Solvation and embedding schemes in quantum chemistry

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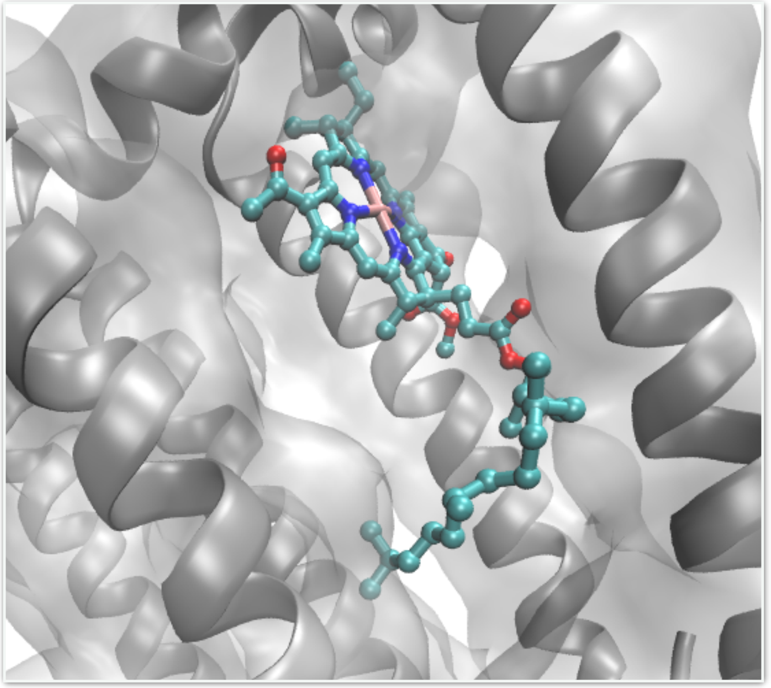
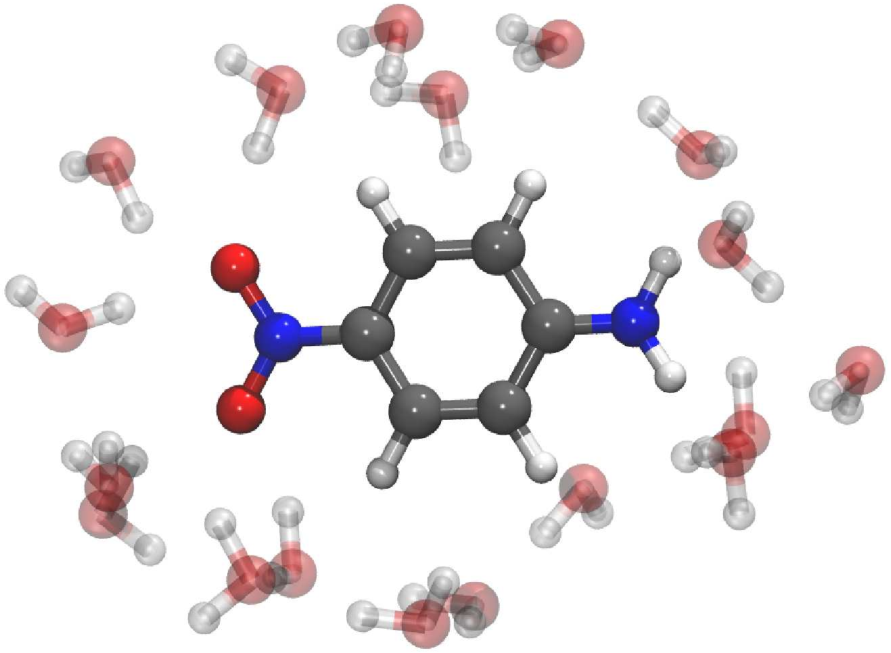
TMCS

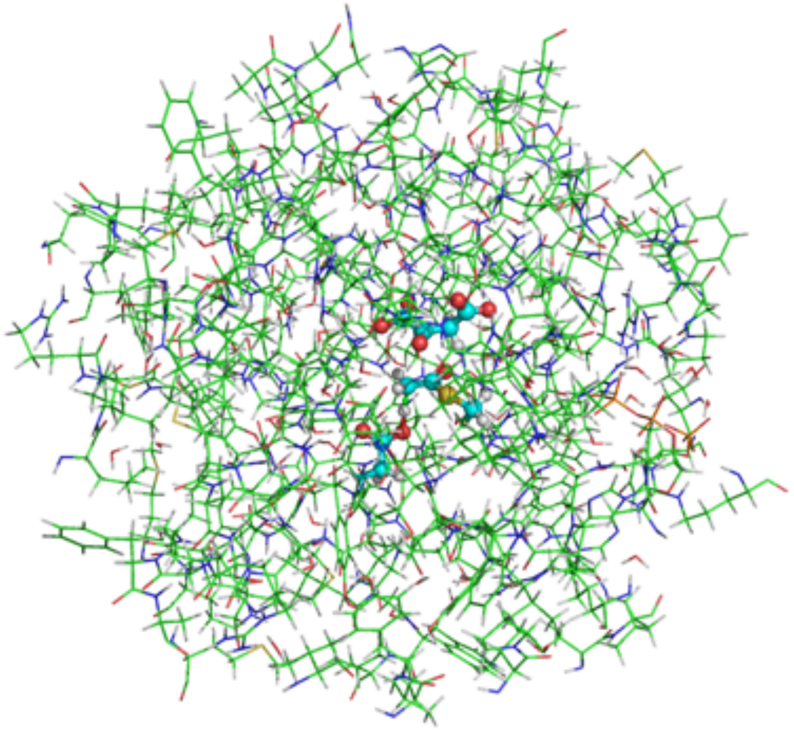
Lecture 1

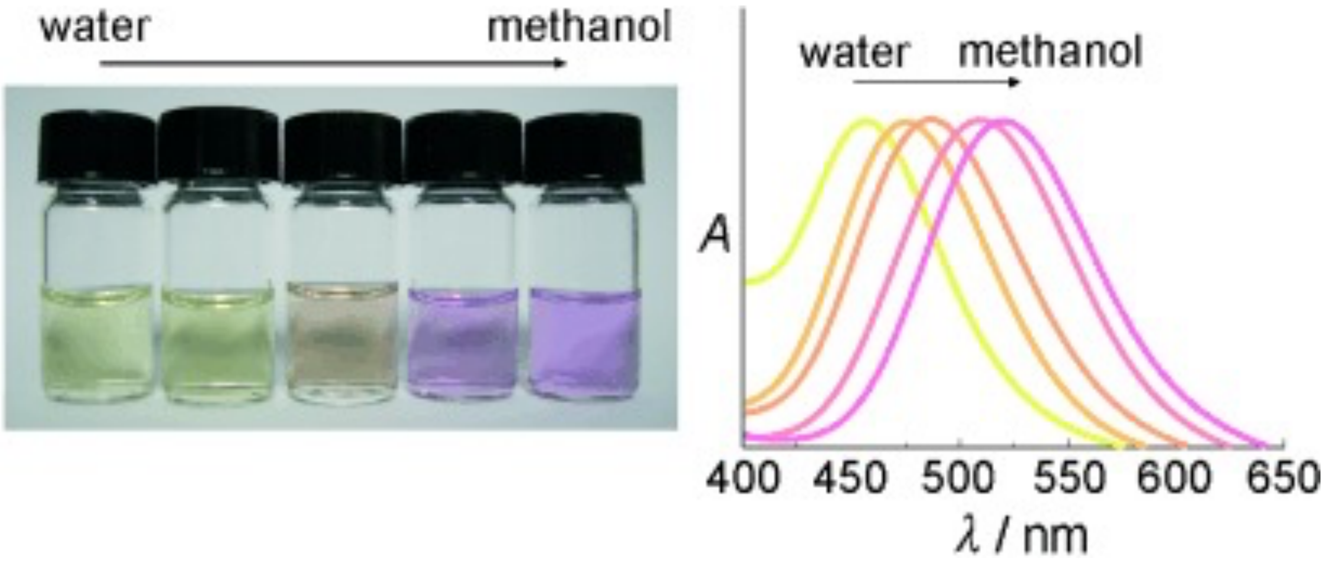
QM/MM and polarizable continuum methods

Motivation









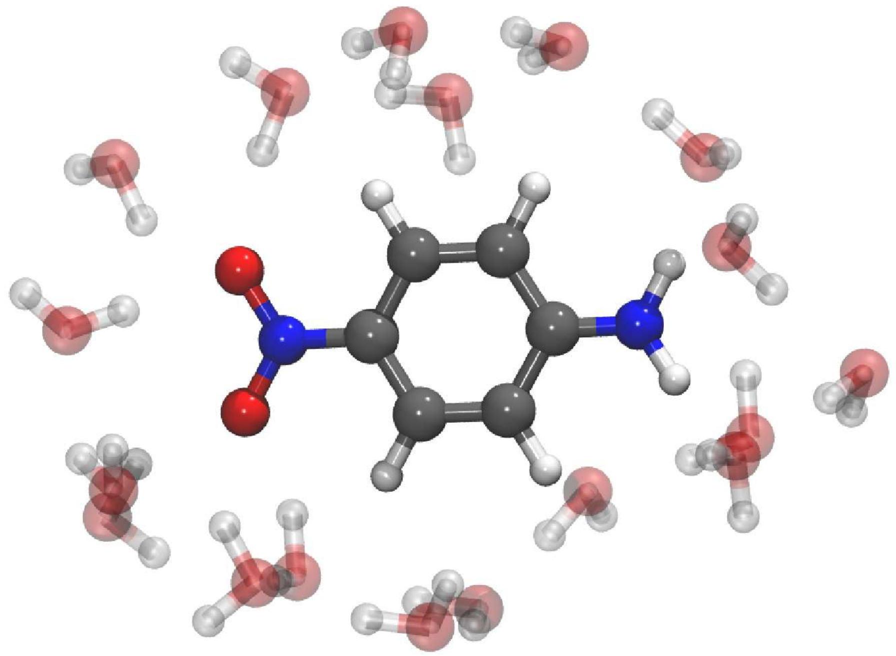
Díez *et al.* Angew. Chem. (2009) doi: 10.1002/anie.200806210

Overview

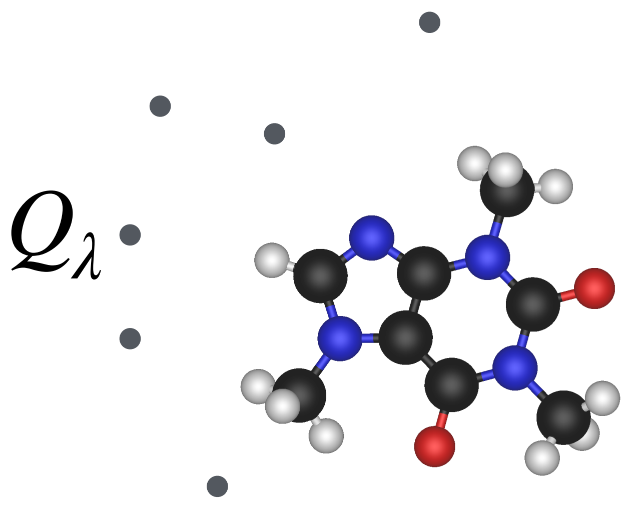
- Key physical effects
- QM/MM
- Polarisable continuum methods

Key physical effects in solvation

- Electrostatics
- Pauli repulsion
- Dispersion
- Dielectric screening



Electrostatics



$$\hat{H}_{\text{elec}} = -\sum_{i\lambda} \frac{Q_\lambda}{|\mathbf{R}_\lambda - \mathbf{r}_i|}$$

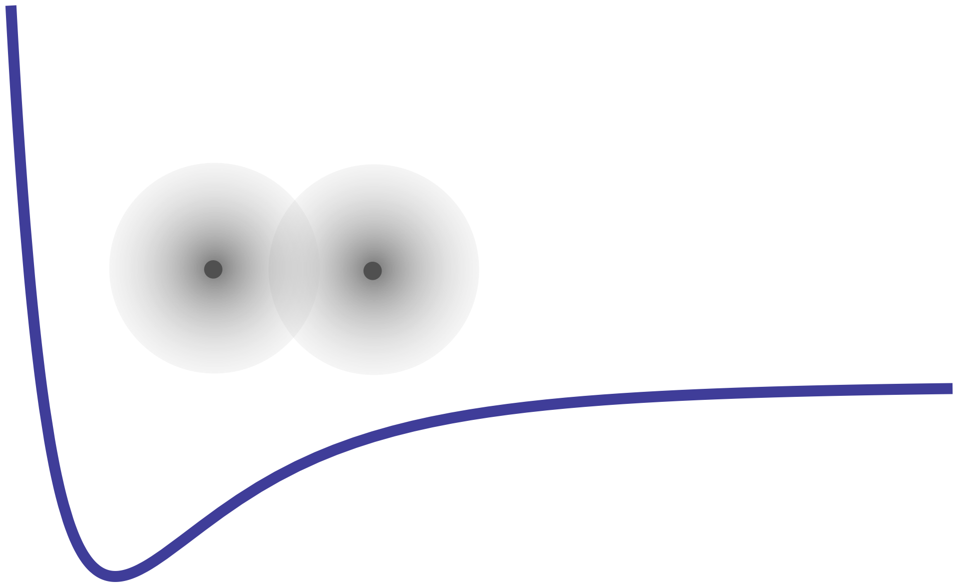
$$E = \langle \Psi | \hat{H}_{\text{elec}} | \Psi \rangle = \int \mathrm{d}\mathbf{r}\, V_{\text{elec}}(\mathbf{r}) \rho(\mathbf{r})$$

$$V_{\text{elec}}(\mathbf{r}) = -\sum_{\lambda} \frac{Q_\lambda}{|\mathbf{R}_\lambda - \mathbf{r}|}$$

- Alternatively, smooth charges can be used
- Multipoles higher than monopoles can be used (Anthony Stone’s book!)
- Polarization can be considered

Pauli repulsion

$$\hat{\mathcal{A}}|\Phi_\mathrm{A}\Phi_\mathrm{B}\rangle \neq |\Phi_\mathrm{A}\Phi_\mathrm{B}\rangle$$

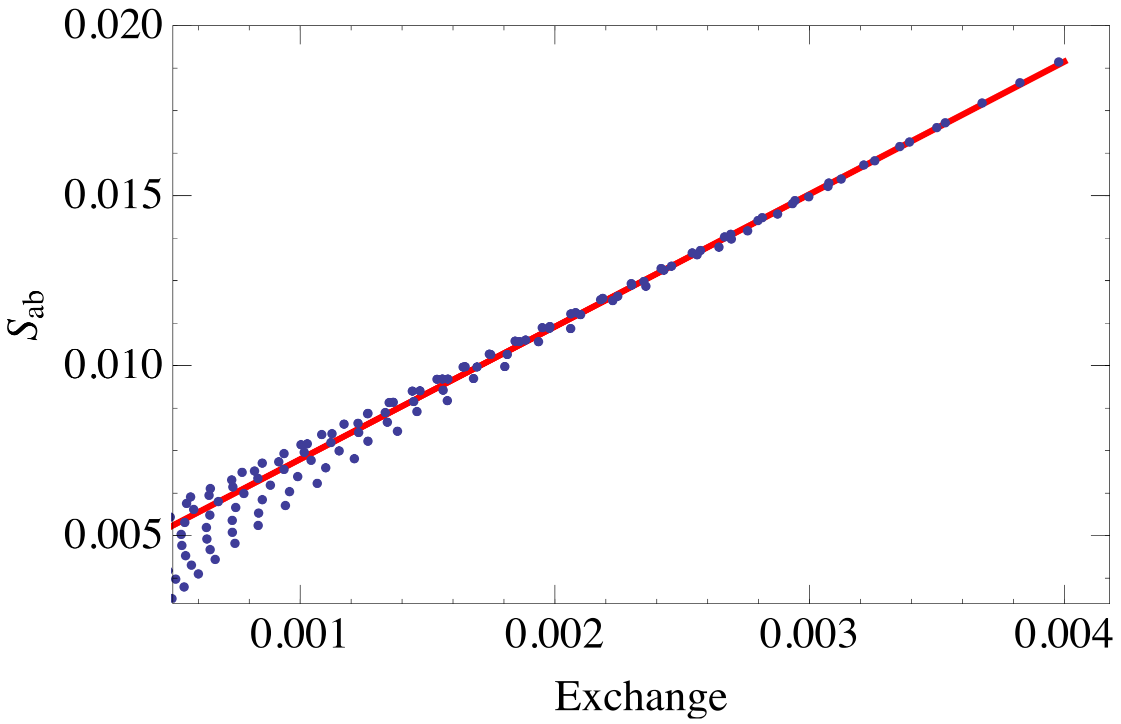


- A very simple model:

$$E_\mathrm{repl} = \kappa \int \mathbf{dr}\, \rho_\mathrm{mol}(\mathbf{r})\, \rho_\mathrm{solv}(\mathbf{r})$$

Wheatley, Price, Mol. Phys., **69**, 507 (1990)

- A repulsive interaction
- Probably about as important as electrostatics over all



A little calculation

- Suppose we have two identical one-electron atoms with Hamiltonians h_1, h_2 and solutions $h_i|\psi_i\rangle = E|\psi_i\rangle$ for $i = 1, 2$
- Dimer has Hamiltonian $H = h_1 + h_2 + V$, and $\langle\psi_1|\psi_2\rangle = S \in \mathbb{R}$
- Energy of product state $|\psi_1\psi_2\rangle$:

$$\langle\psi_1\psi_2|H|\psi_1\psi_2\rangle = \langle\psi_1\psi_2|h_1 + h_2 + V|\psi_1\psi_2\rangle = 2E + \langle V\rangle$$

- This state doesn't obey the Pauli principle, but we can fix that:

$$|\Psi\rangle = \tfrac{1}{2}(1 - p_{12})|\psi_1\psi_2\rangle$$

$$\frac{\langle\Psi|H|\Psi\rangle}{\langle\Psi|\Psi\rangle} = \frac{\langle\psi_1\psi_2|H(1 - p_{12})|\psi_1\psi_2\rangle}{\langle\psi_1\psi_2|1 - p_{12}|\psi_1\psi_2\rangle} = ?$$

A little calculation

- So we get

$$\frac{\langle \psi_1 \psi_2 | H(1 - p_{12}) | \psi_1 \psi_2 \rangle}{\langle \psi_1 \psi_2 | 1 - p_{12} | \psi_1 \psi_2 \rangle} = \frac{2E + \langle V \rangle - 2ES^2 - \langle V p_{12} \rangle}{1 - S^2} = 2E + \frac{\langle \bar{V} \rangle}{1 - S^2}$$

where $\langle \bar{V} \rangle = \langle V \rangle - \langle V p_{12} \rangle$

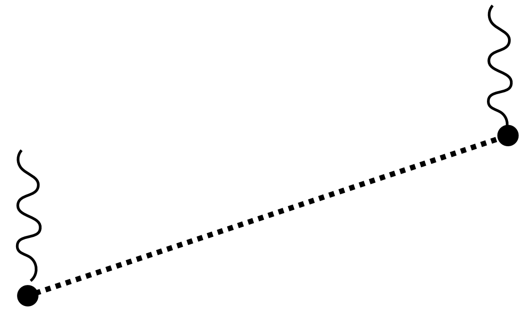
- Taylor expansion of $1/(1 - S^2)$ gives

$$\frac{\langle \psi_1 \psi_2 | H(1 - p_{12}) | \psi_1 \psi_2 \rangle}{\langle \psi_1 \psi_2 | 1 - p_{12} | \psi_1 \psi_2 \rangle} = 2E + \langle \bar{V} \rangle (1 + S^2 + \cdots)$$

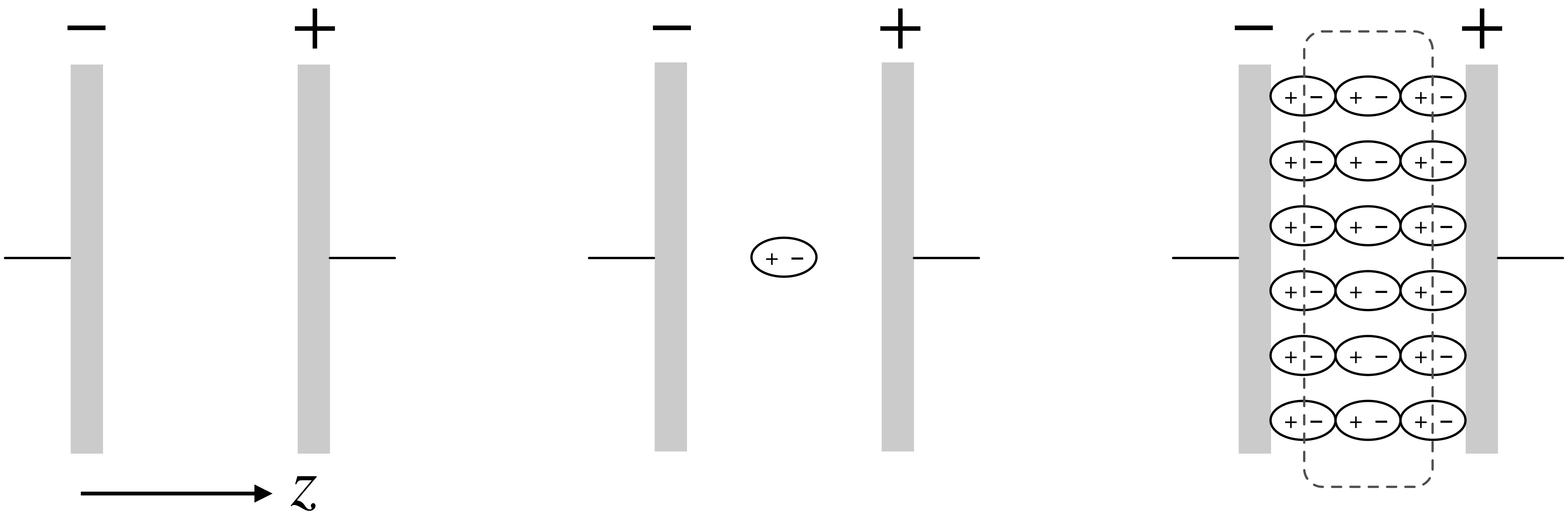
- So where V is repulsive, energy gets more positive as $\mathcal{O}(S^2)$

Dispersion

- Correlated fluctuations between molecule and solvent
- For ground-state energetics simplest to add $-C_6/R^6$ between every atom in molecule and solvent
- But this doesn't affect the state, doesn't include many-body dispersion effects, and has no effect on excitation energies



Dielectric screening



$$V(z) = fz$$

$$V(z) = fz/\varepsilon$$

- Interactions between charges are screened by a polarisable medium

- In an isotropic medium, characterized by dielectric constant ε

QM/MM

- Should be simple: electrostatic embedding with MM point charges
- But a few things need to be considered:
  - Other terms and full energy expression
  - Gradients wrt to QM and MM atom positions
  - Efficiency (there might easily be 10^4–10^5 charges)
  - Link atoms
  - Polarisable MM environment

The QM/MM energy

- QM and MM atoms positions will be (collectively) $\mathbf{R}^{\mathrm{QM}}$ and $\mathbf{R}^{\mathrm{MM}}$
- The MM energy is typically something like

$$U(\mathbf{R}^{\mathrm{MM}}) = U_{\mathrm{bonded}}(\mathbf{R}^{\mathrm{MM}}) + U_{\mathrm{nonbonded}}(\mathbf{R}^{\mathrm{MM}})$$

$$U_{\mathrm{nonbonded}}(\mathbf{R}^{\mathrm{MM}}) = \frac{1}{2}\sum_{\kappa\neq\lambda}\frac{Q_\kappa Q_\lambda}{R_{\kappa\lambda}} + \frac{1}{2}\sum_{\kappa\neq\lambda} V^{\mathrm{LJ}}_{\mathrm{t}(\kappa)\mathrm{t}(\lambda)}(R_{\kappa\lambda})$$

- Here $\mathrm{t}(\kappa)$ refers to the type of atom (eg alkyl carbon, alcoholic hydrogen, etc)
- QM Hamiltonian modified to include electrostatic coupling to MM:

$$H_{\mathrm{QM/MM}} = H_{\mathrm{QM}} - \sum_{i\lambda}\frac{Q_\lambda}{|\mathbf{R}_\lambda - \mathbf{r}_i|}$$

The QM/MM energy

- In practice just add a fixed potential to the core Hamiltonian

$$\mathbf{H}_0^{\mathrm{QM/MM}} = \mathbf{H}_0 + \mathbf{V}^{\mathrm{MM}}$$

where (for example in the AO basis) we have

$$V_{\mu\nu}^{\mathrm{MM}} = -\sum_{\lambda} Q_{\lambda} \left\langle \eta_{\mu} \middle| \, |\mathbf{R}_{\lambda} - \mathbf{r}|^{-1} \middle| \eta_{\nu} \right\rangle$$

- But this is just the form of the nuclear attraction integral, so always available

The QM/MM energy

- Finally the energy is put together as:

$$E^{\text{QM/MM}} = \langle \Psi | H^{\text{QM/MM}} | \Psi \rangle + U(\mathbf{R}^{\text{MM}}) + \sum_{A \in \text{QM}} \sum_{\lambda \in \text{MM}} V^{\text{LJ}}_{\text{t}(A)\text{t}(\lambda)}(R_{A\lambda})$$

this term includes the electrostatic part of the QM/MM interaction

QM/MM gradients

- First we consider the gradient with respect to a QM atom

$$\frac{\mathrm{d}E^{\mathrm{QM/MM}}}{\mathrm{d}X_A} = \frac{\mathrm{d}}{\mathrm{d}X_A}\langle\Psi|H^{\mathrm{QM/MM}}|\Psi\rangle + \frac{\mathrm{d}}{\mathrm{d}X_A}\sum_{\lambda\in\mathrm{MM}} V^{\mathrm{LJ}}_{\mathrm{t}(A)\mathrm{t}(\lambda)}(R_{A\lambda})$$

$$\frac{\mathrm{d}}{\mathrm{d}X_A}V^{\mathrm{LJ}}_{\mathrm{t}(A)\mathrm{t}(\lambda)}(R_{A\lambda}) = \frac{X_A - X_\lambda}{|\mathbf{R}_A - \mathbf{R}_\lambda|}V^{\mathrm{LJ}\,\prime}_{\mathrm{t}(A)\mathrm{t}(\lambda)}(R_{A\lambda})$$

- So this is very straightforward: a normal QM gradient plus simple derivatives of the pairwise interaction function

QM/MM gradients

- Next, gradient with respect to an MM atom:

$$\frac{\mathrm{d}E^{\mathrm{QM/MM}}}{\mathrm{d}X_\lambda} = \frac{\mathrm{d}}{\mathrm{d}X_\lambda}\langle\Psi|H^{\mathrm{QM/MM}}|\Psi\rangle + \frac{\mathrm{d}U(\mathbf{R}^{\mathrm{MM}})}{\mathrm{d}X_\lambda} + \frac{\mathrm{d}}{\mathrm{d}X_\lambda}\sum_{A\in\mathrm{QM}} V^{\mathrm{LJ}}_{\mathrm{t}(A)\mathrm{t}(\lambda)}(R_{A\lambda})$$

- All terms contribute, but the second is the standard MM gradient, and the last is just as we had on the previous slide

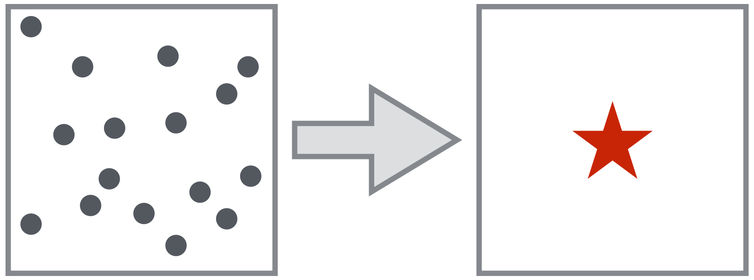
- The energy depends on the position of MM atoms (only) through the electrostatic interaction $\langle\Psi|H^{\mathrm{QM/MM}}|\Psi\rangle \leftarrow \mathrm{tr}\,\mathbf{D}\mathbf{V}^{\mathrm{MM}}$ so (assuming variational QM method)

$$\frac{\mathrm{d}}{\mathrm{d}X_\lambda}\langle\Psi|H^{\mathrm{QM/MM}}|\Psi\rangle = \mathrm{tr}\,\mathbf{D}\left\{\partial\mathbf{V}^{\mathrm{MM}}/\partial X_\lambda\right\}$$

where $$\left\{\partial\mathbf{V}^{\mathrm{MM}}/\partial X_\lambda\right\}_{\mu\nu} = Q_\lambda\left\langle\eta_\mu\middle|\frac{X_\lambda - x}{|\mathbf{R}_\lambda - \mathbf{r}|^3}\middle|\eta_\nu\right\rangle$$

Efficiency

- With cheap DFT or semi-empirical methods, the interaction is easily the bottleneck
- There are three basic techniques to speed it up:
  - Use interaction between MM atoms and atomic charges in QM region (but which charges? sensitivity on basis?)
  - Use some kind of multipole method
  - Do what every quantum chemist spends half their life doing, i.e. change the order of operations to contract early (with density for gradient and with MM charges for energy)



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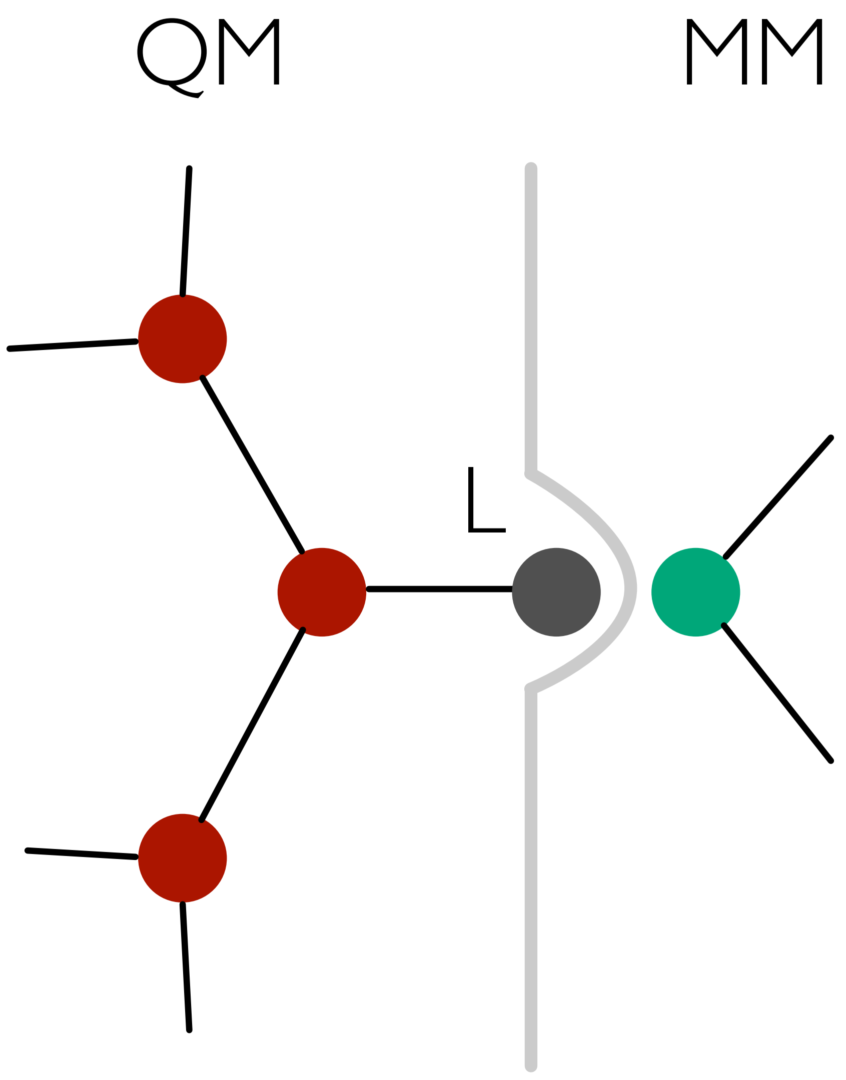
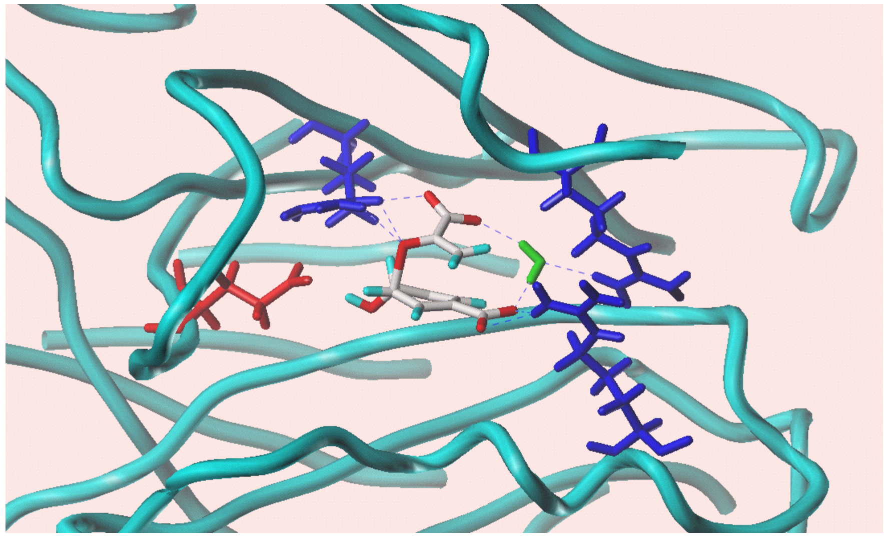
Link atoms

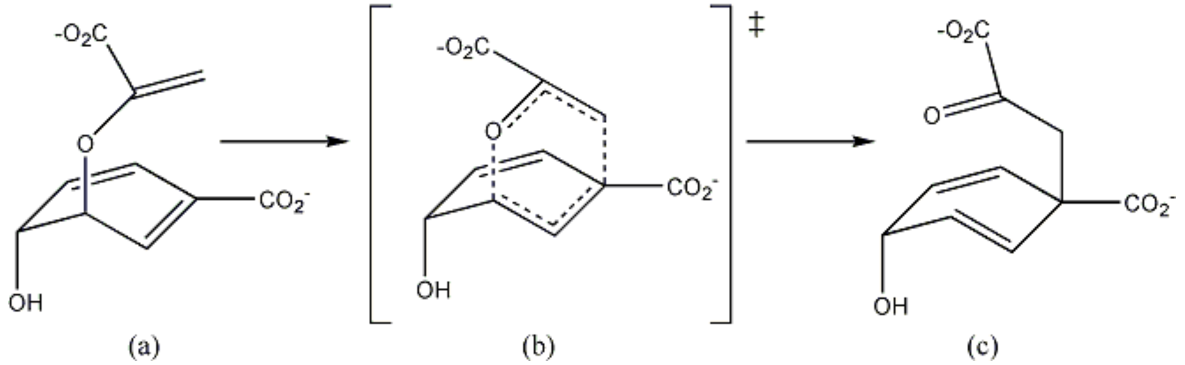


- Add link atom L to QM treatment
- Adds 3 additional degrees of freedom (L position) that are unphysical
- Charge on MM atom very close, so over polarises L
- L is usually hydrogen

If you need the details, Senn and Thiel, *Angew. Chem. Int. Ed.* **48** 1198 (2009) is a great place to start.

QM/MM in practice





Method	CM	PHBH
HF	28.3	36.7
B3LYP	10.2	8.4
LMP2	9.5	10.7
LCCSD(T0)	13.1	13.3
Experiment	12.7[a]	12.0[b]
		14.6[c]

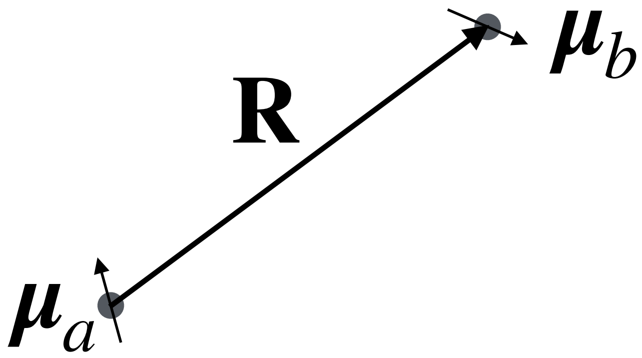
- Plus thousands of other studies
- Enzymes, solids, solvation in liquids, etc

[6] F. Claeyssens, J. N. Harvey, F. R. Manby, R. A. Mata, A. J. Mulholland, K. E. Ranaghan, M. Schütz, S. Thiel, W. Thiel, and H.-J. Werner, "High-accuracy computation of reaction barriers in enzymes", Angew. Chemie - Intl. Ed. **45**, 6856–6859 (2006).

Polarisable embedding

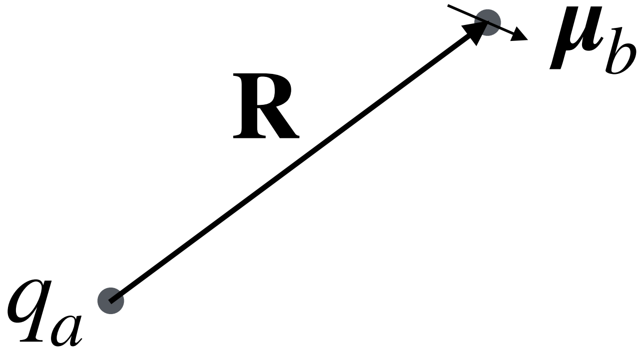
- In standard QM/MM the MM charges polarise the QM region, but not *vice versa*
- A polarisable environment should improve accuracy
- Simplest model: isotropic polarisable point dipoles (or Drude oscs)
- A quick reminder about electrostatics:

$$E = \boldsymbol{\mu}_a^T \mathbf{T}_2(\mathbf{R}) \boldsymbol{\mu}_b$$



$$\mathbf{T}_n(\mathbf{R}) = \underbrace{\nabla\nabla\cdots}_{n\text{ times}} \frac{1}{R}$$

$$E = q_a \mathbf{T}_1(\mathbf{R}) \boldsymbol{\mu}_b$$



$$\mathbf{T}_n(\mathbf{R}) \propto \frac{1}{R^{n+1}}$$

Polarisable embedding

- Electric field produced at position b by a charge at a: $\mathbf{F}_b = -q_a \mathbf{T}_1(\mathbf{R})$
- This induces a dipole at position b according to the polarisability α
- The total induction energy is

$$E = -\tfrac{1}{2}\alpha \mathbf{F}_b^T \mathbf{F}_b = -\frac{1}{2} q_a^2 \alpha \mathbf{T}_1^T(\mathbf{R}) \mathbf{T}_1(\mathbf{R}) \propto -\frac{1}{R^4}$$

- That concludes the analysis of a single molecule and a single polarisable point; next a molecule and a solvent

Polarisable embedding

- So we don't need to do the whole thing, but generalising the electric field at a site b from a single point charge to a density gives

$$\mathbf{F}_b = -\,q_a \mathbf{T}_1(\mathbf{R}) \qquad \longrightarrow \qquad \mathbf{F}_b = \int \mathrm{d}\mathbf{r}\, \rho(\mathbf{r})\, \mathbf{T}_1(\mathbf{r} - \mathbf{R}_b)$$

- So the induced dipole at b can be computed using AO integrals over $(\mathbf{r} - \mathbf{R}_b)/|\mathbf{r} - \mathbf{R}_b|^3$

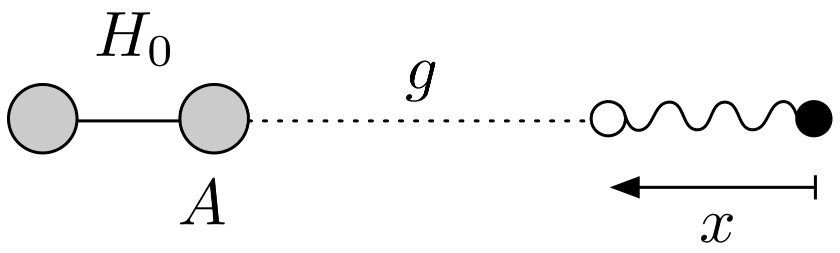
- … and these are the electric field integrals you need for all gradient theories

Polarisable embedding

- Next need to minimize the energy with respect both to parameters n the wavefunction and with respect to the magnitude of induced dipoles

- Papers about this look complicated because of interaction tensors, etc

- But fundamentally it's like this:



$$H(x) = H_0 + gAx + \frac{k}{2}x^2$$

$$E = \min_{x,\psi} \langle \psi | H(x) | \psi \rangle$$

The direct reaction field - exercise

$$H(x) = H_0 + gAx + \frac{k}{2}x^2 \qquad\qquad E = \min_{x,\psi} \langle\psi|H(x)|\psi\rangle$$

- Perturbative approximation – assume eigenstate $|0\rangle$ of H_0 not affected by polarisable site; minimize the energy

(hint: take the Hamiltonian, make expectation value with state $|0\rangle$, minimize this number w.r.t. x)

The direct reaction field - exercise

$$H(x) = H_0 + gAx + \frac{k}{2}x^2 \qquad E = \min_{x,\psi}\langle\psi|H(x)|\psi\rangle$$

- Perturbative approximation – assume eigenstate $|0\rangle$ of H_0 not affected by polarisable site; minimize the energy

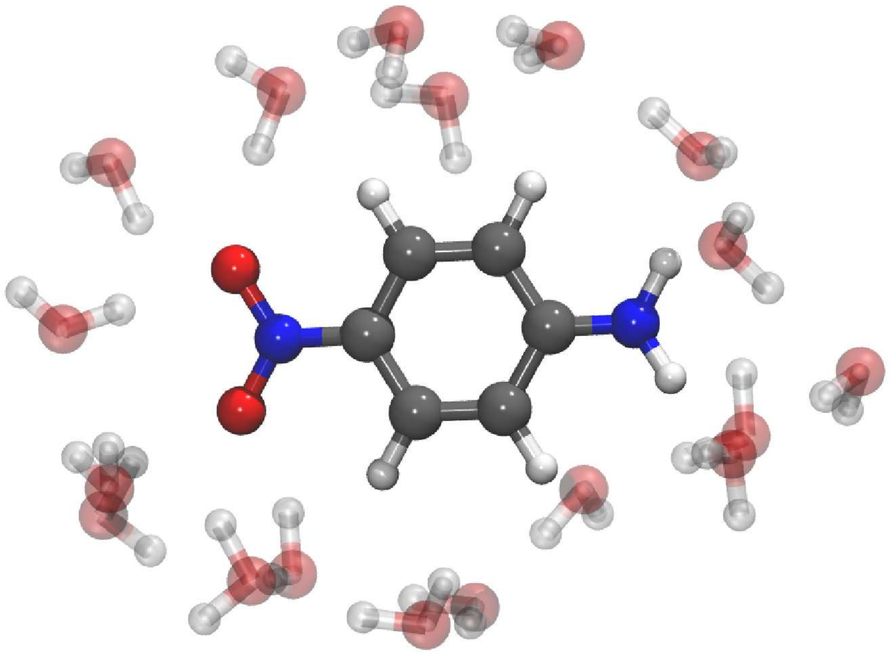
$$E_{\text{min}} = E_0 - \frac{g^2\langle 0|A|0\rangle^2}{2k}$$

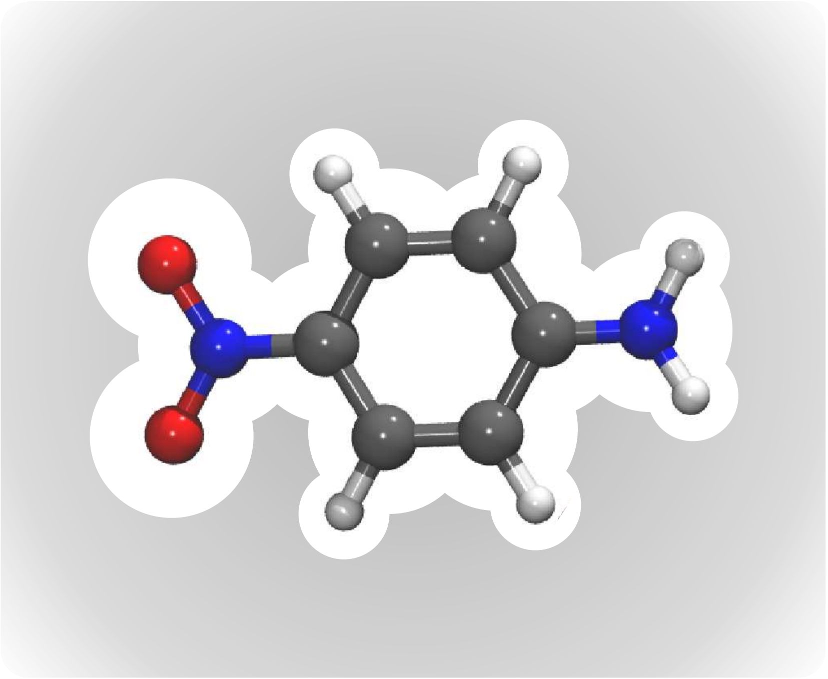
- If we believe the solvent response is instant, we could instead use the Hamiltonian

$$H_{\text{DRF}} = H_0 - \frac{g^2A^2}{2k}$$

- Not the same thing as doing it properly as $\langle A^2\rangle \neq \langle A\rangle^2$

Continuum solvation models





- Takes account of solvent structure
- Requires sampling
- Often with static charges, so no screening

- No need for sampling
- Ignores solvent structure
- Captures screening (but often ignores other effects)

Apparent surface charges

- Put the molecule in a cavity
- The molecule polarises the solvent, inducing a charge density in it
- The electrostatic potential of this charge distribution is modelled as the electrostatic potential of a charged layer at the surface
- In the end you need:
  - A QM/MM-like interaction with point charges on the cavity surface
  - A method to determine these surface charges

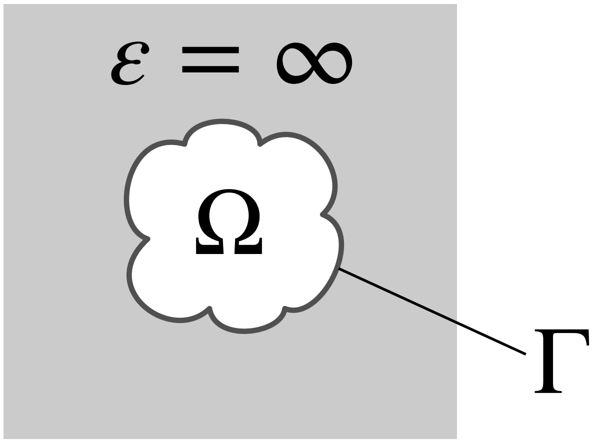
COSMO (conductor-like screening)

- Assume solvent is a perfect conductor ($\varepsilon = \infty$)…

solvent	ε
water	78.5
acetonitrile	36.6
hexane	1.9

$$f(\varepsilon) = \frac{\varepsilon - 1}{\varepsilon + x}, \quad 0 \leq x \leq 2$$

- Then the potential must vanish both in the solvent and at the surface



$$\rho_{\text{tot}} = \rho_{\text{mol}} + \rho_{\text{ind}}$$

$$\Phi_{\text{tot}} = \Phi_{\text{mol}} + \Phi_{\text{ind}}$$

A Klamt, G Schüürmann, *J. Chem. Soc. Perkin Trans.* **2** 799 (1993)

COSMO continued

- Induced density minimizes the total electrostatic energy
- Let

$$(\rho\,|\,\rho') = \int d\mathbf{r} \int d\mathbf{r}' \, \frac{\rho(\mathbf{r})\rho'(\mathbf{r}')}{|\,\mathbf{r}-\mathbf{r}'\,|} = \int d\mathbf{r}\, \Phi(\mathbf{r})\rho'(\mathbf{r}) \equiv (\Phi\rho')$$

- Then the total electrostatic energy is

$$E = \tfrac{1}{2}(\Phi_{\mathrm{tot}}\rho_{\mathrm{tot}}) = \tfrac{1}{2}(\Phi_{\mathrm{mol}}\rho_{\mathrm{mol}}) + (\Phi_{\mathrm{mol}}\rho_{\mathrm{ind}}) + \tfrac{1}{2}(\Phi_{\mathrm{ind}}\rho_{\mathrm{ind}})$$

- Minimizing:

$$\frac{\delta E}{\delta \rho_{\mathrm{ind}}} = \Phi_{\mathrm{mol}} + \Phi_{\mathrm{ind}} = 0 \quad \text{or} \quad \Phi_{\mathrm{ind}} = -\,\Phi_{\mathrm{mol}}$$

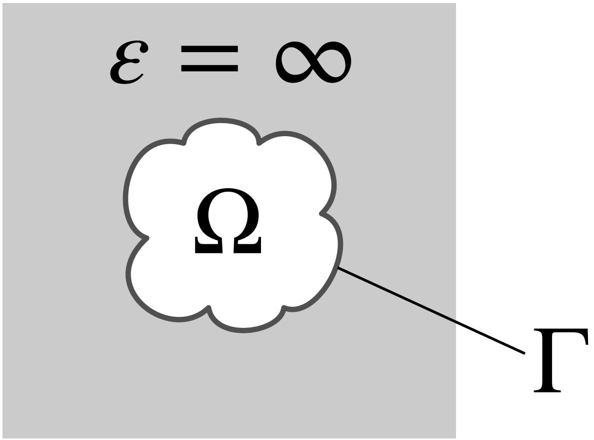
$$E = \tfrac{1}{2}(\Phi_{\mathrm{mol}}\rho_{\mathrm{mol}}) + \boxed{\tfrac{1}{2}}(\Phi_{\mathrm{ind}}\rho_{\mathrm{mol}})$$

COSMO continued

- The total electrostatic potential vanishes at the surface*

$$\Phi_{\mathrm{tot}}(\mathbf{s}) = \Phi_{\mathrm{mol}}(\mathbf{s}) + \Phi_{\mathrm{ind}}(\mathbf{s}) = 0 \quad \forall \mathbf{s} \in \Gamma$$

$$\Phi_{\mathrm{ind}}(\mathbf{s}) = -\,\Phi_{\mathrm{mol}}(\mathbf{s}) \quad \forall \mathbf{s} \in \Gamma$$

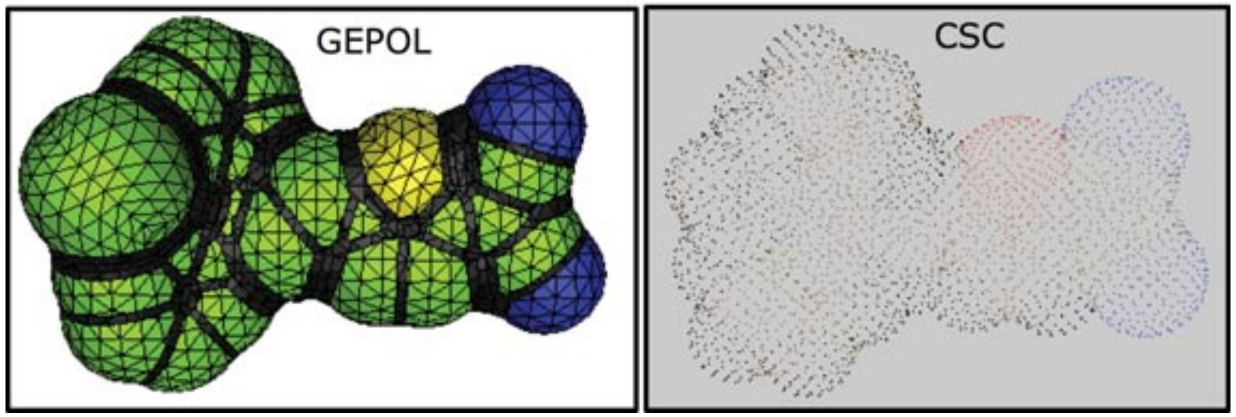


- We only need the electrostatic potential in Ω to be correct

- This can be achieved by representing $\Phi_{\mathrm{ind}}(\mathbf{s})$ as the Coulomb potential of an apparent surface charge $\sigma(\mathbf{s})$

*Strictly the electric field vanishes at the conductor surface, but electric field is gradient of potential, so the potential is a constant; and the boundary condition that the potential vanishes at large distance gives $\Phi_{\mathrm{tot}}(\mathbf{s}) = 0$ on surface

Surface charge models



B Mennucci, *WIREs* **2** 386 (2012)

- Discretize the surface
- Determine surface charges $\boldsymbol{\sigma_i}$
- Add QM/MM-type potential to QM Hamiltonian

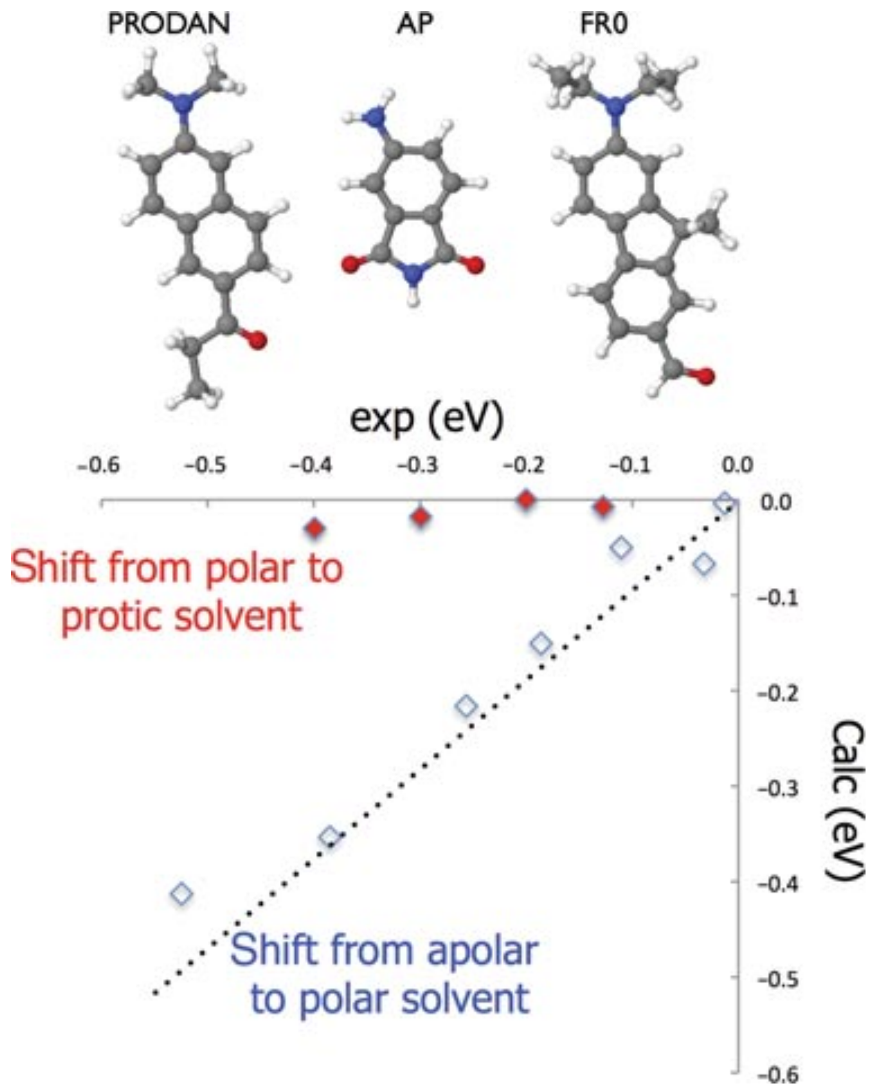
$$\hat{H}_{\text{solv}} = -\sum_{i\lambda} \frac{\sigma_i}{|\mathbf{s}_i - \mathbf{r}_\lambda|}$$

- Calculate total energy at the end using

$$E = \langle\Psi|\hat{H}_{\text{mol}}|\Psi\rangle + \frac{1}{2}\langle\Psi|\hat{H}_{\text{solv}}|\Psi\rangle$$

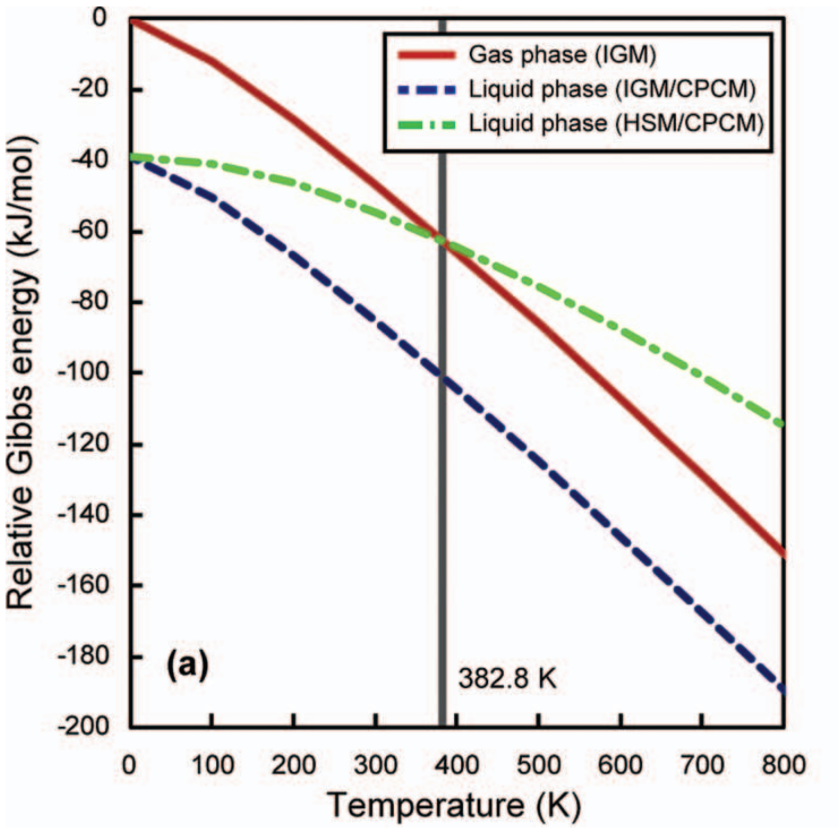
Continuum solvation in operation

solvatochromism



B Mennucci, *WIREs* **2** 386 (2012)

condensed phase properties



H Nakai and A Ishikawa,
J. Chem. Phys. **141** 174106 (2014)

Summary

- Many effects couple a molecule to its chemical environment
- We have focused on the simplest, and seen the two principal ways of treating electrostatic and screening effects through QM/MM and continuum solvation models
- In the next lecture we'll look more deeply into what happens when you partition a quantum system, and I'll tell you a bit about modern quantum embedding methods