Improving the Construction of QM Cluster Modeling using FSAPT Interaction Energies

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Abstract

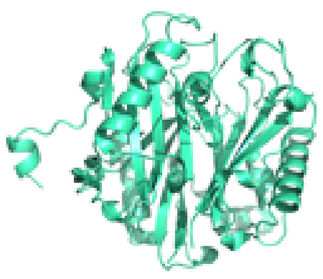
A fundamental part of drug discovery is understanding the mechanism of enzyme-substrate interactions. One focus of the DeYonker lab is the design and application of computational enzymology, specifically using Quantum Mechanical-cluster models. My project utilizes the chorismate mutase enzyme as a case study and extends the results of qualitative contact-based Residue Interaction Networks (RINs) with quantitative interaction energies from functional group symmetry adapted perturbation theory (F-SAPT). We analyzed various types of QM-cluster models from F-SAPT interaction energies based on how far away the amino acid fragment is from the substrate. We built off a qualitative interatomic contact-based model by extending the model from five to twenty-five additional fragments. We will investigate using both a representative frame from molecular dynamics simulation and the X-ray crystal structure. Additionally, we are studying how the energy decomposition of F-SAPT into electrostatic, induction, and dispersion terms is correlated with the residue fragment distance from the TSA. Preliminary results show that side chains of charged residues outside of the contact-based RIN have total interaction energies greater than 20 kcal/mol, even when > 7 Angstroms away from the TSA. Our focus needs to be on how the uncharged side chain fragments impact the model.

Background and Aims

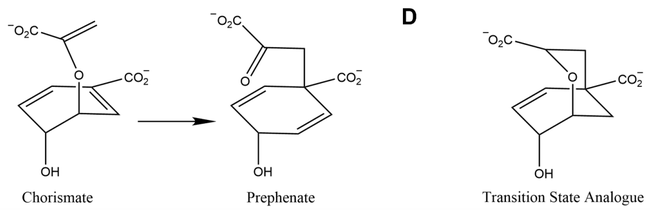
- Chorismate mutase (CM) is an enzyme that catalyzes the conversion of chorismate to prephenate
- Pathway is responsible for the *bacterial* production of tyrosine and phenylalanine
- CM provides a ~2 x 10^6 fold rate enhancement over the uncatalyzed Claisen rearrangement
- Residue Interaction Network ResidUe Selector (RINRUS) is an open-source software developed by our group to automate the construction of QM-cluster models

https://github.com/natedey/RINRUS

- Previous CM case study showed the number of qualitative interatomic contacts with ligand did not correlate with FSAPT interaction energies
- We aim to explore growing the size of the active site model of chorismate mutase
- Charged residues have large interaction energies within the active site
- **Do charged (or other types of) residues also have a large interaction energy with chorismate when farther away from the active site?**

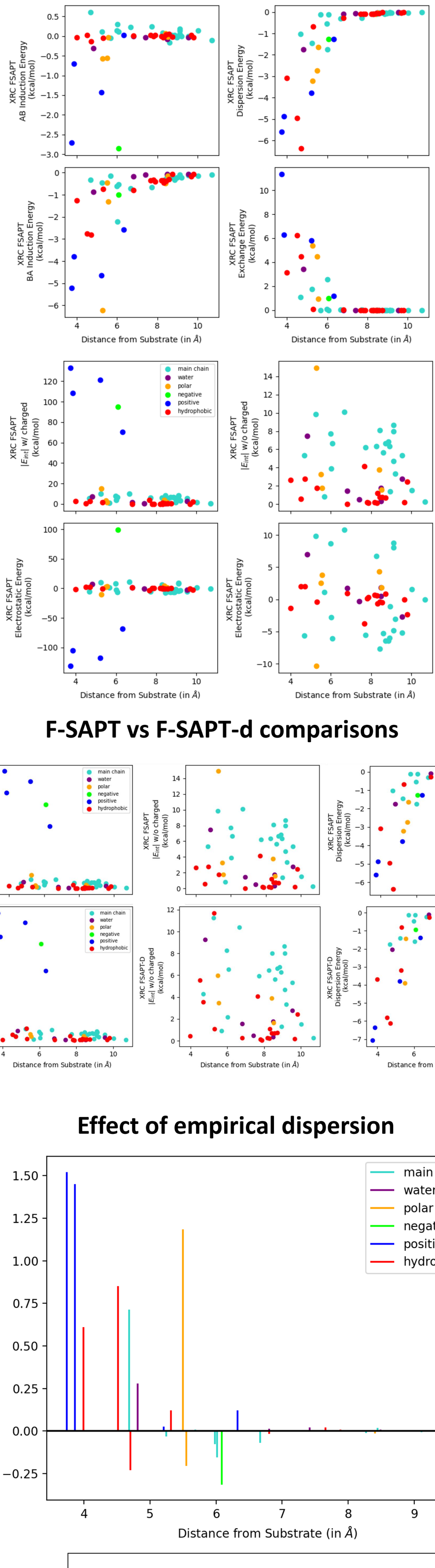


PDB 2CHT



Results

Calculated F-SAPT energies



F-SAPT vs F-SAPT-d comparisons

Effect of empirical dispersion

References

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J. Chem. Phys., **158**, 065101 (2023)
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Methodology

- This work builds upon the *probe* software used within *RINRUS* to construct qualitative contact-based models of the enzyme chorismate mutase
- *Probe* generates contact dots and clashes by rolling a spherical probe along the van der Waals surface of atoms in the protein
- The substrate for chorismate mutase is 8-hydroxy-2-oxa-bicyclo[3,3,1]non-6-ene-3,5-dicarboxylic acid from PDB:2CHT
- RINRUS compiles the information of the contacts and atomic overlaps to generate a **Residue Interaction Network (RIN)**
- Starting from our initial *probe*-based models, we extended five fragments at a time by selecting amino acid residues based upon increasing distance from the substrate *if they were not in the original model*
- F-SAPT computes quantum mechanical protein-substrate interaction energies
- Grew QM-cluster models from original size (13 fragments + chorismate substrate =205 atoms) to a model with 25 extra fragments (485 atoms)
- Most expensive part of F-SAPT is calculation of the dispersion component
- F-SAPT-D uses an empirical correction for dispersion and saves a lot of time and effort!

Conclusions

- *RINRUS* provides an automated computational enzyme workflow to systematically create QM-cluster models
- F-SAPT-D has small differences in dispersion term compared to conventional F-SAPT, but this might show a large shift if total interaction energies are small
- Distant main chain fragments seem to retain competitive interaction energies relative to uncharged side chains
- Charged amino acid side chains have the highest total interaction energies, which is expected due to electrostatic interactions with the di-anionic chorismate substrate
- Induction, dispersion, and exchange terms of the F-SAPT interaction energy asymptotically approach zero as we add more distant fragments to our model
- Electrostatic components do not fizzle out with respect to distance!

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