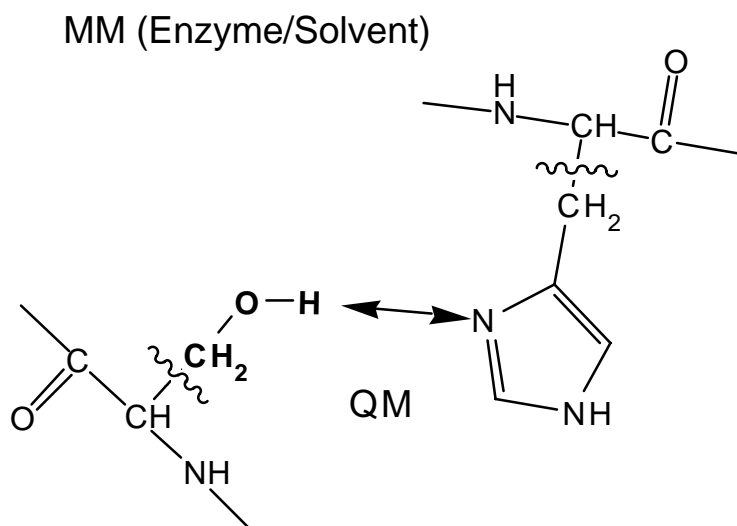


Quantum Mechanical/Molecular Mechanical (QM/MM) Calculations

Investigate chemical reactions in condensed phase environments. Exploit explicit treatment of electrons with QM approaches in combination with computationally cheap MM approach to treat condensed phase environment. (Field *et al.*, 1990; Gao, 1996)



QM

Semiempirical (MNDO, AM1)

Ab initio

Density Functional Methods

In CHARMM

MOPAC (default)

GAMESS, www.msg.ameslab.gov/GAMESS/GAMESS.html

CADPAC

MM

CHARMM

or others (AMBER, GROMOS etc.)

Effective Hamiltonian for QM/MM calculations

$$\hat{H}_{eff} = \hat{H}_{QM/QM} + \hat{H}_{MM/MM} + \hat{H}_{QM/MM}$$

$$E = \langle \Phi | \hat{H}_{eff} | \Phi \rangle = \langle \Phi | \hat{H}_{QM/QM} | \Phi \rangle + \langle \Phi | \hat{H}_{QM/MM} | \Phi \rangle + E_{MM/MM}$$

QM/MM Hamiltonian

$$\hat{H}_{QM/MM} = -\sum_{i,M} \frac{eq_M}{r_{iM}} + \sum_{\alpha,M} \frac{Z_\alpha q_M}{R_{\alpha M}} + \sum_{\alpha,M} 4\epsilon_{\alpha M} \left\{ \frac{R_{\min,\alpha M}^{12}}{R_{\alpha M}^{12}} - 2 \frac{R_{\min,\alpha M}^6}{R_{\alpha M}^6} \right\} + \hat{H}_{QM/MM}^{int-coor}$$

Counters

i: electrons

α : nuclei

M: MM atoms

e: electron charge

q_M : atomic charge on MM atoms

Z: nuclear charge

R/r: distances between particles

ϵ and R_{\min} : well-depth and radius

In solution

Reactants being treated by QM are surrounded by MM waters: no covalent bonds between QM atoms and MM atoms

Enzyme active site

Necessity of including amino acid or coenzyme functional groups in QM region requires treatment of covalent link between QM and MM regions (frontier region). (Reuter *et al.*, 2000)

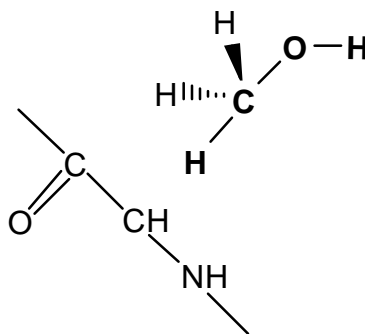
Valences of the frontier atoms of QM region must be filled.

Link Atoms

Frontier Orbitals

Link atom approach

- 1) Include hydrogen to fill valence (or fluorine or methyl).
- 2) Maintain QM to MM covalent terms (bonds, angles, and dihedrals)
- 3) QM sees all MM atoms and vice versa. Omission of link atom to MM atom interactions leads to poor results due to polarization of link atom - carbon bond. (Reuter et al., 2000) This is caused by the carbon "feeling" the MM field while the link atom does not.



Apply constraints to keep link atom along the C-CH bond.

Frontier Orbitals(Assfeld & Rivail, 1996; Gao *et al.*, 1998) (see

nad_qm_surf_1a.inp)

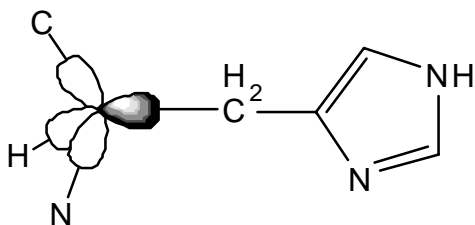
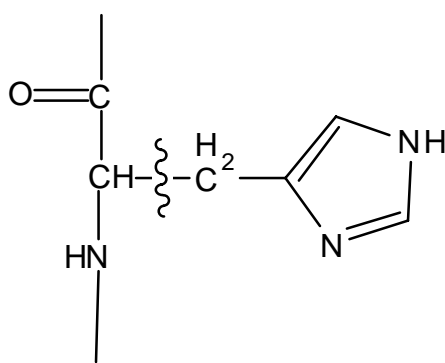
1) Place orbitals on frontier QM atom to fill valence

2) Avoid need for additional link atom

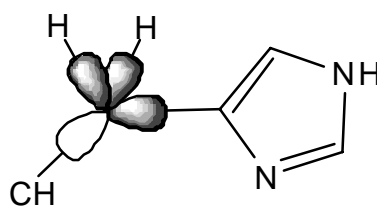
3) Treat orbitals

as Frozen (open orbitals in figure below)

in QM Self-Consistent Field (SCF) procedure (filled orbitals below)



General Hybridized Orbital (GHO)



Local SCF (LSCF) Method

Considerations

Selection of QM region

- 1) Perform test calculations using different QM/MM partitions to see if Mulliken charge distribution (or, ideally, energy surface associated with the gas phase reaction coordinate) reproduces full QM values in the gas phase.
- 2) ALWAYS place QM/MM frontier (link atom or orbital) at an aliphatic carbon as it is desirable to have the smallest possible charge distribution at the frontier.

Accuracy of QM model and QM/MM nonbonded interactions (Bash *et al.*, 1996; Freindorf & Gao, 1996)

1) QM

Compare QM calculated gas phase reaction rate to experimental or high level QM data

Optimize semiempirical (AM1, MNDO) model to reproduce experiment or high level *ab initio* data

2) QM/MM

QM/MM nonbond interactions must be balanced with MM/MM interactions. The balance is often not present due to QM/MM electrostatic interactions based on QM determined charges, which can differ significantly from MM charges.

Optimize Lennard-Jones parameters on QM atoms to reproduce MM/MM model compound - water (or dimer) interaction energies or geometries.

Accuracy of QM/MM covalent connectivity(Gao et al., 1998; Reuter et al., 2000)

- 1) Compare geometry of QM/MM optimized structures with pure QM, pure MM or experiment.
- 2) Compare torsional energy surface with pure QM, pure MM or experiment
see nad_mm_surf_1a.inp and nad_qm_surf_1a.inp
- 3) Optimize bond, angle and dihedral parameters for QM/MM covalent connection to accurately reproduce target data in 1 and 2.

Steps 1 and 2 above are also a good approach to insure that the calculation is being setup properly.

Calculation of energy surface for chemical reaction of interest

1) Define reaction coordinate

2) Minimization alone

potential energy only (AM1 has free energy contributions)

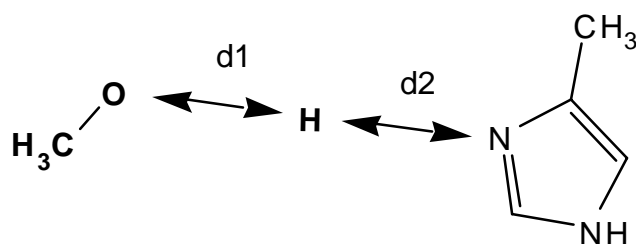
local minima problem

3) MD simulations to sample reaction coordinate (see `nad_pral_qm_dyn_surf_2d.inp`)

Free Energy perturbation or Umbrella sampling to obtain Free Energy

Systematically sample reaction coordinate

Extend simulations and test for convergence of energetics



D1: 1.0 - 3.00 in 0.05 increments

D2: 1.0 - 3.00 in 0.05 increments

From 2D free energy surface extract the 1D reaction coordinate

Comparison of reaction energy profiles in gas phase to solution phase to enzyme environment allows for detailed understanding of chemical catalysis by enzymes.

Contributions of individual amino acids may be determined by

1) recalculating the reaction energy with amino acids mutated

2) component analysis of Free Energy perturbation method is applied.

3) energetic analysis of extended simulations at selected points along the reaction coordinate.

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