Name:_____

CHEMISTRY 4021/8021
MIDTERM EXAM 3 — SPRING 2013 — KEY

Q1) Compare and contrast continuum and explicit solvent models. What strengths and weaknesses are associated with each? Give an example of a study where one model would clearly be more appropriate than the other. (30 points)

The greatest advantage of a continuum solvent model is the degree to which it introduces electrostatic (and possible non-electrostatic) interactions between the solute and the solvent at very low cost (since no new atoms are introduced). For quantum mechanical calculations, this is particularly useful, in so far as polarization of the solute wave function (or density) can arise from first principles. The continuum model assumes full equilibration of the solvent with the solute, which can be a drawback when dynamical behavior in solution would make the equilibrium assumption inaccurate. Separation of the continuum model into dielectric responses having different time scales is possible, however (e.g., for computing solvatochromic effects). A disadvantage of the continuum model is that it is impossible to learn anything about the atomistic behavior of the solvent, as the solvent is not represented explicitly. In addition, charge transfer cannot take place from the solute to the solvent. Finally, the continuum model can be rather sensitive to the paramaterization of variables like the solute atomic radii that define where the solute ends and the solvent begins (such a sharp boundary is moreover a rather severe approximation, justified only by its efficiency).

In some sense, the explicit solvent model has complementary strengths and weaknesses to the continuum. The full representation of a complete solvent is very expensive, even with tricks like periodic boundary conditions, so classical simulations are far more common than quantum mechanical ones, although hybrid models are also possible. Achieving equilibrium (so that accurate averages over phase space can be computed) can also be time consuming, and there is no guarantee that a given sampling scheme will be ergodic. However, explicit solute-solvent interactions (e.g., hydrogen bonding) can be fully characterized.

One can imagine a number of examples where one model would be better than another. Predicting logP values for 10^6 drug database molecules would clearly be impossible for an explicit model but just fine for a continuum model. Studying the role of solvent-solute hydrogen bonding in the conformational equilibrium of 1,2-ethanediol in water and chloroform would clearly need explicit simulations to model the hydrogen bonding interactions accurately. Many other answers are possible.

Q2) Write down a Hamiltonian operator for a QM/MM calculation in which the boundary between the two regions does not cut any covalent bonds. Define all symbols. If you were to use your operator in a Monte Carlo simulation of a quantum solute in a periodic box of classical chloroform molecules, explain what would be involved in a single Monte Carlo step. What would change if you were interested in modeling an excited electronic state of the solute? (40 points)

$$\begin{aligned}
\left\langle \Psi \middle| H_{\text{complete}} \middle| \Psi \right\rangle &= \left\langle \Psi \middle| H_{\text{QM}} \middle| \Psi \right\rangle + \left\langle \Psi \middle| H_{\text{MM}} \middle| \Psi \right\rangle + \left\langle \Psi \middle| H_{\text{QM/MM}} \middle| \Psi \right\rangle \\
&= \left\langle \Psi \middle| \sum_i^N -\frac{1}{2}\nabla_i^2 - \sum_i^N \sum_k^K \frac{Z_k}{r_{ik}} + \sum_{i<j} \frac{1}{r_{ij}} + \sum_{k<l} \frac{Z_k Z_l}{r_{kl}} \middle| \Psi \right\rangle + \langle \Psi | \Psi \rangle H_{\text{MM}} \\
&\quad + \left\langle \Psi \middle| -\sum_i^N \sum_m^M \frac{q_m}{r_{im}} \middle| \Psi \right\rangle + \langle \Psi | \Psi \rangle \sum_k^K \sum_m^M \left[\frac{Z_k q_m}{r_{km}} + 4\varepsilon_{ij} \left(\frac{\sigma_{km}^{12}}{r_{km}^{12}} - \frac{\sigma_{km}^{6}}{r_{km}^{6}} \right) \right] \\
&= \left\langle \Psi \middle| \sum_i^N -\frac{1}{2}\nabla_i^2 - \sum_i^N \sum_k^K \frac{Z_k}{r_{ik}} - \sum_i^N \sum_m^M \frac{q_m}{r_{im}} + \sum_{i<j} \frac{1}{r_{ij}} + \sum_{k<l} \frac{Z_k Z_l}{r_{kl}} \middle| \Psi \right\rangle \\
&\quad + H_{\text{MM}} + \sum_k^K \sum_m^M \left[\frac{Z_k q_m}{r_{km}} + 4\varepsilon_{ij} \left(\frac{\sigma_{km}^{12}}{r_{km}^{12}} - \frac{\sigma_{km}^{6}}{r_{km}^{6}} \right) \right]
\end{aligned}$$

where i and j run over N QM electrons, k and l run over the K nuclei in the QM fragment, and m runs over the M molecular mechanics atoms. The second equality simply expands the QM Hamiltonian into its usual individual terms (electronic kinetic energy, electron-nuclear attraction, electron-electron repulsion and, nuclear-nuclear repulsion. The terms having no dependence on the electronic coordinates—H_{MM}, the QM-nuclei/MM-atom electrostatic interactions, and the Lennard-Jones interactions—may be taken outside of expectation value integrals, which are then simply one by normalization of the wave function. The third equality simply collects terms together in a convenient fashion.

One MC step would involve moving either the solute or a solvent (or an atom thereof, if the molecules are taken to be flexible), evaluating the energy expression (which, unfortunately, must be evaluated *in full*, for the QM part, not just as a change associated only with the moved solvent molecule, if it *was* a solvent molecule), compare the energy to a Boltzmann probability function, and accept or decline the step appropriately.

For an excited electronic state, the model would need to use some excited state QM method to determine the wave function, e.g., CIS (reasonably simple to express), TD-DFT (not a wave function, per se, but operationally similar), EOM CCSD, etc.

Q3) What is a primary kinetic isotope effect? Computationally, what is required to compute the primary kinetic isotope effect for a given reaction? Does quantum mechanical tunneling *increase* or *decrease* a primary isotope effect? For a reaction where tunneling plays no role, would you expect a primary kinetic isotope effect computed at the *ab initio* Hartree-Fock level to be too large or too small (justify your answer)? (30 points)

A primary kinetic isotope effect (KIE) is the ratio of rate constants for a reaction involving making or breaking a bond that varies in isotopic substitution of one of the two atoms in the bond. The KIE is reported as

$$\frac{k_{\text{light}}}{k_{\text{heavy}}} = \frac{\dfrac{Q^{\ddagger}_{\text{light}}}{Q_{\text{R,light}}} e^{-\Delta V^{\ddagger}_{\text{light}} / k_{\text{B}}T}}{\dfrac{Q^{\ddagger}_{\text{heavy}}}{Q_{\text{R,heavy}}} e^{-\Delta V^{\ddagger}_{\text{heavy}} / k_{\text{B}}T}}$$

$$= \frac{Q^{\ddagger}_{\text{light}}}{Q^{\ddagger}_{\text{heavy}}} \frac{Q_{\text{R,heavy}}}{Q_{\text{R,light}}} e^{-\left(\Delta \text{ZPVE}^{\ddagger}_{\text{light}} - \Delta \text{ZPVE}^{\ddagger}_{\text{heavy}}\right) / k_{\text{B}}T}$$

From a theoretical perspective, isotope effects are fairly trivially computed. The stationary points on the PES and their electronic energies are independent of atomic mass, as are the molecular force constants. Thus, one simply needs to compute the isotopically dependent zero-point energies and translational, rotational, and vibrational partition functions, and evaluate the above equation.

Tunneling *increases* a KIE since light atoms tunnel more effectively than heavy atoms.

If tunneling plays no role, an HF calculation would be expected to *over*estimate a KIE, because HF theory systematically overestimates frequencies, and hence also zero-point energies, which will make the argument of the exponential a larger, positive value above.