

# **Investigation of Complex Systems by Hybrid QM/MM Molecular Dynamics Simulations**

PhD Thesis

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## I. Introduction

Complex systems with important electronic degrees of freedom can be investigated by hybrid quantum mechanical-molecular mechanical (QM/MM) methods. During my PhD study, I was working on two problems inherent to QM/MM simulations: development of a pseudopotential and improvement of sampling. In the first project I developed an appropriate QM/MM potential surface to investigate the properties of negatively charged methanol clusters. In the other work, I applied a special general reaction coordinate to investigate the chloride – methyl-chloride substitution reaction in aqueous solution. Although the reaction coordinate is originally defined on a classical potential energy surface, I was able to use it successfully on higher level of theory (i.e. QM/MM level).

## II. Study of Negatively Charged Methanol Clusters

### II.1. Introduction and Scientific Aims

Solvated electron has long been investigated because of its importance in fundamental chemistry and several biological processes<sup>1</sup>. In a more general sense, the solvated excess electron serves as the simplest model system in solutions with a solute having a single electronic degree of freedom. Besides the aqueous case, which has been the most extensively studied, experimental results for excess electrons in methanol are also available<sup>2</sup>. Methanol, similarly to other polar solvents, localizes the excess electron in a solvent cavity surrounded by properly oriented methanol molecules.

Due to the rapid advance of the experimental techniques, nowadays the scientific interest turned again to the finite size solvated electron systems. The theoretical interest is based on the fact that cluster anions can be considered as a transition between the gaseous species and the bulk solvated electron. Despite the finite size and the anticipated relative simplicity of cluster anions compared to bulk condensed phases, up to now there is still no consensus on the most basic structural properties of water cluster anions<sup>3</sup>. The most delicate unexplained problem is the

appearance of at least three characteristic cluster anion classes reflected by three distinctly different trends in the variation of the vertical electron detachment energy with cluster size. A straightforward approach to solve the problematic issues is to extend the investigations to other polar solvents. Recent study of negatively charged methanol clusters by photoelectron imaging revealed two different sequences in the excess electron vertical detachment energy (VDE) with cluster size suggesting appearance of two different types of cluster isomers.

The primary purpose of my study was to identify and investigate the two isomers using hybrid QM/MM molecular dynamics simulations. The study required the development of a new pseudopotential that describes the interaction between the excess electron and the classical methanol molecules. In contrast to previous potentials, the new pseudopotential is an all-site model that expectedly improves its atomistic character. As an addition purpose to develop a new pseudopotential is the transferability. For the more general use of the pseudopotential, it is desirable to develop such atomic parameters of the potential, which are transferable from one molecule to other making the calculations easier in other solvents.

## II.2. Methods

To investigate the physical properties of the negatively charged methanol clusters, QM/MM single point calculations and molecular dynamics simulations were performed. The quantum zone included the excess electron, while the methanol molecules were treated classically. The interaction between the excess electron and the methanol molecules was described by a newly developed pseudopotential.

The generation of the new electron-methanol pseudopotential followed the Turi-Borgis protocol employed for the electron-water pseudopotential<sup>4</sup>. The method is based on the static exchange (SE) approximation<sup>5</sup>. As a first step, the  $N$ -electron problem was reduced to a one-electron problem using the Phillips-Kleinman repulsion operator<sup>6</sup>. Secondly, to remove large oscillations of the wave function of the excess electron in the core region, the excess state was mixed appropriately with the core states<sup>7</sup>. The procedure resulted in the exact pseudowave function. In the third step, the local approximation of the nonlocal operators was carried out<sup>8</sup>. In this method the polarization part is added to the potential *a posteriori*<sup>9</sup>. The polarization

parameters were tuned to reproduce the most important properties of the solvated excess electron in methanol bulk using QM/MM MD simulations.

Using the developed potential, the investigation of several methanol cluster anions was carried out. As the first step, the “static” examination of the systems was performed. In this study the initial binding of the excess electron to neutral clusters was modeled. The neutral configurations were generated from classical MD simulations. Correlation analysis of the binding energy of the excess electron and several cluster properties were also carried out. In the second step, the “dynamic” behavior of the system was studied. Both the surface- and interior-type states were modeled by QM/MM MD simulations starting the systems from different initial conditions.

### *II.3. Results and Conclusions*

#### *II.3.1. The New Electron-Methanol Pseudopotential*

After the application of the Phillips-Kleinman theorem<sup>6</sup> in the framework of SE approximation<sup>5</sup>, the core oscillations of the excess electron state were removed by minimizing the kinetic energy of the excess state<sup>7</sup>. The resultant exact pseudo wave function is relatively smooth at the core region but has the same asymptotic behavior similarly to the SE excess state.

Because of computational purposes, the nonlocal operators were approximated by local ones. After the application of the Schnitker-Rosky repulsion operator (SRR), the pseudo wave function kept its good asymptotic behavior and moderate fluctuations in the core region, and its eigenenergy was also well approximated. For the exchange operator, four different approximations were tested. Among the investigated scenarios, the semiclassical exchange potential (SCE) was chosen since the SRR-SCE potential<sup>8</sup> approximated the eigenenergy and the electron density of the excess state the best.

A numerical fitting procedure was carried out to obtain the final form of the potential applicable for the molecular dynamics simulation. The parameters of oxygen and hydroxyl hydrogen atoms were taken from the electron-water potential developed previously with the same procedure, while the parameters of the carbon and methyl hydrogen atoms were optimized. This selective optimization of the parameters made the new potential transferable.

The induced polarization effect was introduced as an additive *a posteriori* term to the potential. The values of the adjustable parameters were set to reproduce the expected position of the maximum of the absorption spectrum of the solvated electron in methanol using molecular dynamics simulations.

To investigate the basic physical properties of the solvated electron in bulk methanol, molecular dynamics simulations were performed in equilibrium with the developed pseudopotential. The binding energy was found to be significantly higher than computed with a previous three-site model<sup>10</sup> showing that the explicit treatment of the methyl hydrogens may have crucial role in bulk. Although the stabilization of the electron is slightly weaker in methanol than in water, the ground state electron occupies also a quasispherical (*s*-like) cavity as it was observed in water. The calculated radius of gyration of the ground state electron was also very similar (although less diffuse) to that found in water<sup>4</sup>. Electron-site radial distribution functions revealed that the electron is surrounded by OH bonds oriented toward the electron. The radial distribution function of methyl hydrogen – electron has a broad peak due to the rotation of the methyl group. However, the position of the beginning of the peak indicates that methyl hydrogen atoms can also participate slightly to the stabilization of the excess electron. The coordination number of the first shell calculated from the center-of-mass – electron distribution agrees also well with the experiments. One of the major goals of the model is to reproduce the proper position of the optical spectrum, which was slightly redshifted in a previous model.

### *II.3.2. Static Study of Electron-Methanol Clusters*

As a first step to study solvated electron in methanol clusters, the electron localization route was modeled using equilibrated neutral methanol clusters in the range of cluster size of 50-500 molecules. I found as a first conclusion, similarly to water, that the electron binding strength and the degree of localization are mainly determined by the dipole moment of the neutral clusters. Since the dipole moments of the methanol clusters are similar to those of the water clusters, the electron binding energies are also similar in both systems and increase with the size. Electron localization takes places solely at the surface of methanol clusters, and the electron is more diffuse than on the surface of water clusters. Surface analysis of the atoms of the methanol

clusters revealed that the surface is covered mostly by methyl hydrogens in contrast to water clusters, where ~20% of surface water molecules have one free OH pointing to the vapor. Methyl hydrogen atoms can bind the excess electron much weaker than hydroxyl hydrogens that leads to a weakly bound surface state. Possible interior localization states were also investigated enforcing the excess electron to localize in neutral equilibrated bulk methanol. The experiment showed that the electron does not find favorable cavities even in liquid methanol. While the initial stabilization of the excess electron on the surface is energetically weakly favorable, the electron is unbound in the case of interior localization.

### *II.3.3. Dynamic Study of Electron-Methanol Clusters*

Experimental data suggest that for larger clusters besides the weakly bound surface state there exists another state of the excess electron that has a significantly larger vertical detachment energy. It can be imagined, that the initially surface bound electron enters into the cluster resulting in an interior state. To investigate this possible scenario, hybrid QM/MM molecular dynamics simulations were performed. The results revealed that the electron remains on the surface for smaller clusters (50-85 molecules). In the case of middle size clusters (103-161 molecules) the electron is able to enter into the inner space of the clusters but it cannot stay there for a long time. For larger clusters (205-500 molecules), the electron penetrates into and stays in the interior of the cluster. The electron binding energy of these interior states increases also with the cluster size and is significantly stronger than that on the surface in a good qualitative agreement with the experimental data.

### III. Extension of $E_{gap}$ as a General Reaction Coordinate on Higher Level of Theory

#### III.1. Introduction and Scientific Aims

In many cases, especially in chemical reactions of complex systems, QM/MM molecular dynamics is not able to perform an effective exploration of the PES and special bias of the dynamics is required. The technical implementation of this bias depends on the so called potential of mean force (PMF) method. These techniques differ in numerous technical properties allowing one to choose the most appropriate one for the investigated problem. However, the applied PMF method in itself cannot guarantee the sufficient sampling, as all of the PMF methods apply one or more reaction coordinates (or collective variables), which are functions of the coordinates of nuclei and along which the system is biased and sampled. In contrast to the sampling methods, the proper choice of the reaction coordinate(s) is not obvious.

Because of their relatively easy implementation and interpretation, the most often applied reaction coordinates are the so called geometrical coordinates, which depend only on a few coordinates of the system. However, application of geometrical coordinates in complex systems can fail easily. The reason is that reaction coordinates, which are lacking in indispensable degrees of freedom, lead to insufficient sampling and serious hysteresis as the “correct” variable is not biased.

Obviously, there is a need for having such a universal reaction coordinate that does not suffer from such problems. Energy gap ( $E_{gap}$ ), which is the difference between two (e.g. reactant and product) classical valence states in the framework of Empirical Valence Bond (EVB) theory<sup>11</sup>, seems to be a potential candidate for serving as general reaction coordinate. As an energy variable,  $E_{gap}$  depends on all important degrees of freedom of the system. However,  $E_{gap}$  is originally defined on classical level and its use on higher level of theory (i.e. QM and QM/MM) is not apparent since molecular orbital based quantum theories cannot define valence states. During my work I showed how to solve this discrepancy in a straightforward manner and calculate  $E_{gap}$  dependent free energy profile of chemical reactions on higher level of theory.

The chosen model system was a very simple symmetric nucleophilic substitution: the chloride exchange in methyl-chloride in gas phase and water solution. Accuracy of  $E_{gap}$  was compared to that of a geometrical coordinate  $DD$ , which is the difference between the attacking

chloride – carbon and leaving chloride – carbon distances and widely applied to describe this reaction.

### III.2. Methods

For the QM/MM calculations, the methyl chloride and the chloride ion were described using the semiempirical PM3 Hamiltonian<sup>12</sup> and water by the classical TIP3P model<sup>13</sup> with the full electrostatic coupling between quantum and classical regions<sup>14</sup>. The PM3 QM/MM Hamiltonian is chosen here only because at this simple level of description it was possible to perform extensive tests and to converge the free energies up to statistical accuracy.

Both possible ways were investigated to evaluate the free energy profiles on a QM surface using *Egap* as a reaction coordinate. In the indirect implementation the simulation was governed by *Egap* on the classical potential by the EVB method. The differences between the classical and the QM potential energy surfaces are taken into account by postprocessing the configurations derived from the classical simulations. To calculate the free energy profile associated to the QM surface, the free energy perturbation/umbrella sampling (FEP/US) method was used. In the direct implementation, simulations are performed on the QM potential surface, computing the potential of mean force as a function of *Egap* evaluated on the classical potential energy surface.

Convergence of free energy profile of *Egap* and *DD* was investigated by using modern fast PMF methods such as metadynamics<sup>15</sup> and adaptive biasing force<sup>16</sup>, which are able to evaluate the free energy profile during the simulations (on the fly). The efficiency of the sampling on the QM potential energy surface using different reaction coordinates was assessed by two measures (hysteresis and efficiency). The calculation of these measures is based on the standard deviation of the current free energy estimation compared to the fully converged free energy profile, evaluated with the constrained dynamics approach<sup>17</sup>.

Finally, to investigate the correct indication of the transition state (TS) by *Egap* and *DD*, the committor analysis was performed<sup>18</sup>.

### *III.3. Results and Conclusions*

#### *III.3.1. Implementation of $E_{gap}$ into Free Energy Calculations*

Results of the two possible techniques showed that although the indirect method requires computationally much less effort (as the dynamics is propagated on classical surface), it leads to systematic errors when the QM and classical surfaces deviate by more than 2-3 RT. Contrarily, direct method (using constrained dynamics) resulted in a reliable, converged profile. Besides its accuracy, the direct implementation has the additional advantage that it can be combined with any sampling methods. Therefore, a special chimera program was constructed by combining two program packages. The philosophy behind the combination is that the quantum dynamic program package provides the QM or QM/MM surface and propagates the dynamics, while an appropriate classical program package is responsible for the calculation of  $E_{gap}$  and the evaluation of the free energy profile associated to the applied PMF method. Besides the combination of the AMBER<sup>19</sup> and XdynBP program packages that was used in my study, I contributed to the development of the connection of the DFT based CPMD<sup>20</sup> and XdynBP.

#### *III.3.2. Comparison of Free Energy Profiles of $E_{gap}$ and $DD$*

In vacuum, the free energy curves for both coordinates were symmetric. The activation barriers were in a good agreement of the experimental value. In solutions, a larger deviation between the  $E_{gap}$  and  $DD$  reaction coordinates could be observed. The profile of  $E_{gap}$  evaluated by constrained dynamics was also symmetric, while using  $DD$  resulted in a slightly asymmetric profile. The profile of  $E_{gap}$  approximated slightly better the experimental value of the activation barrier.

Metadynamical hysteresis of the free energy profiles was much larger for  $DD$  than for  $E_{gap}$ . The error of the current curves (compared to the profiles evaluated by constrained dynamics) as a function of time showed that the convergence of the free energy profile is much faster for  $E_{gap}$  compared to  $DD$  in both metadynamics and adaptive biasing force methods.

### III.3.3. Localization of the Transition State on a High-Level Surface Using Egap

Although DD is a widely applied reaction coordinate for this reaction, it has failed the committor test in water solution, while Egap behaved as a good reaction coordinate and indicated the TS correctly.

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