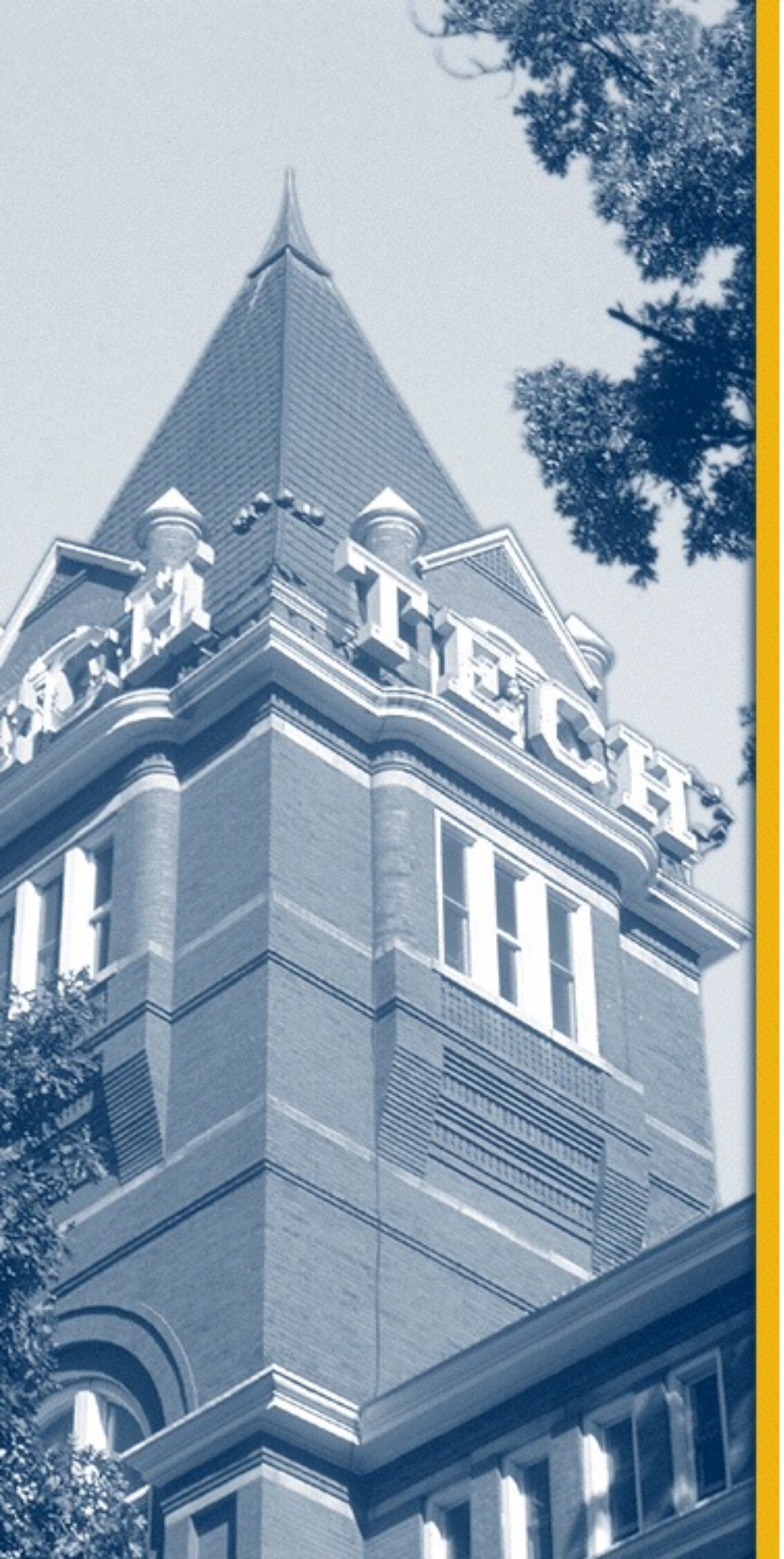
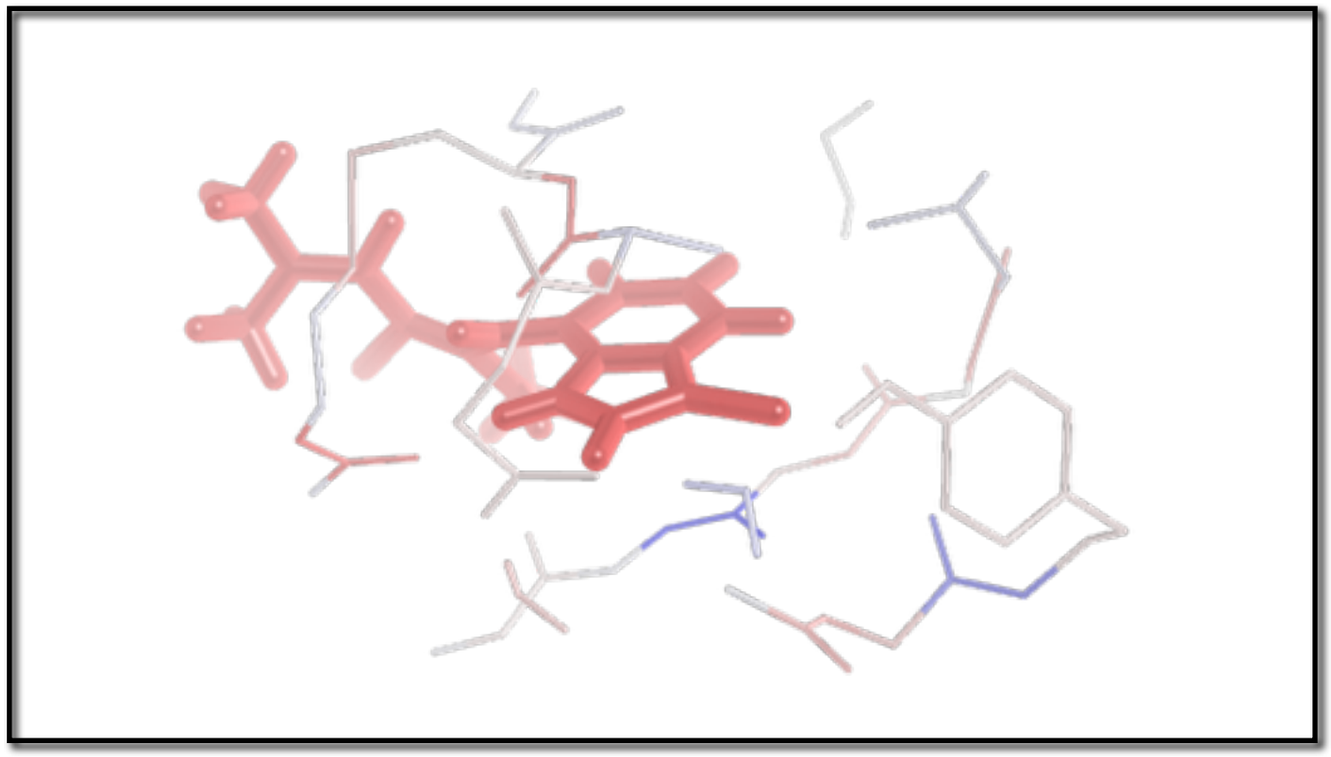


Partitioned SAPT:

A New Tool for Robust Analysis of Noncovalent Interactions



Robert M. Parrish and C. David Sherrill,

Georgia Institute of Technology

July 30, 2015

DOE CSGF

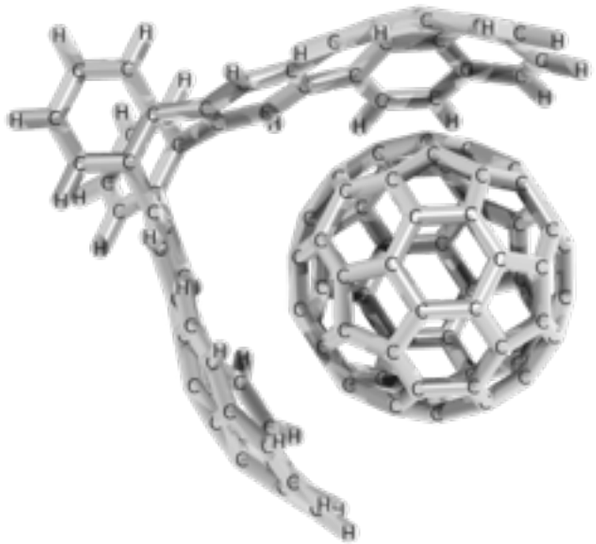
The Sherrill Group

PSI4 AB INITIO QUANTUM CHEMISTRY

Join the DOE CSGF and See the World!

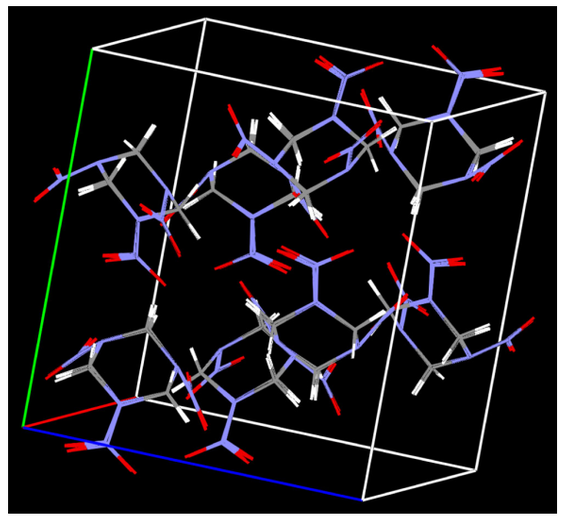
Noncovalent Interactions: Where are they?

Nanotechnology



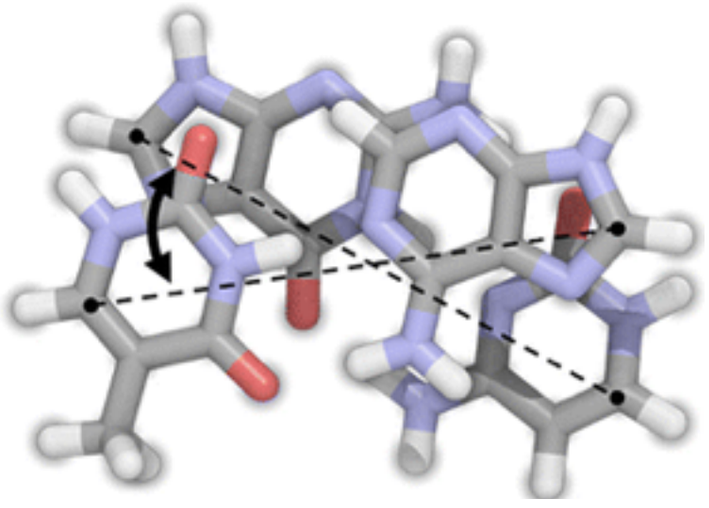
A. Sygula, F.R. Fronczek, R. Sygula, P.W. Rabideau, and M.M. Olmstead,
J. Am. Chem. Soc. **129**, 3842 (2007).

Organic Crystal Packing



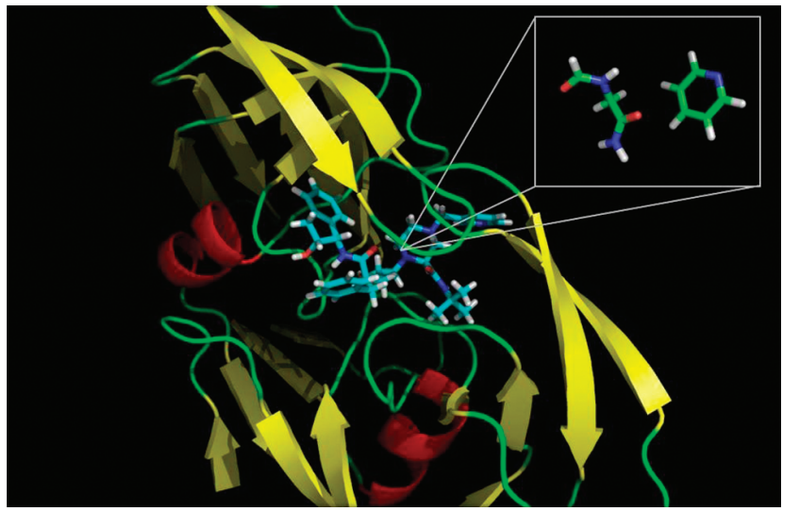
R. Podeszwa, B.M. Rice, and K. Szalewicz,
Phys. Rev. Lett. **101**, 115503 (2008).

DNA Structure/Function



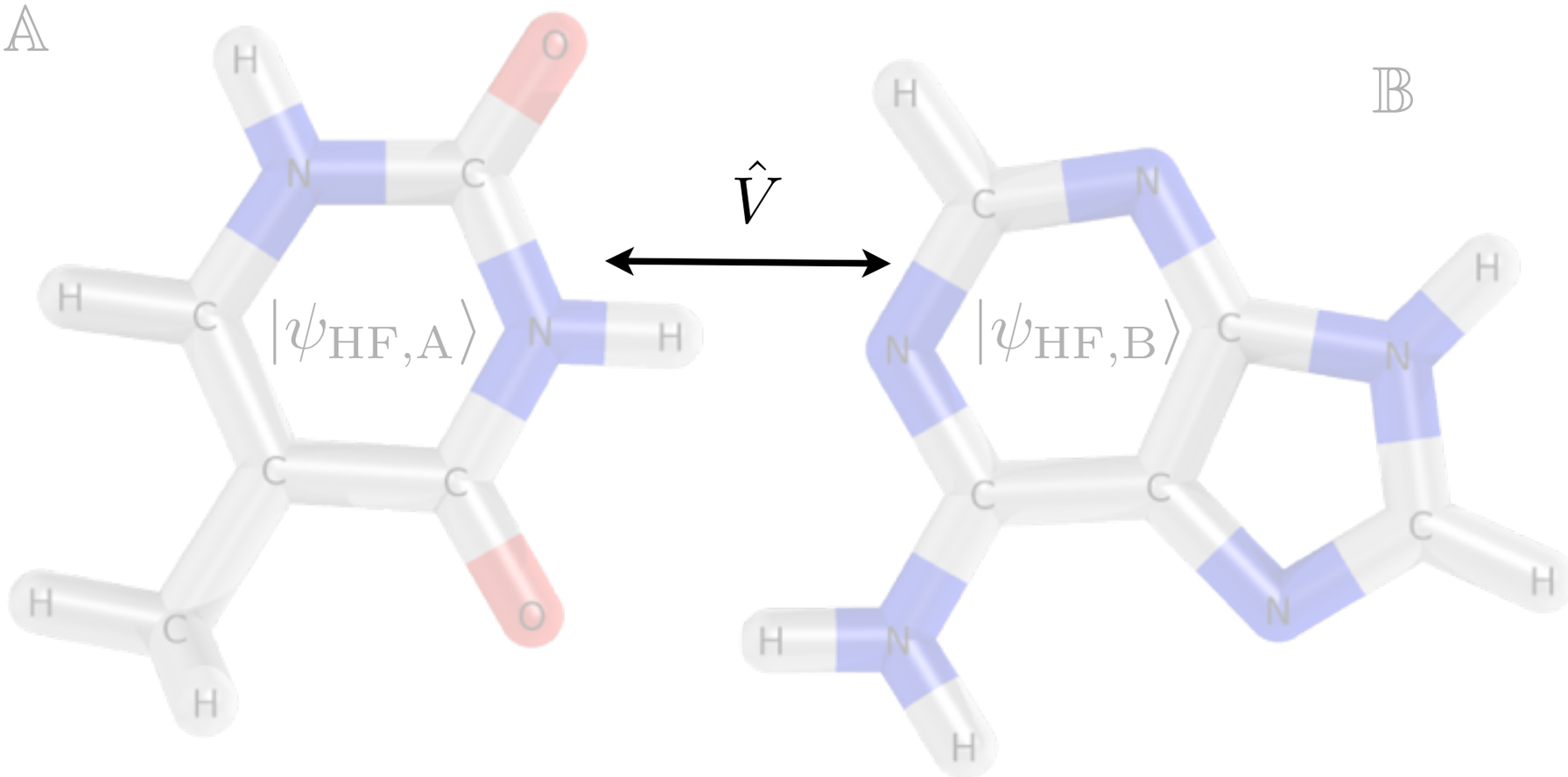
T.M. Parker, E.G. Hohenstein, R.M. Parrish, N.V. Hud, and C.D. Sherrill,
J. Am. Chem. Soc. **135**, 1306 (2013).

Drug-Protein Interactions



J.C. Faver et. al,
J. Chem. Theory Comput. **7**, 790-797 (2011)

SAPT Formalism



$$E_{\mathrm{int}} = E_{\mathrm{elst}} + E_{\mathrm{exch}} + E_{\mathrm{ind}} + E_{\mathrm{disp}}$$

B. Jeziorski, R. Moszyński, and K. Szalewicz, *Chem. Rev.* **94**, 1887 (1994).

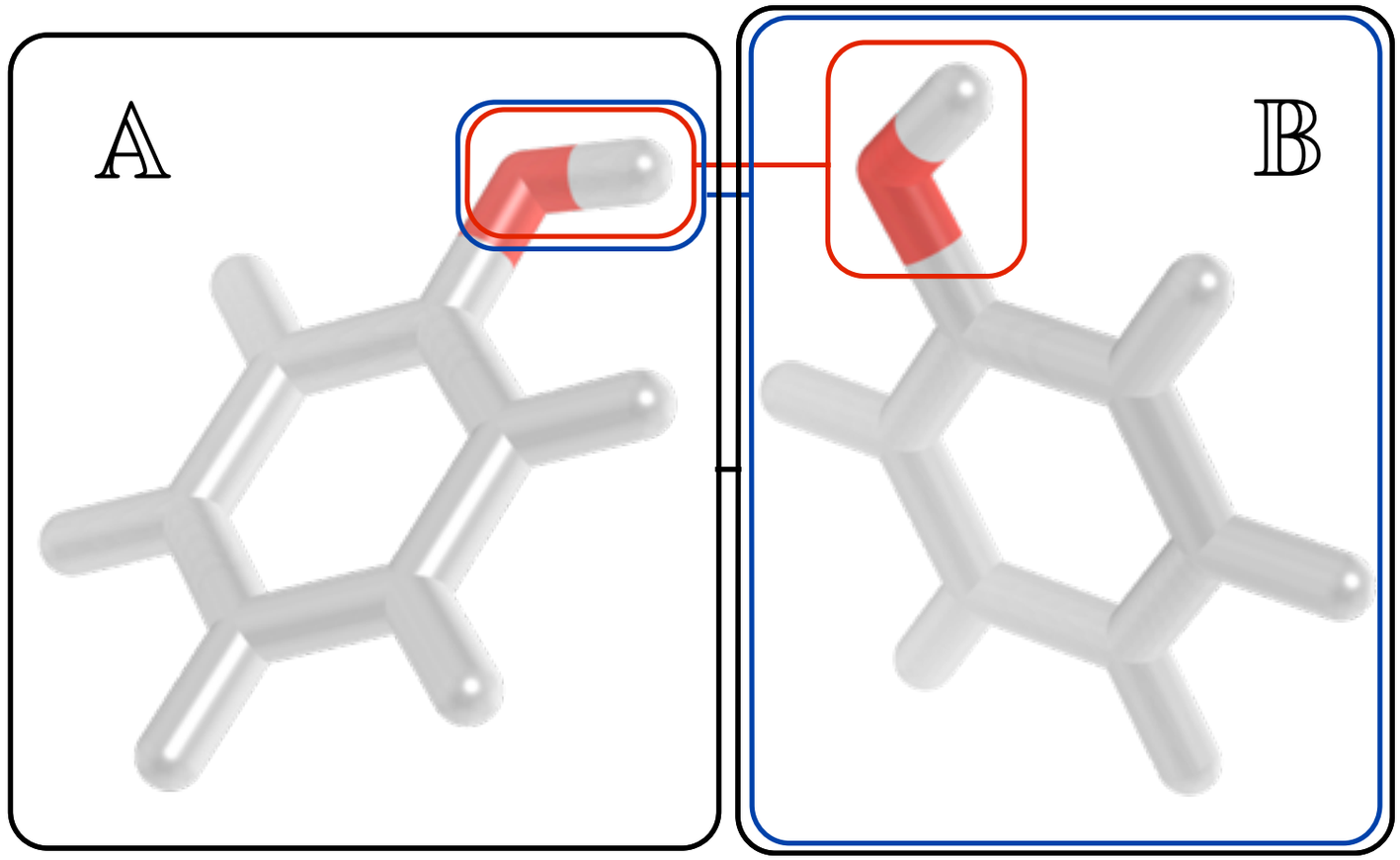
Spatially Partitioned SAPT Philosophy

Partitioned SAPT Motivation:

Order-2: $E_{\text{int}} \rightarrow E_{\text{int}}^{\mathbf{AB}}$

Order-1: $E_{\text{int}}^{\mathbf{A}} = \sum_{\mathbf{B}} E_{\text{int}}^{\mathbf{AB}}$

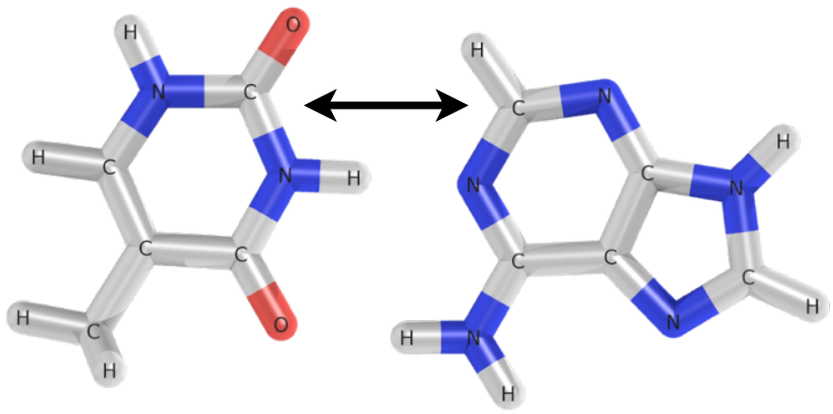
Order-0: $E_{\text{int}} = \sum_{\mathbf{A}} E_{\text{int}}^{\mathbf{A}}$



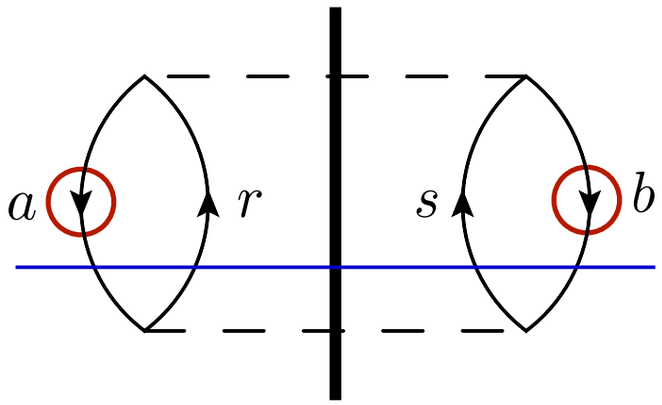
$E_{\text{int}}^{\mathbf{AB}}$ $E_{\text{int}}^{\mathbf{A}}$ E_{int}

Spatially Partitioned SAPT Development

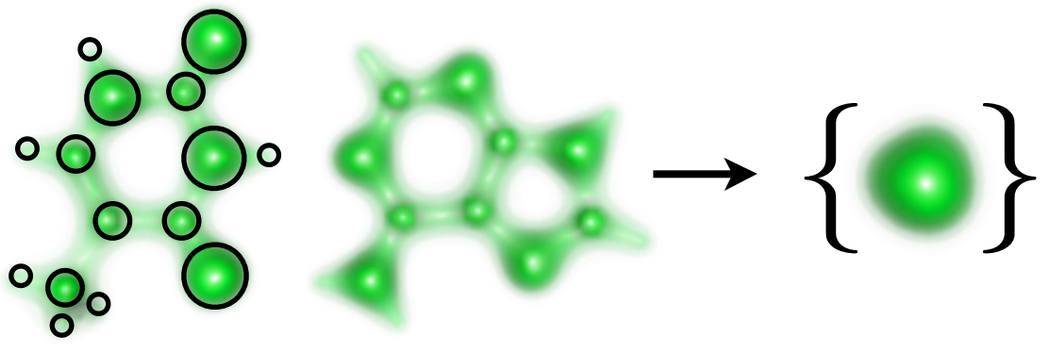
1) Allow the many-body interaction to occur naturally (SAPT0/jDZ for now).



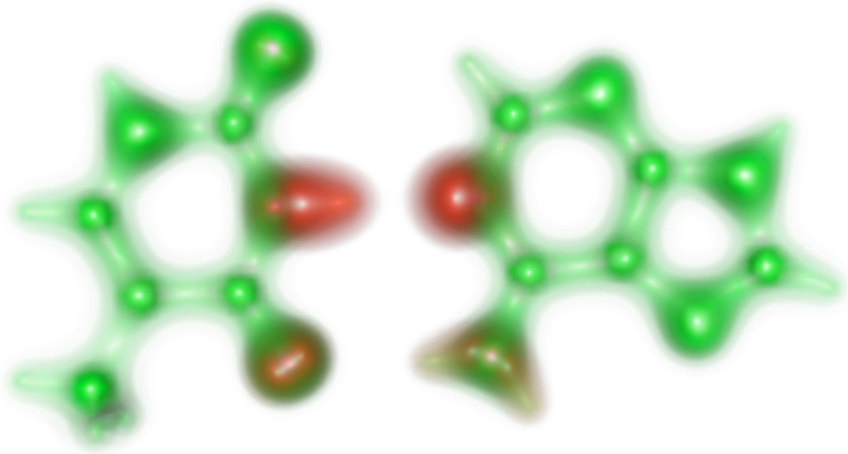
2) Identify two key occupied bodies in each many-body interaction term.



3) Perform key two-body occupied summations with local quasiparticles.



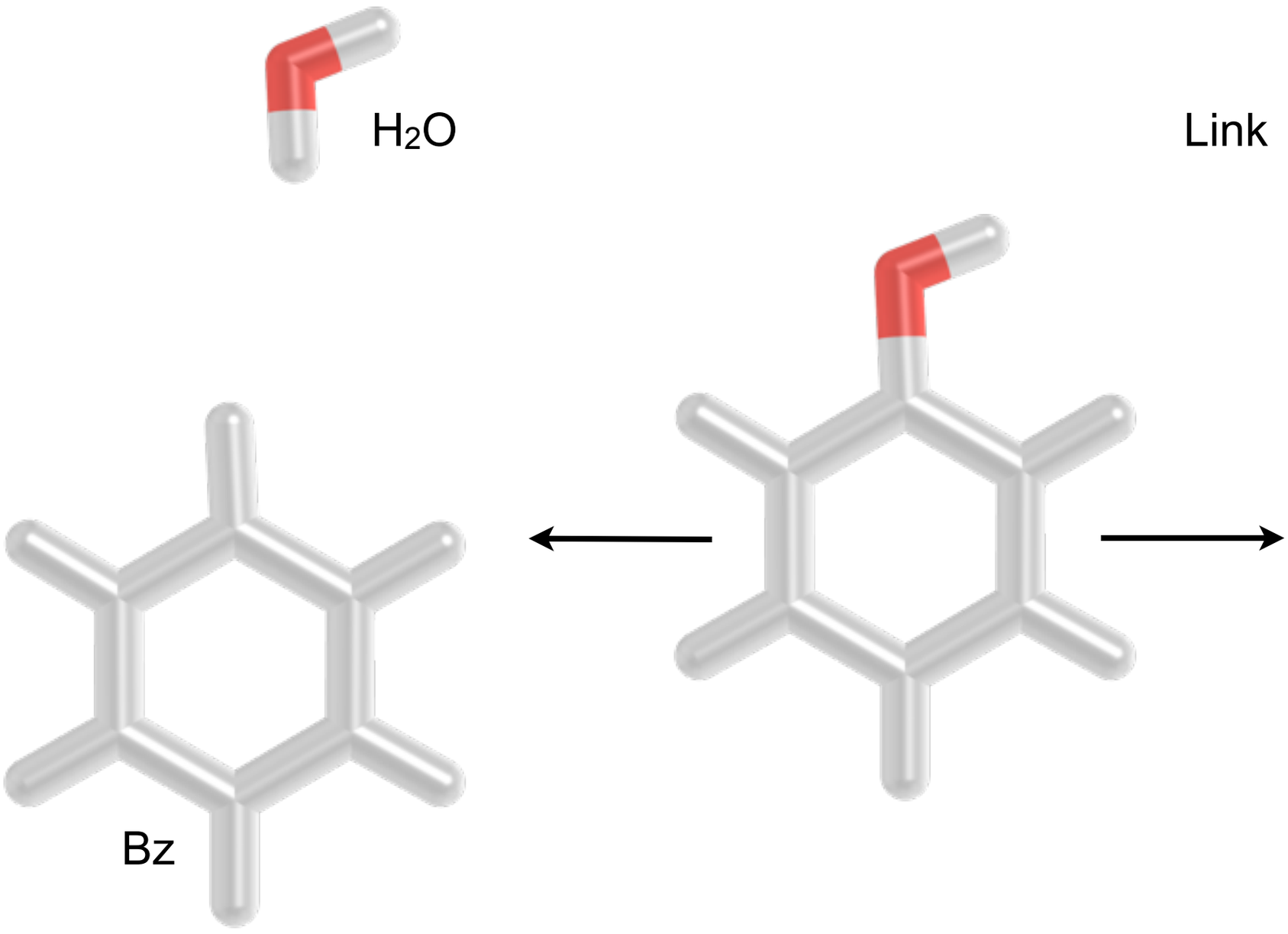
4) Analyze and visualize results.



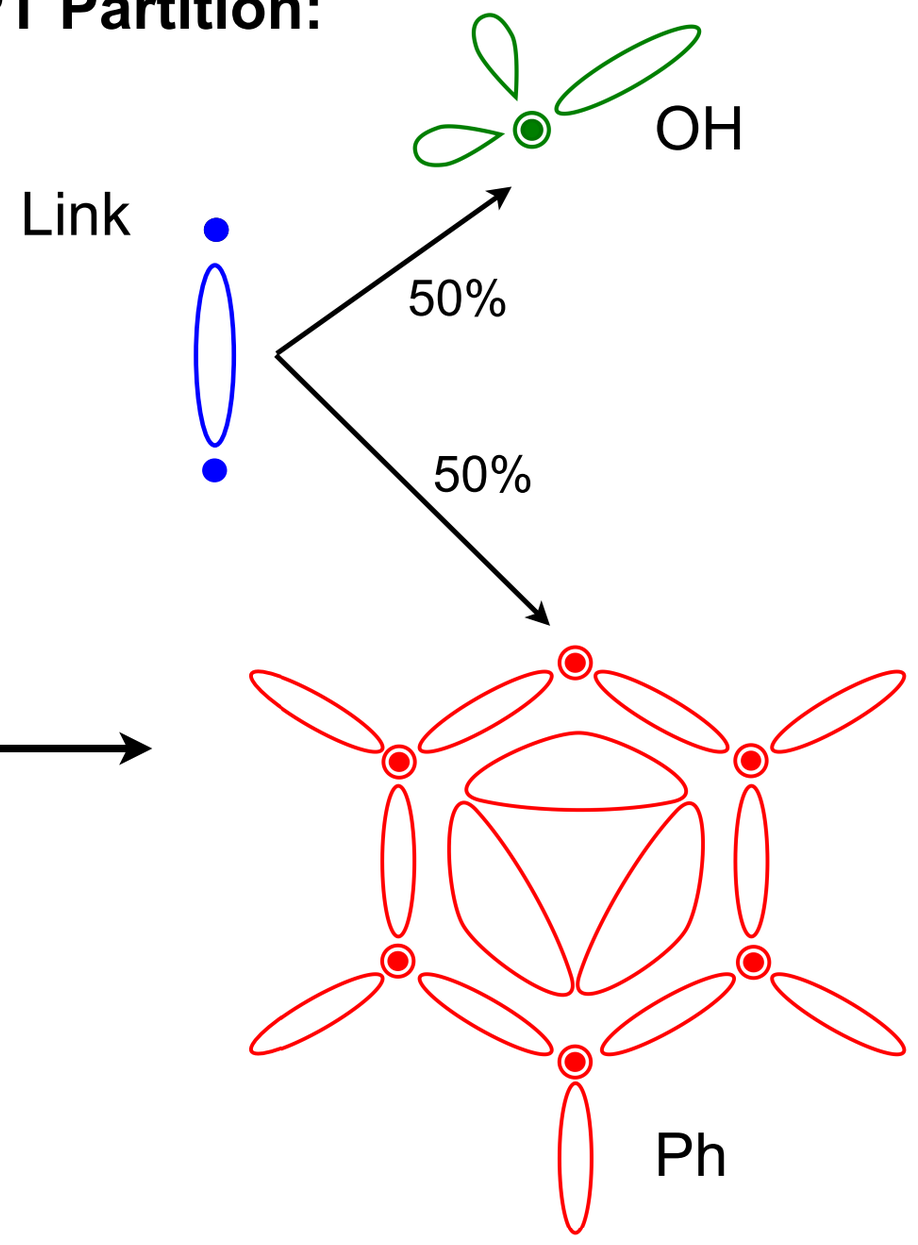
R.M. Parrish and C.D. Sherrill, *J. Chem, Phys*. **141**, 044115 (2014).

Functional Groups as Fragments (F-SAPT)

Cut-Cap Partition:

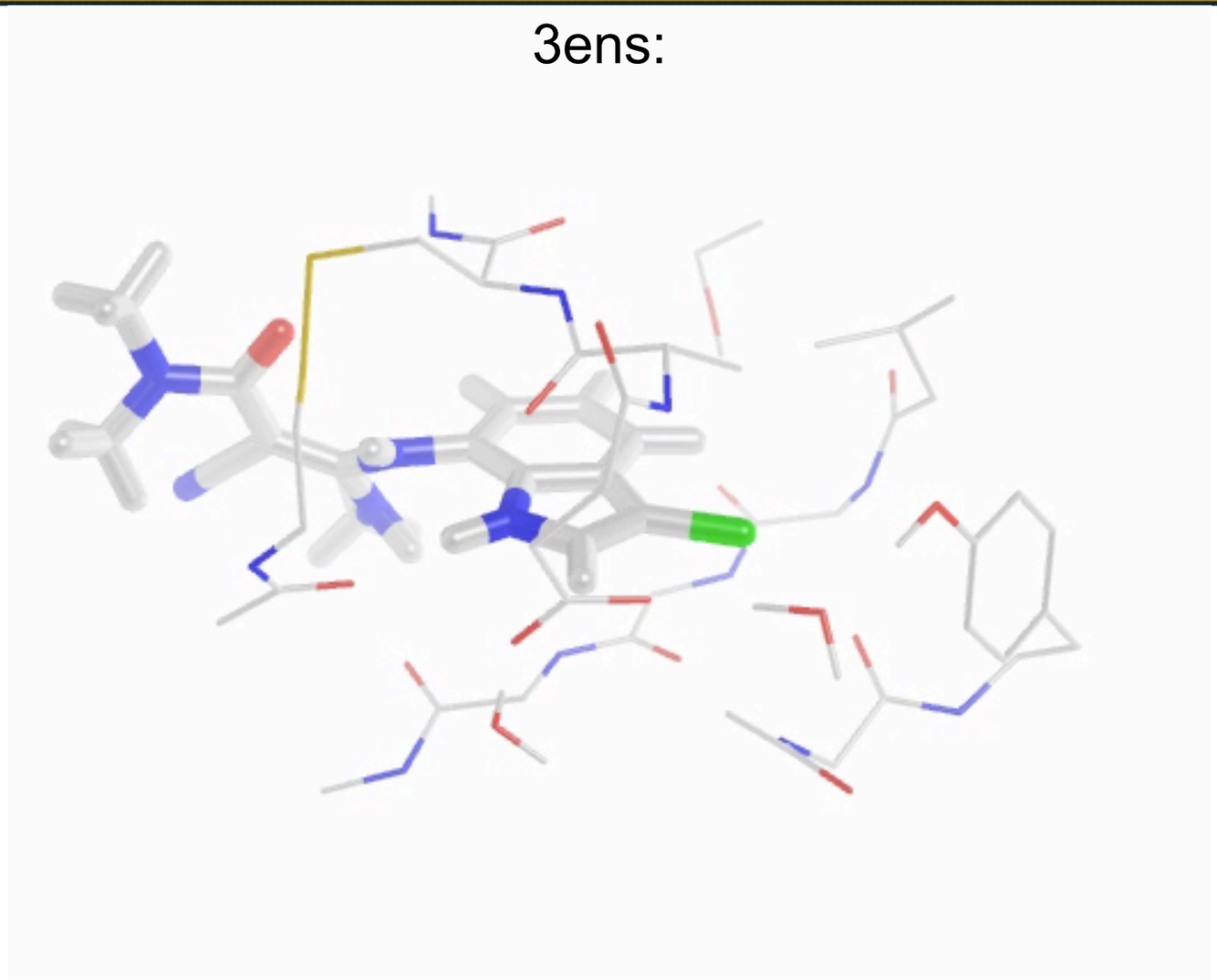


F-SAPT Partition:



Drug Design: Factor Xa S1 Pocket - Cl vs. Me

3ens:



Cl variant binds effectively, Me variant does not. Why?

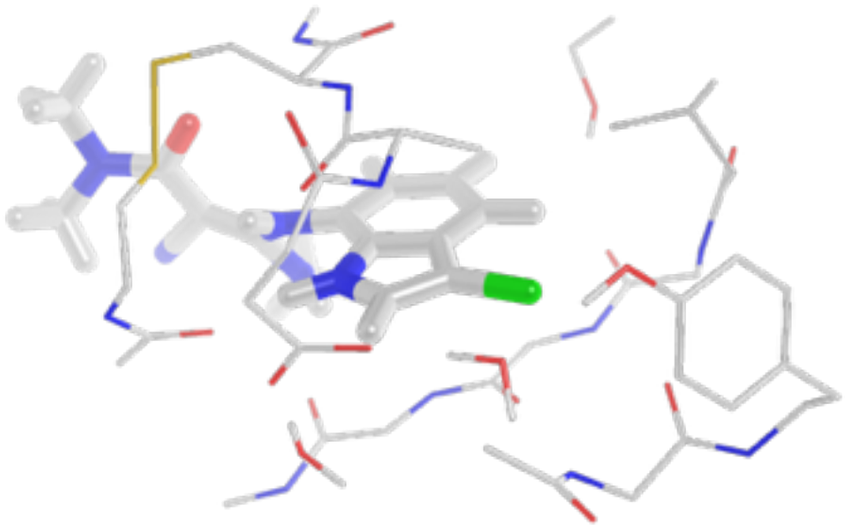
Proposed Explanations:

A. Halogen-π Interaction
B. Dipole-Aspartate Interaction
C. Unknown Effect

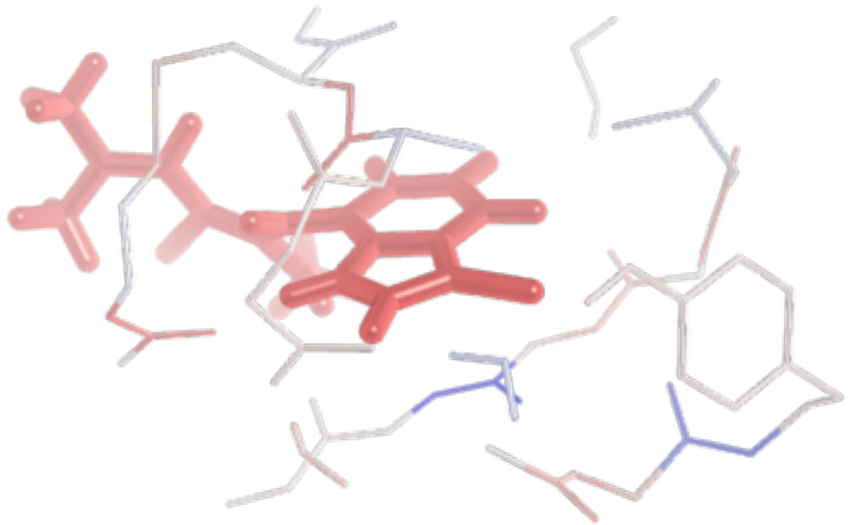
R.M. Parrish, C.D. Sherrill, D. Sitkoff and D. Cheney, *In Progress,* (2015).

Difference F-SAPT Scheme

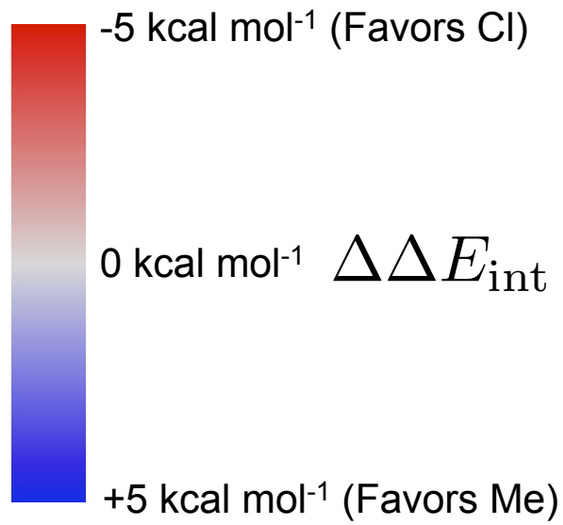
3ens-Cl: Geometry



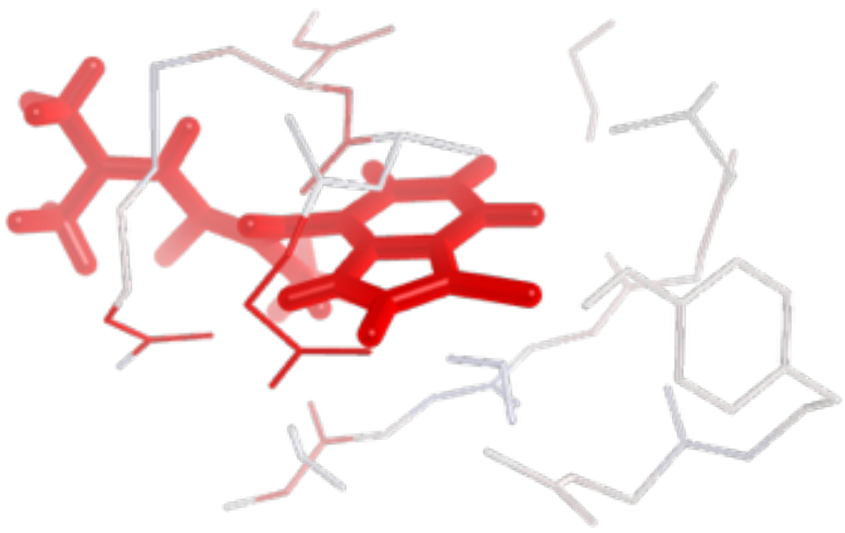
Difference: -2.46 kcal mol^{-1}



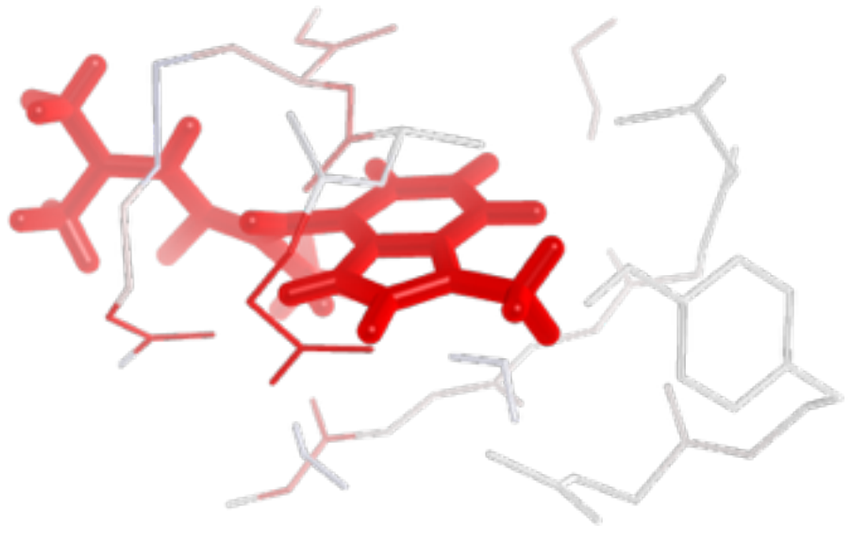
Color Scale (Top):



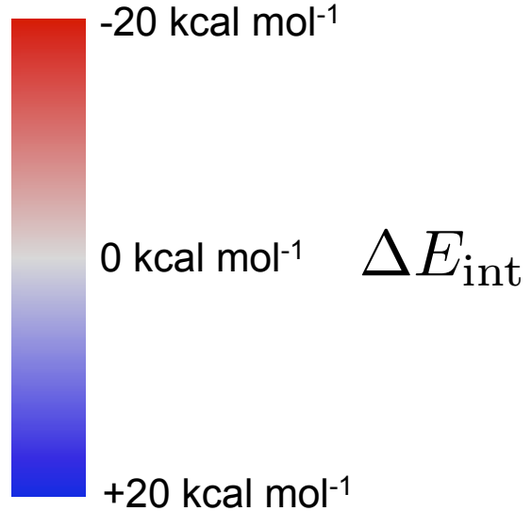
3ens-Cl: -57.46 kcal mol^{-1}



3ens-Me: -55.00 kcal mol^{-1}



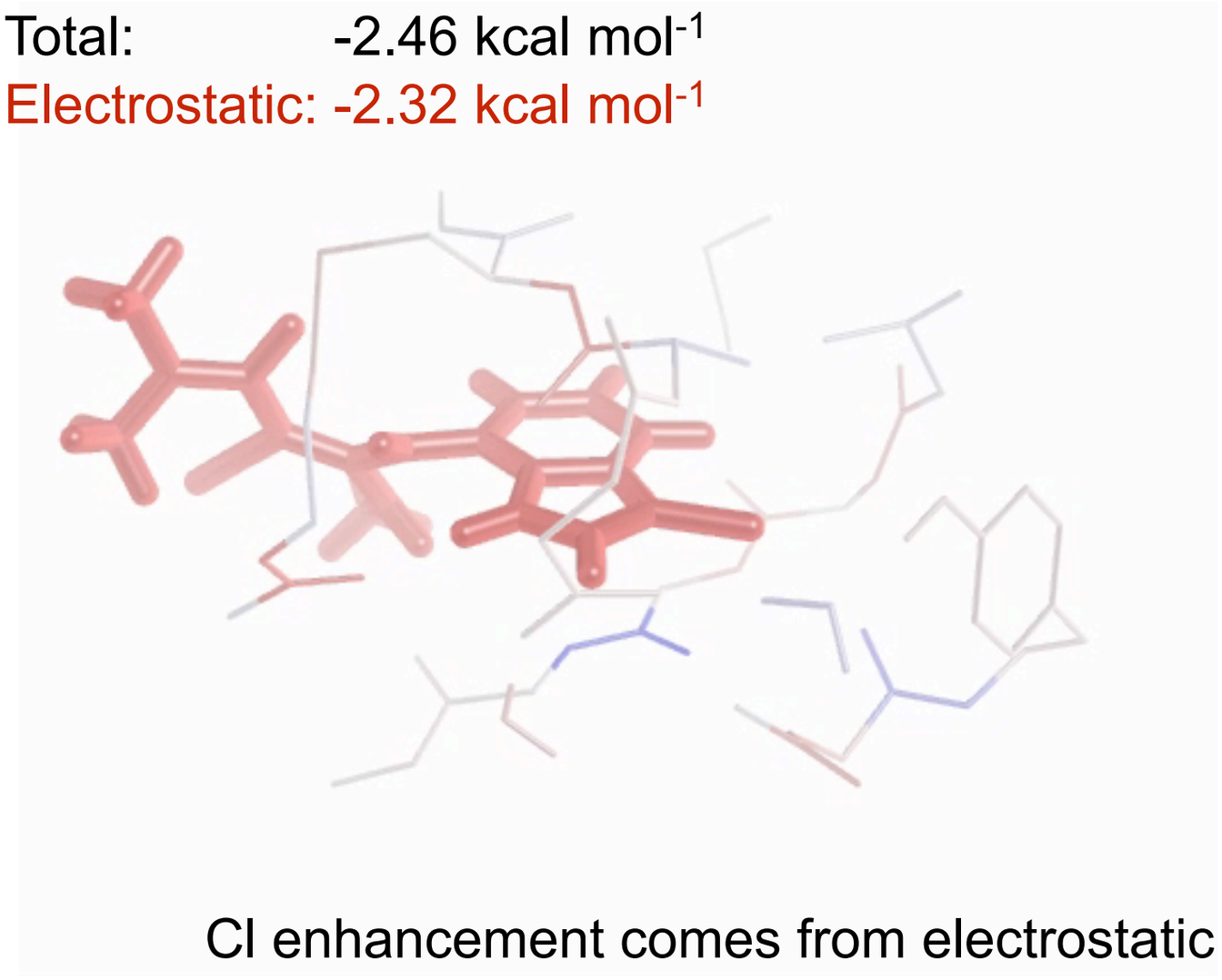
Color Scale (Bottom):



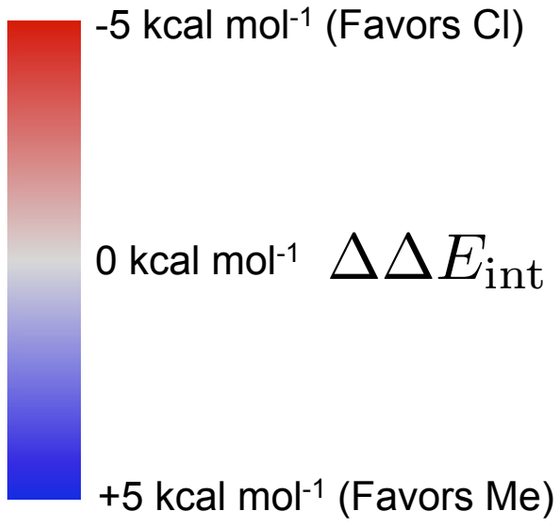
R.M. Parrish, C.D. Sherrill, D. Sitkoff and D. Cheney, *In Progress,* (2015).

Difference F-SAPT Results

CI Enhancement:
Total: -2.46 kcal mol^{-1}
Electrostatic: -2.32 kcal mol^{-1}



Color Scale:

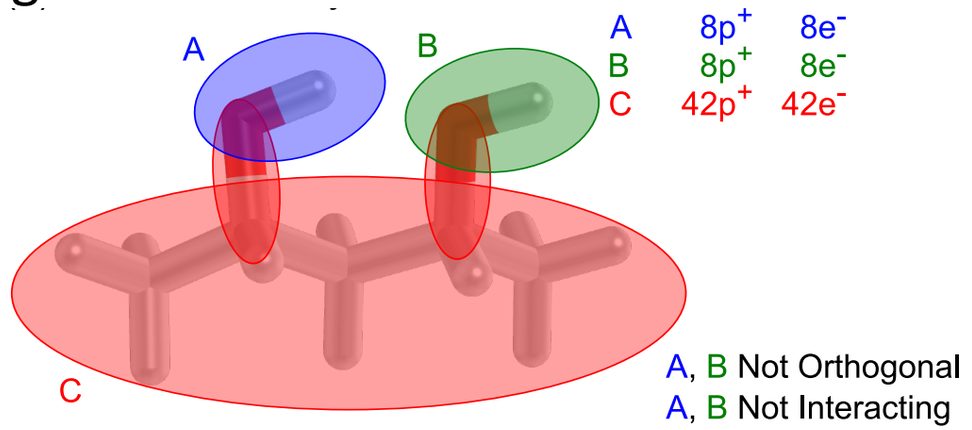


CI enhancement comes from electrostatic interactions with peptide backbone!

R.M. Parrish, C.D. Sherrill, D. Sitkoff and D. Cheney, *In Progress,* (2015).

Summary and Outlook

- Partitioned SAPT Methods:
  - Partitions interaction energy contributions to pairs of fragments
  - Uses rigorous SAPT methodology
  - Developed in A-SAPT, F-SAPT, I-SAPT flavors
- Application to S1 Pocket in Factor Xa:
  - Results are **not** in line with standard intuition
  - Pairwise contacts from all over the pocket are significant
  - Peptide bond dipoles may be very important
  - Unexpected effects are largely electrostatic in nature
- Outlook:
  - Chemical intuition cannot be trusted
  - SAPT/F-SAPT can help!



R.M. Parrish, Jérôme F. Gonthier, Clémence Corminbœuf, and C.D. Sherrill, *J. Chem. Phys.*, In Press (2015).

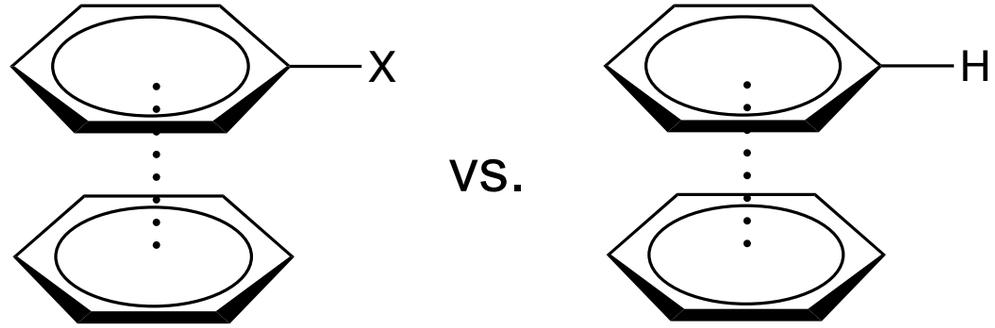
Acknowledgements

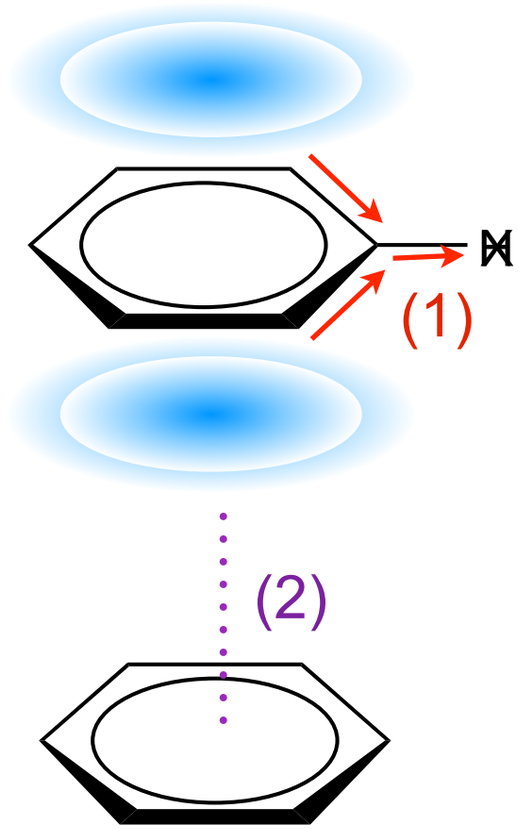
- Funding:
  - DOE CSGF
- Collaborators/Coauthors:
  - David Sherrill (Georgia Tech)
  - The Sherrill Group (Georgia Tech)
  - Ed Hohenstein (CCNY)
  - Sara Kokkila (Stanford)
  - Todd Martínez (Stanford)
  - Nicholas Schunck (LLNL)
  - Justin Turney (UGA)
  - Andy Simonnett (Utah/NIH)
  - Francesco Evangelista (Emory)
  - Daniel Smith (Auburn)
  - Thomas Körzdörfer (Potsdam)
  - John Sears (Wake Forest)
  - Jean-Luc Brédas (KAUST)
  - Daniel Cheney (BMS)
  - Doree Sitkoff (BMS)

DOE CSGF

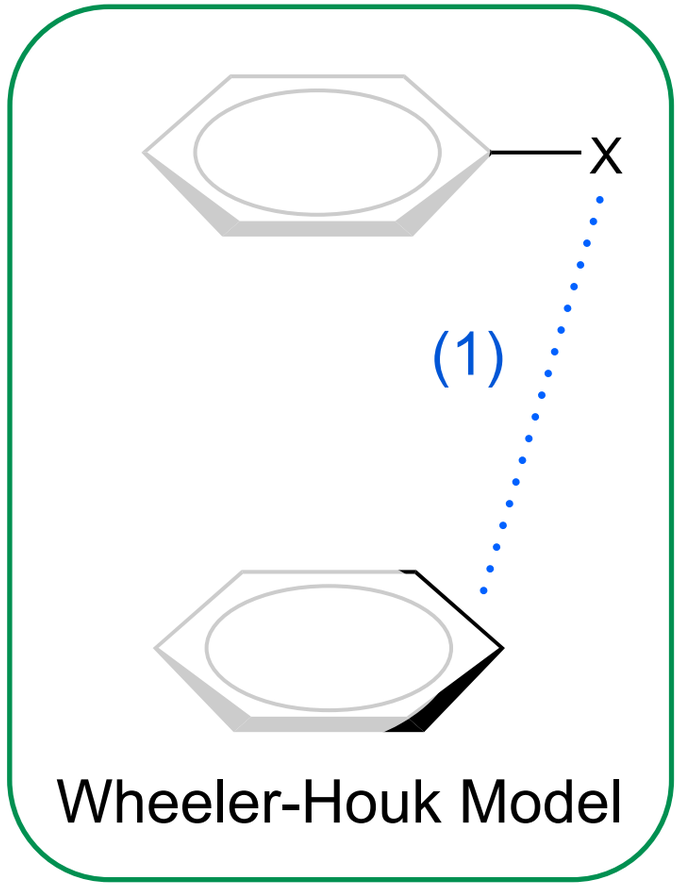
PSI4
AB INITIO QUANTUM CHEMISTRY

F-SAPT Application: Substituent Effect in Bz2

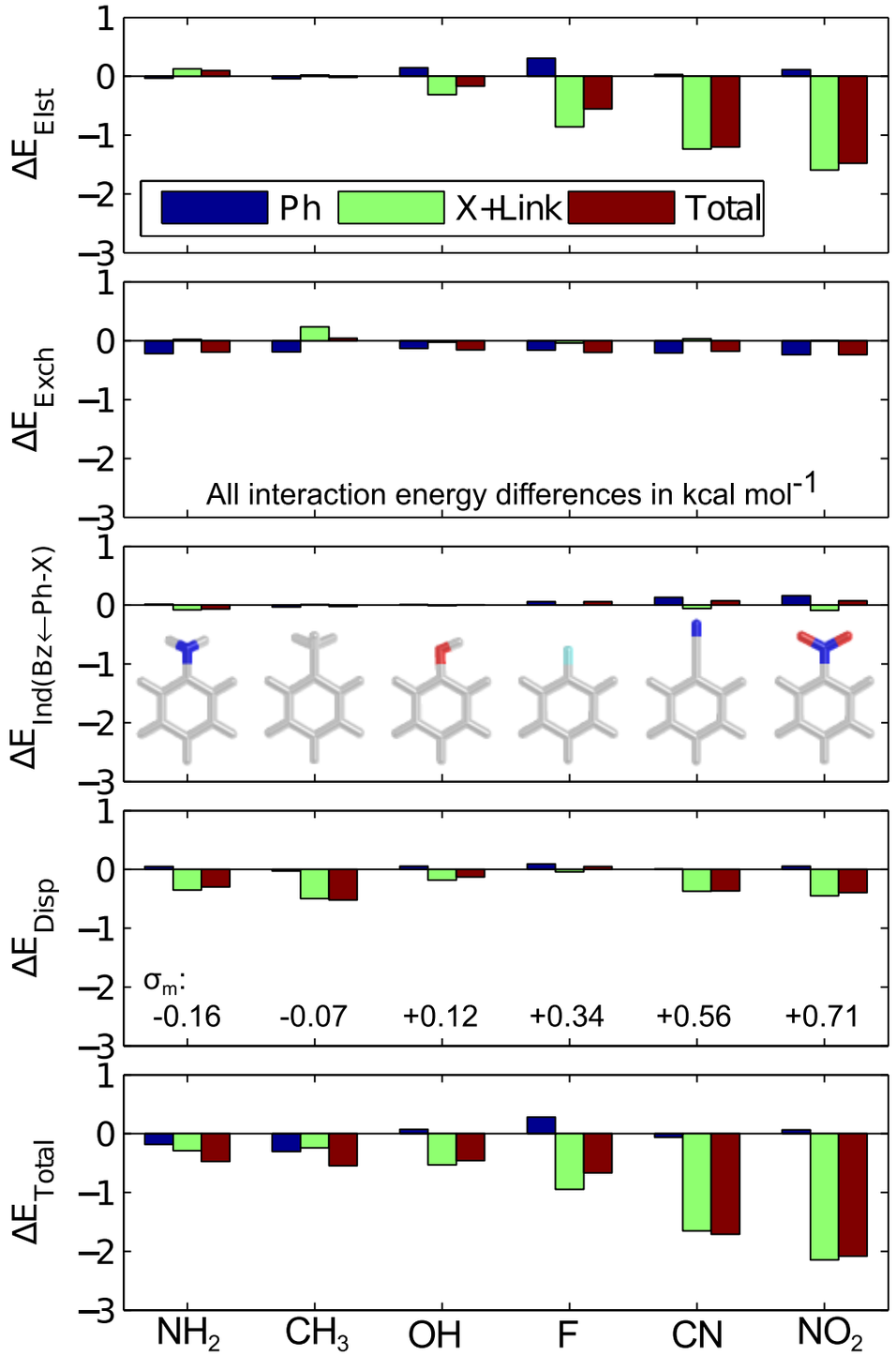




Hunter-Sanders Model



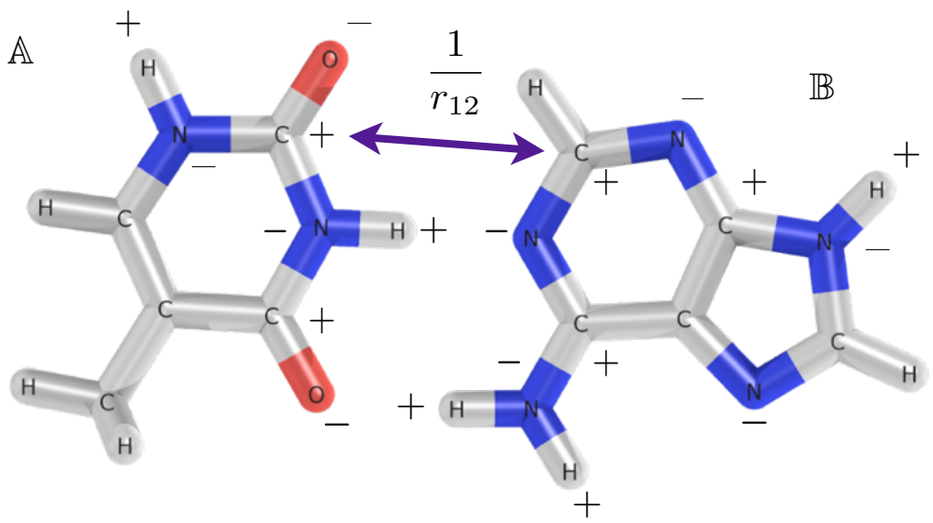
Wheeler-Houk Model



R.M. Parrish and C.D. Sherrill, *J. Am. Chem. Soc.* **136**, 17386 (2014).

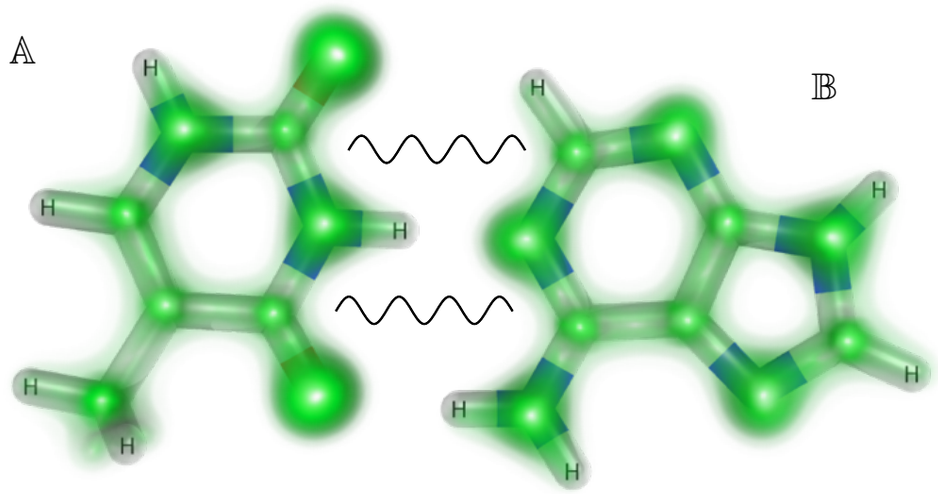
SAPT Interaction Energy Components

Electrostatics:



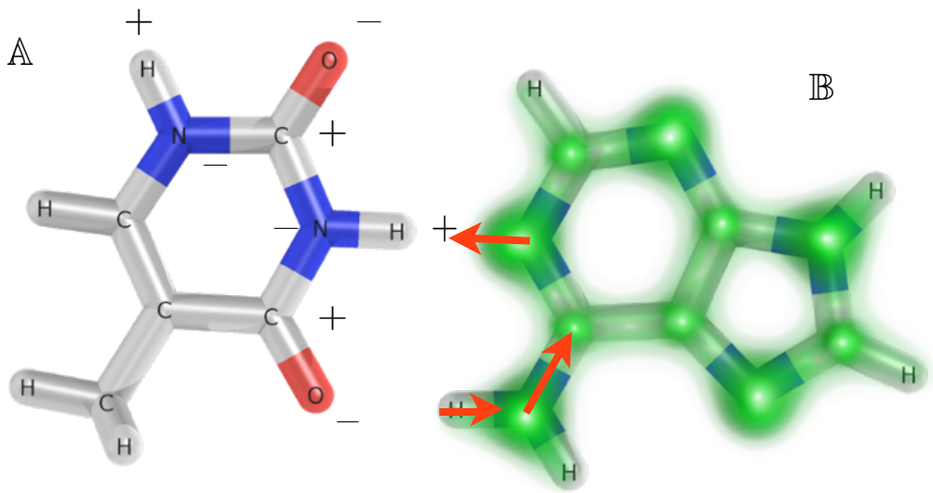
"Dipole-Dipole," "Hydrogen Bonding," etc.

Exchange:



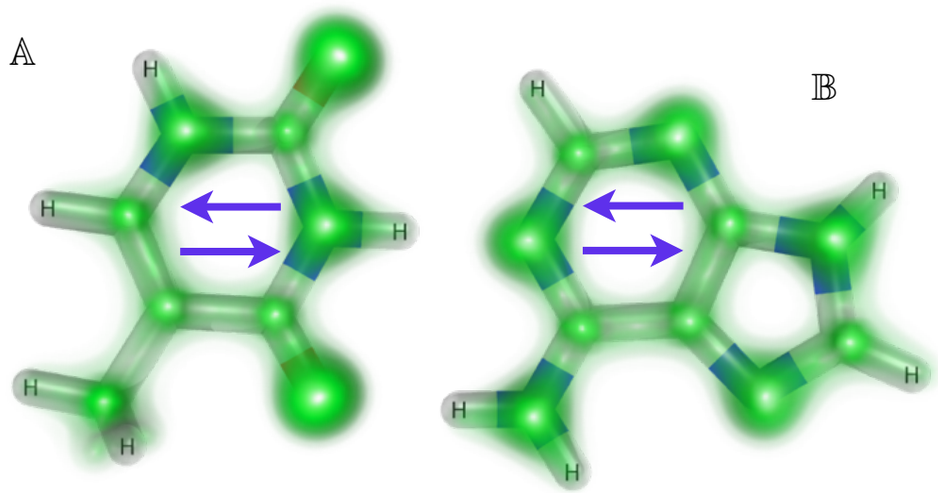
"Steric Repulsion" or "Pauli Exclusion"

Induction:



"Polarization" or "Dipole-Induced Dipole"

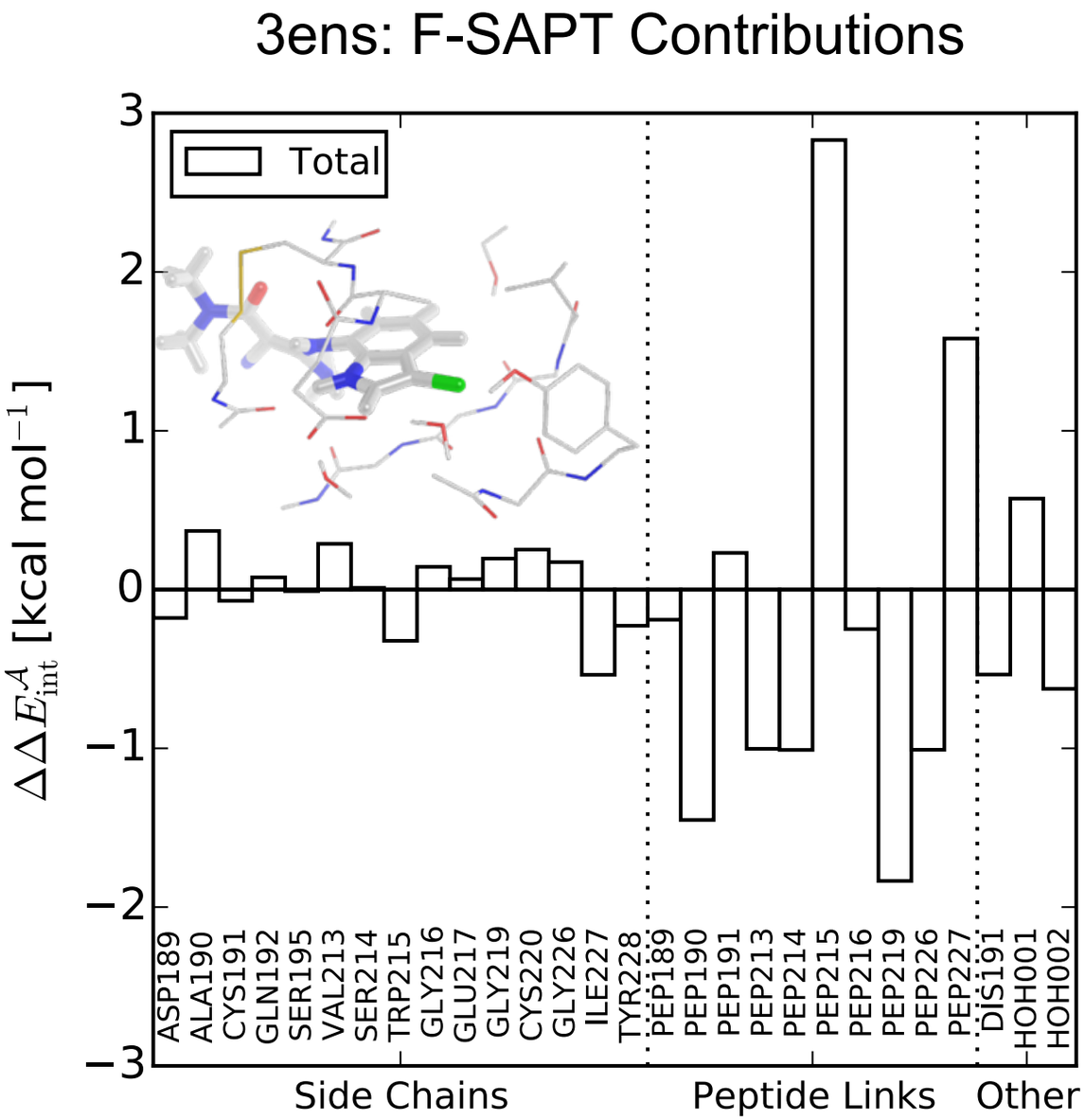
Dispersion:

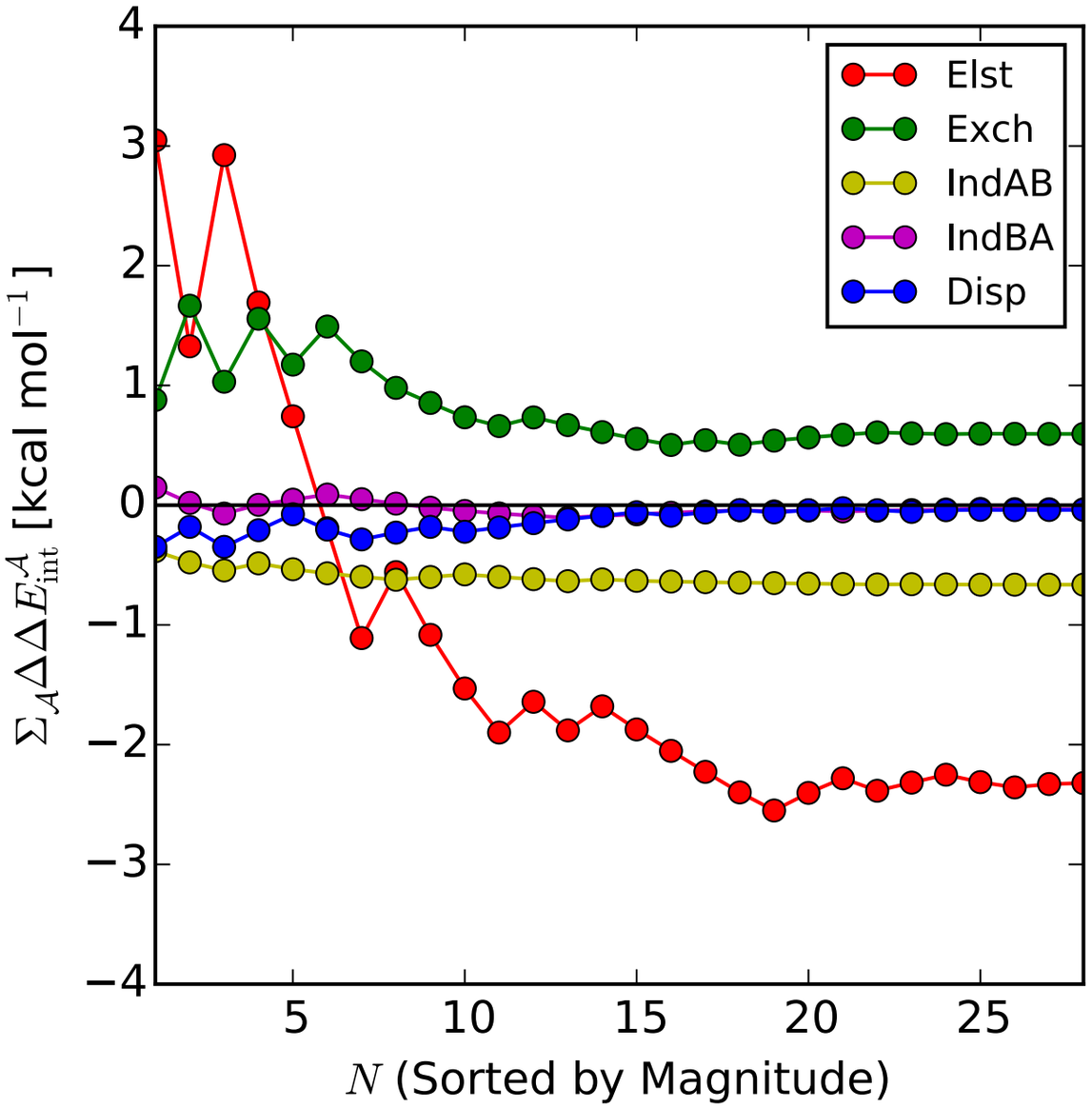


"London Dispersion"

B. Jeziorski, R. Moszyński, and K. Szalewicz, *Chem. Rev.* **94**, 1887 (1994).

Quantitative F-SAPT Results

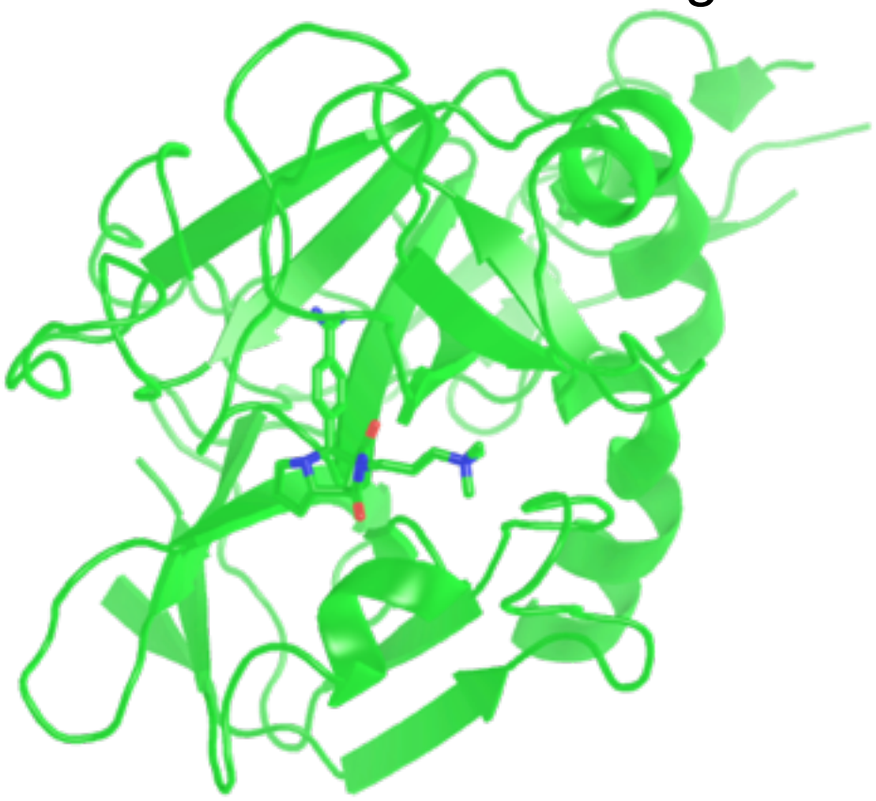




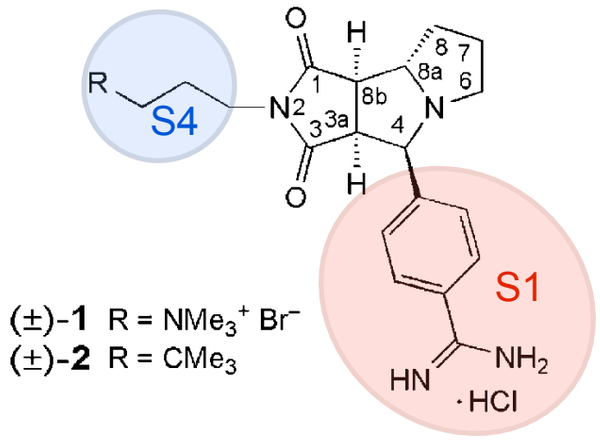
R.M. Parrish, C.D. Sherrill, D. Sitkoff and D. Cheney, *In Progress,* (2015).

Direct Factor Xa Inhibitors

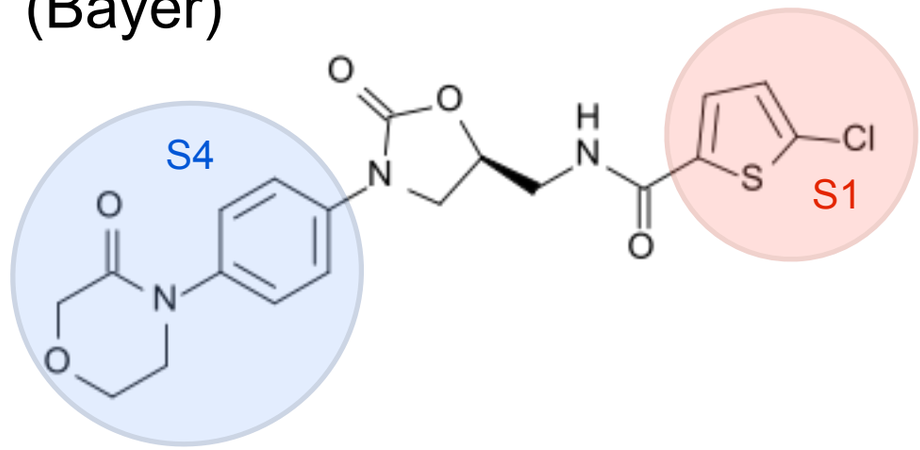
PDB ID 2bok: Factor Xa + Ligand:



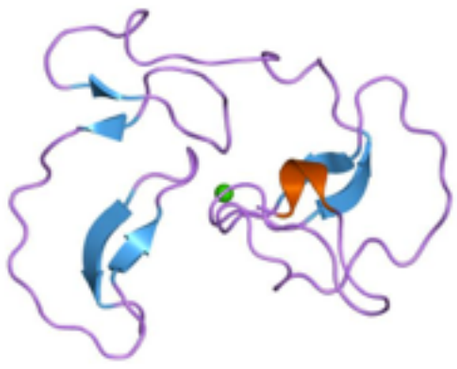
2bok:(Diederich, ETH)



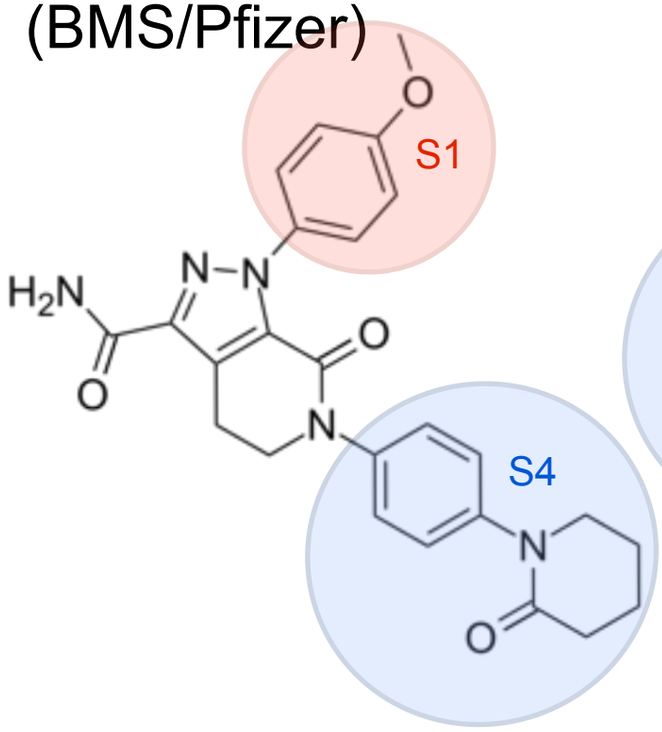
Rivaroxaban (Xarelto): (Bayer)



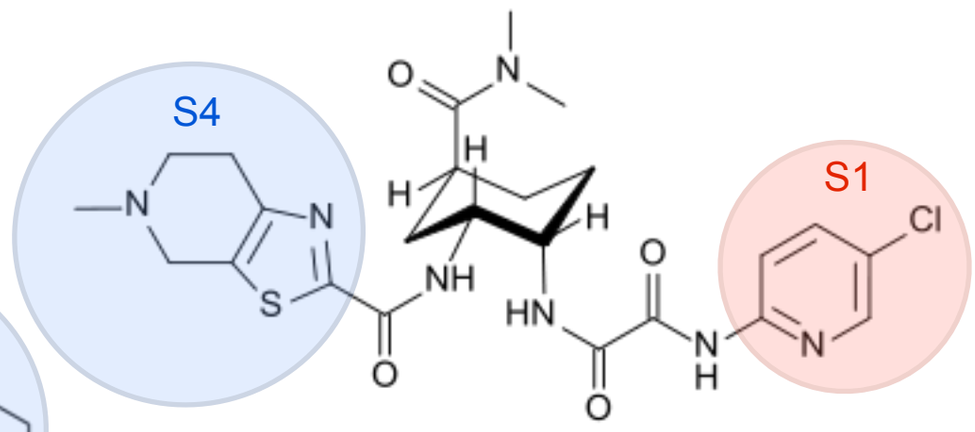
Antistasin: (Mexican Leech)



Apixaban (Eliquis): (BMS/Pfizer)



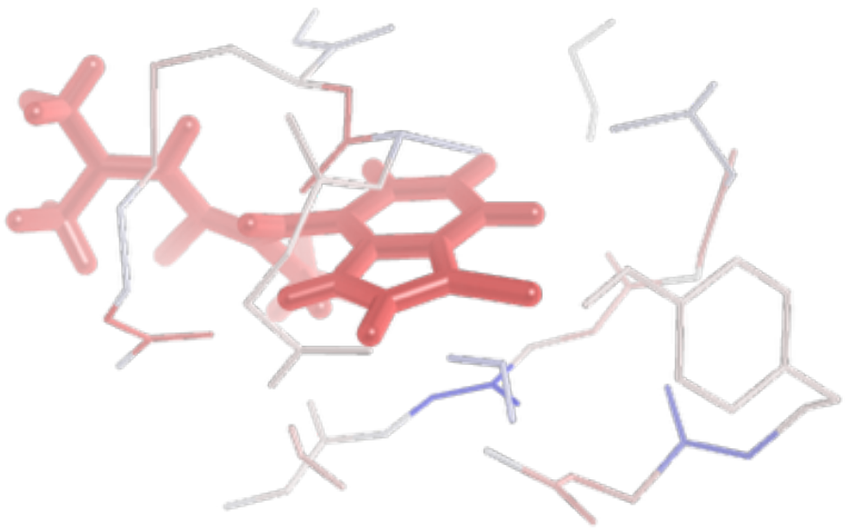
Edoxaban (Lixiana): (Daiichi)



Many others (~220 publicly available!)

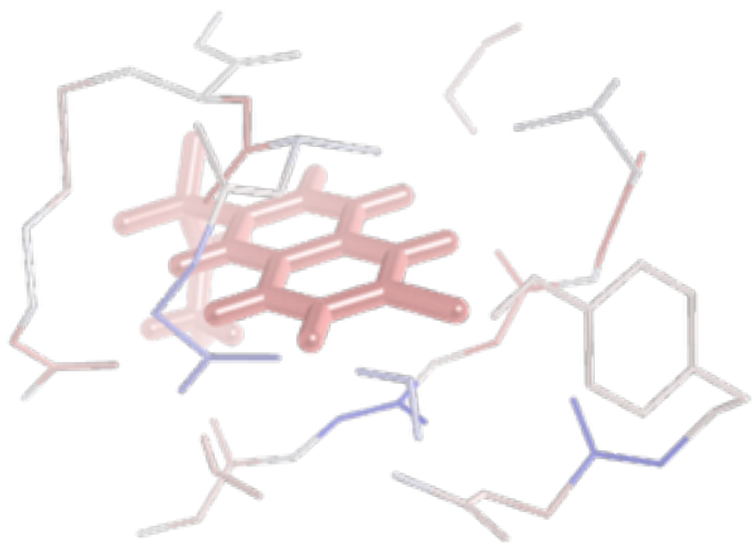
More Difference F-SAPT Results

3ens: -2.46 kcal mol^{-1}



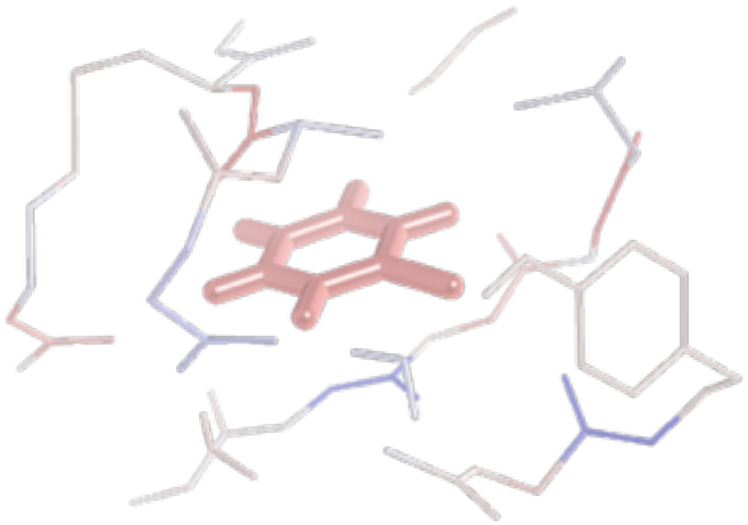
IC_{50} = 2.4 nM vs. 118 nM: 49x

2cji: -1.30 kcal mol^{-1}



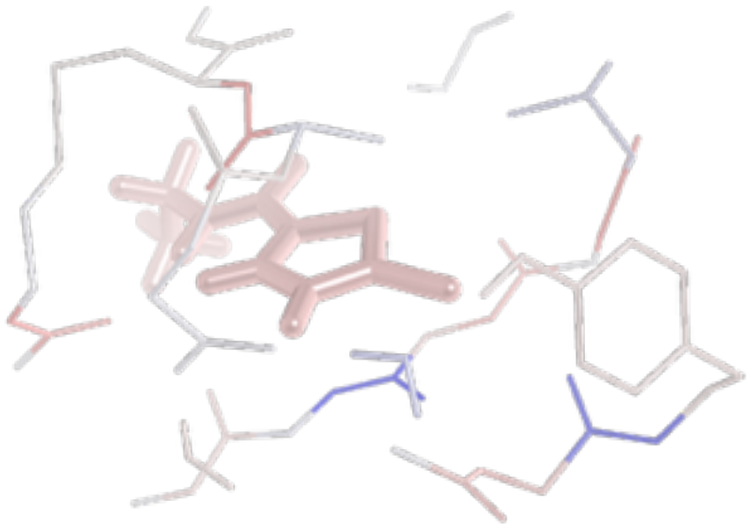
K_i = 6 nM vs. 109 nM: 18x

2pr3: -1.28 kcal mol^{-1}



(IC_{50} = 36 nM vs. 389 nM: 11x)

2w26: -0.71 kcal mol^{-1}



IC_{50} = 0.7 nM vs. 4.2 nM: 6x

Color Scale:

-5 kcal mol^{-1} (Favors Cl)

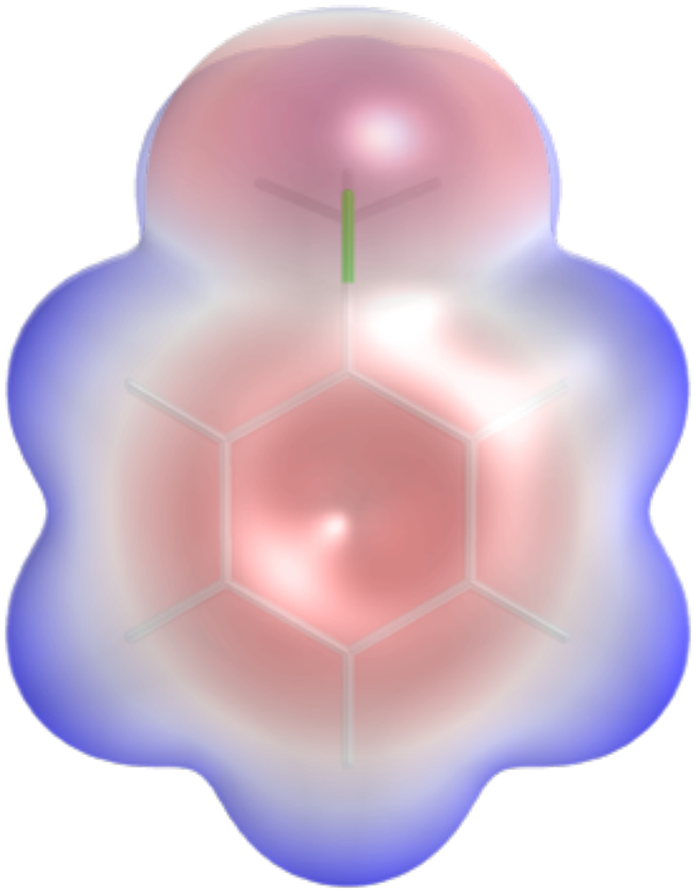
0 kcal mol^{-1} $\Delta\Delta E_{\mathrm{int}}$

+5 kcal mol^{-1} (Favors Me)

R.M. Parrish, C.D. Sherrill, D. Sitkoff and D. Cheney, *In Progress*, (2015).

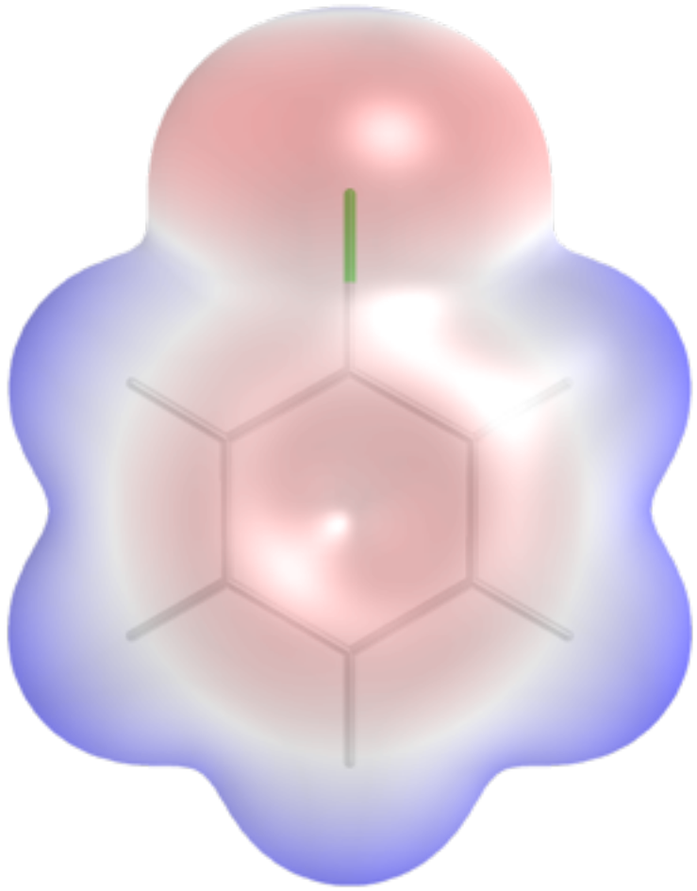
Toluene vs. Chlorobenzene

Toluene:



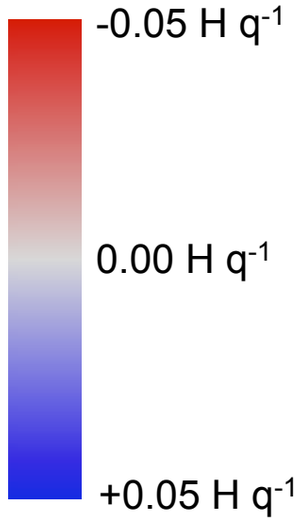
Dipole: +0.42 Debeye

Chlorobenzene



Dipole: +2.07 Debeye

Color Scale:

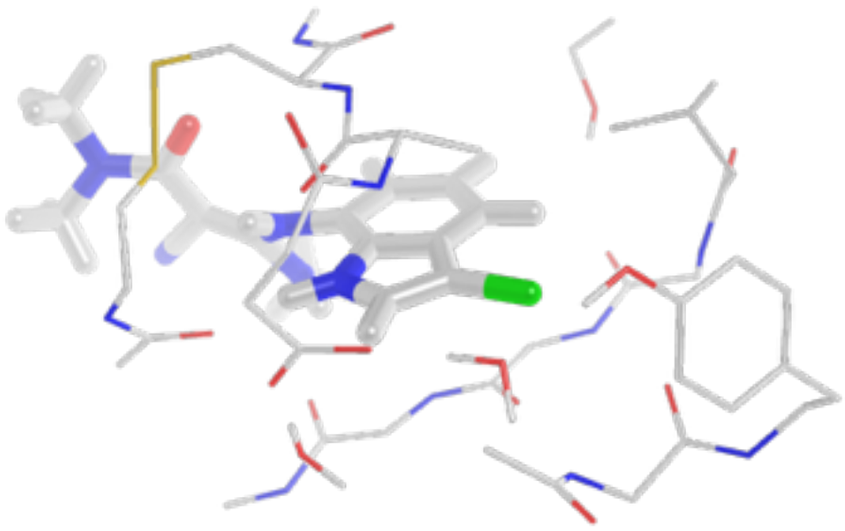


$\Delta\Delta E_{\text{int}}$

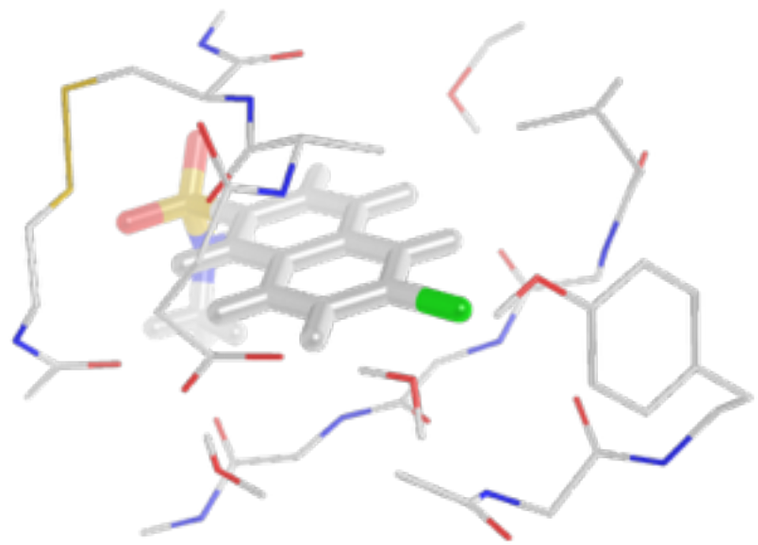
R.M. Parrish, C.D. Sherrill, D. Sitkoff and D. Cheney, *In Progress,* (2015).

Geometries

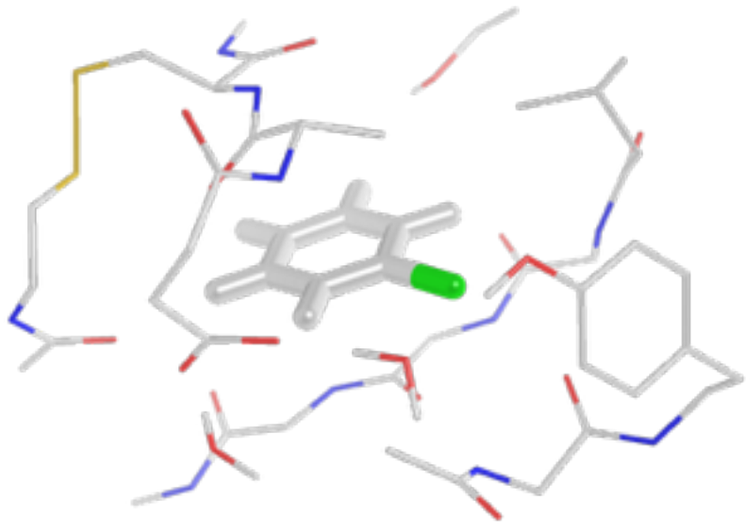
3ens: -2.46 kcal mol^{-1}



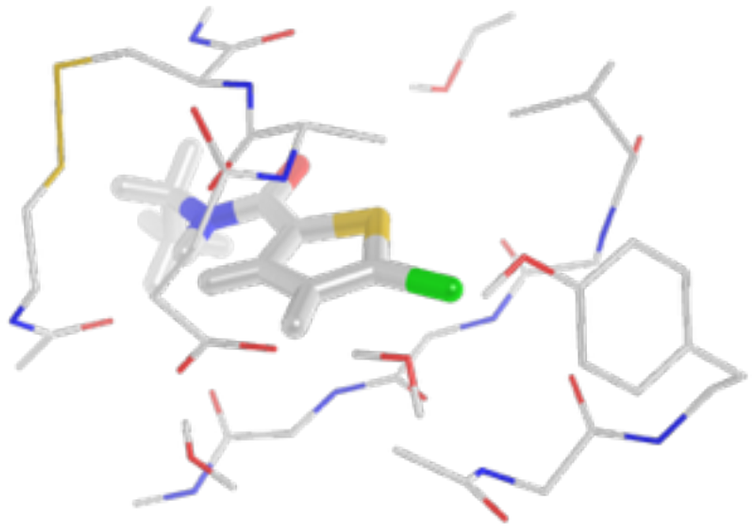
2cji: -1.30 kcal mol^{-1}



2pr3: -1.28 kcal mol^{-1}



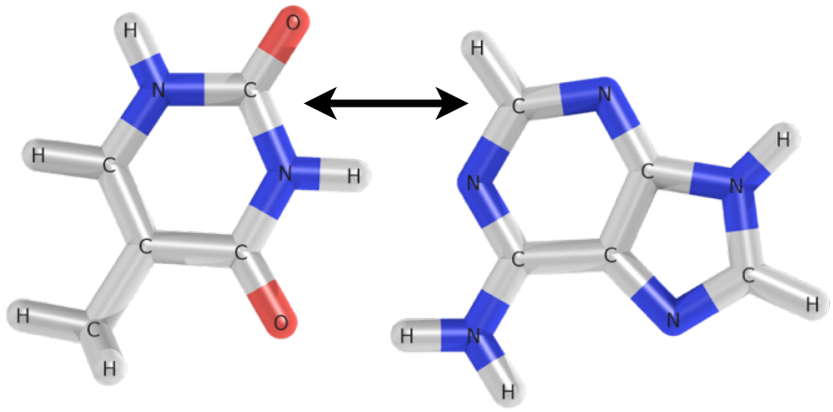
2w26: -0.71 kcal mol^{-1}



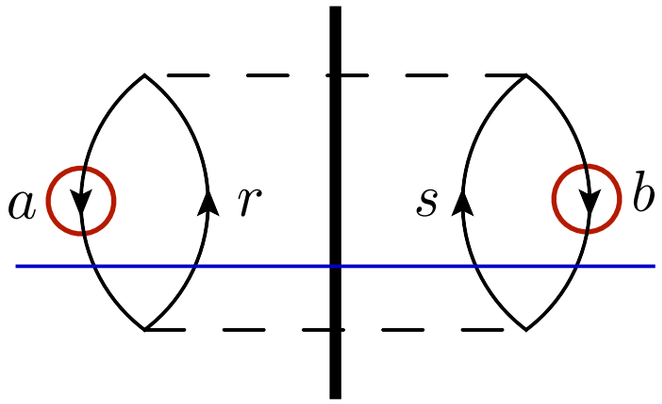
R.M. Parrish, C.D. Sherrill, D. Sitkoff and D. Cheney, *In Progress,* (2015).

Spatially Partitioned SAPT Development

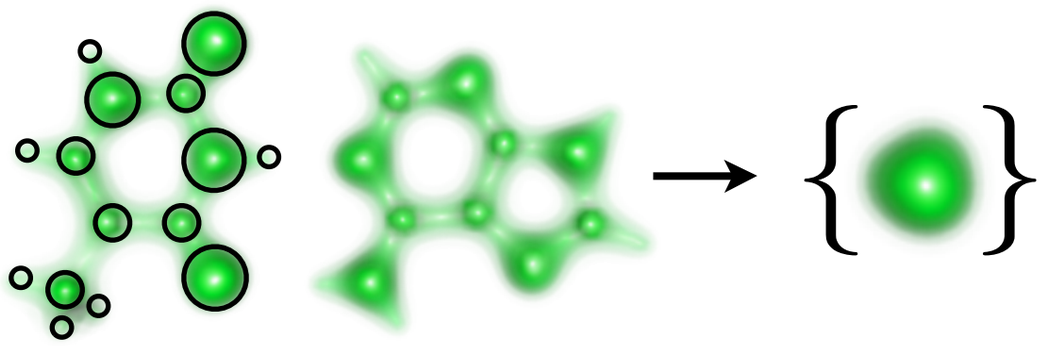
1) Allow the many-body interaction to occur naturally (SAPT0/jDZ for now).



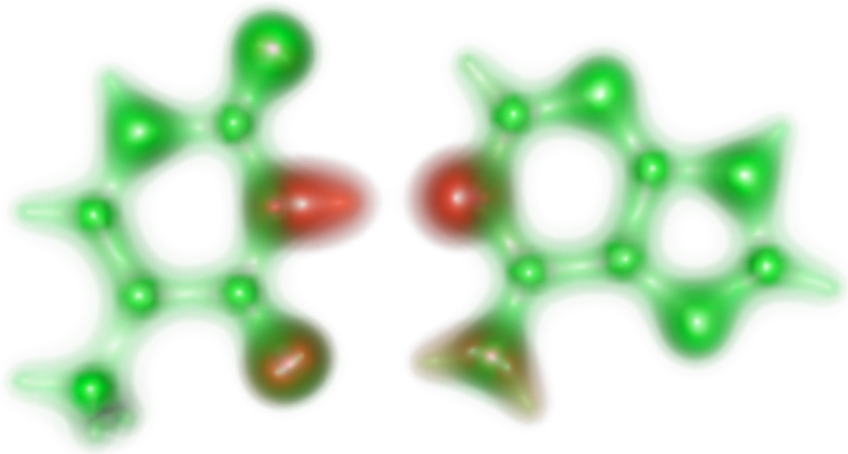
2) Identify two key occupied bodies in each many-body interaction term.



3) Perform key two-body occupied summations with local quasiparticles.



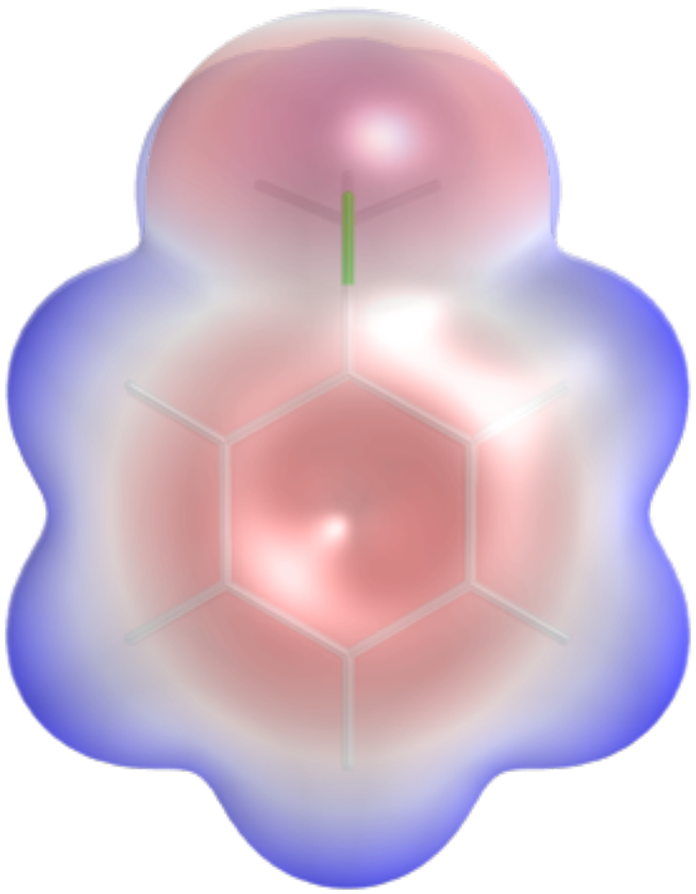
4) Analyze and visualize results.



R.M. Parrish and C.D. Sherrill, *J. Chem, Phys*. **141**, 044115 (2014).

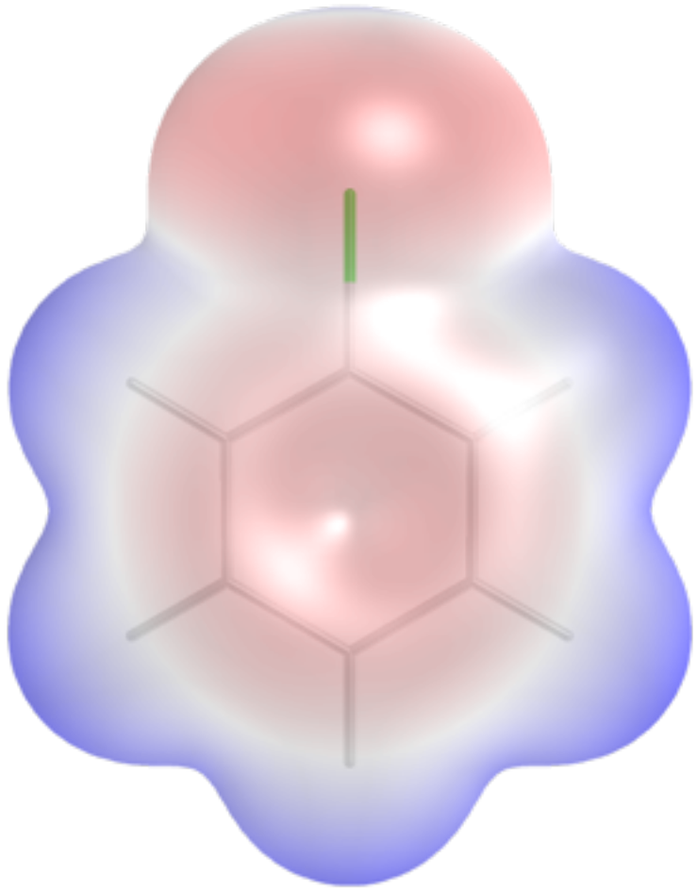
Factor Xa: S1 Pocket - Halogen-π Checks

Toluene:



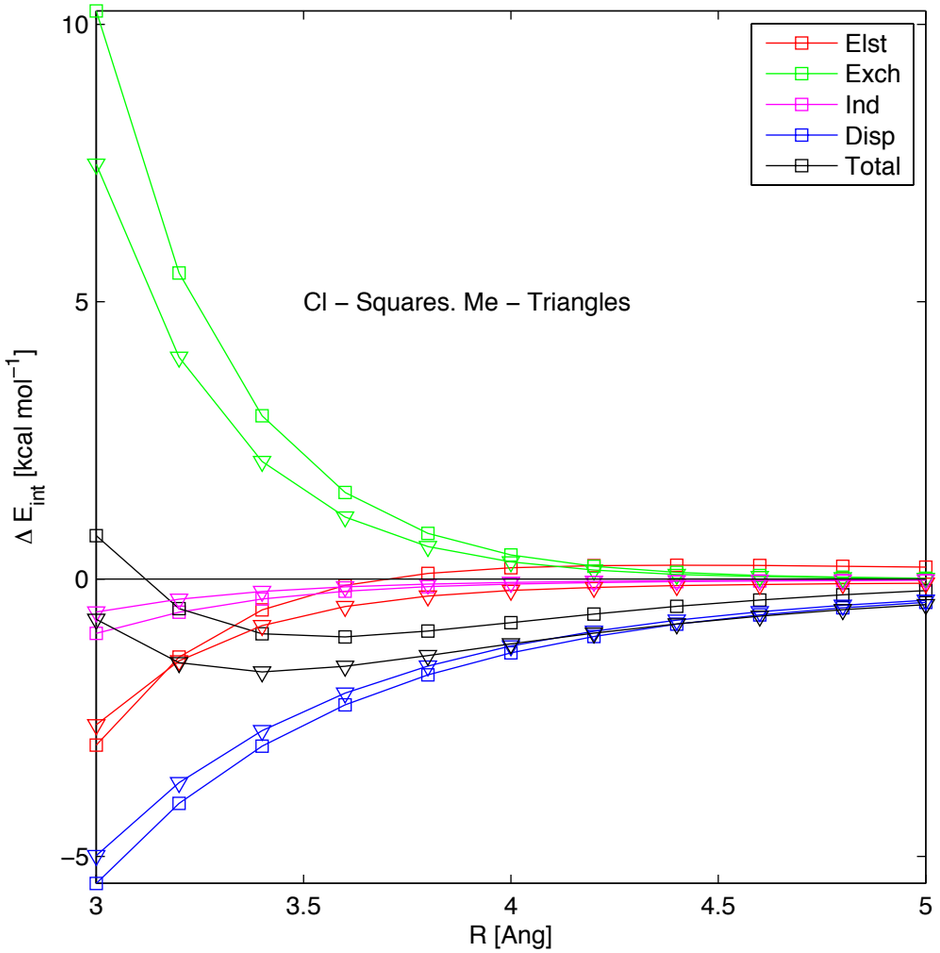
Dipole: +0.42 Debeye

Chlorobenzene



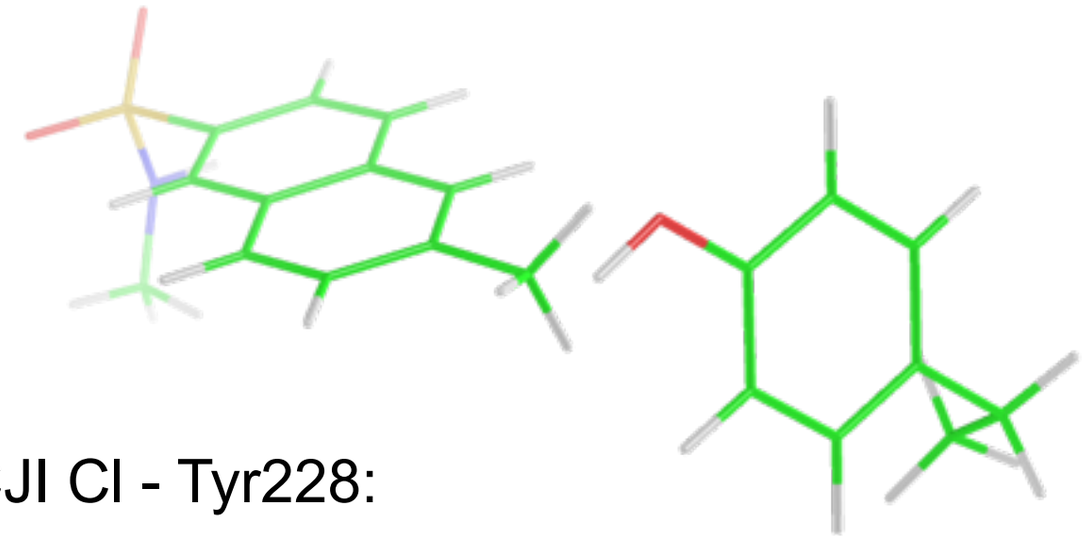
Dipole: +2.07 Debeye

Model PES with Tyr228 (Phenol):

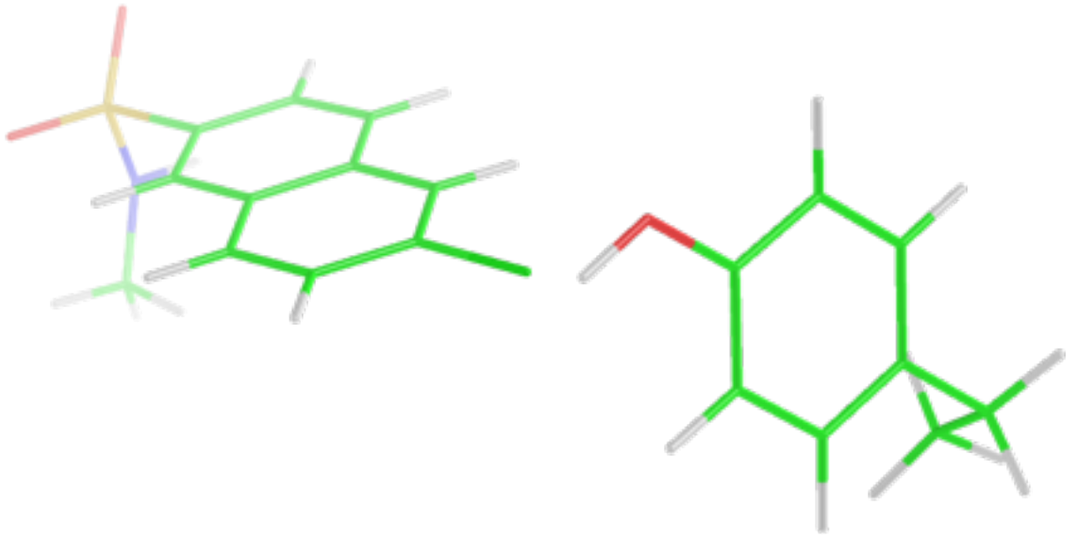


Factor Xa: S1 Pocket - Halogen-π Checks

2CJI Me - Tyr228:



2CJI Cl - Tyr228:

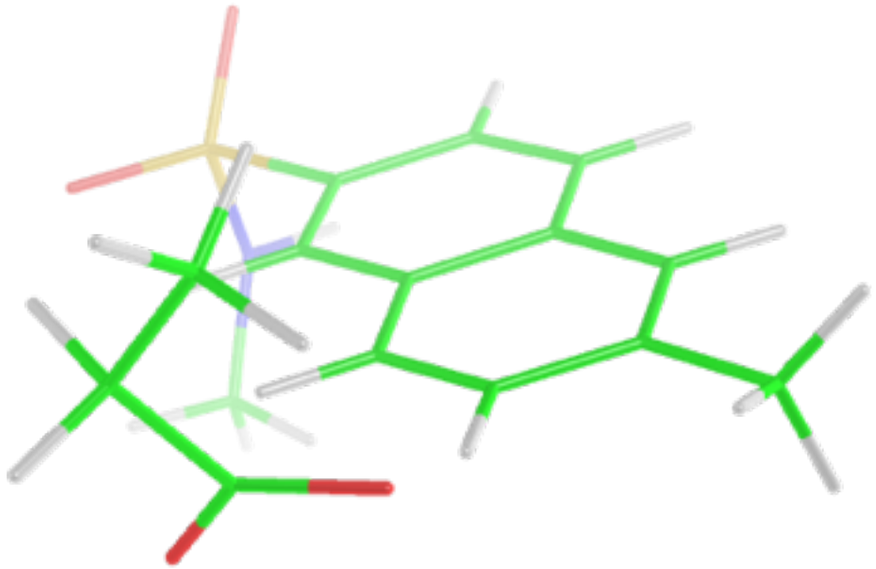


SAPT0/jun-cc-pVDZ Results:

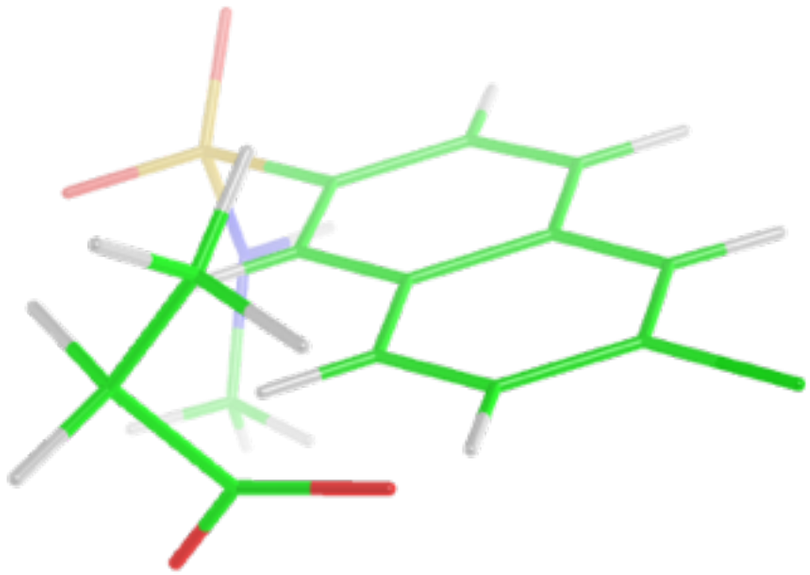
(kcal mol^{-1})	F-SAPT	Cut-Cap
Me	-1.04	-1.52
Cl	-1.33	-1.37
Diff	-0.29	+0.15

Factor Xa: S1 Pocket - Dipole-Aspartate Checks

2CJI Me - Asp189:



2CJI Cl - Asp189:

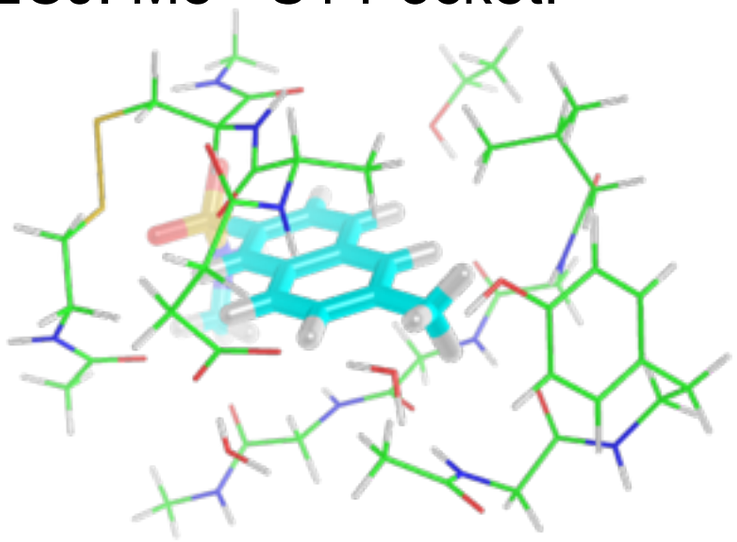


SAPT0/jun-cc-pVDZ Results:

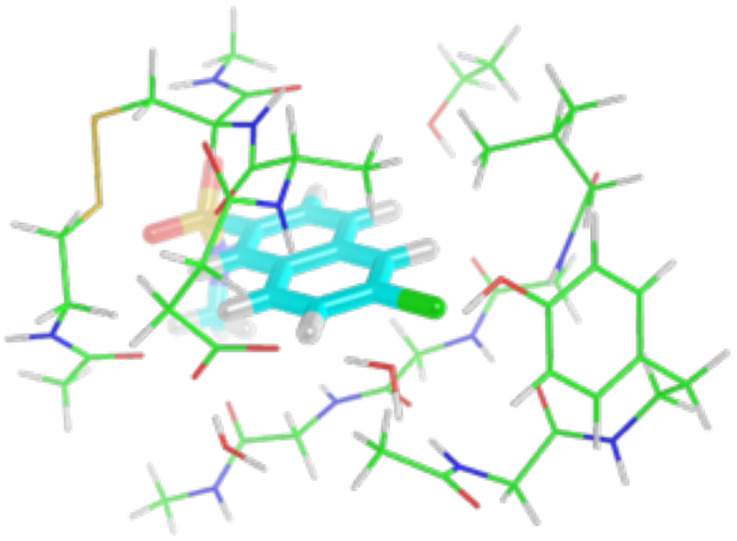
(kcal mol^{-1})	F-SAPT	Cut-Cap
Me	-13.05	-14.10
Cl	-12.05	-13.16
Diff	+1.00	+0.94

Factor Xa: S1 Pocket - Point Charge Model

2CJI Me - S1 Pocket:



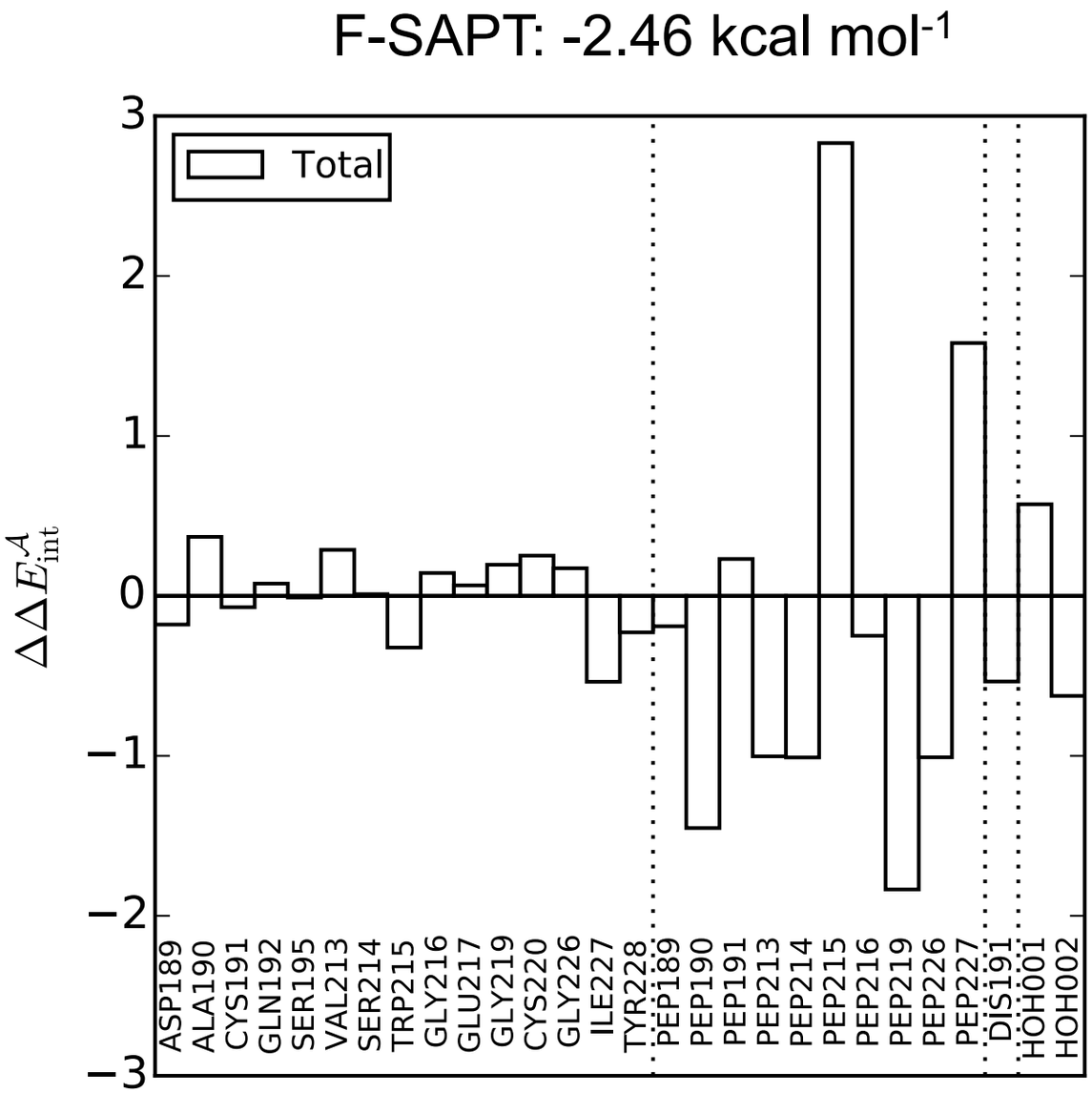
2CJI Cl - S1 Pocket:

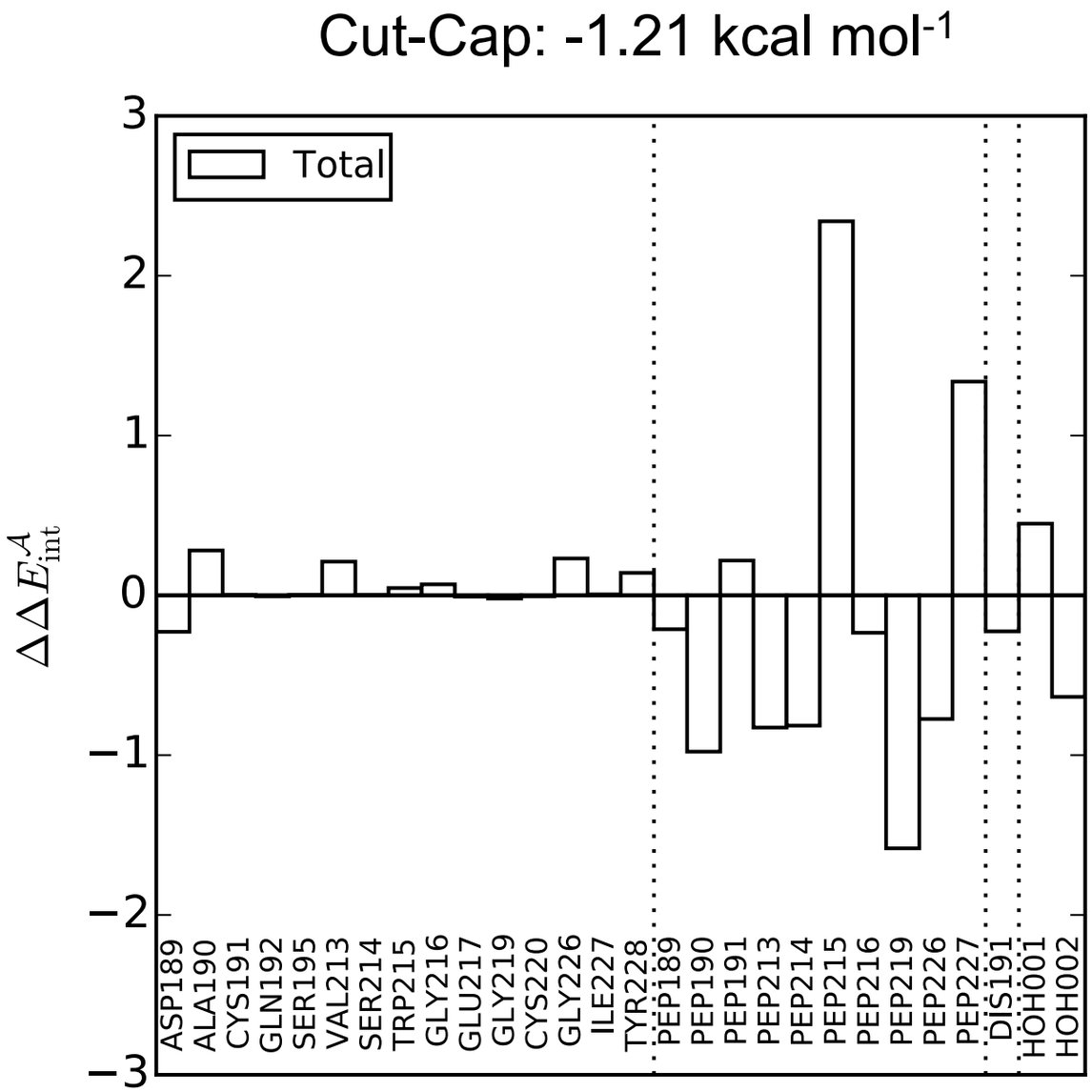


SAPT0/jun-cc-pVDZ Results:

(kcal mol^{-1})	Total (F-SAPT)	Elst (F-SAPT)	Elst (Charges)
Me	-38.84	-21.26	-32.23
Cl	-40.14	-22.89	-33.12
Diff	-1.30	-1.63	-0.91

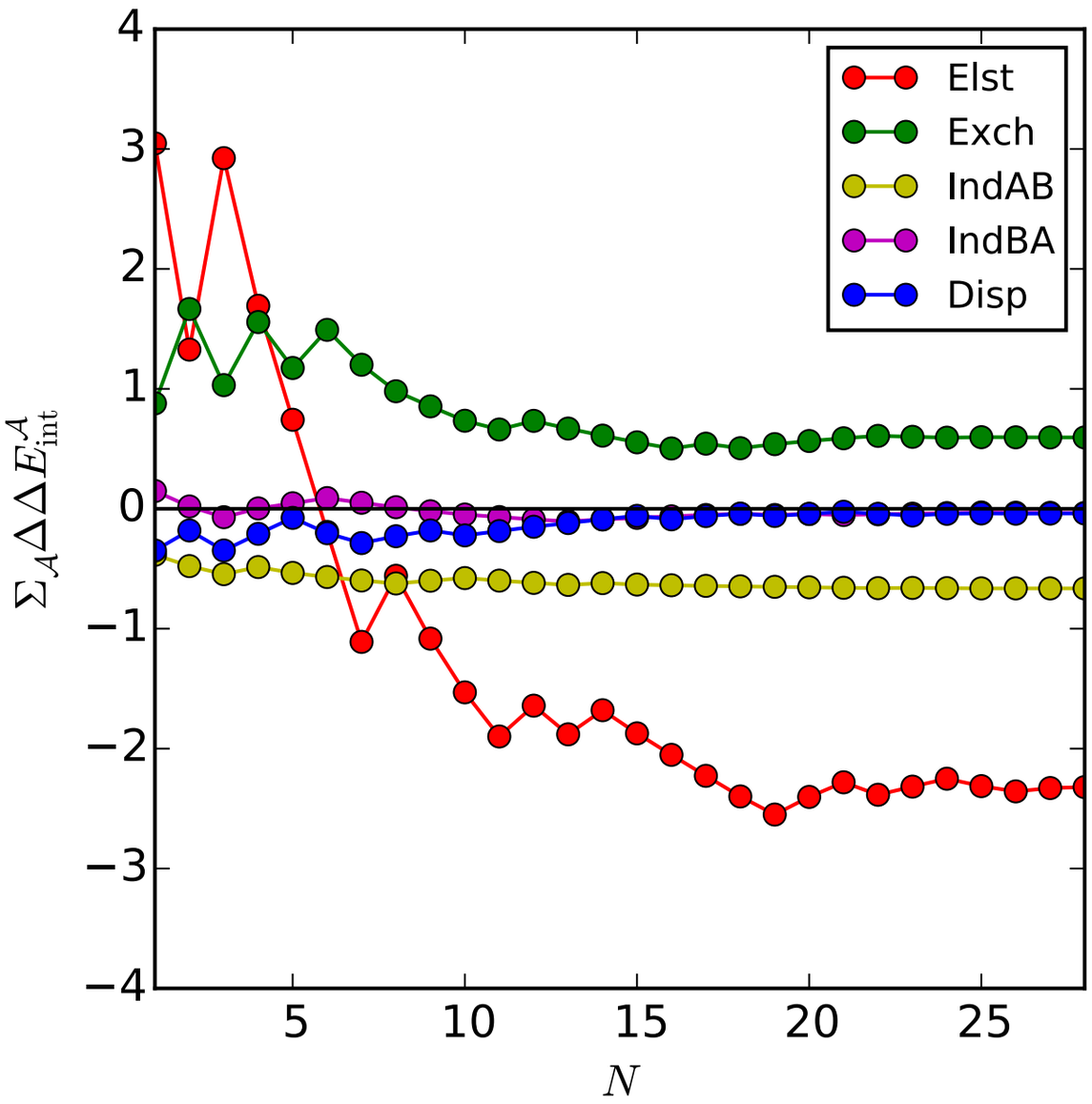
3ens: F-SAPT vs. Cut-Cap Totals

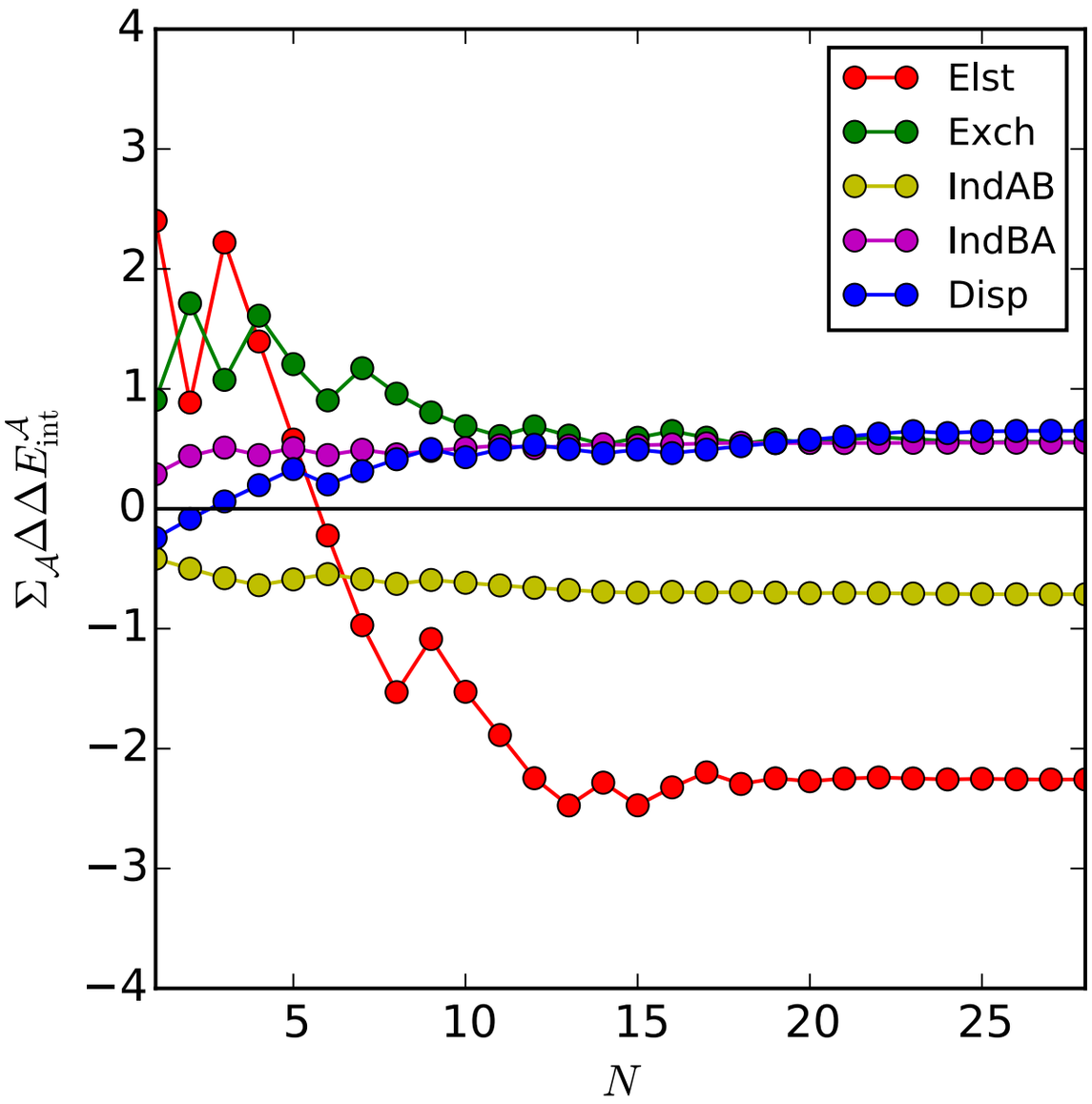




R.M. Parrish, C.D. Sherrill, D. Sitkoff and D. Cheney, *In. Progress,* (2015).

3ens: F-SAPT vs. Cut-Cap Contributors





R.M. Parrish, C.D. Sherrill, D. Sitkoff and D. Cheney, *In. Progress*, (2015).