



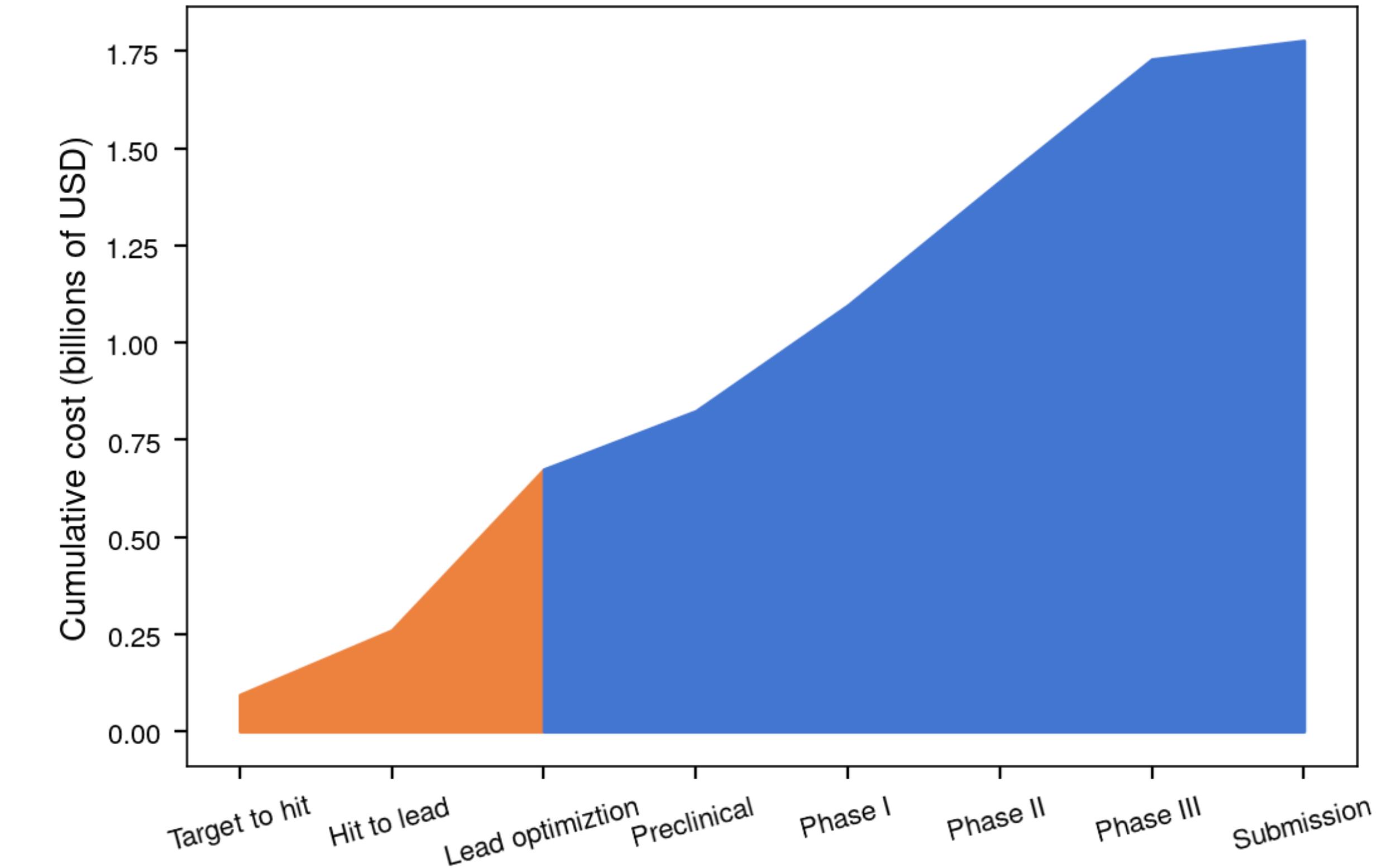
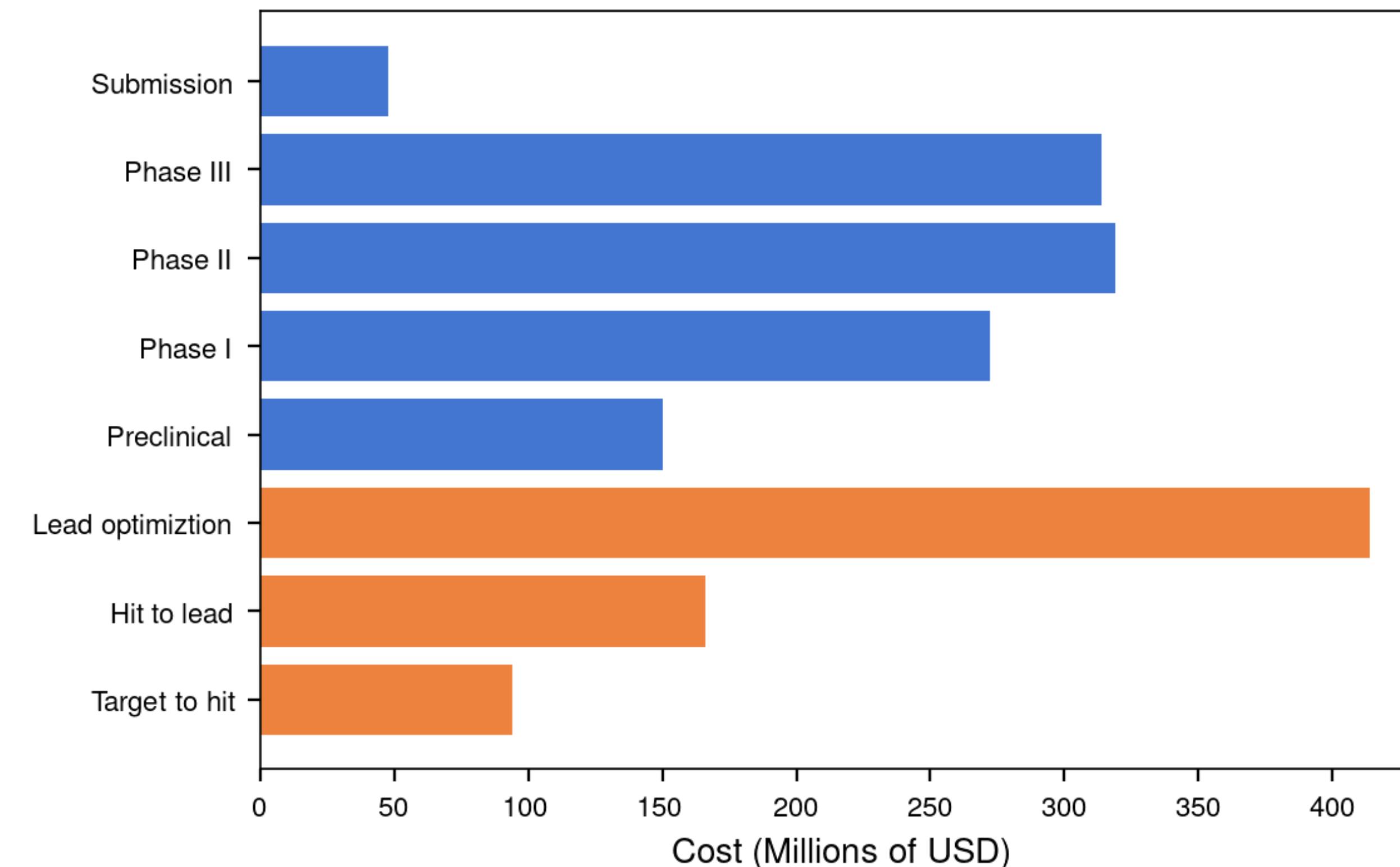
# Benchmarking emerging force fields with binding thermodynamics calculations

**David Slochower**, Niel Henriksen, and Michael K. Gilson  
UCSD

University of California Chemical Symposium, March 25th 2019

**Our goal is to develop efficient and inexpensive access to the design of potent ligands.**

Drug discovery is extremely expensive and virtual screening has to be repeated many times before finding a suitable drug candidate.



Computational chemistry faces an uphill battle.

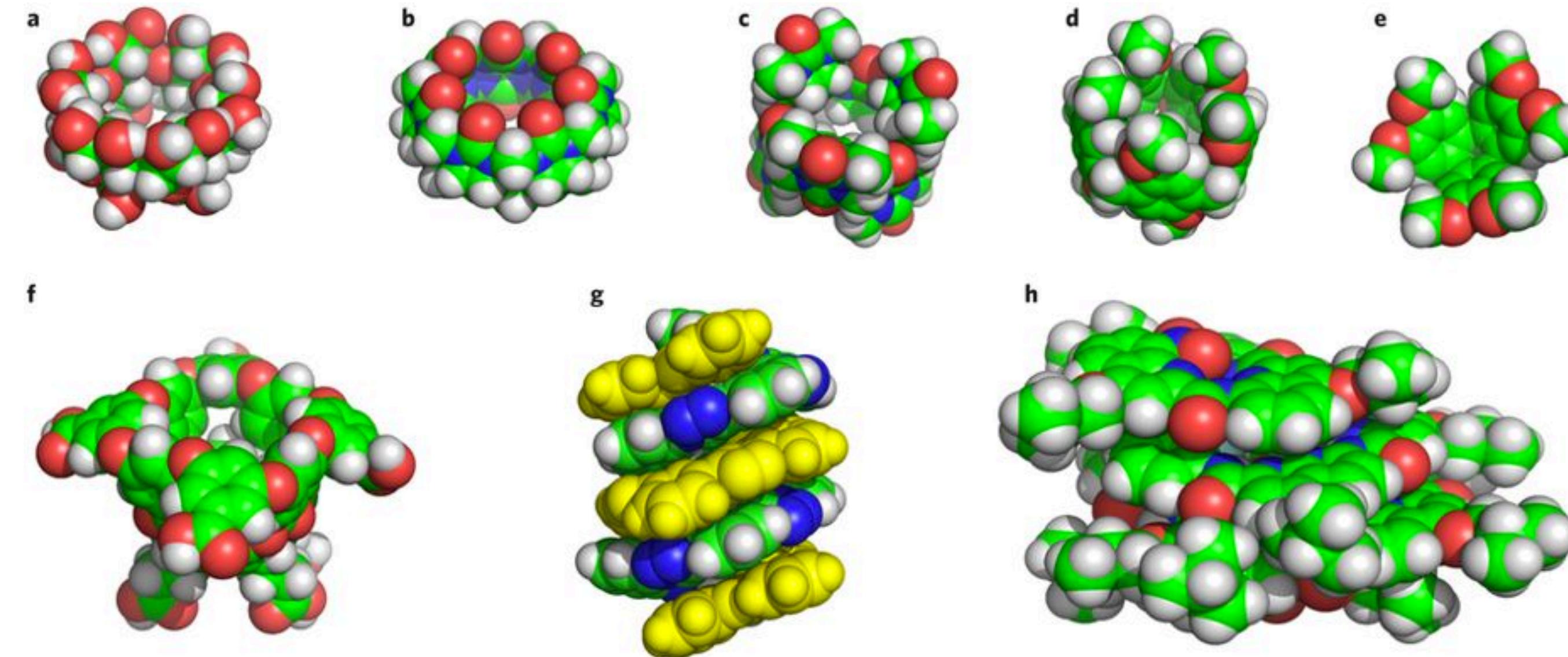
- Folded proteins should **fold correctly**.
- Disordered proteins should stay **disordered**.
- Solvents should adopt the **correct structure** both near complexes and in bulk.
- Ligands should be in the **correct orientation** and with the **correct affinity**.

## What are the sources of error in our simulations?

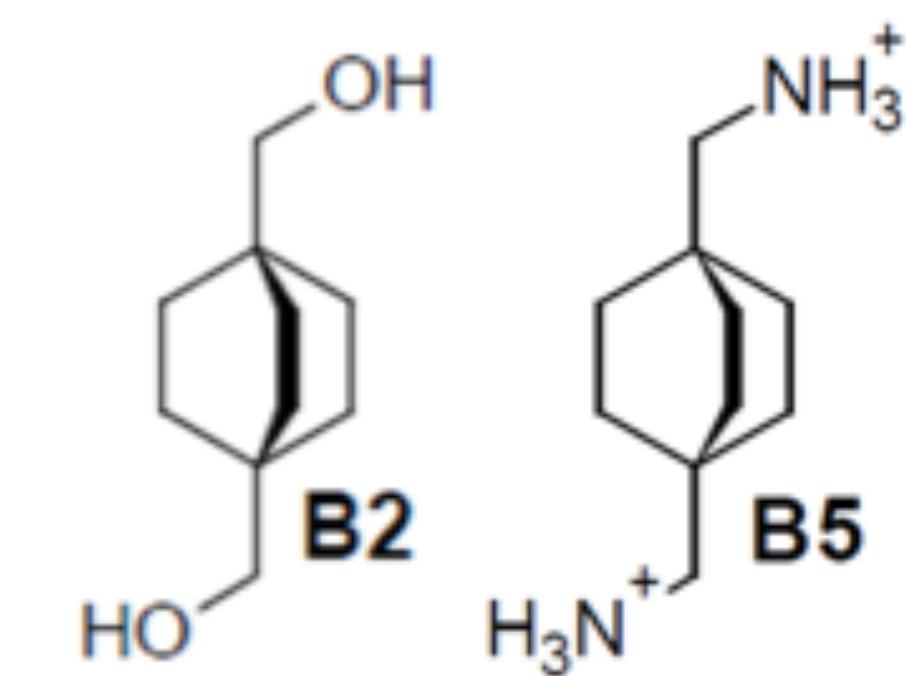
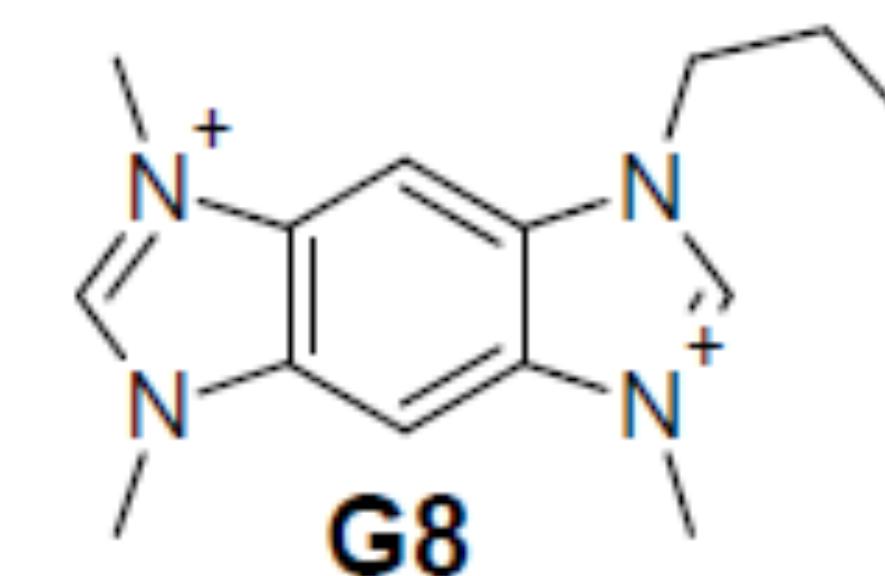
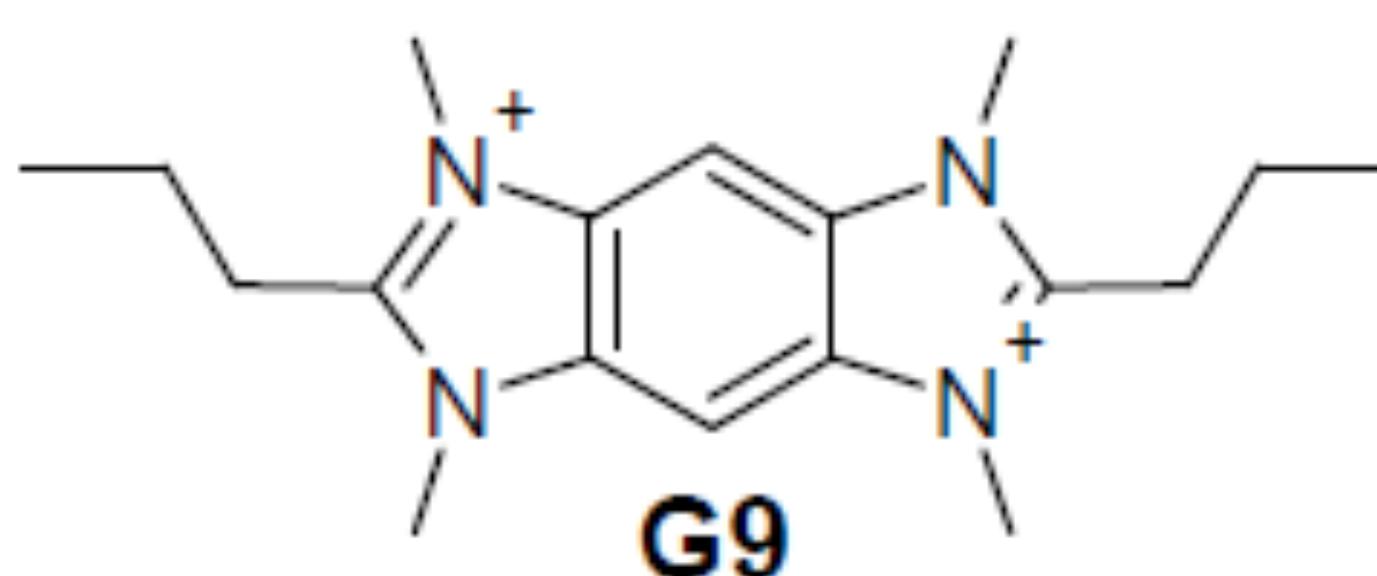
- Simulations aren't long enough.
- Protonation or tautomer states are wrong.
- Force field errors.

**We can use host-guest systems to test force field accuracy.**

Host-guest pairs are ideal binding model systems.

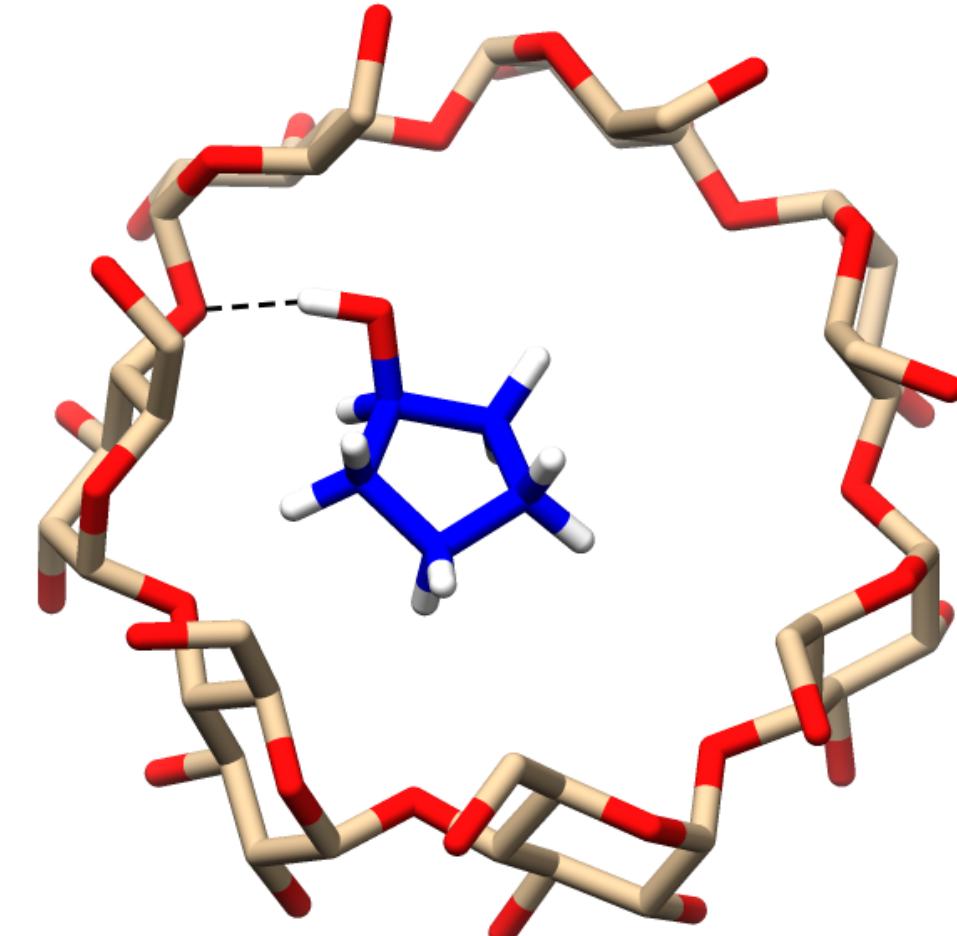


Hosts are cavity-containing molecules (Gibb's Deep Cavity Cavitands)

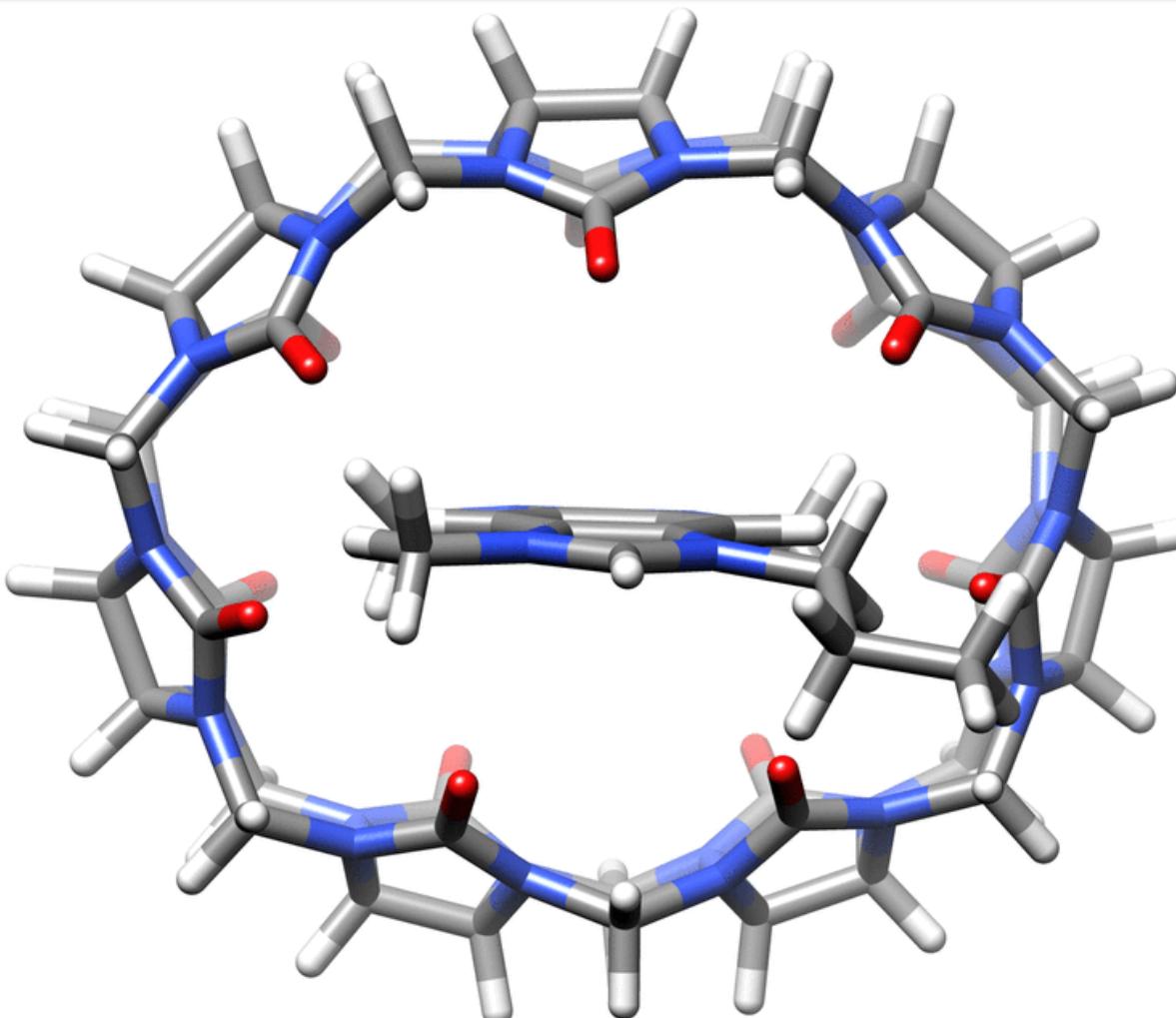


Guests are drug-like small molecules (ligands)

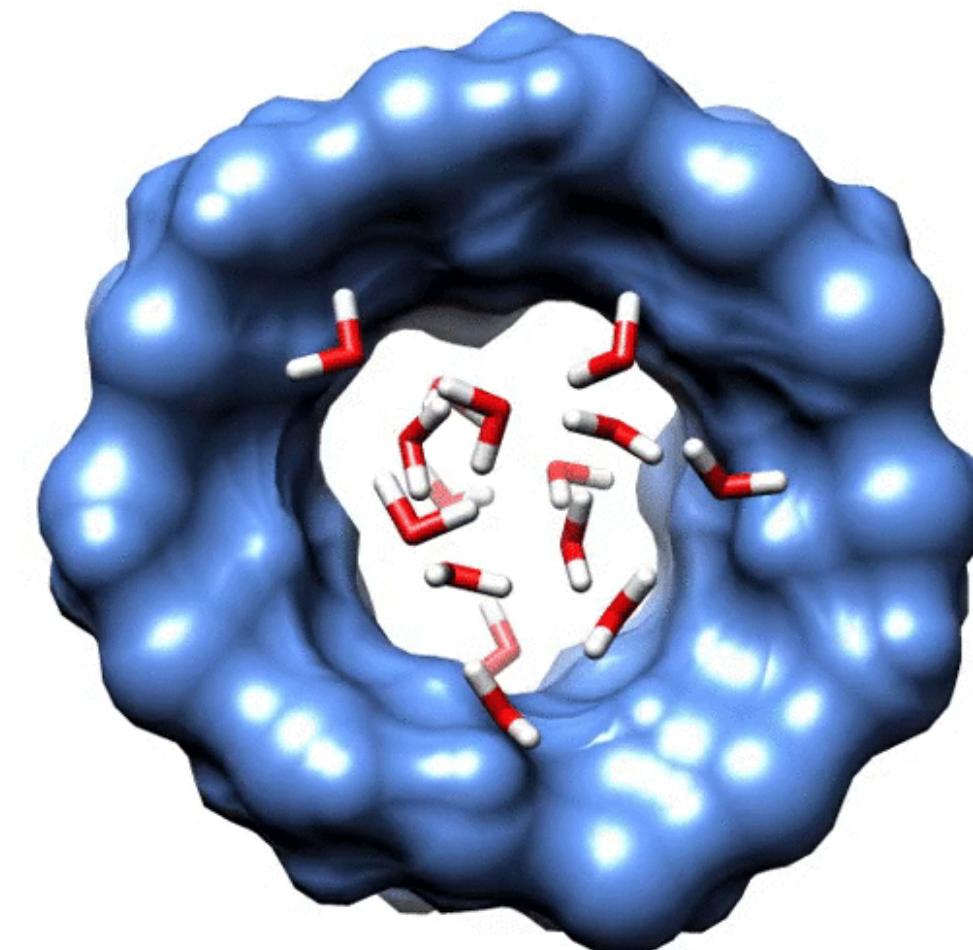
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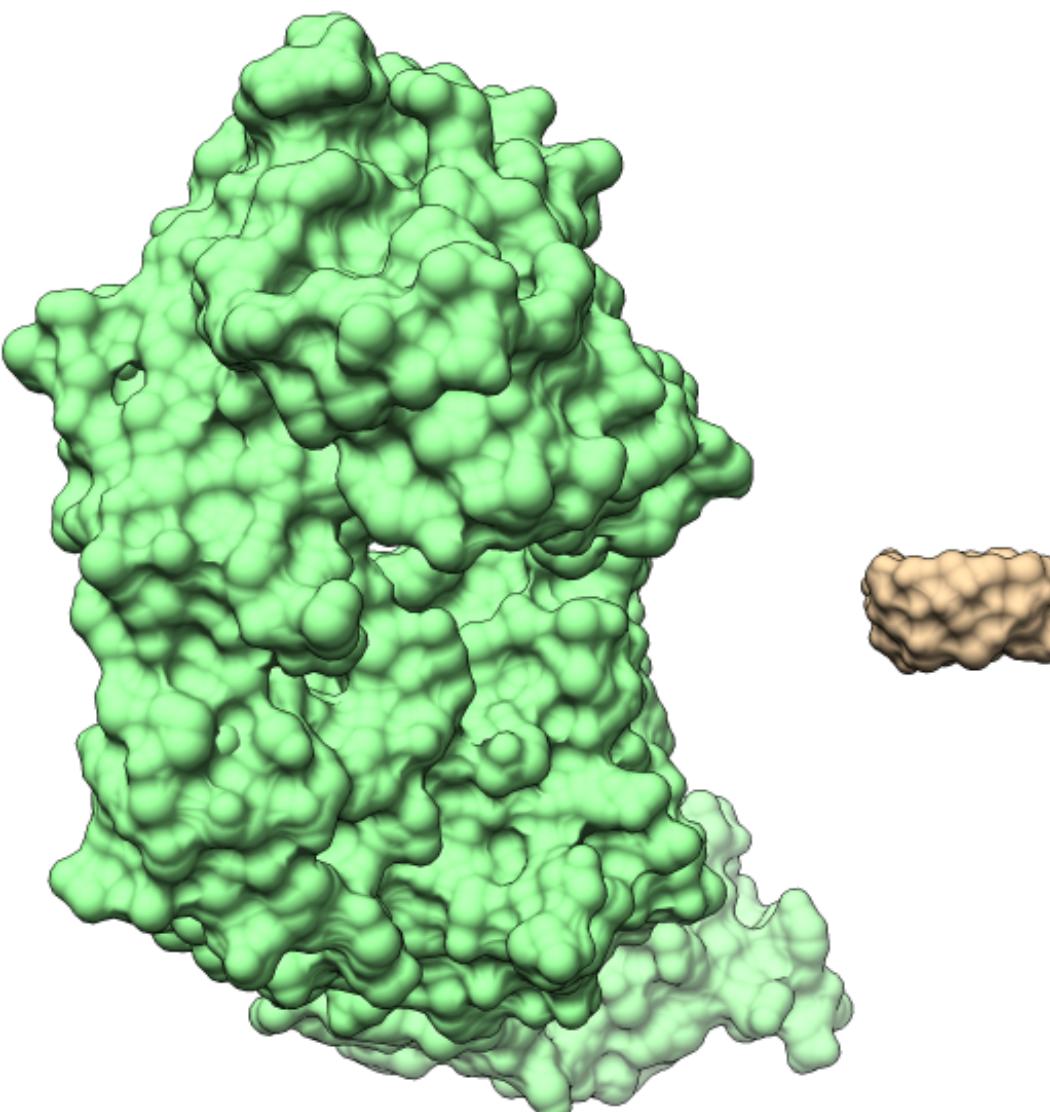
Hydrophilic & hydrophobic interactions



Conformational changes upon binding

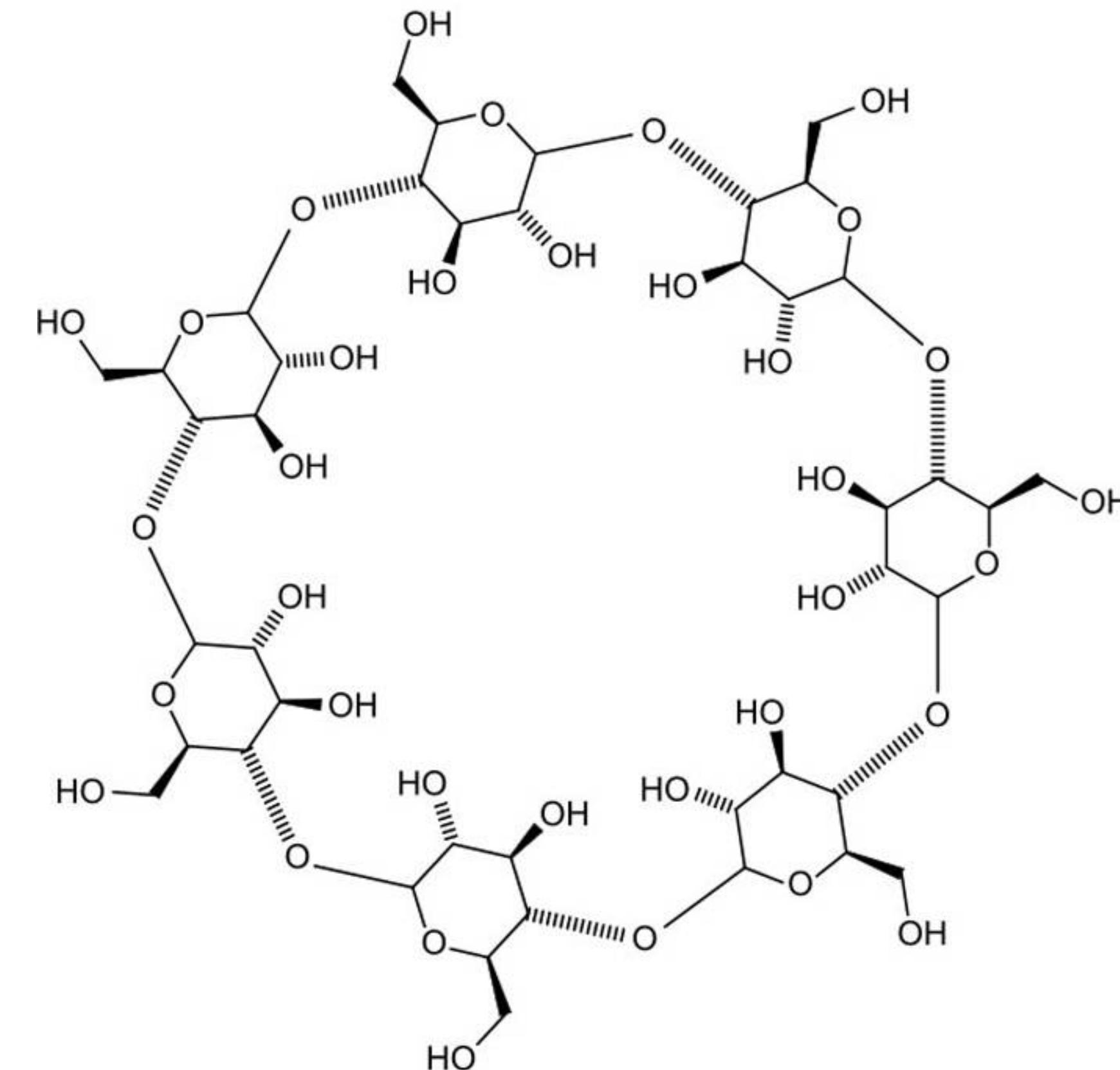
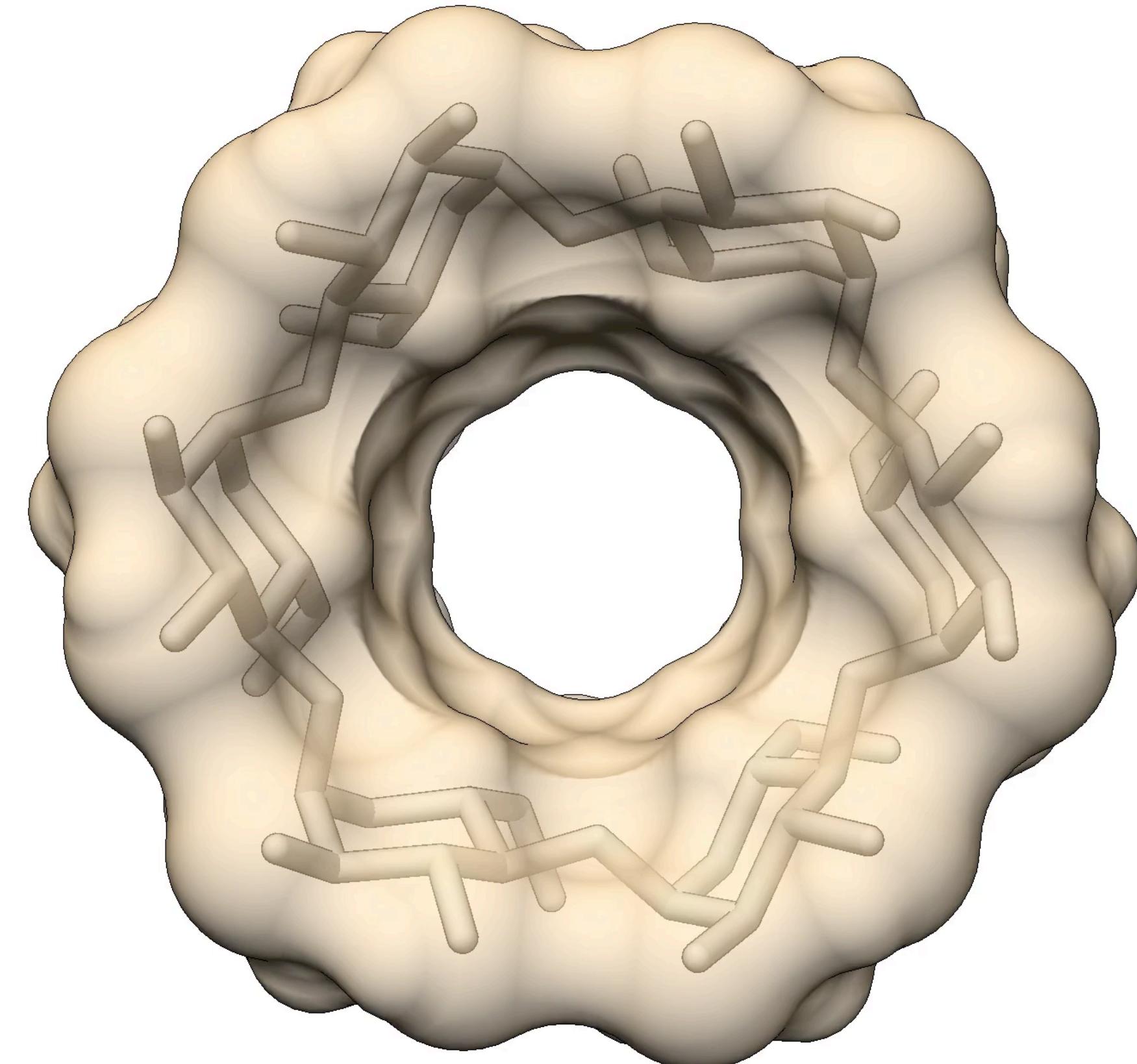


Regions of structured solvent



Simulations are quicker and can run longer

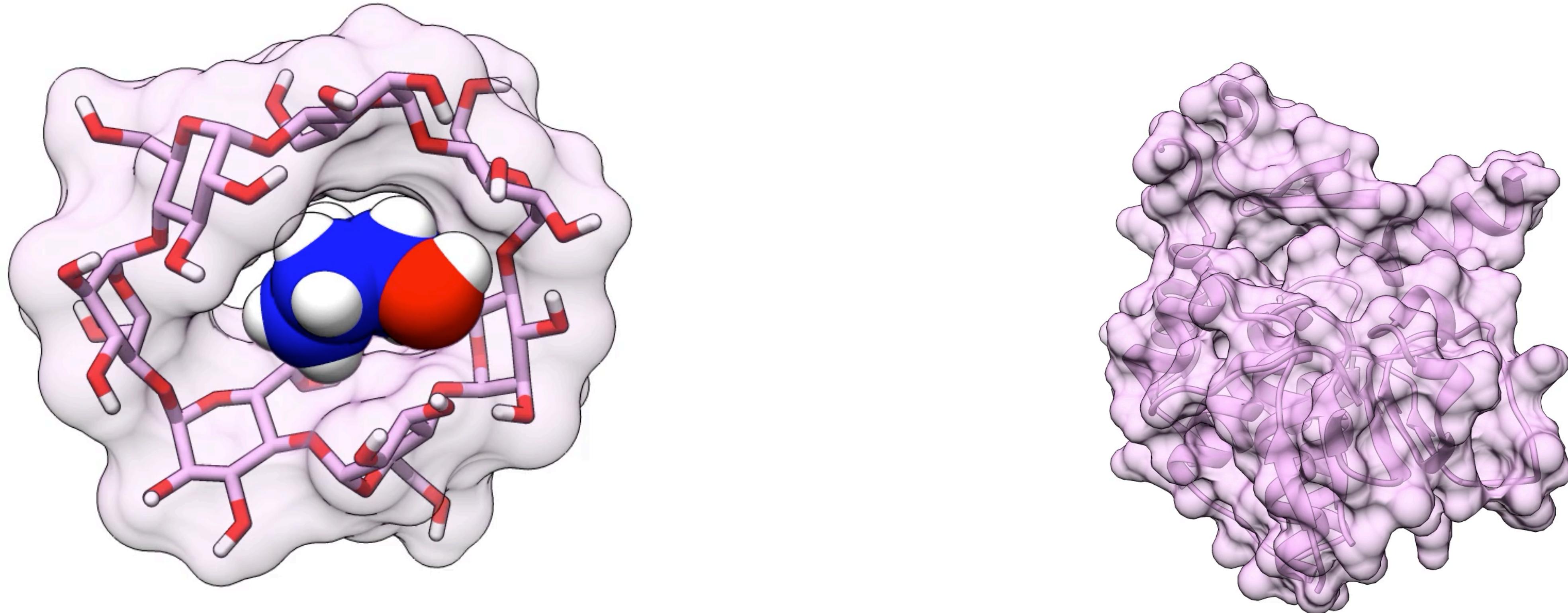
Today I'm going to focus on alpha-cyclodextrin and beta-cyclodextrin.



We develop new methods of computing binding free energies: *computational calorimetry*.

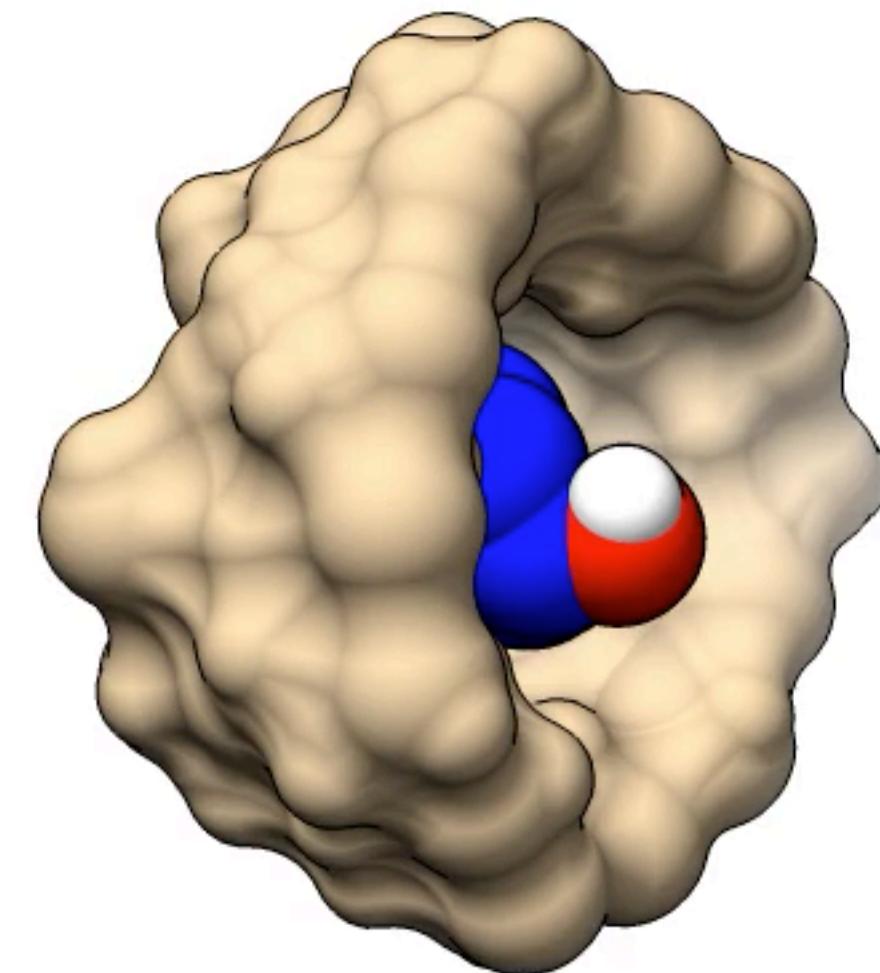
The binding affinity is the reversible work of pulling the ligand out of the host.

We compute binding free energies via a method called attach-pull-release.



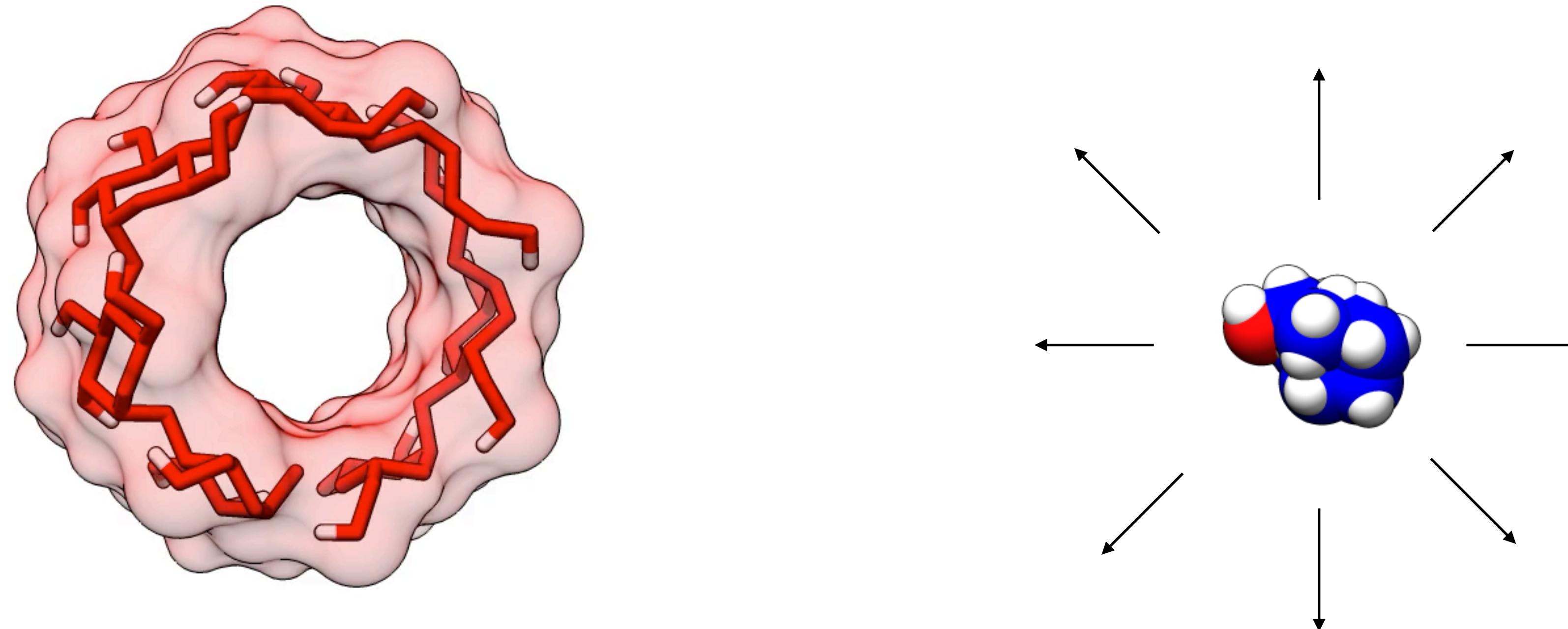
$$\Delta G^\circ = -(W_{\text{attach}} + W_{\text{pull}} + W_{\text{release}})$$

We compute binding free energies via a method called attach-pull-release.



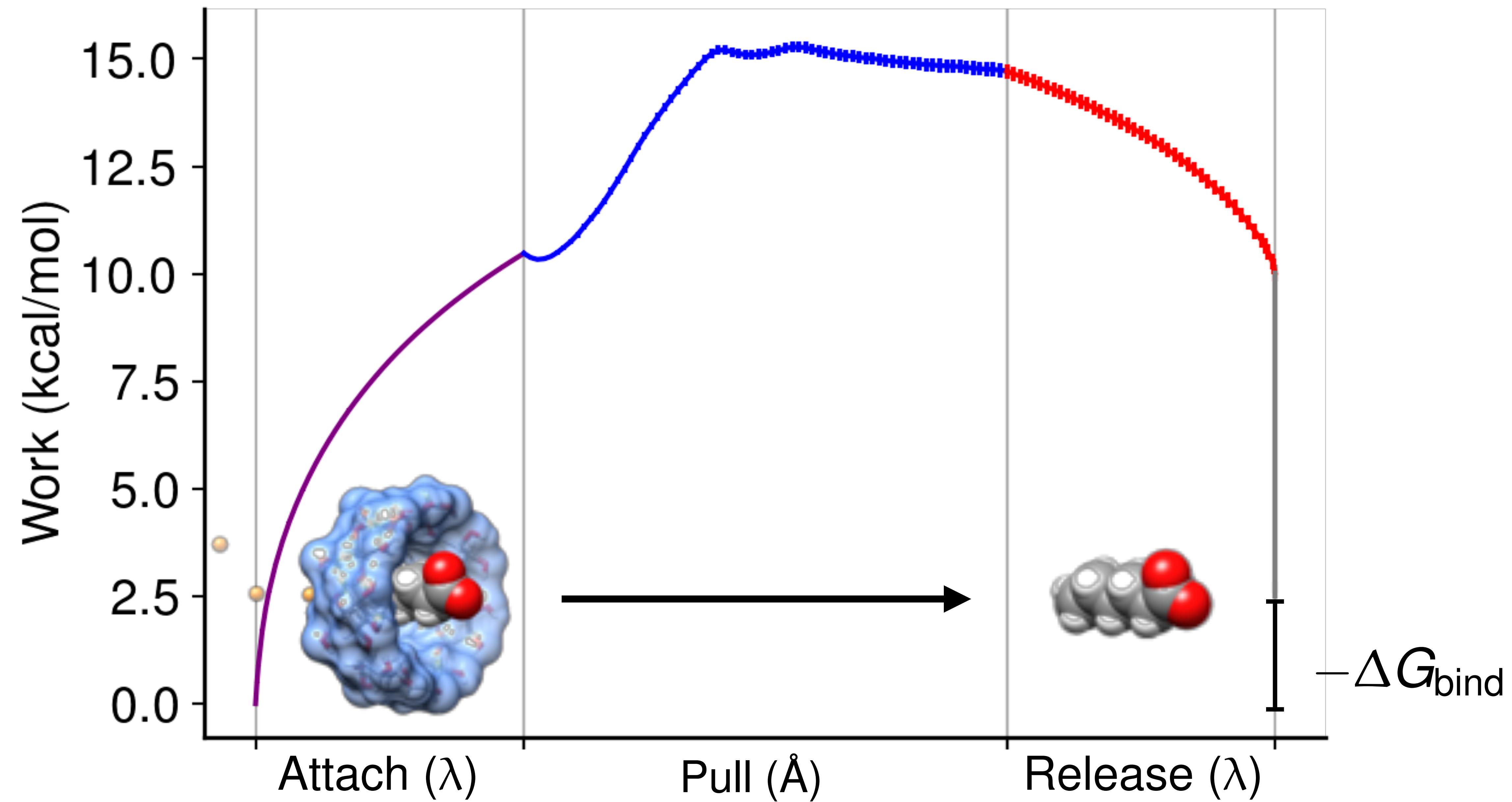
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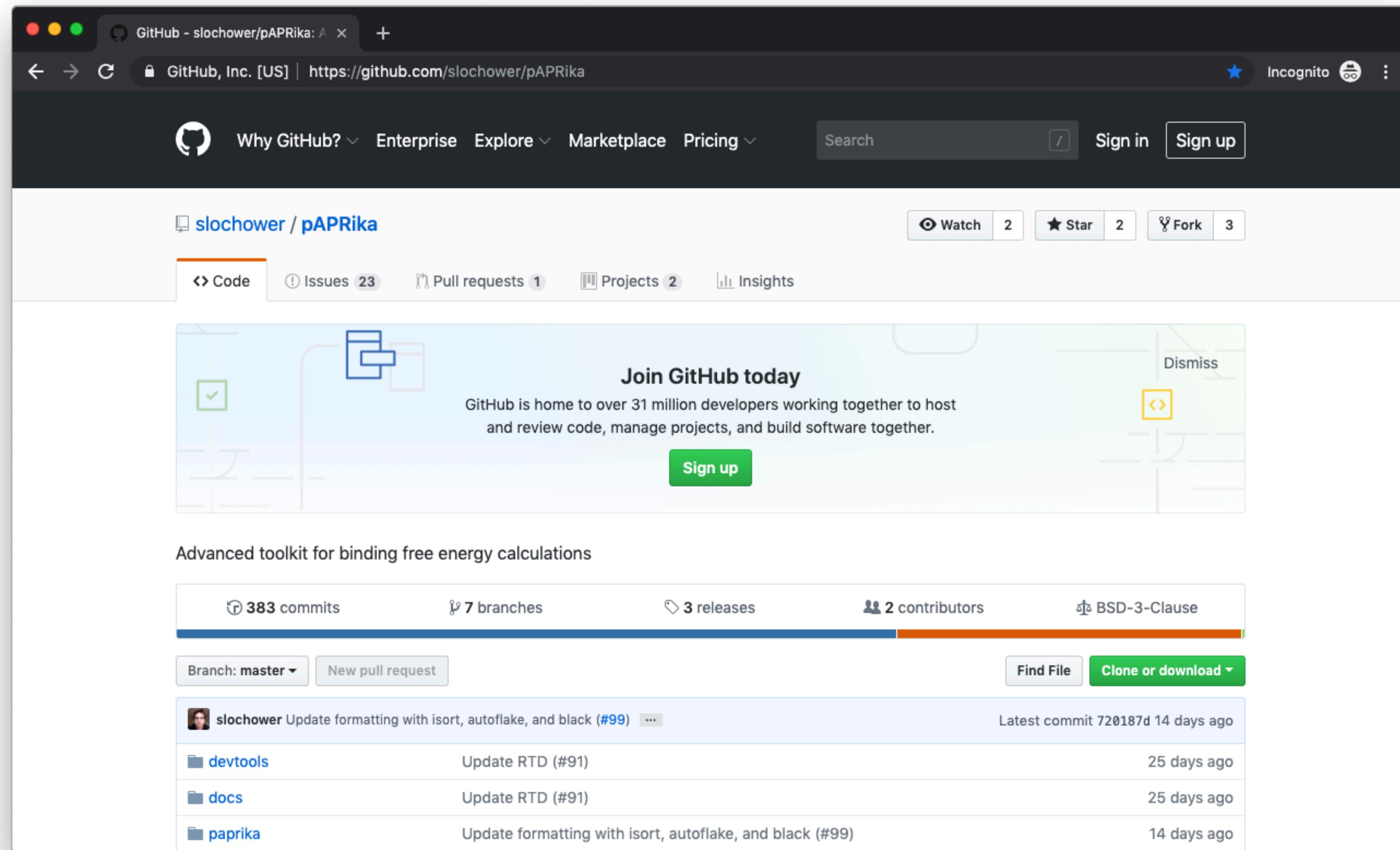
We can also compute the binding enthalpy.

The binding enthalpy is the difference in the partial molar enthalpies of the complex and the free molecules.

N. M. Henriksen, A. T. Fenley, M. K. Gilson, Computational Calorimetry: High-Precision Calculation of Host-Guest Binding Thermodynamics. *J. Chem. Theory Comput.* **11**, 4377–4394 (2015).

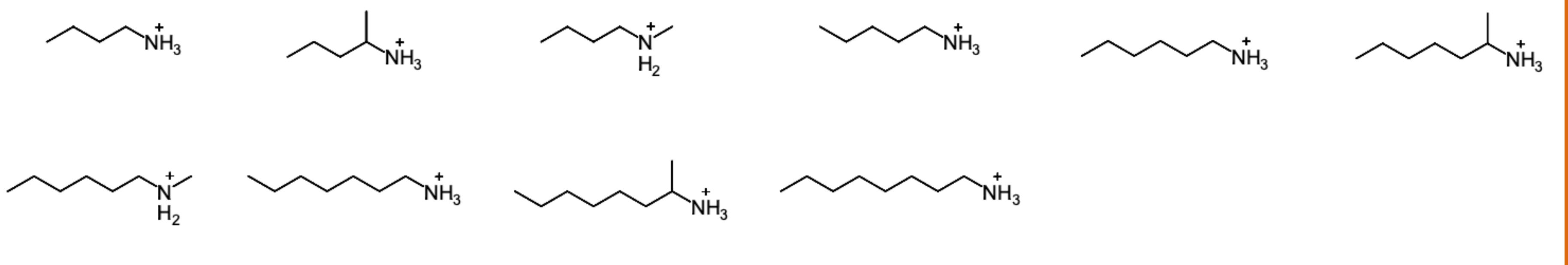
A. T. Fenley, N. M. Henriksen, H. S. Muddana, M. K. Gilson, Bridging Calorimetry and Simulation through Precise Calculations of Cucurbituril-Guest Binding Enthalpies. *J. Chem. Theory Comput.* **10**, 4069–4078 (2014).

# We have implemented attach-pull-release in a Python toolkit called pAPRika.

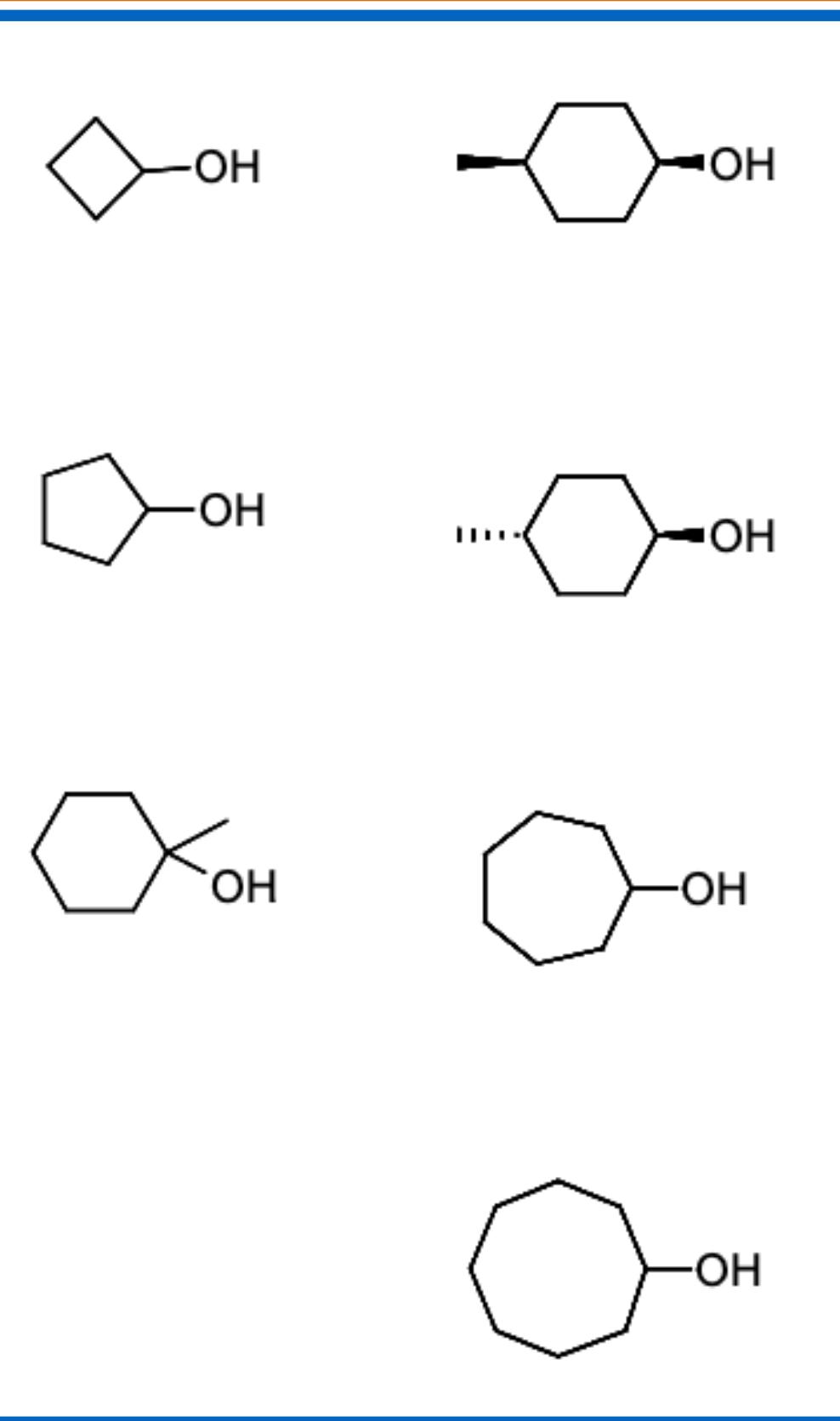


Available on conda-forge and working with AMBER or OpenMM (mostly).

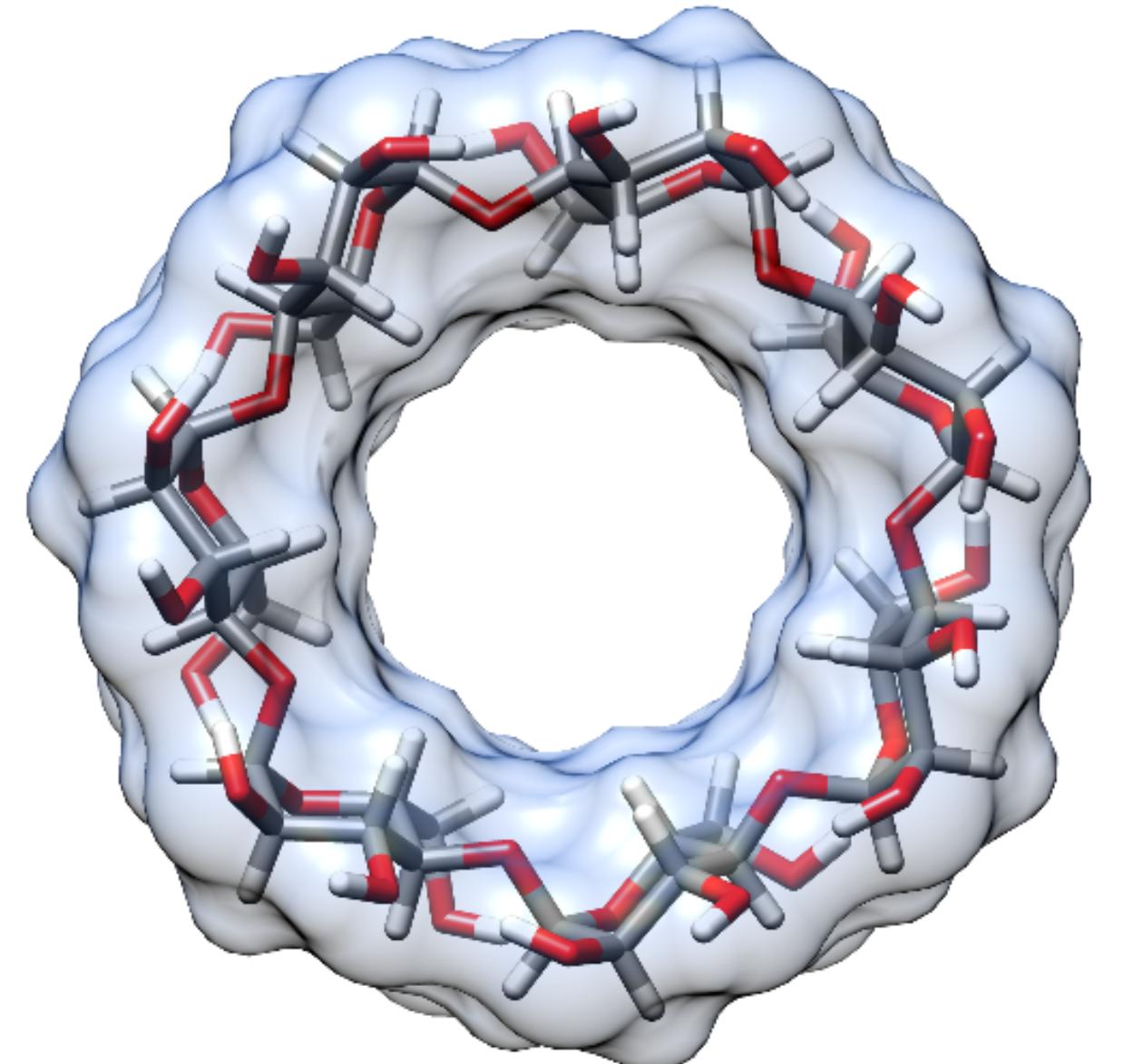
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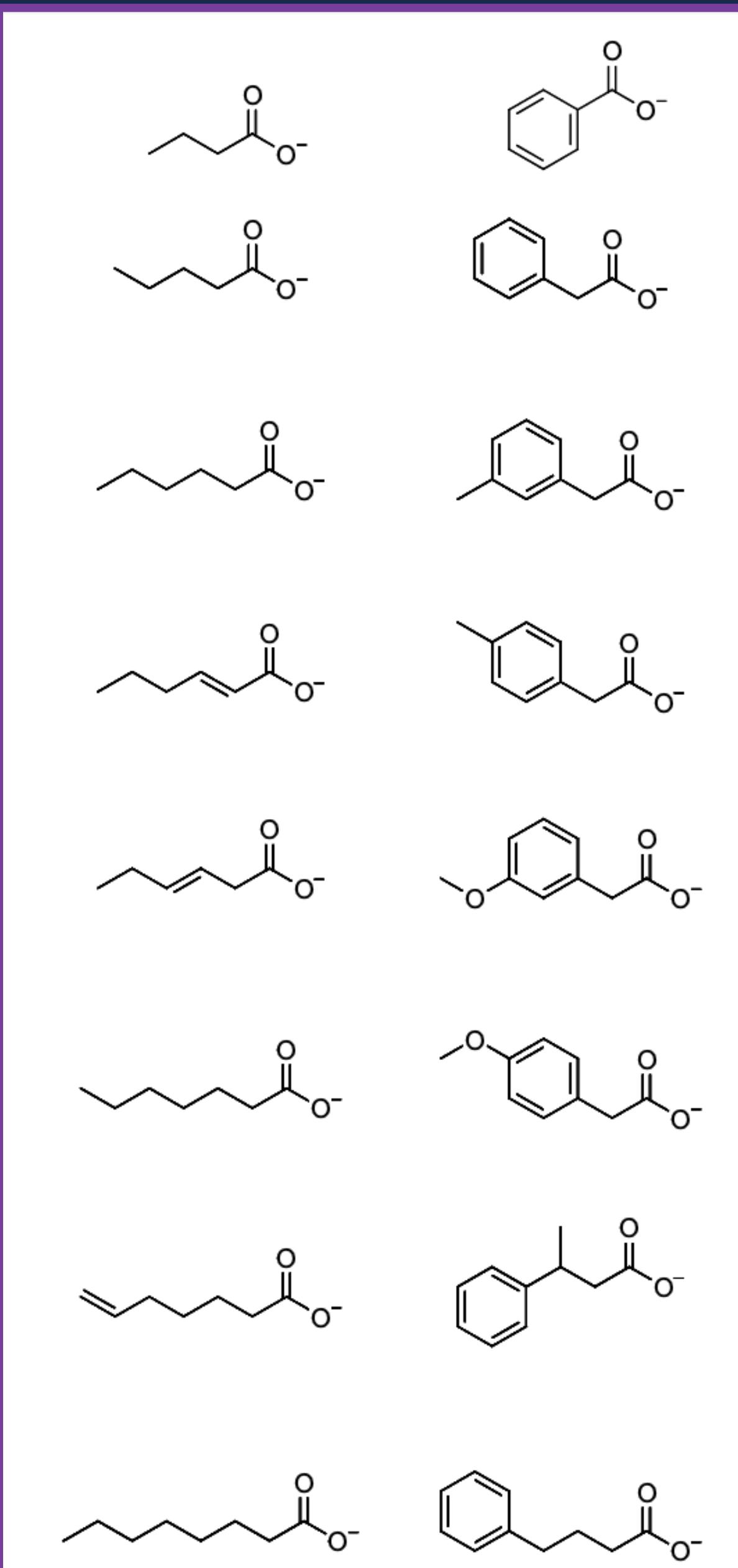
Amines  
(+1)



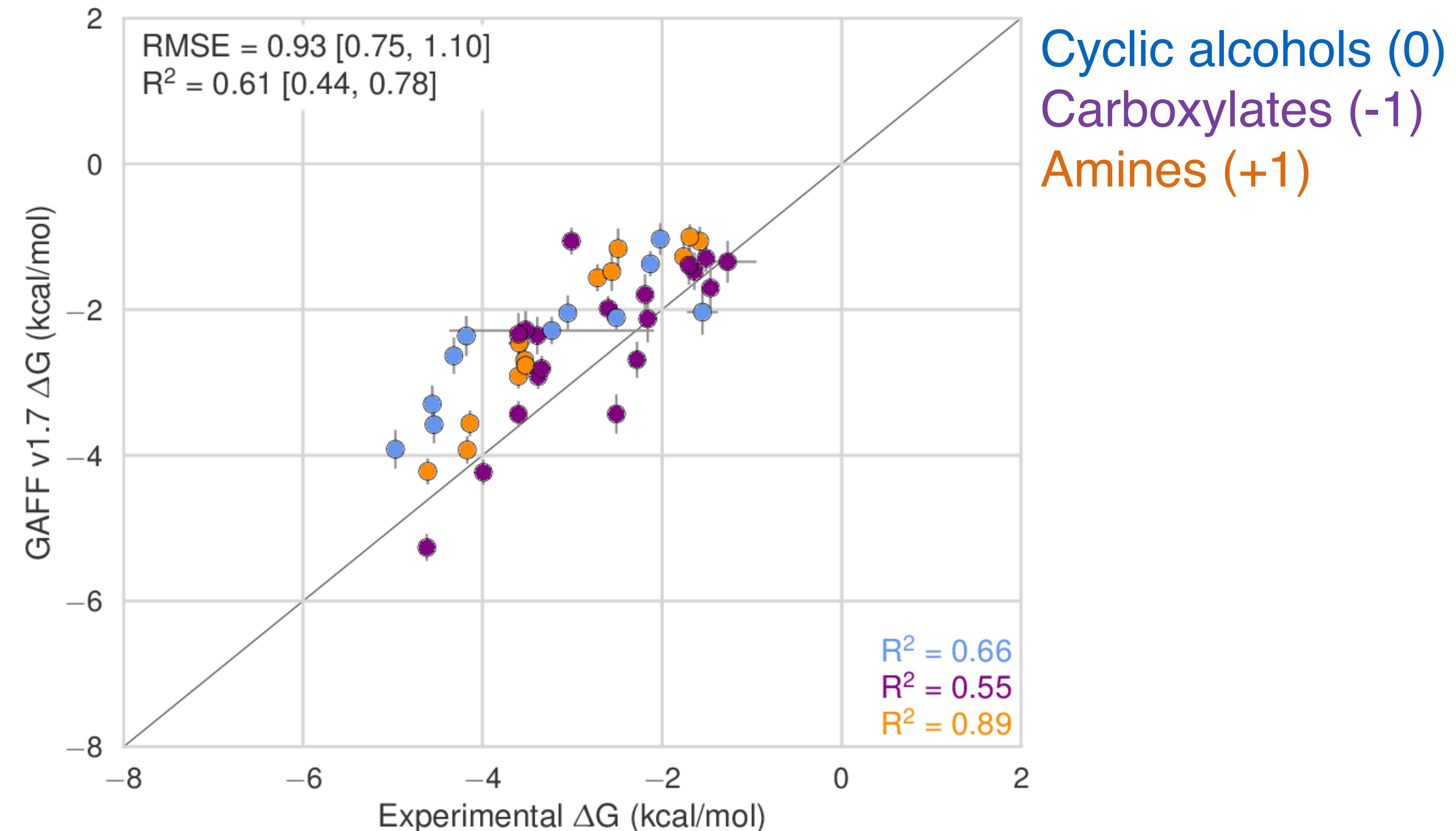
Cyclic alcohols  
(0)



Carboxylates  
(-1)



Our simulations can predict experimental binding free energies to  $\sim$ 1 kcal/mol accuracy.



M. V. Rekharsky *et al.*, Thermodynamic and Nuclear Magnetic Resonance Study of the Reactions of A- and B-Cyclodextrin with Acids, Aliphatic Amines, and Cyclic Alcohols. *J. Phys. Chem. B.* **101**, 87 (1997).

**This work is part of a new effort to systematically generate and improve force fields.**

**Open source**

Software available on GitHub and permissively licensed

**Open data**

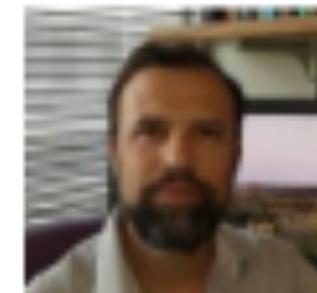
Curated physical property and quantum chemical data sets

**Open science**

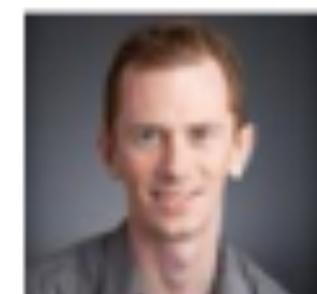
Papers available on bioRxiv and chemRxiv



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**MICHAEL SHIRTS**  
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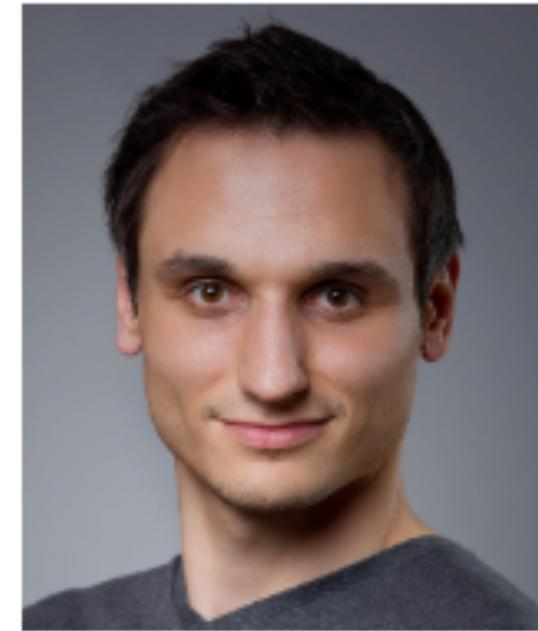
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**CHRISTOPHER BAYLY**  
**OPENEYE SCIENTIFIC**



**KENNETH KROENLEIN**  
**NIST THERMODYNAMICS  
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### Michael Schauperl (Researcher)

Postdoctoral Fellow, University of California, San Diego

*Fitting of new electrostatics models for force fields with a focus on polarization*

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In 1 hour

## Advanced Electrostatic Potential Based Methods to Derive Atomic Charges and Polarizabilities

# SMIRNOFF99Frosst is a new kind of force field.

Fewer numerical parameters than GAFF

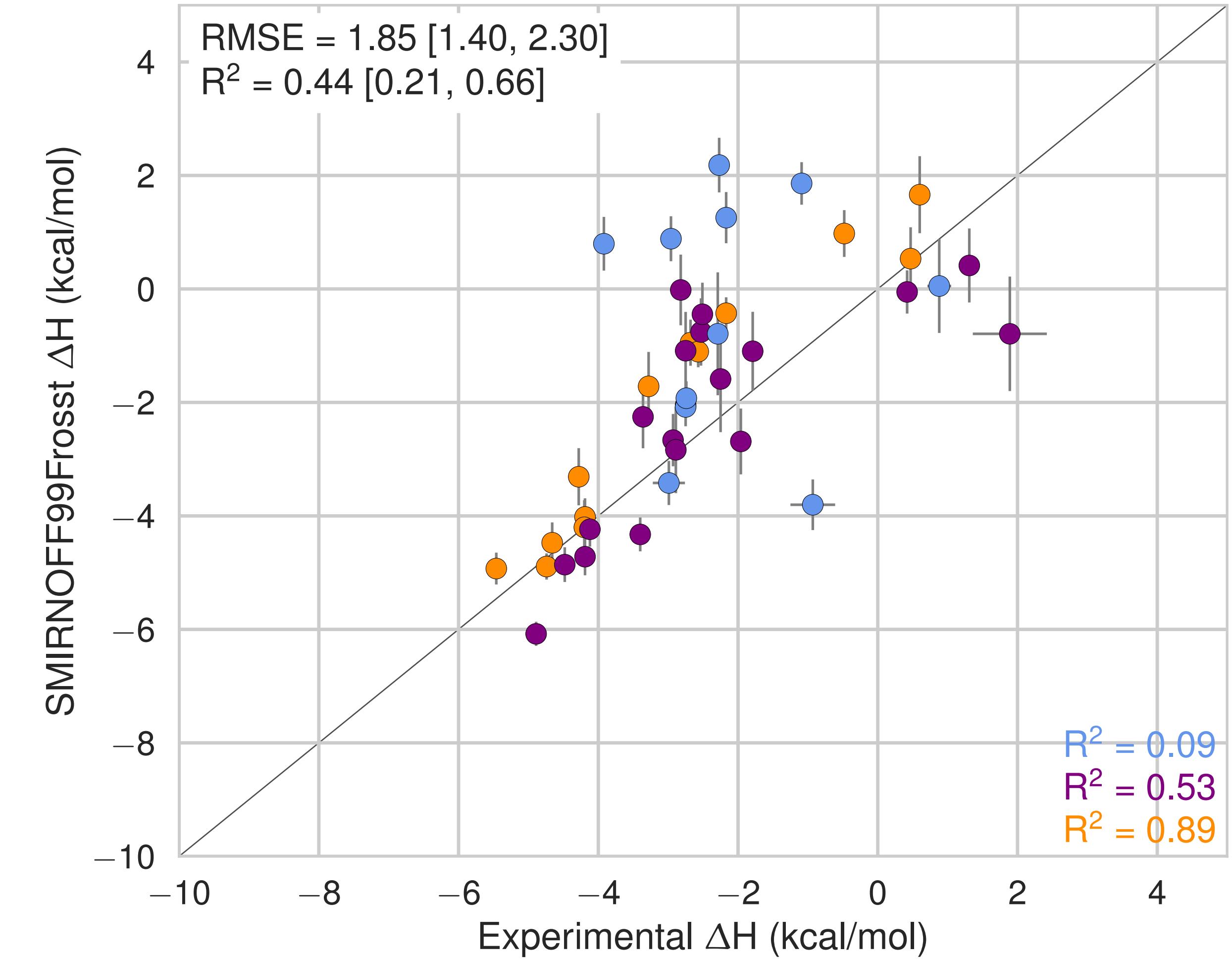
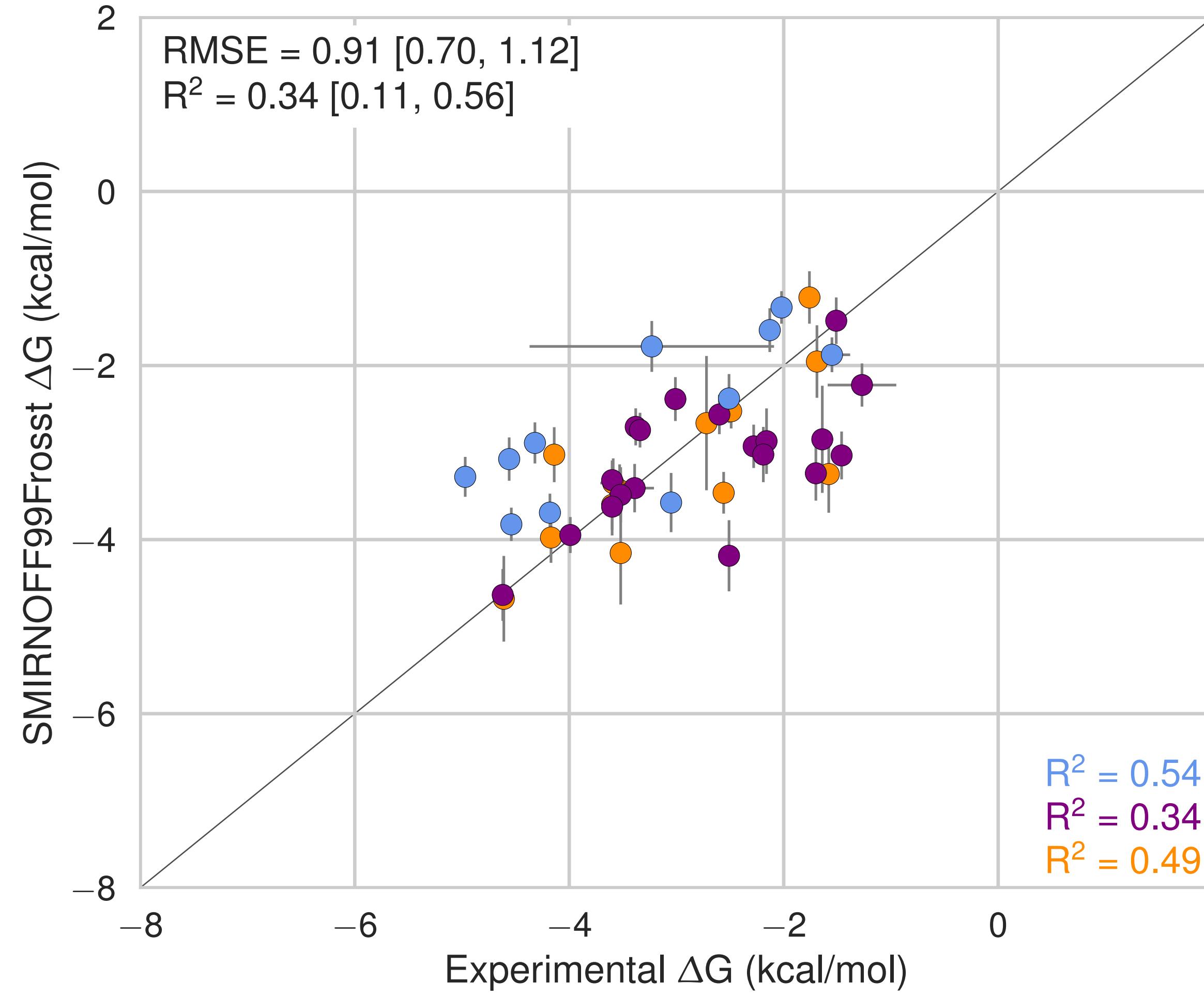
GAFF: 6,700

SMIRNOFF99Frosst: 330

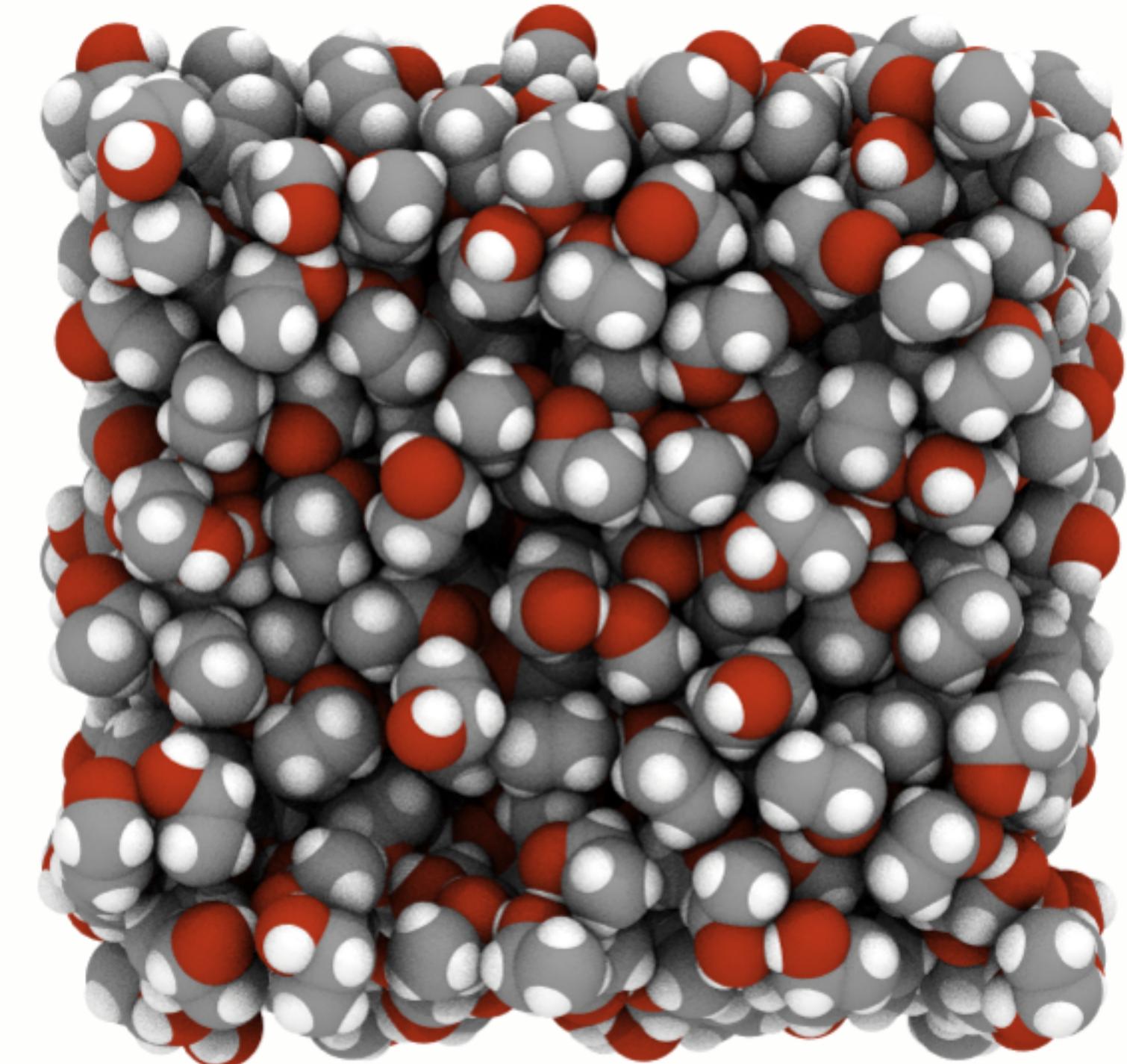
Larger chemical space coverage than GAFF

Usable in multiple simulation codes

With 5% the number of parameters, we can do as well as existing force fields.



# How can we build force fields that are accurate for drug discovery?



**Usually**

Force fields are built using pure liquid properties.

**But**

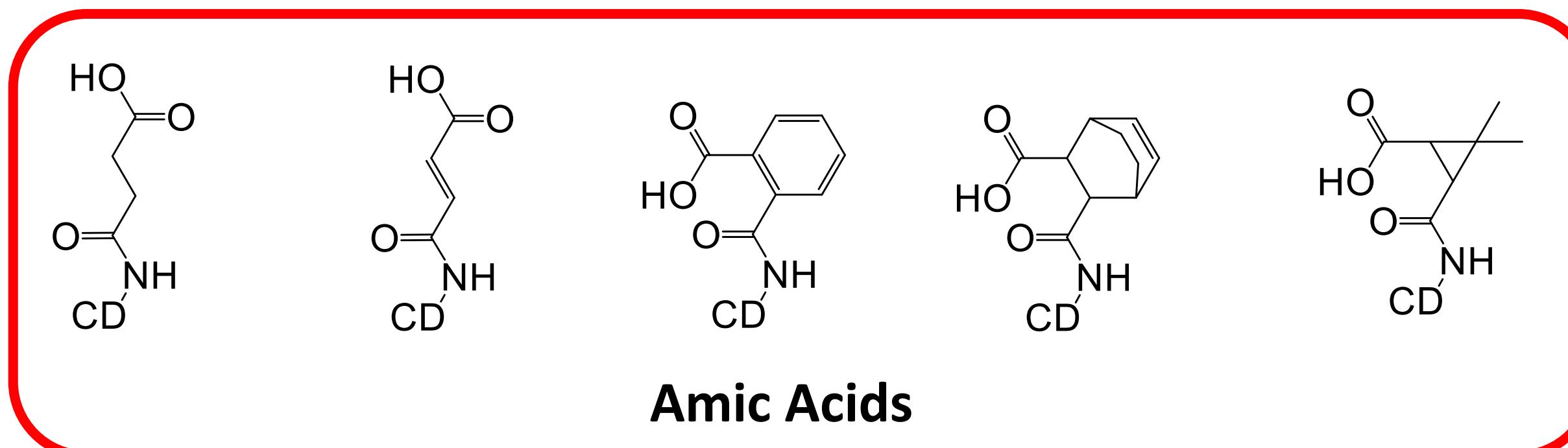
We want to use host-guest data to build force fields.

We want to use systematic data to drive the optimization of force fields.

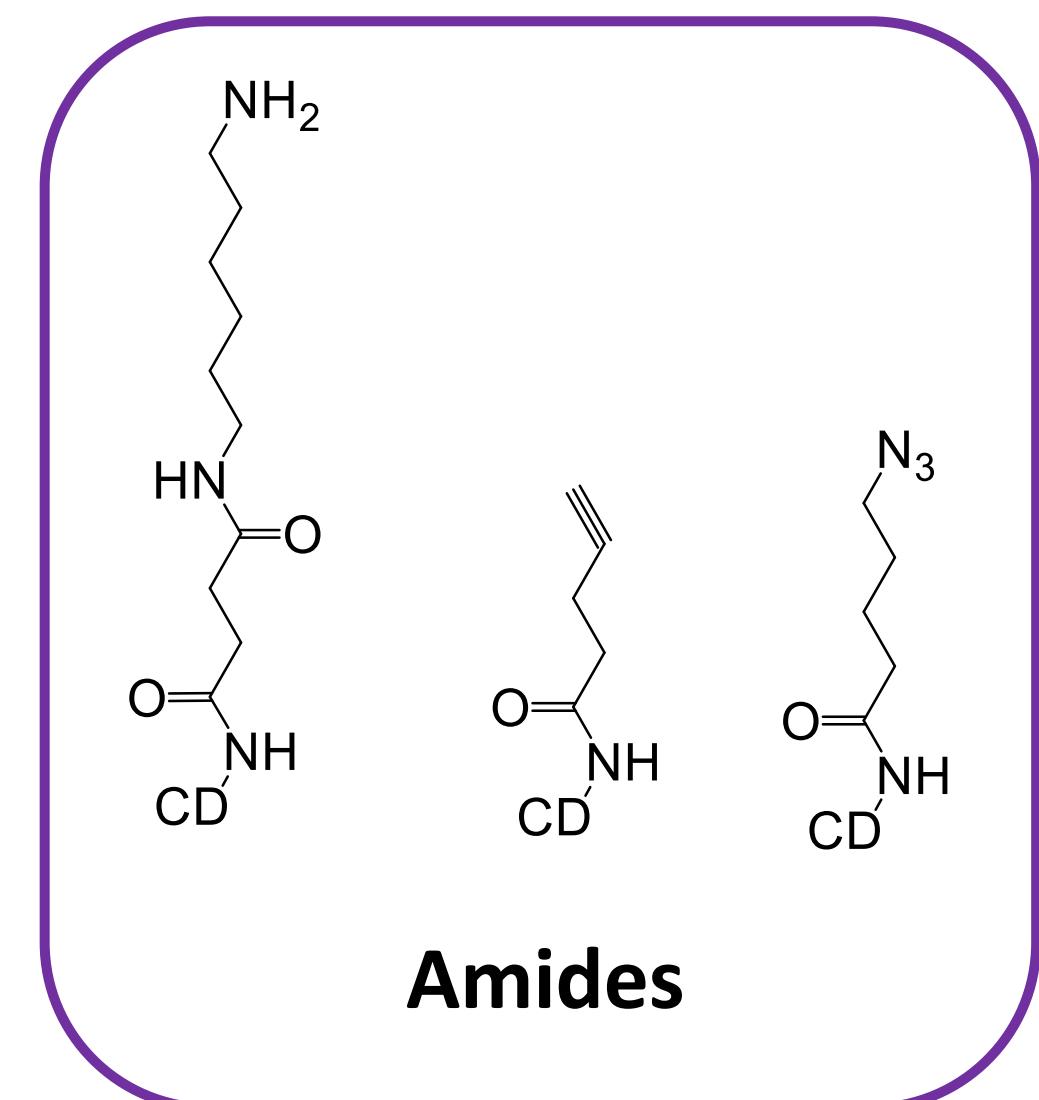
J. Yin *et al.*, Overview of the SAMPL5 host-guest challenge: Are we doing better? *J. Comput. Aided Mol. Des.* **31**, 1–19 (2017).

A. Rizzi *et al.*, Overview of the SAMPL6 host–guest binding affinity prediction challenge. *J. Comput. Aided Mol. Des.* **32**, 937–963 (2018).

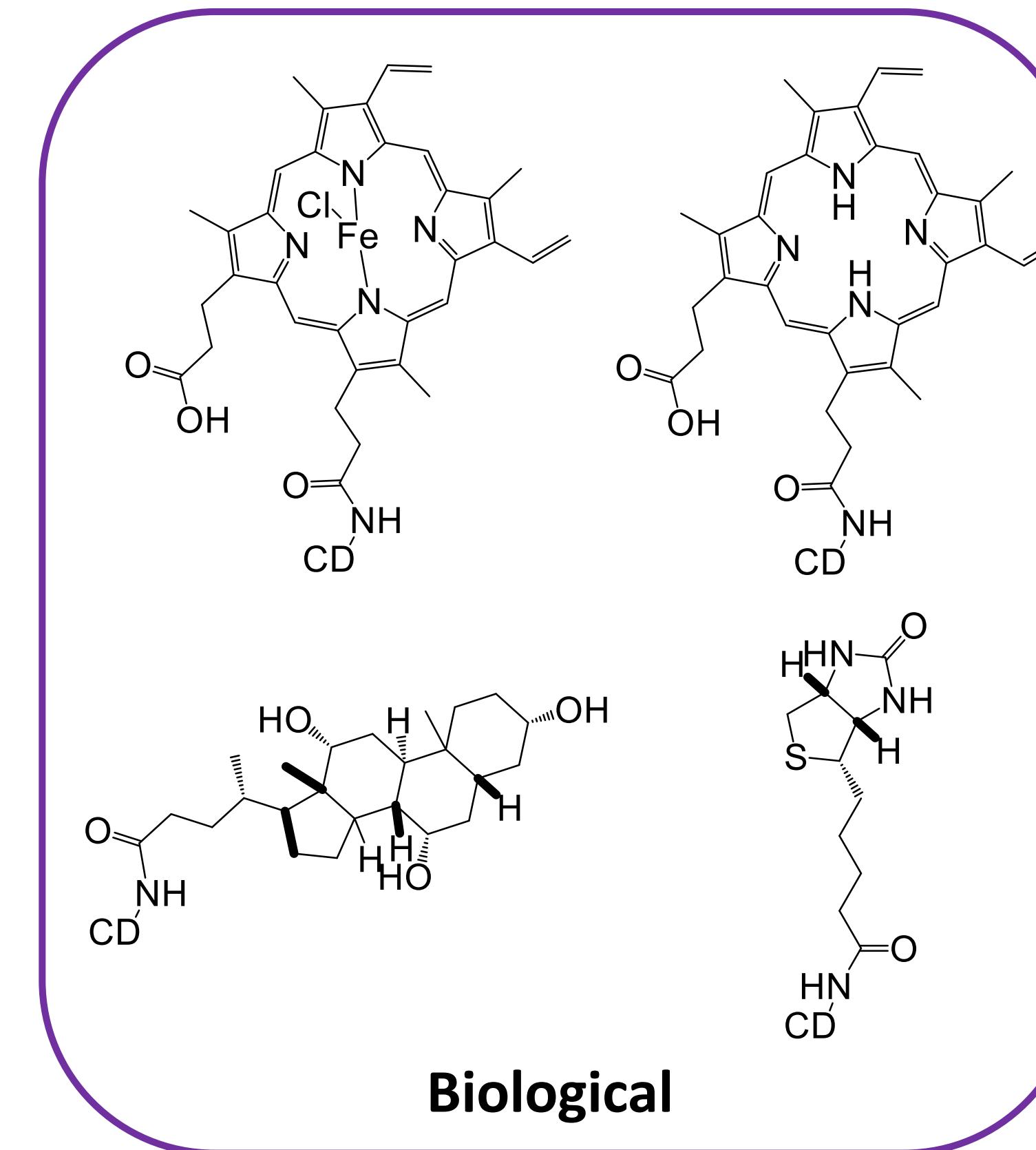
# A large chemically diverse data set of high-quality host-guest binding thermodynamics.



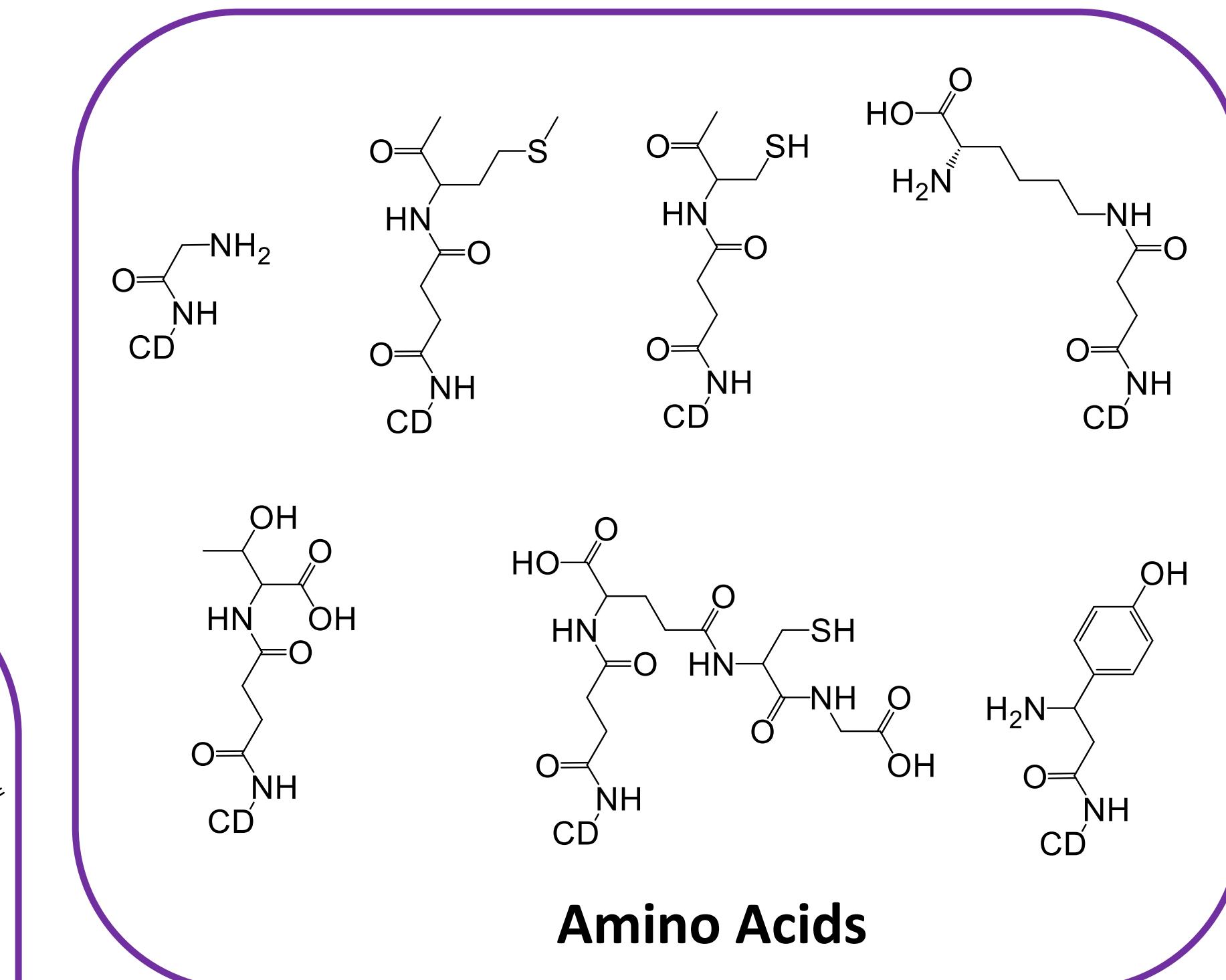
# Amic Acids



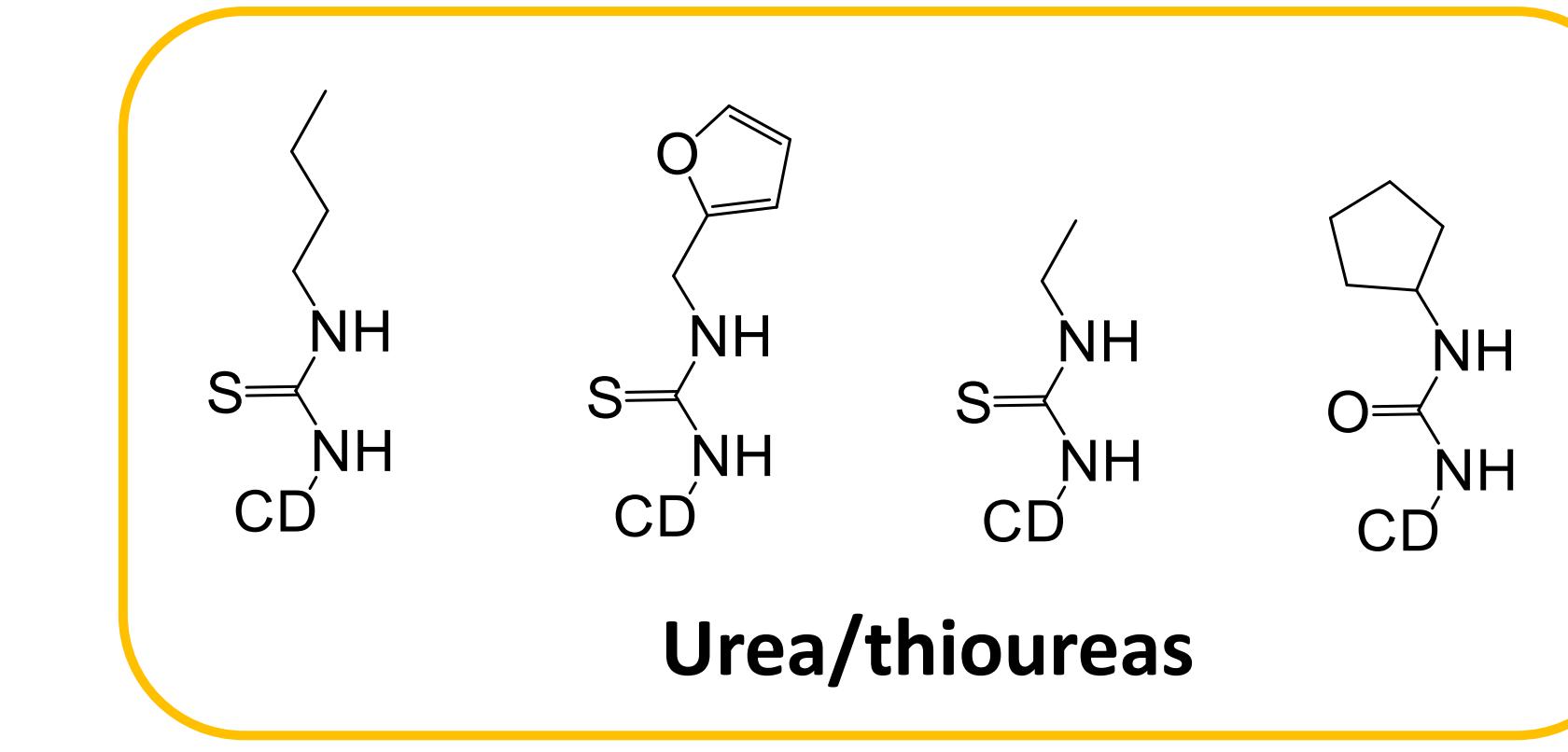
# Amides



# Biologica



# Amino Acids



# Urea/thioureas



## Katy Kellett (Researcher)

Postdoctoral Researcher, University of California, San Diego

*Synthesis and binding studies of novel host-guest systems*

web: [https://www.researchgate.net/profile/Katy\\_Kellett](https://www.researchgate.net/profile/Katy_Kellett)

ORCID: [0000-0001-9618-944X](#) | [Google Scholar](#)

Today, 4:50 pm in Lakeview B

Facile Synthesis of a Diverse Library of Mono-3-substituted  $\beta$ -Cyclodextrin Analogues and Their Applications

## Conclusions

Host-guest complexes are ideal model systems to evaluate force field performance.

Computational calorimetry is approaching the accuracy necessary to accelerate drug discovery.

The Open Force Field Initiative is building new force fields, which will be optimized and tested using binding thermodynamics.



Michael K. Gilson, M.D., Ph.D.

## Gilson group

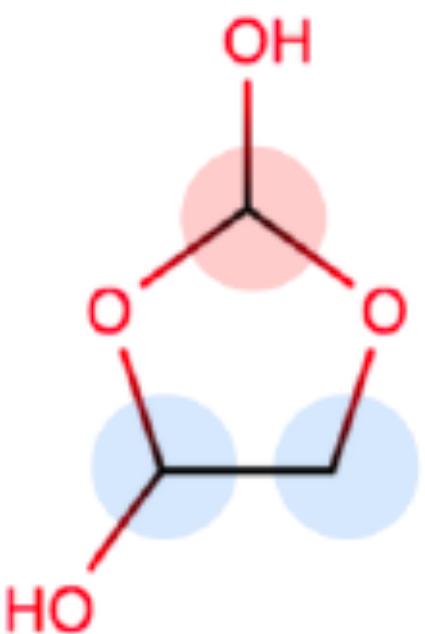
Ido Ben-Shalom, Ph.D.  
Mudong (Winter) Feng  
Samuel Kantonen  
Katy Kellett, Ph.D.  
Tiqing Liu, Ph.D.  
John Lomibao  
Michael Schauperl, Ph.D.  
Felix Yang

Niel Henriksen, Ph.D. (Atomwise)  
Jane Yin, Ph.D. (XtalPi)

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