

Three-Year Progress Report: NSF Research April 7, 2007

This document summarizes some of the progress made on research supported in whole or in part by NSF over the past three years in the Truhlar group. The work in this report may be classified into six areas: (i) enzyme kinetics, (ii) quantum photochemistry, (iii) density functional theory, (iv) computational thermochemistry, (v) converged quantum dynamics, and (vi) molecular modeling of solvation, electrostatics, molecular mechanics, condensed-phase reaction dynamics, electrochemistry, and quantum wells. This summary focuses on the most outstanding themes and highlights. Details of this work and names of researchers and collaborators are provided in the full publications (see separate list of publications).

Enzyme kinetics. In recent years we have made significant progress in understanding how enzymes work and in incorporating quantum mechanical effects into enzyme kinetics. The incorporation quantum effects has in practice constituted a major stride forward in that we have successfully developed and applied methods for incorporating both quantized vibrational energies of a large number of active site modes and also multidimensional tunneling, both in the context of an ensemble average over reaction paths, and this has allowed us to explain several kinetic isotope effects. (The extension of multidimensional tunneling methods to enzymes was entirely supported by NSF, but it provides an example of leverage since it builds on our group's work in applying variational transition state theory with well validated multidimensional-tunneling transmission coefficients to gas-phase reactions, which is supported by DOE.) Because we include quantum effects on more than one particle, we can predict secondary as well as primary kinetic isotope effects, and in one case we predicted an unmeasured KIE that was later confirmed by experiment. There are no other available methods with this capability at the present time.

A particularly dramatic example of an intriguing problem in the temperature dependence of kinetic isotope effects is the observation that, even when the energy of activation is large, the kinetic isotope effect is often (surprisingly) nearly independent of temperature. We studied one such case, and our calculations yielded a kinetic isotope effect that is almost independent of temperature, which agrees with

experiment for the system studied. Furthermore our calculations showed how variational effects on the location of the dynamical bottleneck can partially affect the “natural” or expected temperature dependence. In addition we found that the enthalpy of activation is considerably lower than the free energy of activation, again in good agreement with experiment, showing that our formalism of ensemble-averaged variational transition state theory (developed under NSF support) can handle the enzyme-specific entropic contributions quite well. We extended the treatment of dihydrofolate reductase to the hyperthermophilic enzyme from the bacterium *Thermatoga maritima*, and we showed that the reaction catalyzed by this enzyme is dominated by quantum mechanical tunneling and is promoted by both inter- and intramonomeric correlated motions.

We also analyzed the origin of convex Arrhenius plots, which provides another intriguing issue in the temperature dependence of enzyme-catalyzed reactions, but is also more general.

Quantum Photochemistry–Electronic Structure and Potential Energy Surfaces. We have developed promising methods for treating electronically excited potential energy surfaces and their couplings, in particular the fourfold way for generating diabatic potential energy surfaces and their couplings. The fourfold way allows one to calculate diabatic surfaces and their couplings directly without following a path through configuration space. This is very powerful for obtaining surfaces and couplings for dynamics because the non-Born-Oppenheimer coupling is a smooth scalar function in the diabatic representation, that is, direct diabatization eliminates the need to work with nonsmooth (even singular) vector nonadiabatic couplings. We have now employed the fourfold way successfully for the photodissociation of ammonia, bromoacetyl chloride, bromochloromethane, and the reaction of hydroxyl radical with dihydrogen, which yields water and a hydrogen atom. Three of the four systems were selected because of high-quality and challenging experimental data that is available. The ability of the fourfold way to map out global coupled surfaces and their couplings allows a high level of detail in modeling photochemical dynamics with converged sampling of initial conditions. For example, we have already mapped out the multidimensional conical intersection seam in ammonia in unprecedented detail. Furthermore, in bromoacetyl chloride the surfaces and couplings we obtained, even before calculating

the dynamics, have suggested an alternative interpretation of the experiments.

Quantum Photochemistry–Dynamics. We have also developed promising methods for treating the dynamics of photochemical reactions involving electronically excited reactants, in particular, a new semiclassical trajectory method called decay of mixing with coherent switches (CSDM). This is an Ehrenfest-like method that involves propagation of the electronic wave function or electronic density matrix according to a nondissipative Liouville-von Neumann equation, including non-Markovian dissipation and decoherence caused by the nuclear degrees of freedom. A key reason to include decoherence is so that the simulation produces physical final states. The CSDM method has been validated against accurate quantum dynamics calculations (using our own quantum dynamics methods, which are powerful enough to obtain converged results for three-body electronically nonadiabatic systems) and has proved to be more accurate than surface hopping and other approximate methods applicable to complex systems. Furthermore, we have used the theoretical interpretation of the origin of decoherence, developed by the astrophysical community, to derive an expression for the decoherence rate of molecular electronic density matrices based on a semiclassical wave packet treatment of the nuclear motion.

Density functional theory. The development of the B3LYP density functional in 1993–1994 revolutionized the applications of density functional theory to chemistry. B3LYP achieves its success in part by mixing in nonlocal Hartree-Fock exchange; this is called a hybrid functional. Although B3LYP is by far the most widely used functional, it does have some serious shortcomings: (i) it is better for main-group chemistry than for transition metals; (ii) it systematically underestimates reaction barriers; (iii) it is very inaccurate for interactions dominated by medium-range correlation energy, such as pi–pi stacking and alkane isomerization energies. We developed a suite of four new functionals that overcome these difficulties: (a) M06, a hybrid functional, is (along with its predecessor M05, also developed under NSF support), the first functional with uniformly good accuracy for transition metals, main group thermochemistry, medium-range correlation energy, and barrier heights. (b) M06–2X, another hybrid functional, is not good for transition metals but has excellent across-the-board performance for the

main group. M05-2X (along with our earlier PWB6K and M05-2X functionals) is the first functional to predict accurate pi-pi stacking interactions. M06-2X has also proved accurate for a number of difficult cases that have been put forward as challenges to density functional theory. (c) M06-L is not as accurate as M06 for barrier heights but is the most accurate functional for transition metals and is the only local functional (no Hartree-Fock exchange) with better across-the-board average performance than B3LYP; this is very important because only local functionals (when combined with density fitting, also called resolution of the identity) are affordable for many demanding applications on very large systems. All three functionals have good performance for noncovalent interactions, which is a major breakthrough that opens up a variety of new applications in biology, solvation, and soft materials. We achieved the excellent performance of all three functionals by assembling a broad set of more than two dozen databases (a multi-year effort where our NSF-supported research was leveraged in part by other grants), developing new functional forms for dependence of the exchange-correlation functional on kinetic energy density, and designing and carrying out careful global parameterizations. A fourth functional in the suite, M06-HF, has good performance for valence, Rydberg, and charge transfer excited states with minimal sacrifice of ground-state accuracy. We also developed so called fifth-rung functionals that depend on unoccupied orbitals.

A particularly dramatic example of the success of the new density functionals for noncovalent interactions is provided by their performance on the test set of Hobza and coworkers for 22 noncovalent binding energies in biological molecules. The mean unsigned error in kcal/mol is 1.00 for PWB6K, 0.85 for M06-L, 0.75 for M05-2X, 0.71 for M06-HF, and 0.47 for M06-2X, whereas the mean unsigned error in Moller-Plesset second-order perturbation theory, which was previously considered to be the method of choice (when affordable) for this kind of problem, is 1.63, and the mean unsigned error for B3LYP is 3.54. The ability to handle this kind of problem results from the consistent inclusion of spin kinetic energy density in the exchange and correlation functionals in such a way that they account for medium-range correlation energy. The inclusion of medium-range correlation energy has also been shown to be essential for predicting the isomerization

energies of alkanes, which have important interactions between geminal methylene and CH groups.

The ability of the new density functionals to treat complex interactions in large molecules is demonstrated by our recent explanation of the relative rates of formation of first- and second-generation Grubbs Ru catalysts for olefin metathesis.

Another recent application of density functional theory to a complex problem is its use to analyze the bonding of carbon monoxide to a group-10 metal, which is a critical issue for fuel cell poisoning.

Path integrals. We developed new Monte Carlo techniques (adaptive stratified sampling, importance sampling based on model probability densities, extended zigurat sampling, and path-by-path monotone extrapolation) that have allowed completely converged quantum path integral calculations even for four-body systems at room temperature (convergence is much easier at high temperature). This allowed, for example, the first ever converged vibrational-rotational partition functions for a molecule with a torsion, which would be hard to converge with conventional methods because of the large-amplitude motion and the vibration-rotation coupling. The resulting accurate partition functions were used to test practical approximation schemes for calculating partition functions of torsional modes against accurate quantum mechanical results for hydrogen peroxide and six isotopically substituted hydrogen peroxides; in particular we tested separable and almost-separable methods as well as an improved Pitzer-Gwinn-type method that we proposed for this kind of problem.

Converged polyatomic partition functions and quantum dynamics by vibrational configuration interaction. We used vibrational configuration interaction with hierarchical expansions of the potential energy to compute converged vibrational partition functions for ethane, which has eight atoms; this is the only converged calculation of a vibrational partition function for a molecule with more than five atoms. We also pioneered the application of vibrational configuration interaction to dynamics, in particular computing converged rate constants for zero total angular momentum for OH reacting with hydrogen molecule to make water and an H atom, which is the only converged quantum rate constant calculation for a system with more than three atoms that is not based on wave packets—thereby opening a new line of attack on quantum dynamics.

Molecular modeling. I will give here four examples of our progress in molecular modeling:

1. We found evidence, in collaboration with the experimental group of Xiaoyang Zhu, for evidence of an unoccupied molecular quantum well in epitaxial thin films of buckminsterfullerene on Au. We characterized this quantum well by tight-binding theory and time-dependent density functional theory.

2. Inspired in part by the recent work of Federov and Kitaura, we have developed a simple, but generally new approach to electronic structure calculations on large systems, called the electrostatically embedded many-body (EE-MB) expansion. In the case of a water 21-mer, even the lowest-order version, the electrostatically embedded pairwise additive approximation, leads to an error in the binding energy of only 1.5%, and the electrostatically embedded three-body approximation reduces this to only 0.2%, at a cost that is still 8 times less than a full MP2/aug'-cc-pVTZ calculation. Furthermore, the computational cost of the EE-MB approximation scales better than MP2 as system size is increased further. A number of avenues of further improvement are also available.

3. We have derived the absolute solvation free energy of the proton in three nonaqueous solvents, allowing us to put other ionic solvation energies in these nonaqueous media on an absolute basis. With the new scale of absolute nonaqueous ionic free energies of solvation, we have re-parameterized a generalized-Born-plus-surface-tension solvation model, and we find very good agreement with experiment for both ions and neutral solutes.

4. We have developed a redistributed charge and dipole scheme for combined quantum mechanical and molecular mechanical (QM/MM) calculations. The QM/MM method has been further improved by allowing for polarization of the MM side of the QM-MM boundary. In addition we have combined the QM/MM method with multi-configuration molecular mechanics to allow efficient use of higher-level quantum mechanical electronic structure methods.