Solvation in the Cramer-Truhlar Groups

Developing solvation models that permit the accurate study of dynamical processes in aqueous and nonaqueous solution

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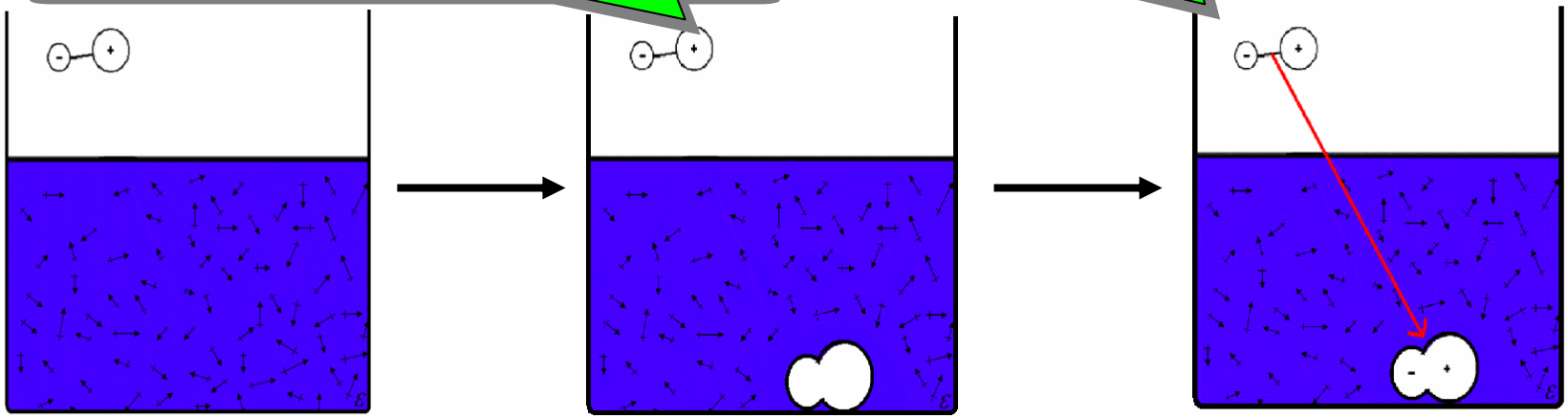
What is solvation?

The process of moving a molecule from the gas phase to a condensed phase.

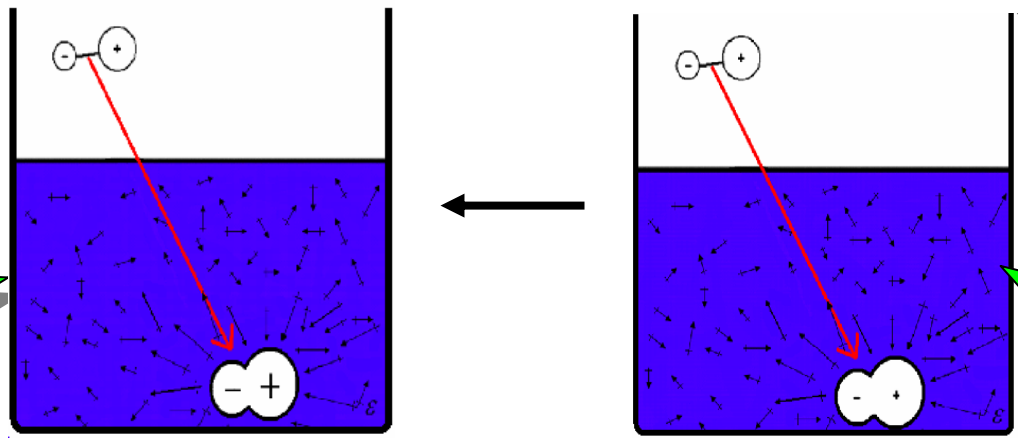
A solute shaped cavity of vacuum is introduced into the solvent.

The solute charge density is placed in the solute cavity.



The solvent molecules reorient and polarize in response to the solute charge density

The solute polarizes in response to the solvent polarization



Objective

To develop a simple and general model to predict the solubility of high-energy compounds in binary supercritical solvents

Milestones

1. Develop a simple and general solvent model to predict solvent properties at 298 K for a broad variety of compounds including ions in a broad variety of solvents
2. Extend the model to apply to a broad range of temperatures

Work In Progress

1. Extend our temperature dependent solvation model (SM6T) to handle *N*-containing compounds and multiple solvents
2. Modify the model to work with binary solvents
3. Extend the model to apply to a range of pressures
4. Improve the accuracy of the model for ionic compounds in non-aqueous solvents

Solvation Model 6 (SM6)

SM6 calculates aqueous solvation free energies based on gas or liquid-phase optimized geometries.

$$\Delta G_S^\circ = \Delta G_{ENP} + G_{CDS}$$

ENP: Electronic, Nuclear, Polarization

CDS: Cavitation, Dispersion, Structure

Change in the solute free energy due to electrostatic interactions between the solute and the bulk solvent and distortion of the solute's electronic structure in solution

The solvent is modeled as a dielectric continuum.

Non-bulk electrostatic contributions to the free energy of hydration: first solvation shell effects

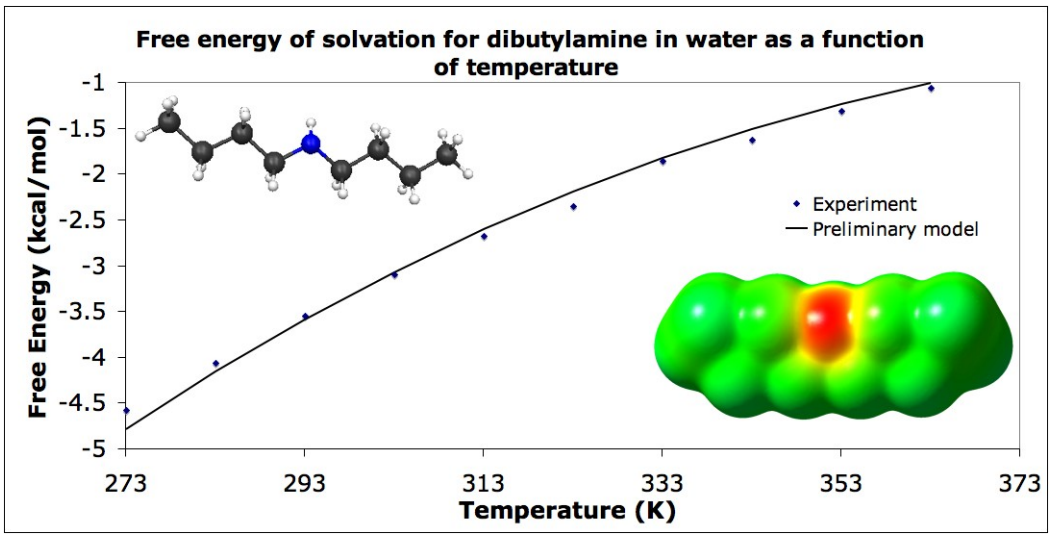
The G_{CDS} term is a parameterized term intended to minimize the deviation between the predictions and experiment.

It involves atomic surface tensions.

Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. *J. Chem. Theory Comput.* **2005**, *1*, 1133

Temperature Dependence of Implicit Solvation Models

- Implicit solvation models can be used to predict free energies of partitioning between different phases
- However, the temperature dependence of the solvation free energy has typically not been addressed with such models
  ⇒ Biological processes occurring at basal body temperature are often modeled with room-temperature data
- We have developed a solvation model with temperature dependence (SM6T)
- We are developing a model to treat a wide range of solutes and solvents of biological importance including olive oil and Caco-2 cell membranes
- We are applying the model to study the neurochemistry of polyamines. In particular, we are investigating the solution phase structure and charge of putrescine, spermidine, spermine, and their metabolites



Predicting Partition Coefficients for Modeling Bioavailability of Drugs

Important pharmacologic applications

- Brain-air partition coefficients correlate well with oil/air partition coefficients
- The passage of drugs through the blood-brain barrier correlates with permeability of Caco-2 cell membranes

» We develop descriptors that characterize the Caco-2 cell membrane and olive oil in order to estimate first-solvation-shell effects on cell membrane permeabilities and partitioning effects

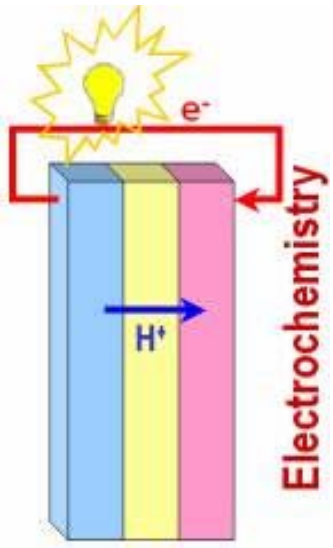
Prediction of the biological activity of drug candidates using partition coefficients leads to

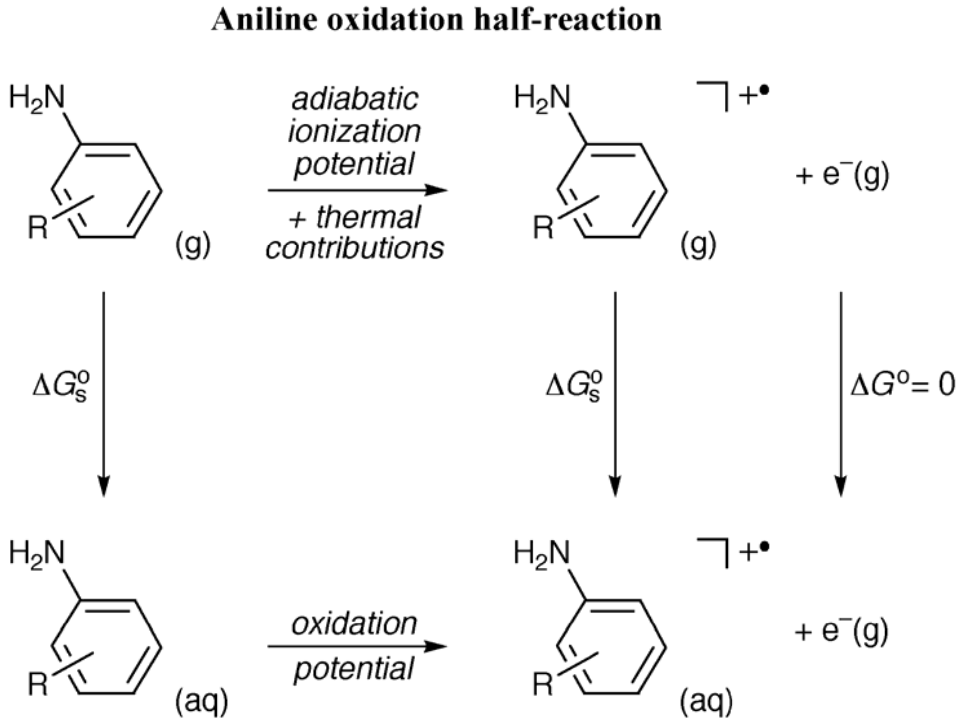
⇒ Reduced use of laboratory test subjects

⇒ Faster drug development

Note: A key variable controlling bioavailability of potential drug molecules is their apparent permeability across Caco-2 cell membranes. Physicochemical models for their permeability depend, inter alia, on the molecular volume and the partitioning of the molecules between aqueous and lipid-like phases.

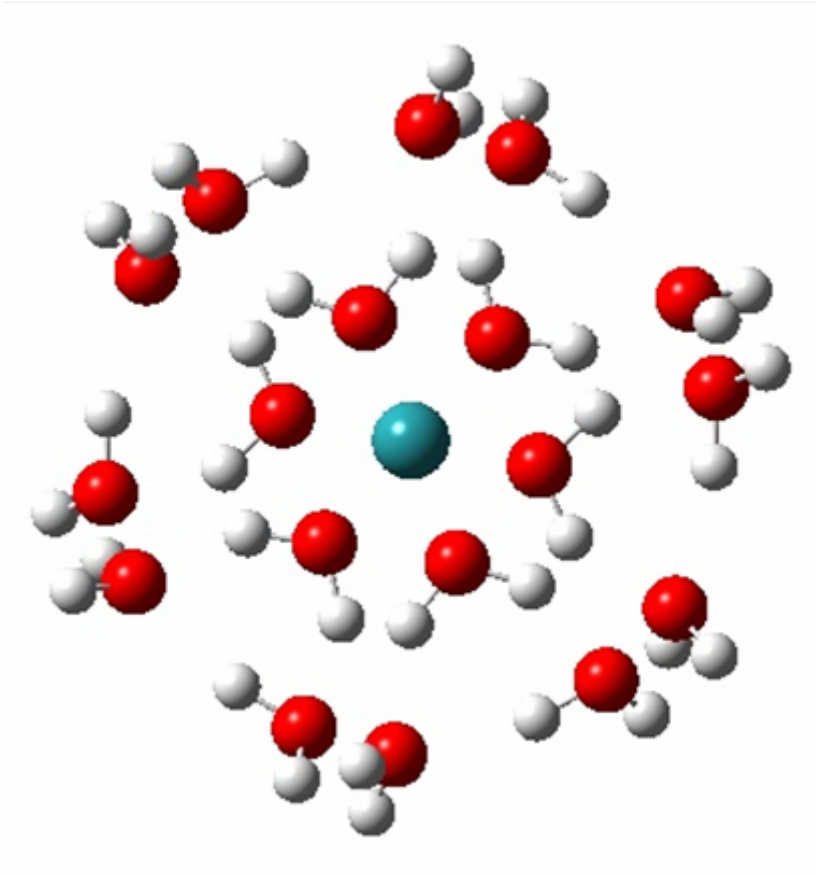
Computational Electrochemistry





Many chemical reactions include steps where a single electron is transferred, actually or formally, from one reacting partner to another, resulting in oxidation or reduction. Such reactions are important in environmental chemistry, where many strategies for cleaning up contaminated soils and other media involve oxidations or reductions of contaminants.

Theoretical Prediction of Redox Potentials

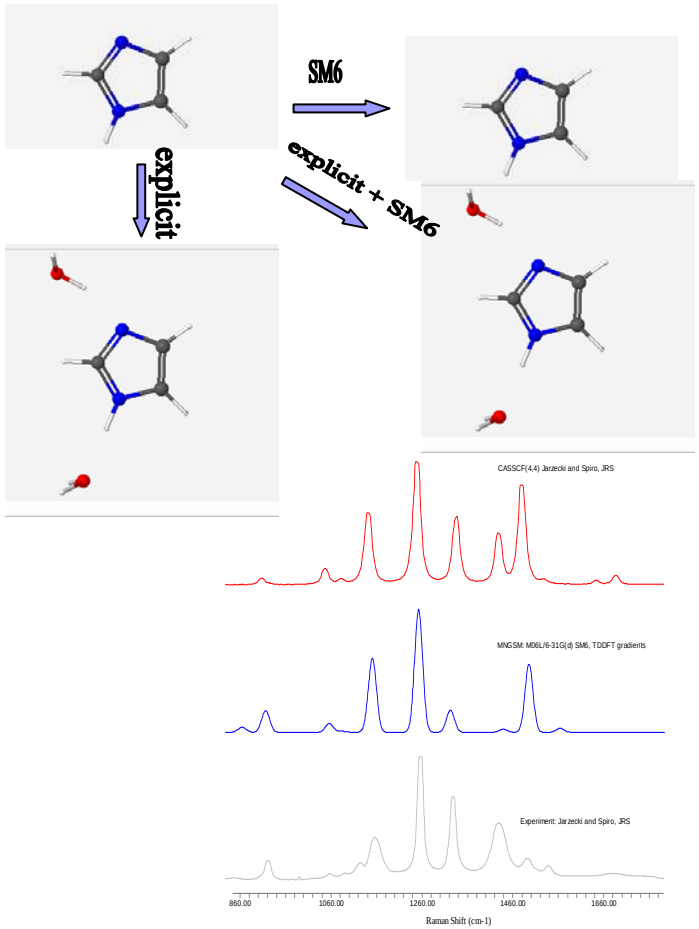


Our most recent study in this field showed that accurate calculation of the $Ru^{3+}|Ru^{2+}$ potential in aqueous solution requires that the cations be surrounded by continuum solvent with the explicit quantum chemistry treatment of up to 18 water molecules.

Simulation of Resonance Raman Spectra Using Consistent Excited-State Gradients with Inclusion of Solvent Effects on Gradients and Vibrational Frequencies

Jonathan Smith, Donald G. Truhlar, and Christopher J. Cramer

- Resonance Raman spectroscopy can be used to probe molecular structure and excited-state dynamics in solution. Imidazole is a good test case because of the strong influence of solvent on spectra.
- To obtain maximal information from resonance Raman spectra, we couple this work to electronic structure calculations that can be used to generate a simulated resonance Raman spectrum. Close agreement between the simulation and experiment validates the theoretical treatment and permits a closer examination of the detailed molecular conformation, electronic structure, and molecular interactions revealed by the computation. Part of this calculation requires accurate prediction of solvent shifts of vibrational frequencies and the corresponding impact on Hessians.
- We have sought to develop a consistent approach that includes explicit and implicit solvent as well as the use of new DFT functions coupled to TDDFT to provide a consistent treatment of the ground state and resonant excited state combining explicit and implicit solvation models. We are applying the SM6 solvation model coupled with the M06-L local functional as executed in the MN-GSM/MN-GFM local Minnesota versions of *Gaussian 03*.*



Imidazole resonance Raman: Experiment** and theory

*C. P. Kelly, C. J. Cramer and D. G. Truhlar, SM6: A Density Functional Theory Continuum Solvation Model for Calculating Aqueous Solvation Free Energies of Neutrals, Ions, and Solute Water Clusters, *J.Chem. Theory Comput.*, **2005**, 1, 1133-1152.

Jarzecki, A. A.; Spiro, T. G. *Journal of Raman Spectroscopy* **2001, *32*, 599.