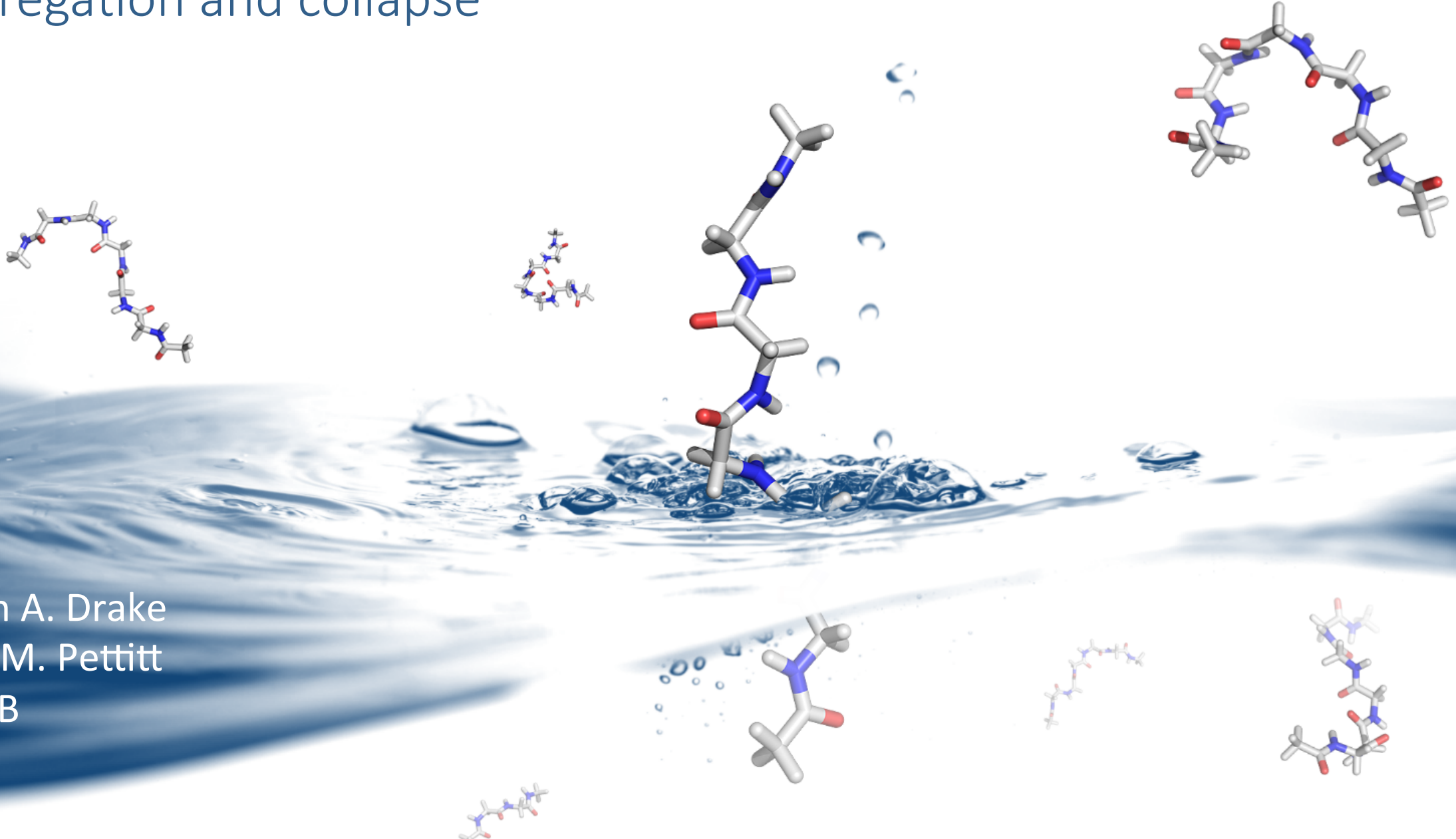
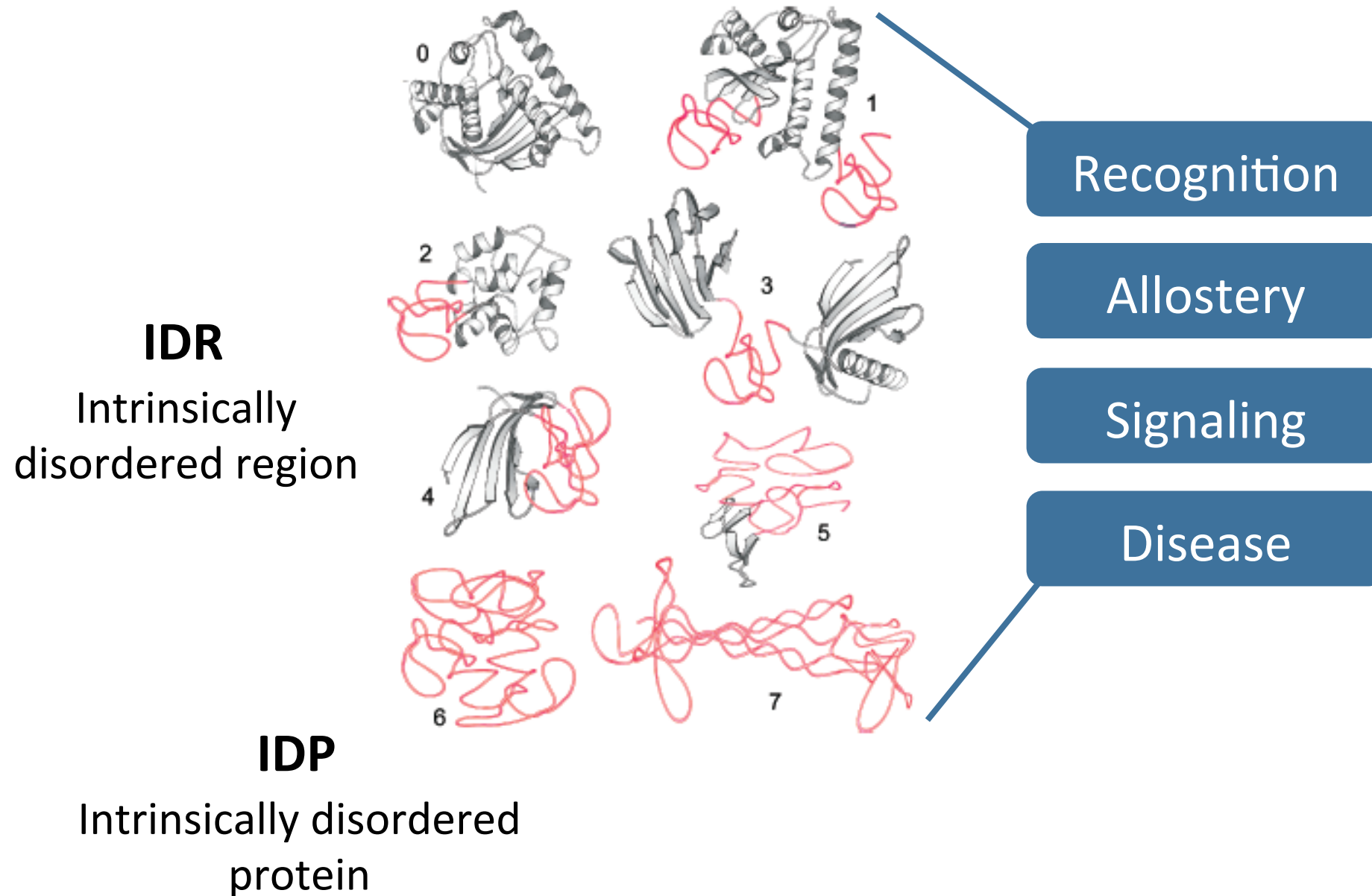


# Solvation thermodynamics of oligoglycine: implications for aggregation and collapse



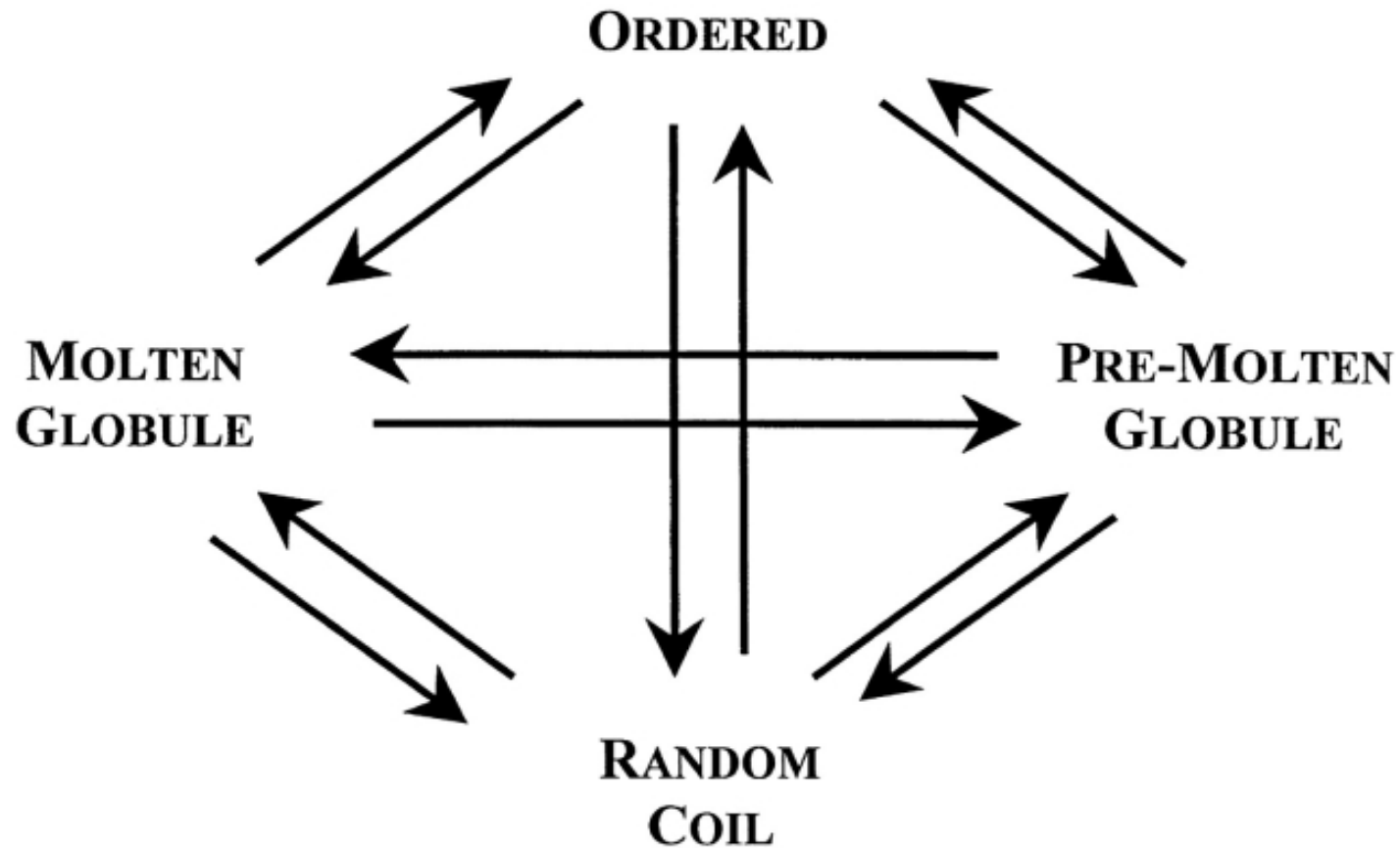
Justin A. Drake  
PI: B.M. Pettitt  
UTMB

# Disorder in proteins

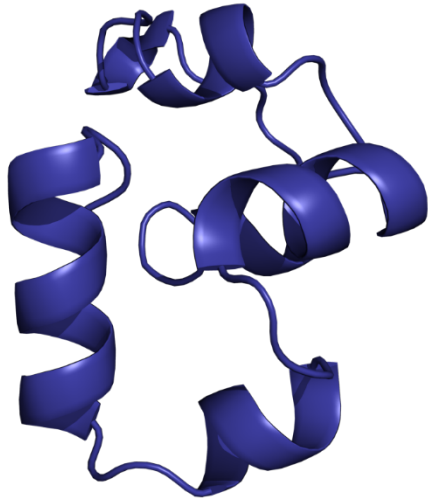
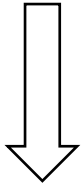


# Disorder in proteins

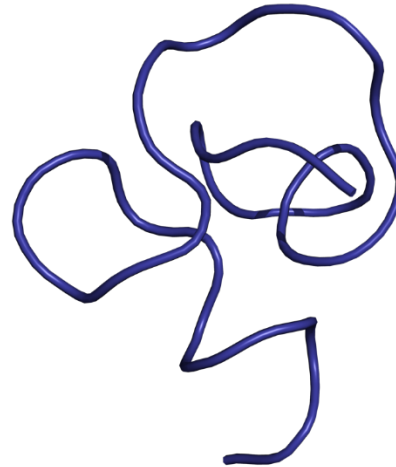
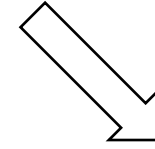
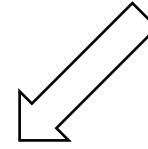
Structural properties of IDRs depend, in part, on chain length and sequence composition



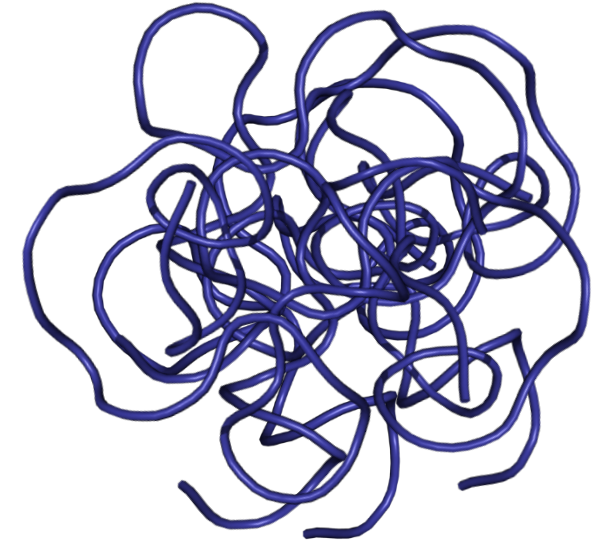
Are the thermodynamic mechanisms that drive folding similar to those that drive IDR collapse?



**Folding**

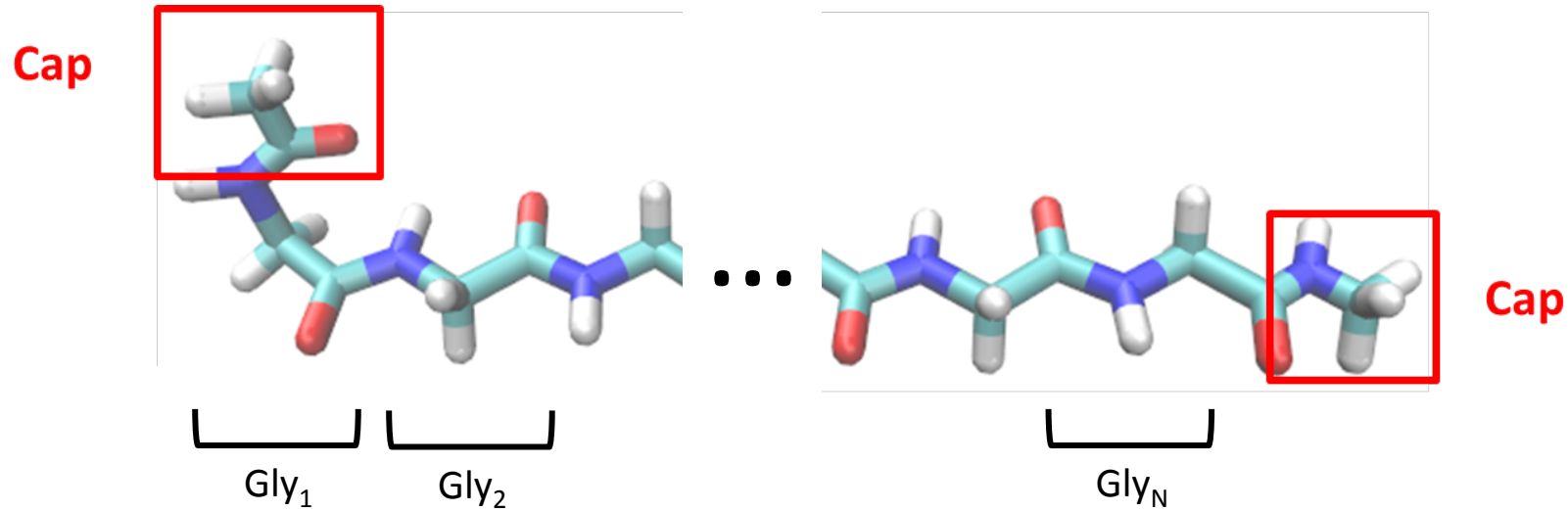


**IDR Collapse**



**Aggregation**

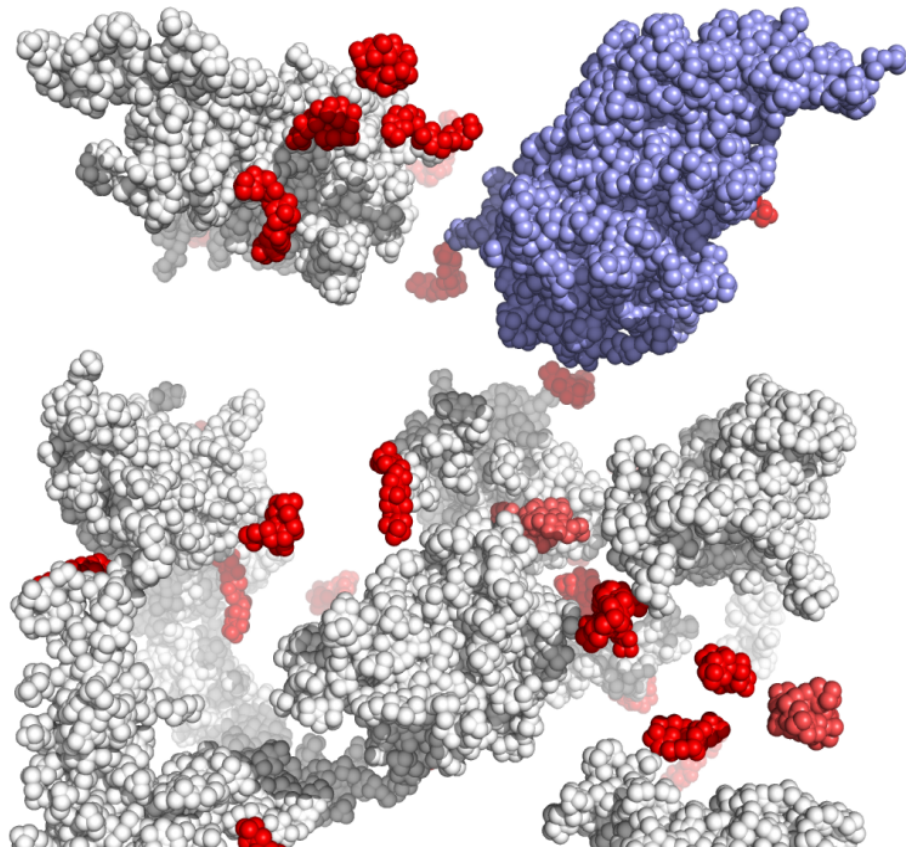
# Oligoglycine Model



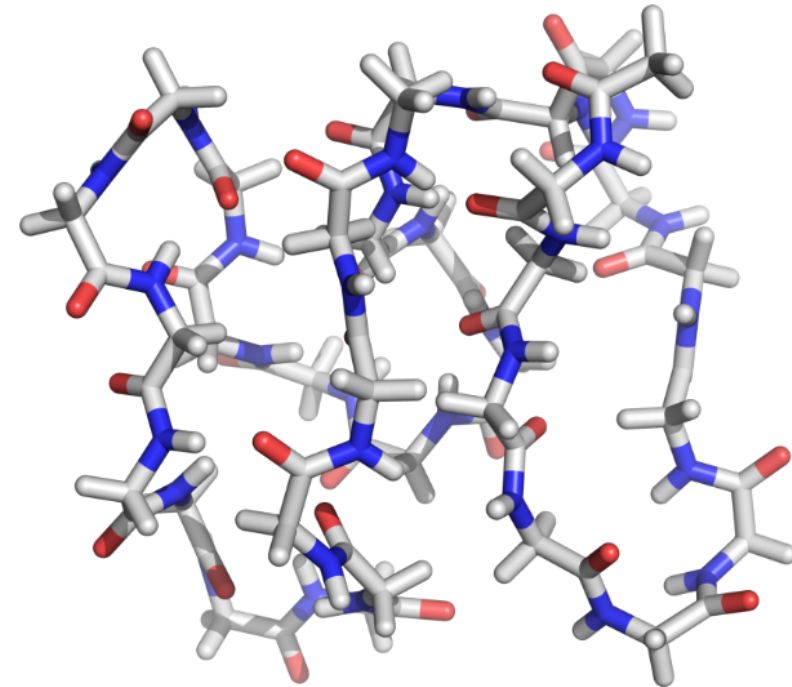
- Protein backbone
- IDRs enriched in glycine and oligoglycine tracts
- High glycine content associated with compact IDRs

# Oligoglycine Model

Experiment and simulation demonstrate the aggregation (insolubility) of short oligoglycines and collapse of long oligoglycines



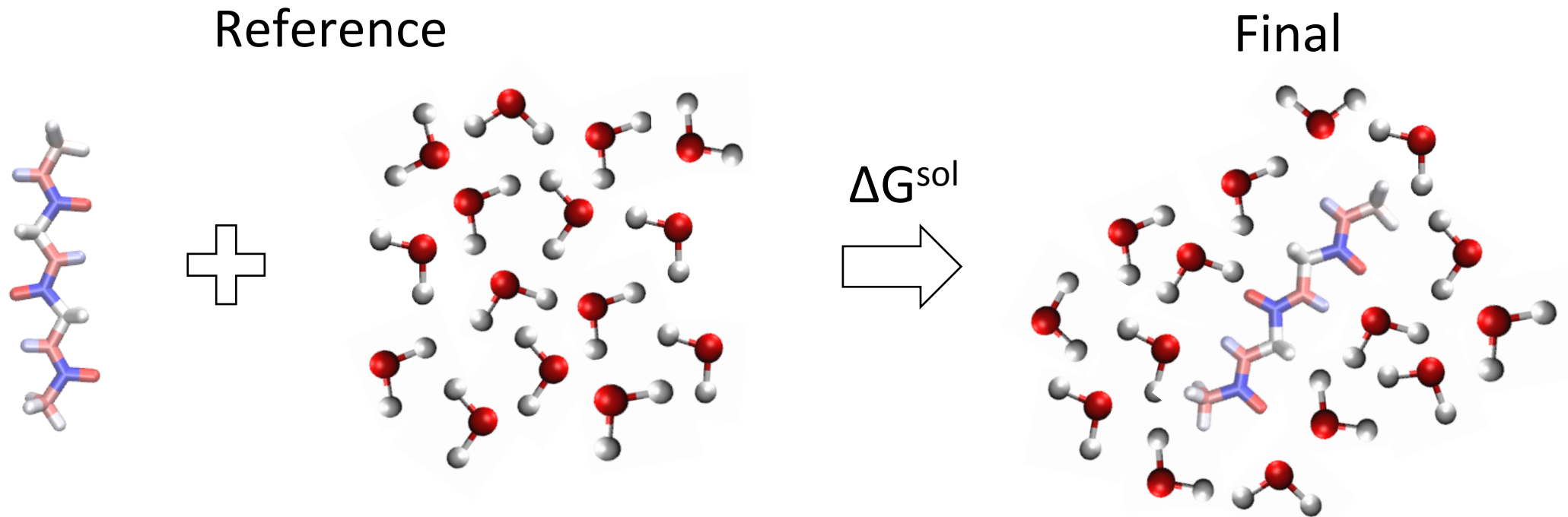
Karandur, 2014



Karandur, 2016  
Neuweiler, 2011  
Auton, 2004



# Approach – computational free energy method



$$U=0$$

$$U=U^{\text{vdw}} + U^{\text{elec}}$$

$$U(\lambda^{\text{vdw}}, \lambda^{\text{elec}}) = \lambda^{\text{vdw}} U^{\text{vdw}} + \lambda^{\text{elec}} U^{\text{elec}}$$

$$\Delta G^{\text{vdw}} = \int_0^1 \langle dU^{\text{vdw}} / d\lambda^{\text{vdw}} \rangle d\lambda^{\text{vdw}}$$

$$\Delta G^{\text{elec}} = \int_0^1 \langle dU^{\text{elec}} / d\lambda^{\text{elec}} \rangle d\lambda^{\text{elec}}$$

# Approach – free energy pathway

**Path 1:**  $\lambda^{\text{vdw}} \cdot U^{\text{vdw}}$

$f \uparrow$

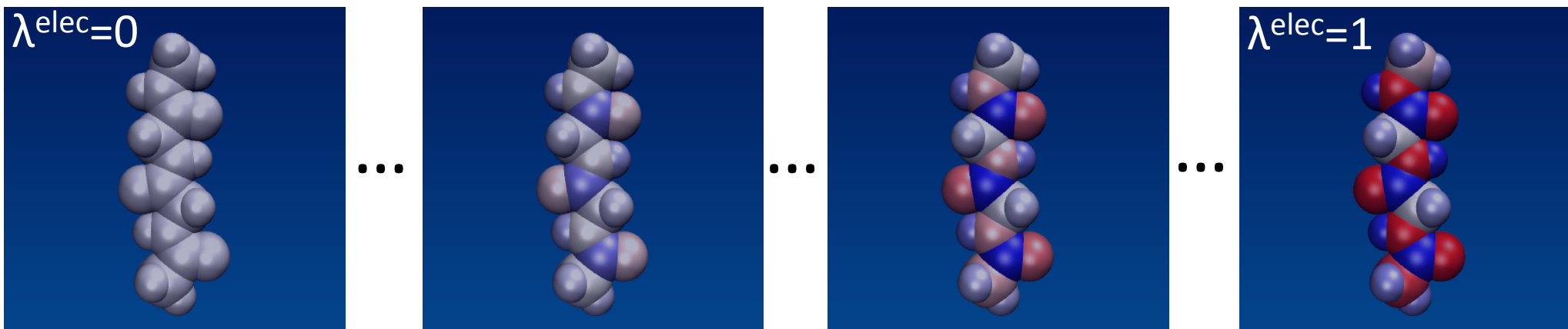


$\Rightarrow \Delta G^{\text{vdw}}$

+

**Path 2:**  $U^{\text{vdw}} + \lambda^{\text{elec}} \cdot U^{\text{elec}}$

$f \uparrow$



$\Rightarrow \Delta G^{\text{elec}}$

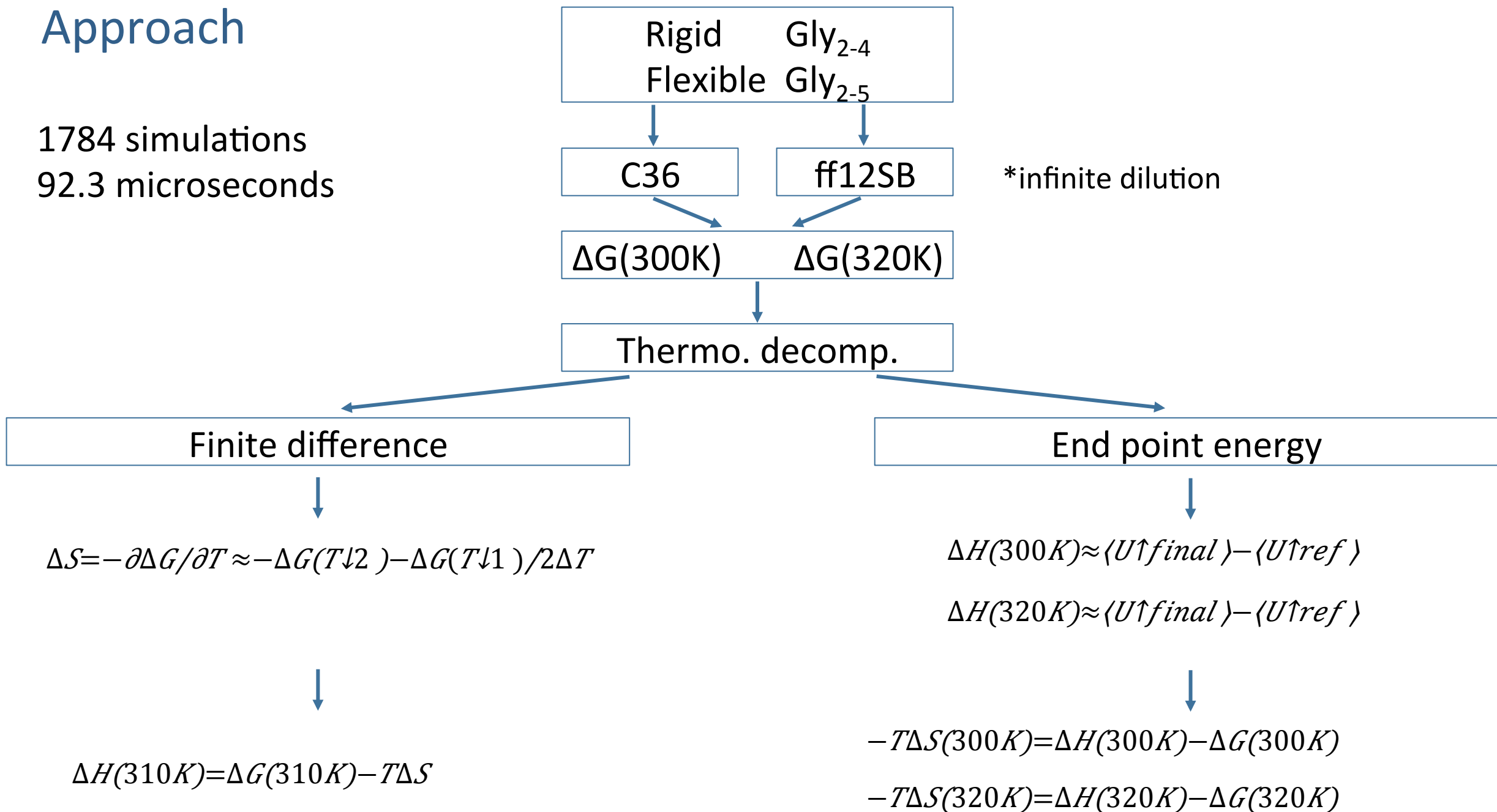
||

$\Delta G^{\text{sol}}$



# Approach

1784 simulations  
92.3 microseconds



# Approach

1784 simulations  
92.3 microseconds

Rigid Flexible  
Gly<sub>2-4</sub> Gly<sub>2-5</sub>

C36

ff12SB

\*infinite dilution

$\Delta G(300K)$

$\Delta G(320K)$

Thermo. decomp.

Finite difference

End point energy

$$\Delta S = -\partial\Delta G/\partial T \approx -\Delta G(T\downarrow 2) - \Delta G(T\downarrow 1) / 2\Delta T$$

$$\Delta H(300K) \approx \langle U \uparrow final \rangle - \langle U \uparrow ref \rangle$$

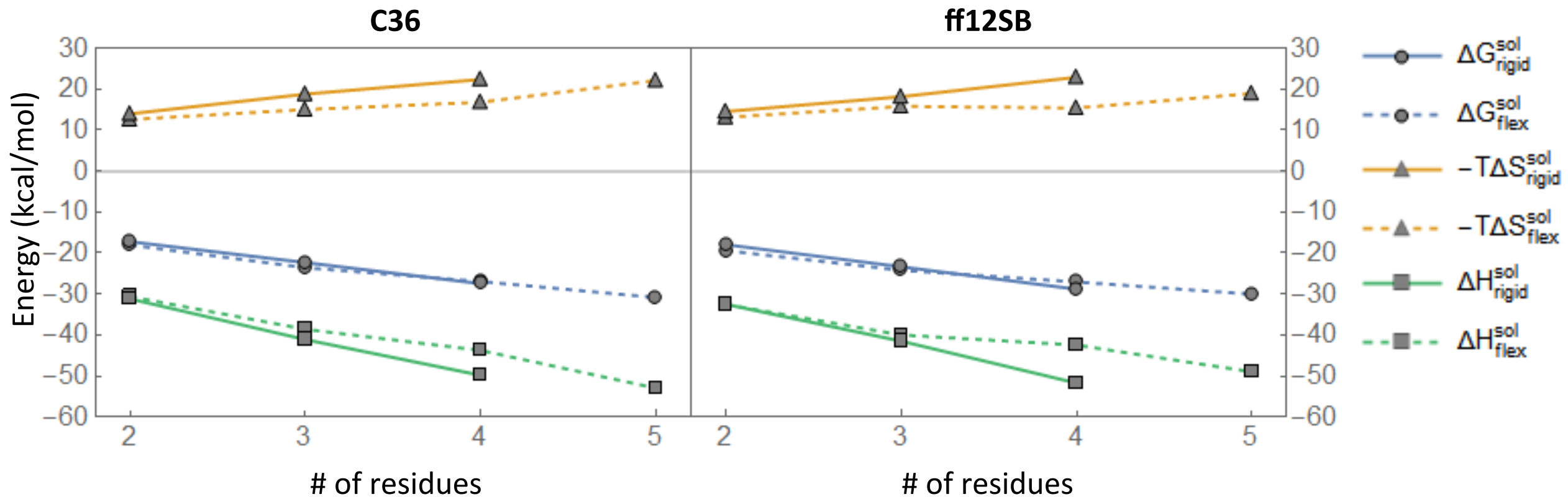
$$\Delta H(320K) \approx \langle U \uparrow final \rangle - \langle U \uparrow ref \rangle$$

$$\Delta H(310K) = \Delta G(310K) - T\Delta S$$

$$-T\Delta S(300K) = \Delta H(300K) - \Delta G(300K)$$

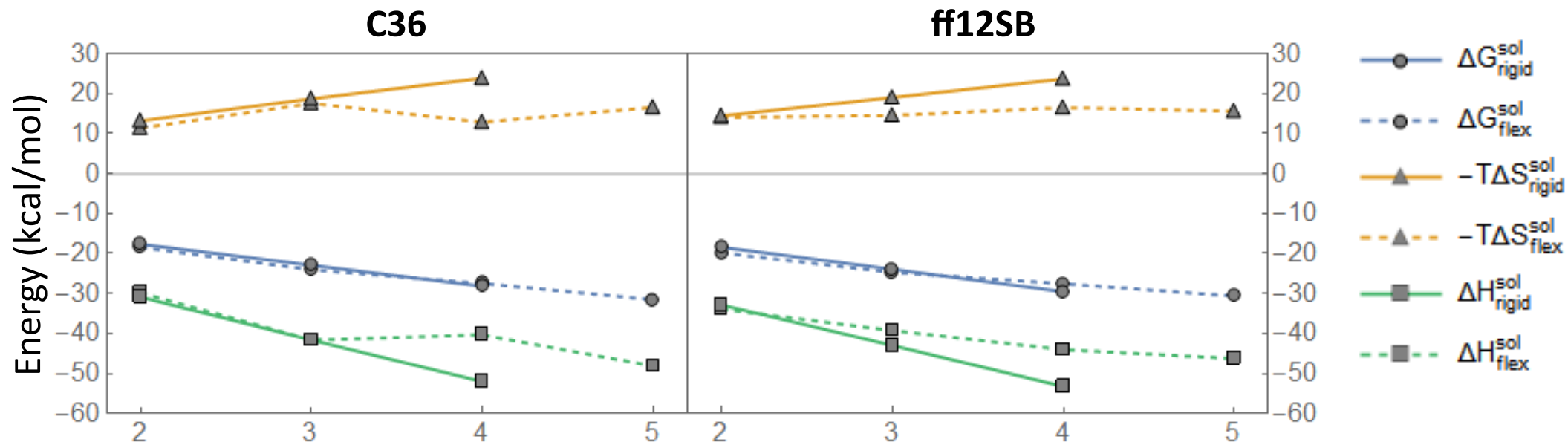
$$-T\Delta S(320K) = \Delta H(320K) - \Delta G(320K)$$

# Results: finite difference approach

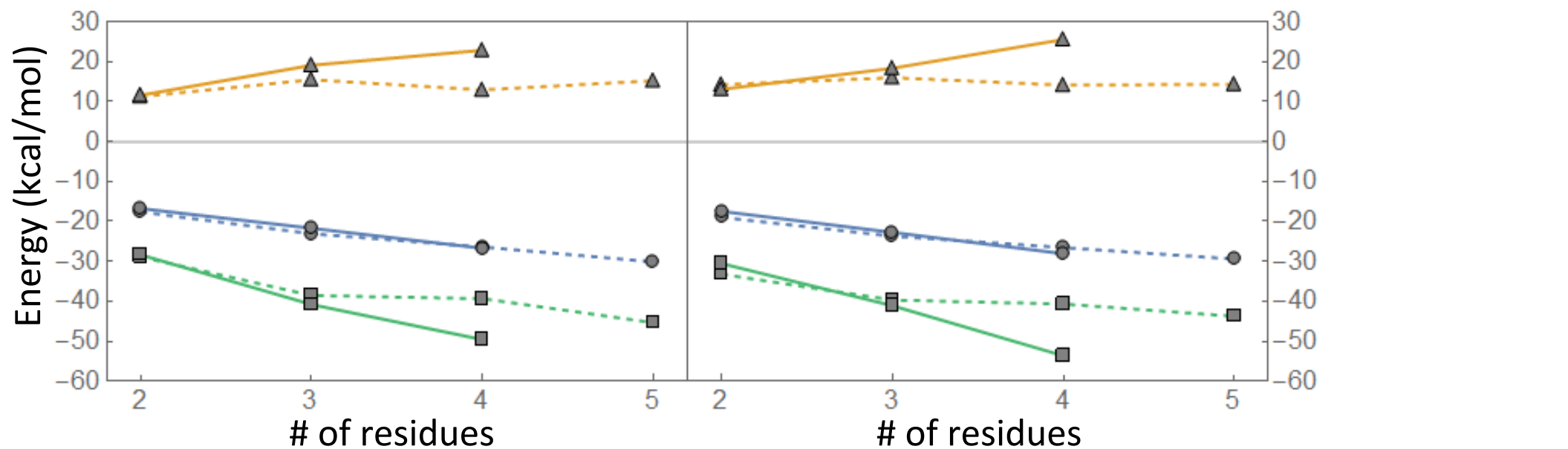


# Results: end point energy approach

300K

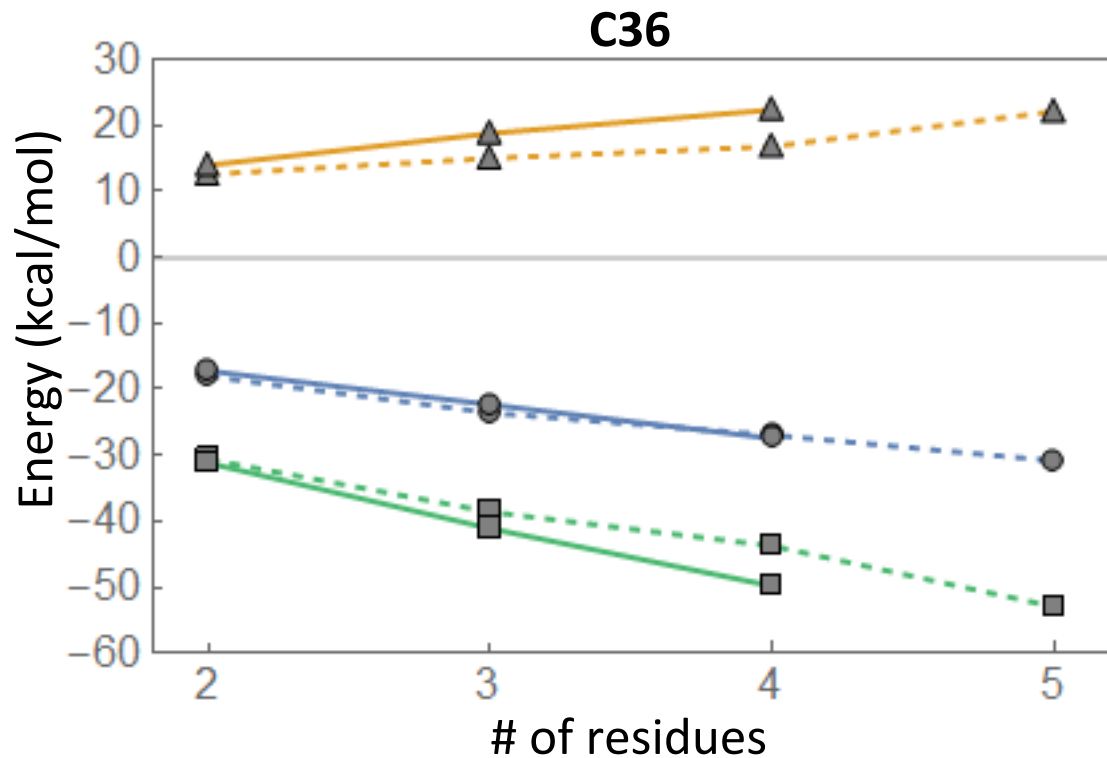


320K

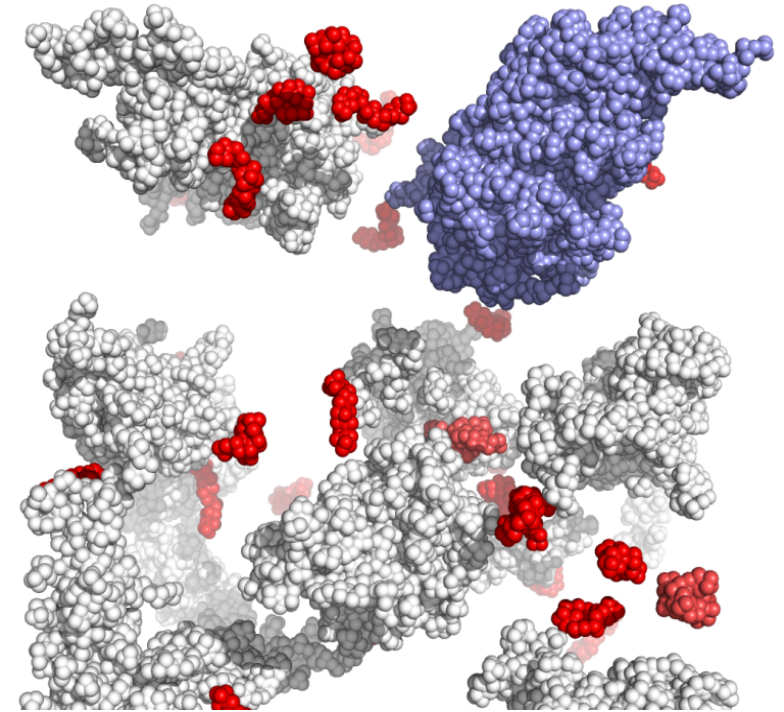


# Implication for the aggregation (insolubility) of Gly<sub>5</sub>

Infinite dilution



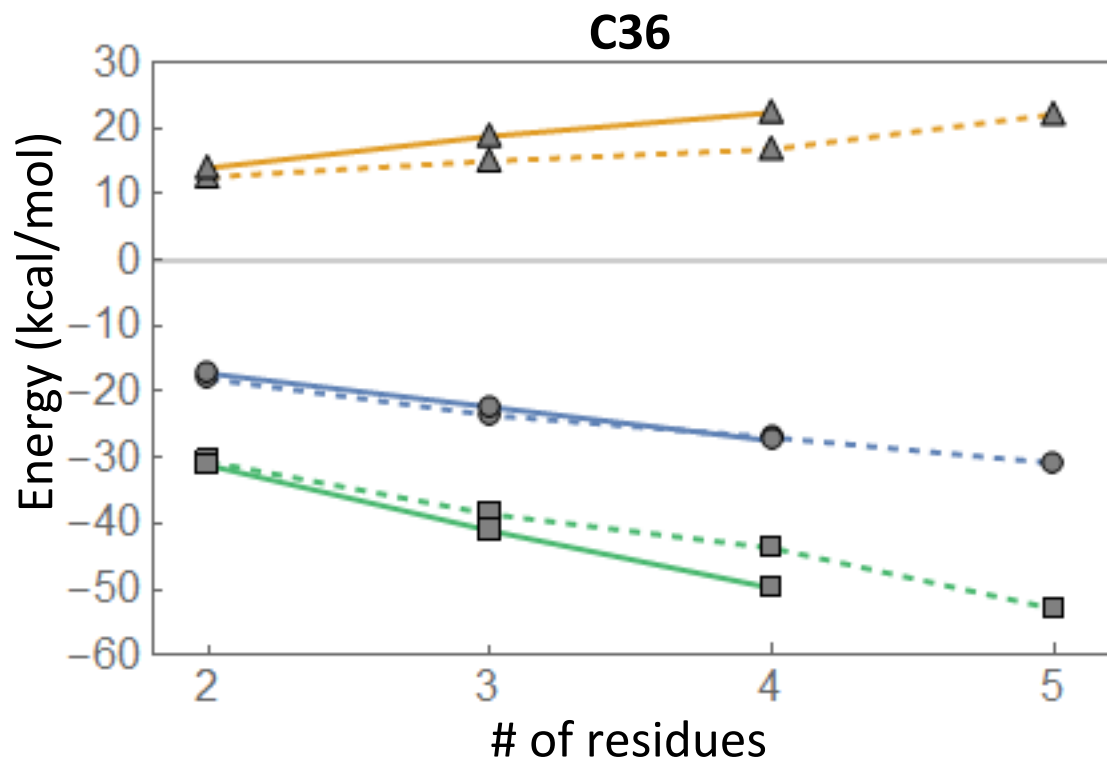
Finite concentration



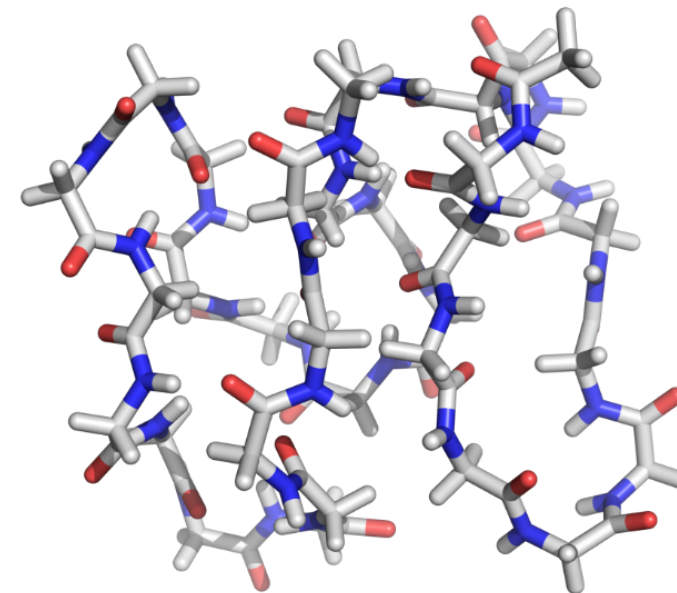
Peptide-peptide interactions outcompete favorable peptide-solvent interactions

# Implication for the collapse of long oligoglycines ( $\sim\text{Gly}_{10-30}$ )

Infinite dilution



Highly dilute

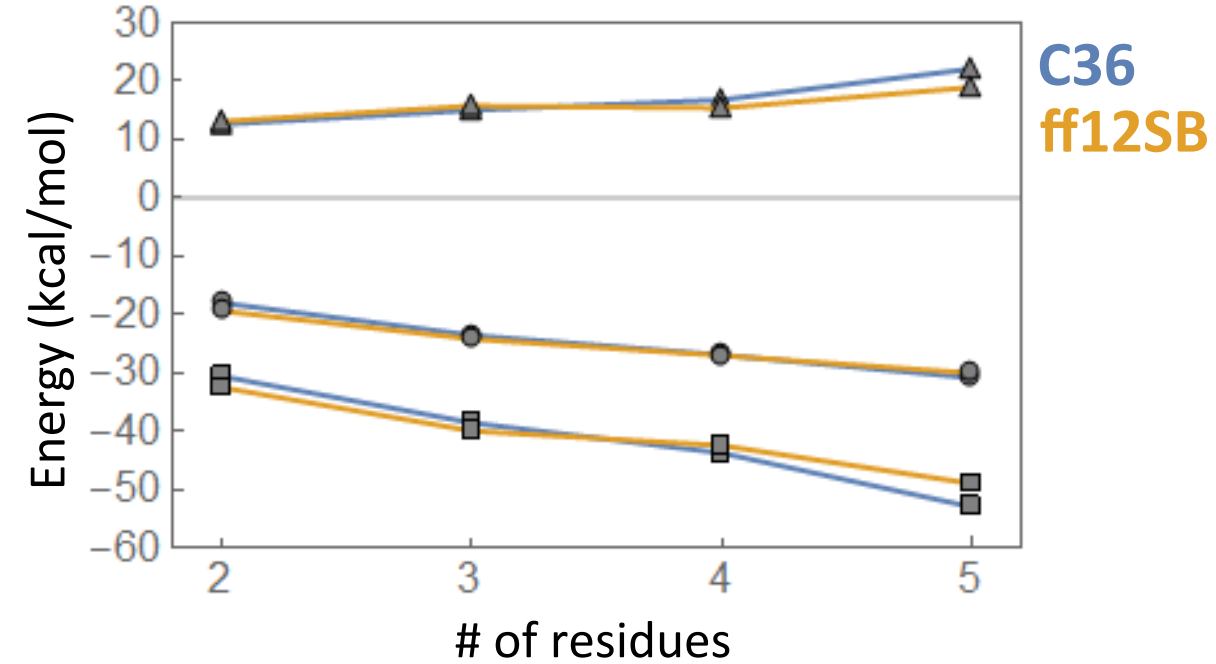


Case 1: scaling relationship holds (driven by peptide-peptide interactions)

Case 2: thermodynamic transition at some longer length (entropically driven)

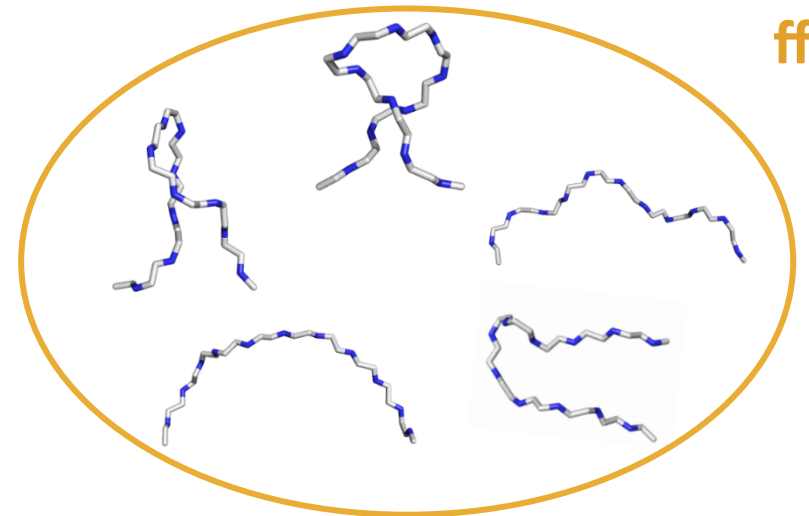
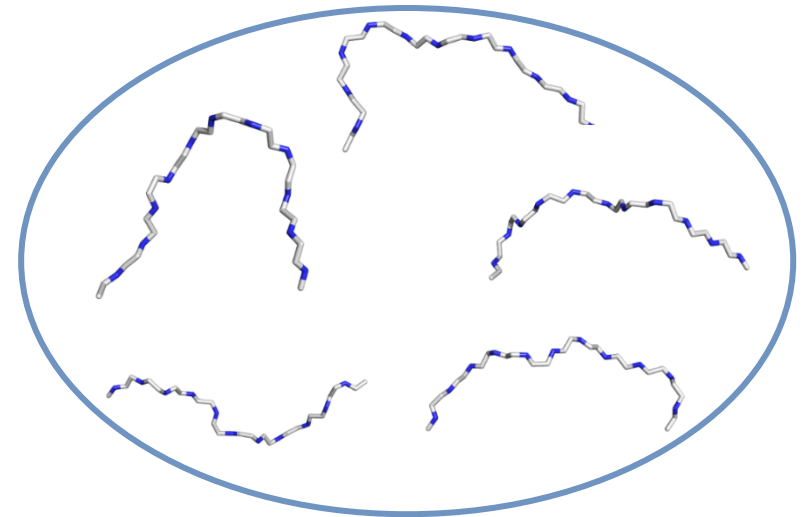
# Different structural ensembles yield similar solvation thermo?

## Solvation Thermo.



Degenerate ensemble – thermo. relationship

## Gly<sub>10</sub> ensemble





# Acknowledgements

PI: Dr. B. Montgomery Pettitt

Admin: Angelina Johnson

## Pettitt Research Group

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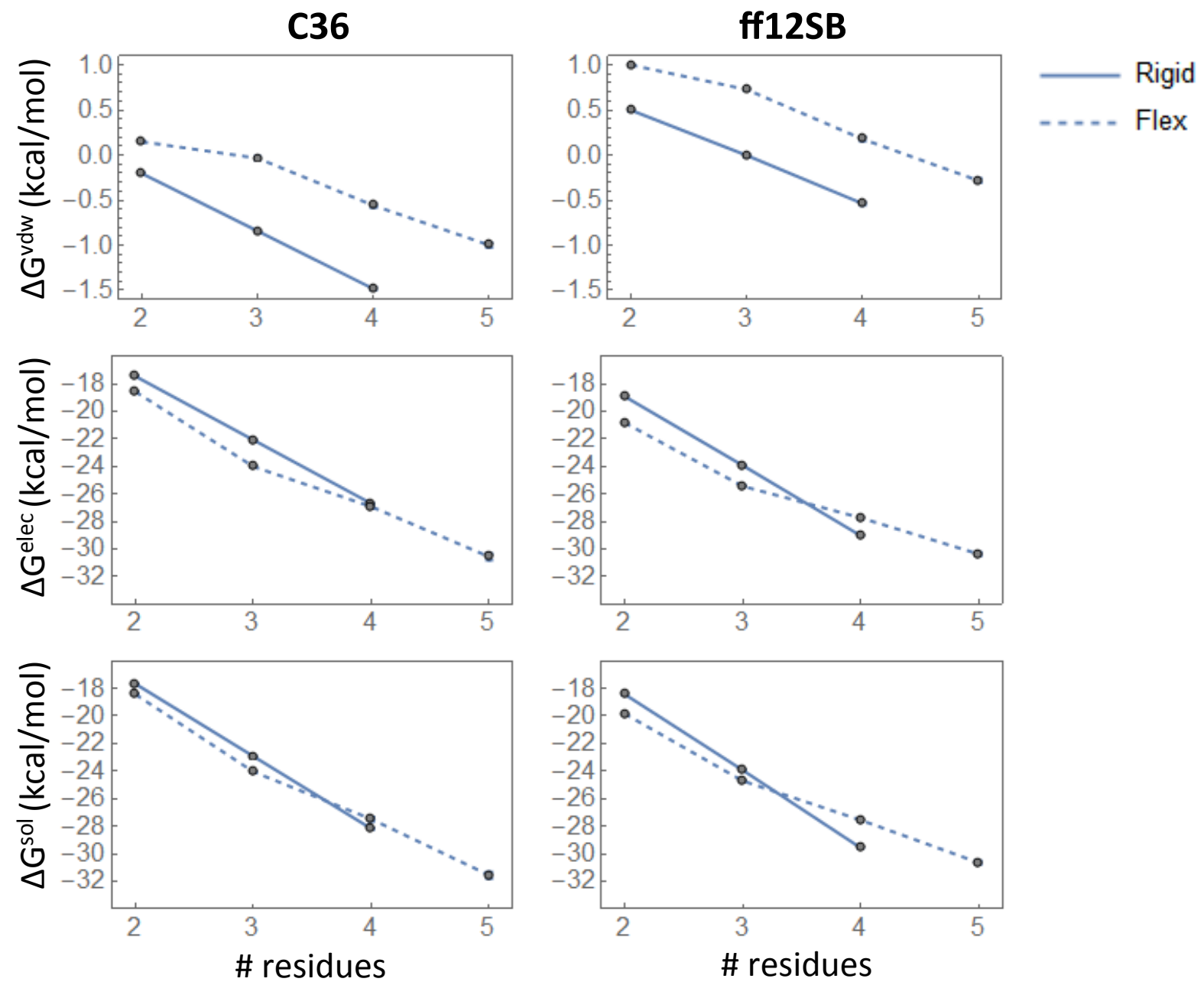
G. Rudenko

S. Bondos

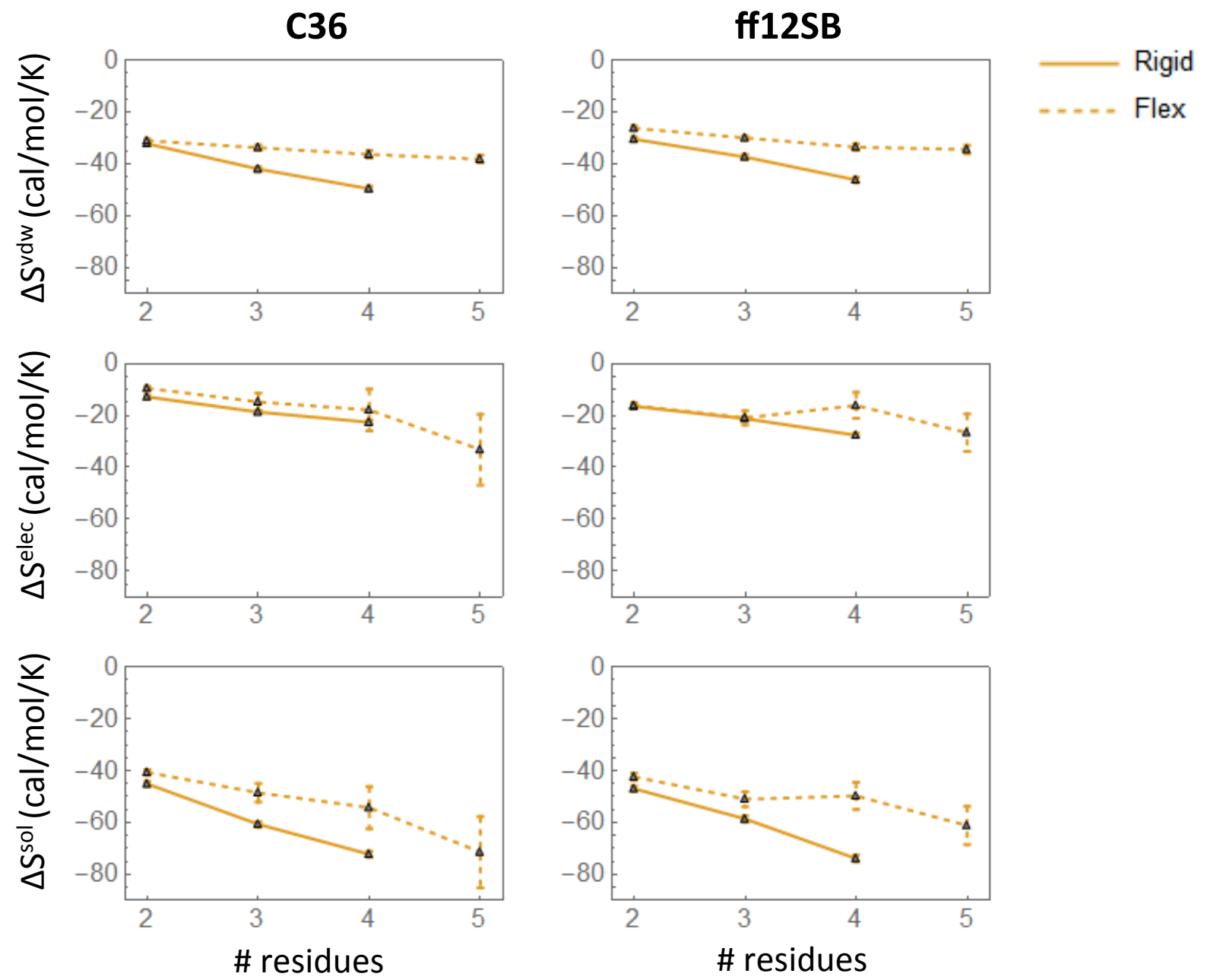


# Supplemental Slides

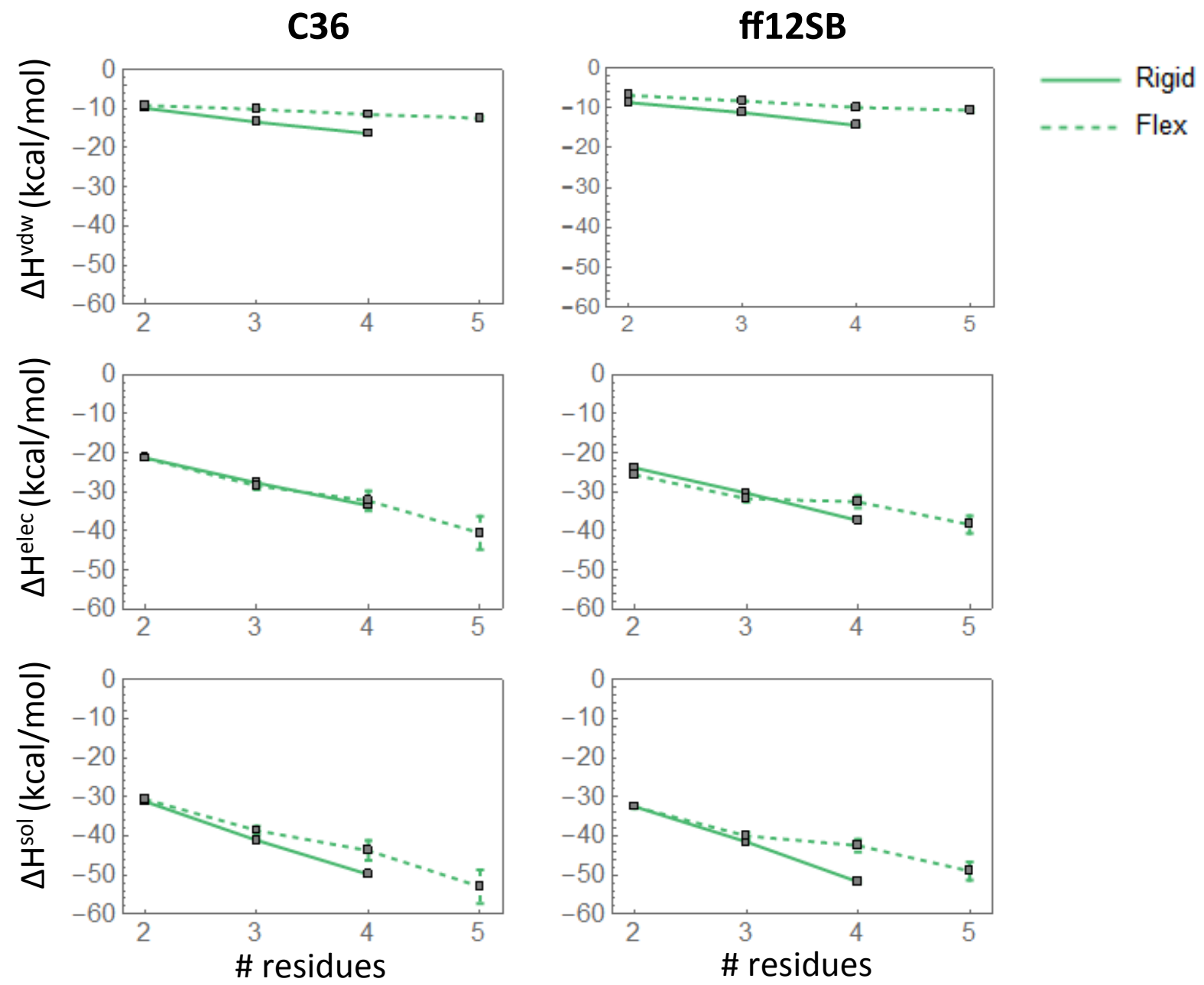
# Solvation free energy: components



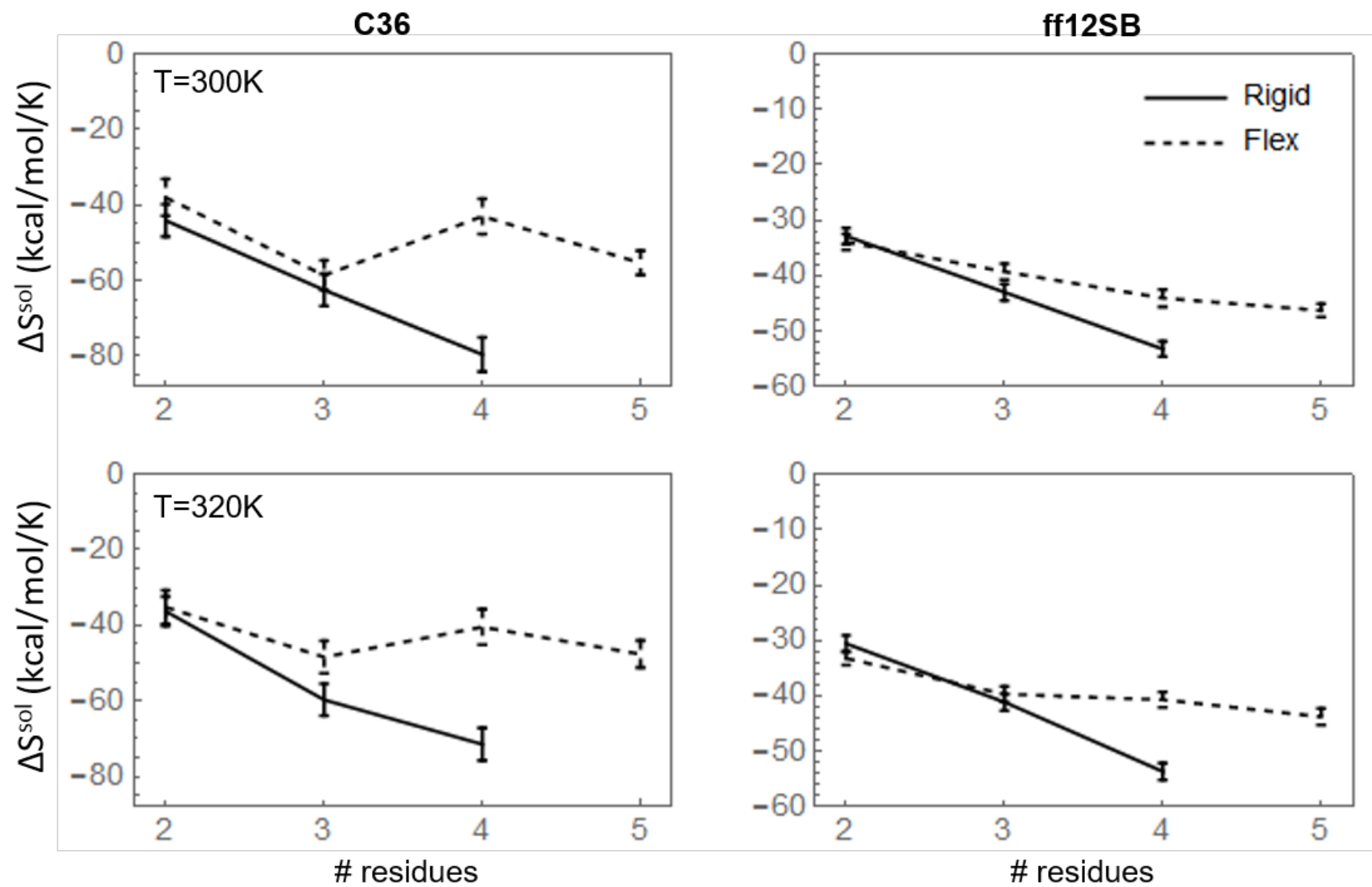
# Solvation entropy FD: components



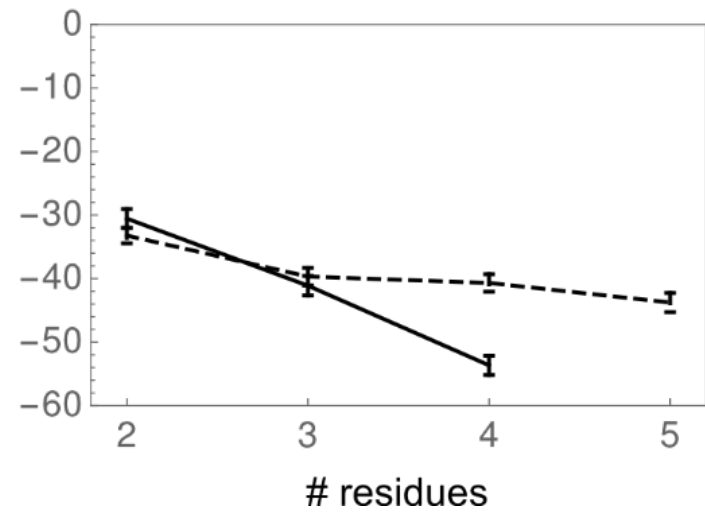
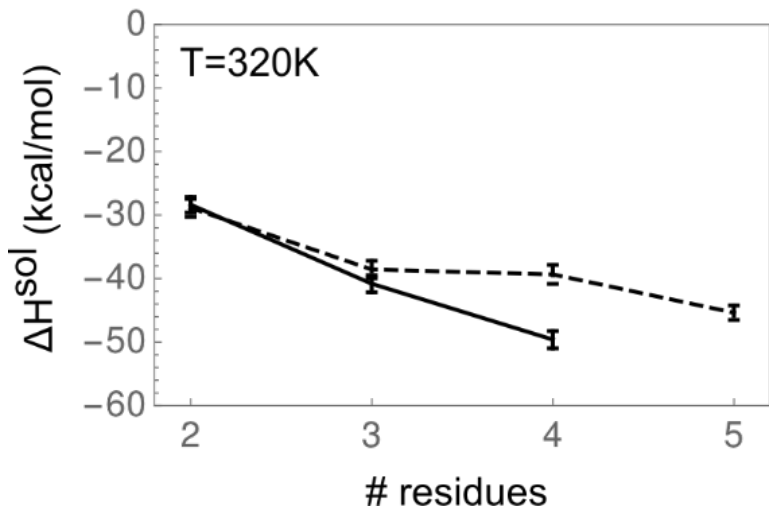
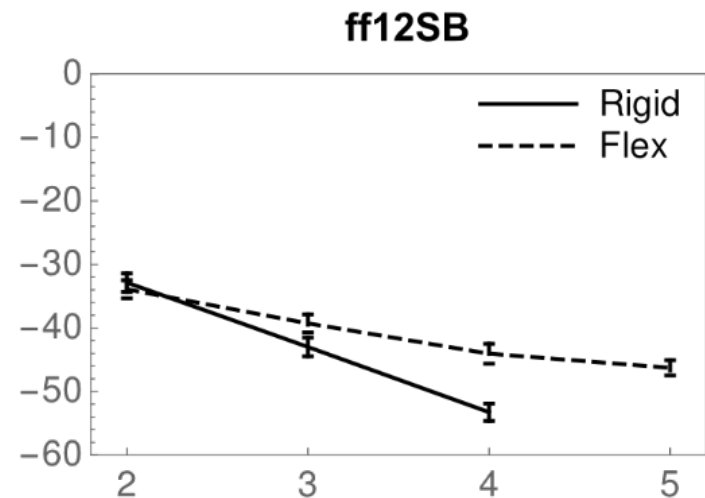
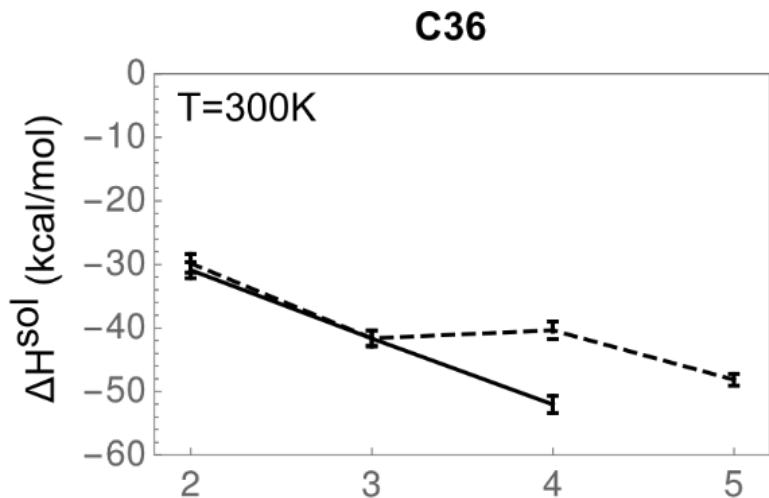
# Solvation enthalpy FD: components



# Solvation entropy EP: components

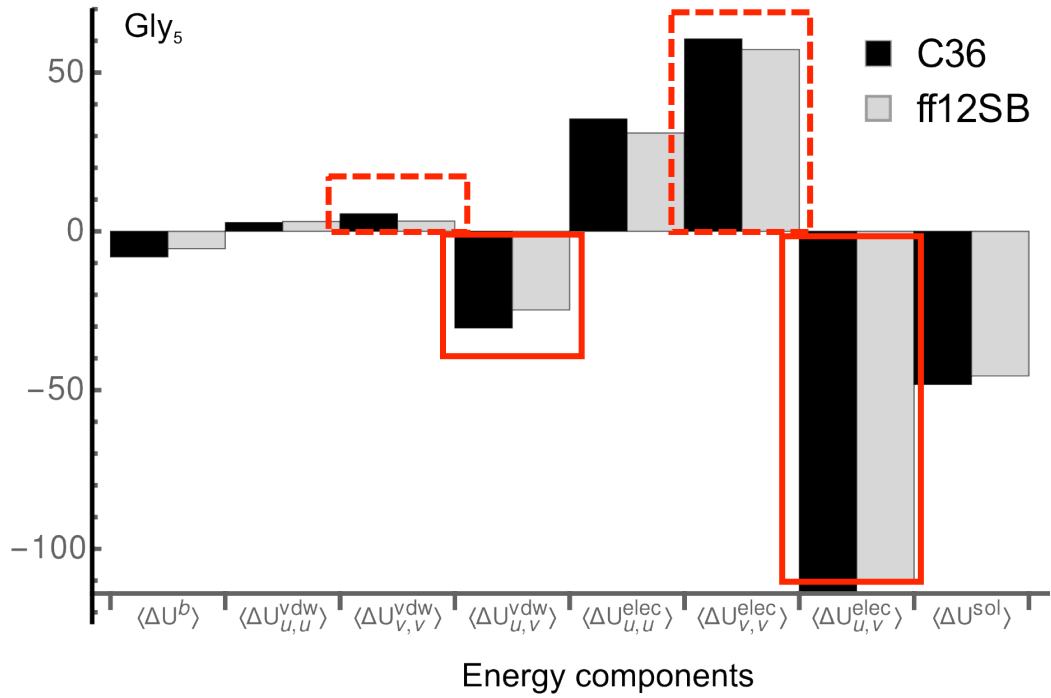
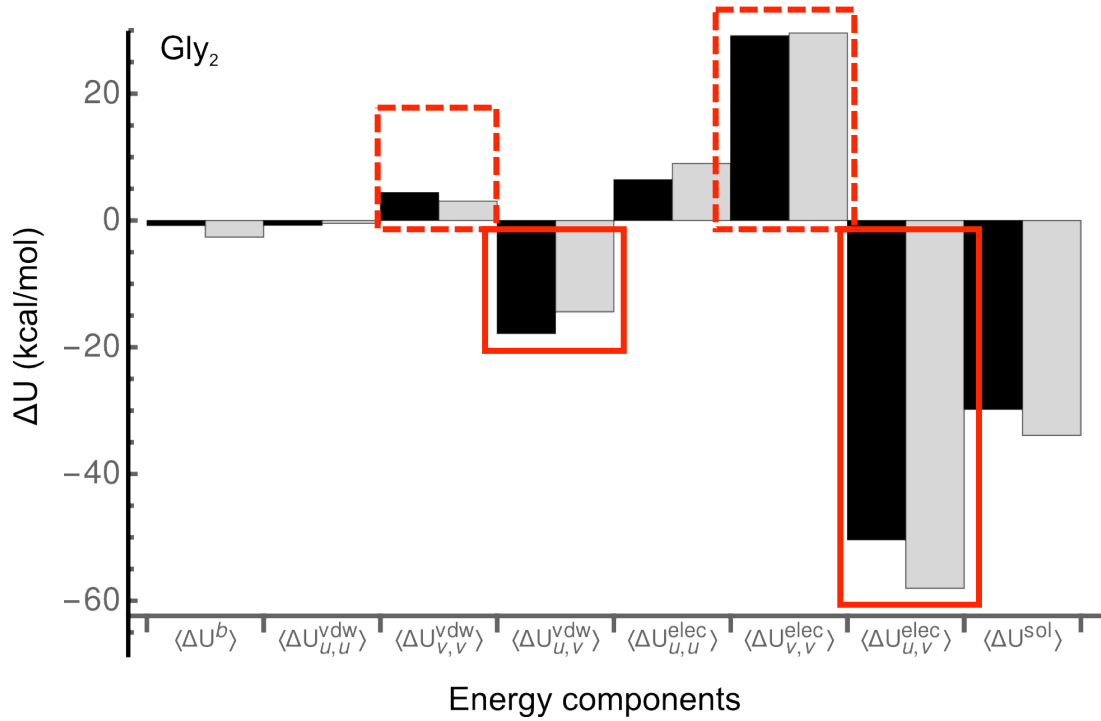


# Solvation enthalpy EP: components

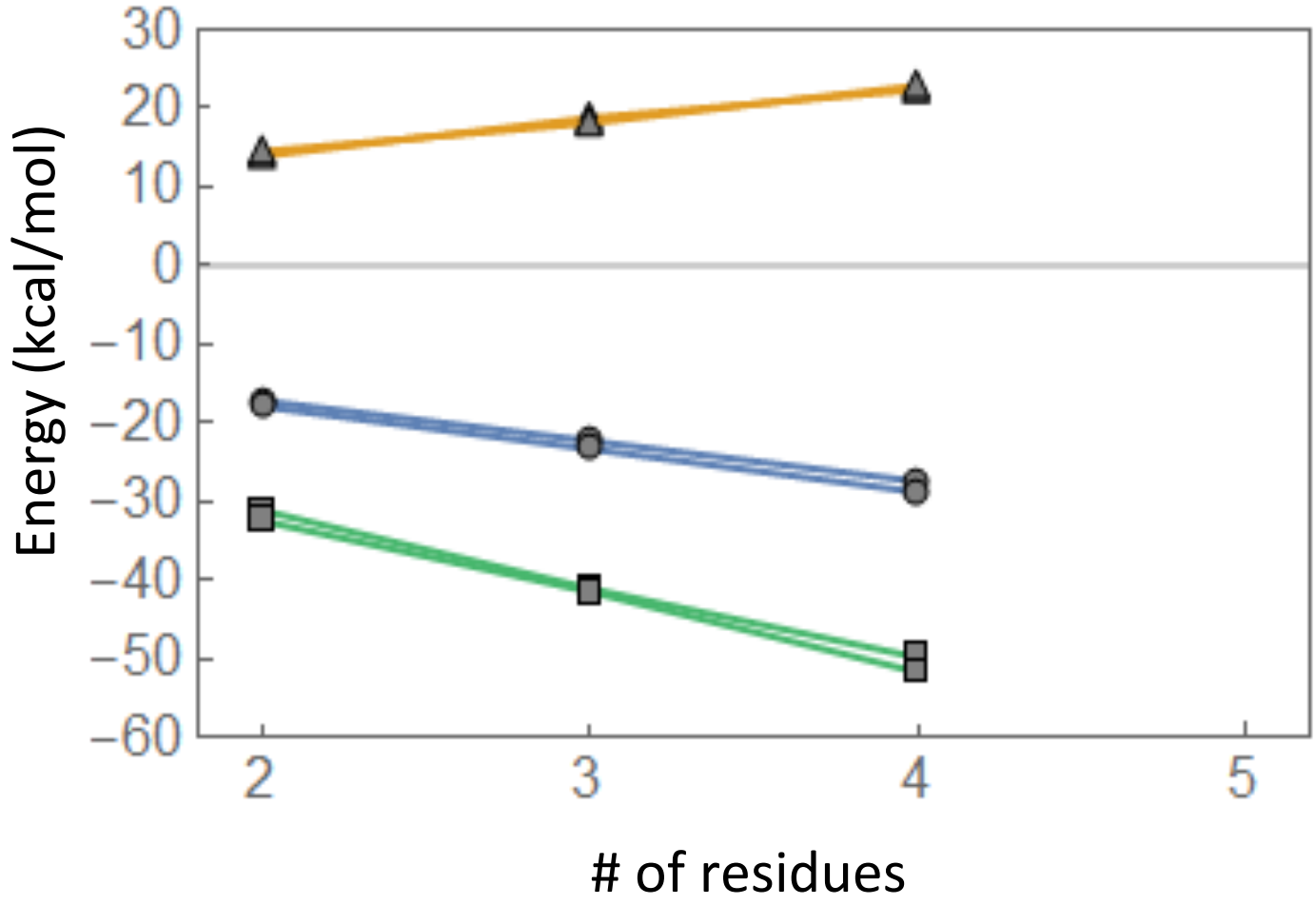




# Solvation enthalpy EP: pair interactions



# Solvation free energy: rigid oligoglycine force field comparison



# Approach – solvation free energy

Computational free energy method: free energy perturbation

