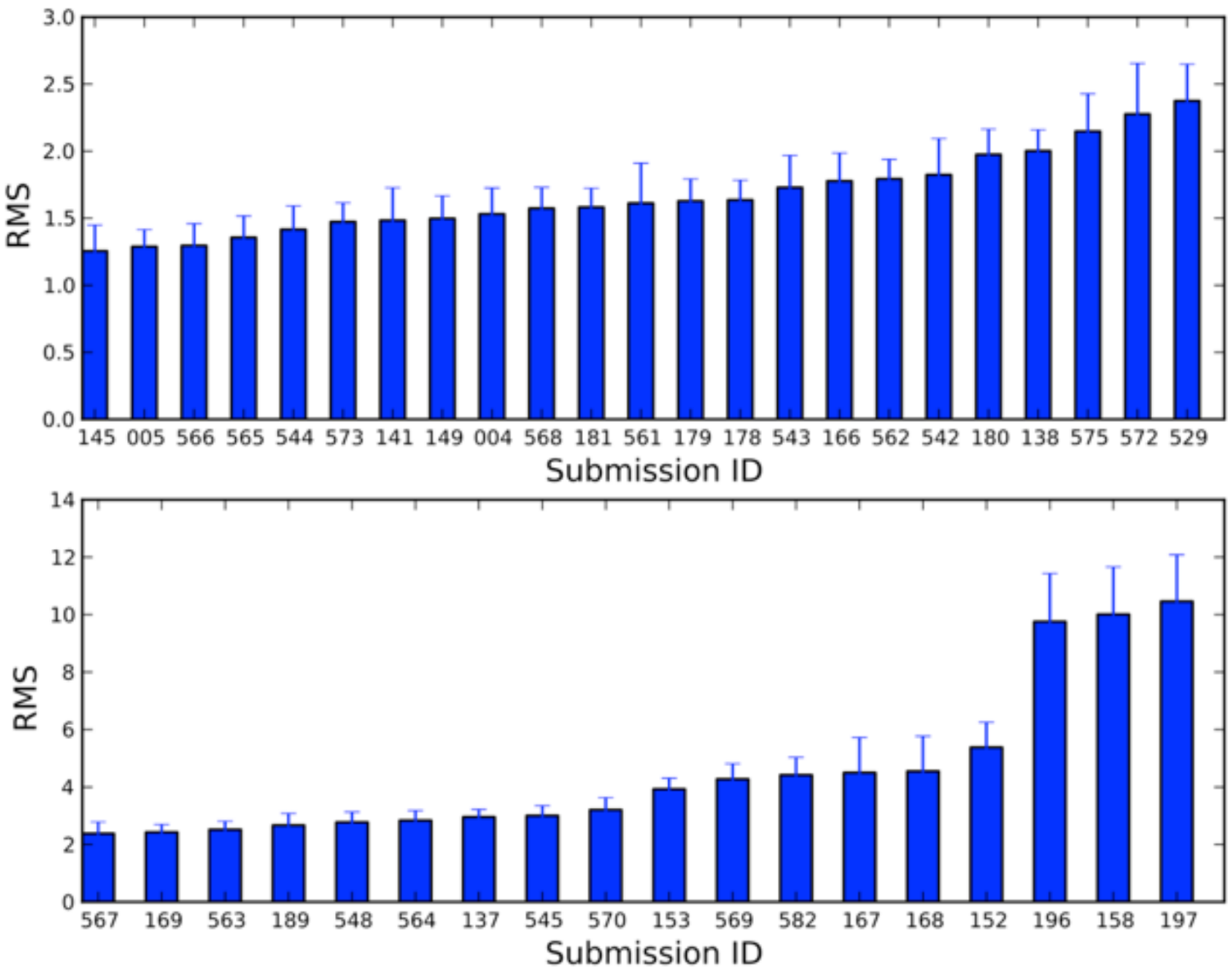




Hydration free energy predictions have improved greatly over the years



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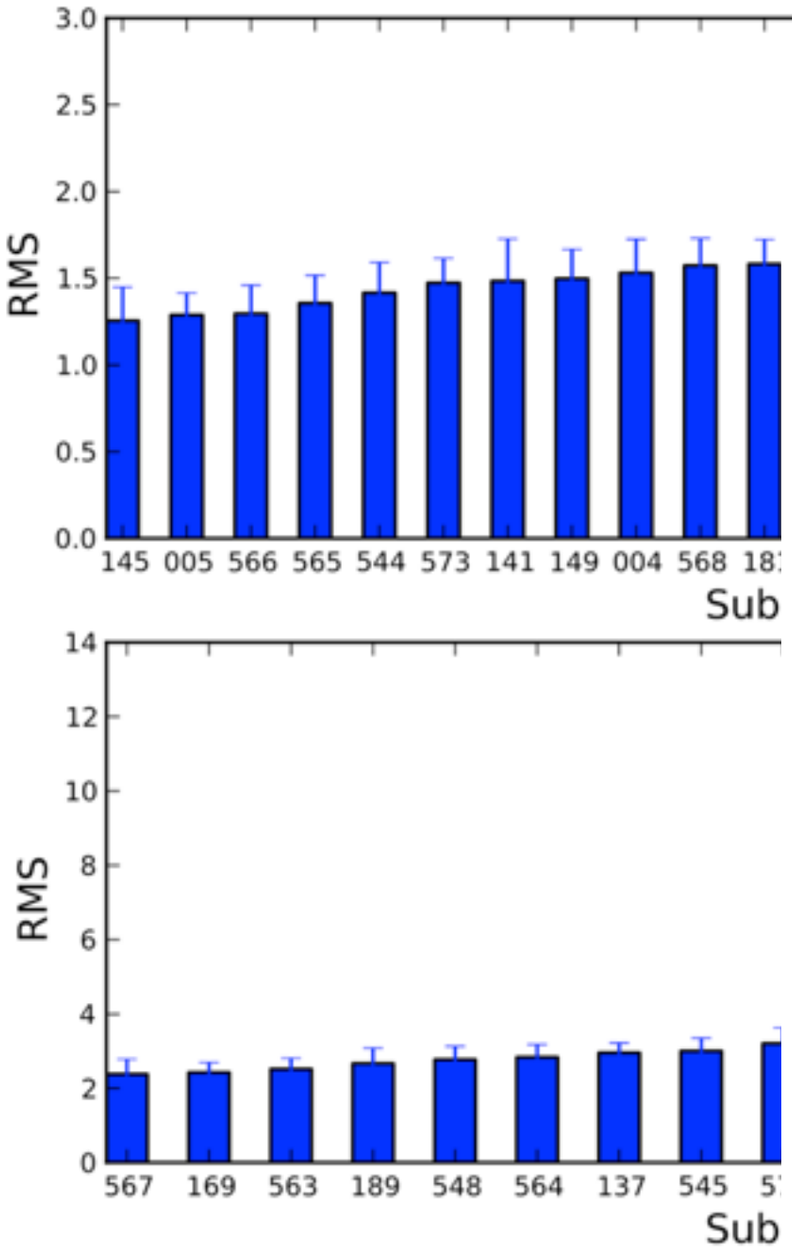

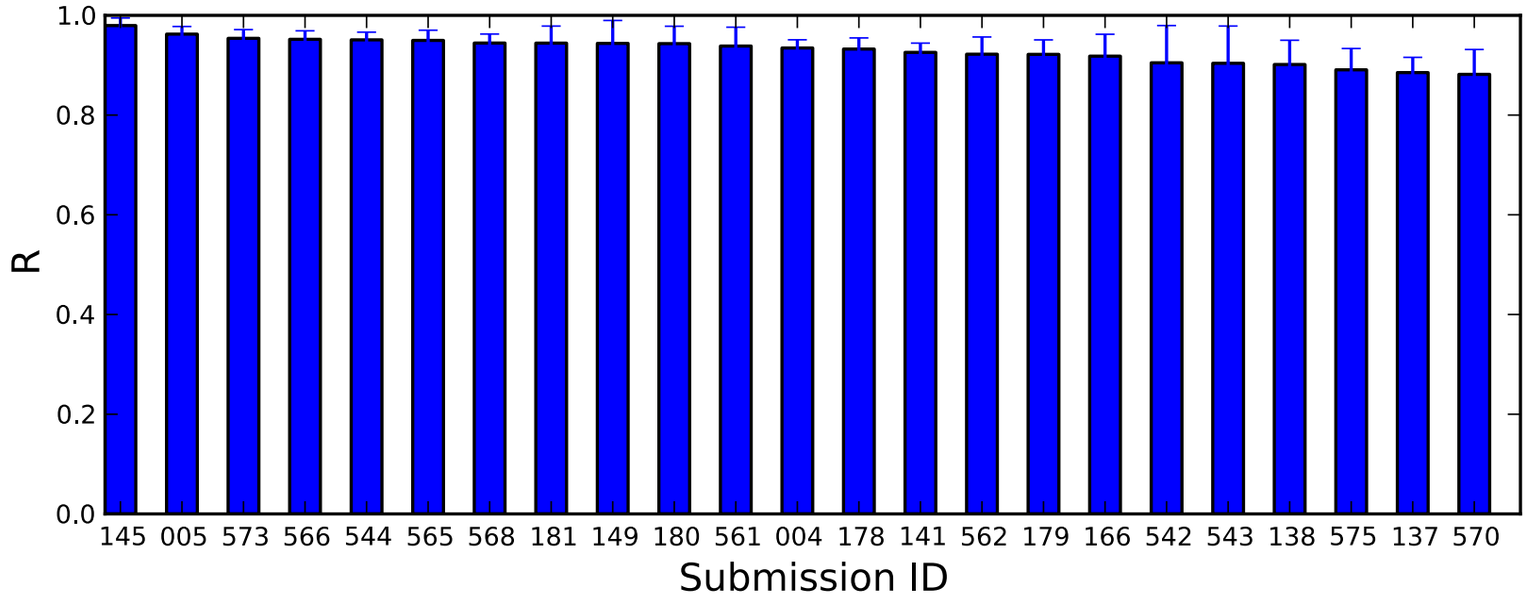

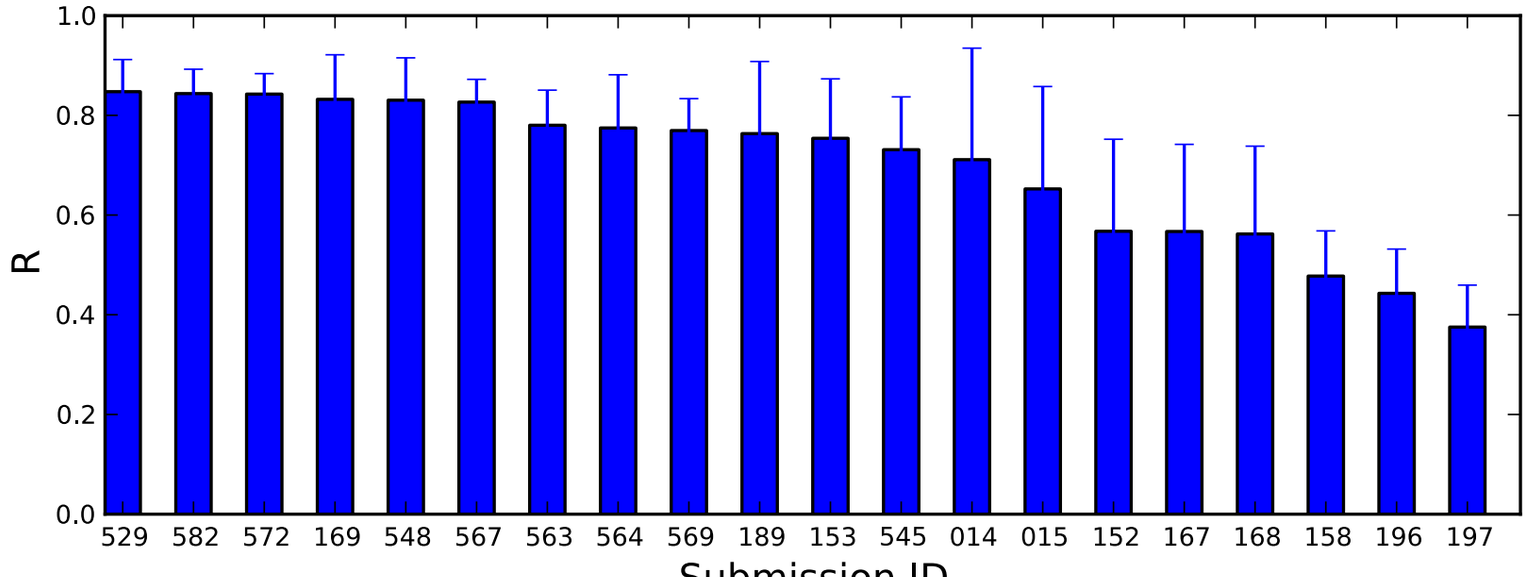

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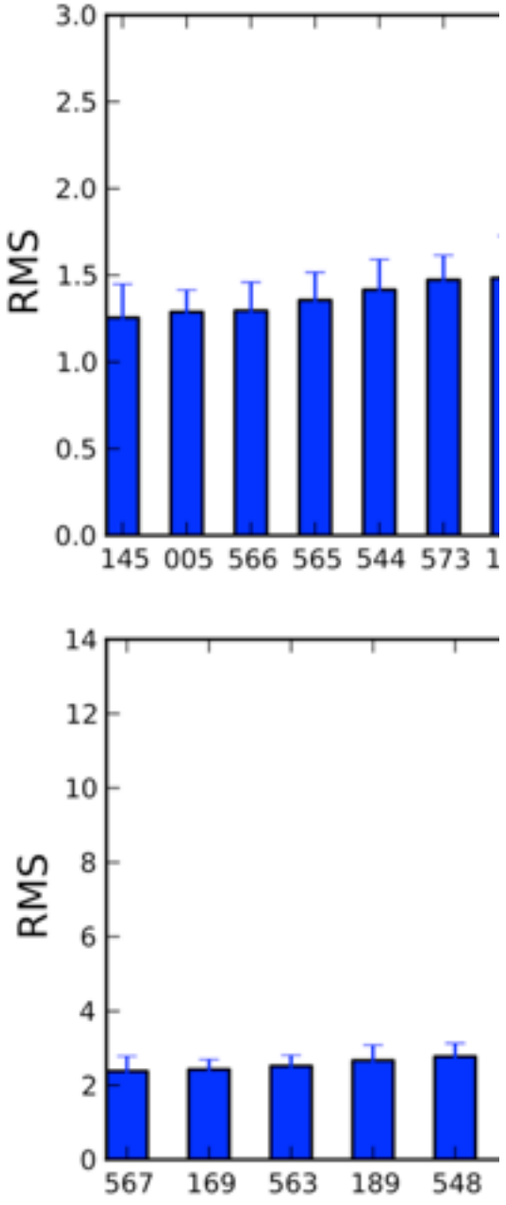
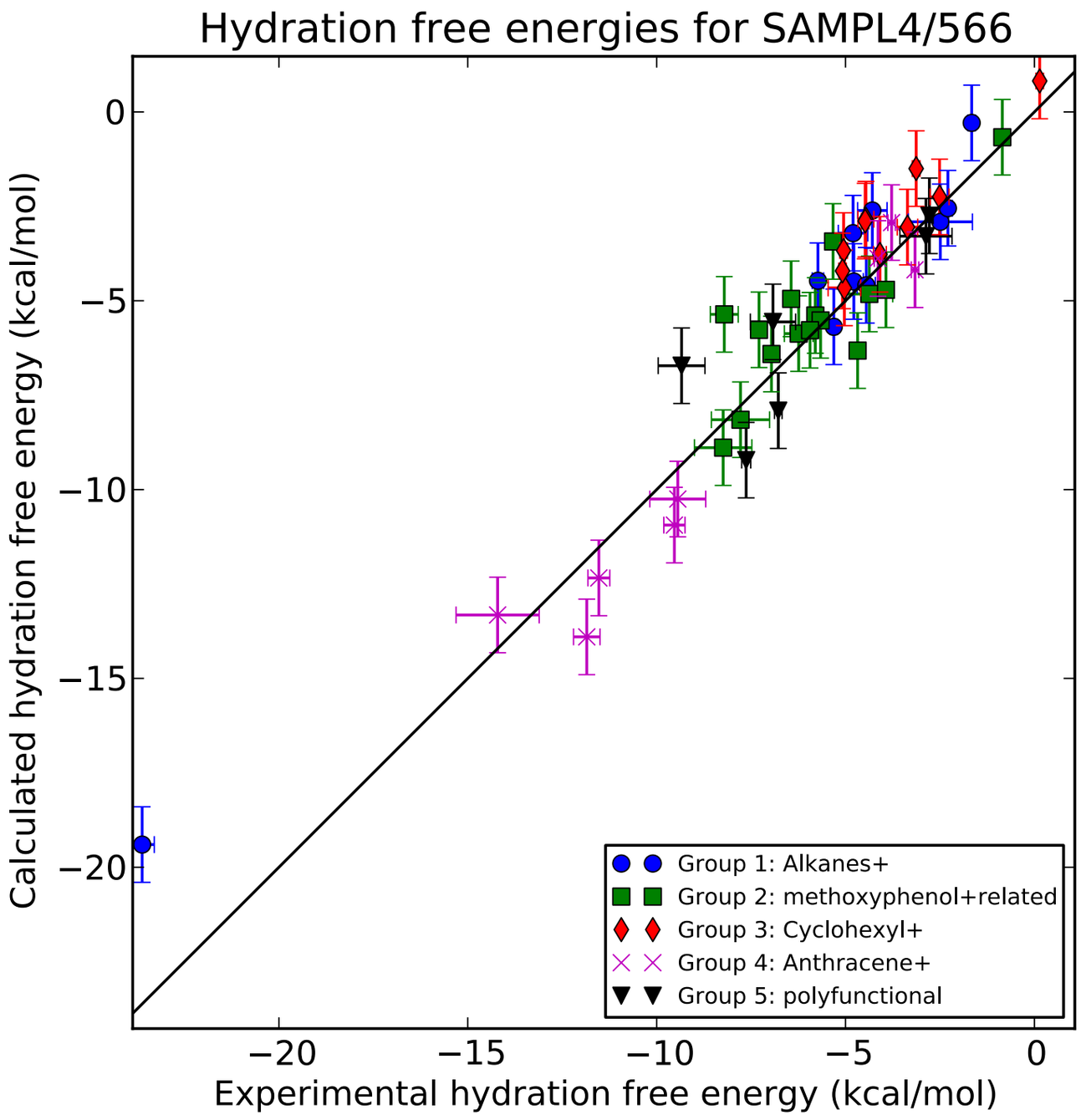
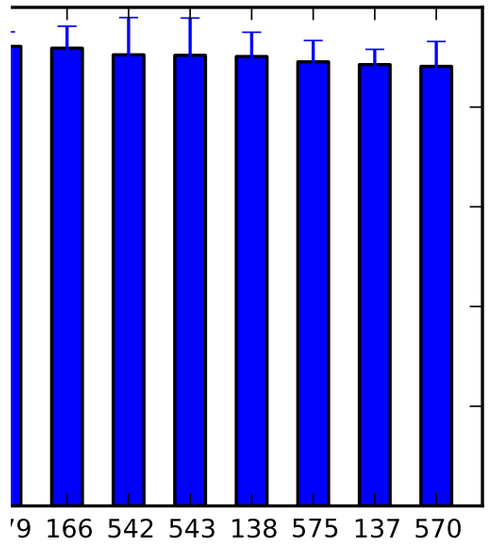
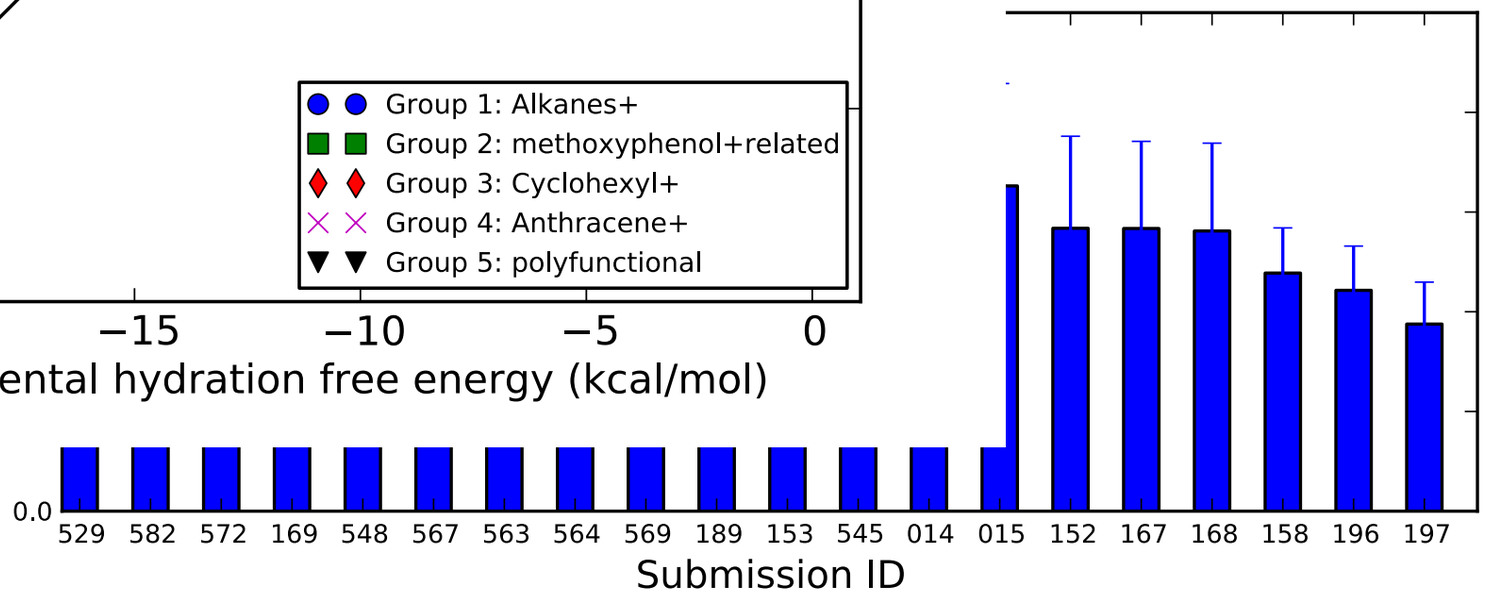


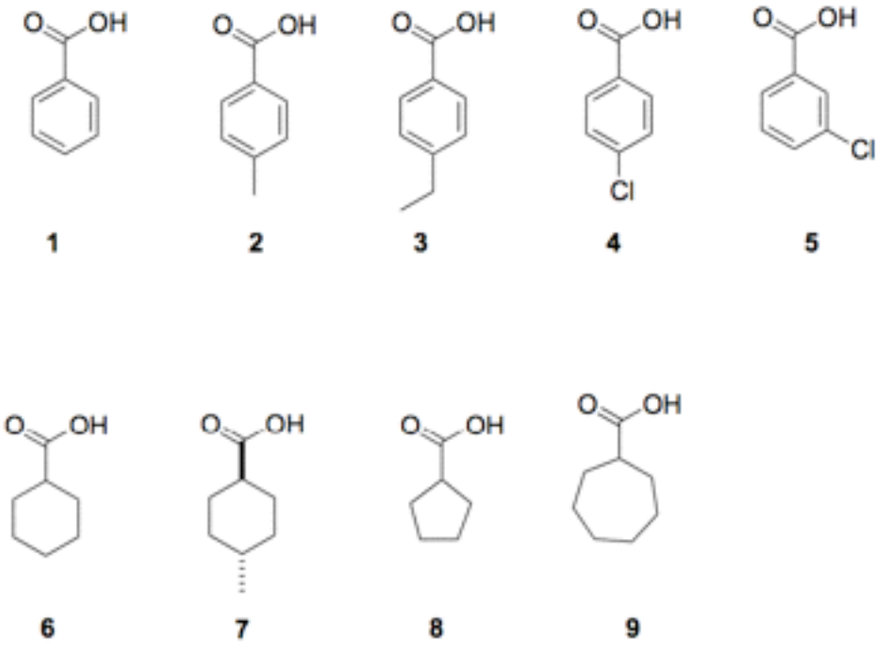


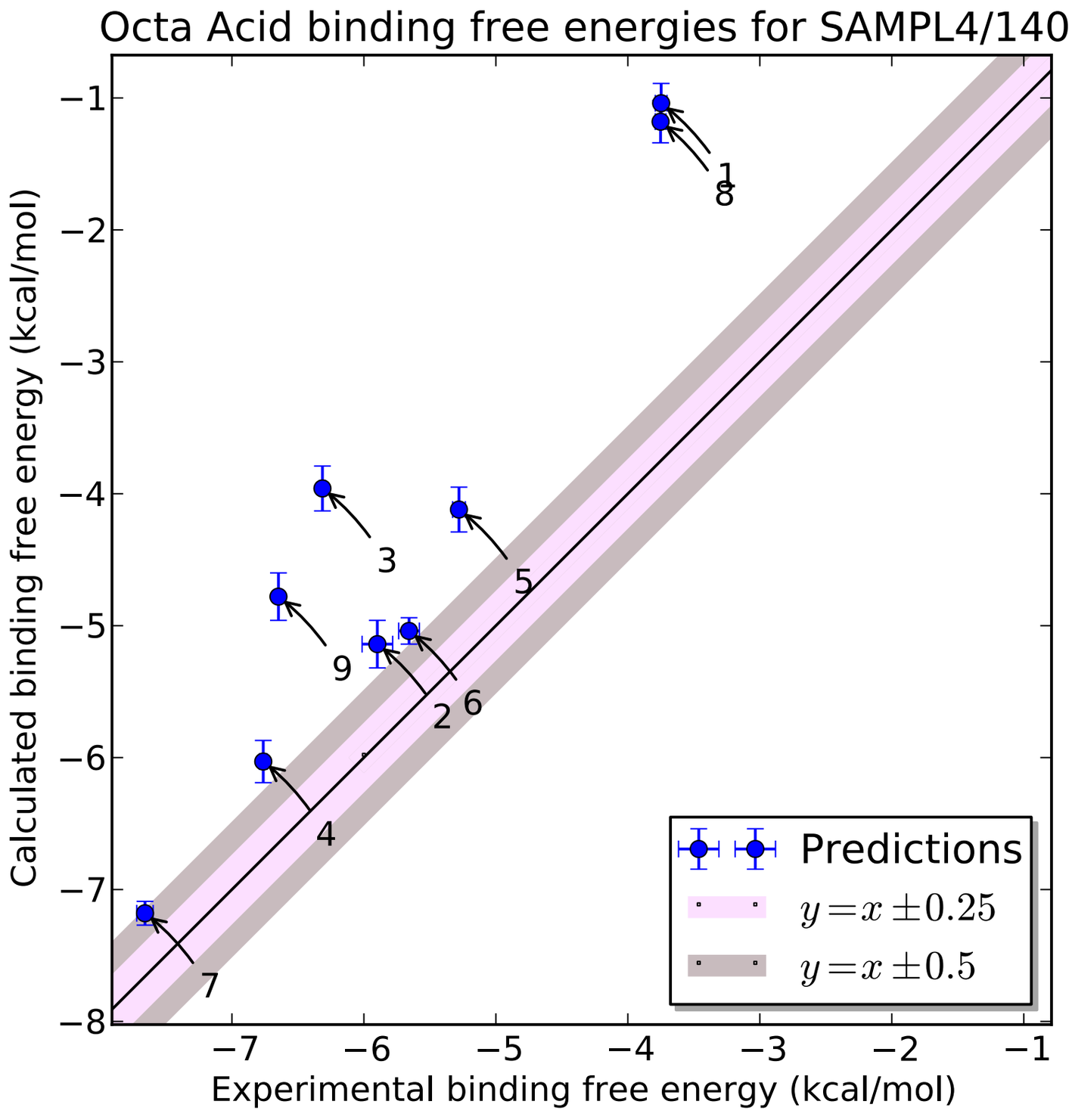




In SAMPL4, the Octa Acid HG system was somewhat tractable

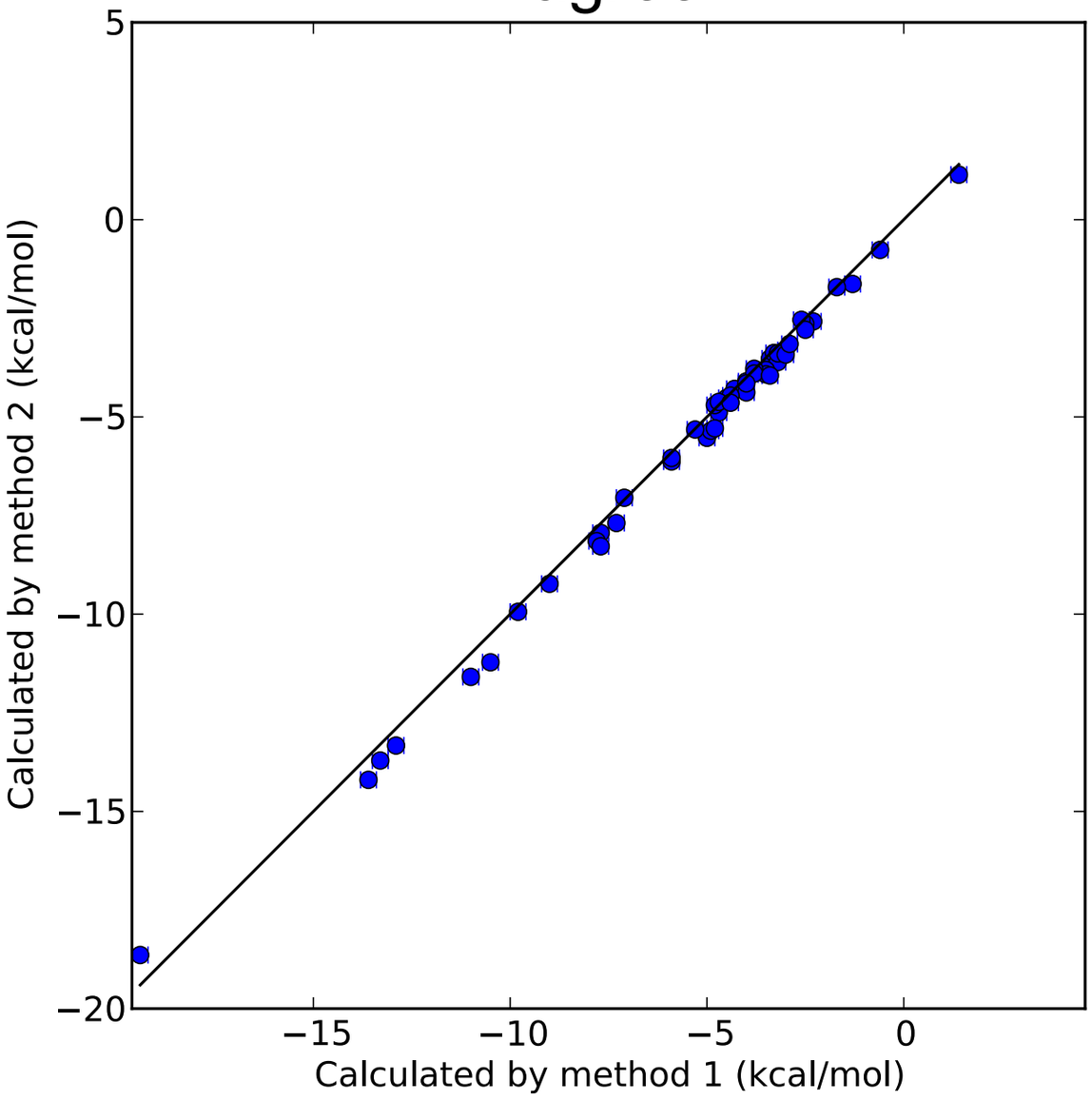
Alchemical relative free energies, TIP3P, GAFF, RESP HF6-31G*



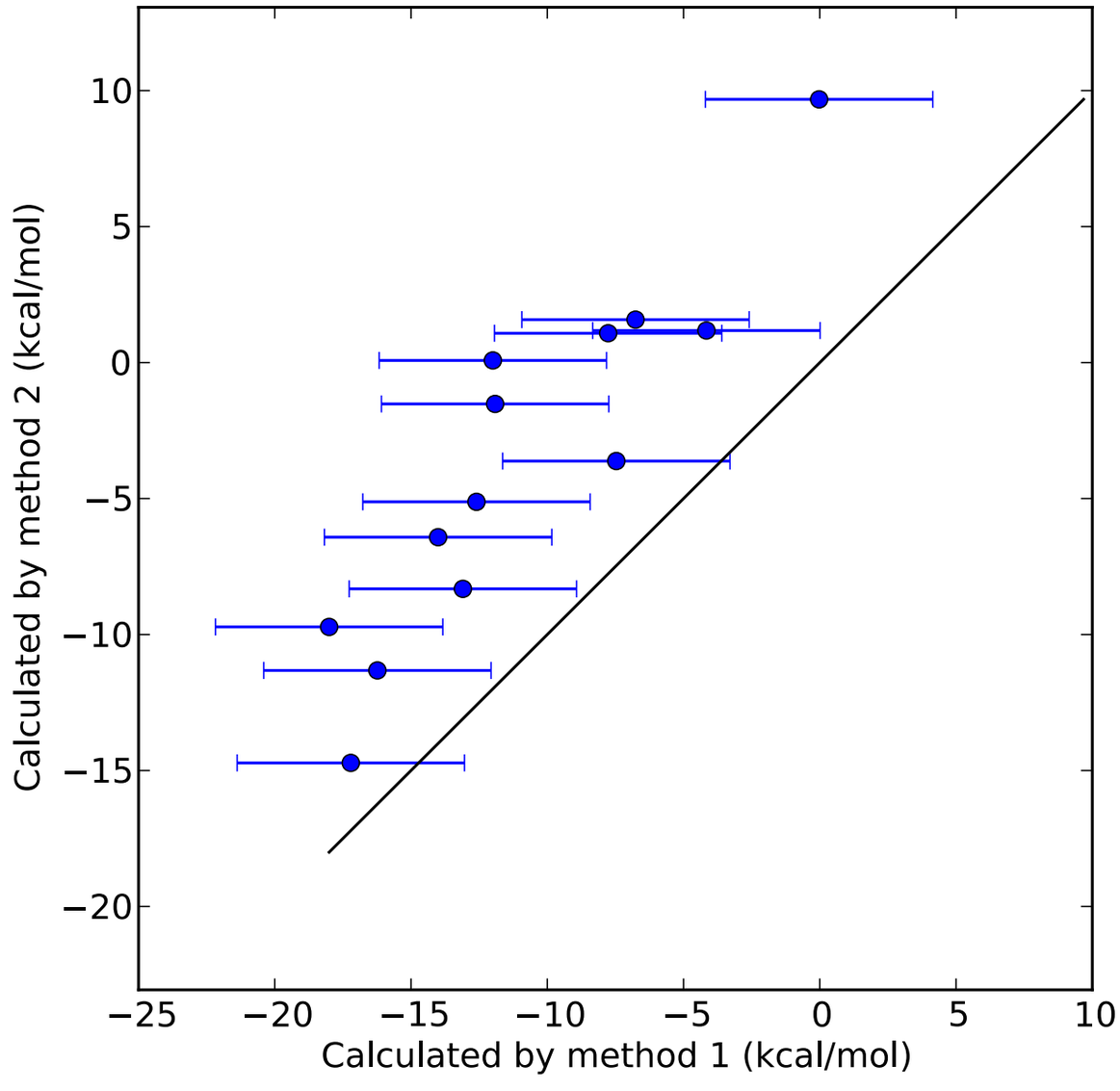


This year, we have “standard calculations”, a new element to separate methods from setups

For SAMPL4 hydration, methods which are the same agree



For HG systems, things are not necessarily so simple

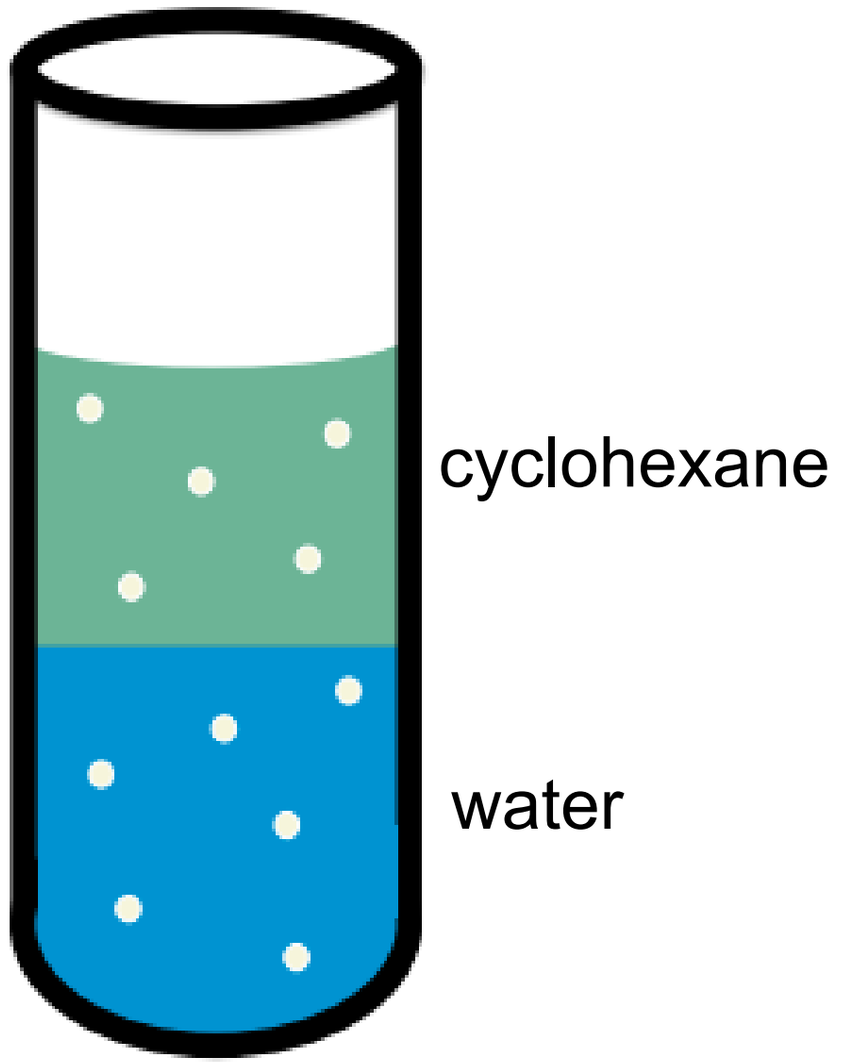


At Genentech, distribution coefficients were obtained for 53 compounds

Partition coefficients and distribution coefficients are similar, but the latter includes all species:

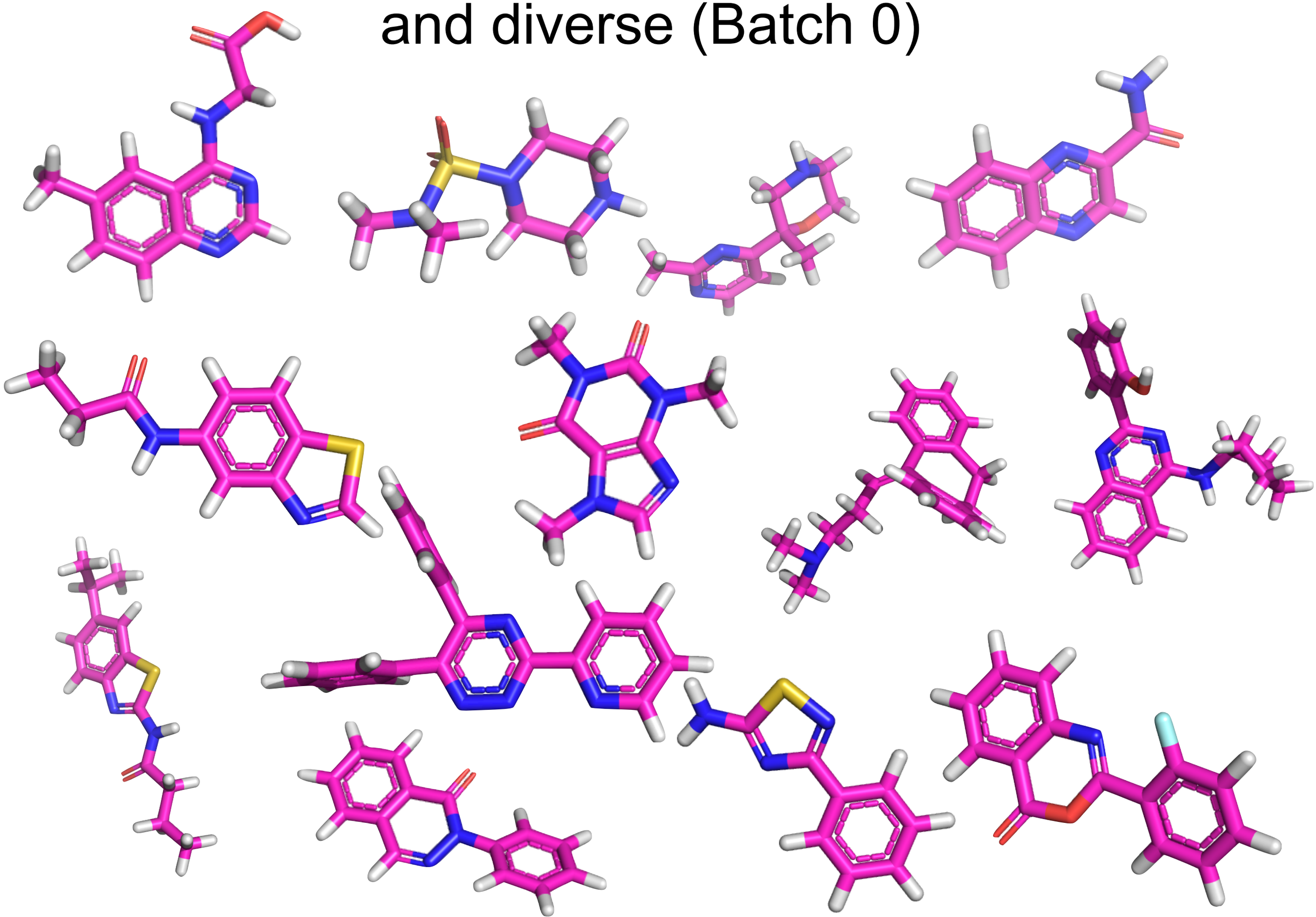
$$P_{cyc} = \frac{[Neutral\ solute\ in\ cyclohexane]}{[Neutral\ solute\ in\ water]}$$

$$D_{cyc} = \frac{[Solute\ in\ cyclohexane]}{[Solute\ in\ water]}$$

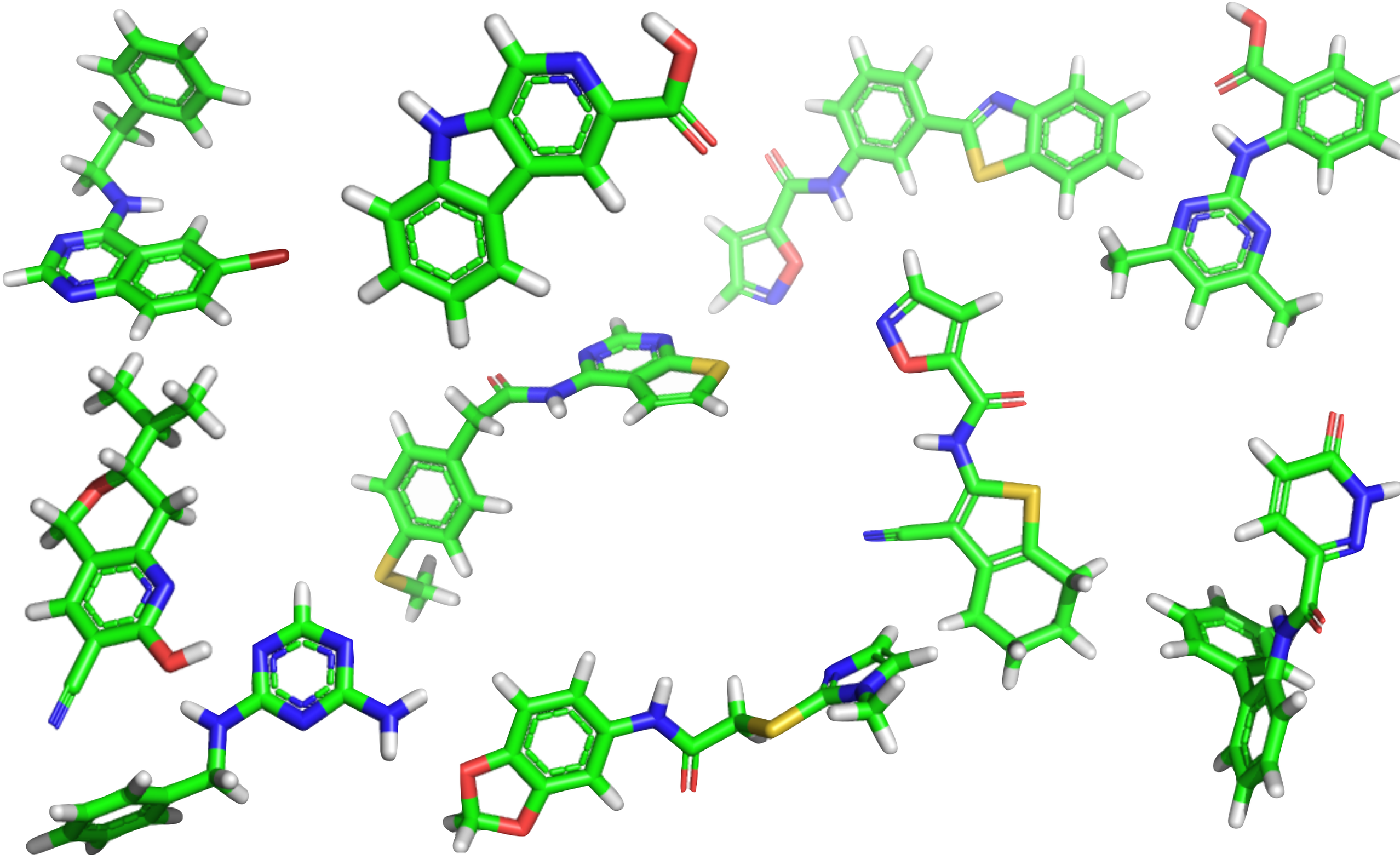


pH dependent, so we report $\log D_{7.4}$ at pH 7.4

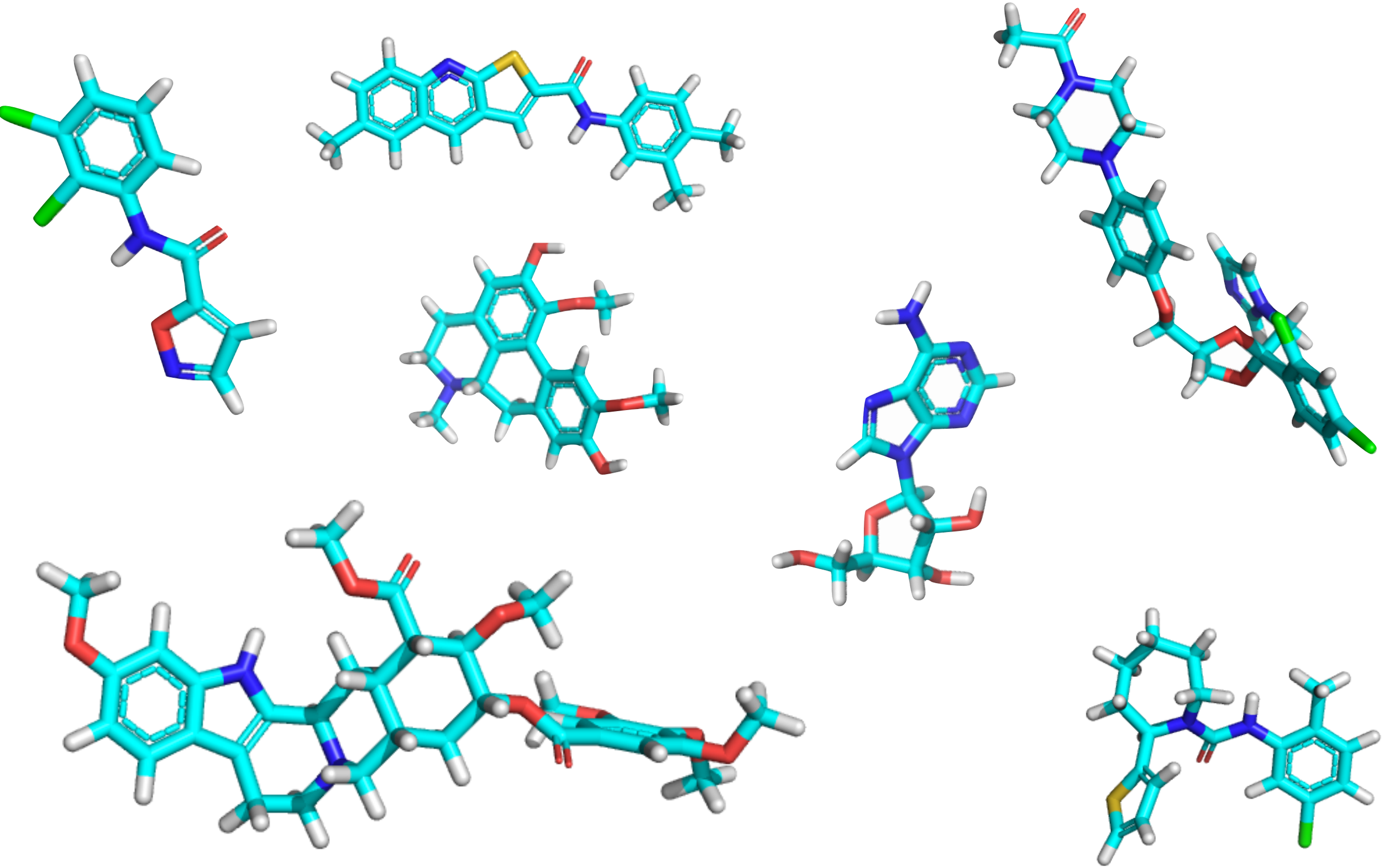
The set is drug-like (from Genentech's library) and diverse (Batch 0)



The set is drug-like (from Genentech's library) and diverse (Batch 1)



The set is drug-like (from Genentech's library) and diverse (Batch 2)



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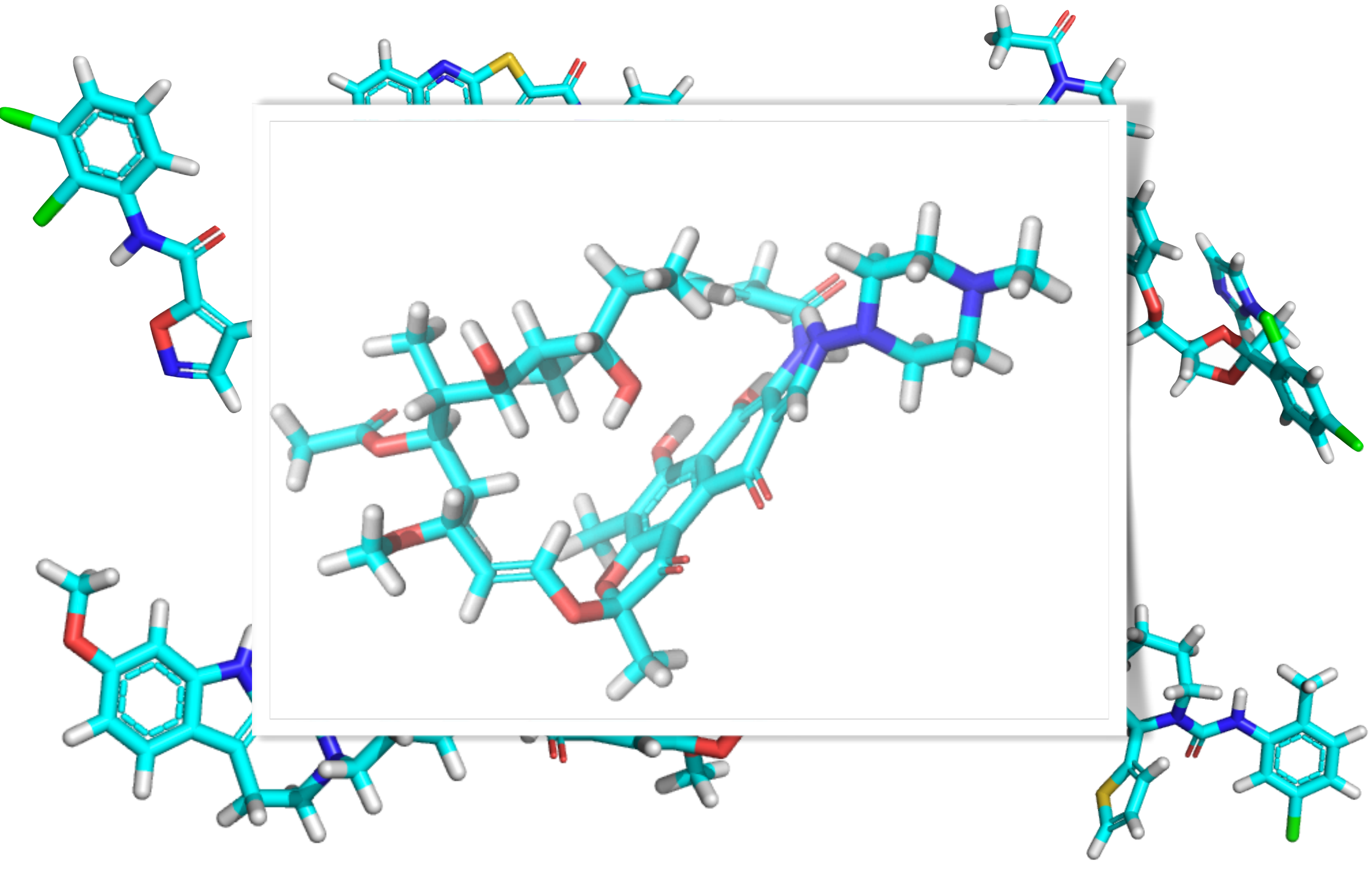


How should we expect people to do?

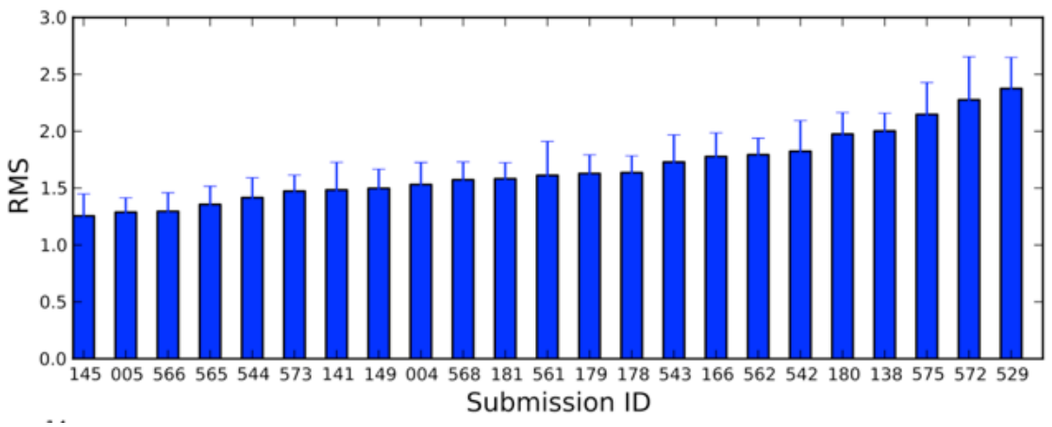
For partition coefficients at infinite dilution, we could calculate

$$\log P = \frac{-\Delta G_{transfer}}{RT\ln(10)} = \frac{\Delta G_{hyd.} - \Delta G_{cyc.}}{-RT\ln(10)}$$

Let's assume a typical method makes equal errors in cyclohexane and water solvation free energies, so we expect an error in log P values of

$$\delta(\log P) = \frac{\sqrt{2} \times \delta\Delta G_{solv}}{RT\ln(10)}$$

If we take a error of 1.5 kcal/mol as typical from last SAMPL:



We would expect the typical error in log P to be 1.54 log units.

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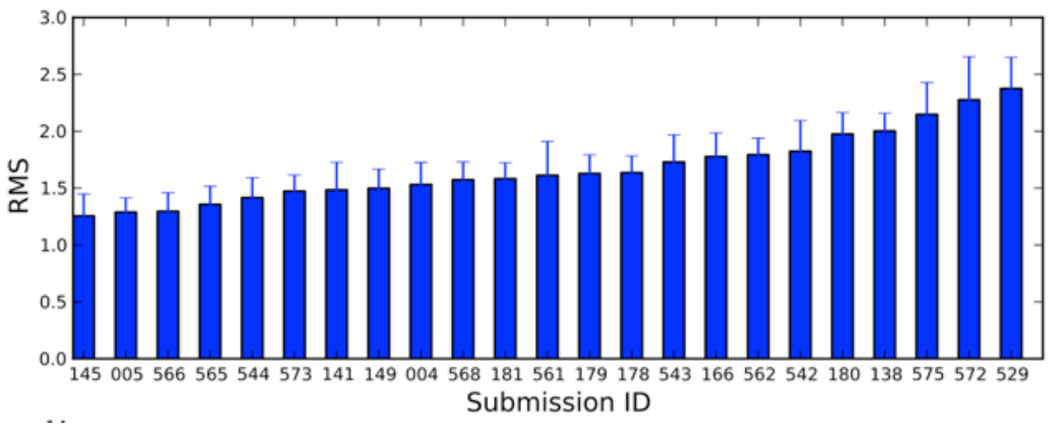

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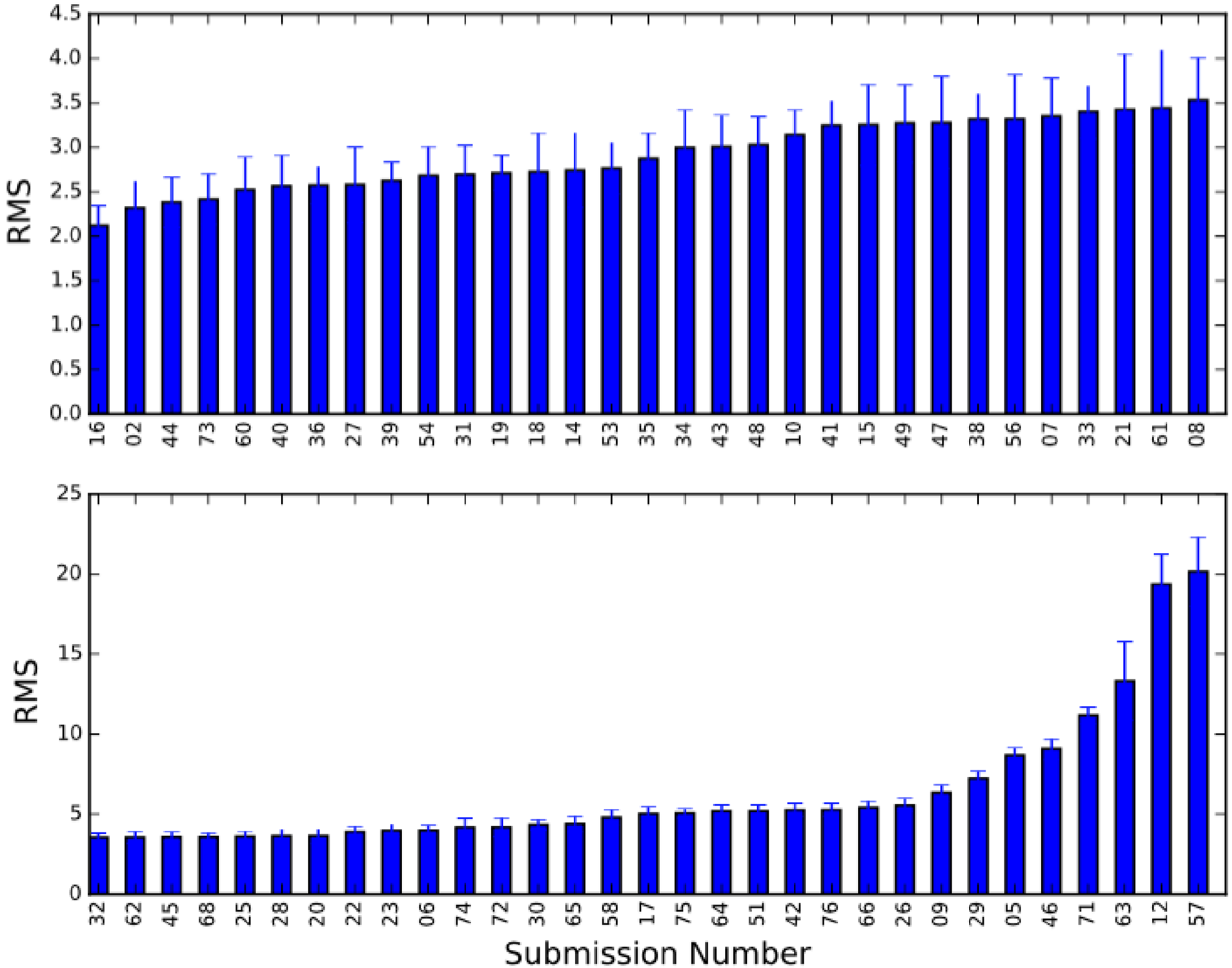
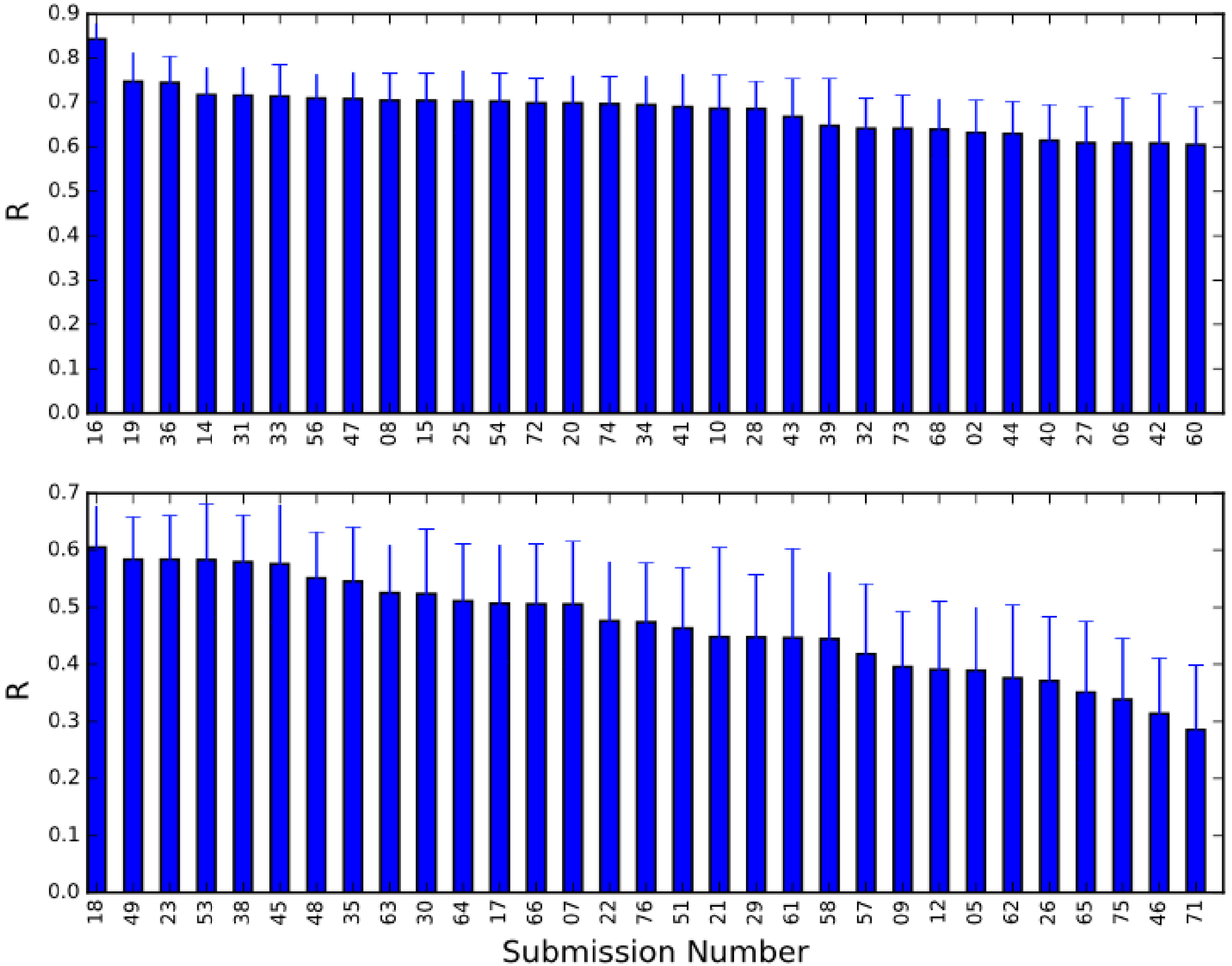
EXCEPT this set is substantially more complex/polyfunctional…

In reality, people do a bit worse than 1.5 log units - but not that much worse



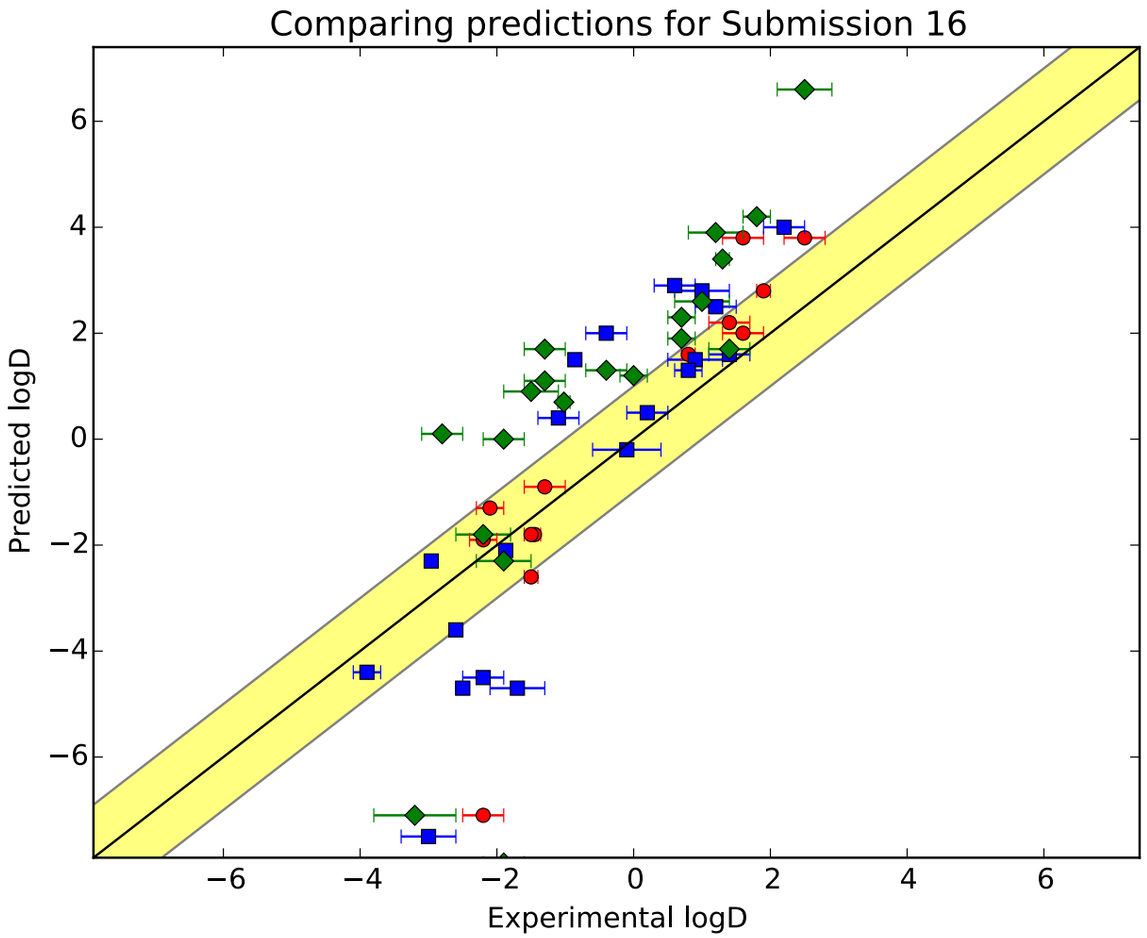
Top few: 16, 02, 44, 73, 60, 40 36

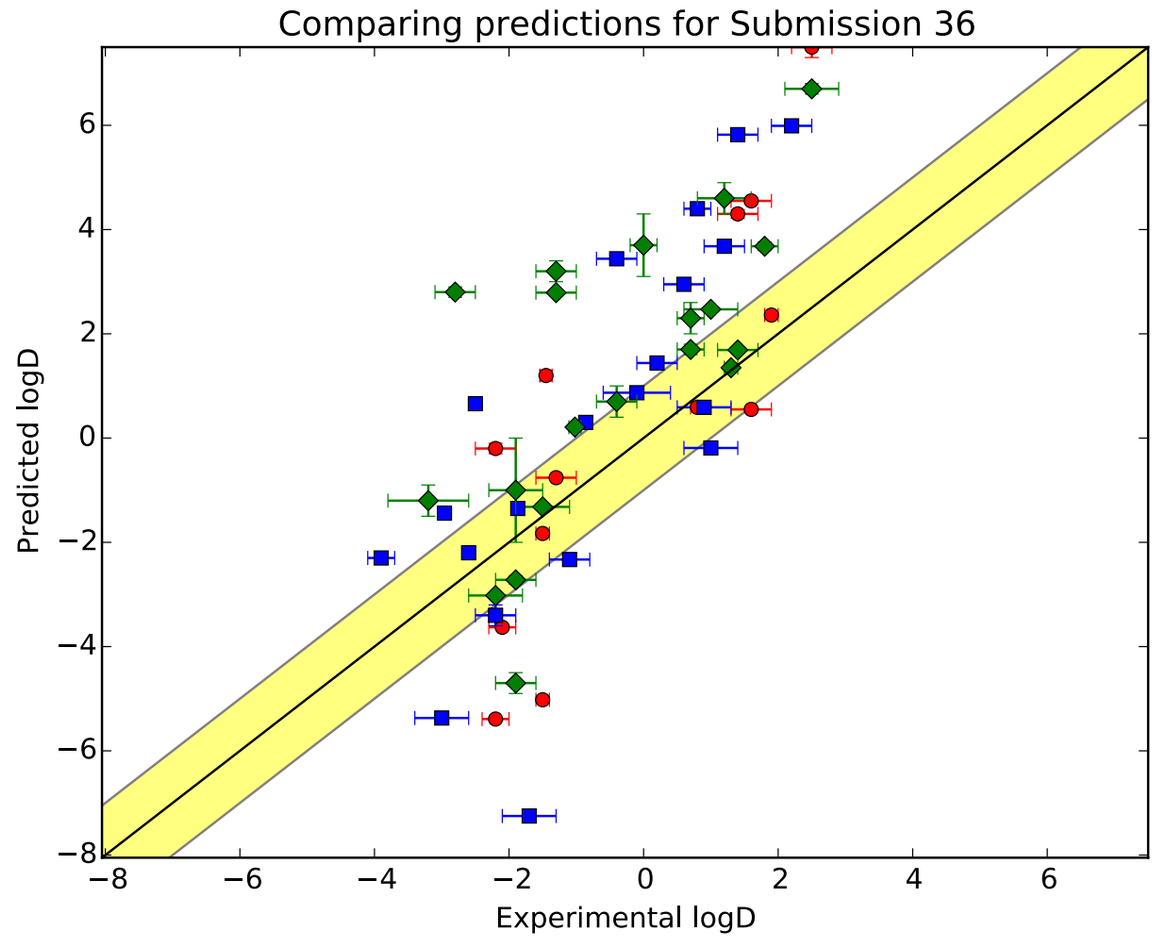
We use several metrics; here let's check against correlation



Top few: **16**, 19, **36**, 14, 31, 33

Let’s take a look at some of these predictions





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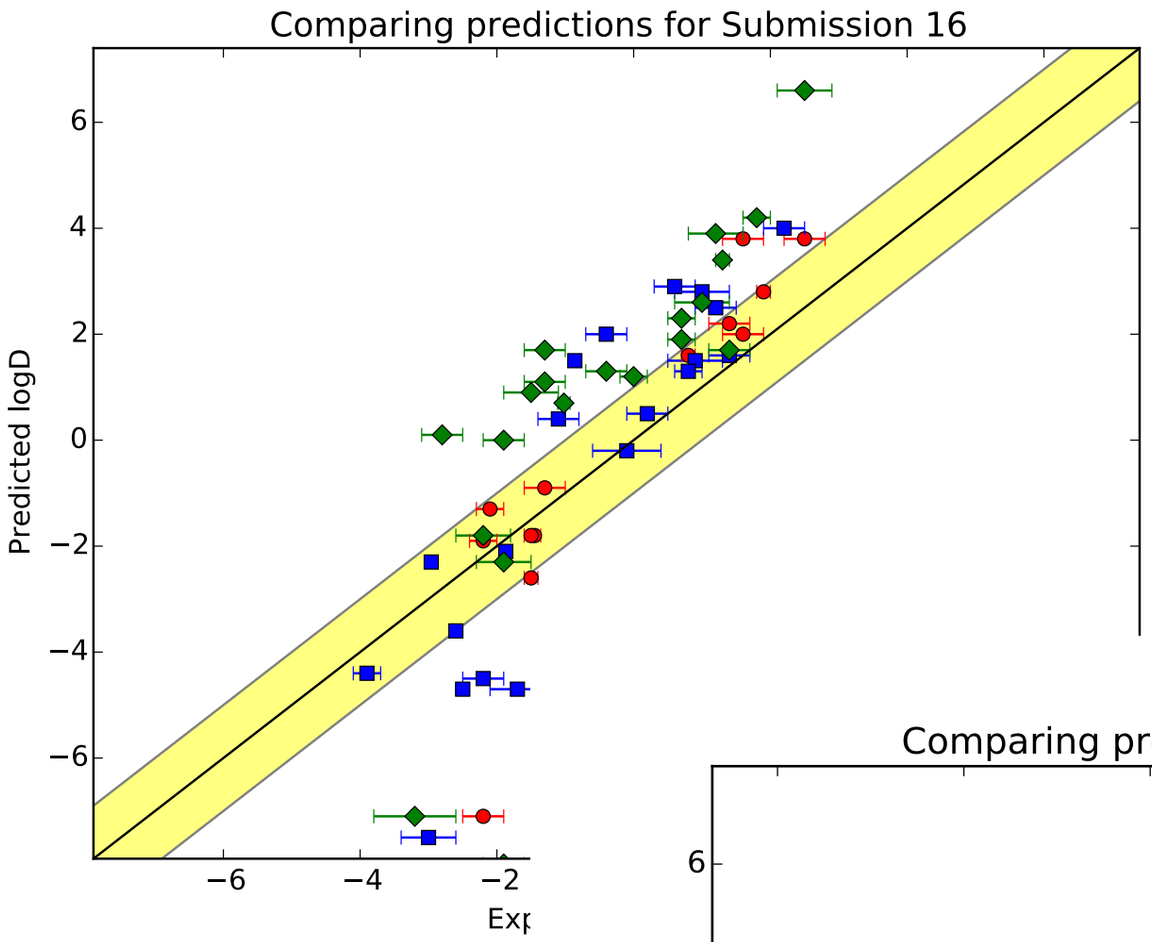
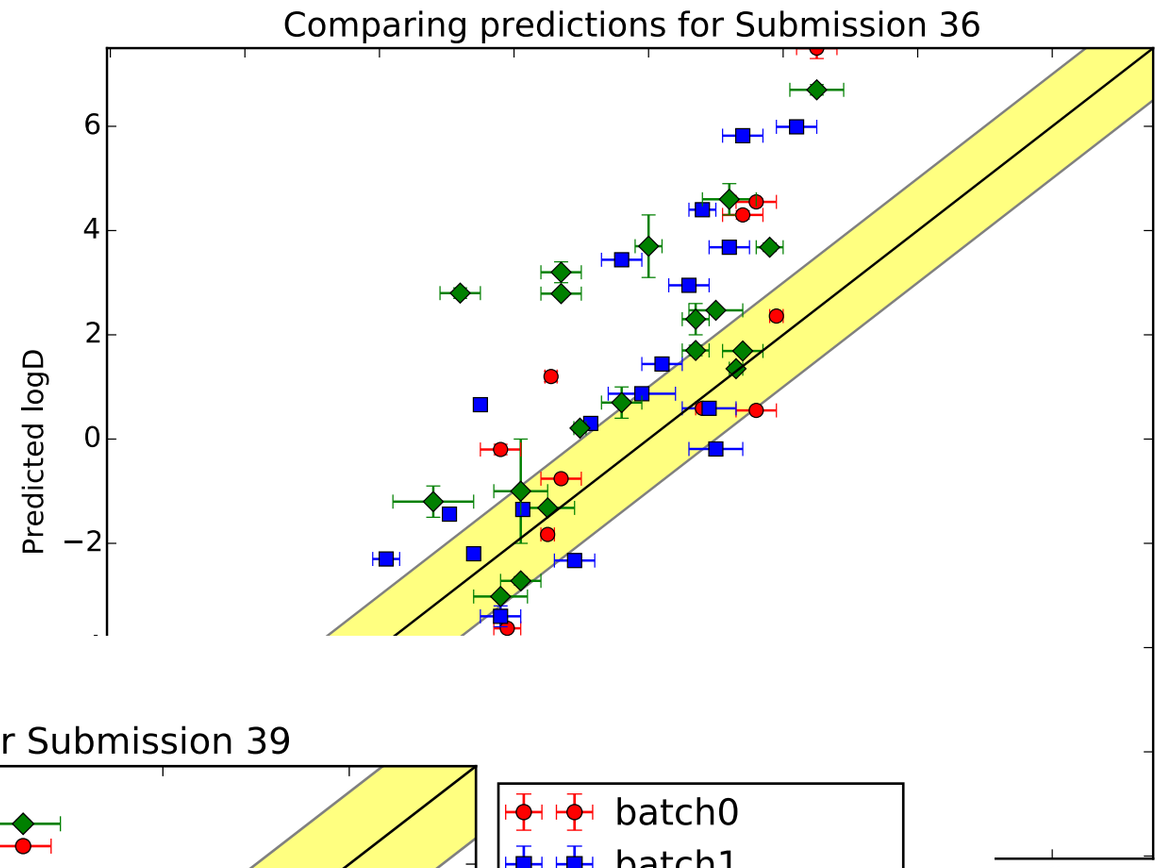
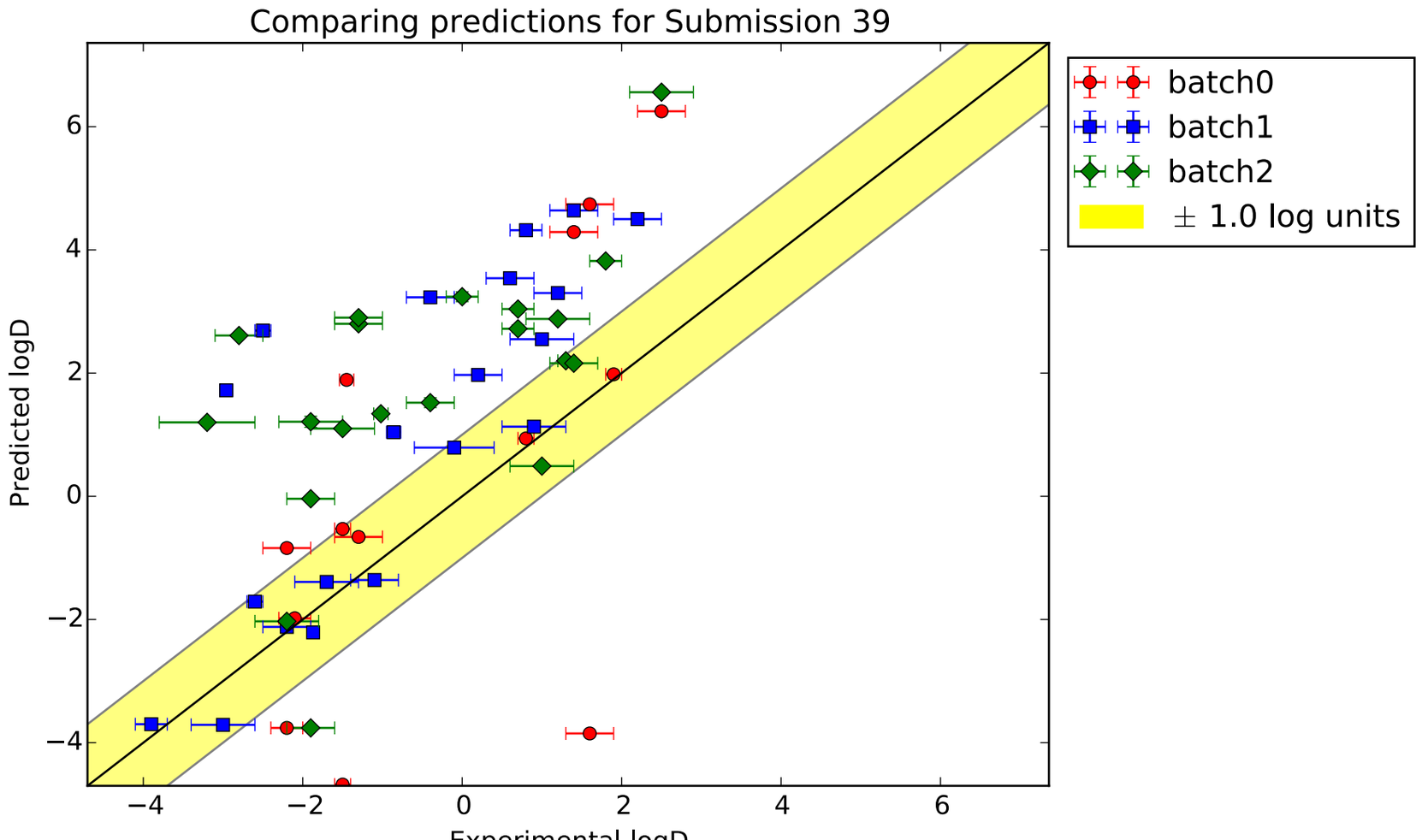
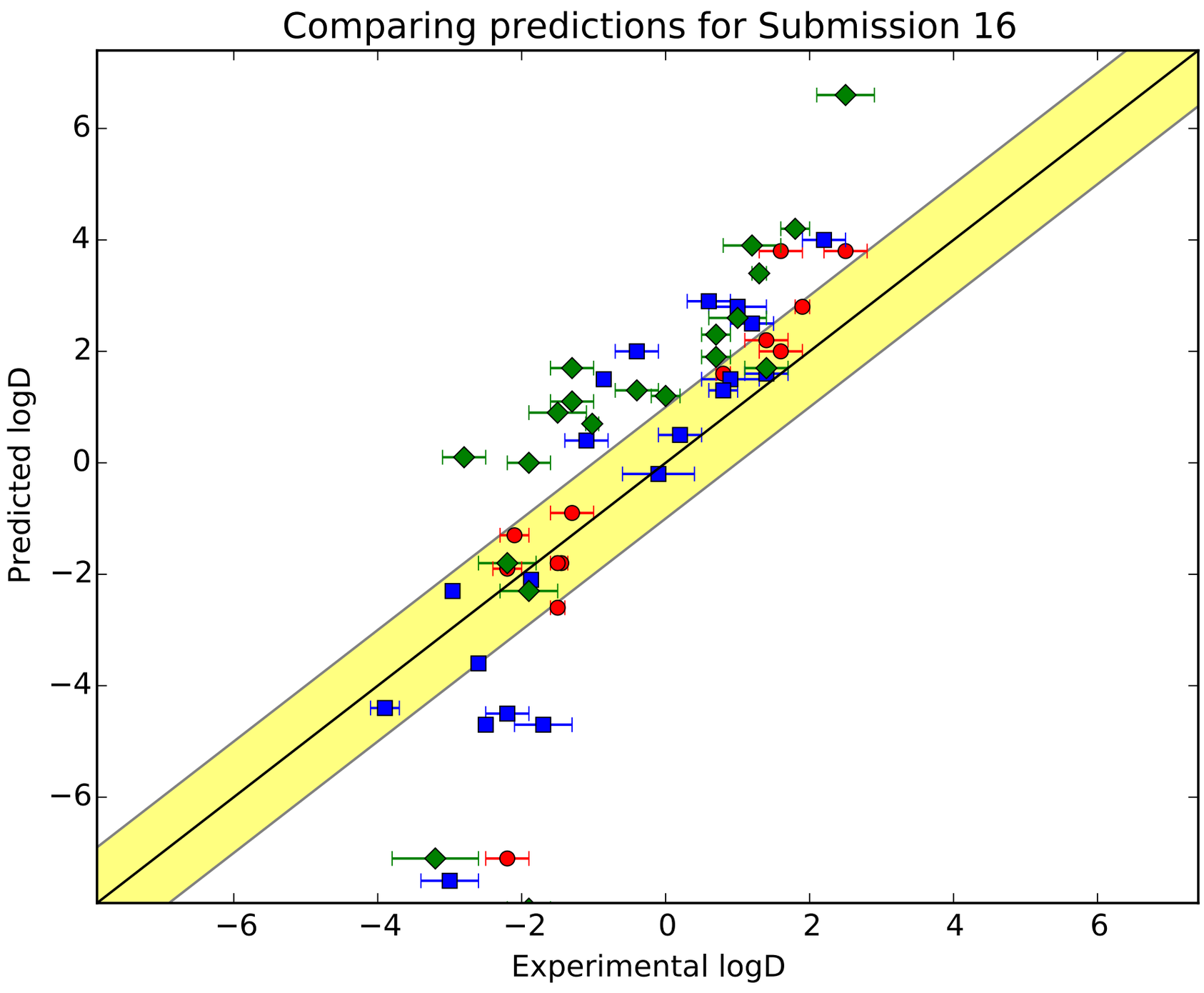






We'll hear from Andreas Klamt later about submission 16



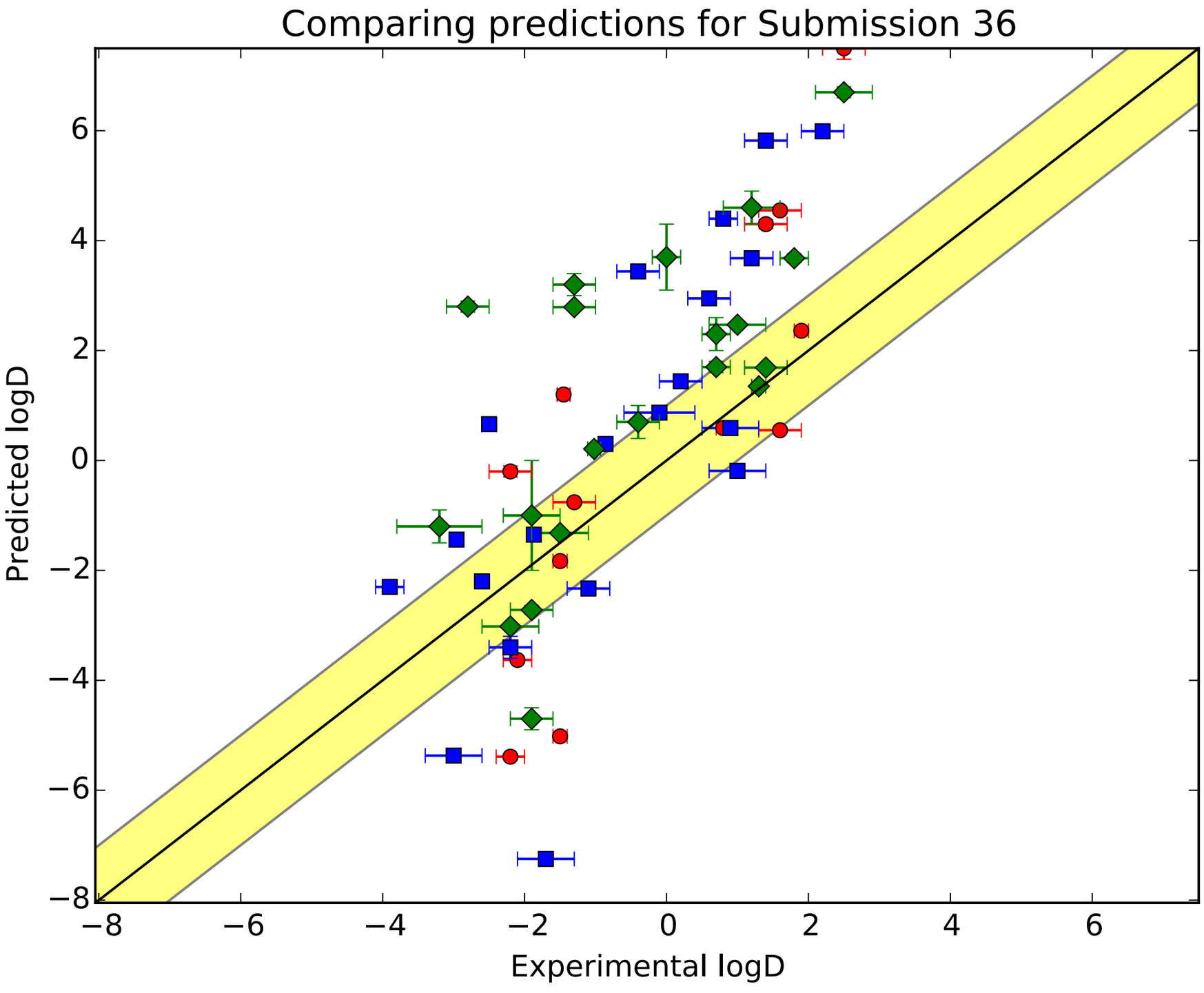
COSMO-RS/ COSMOtherm

COSMO-RS log P calculations, adjusted to log D using proton dissociation/ protonation constants

Includes multiple tautomers (050, 056, 065, 083) and accounting for zwitterions

Andreas Klamt

Modified GAFF/AM1-BCC with dielectric corrections worked quite well



MD/thermodynamic integration with GAFF-DC

Custom UA cyclohexane

Dielectric corrected water (custom)

LJ scaling coupled with condensed phase charge changes in an environment-dependent manner (fixes neat liquid and partition properties)

Christopher Fennell

Our reference calculations were also in the top 25% by most metrics

Log P calculations (deliberately) based on infinite dilution solvation free energy calculations in water and cyclohexane

GAFF+AM1-BCC

Blind predictions by Kalli Burley and Caitlin Bannan (not competing, but submitted)

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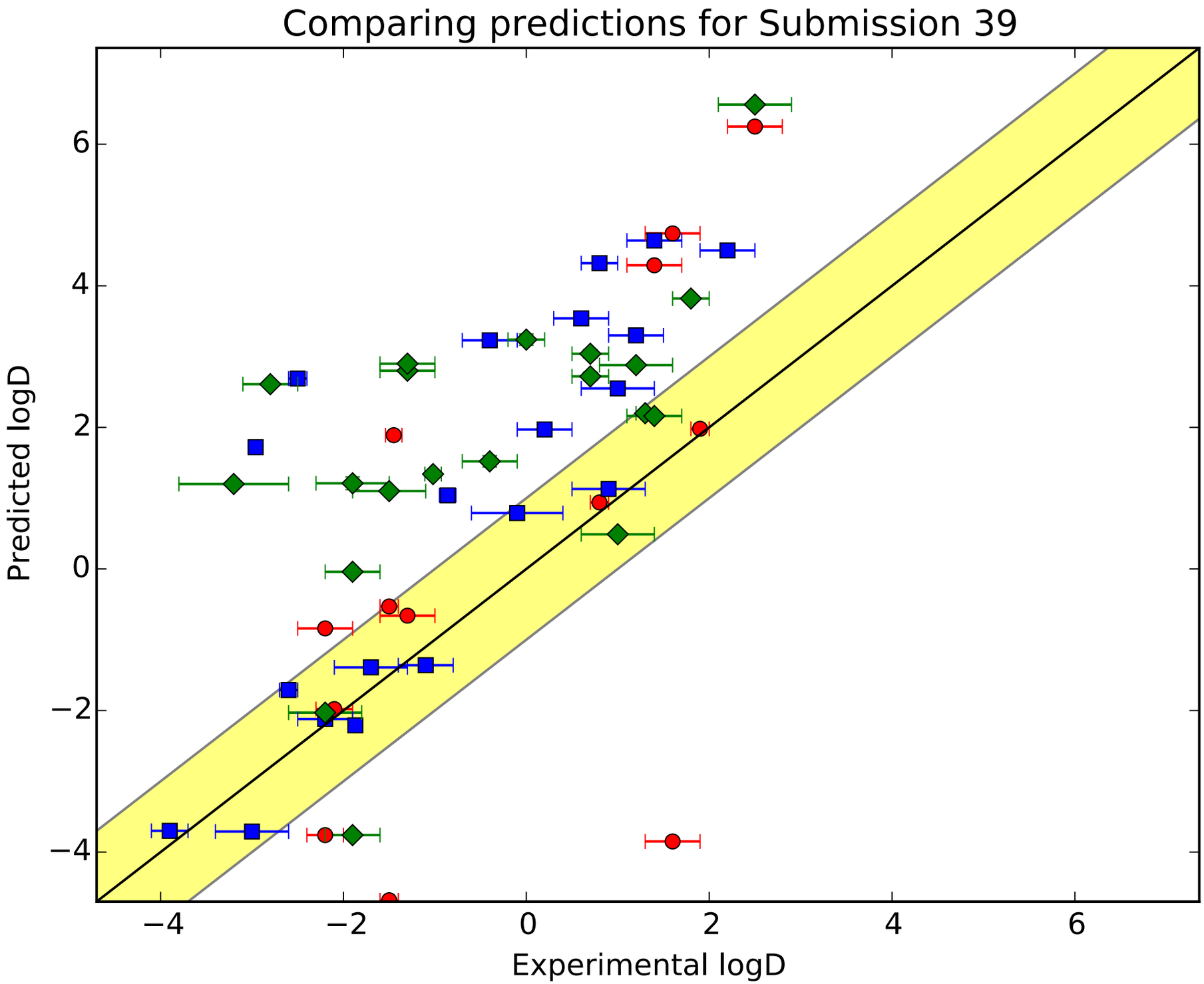

Log P calculations (deliberately) based on infinite dilution solvation free energy calculations in water and cyclohexane

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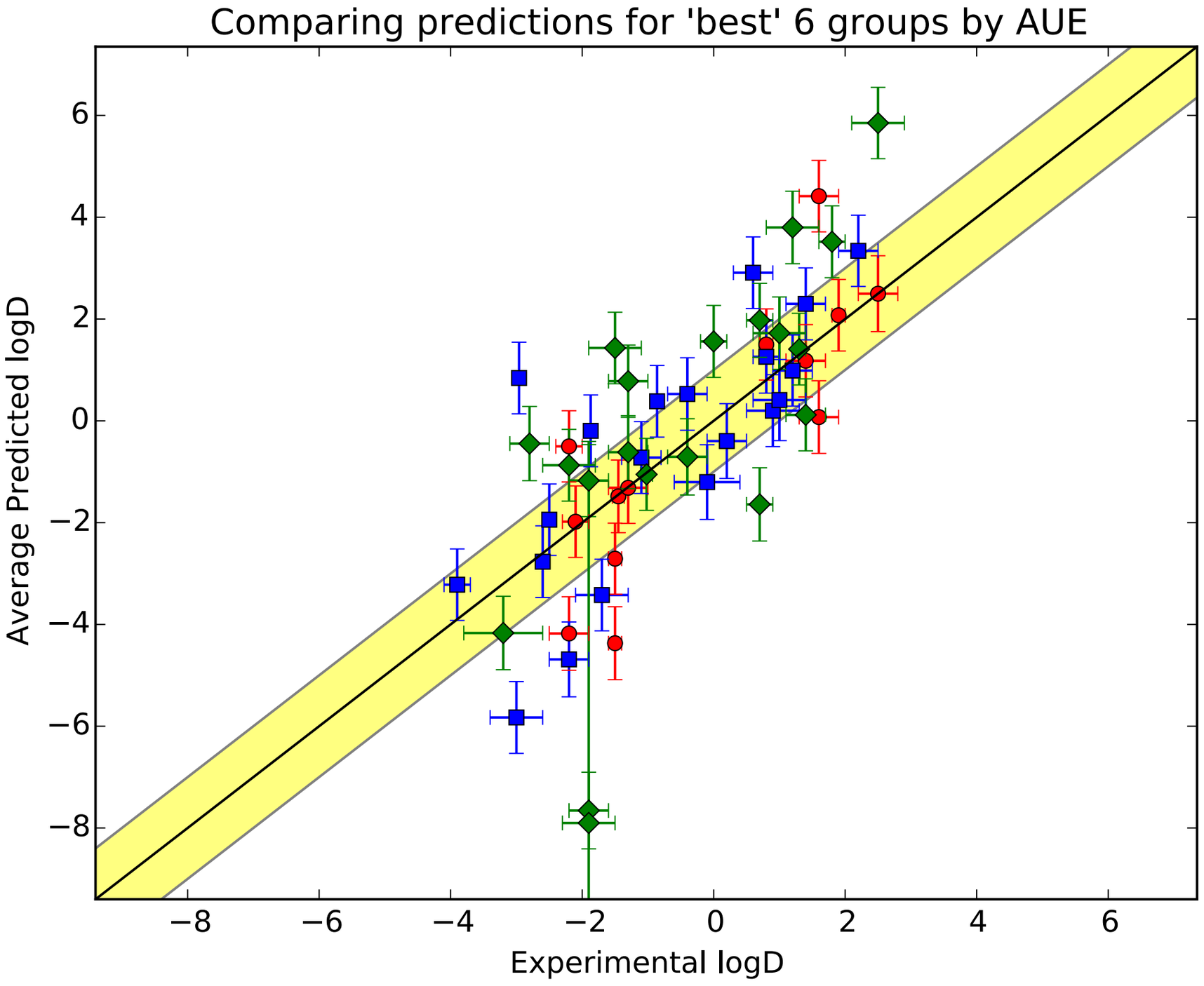
Do the predictions suggest any issues with the experimental data? Maybe



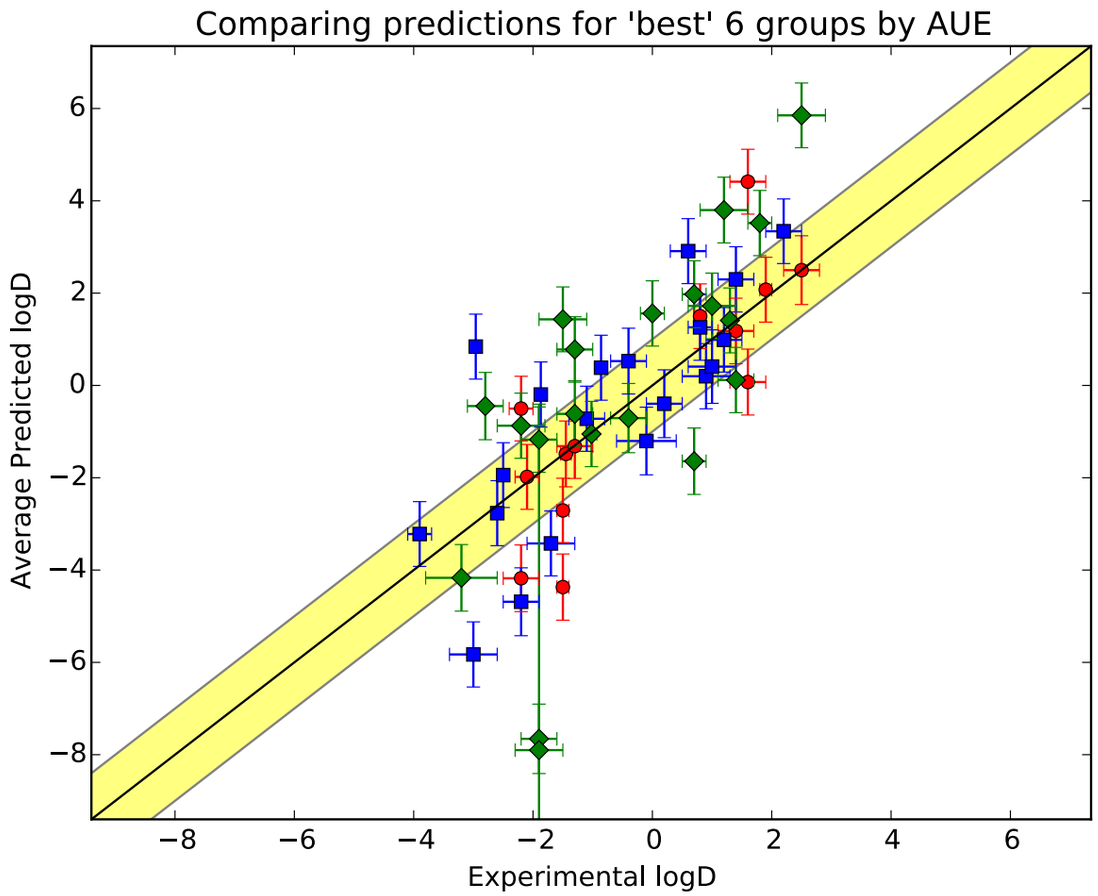
Across best 6 predictions:

Compounds 74 and 83 are particularly problematic

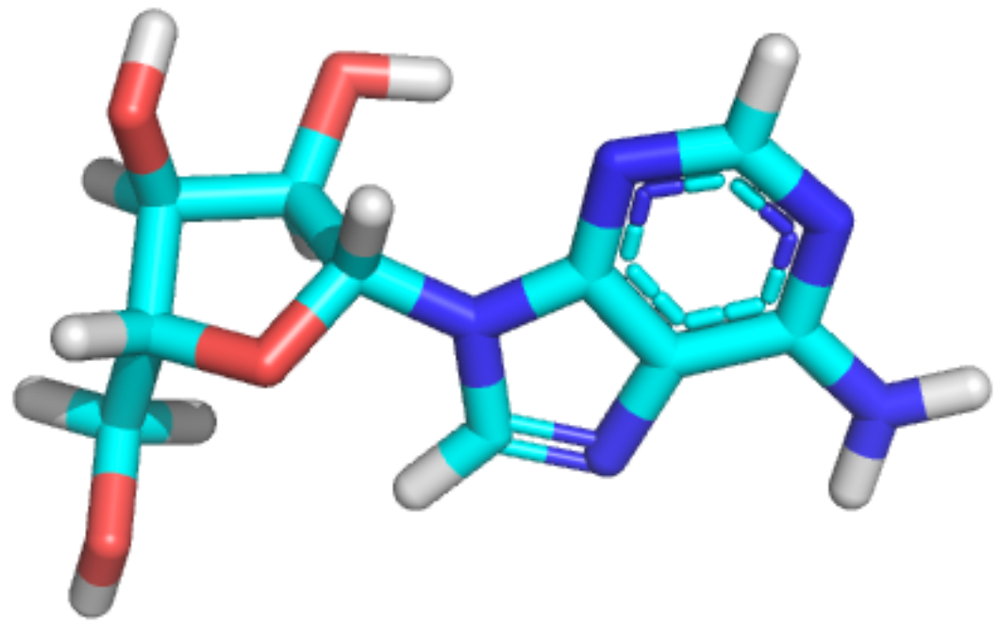
BUT, value for 83 is log D = -8+/-7 whereas for 74 it's -7.5+/-0.8

Consensus for 74; no consensus for 83

SAMPL5_074 is extremely polar and the calculated value much more strongly prefers water than experiment



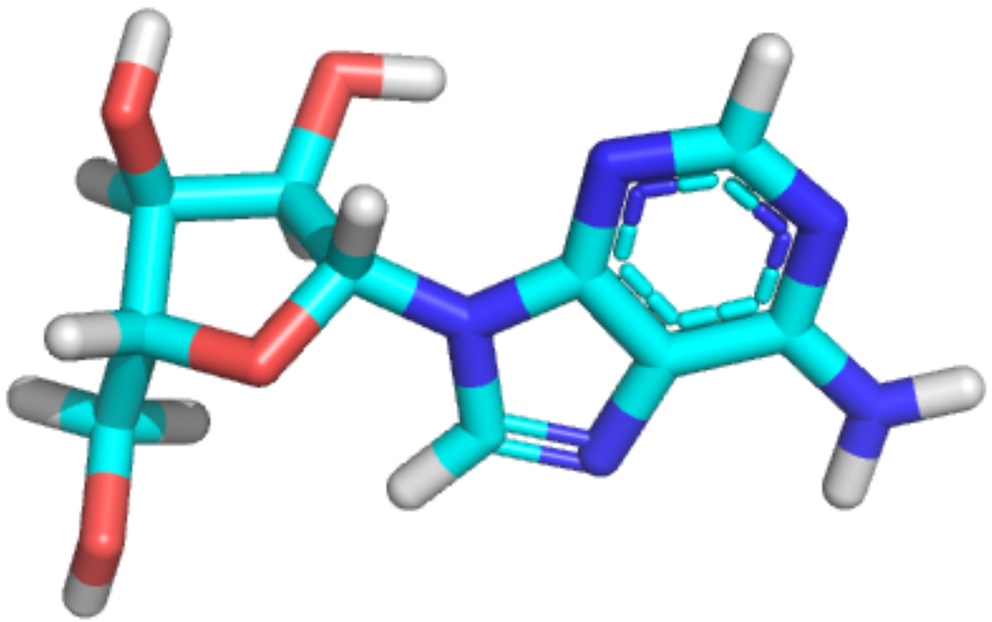
Average Log D for top 6 predictions for SAMPL5_74 is -7.5+/-0.8



No apparent pKa/tautomer issues

Cyclohexane water content could be an issue? Or dimer/oligomerization?

The water content of cyclohexane can make a huge difference, at least in extreme cases



Black et al., (JCP 16:537 (1948)) report solubility of cyclohexane in water as 0.0449 mole fraction

We obtained:

Log D (pure cyclohexane): -3.76+/-0.04

Log D (with 0.045 mf water): -1.73+/-0.04

Experiment: -1.9+/-0.03

Change of 2 log units based on 0.045 mole fraction water!

In our standard calculations, we did log P values. What if we'd done log D?

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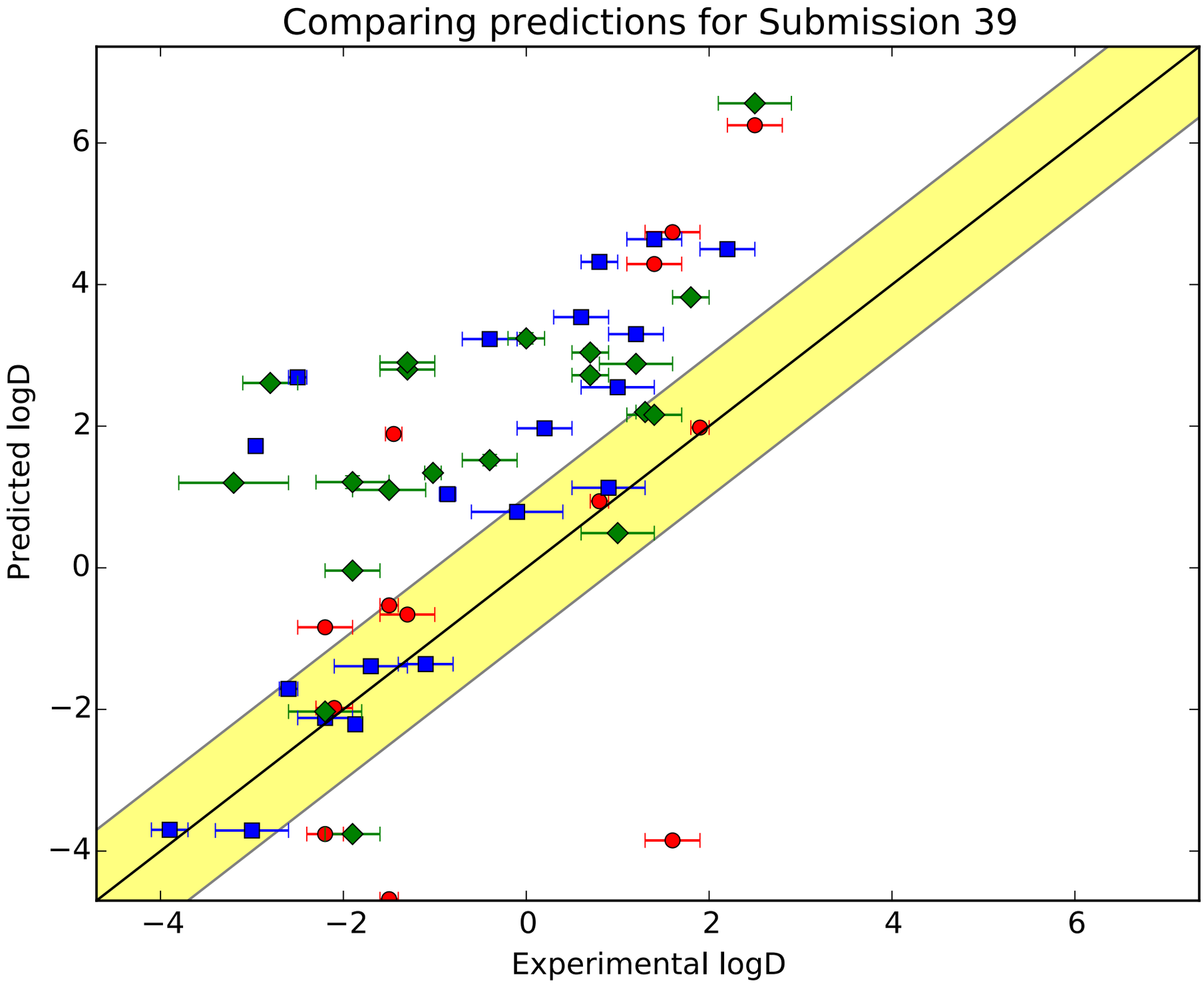
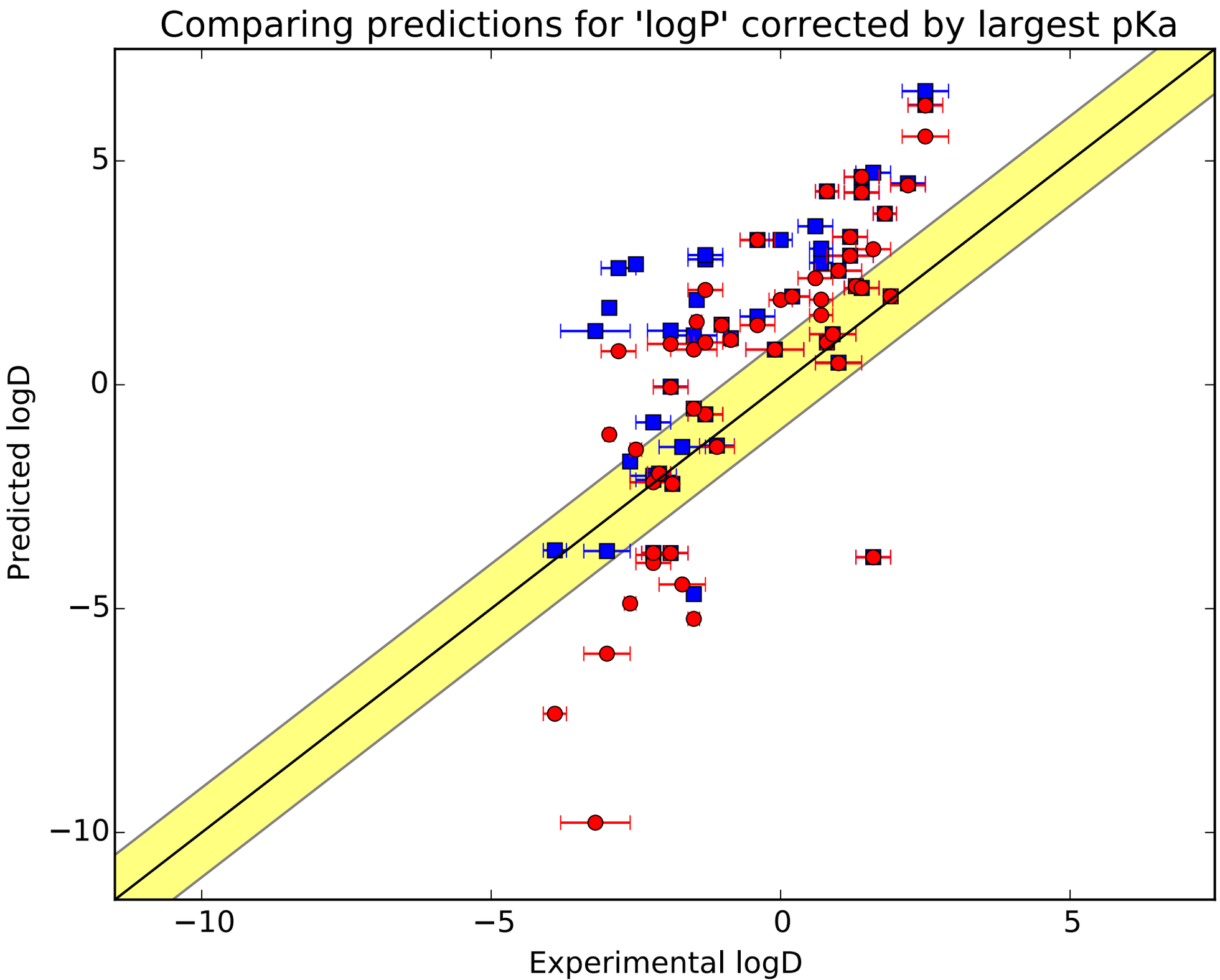
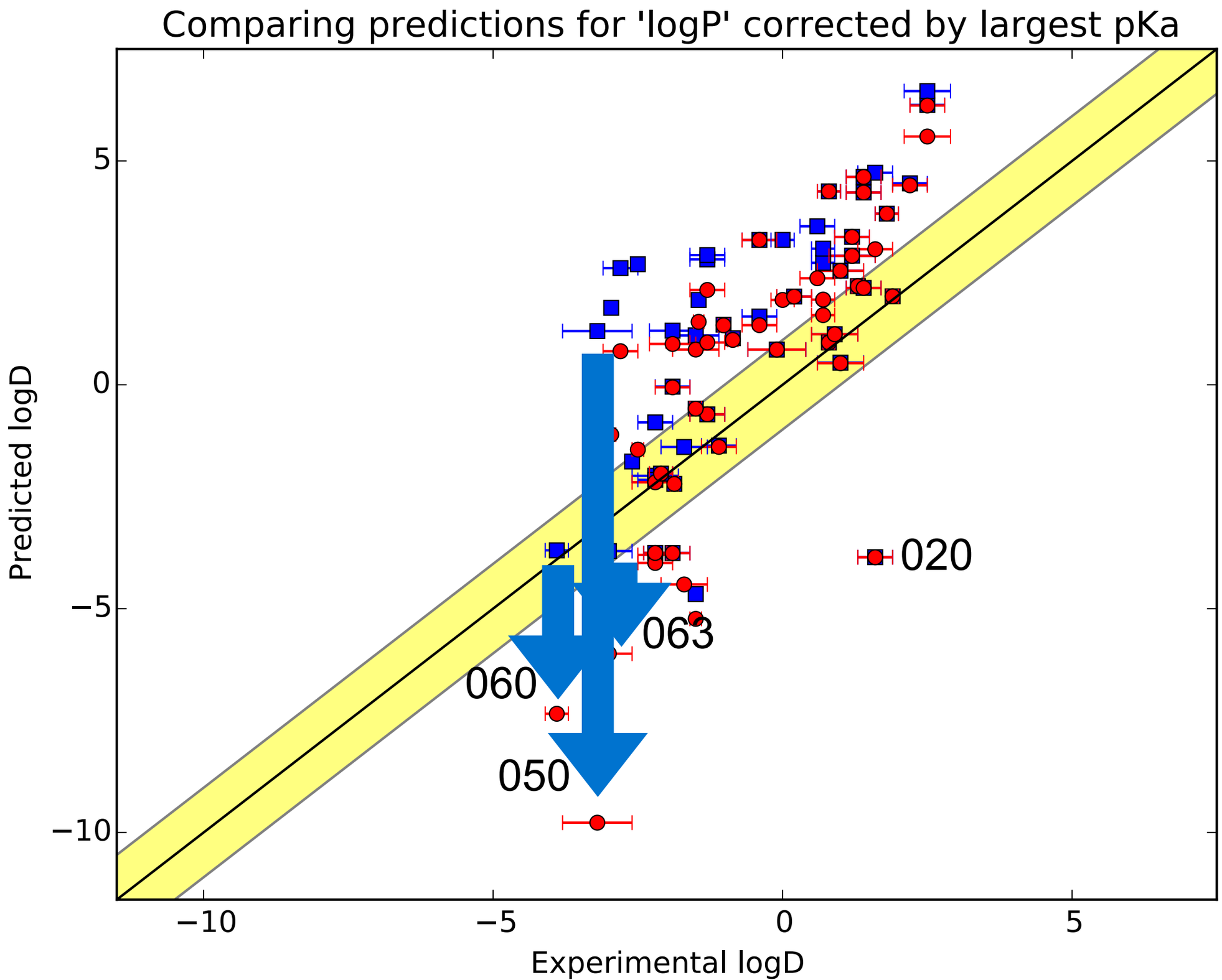


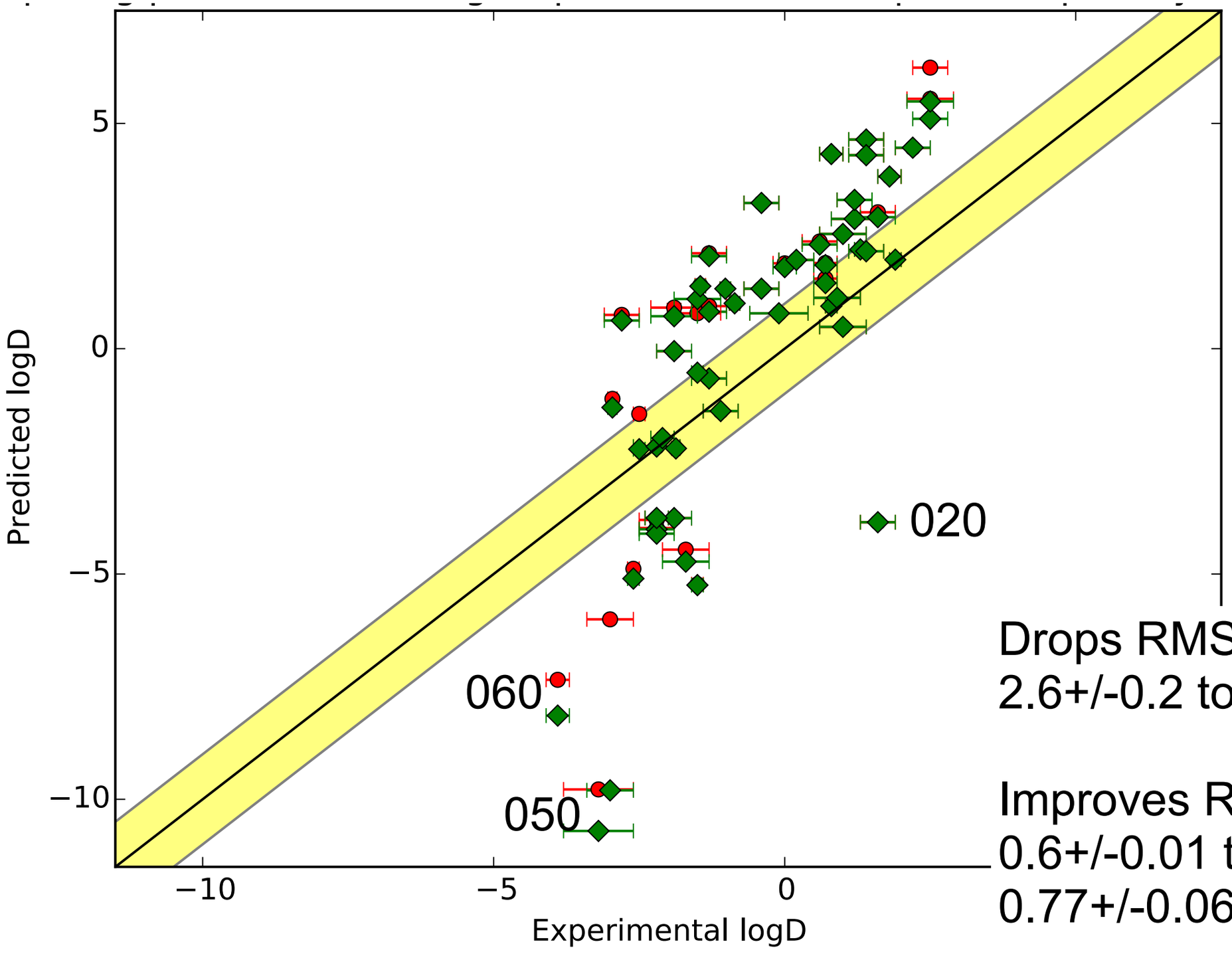
A first pass is to correct for pKa's, which improves things modestly



A first pass is to correct for pKa's, which improves things modestly (except…)



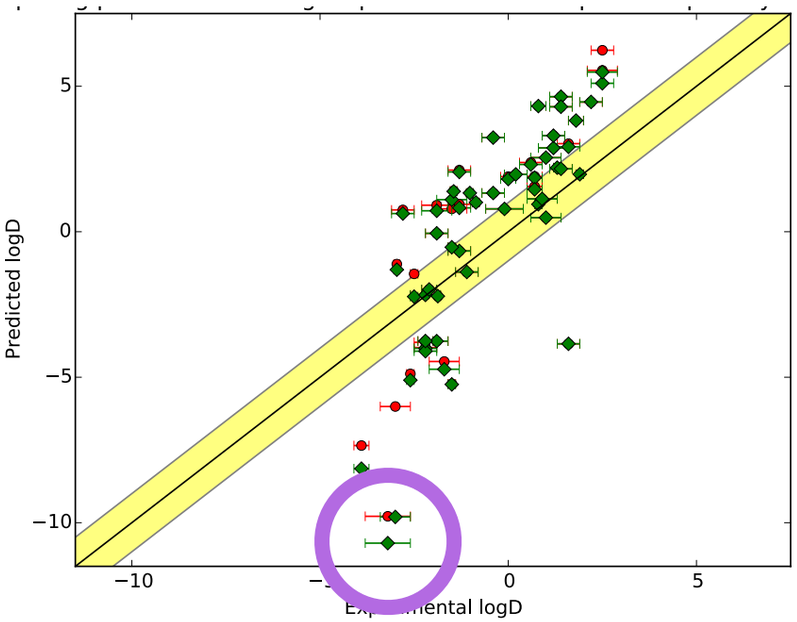
More properly, we should be handling the populations of all states based on predicted energetics



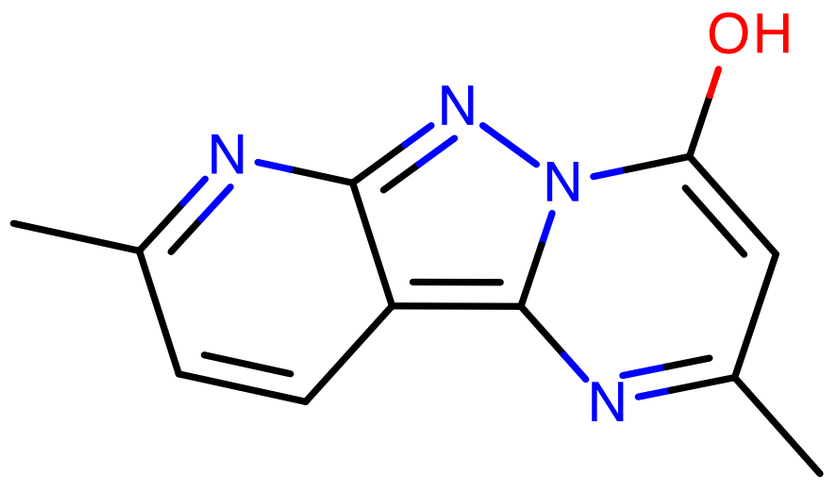
Drops RMS from
2.6+/-0.2 to 2.1+/-0.2

Improves R from
0.6+/-0.01 to
0.77+/-0.06

One reason pKa/state corrections can make things worse is that we're only doing them for water



SAMPL5_050



Experiment -3.2
Our log P: 1.2
Epik state penalty: -11.9
logD = -10.7

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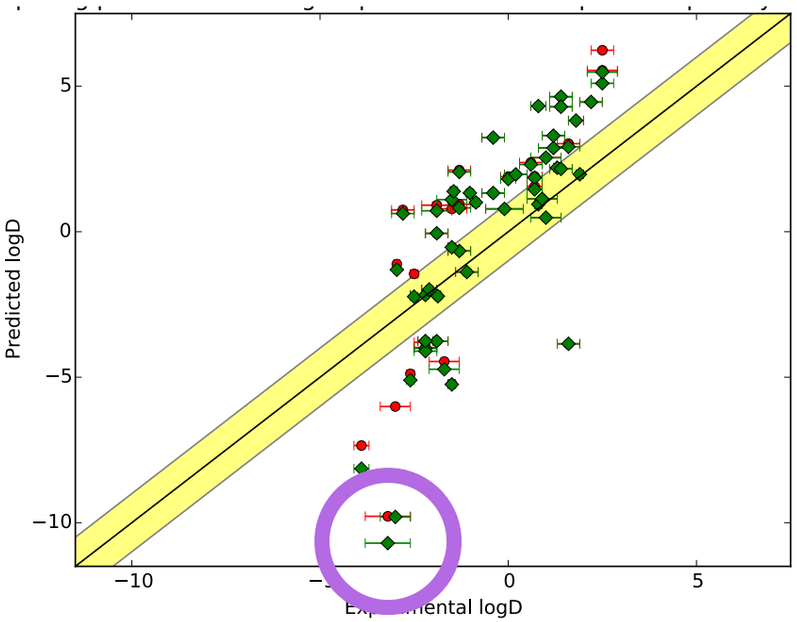
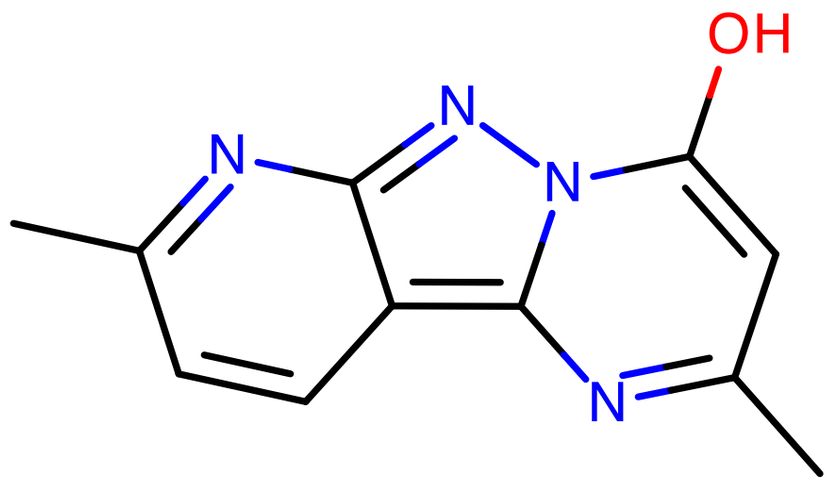


SAMPL5_050



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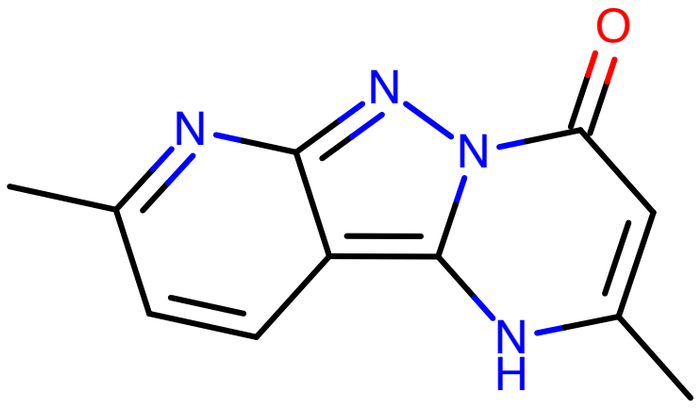

Our log P: -6.04
Epik state penalty: -0.453
logD = -6.49

It turns out that a “guess zero” model would have done relatively well here

RMS error 1.8+/-0.1
AUE 1.6+/-0.1

Best by both metrics
Also smallest max error

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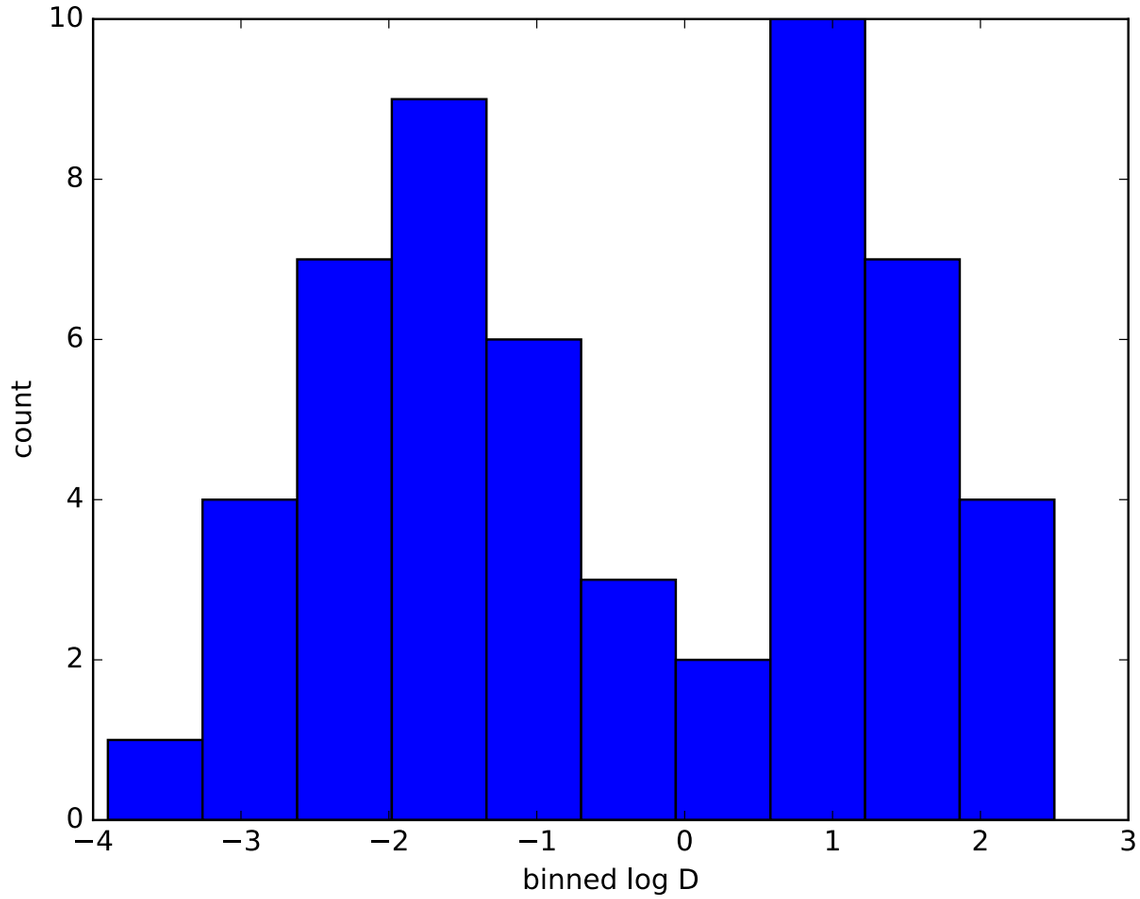
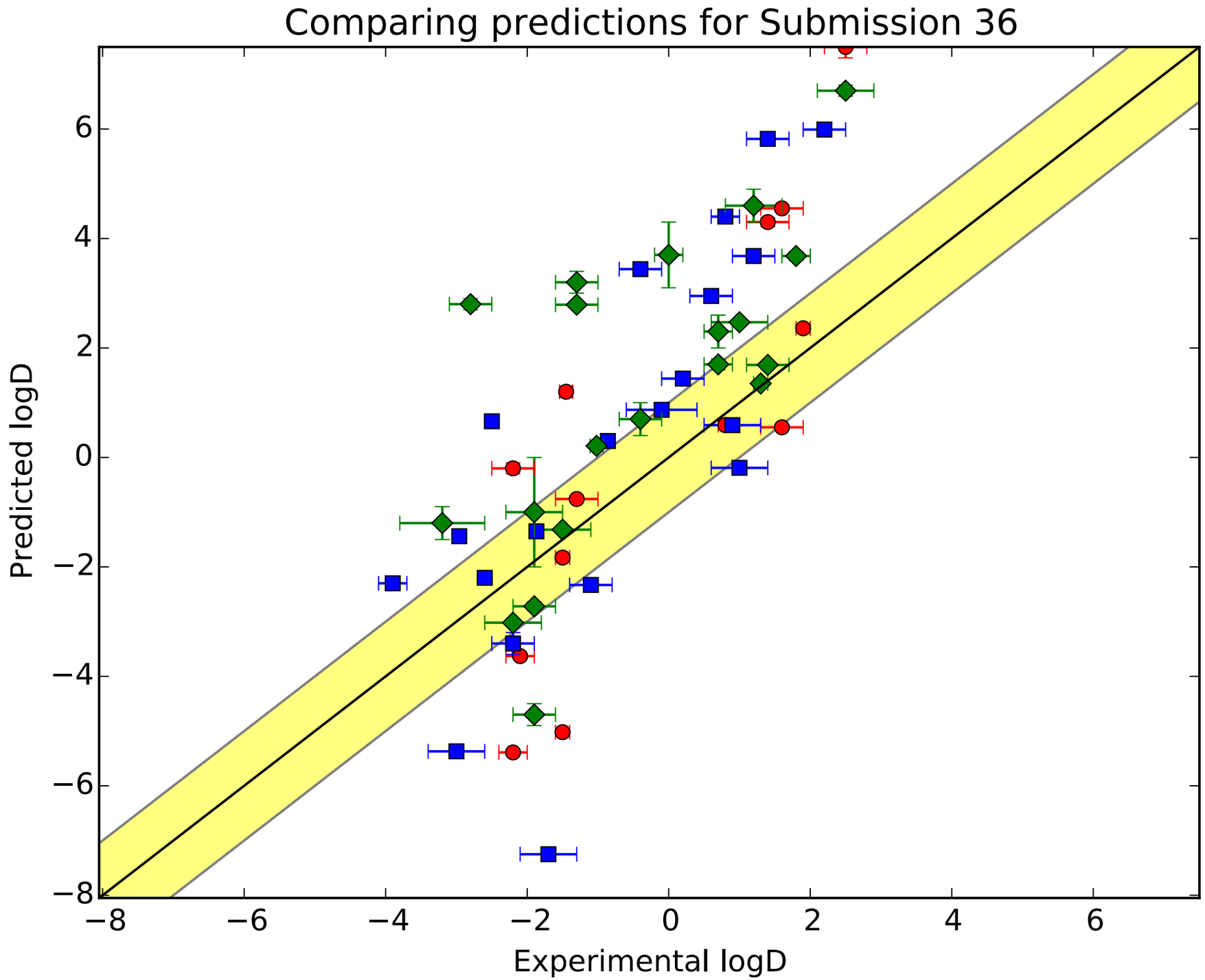
Why? Dynamic range is not huge here and compounds are fairly clustered near zero



This means that some methods suffer from “overprediction”



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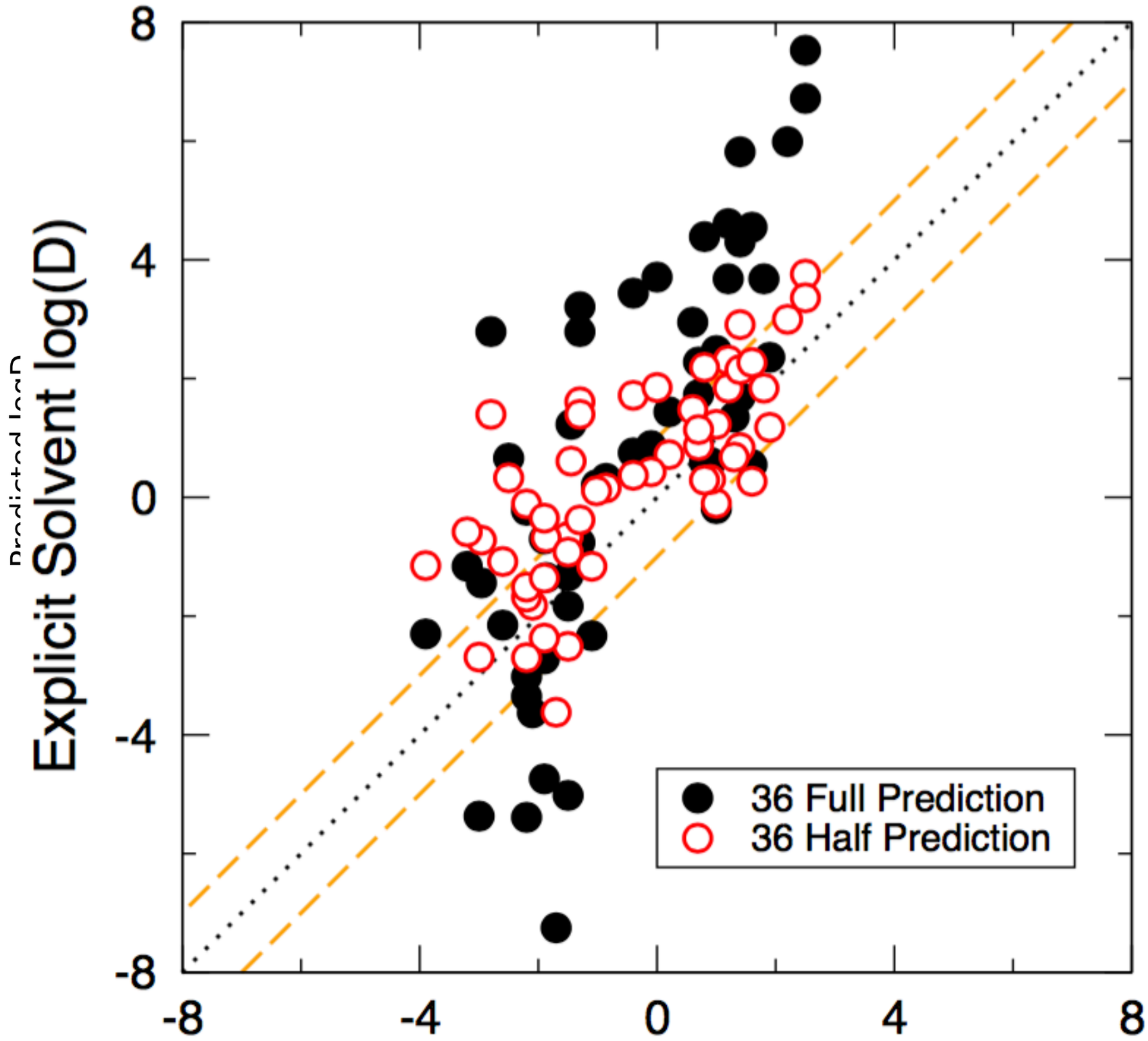
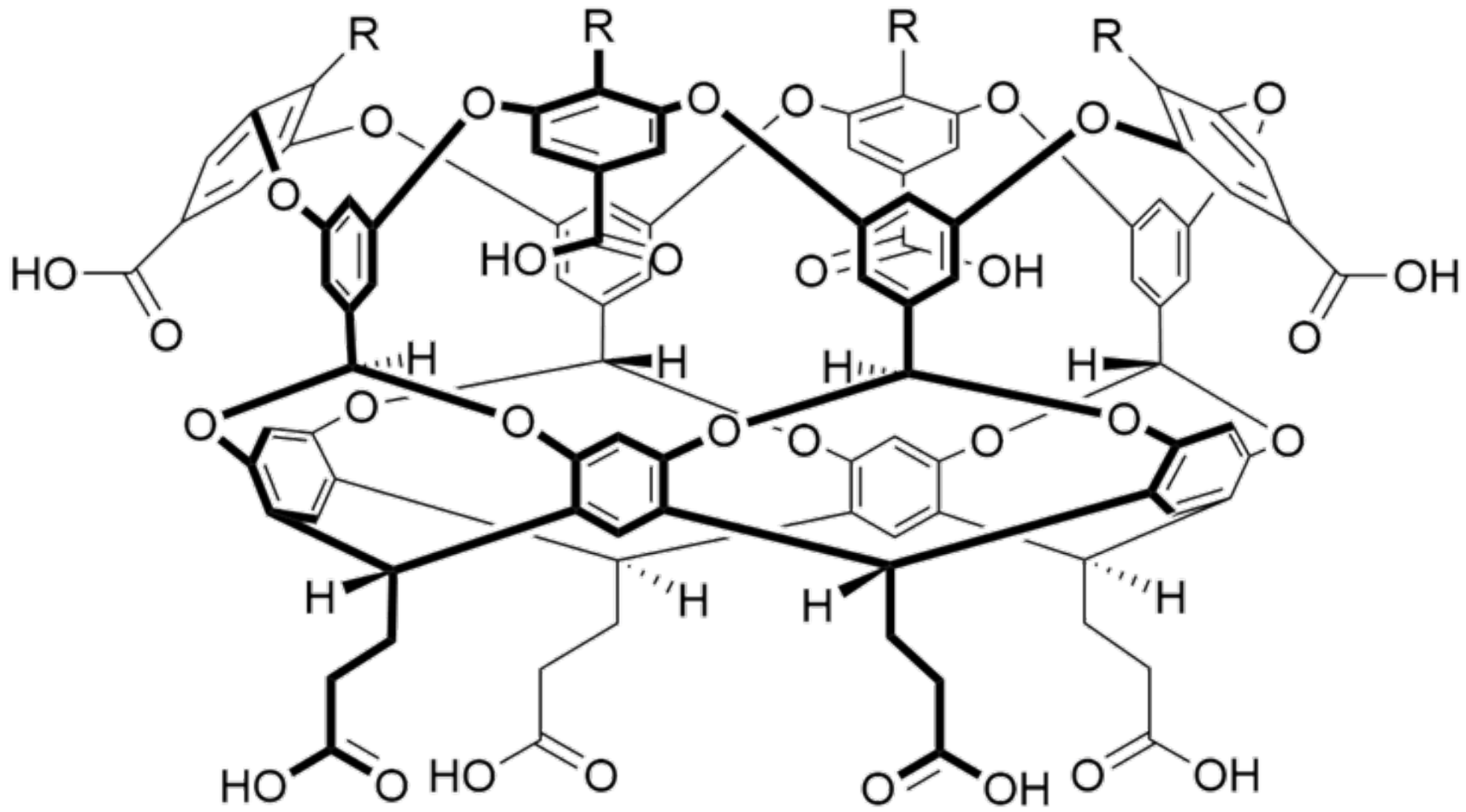


Better even than "guess zero":

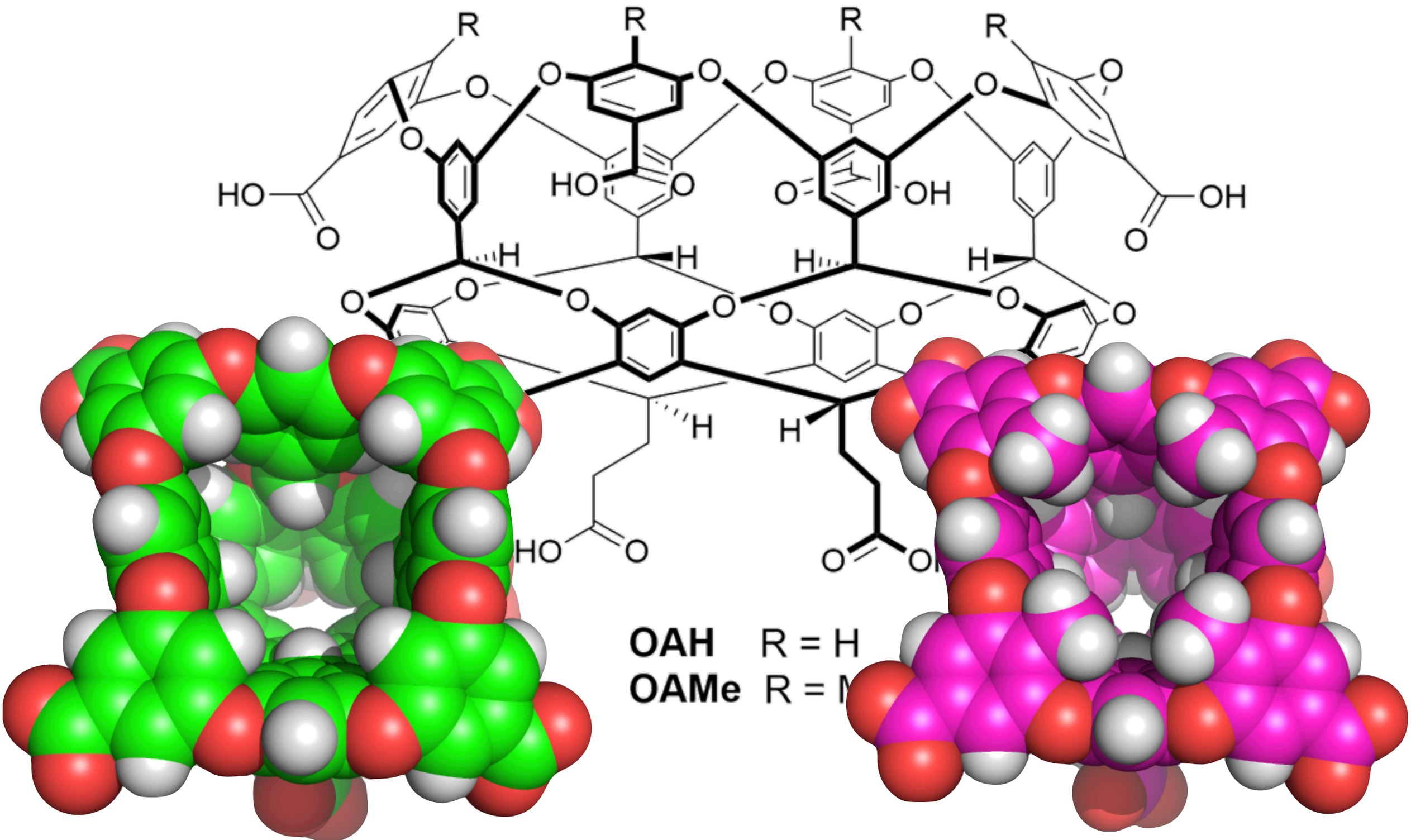
RMS 1.4
AUE 1.2

The host-guest challenge involved the familiar OctaAcid, and a new methylated (OAMe) version

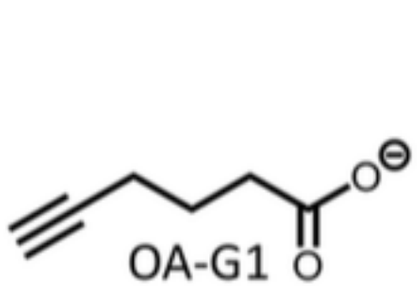


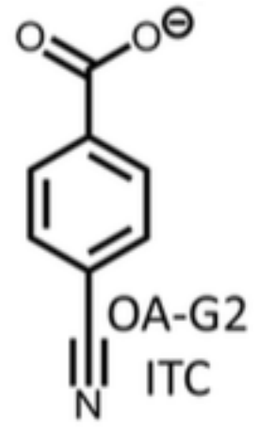
OAH R = H
OAMe R = Me

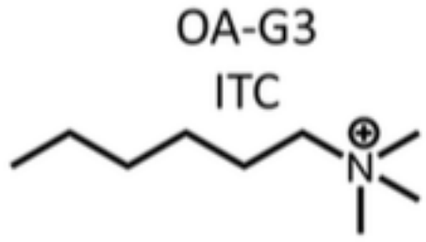
The host-guest challenge involved the familiar OctaAcid, and a new methylated (OAMe) version

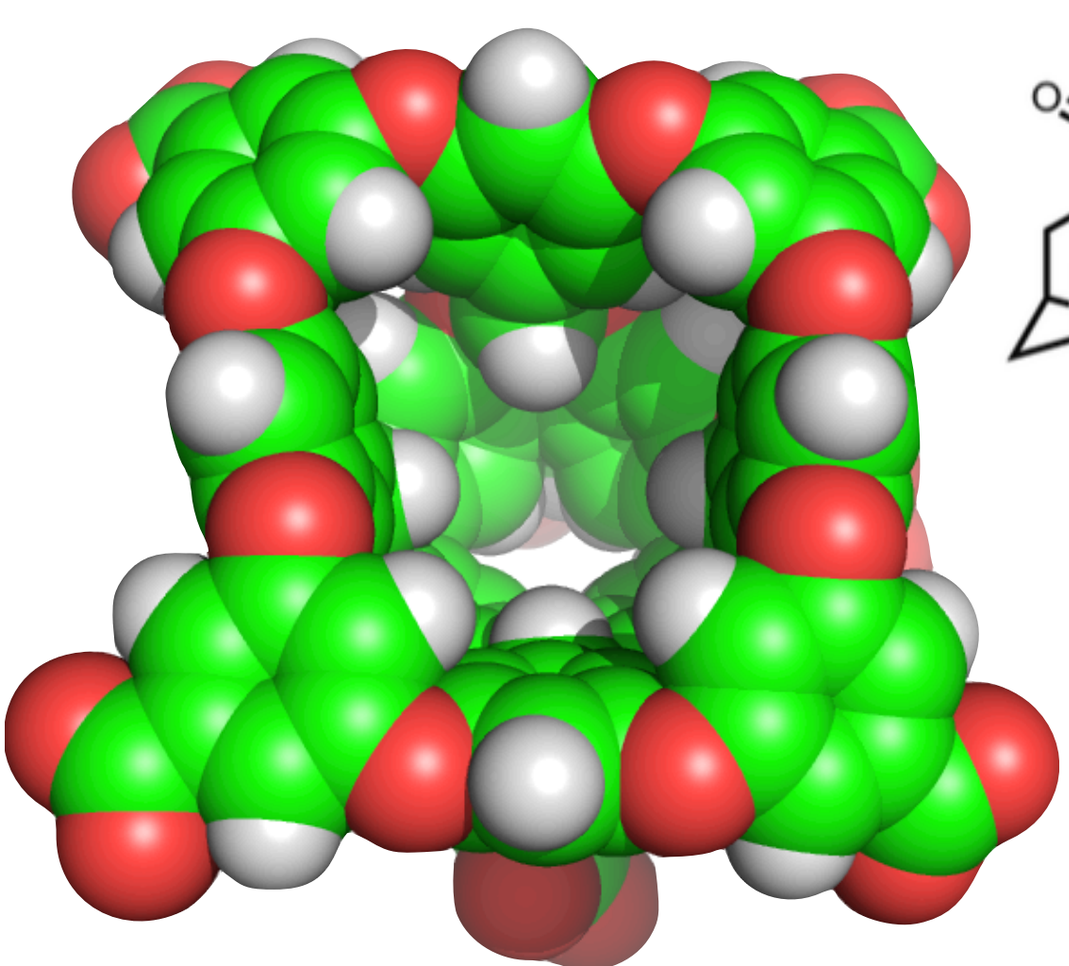


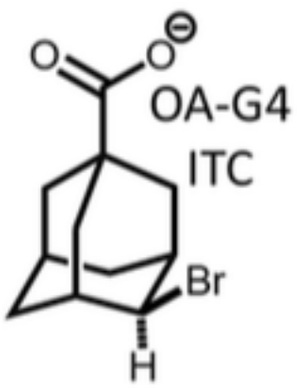
The challenge focused on binding of the same six guests to both hosts

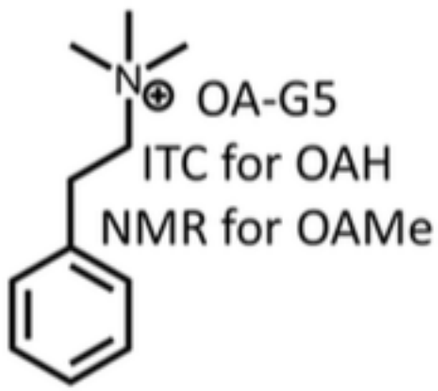


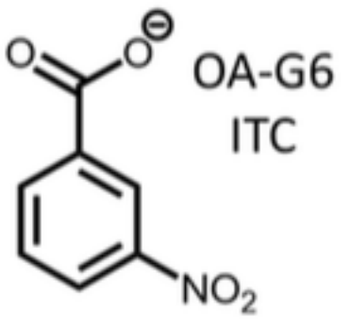




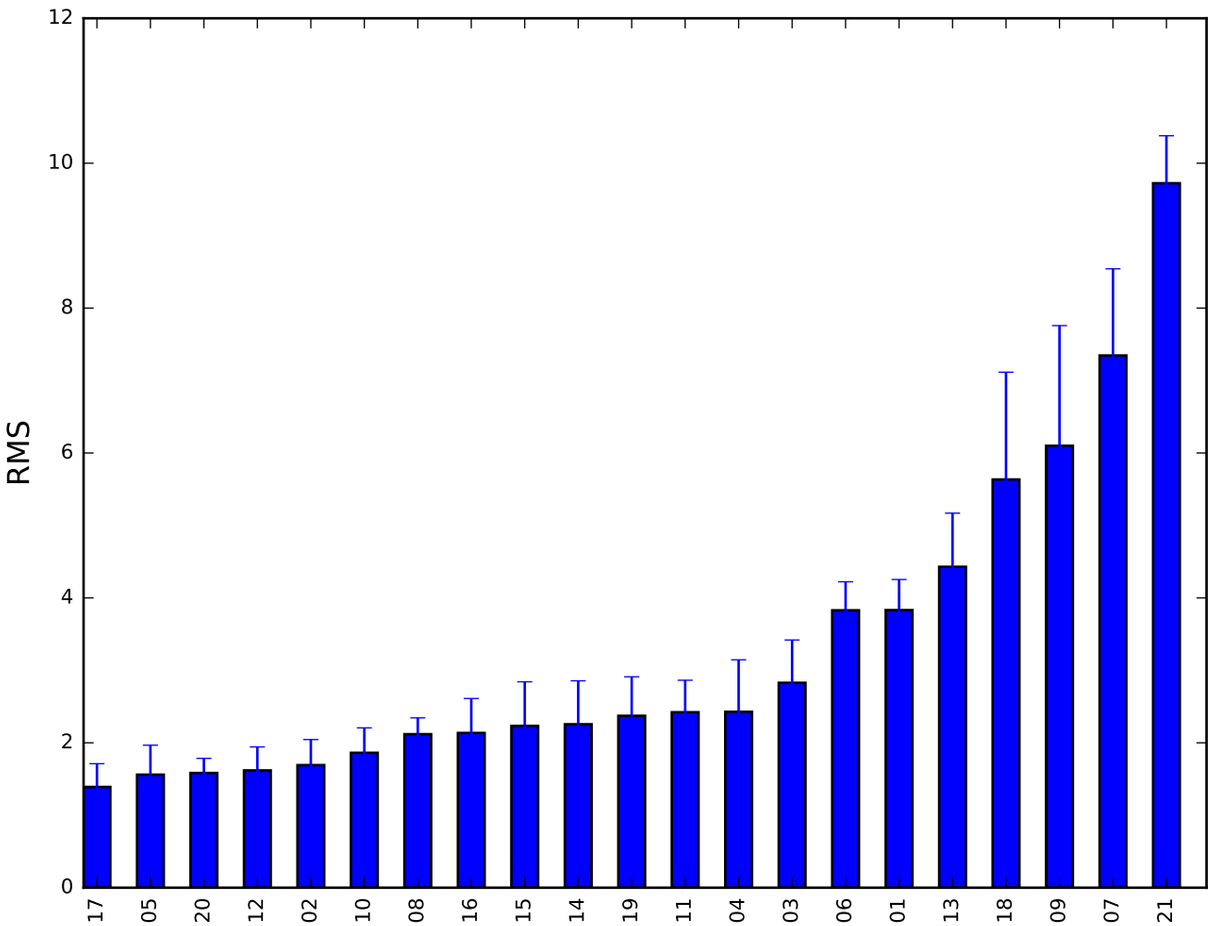








The Octa Acid systems proved still to be quite challenging: OAH



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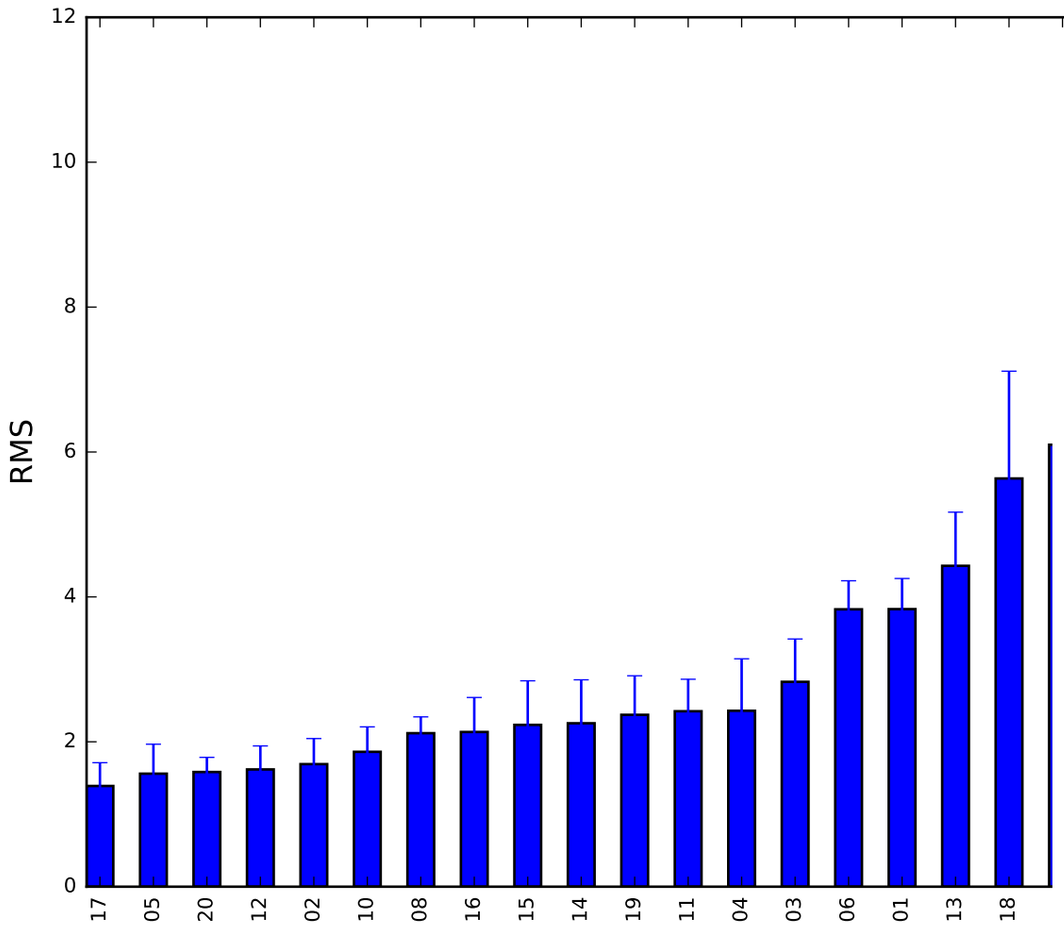
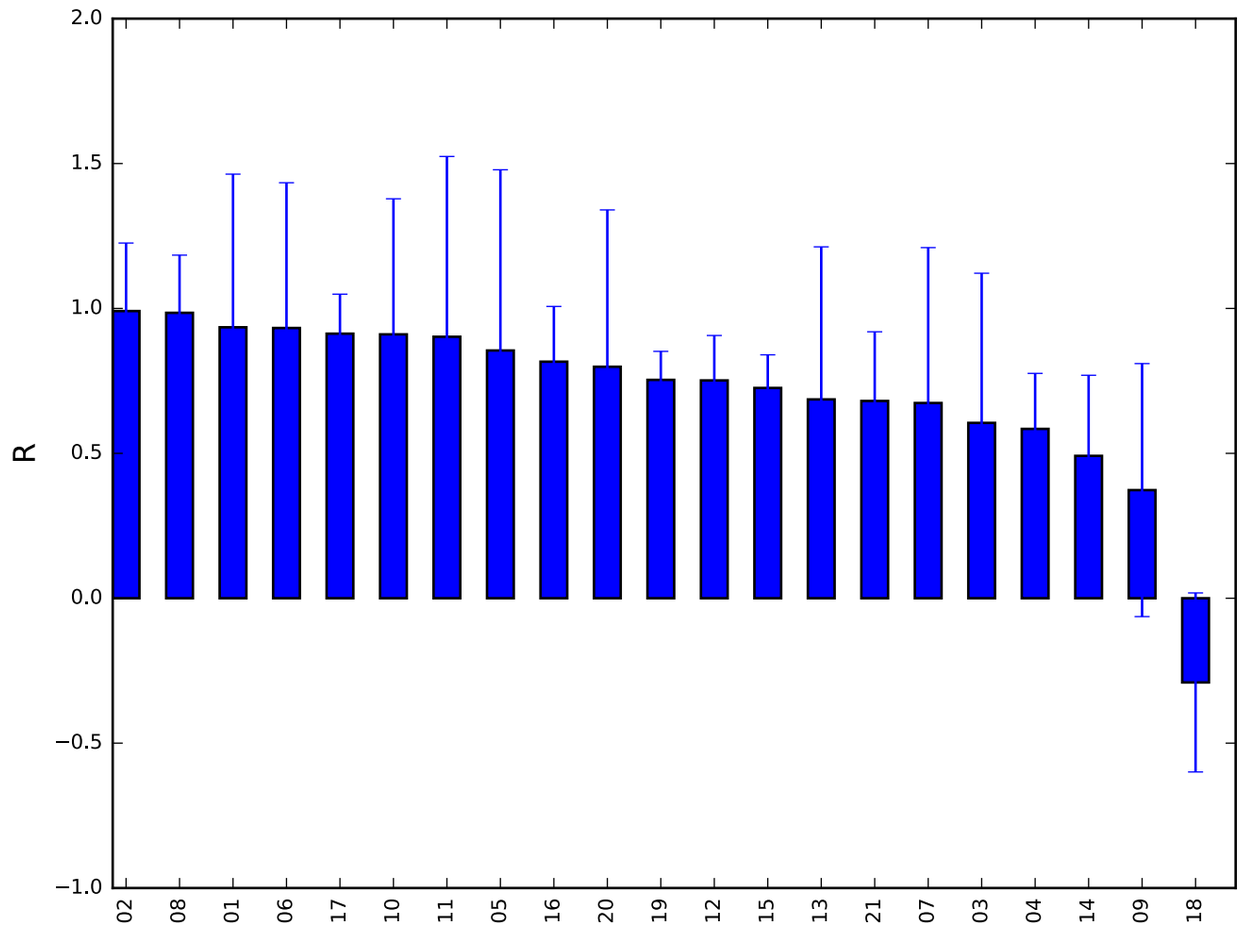
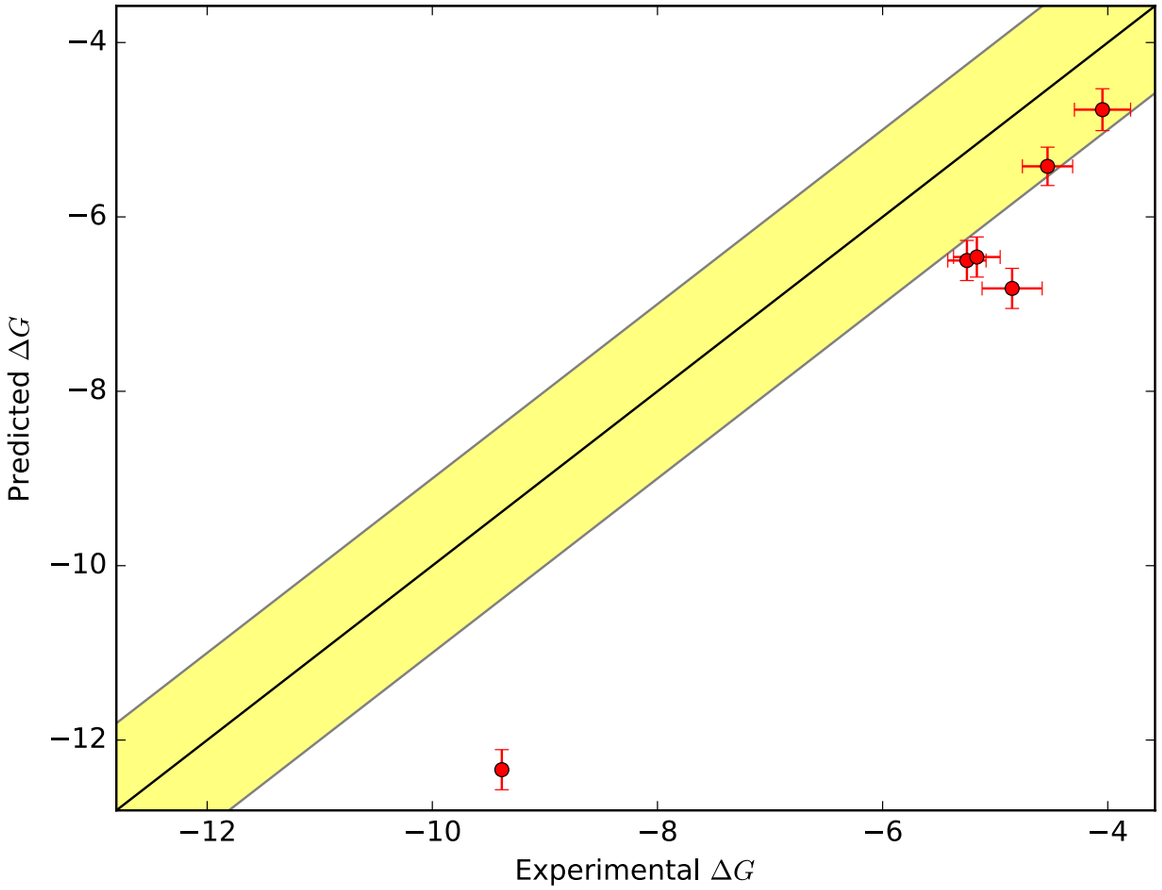




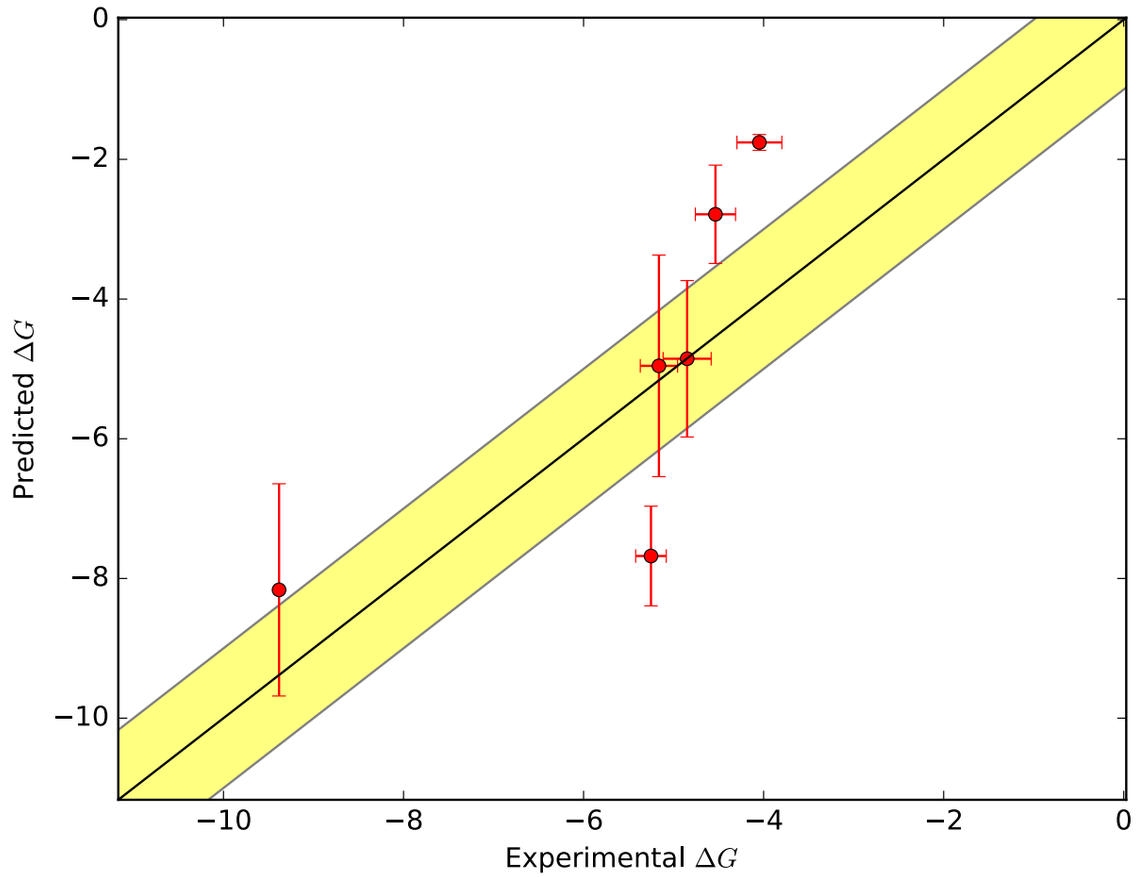
The Octa Acid systems proved still to be quite challenging: OAH

Submission 02



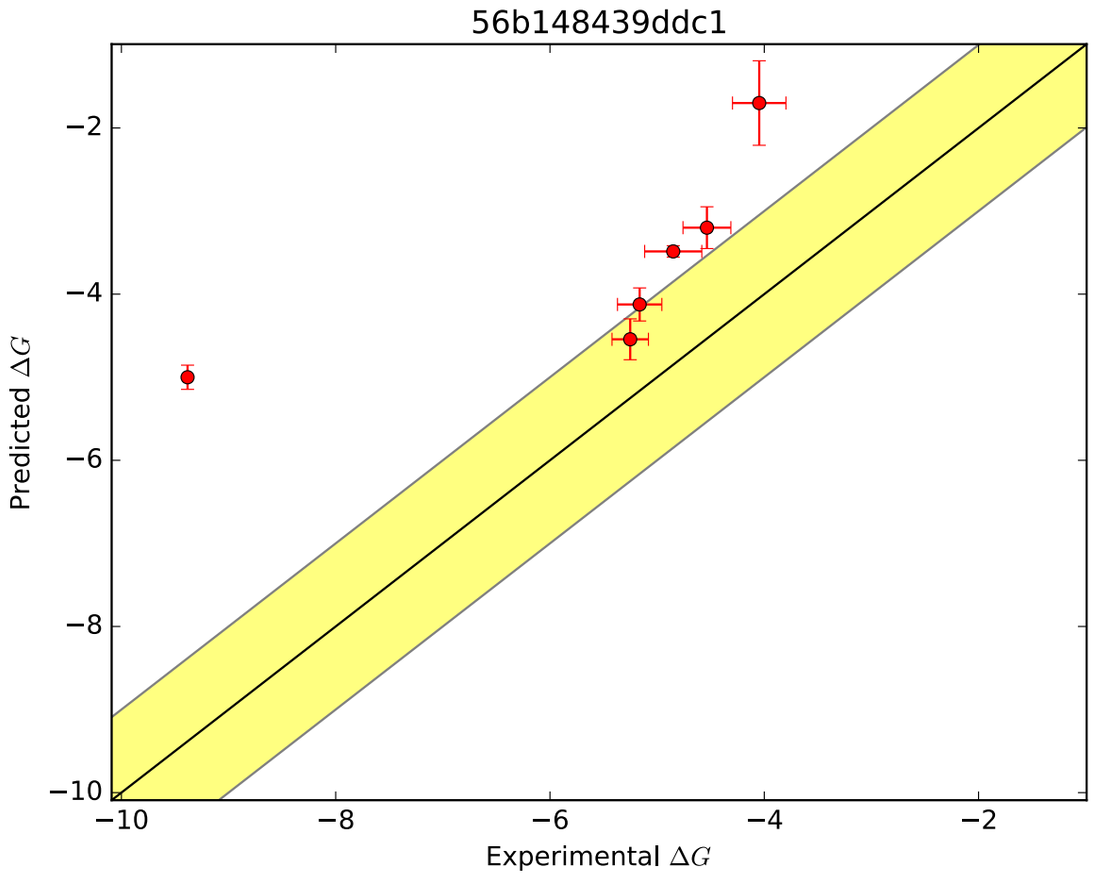
Jane Yin, Gilson lab, standard/reference calculation MD free energy via “attach pull release”

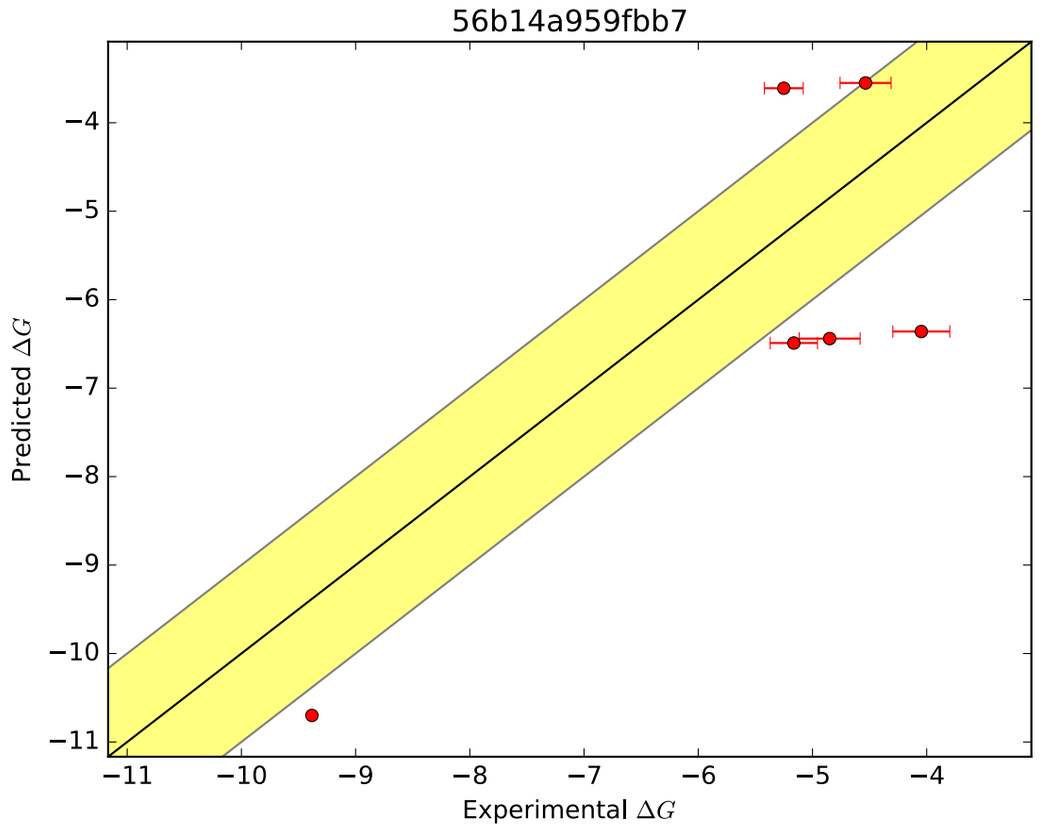
Submission 12



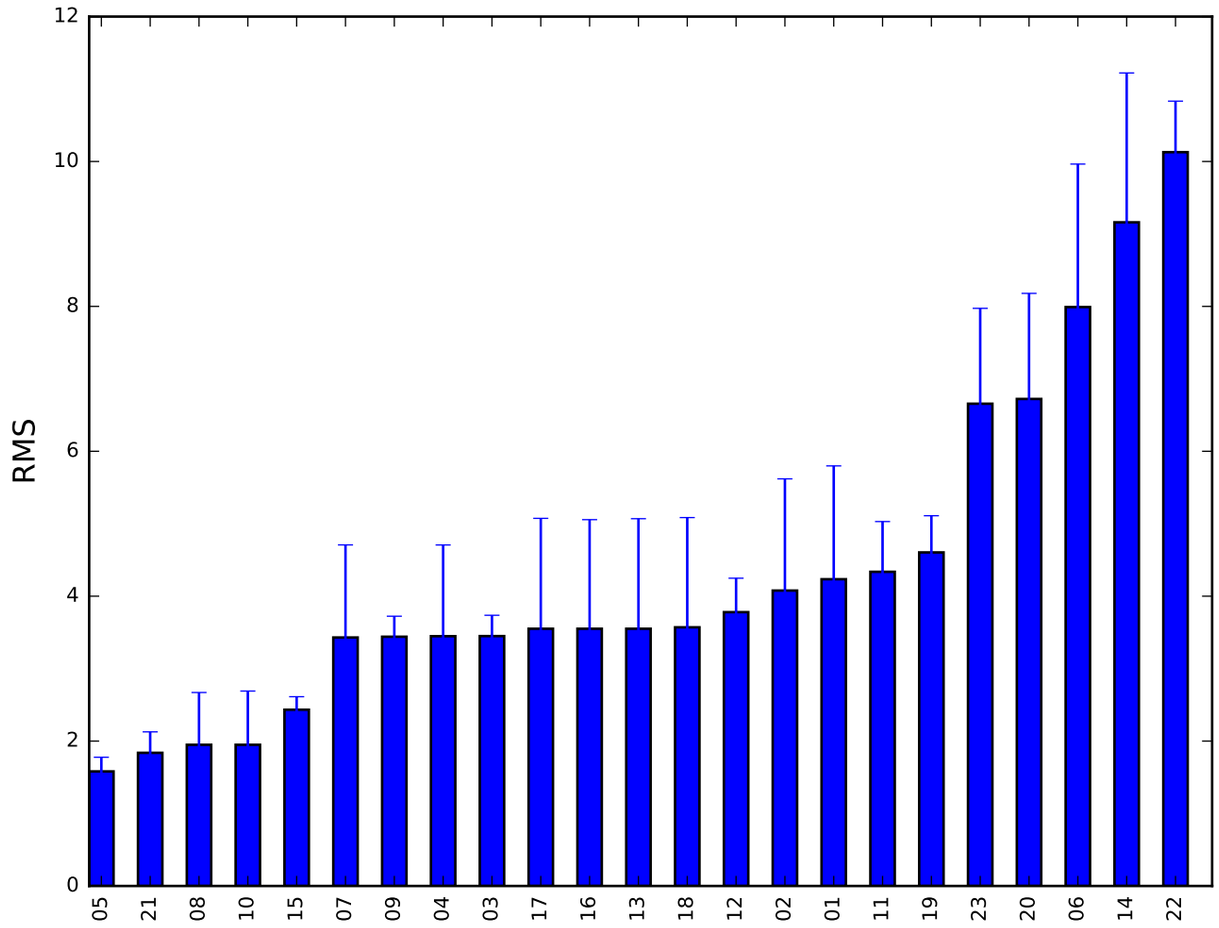
Florentina Tofoleanu, Brooks group, alchemical absolute calculations

But for more typical submissions, things were a good deal worse

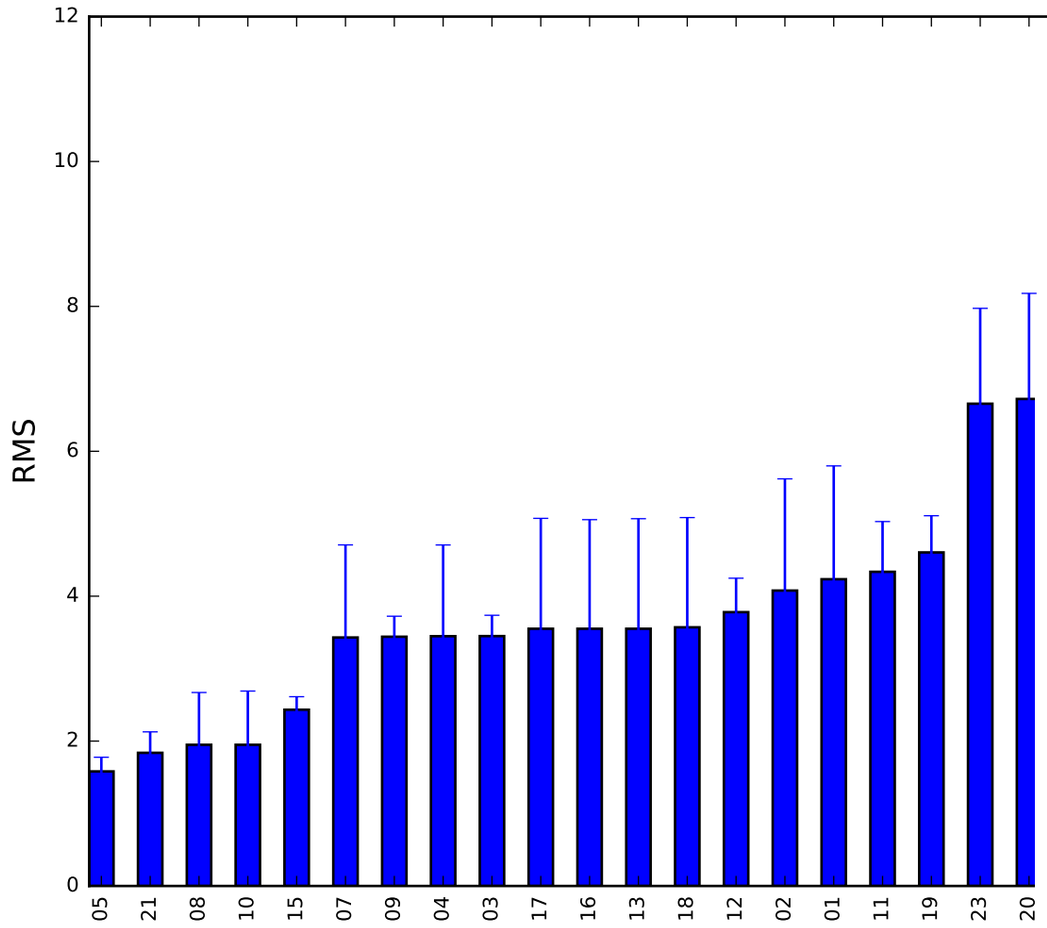


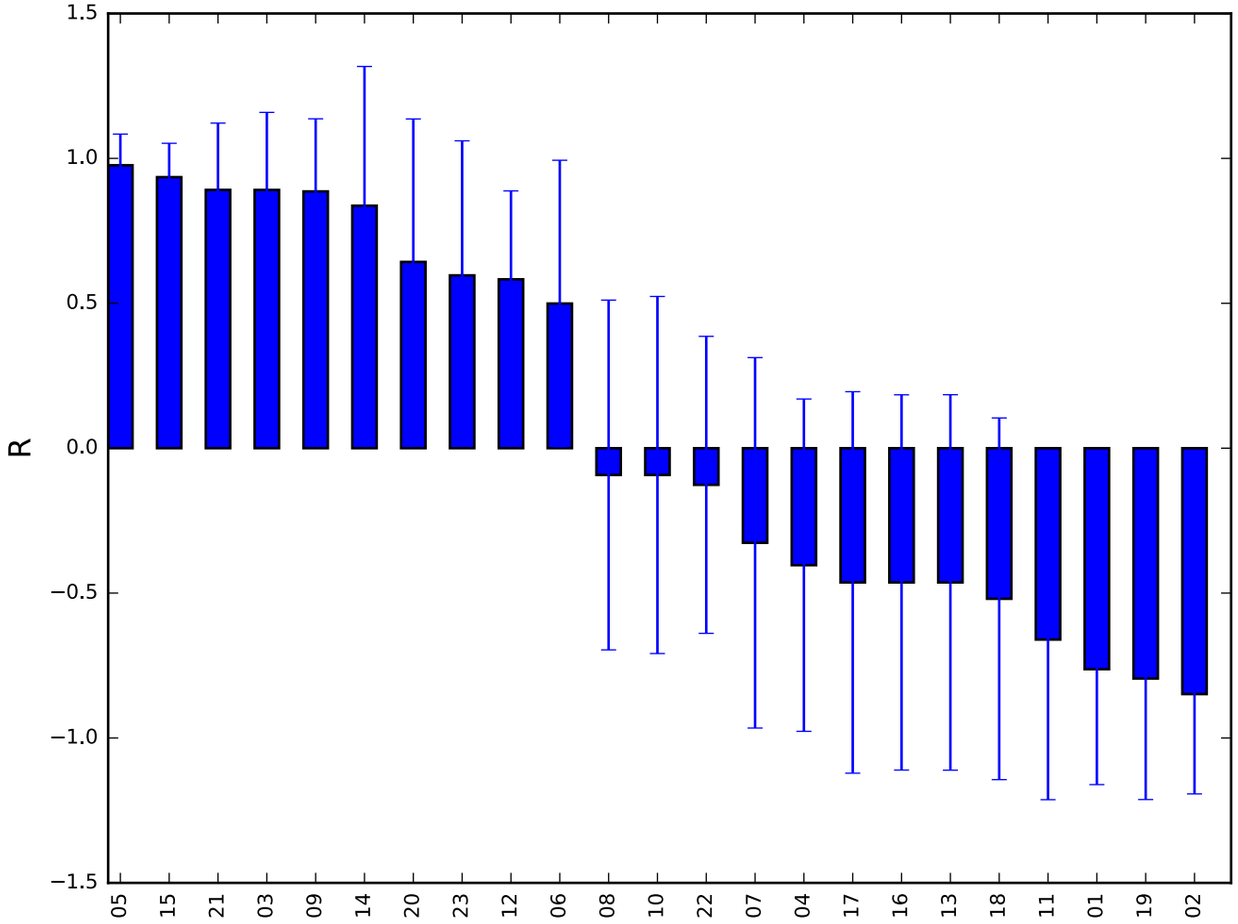


The methylated version seemed to be more challenging still



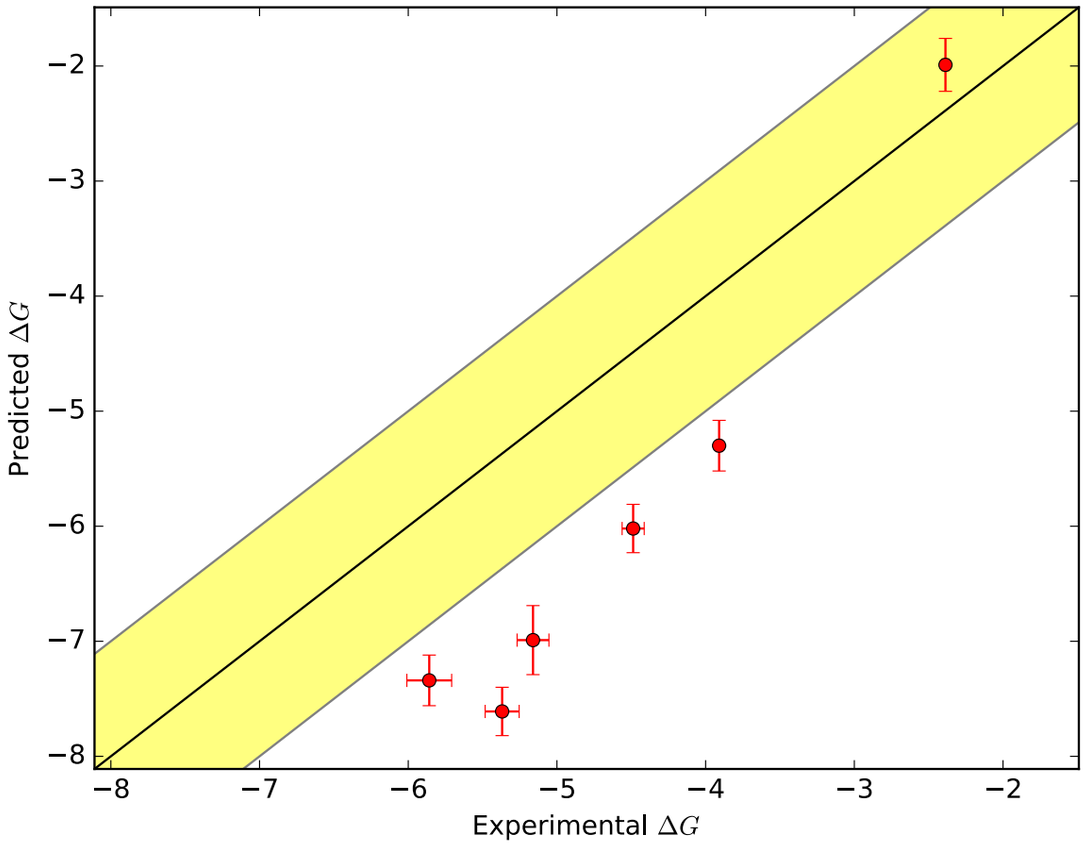
The methylated version seemed to be more challenging still





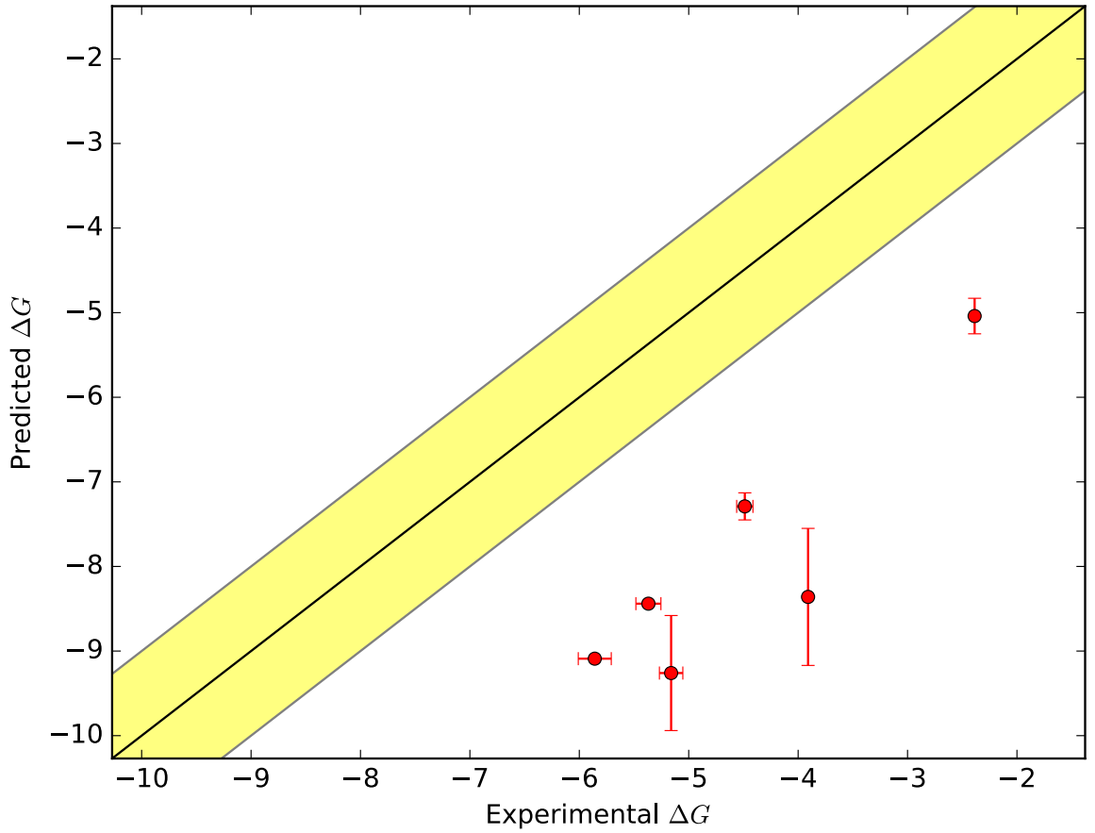
Again, the best submissions seem reasonable, but some systematic error?

Submission 05



Jane Yin, Gilson lab, standard/reference calculation MD free energy via “attach pull release”

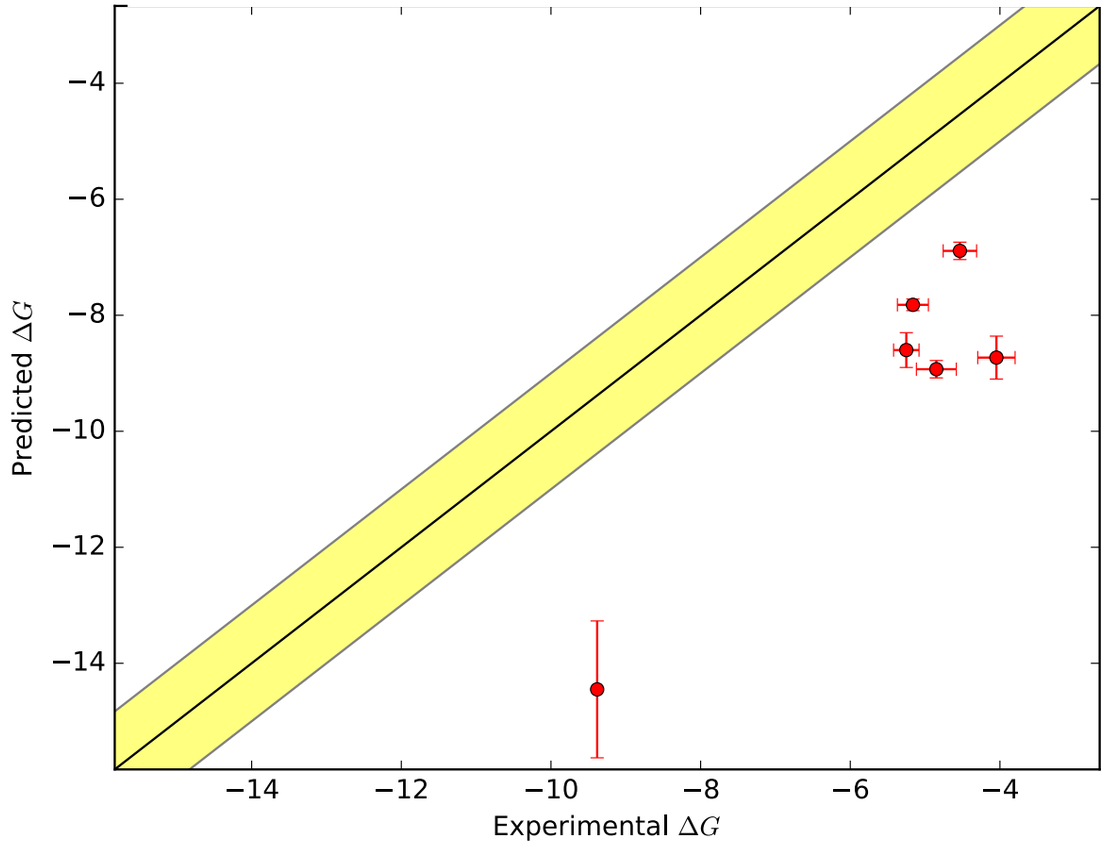
Submission 03



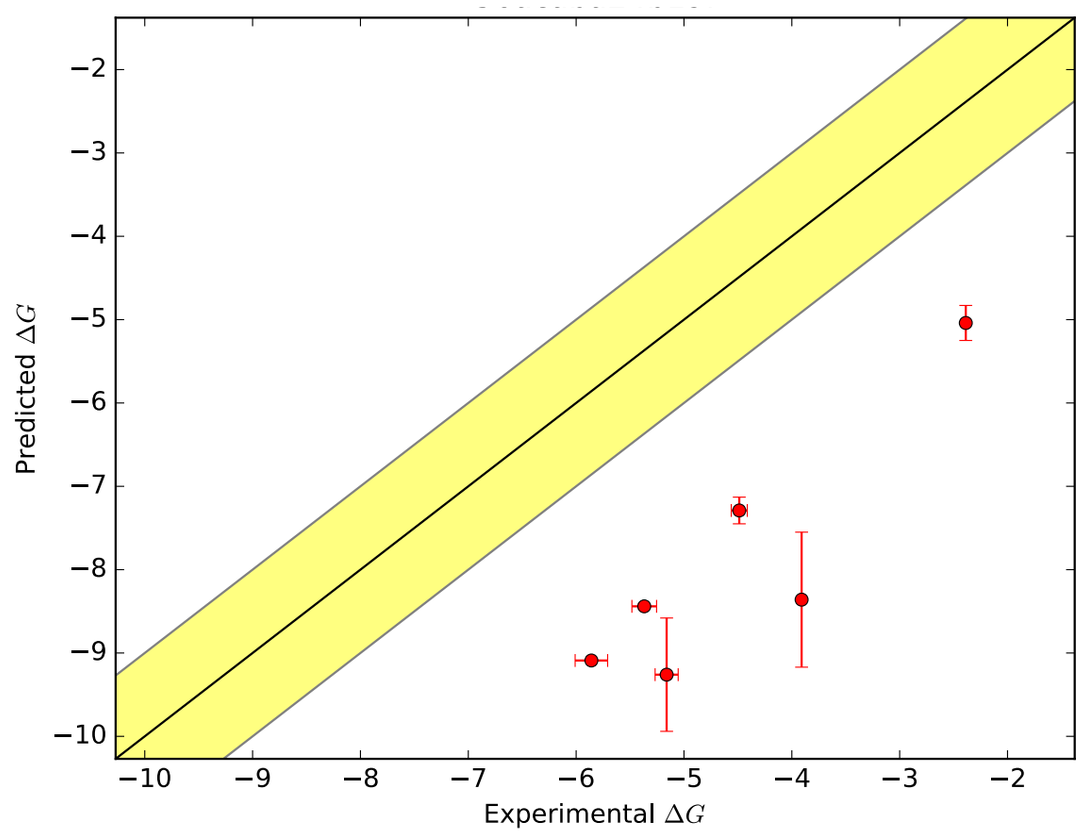
Julien Michel group, SOMD AM1-BCC/GAFF/MBAR

A method might be ranked “well” in OAMe and not OAH, and vise versa

Submission 01, OAH



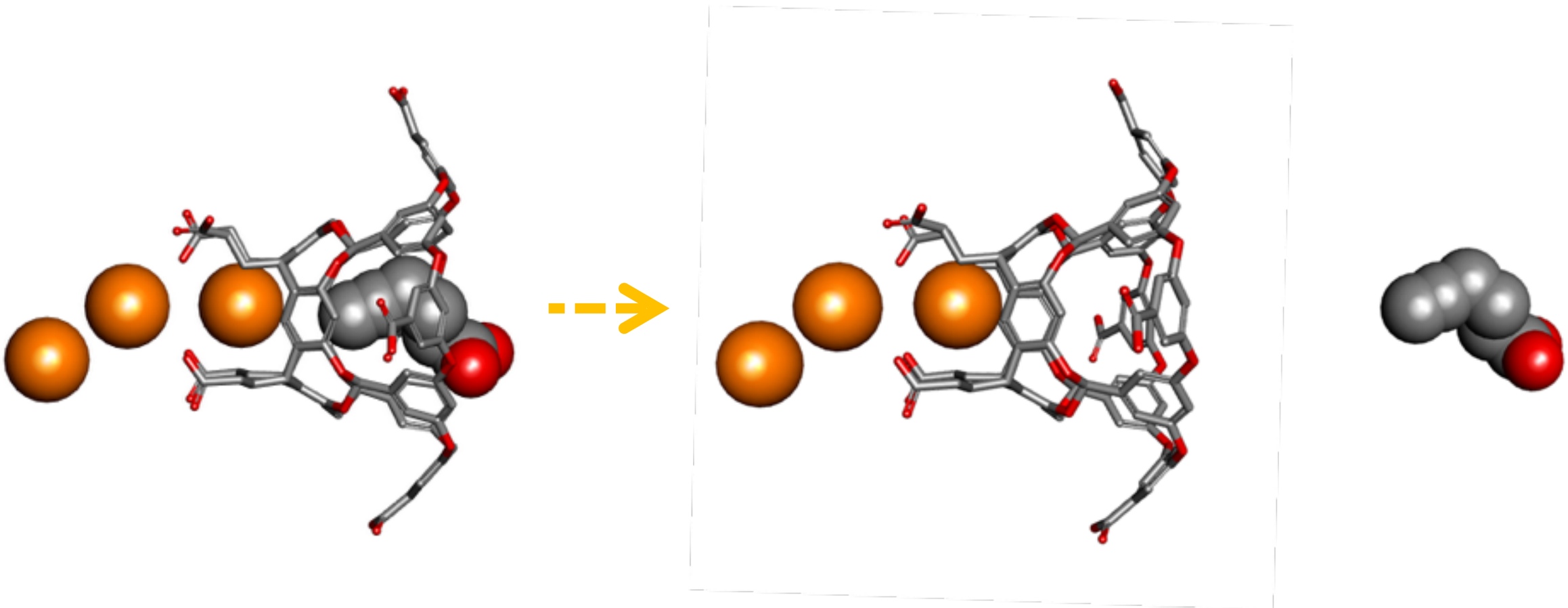
Submission 03, OAMe



Julien Michel’s group; absolute binding free energy calculations with restraints using MD (Sire/OpenMM); analyzed via MBAR

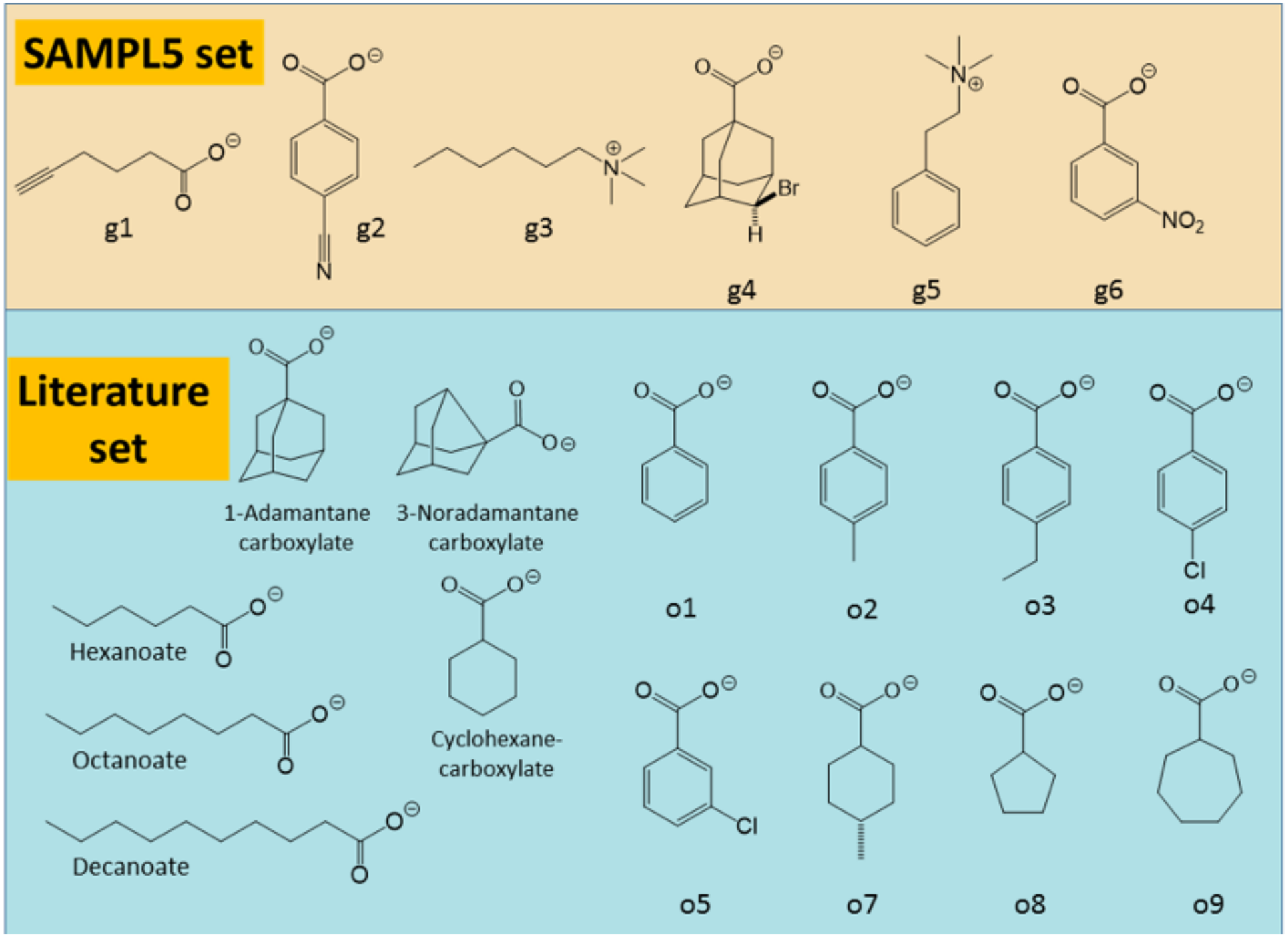
Attach-Pull-Release (APR) Approach

$$\Delta G^0_{bind} = -(W_{attach} + W_{pull} + W_{release-conf} + W_{release-std})$$



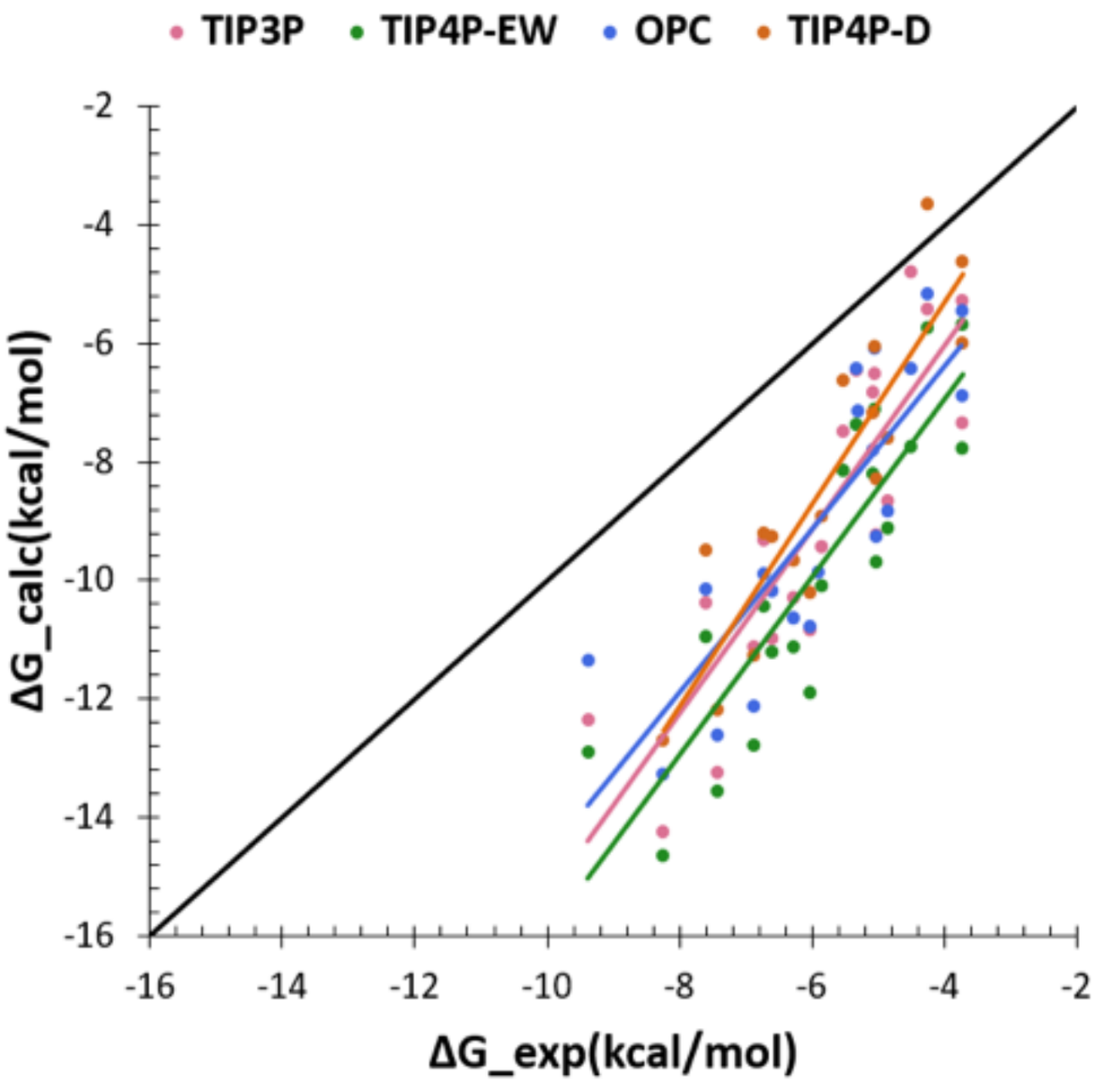
Henriksen, N. M., Fenley, A. T., & Gilson, M. K. (2015). *J. Chem. Theory Comput.*, *11*(9), 4377-4394.
Velez-Vega, C., & Gilson, M. K. (2013). *J. Comput. Chem.*, *34*(27), 2360-2371.

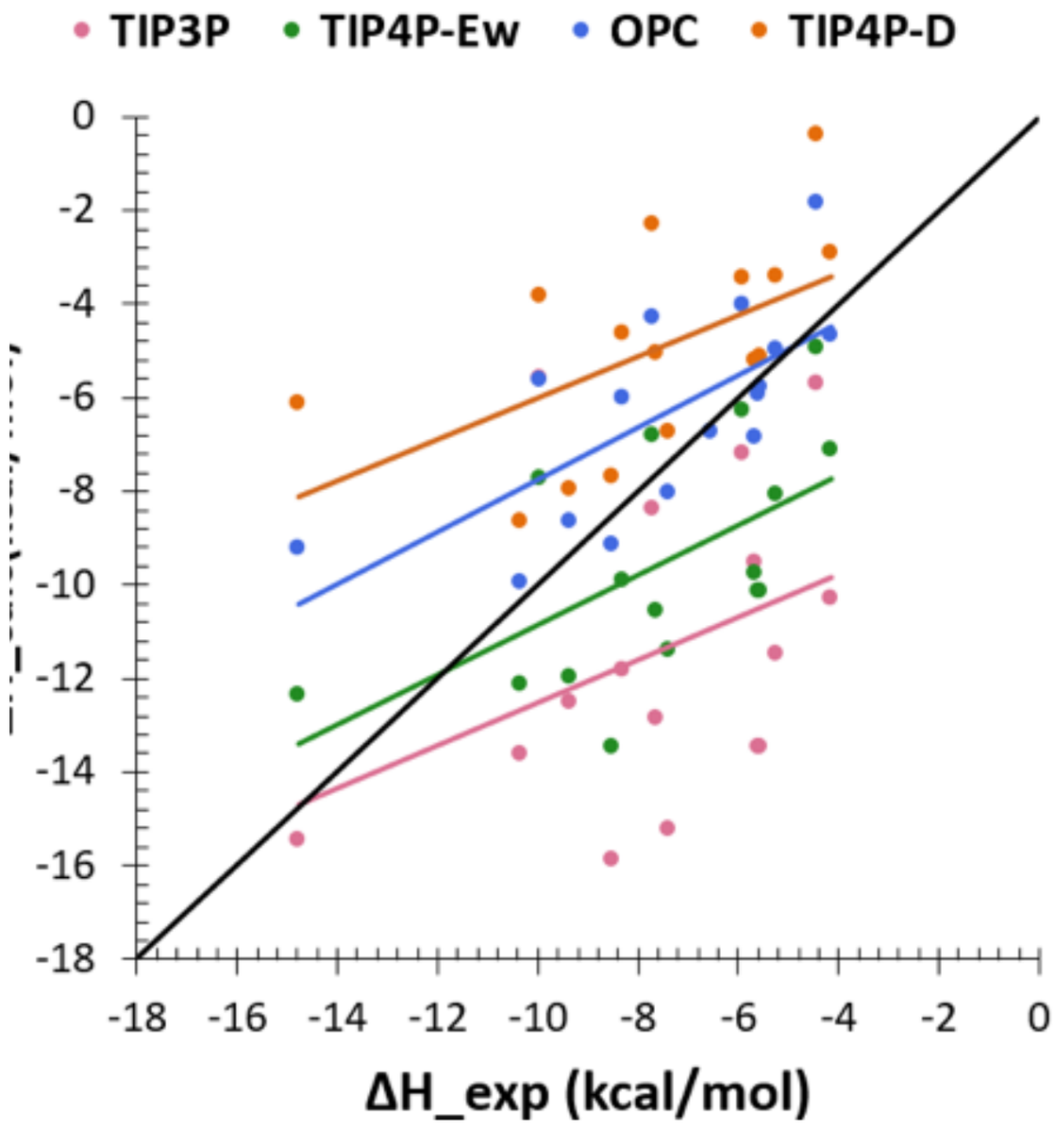
Structures of Octa Acid Guests



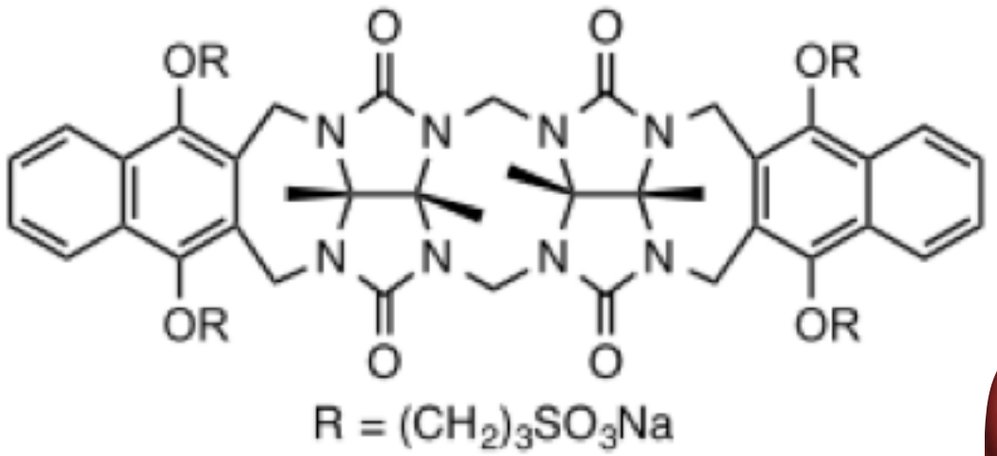
Sun, H., Gibb, C. L., & Gibb, B. C. (2008). Supramol. Chem., 20(1-2), 141-147
Gibb, C. L., & Gibb, B. C. (2014). J. Comput.-Aided Mol. Des., 28(4), 319-325.

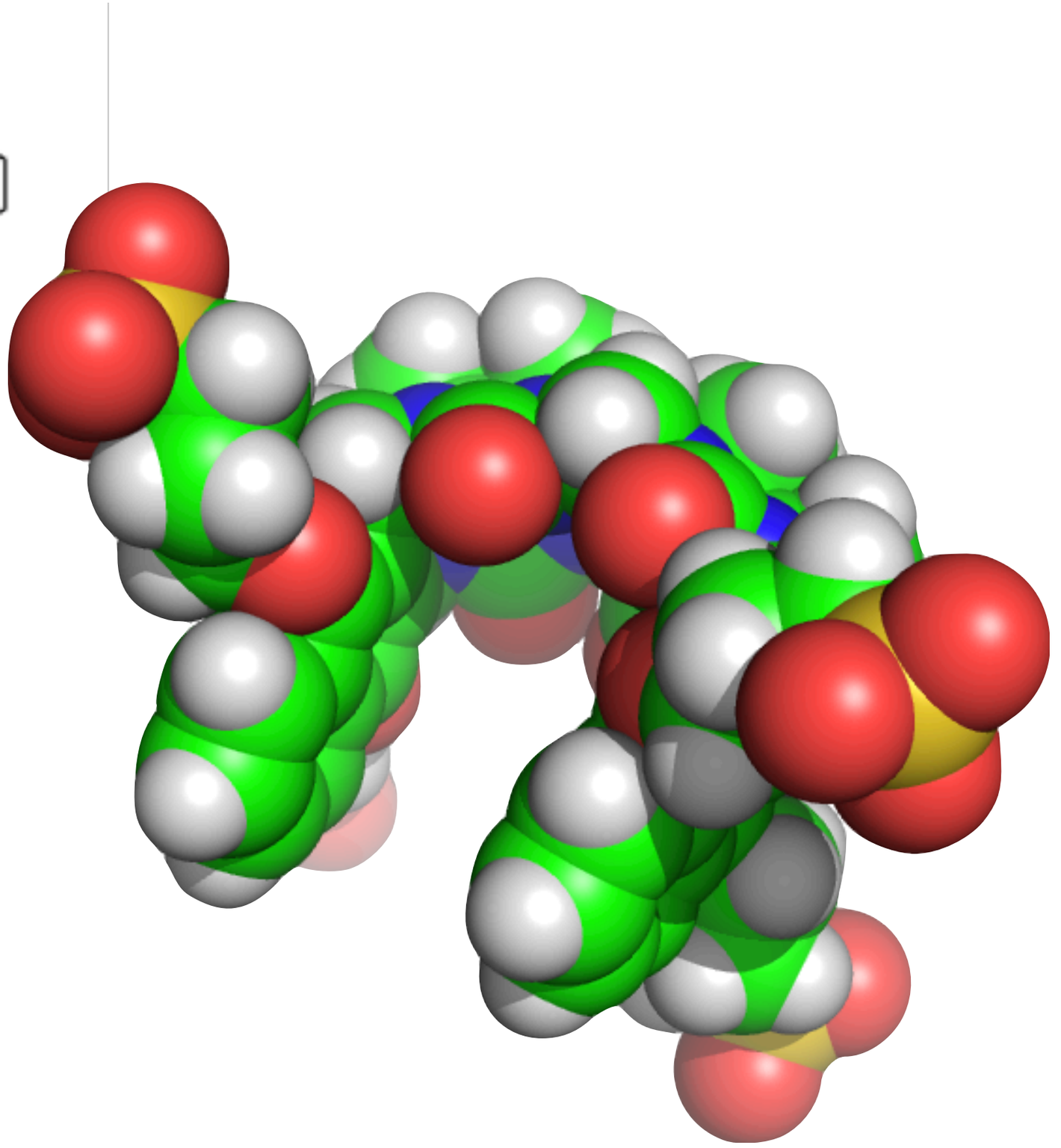
Four Water Models Behave Differently on Binding Enthalpies, but Similarly on Binding Free Energies





CBClip is a new host for the SAMPL challenge





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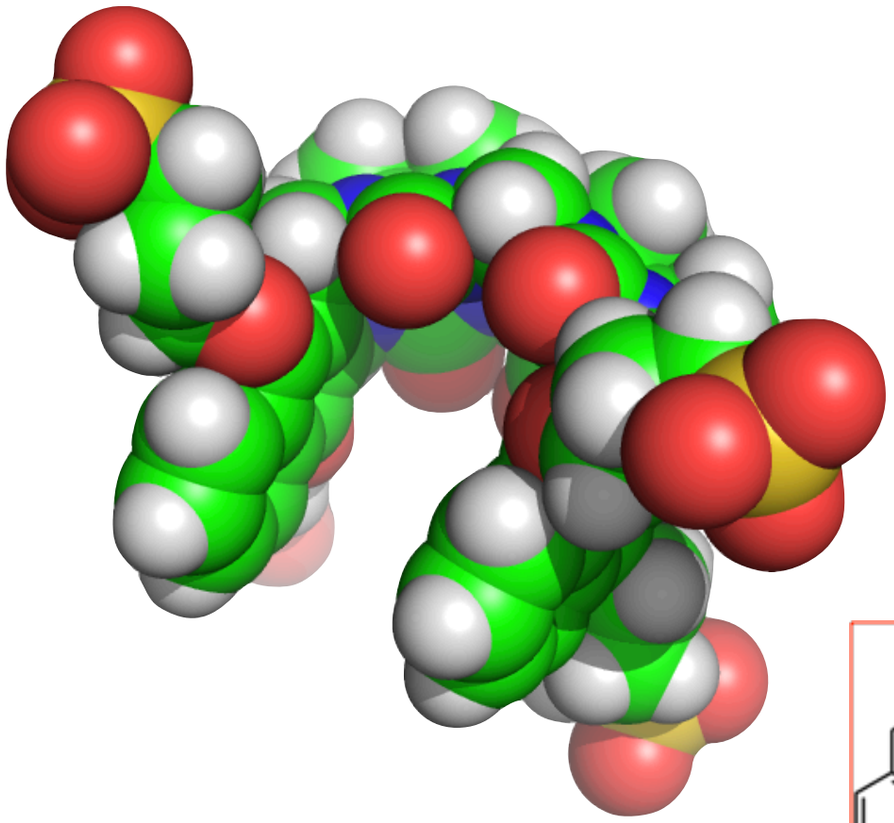
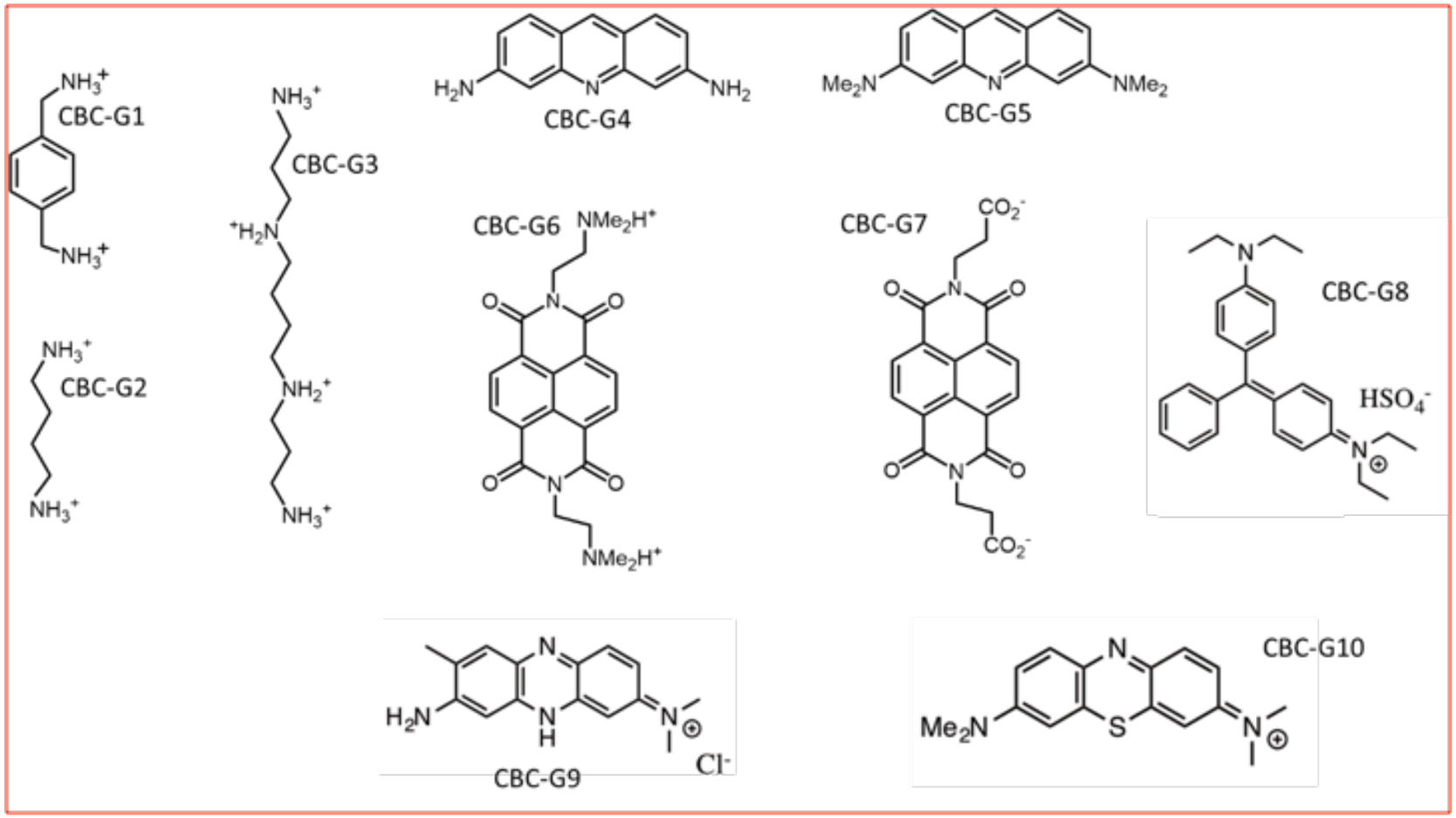
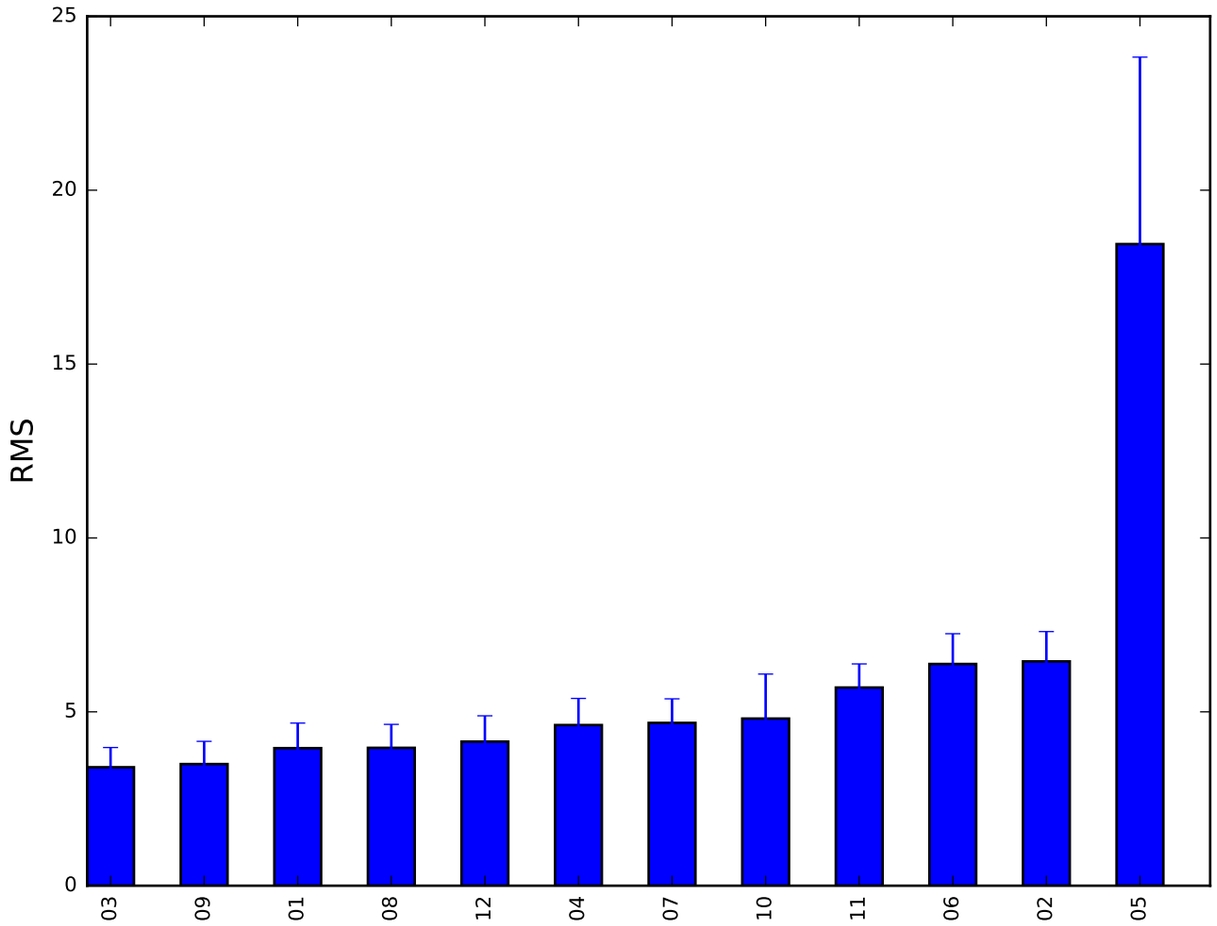




This seems to be far more challenging than the Octa Acid systems



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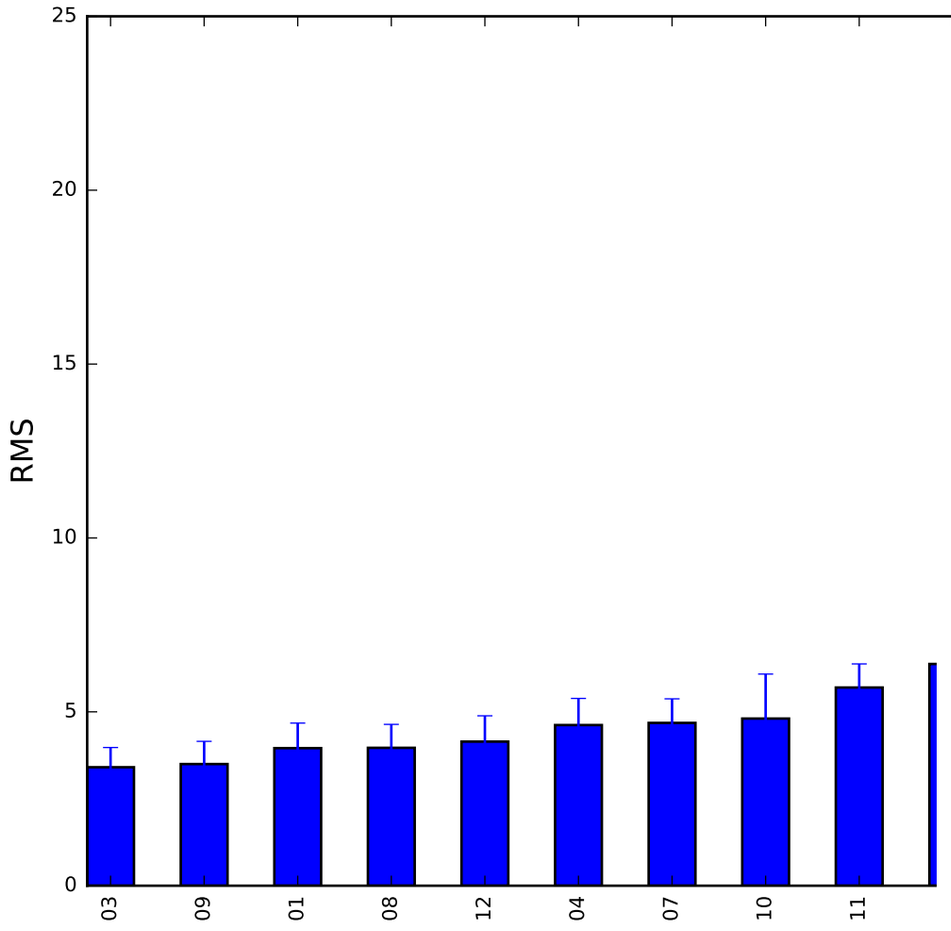
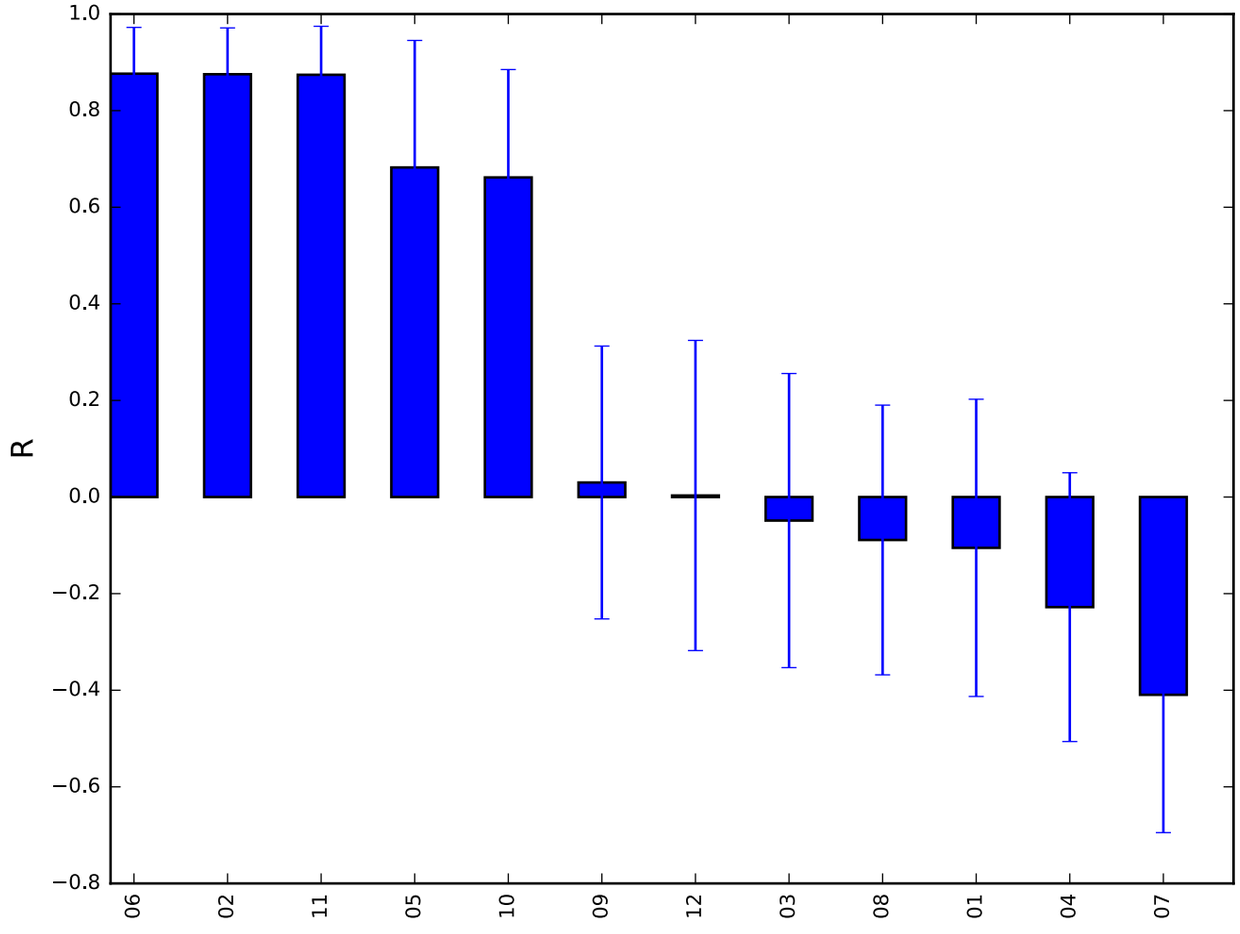
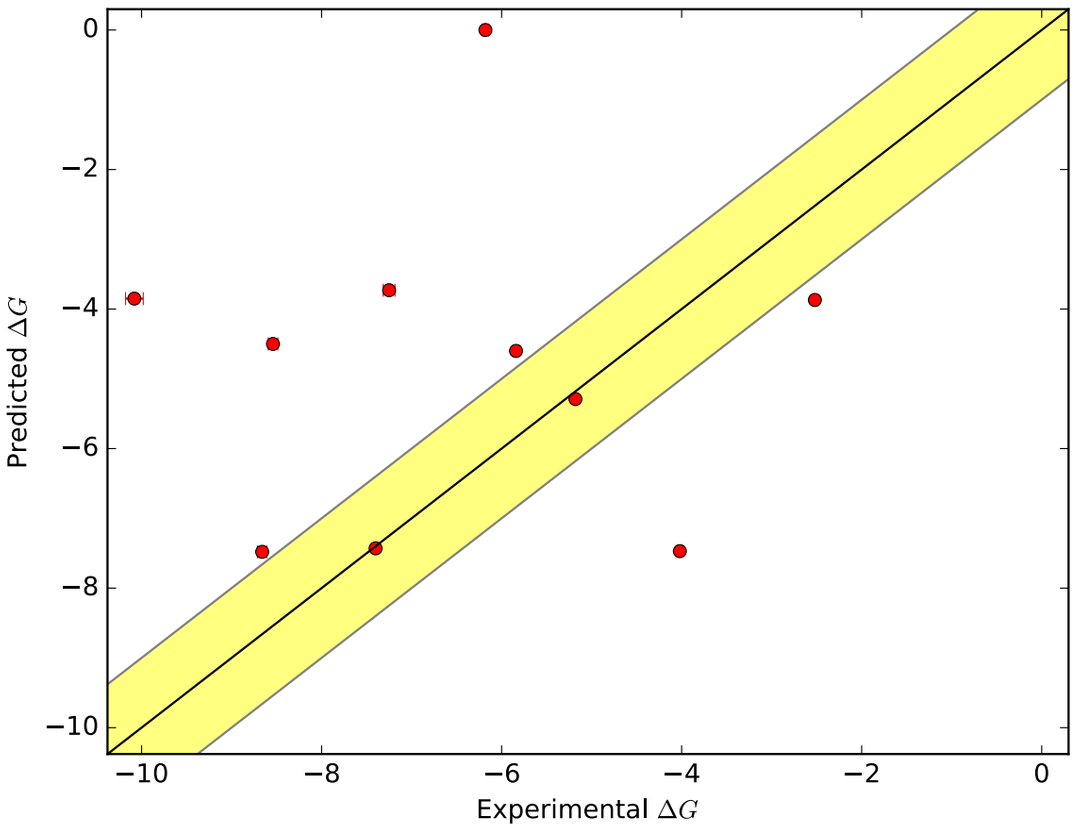


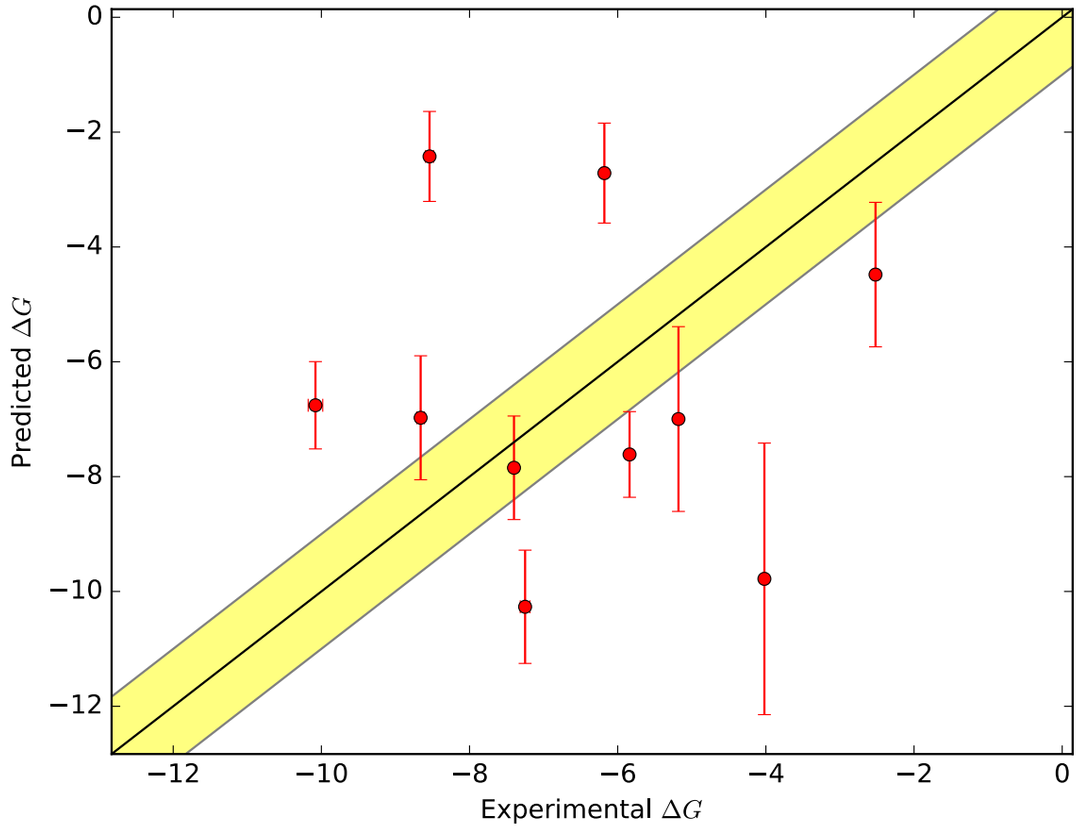


Here, the top methods by RMS/AUE have near zero correlation

Submission 09

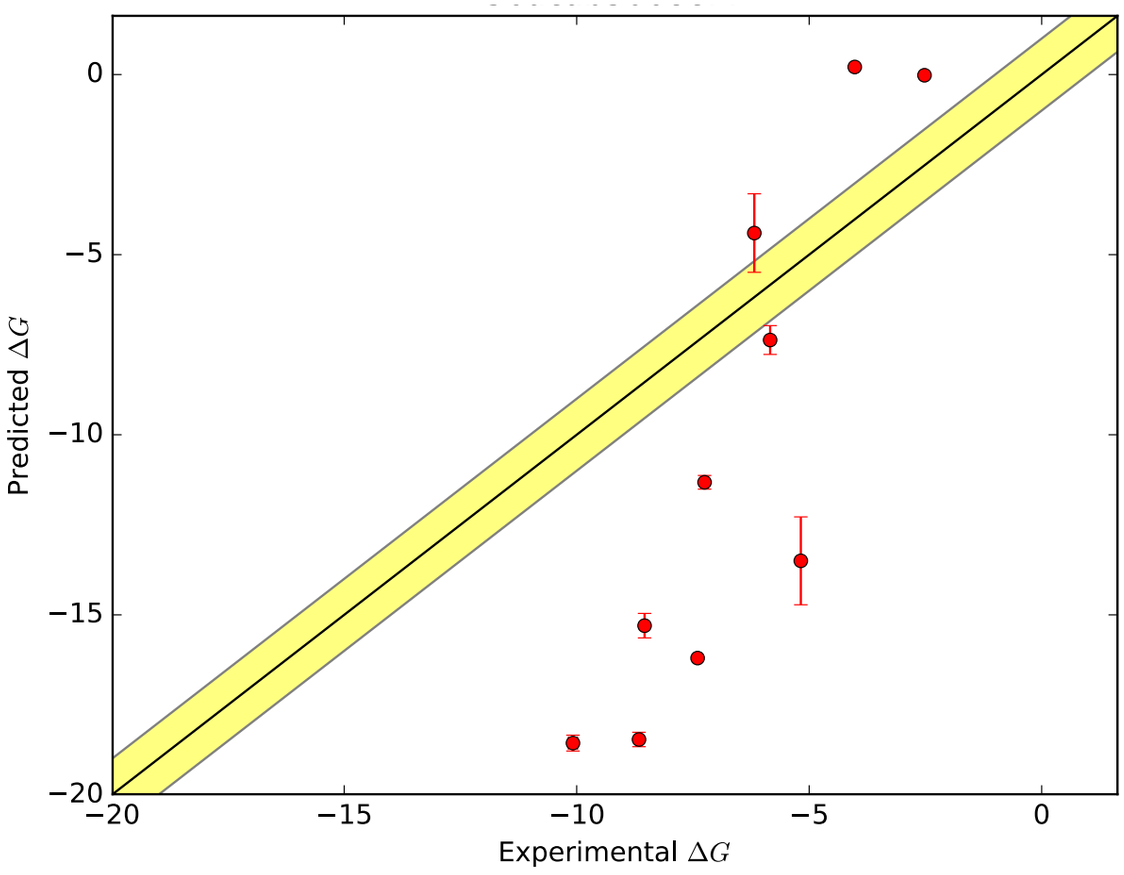


Submission 03

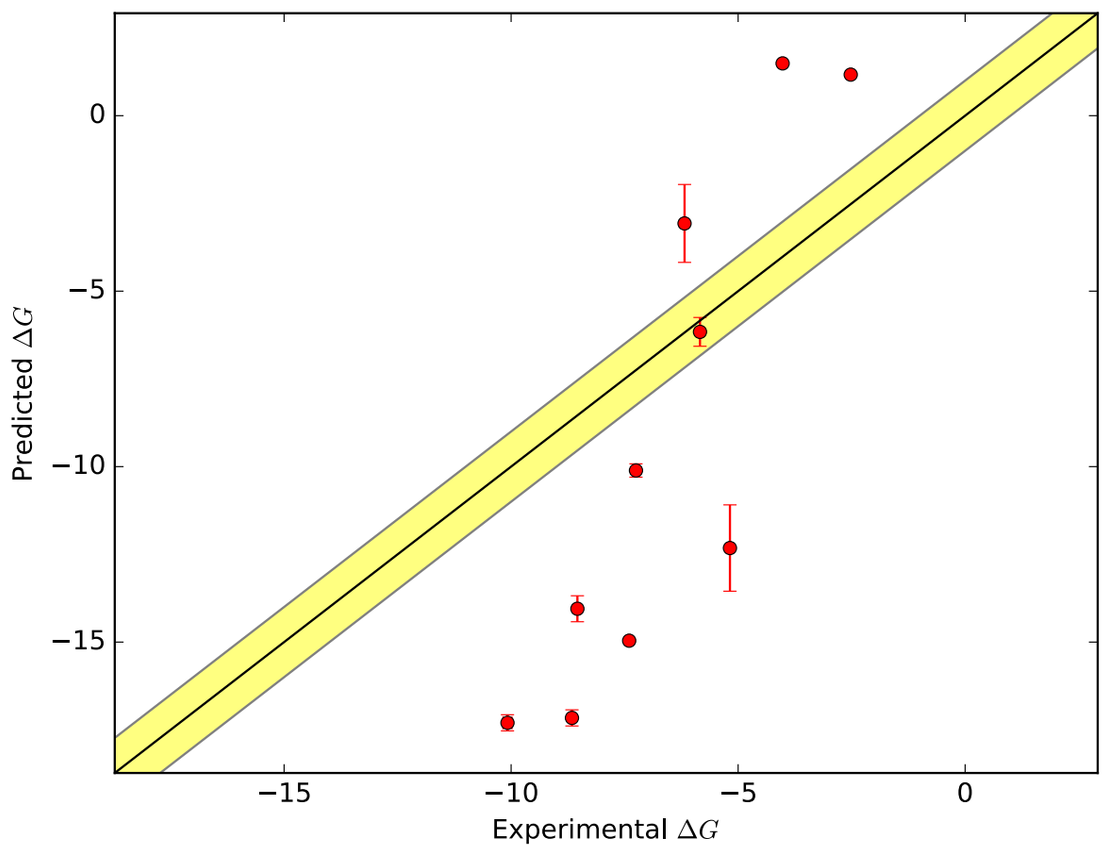


But runners up from the Michel group achieve some correlation here (and lead on tau/R)

Submission 06

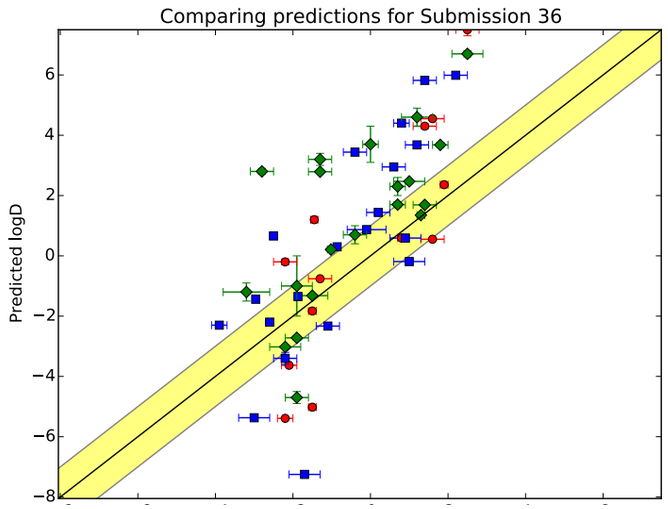


Submission 11



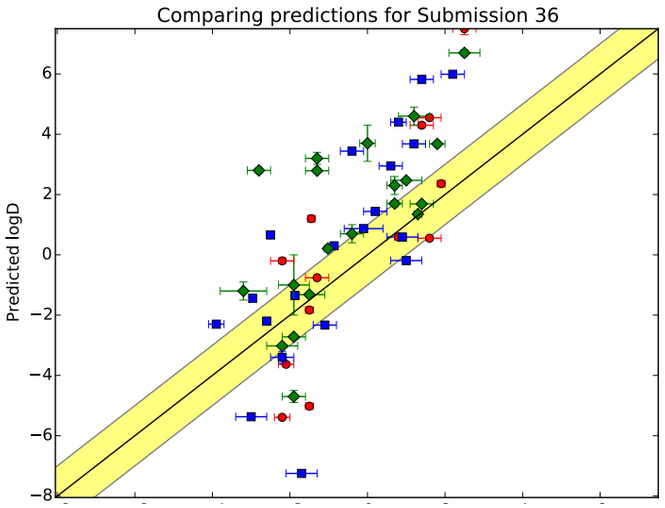
What did we learn?

What did we learn?



DC’s are challenging but tractable

What did we learn?



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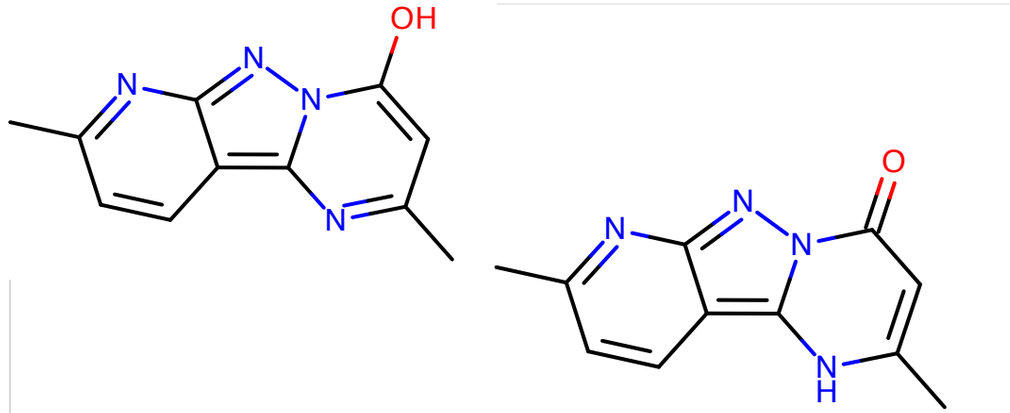
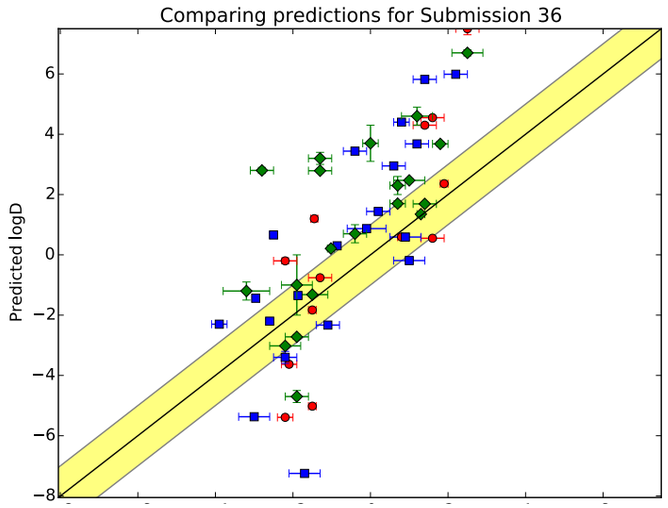


They challenge in many of the same ways as binding calculations

What did we learn?



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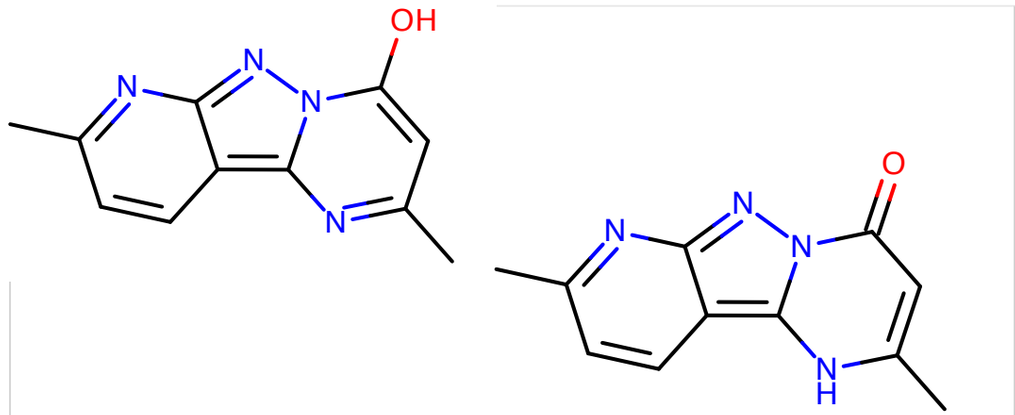

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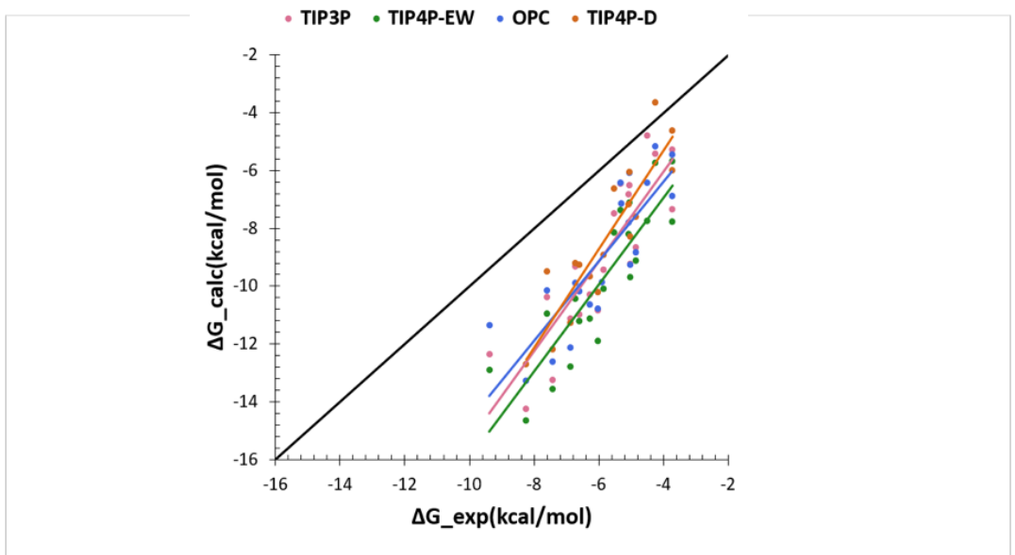
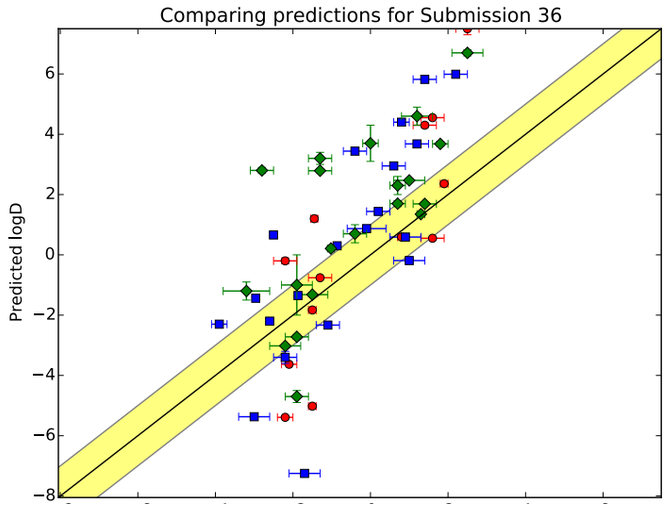
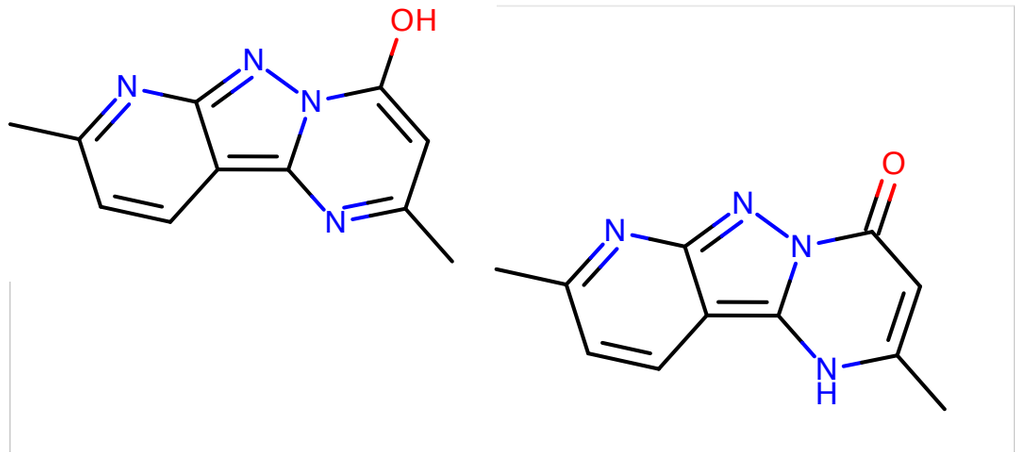


HG calculations are still very difficult

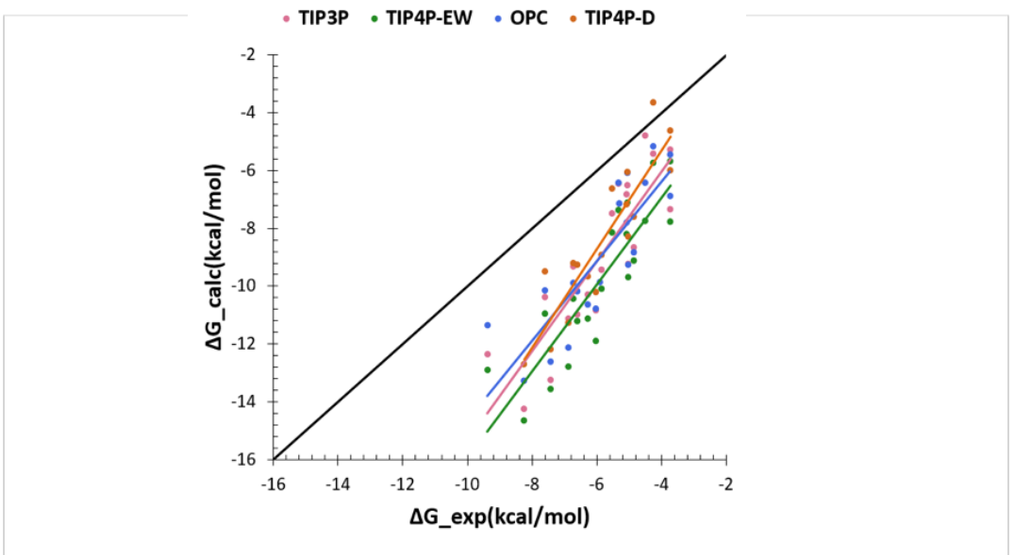
What did we learn?



DC’s are challenging but tractable



They challenge in many of the same ways as binding calculations



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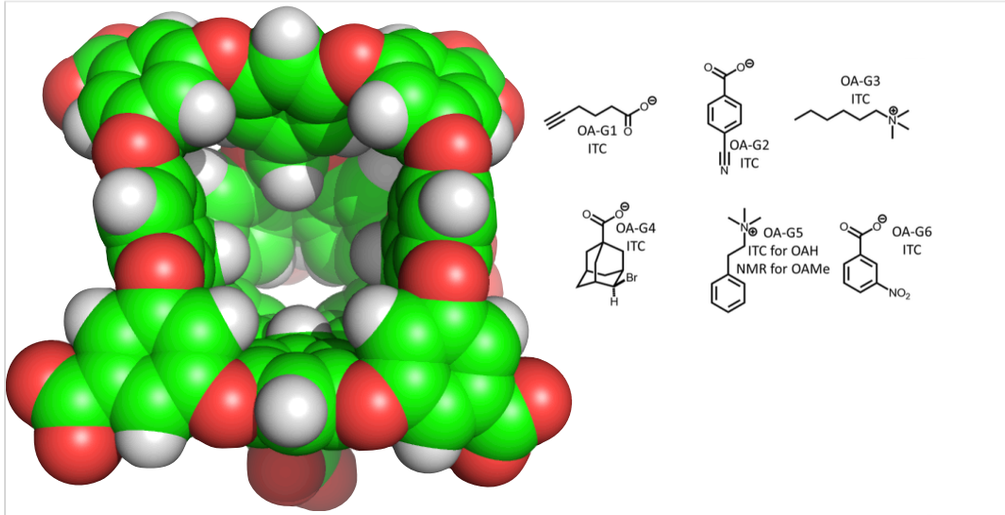

We still have much to learn that’s relevant to biomolecular binding

Acknowledgments

- Genentech for sponsoring DC experiments/internship, especially JW Feng, Baiwei Lin, Dan Ortwine, Joe Pease, Justin Dancer
- Mike Gilson (UCSD) for involvement in all aspects of SAMPL
- Michael Shirts for reference calculation input format conversion
- DC experiments: Bas Rustenberg and John Chodera (MSKCC)
- DC reference calculations/analysis: Caitlin Bannan, Kalli Burley (UCI)
- HG experiments: Bruce Gibb (Tulane), Lyle Isaacs (Maryland) and their group members
- HG analysis: Shuai Liu, Mike Gilson (UCSD)
- HG reference calculations: Jian Yin (UCSD)
- Helpful comments/input/etc.: Andreas Klamt, Chris Fennell, John Chodera
- NIH for D3R support, D3R for support of SAMPL
- NSF for support of my group's work on solvation