I-H Electronic Structure of a Molecule in Solution

Chemical reaction is undoubtedly the most important issue in the theoretical chemistry, and the electronic structure is a key to solve the problem. As long as molecules in the gas phase are concerned, the theory for the electronic structure has been enjoying its great success. However, when it comes to molecules in solution, the stage of theory is still an infant. Thirteen years ago, we have proposed a method refereed to as RISM-SCF based on the integral equation theory of molecular liquids (RISM) and the ab initio electronic structure theory (SCF).[1)] The method was applied successfully to a variety of chemical processes in solution including a number of different types of chemical reactions, S_N2, acid-base, redox, and so on.

More recently, we have revised the theory so that the theory can account for the three dimensional distribution of solvent around solute.[2)] (3D-RISM) This revision turns out to be essential when one tries to treat the solvent distribution around the native state of protein. The new theory allows us to handle the electronic structure of protein in water with appropriate theories for quantum chemistry.

One of the most complicated chemical reactions is that taking place in protein, or the enzymatic reaction. The reaction involves not only the electronic structure change of chemical species, but also recognition of substrates by host protein. The latest progress in our group is to develop a new approach for molecular recognition in host-guest systems. The progress is reported in the section I-I. Combining the approach with the 3D-RISM/SCF type theory will enable us to treat enzymatic reactions.

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I-H-1 A New Method to Determine Electrostatic Potential around a Macromolecule in Solution from Molecular Wave Function

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[*J. Comput. Chem.* **27**, 453 (2006)]

The three dimensional reference interaction site model integral equation theory (3D-RISM) combined with the *ab initio* molecular orbital method (3D-RISM-SCF) is applied to a solvated macro molecular system. The solvation structure around a solute molecule is obtained from the 3D-RISM integral equation under the electrostatic potential of the solute molecule, calculated by the *ab initio* molecular orbital theory.

The electrostatic potential should be calculated on each grid point in the three dimensional real space. Therefore, the calculation of the electrostatic potential is the most time consuming part in this method. In this paper, we propose a new procedure to save the computational cost for calculating the electrostatic potential and the solvated fock matrix.

I-H-2 Ab Initio Theoretical Study of Temperature and Density Dependence of Molecular and Thermodynamic Properties of Water in the Entire Fluid Region: Autoionization Processes

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[*J. Phys. Chem.* **110**, 8451 (2006)]

The temperature and density dependence of the molecular and thermodynamic properties of water is investigated theoretically by means of the *ab initio* electronic structure theory combined with the reference interaction site model method, so called as RISM-SCF. We consider the autoionization process ($H_2O + H_2O = H_3O^+ + OH^-$) by regarding H_2O, H_3O^+ and OH^- as "solute" molecules in an aqueous solution and evaluate molecular geometries, electronic structure, solvation structure, and ionic product of water (pK_w) of these species as functions of thermodynamical conditions. In our previous paper, we calculated these properties by using essentially the same method in a wide range of density (0.6–1.4 g/cm^3). However, the calculation was limited in rather higher density (> 0.6 g/cm^3) due to the difficulty of convergence, which is inherent to the hypernetted chain (HNC) closure. The problem is overcome in this study by employing the Kovelenko-Hirata (KH) closure which hybridizes the HNC and mean spherical approximation (MSA). Here, we present the results for the thermodynamic range 0.025 g/cm^3 to 1.0 g/cm^3 and from 300 K to 800 K including a supercritical point.

I-H-3 Conformational Equilibrium of 1,2-Dichloroethane in Water: Comparison of PCM and RISM-SCF Methods

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[*J. Phys. Chem. B* **110**, 16018 (2006)]

The RISM-SCF and polarizable continuum model (PCM) approaches have been applied to study the conformational equilibrium of 1,2-dichloroethane (DCE) in water. Both the electron correlation effect and basis sets play an important role to the relative energies of the gauche and trans conformers in gas and solution phases. Both PCM and RISM-MP2 methods resulted in the consistent trend with the previous experimental and theoretical studies that the population of the gauche

conformer increases in going from the gas phase to the aqueous solution. However, the PCM treatment could not describe the solvent effect completely in that the sign of relative free energy of the gauche and trans forms is opposite to the most recent experimental and theoretical data, while it is in good agreement by the RISM-MP2 method. We found that the larger excess chemical potential gain (by ~–4.1 kcal/mol) for the gauche conformer is large enough to result in the gauche preference of DCE in water, though it has to compensate the more solute reorganization energy (~1.7 kcal/mol) and overcome the energy difference (~1.6 kcal/mol) in the gas phase. The radial distribution functions between DCE and the nearest water shows that the electrostatic repulsion between chlorine and oxygen atoms is higher in trans conformer than gauche one, while the attractive interaction between chlorine and hydrogen of water is higher in gauche conformer.

I-I Solvation Thermodynamics of Protein and Related Molecules

Concerning biomolecules such as protein, it is a final goal for the biochemistry and biophysics to explore the relation between conformations and biological functions. The first important step toward the goal would be to explain the conformational stability of biomolecules in terms of the microscopic structure of the molecules in solvent. It is an extremely difficult problem by any means due to the overwhelmingly large degrees of freedom to be handled, including protein and solvent.

In the past 11 years, we have been developing a method to attack the problem based on the statistical mechanics of liquids, especially, on the RISM theory.[1)] Recently, we put forward our effort to apply the three dimensional (3D) RISM theory to biomolecules, and have succeeded for the first time to obtain thermodynamic quantities of "real" protein, which is in agreement with experiments not only qualitatively but also quantitatively in case of the partial molar volume.[2)] The 3D-RISM theory turns out to be even more powerful to explore water molecules trapped in a cavity of protein.[3)]

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I-I-1 Locating Missing Water Molecules in Protein Cavities by the Three-Dimensional Reference Interaction Site Model (3D-RISM) Theory of Molecular Solvation

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[*Protein* in press]

Water molecules confined in protein cavities are of great importance in understanding the protein structure and functions. However, it is a nontrivial task to locate such water molecules in protein by ordinary molecular simulation and modeling techniques as well as experimental methods. The present study proves that the three-dimensional reference interaction site model (3D-RISM) theory, a recently developed statistical-mechanical theory of molecular solvation, has an outstanding advantage in locating such water molecules. In this paper, we demonstrate that the 3D-RISM theory was able to reproduce the structure and the number of water molecules in cavities of hen egg-white lysozyme observed commonly in the X-ray structures of different resolutions and conditions. Furthermore, it is shown that the theory successfully identified a water molecule in a cavity, even the existence of which had been ambiguous from the X-ray results. In contrast, it was confirmed that molecular dynamics simulation is helpless to find such water molecules because the results substantially depend on the initial coordinates of water molecules. Possible applications of the theory to problems in the field of molecular biology are also discussed.

I-I-2 Conformational Equilibria in Liquids Consisting of Small Chain Molecules

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[*Chem. Phys. Lett.* **420**, 135 (2006)]

The conformational equilibrium in neat liquids consisting of small chain molecules, *n*-butane and 1,2-dichloroethane, are studied by means of a RISM-type integral equation theory formulated by Yoshida, Munakata and Hirata. Conformational shift toward the *gauche* isomer was observed upon transferring from gas to liquid phases in the both fluids in harmony with experiments. The equilibrium constant for 1,2-dichloroethane shows very small temperature dependence. The pressure dependence of the equilibrium constant indicates that the *gauche* isomer is in favor at higher temperature. The theoretical results are consistent with the experimental observations.

I-I-3 Theoretical Study of Volume Changes Accompanying Xenon-Lysozyme Binding: Implication for Molecular Mechanism of Pressure Reversal of Anesthesia

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[*J. Phys. Chem. B* **110**, 12149 (2006)]

The change in partial molar volume (PMV) accompanying the xenon-lysozyme binding was investigated for elucidating the molecular mechanism of the pressure reversal of general anesthesia, using the three-dimensional reference interaction site model (3D-RISM) theory. An increase of the PMV from xenon binding to the substrate binding site of lysozyme was found, and the binding is suppressed by pressure, while the internal site binding did not change the PMV. From the decomposition of the PMV change, combined with the analysis of the hydration change due to the binding, we propose a molecular mechanism of the PMV increase from anesthetic-protein binding, that is the mechanism of pressure reversal of general anesthesia.

I-I-4 A Theoretical Analysis on Hydration Thermodynamics of Proteins

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[*J. Chem. Phys.* **125**, 024911 (2006)]

The hydration free energy (HFE) is calculated for several proteins using the three-dimensional reference interaction site model (3D-RISM) theory, a recently developed integral equation theory of molecular solvation, combined with the all-atom potentials. The HFE is decomposed into the energetic and entropic components under the isochoric condition. The former comprises the protein-water interaction energy and the water reorganization energy (the energy arising from the structural changes induced in water). Each component is further decomposed into the non-electrostatic and electrostatic contributions. It is found that the HFE is governed by the non-electrostatic hydration entropy and the electrostatic hydration energy. The non-electrostatic hydration entropy is almost exclusively ascribed to the translational entropy loss of water upon the protein insertion. It asymptotically becomes proportional to the excluded volume (EV) for water molecules with increasing the protein size. The hydration energy is determined by the protein-water interaction energy which is half compensated by the water reorganization energy. These energy terms are approximately proportional to the water-accessible surface area (ASA). The energetic and entropic contributions are balanced with each other, and the HFE has no apparent linear relation with the EV and ASA.

I-I-5 Selective Ion-Binding by Protein Probed with the 3D-RISM Theory

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[*J. Am. Chem. Soc.* in press]

Selective ion-binding by human lysozyme and its mutants is probed with the three-dimensional interaction site model theory, which is the statistical mechanical integral equation theory. The three- dimensional distribution of ions as well as water molecules was calculated for aqueous solutions of three different electrolytes $CaCl_2$, NaCl and KCl, and for four different mutants of the human lysozyme: wild type, Q86D,A92D, Q86D/A92D that have been studied experimentally. For the wild type of the protein in the aqueous solutions of all the electrolytes studied, there are no distributions observed for the ions inside the active site. The A92D and Q86D/A92D mutants show a large peak of Na^+ in the recognition site. Especially, holo-Q86D/A92D, one of the mutants, shows conspicuous peak of Ca^{2+}. These behaviors are in accord with the experimental results.

I-J Collective Density Fluctuations in Polar Liquids and Their Response to Ion Dynamics

As to the model for molecular diffusion in polar liquids, there are two quite different points of view. One is the conventional rot-translation model, and the other the interaction-site description which sees the diffusion of a molecule as a correlated motion of each atom (site).[1)] It is clearly advantageous to use the interaction-site description compared to the rot-translation model to account for chemical characteristics of solvent as well as solute dynamics. However, the interaction-site description has its own disadvantage in interpreting physical meaning of the results, since it does not give an explicit picture for the rotational relaxation of molecules, which can be directly probed by many experimental means including the dielectric and NMR relaxation. We have solved the problem by extracting collective modes of the density fluctuation from the site-site density correlation functions. In our recent study for dynamics of molecular liquids based on the interaction-site model, we have succeeded to abstract the collective excitations in liquids, which can be identified as optical and acoustic modes, by diagonalizing the collective

frequency matrix appearing in the generalized Langevin equation. The two modes arise essentially from the rotational and translational motions of molecules.[2)] We applied the method to the ion dynamics in a dipolar liquid, and could have explained successfully the peculiar size dependence of friction of alkali and halide ions in terms of response of the collective excitations in solvent to the solute displacement.[3)]

In the past year, we have elaborated the memory kernel in our generalized Langevin equation base on the mode coupling theory. We have also extended our treatment to dynamics of water and hydrated ions. Those studies as well as other related topics are reviewed below.

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I-J-1 Study of Anomalous Mobility of Polar Molecular Solutions by Means of the Site-Site Memory Equation Formalism

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[*J. Mol. Liq.* **125**, 14 (2006)]

In this work, the memory equation approach is applied for theoretical study of dynamics of polar molecular liquids described by the interaction site model. The study includes the temperature-density(pressure) dependence of the translational diffusion coefficients *D* and orientational relaxation times tau for infinitely dilute solutions of acetonitrile and methanol in water, and methanol in acetonitrile. Calculations are performed overthe range of temperatures and densities employing the SPC/E model for water and optimized site-site potentials for acetonitrile and methanol. Despite an approximate character of the model potentials and closure relation used, the theory is able to reproduce qualitatively all mainfeatures of temperature and density dependences of *D* and τ observed in computer and real experiments. In particular, anomalous behavior, *i.e.*, the increase in mobility with density(pressure), is obtained for *D* and τ of methanol in water, while acetonitrile in water or methanol in acetonitrile do not show deviations from the usual. The observed enhancement in the molecular mobility is interpreted in accordance with the concept by Yamaguchi *et al.* [*J. Chem. Phys.* **119**, 1021 (2003)], *i.e.*, in terms of two competing origins of friction, which interplay with each other as density increases: the collisional and dielectric frictions that have tendency, respectively, to strengthen and weaken with increasing density.

I-K Statistical Mechanics of Interfacial Fluids

Microscopic structure of fluid interfaces has been drawing a lot of attention due to recent development in the experimental techniques devised particularly to probe the interface. However, there are many open questions remained unanswered. For example, how wide is the interfacial region, how does it depend on the chemical species consisting the solution? Is the interface more or less homogeneous in terms of density or concentration of the two fluids, or is it spatially inhomogeneous? If it is inhomogeneous, what is the spatial extent of the inhomogeneity? Answering those questions is the most difficult and challenging tasks for theoretical physics and chemistry, and not much progress has been made in the past, especially from a molecular view point. We have been developing statistical mechanics for two different types of interfacial fluids: fluid-fluid interface and fluids in porous media. Following are the latest achievement in that direction.

I-K-1 Criticality of a Liquid-Vapor Interface from an Inhomogeneous Integral Equation Theory

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[*Phys. Chem. Chem. Phys.* **7**, 4132 (2005)]

A microscopic theory is developed to study the liquid–vapor interfacial properties of simple fluids with ab initio treatment of the inhomogeneous two-body correlation functions, without any interpolation. It consists of the inhomogeneous Ornstein-Zernike equation coupled with the Duh-Henderson-Verlet closure and the Lovett-Mou-Buff-Wertheim equation. For the liquid–vapor interface of the Lennard-Jones fluid, we obtained the density profile and the surface tension, as well as their critical behaviour. In particular, we identified non-classical critical exponents. The theory accurately predicts the phase diagram and the interfacial properties in a very good agreement with simulations. We also showed that the method leads to true capillary-wave asymptotics in the macroscopic limit.