Theory of Hybrid Quantum Mechanics/Molecular Mechanics Methods (QM/MM)

CHEM 4021/8021

Video VII.i

Motivation

Gain an understanding of solvent structure

…or protein environment, etc.

While maintaining the ability to make and break bonds

What about solvent structure?

- Can we treat the solvent with MM and the solute with QM?

Energy Expression:

$$E_{complete} = E_{QM} + E_{MM} + E_{QM/MM}$$

Partion the Energy Expression

Energy Expression:

$$E_{complete} = E_{QM} + E_{MM} + E_{QM/MM}$$

- E_{QM} → $$H^{QM} = -\frac{1}{2}\sum_i \langle \mu | \nabla_i^2 | \upsilon \rangle - \sum_k \left\langle \mu \left| \frac{Z_k}{r_k} \right| \upsilon \right\rangle + G_{\mu\upsilon}$$
- E_{MM} → usual Force Field Terms

Partion the Energy Expression

Energy Expression:

$$E_{complete} = E_{QM} + E_{MM} + E_{QM/MM}$$

- E_{QM} → $$H^{QM} = -\frac{1}{2}\sum_i \langle \mu | \nabla_i^2 | \upsilon \rangle - \sum_k \left\langle \mu \left| \frac{Z_k}{r_k} \right| \upsilon \right\rangle + G_{\mu\upsilon}$$
- E_{MM} → usual Force Field Terms
- $E_{QM/MM}$ → Core challenge in QM/MM methods

Partion the Energy Expression

Energy Expression:

$$E_{complete} = E_{QM} + E_{MM} + E_{QM/MM}$$

- $E_{QM/MM}$ → $$H^{QM/MM} = -\sum_{k}\left\langle \mu \left| \frac{Z_k}{r_k} \right| \upsilon \right\rangle + \sum_{K,k}^{MM,QM} \frac{Z_K Z_k}{r_K r_k}$$

- One electron interaction terms and electrostatics for interaction between QM and MM regions
- Point Charges! Must add non-bonded terms

Partion the Energy Expression

Energy Expression:

$$E_{complete} = E_{QM} + E_{MM} + E_{QM/MM}$$

- Boundaries Through Space
- Boundaries Through Bonds

Unpolarized Interactions

$$H^{QM/MM} = \sum_{i}^{Solute} \sum_{j}^{Solvent} \frac{\alpha q_i^{CM1} q_j}{r_{ij}} + 4\varepsilon_{ij}\left(\frac{\sigma_{ij}^{12}}{r_{ij}^{12}} - \frac{\sigma_{ij}^{6}}{r_{ij}^{6}}\right)$$

- Compute the QM/MM interaction energy in a similar way to non-bonded FF interactions
- Use standard Lennard-Jones combining rules and assume the QM σ and ε values are the same for the atom type in the FF.
- α is a parameter to deal with charged versus neutral molecules to treat solvent polarization

Unpolarized Interactions

$$H^{QM/MM} = \sum_{i}^{Solute} \sum_{j}^{Solvent} \frac{\alpha q_i^{CM1} q_j}{r_{ij}} + 4\varepsilon_{ij}\left(\frac{\sigma_{ij}^{12}}{r_{ij}^{12}} - \frac{\sigma_{ij}^{6}}{r_{ij}^{6}}\right)$$

- Example: Kaminski and Jorgensen's AM1/OPLS/ CM1 (AOC)
  - AM1 for the solute (Perform MC simulation)
  - OPLS for the solvent
  - Charges (q_i) for the solute are from the CM1 charge model
  - Treats polar solvation effects well (e.g. rotameric equilibria) but not as good for non-polar solvents
  - Treats solvation free energy effects along a reaction coordinate

Polarized/Unpolarized Interactions

$$H^{QM/MM} = \sum_{i}^{\substack{Solute\\Electrons}} \sum_{m}^{\substack{MM\\Atoms}} \frac{q_m}{r_{im}} + \sum_{k}^{\substack{Solute\\nuclei}} \sum_{k}^{\substack{MM\\Atoms}} \left[\frac{Z_k q_m}{r_{km}} + 4\varepsilon_{km} \left(\frac{\sigma_{km}^{12}}{r_{km}^{12}} - \frac{\sigma_{km}^{6}}{r_{km}^{6}} \right) \right]$$

- Allow the environment (MM part) to polarize the QM part
- Separate the interaction of the MM part with the solute electrons and the solute nuclei

Polarized/Unpolarized Interactions

$$H_{complete} = H_{QM} + H_{MM} + H_{QM/MM}$$

- H_{MM} (Traditional FF)
- $H_{QM/MM}$ (Separated electrostatic + nonbonded part)
- How does H_{QM} change?

$$H^{QM} = -\frac{1}{2}\sum_i \langle \mu | \nabla_i^2 | \upsilon \rangle - \sum_k \left\langle \mu \left| \frac{Z_k}{r_k} \right| \upsilon \right\rangle + G_{\mu\upsilon}$$

Recall from earlier

$$H^{QM} = -\frac{1}{2}\sum_i^N \nabla_i^2 - \sum_i^N \sum_k^{\substack{Solute \\ Nuclei}} \frac{Z_k}{r_{ik}} - \sum_i^N \sum_m^{\substack{MM \\ Atoms}} \frac{q_m}{r_{im}} + \sum_{i<j} \frac{1}{r_{ij}} + \sum_{k<l} \frac{Z_k Z_l}{r_{kl}}$$

Fully Polarized Interactions

- Use a polarizable FF where each MM atom type/molecule is assigned a polarizability tensor, α
- Allow for induced dipoles, $\mu_{ind}=\alpha\mathbf{E}$, where $\mathbf{E}$ is the electric field
- Allow the induced dipoles to interact with QM system

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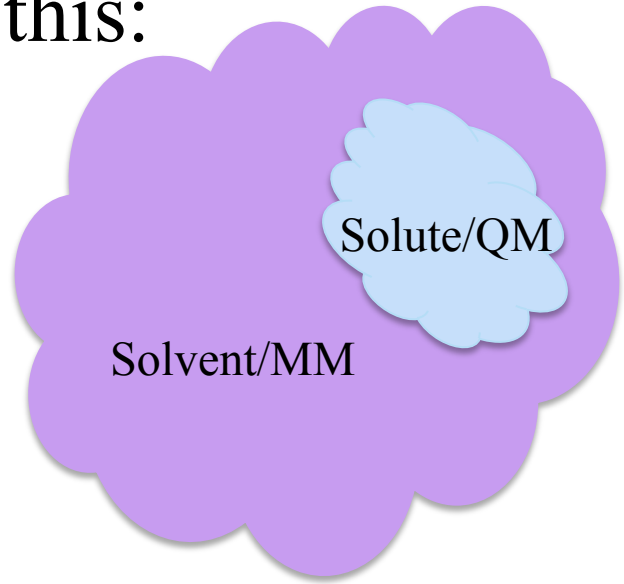
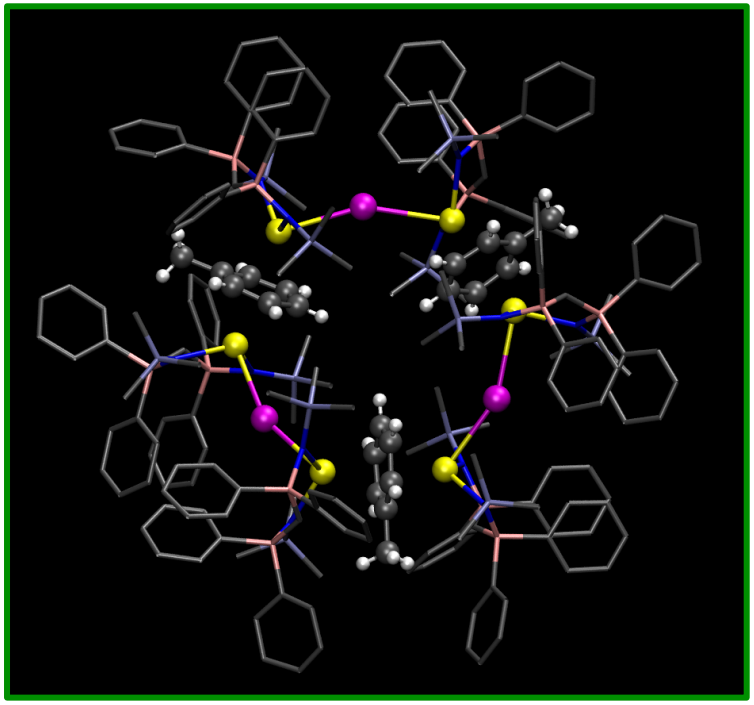
Partitions that cross covalent bonds

- What if we don't want to treat this:



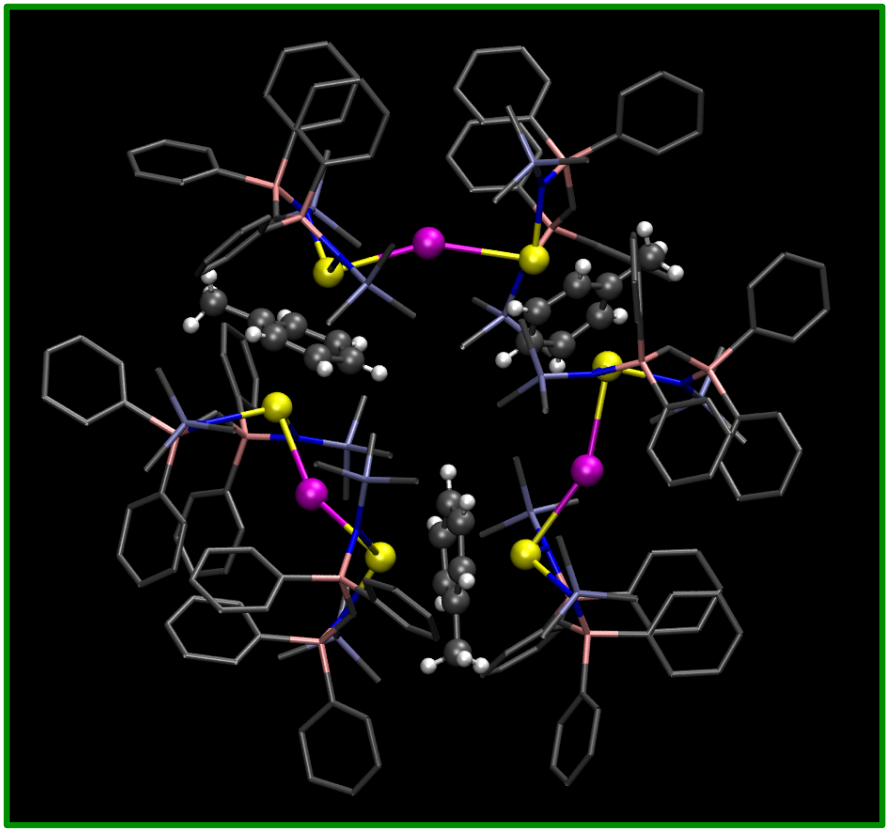
- But THIS!



Partitions that cross covalent bonds

Can we consider the bulky portions of the ligand as MM?

How will we compute the energy if the partition crosses covalent bonds?



Partitions that cross covalent bonds

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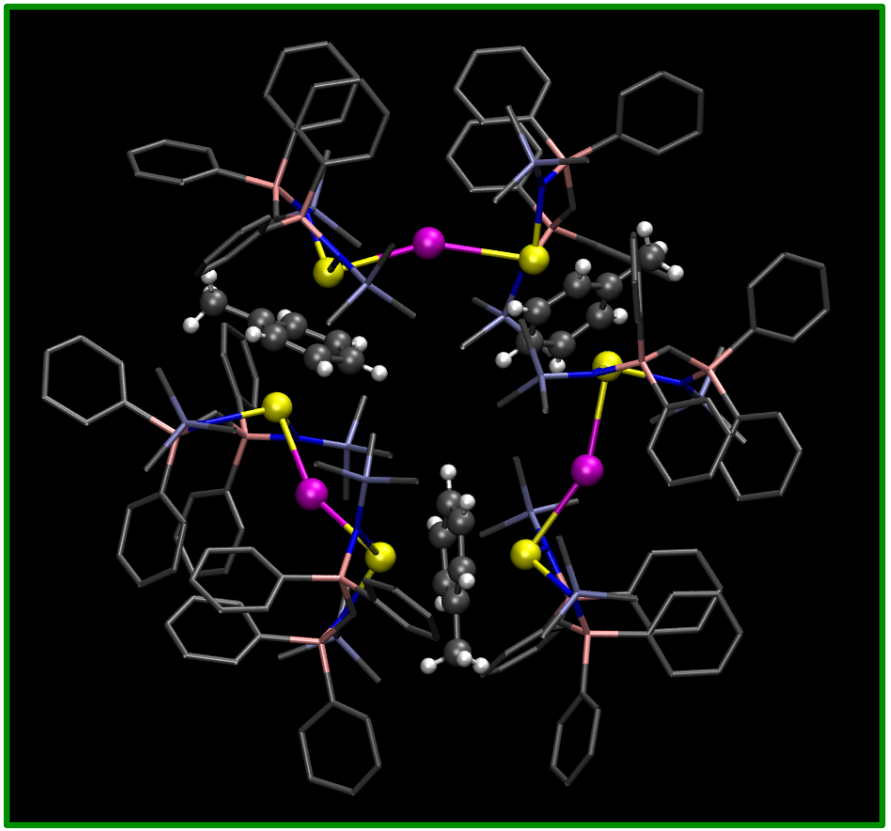
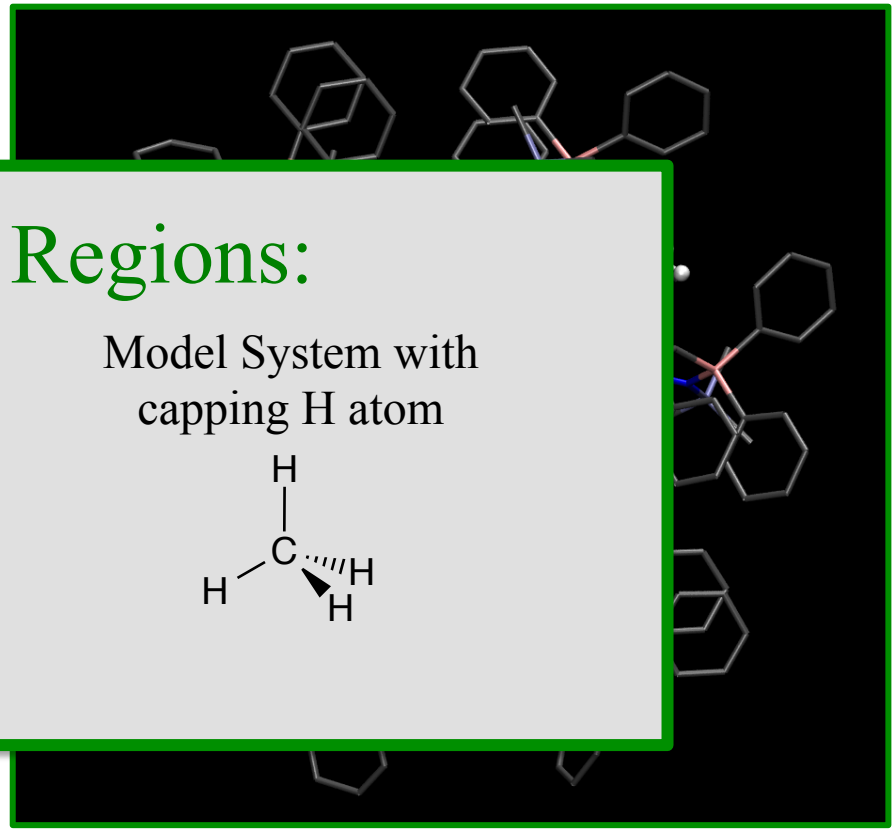


Mechanical Embedding

$$E_{complete} = E_{QM}^{small} + \left(E_{MM}^{big} - E_{MM}^{small} \right)$$

Partitions that cross covalent bonds

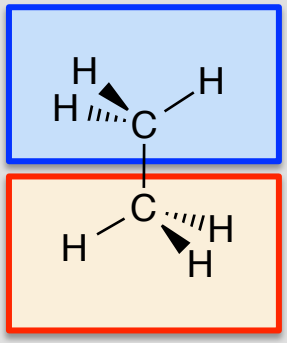
How will we compute the energy if the partition crosses



Linking Regions:

MM Region

QM Region



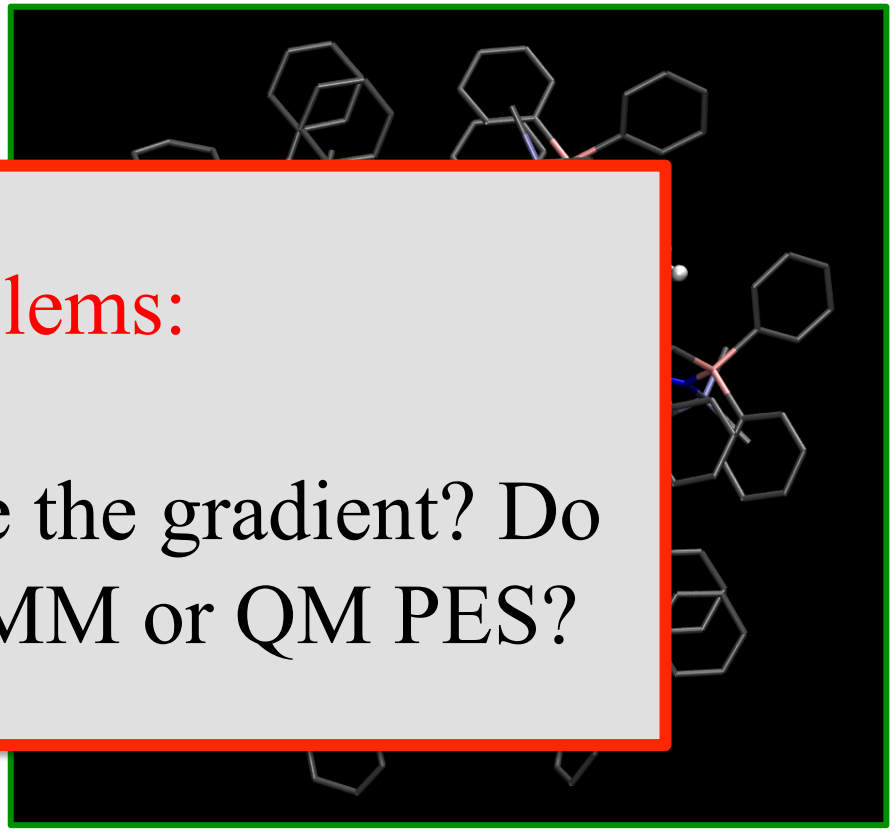
Model System with capping H atom

Embedding

$$E_{complete} = E_{QM}^{small} + \left(E_{MM}^{big} - E_{MM}^{small} \right)$$

Partitions that cross covalent bonds

How will we compute the energy if the partition crosses



Problems:

How do you take the gradient? Do you follow the MM or QM PES?

M

Embedding

$$E_{complete} = E_{QM}^{small} + \left(E_{MM}^{big} - E_{MM}^{small} \right)$$

Integrated Molecular Orbital Molecular Mechanics Method (IMOMM)

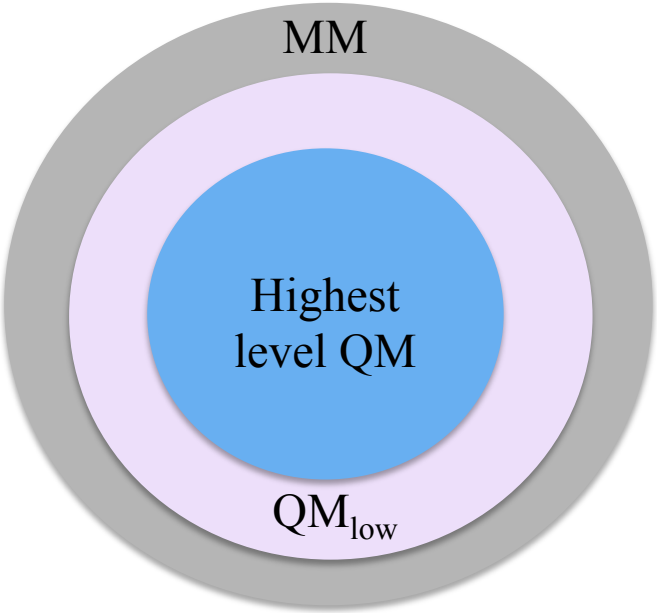
- Align the atoms that the small and large region have in common (e.g. force cut bonds to be along the same vector)

- Within these constraints, write expressions for the gradient as sums of the MM and QM gradients

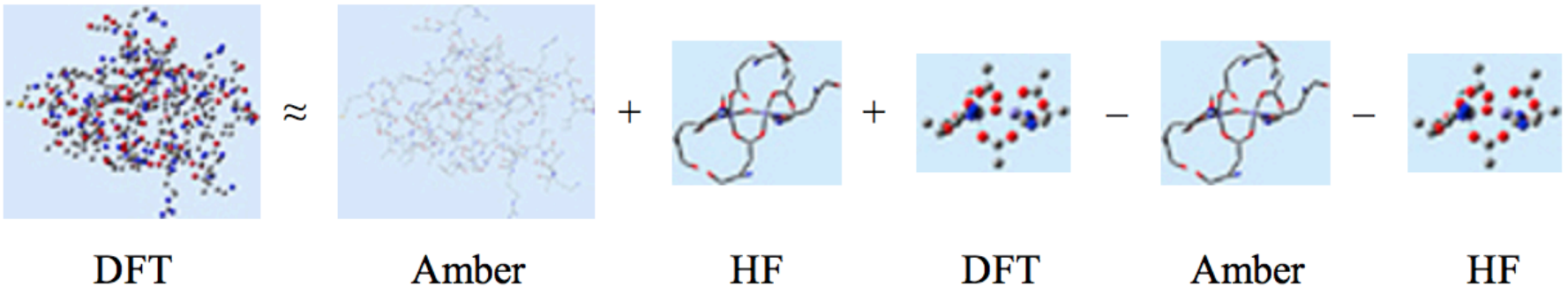
- Has also been generalized for QM/QM'

Our own N-layered Integrated molecular Orbital and molecular Mechanics (ONIOM)

This idea can be extended beyond two layers



$$E^{high}(Real) \approx E^{ONIOM} = E^{low}(Real) + E^{medium}(Intermediate) + E^{high}(Small) - E^{low}(Intermediate) - E^{medium}(Small)$$



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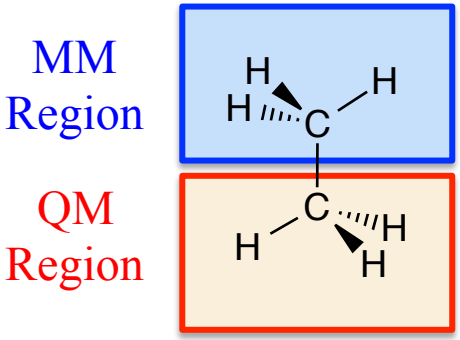
Beyond Sterics: Electrostatic Embedding

- Example: A large protein where charged residues in the MM region will polarize the QM region
- Extend our idea of a polarized/unpolarized partition for non-bonded terms
- Include terms for the bonds cut by the QM/MM boundary!



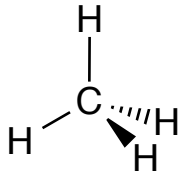
Beyond Sterics: Electrostatic Embedding

- Cap QM region with H's. Compute H^{QM} like before.

$$H^{QM} = -\frac{1}{2}\sum_{i}^{N}\nabla_i^2 - \sum_{i}^{N}\sum_{k}^{\substack{Solute\\Nuclei}}\frac{Z_k}{r_{ik}} - \sum_{i}^{N}\sum_{m}^{\substack{MM\\Atoms}}\frac{q_m}{r_{im}} + \sum_{i<j}\frac{1}{r_{ij}} + \sum_{k<l}\frac{Z_k Z_l}{r_{kl}}$$

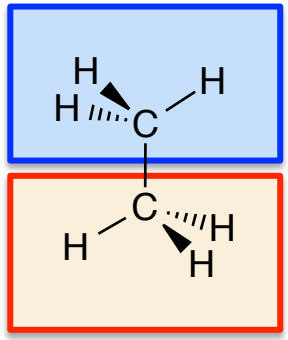
- Don't compute for capping H atoms

Model System with capping H atom



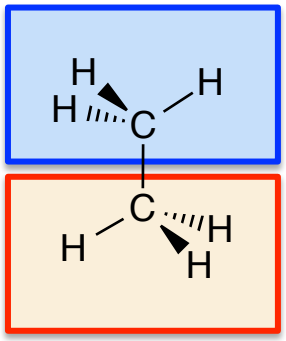
MM Region

QM Region



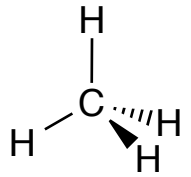
MM Region

QM Region



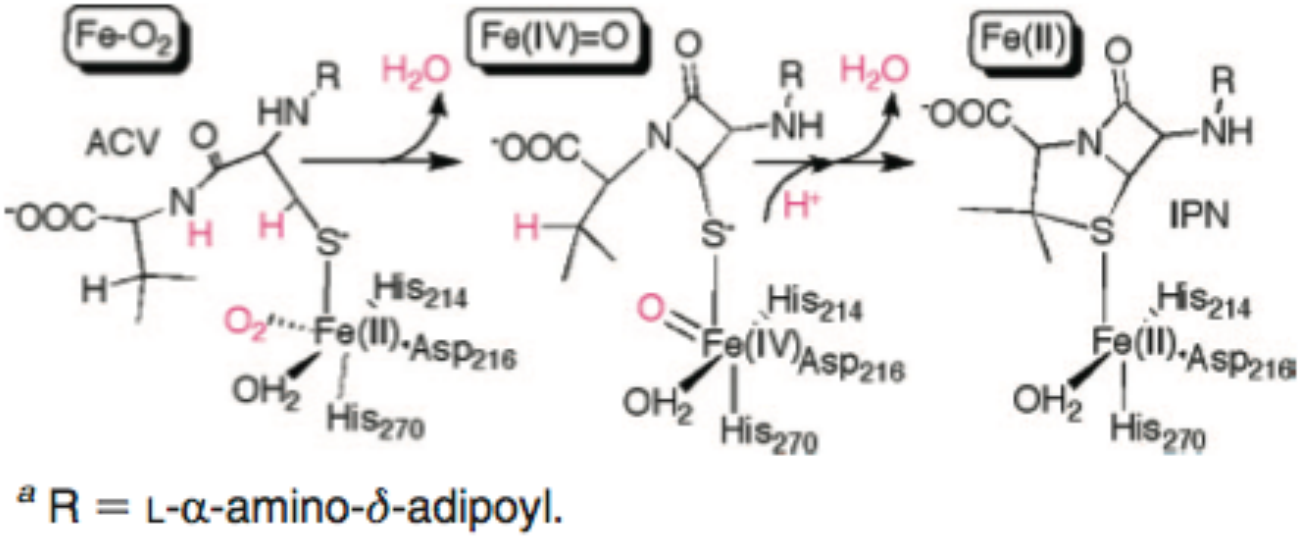
Beyond Sterics: Electrostatic Embedding

Model System with capping H atom



- Bond stretching for bonds cut by the QM/MM boundary are treated with MM potential
- Angle bending ($atom_{MM}$-$atom_{MM}$-$atom_{QM}$) are treated with MM potential
- Fictitious bond angles involving capping atom (e.g. $atom_{QM}$-$atom_{MM}$-$H_{capping}$) have very large force constants
- Torsions also use MM potential when 2 MM and 2 QM or 3 MM and 1 QM atoms are involved.
- Sometimes charges must be modified as well

Case Study: Transition States in a Protein Environment - ONIOM QM:MM Modeling of Isopenicillin N Synthesis



Scheme 1. General Reaction for Isopenicillin N Synthase Including the Proposed [Fe(IV)dO] Intermediate[a]

Two layer ONIOM calculations:
B3LYP is the high level of AMBER is the low level

Lundberg, Kawatsu, Vreven, Frisch, and Morokuma. *J. Chem. Comput. Chem.* **2008**, 5, 220-234.

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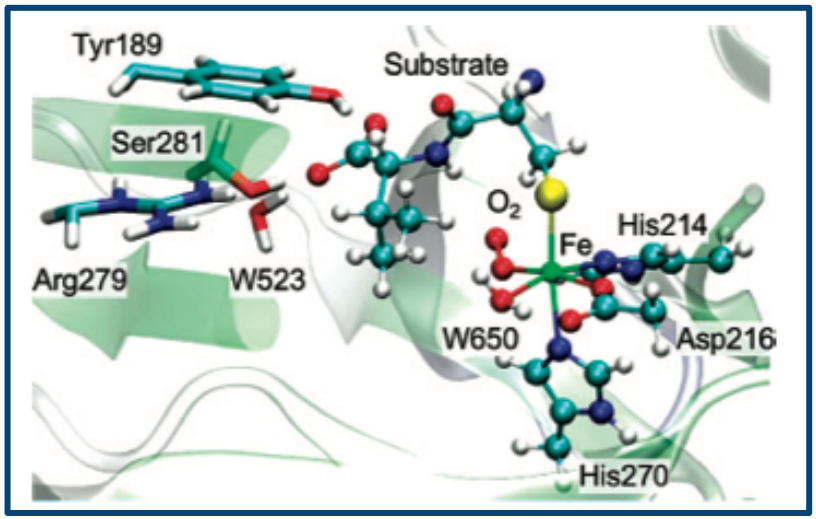
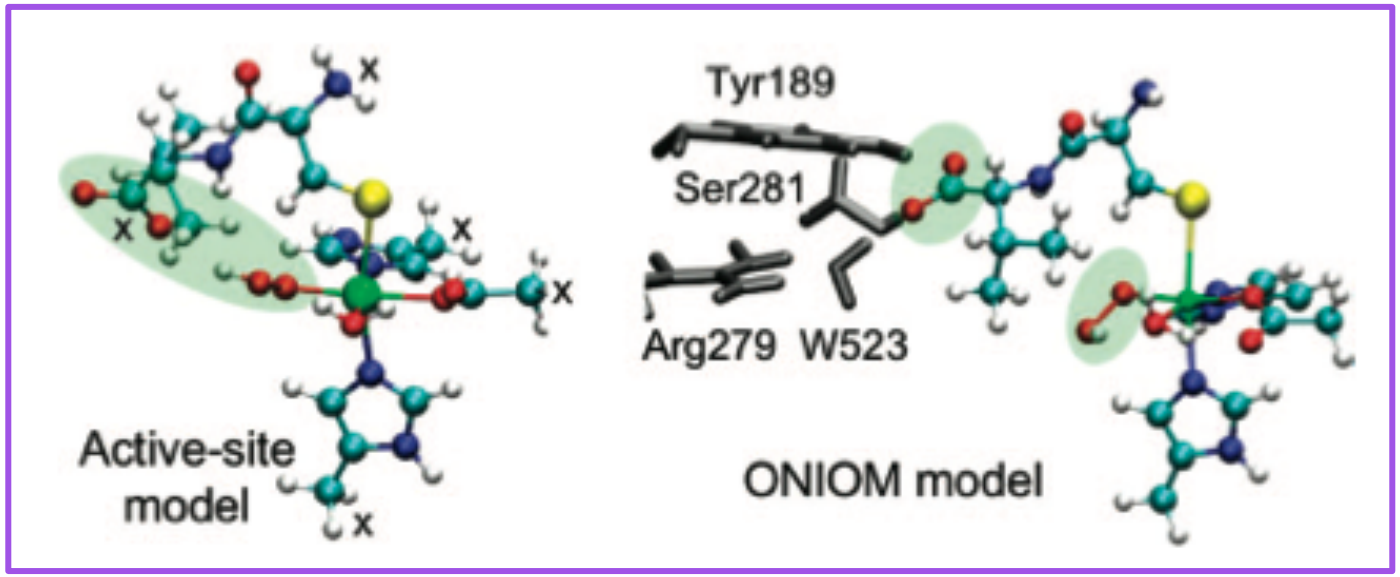


Choosing the Size of the QM Space



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Case Study: Transition States in a Protein Environment - ONIOM QM:MM Modeling of Isopenicillin N Synthesis

Example of how the size of the QM region can impact your results

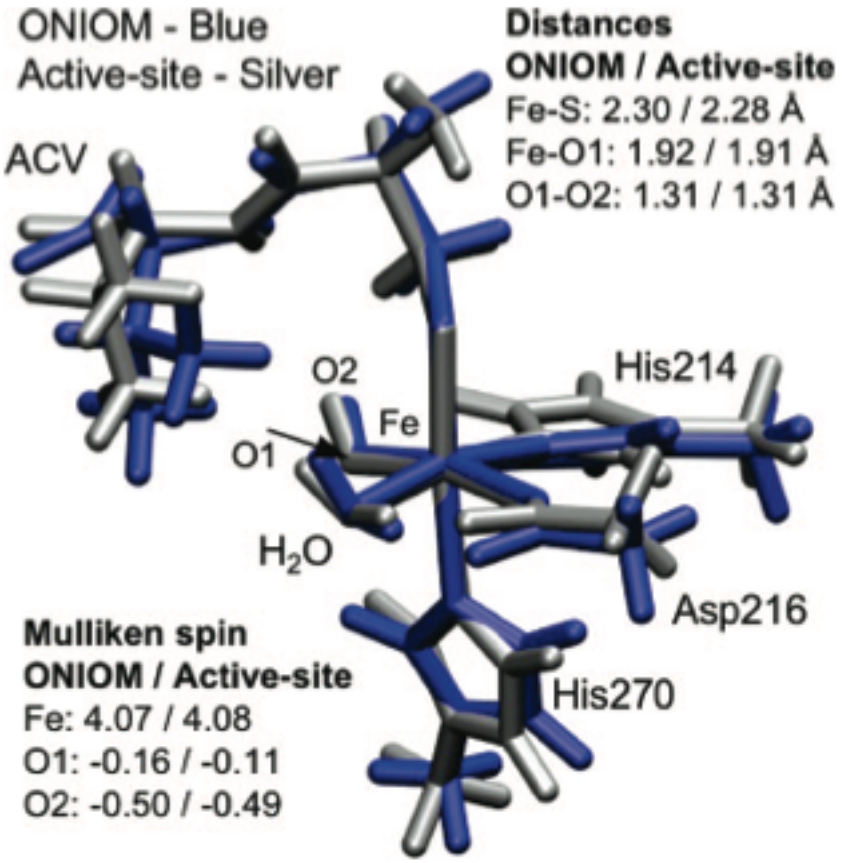

Figure 2. Geometries and spin populations for the intermediate with end-on bound dioxygen in the quintet state (^{5}**2** INT) optimized using the active-site model (silver) and the ONIOM QM:MM model (blue).

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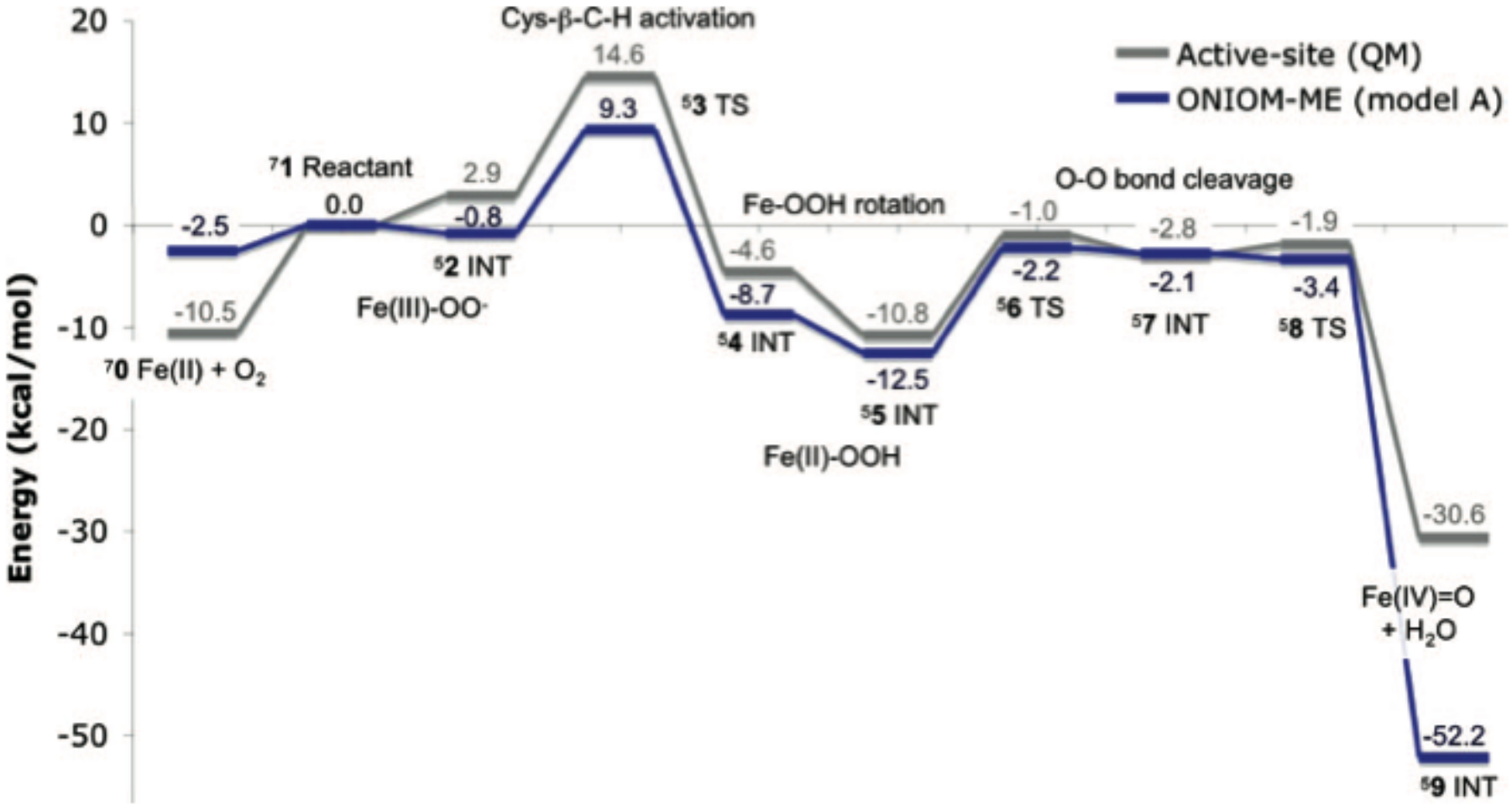

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