I-L 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. About 15 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.

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I-L-1 Electronic Structure Calculation of a Solvated Macro Molecule by Using Three-Dimensional Reference Interaction Site Model Combined with *Ab Initio* Molecular Orbital Theory

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[*J. Comput. Chem.* submitted]

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. Hence the solvated fock matrix are also prepared on each grid point. Therefore, the calculation of the electrostatic potential and the solvated fock matrix 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. The strategy of this procedure is to divide the space into three regions: (I) the inside of the repulsive cores, and (II) the region excluding(I), where the electron density is distributed, and (III) the remaining part in the super cell after applying the (I) and (II).

In the first region, it is possible to avoid the calculation of electrostatic potential and solvated Fock matrix by assuming the potential to be infinity.

In the second region, the electrostatic potential is evaluated directly by integrating the molecular orbitals. In the outermost region, it is evaluated approximately by putting the effective point charge on each atomic site.

The electronic structure and the energy gradient of Methionine-Enkephalin and solvation structure are estimated by using this procedure in aqueous solution, and are compared with the results from other procedures. The results are compared also with those from the continuum model.

I-L-2 New Theoretical Approach for the Diastereoselectivity of H/D Exchange Reaction on Methyl 3-Fluorobutanoate Anion

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[*Tetrahedron Lett.* submitted]

The origin of closed to si-face stereochemistry in the protonation of β-substituted ethyl butanoates in ethanol-*d*, which has been studied by Mohrig and co-workers, was examined with Me 3-fluoro butanoate anion as a computational model. It was found that the prediction of the selectivity was achieved with the solvent effect arround substrate and the population fo the ground state species. The transition state to si-face streochemistry is found to be the most favorable process in ethanol.

I-M 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 10 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.

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I-M-1 Hydrophobic Effects on Partial Molar Volume

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[*J. Chem. Phys.* **122**, 94509 (2005)]

The hydrophobic effects on partial molar volume (PMV) are investigated as a PMV change in the transfer of a benzene-like non-polar solute from the non-polar solvent to water, using an integral equation theory of liquids.

The volume change is divided into two effects. One is the "packing" effect in the transfer from the non-polar solvent to hypothetical "non-polar water" without hydrogen bonding networks. The other is the "iceberg" effect in the transfer from "non-polar water" to water. The results indicate that the "packing" effect is negative and a half compensated by the positive "iceberg" effect. The "packing" effect is explained by the difference in the solvent-compressibility. Further investigation shows that the sign and magnitude of the volume change depends on the solute-size and the solvent-compressibility. The finding gives a significant implication that the exposure of a hydrophobic residue caused by protein denaturation can either increase or decrease the PMV of protein depending on the size of the residue and the fluctuation of its surroundings. Possible applications of the method to problems related to the solvation thermodynamics of protein are discussed.

I-M-2 Partial Molar Volume of Proteins Studied by the 3D-RISM Theory

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[*J. Phys. Chem. B* **109**, 6658 (2005)]

The three-dimensional reference interaction site model (3D-RISM) theory is applied to the analysis of hydration effects on the partial molar volume of proteins. For the native structure of some proteins, the partial molar volume is decomposed into geometric and hydration contributions using the 3D-RISM theory combined with the geometric volume calculation.

The hydration contributions are correlated with the surface properties of protein. The thermal volume, which is the volume of voids around the protein induced by the thermal fluctuation of water molecules, is directly proportional to the accessible surface area of protein. The interaction volume, which is the contribution of electrostatic interactions between the protein and water molecules, is apparently governed by the charged atomic groups on the protein surface. The polar atomic groups does not make any contribution to the interaction volume. The volume differences between low- and high-pressure structures of lysozyme are also analyzed by the present method.

I-M-3 Theoretical Study of Volume Changes Associated with the Helix-Coil Transition of an Alanine-Rich Peptide in Aqueous Solution

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The changes in the partial molar volume (PMV) associated with the conformational transition of an alanine-rich peptide AK16 from the α-helix structure to various random coil structures are calculated by the three-dimensional interaction site model (3D-RISM) theory coupled with the Kirkwood-Buff theory. The volume change is analyzed by decomposing it into contributions from geometry and hydration: the changes in the van der Waals, void, thermal, and interaction volume. The total change in the PMV is positive. This is primarily due to the growth of void space within the peptide which is cancelled in part by the volume reduction resulting from the increase in the electrostatic interaction between the peptide and water molecules. The changes in the void and thermal volume of the coil structures are widely distributed and tend to compensate each other. Additionally, the relations between the hydration volume components and the surface properties are investigated. We categorize coil structures into extended coils with the PMV smaller than helix and general coils with the PMV larger than helix. The pressure therefore can both stabilize and destabilize the coil structures. The latter seems to be a more proper model of random coil structures of the peptide.

I-M-4 Combination of the Replica-Exchange Monte Carlo Method and the Reference Interaction Site Model Theory for Simulating a Peptide Molecule in Aqueous Solution

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[*J. Phys. Chem. B* **108**, 19002 (2004)]

This article reports the first attempt to combine the replica-exchange Monte Carlo method and the reference interaction site model (RISM) theory for simulating a peptide molecule in aqueous solution. The energy function is the sum of the conformational energy and the solvation free energy. The solvation free energy for a fixed conformation of the peptide molecule is calculated using the RISM theory. The replica-exchange method is modified so that the dependence of the energy function on the temperature can be incorporated. The effectiveness of the combined approach is demonstrated for Met-enkephalin in water. It is argued that the number of replicas required for a peptide molecule immersed in water is drastically reduced by emplying the combined approach. Solvation properties and free energy surfaces of Met-enkephalin in water are discussed.

I-M-5 Water Molecules in a Protein Cavity Detected by a Statistical-Mechanical Theory

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[*J. Am. Chem. Soc. communication*, submitted]

Water molecules confined inside cavities in a protein are of great importance in understanding the structure, stability, and functions of the biomolecule. Considerable efforts have been devoted to observe such water molecules by experiments, but it is still a nontrivial task.

It is virtually impossible to “find” water molecules in a protein cavity by the ordinary molecular simulation, because they are most likely trapped in the biomolecule through a process of large conformational fluctuation or “folding.” The simulation of such water molecules is as difficult as the protein folding itself.

Surprisingly enough, in the present study, we could have detected water molecules in a protein cavity by means of a recently developed statistical mechanics of molecular solutions, or the three-dimensional reference interaction site model (3D-RISM) theory. This paper reports how the water molecules are detected by the 3D-RISM calculation.

The results may have great impact on biochemistry and biophysics including molecular recognition, enzymatic reaction, and so on.

I-N 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-N-1 Site-Site Memory Equation Approach in Study of Density/Pressure Dependence of Translational Diffusion Coefficient and Rotational Relaxation Time of Polar Molecular Solutions: Acetonitrile in Water, Methanol in Water, and Methanol in Acetonitrile

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[*J. Chem. Phys.* **122**, 184511 (2005)]

We present results of theoretical study and numerical calculation of the dynamics of molecular liquids based on combination of the memory equation formalism and the reference interaction site model—RISM. Memory equations for the site-site intermediate scattering functions are studied in the mode-coupling approximation for the first order memory kernels, while equilibrium properties such as site-site static structure factors are deduced from RISM. The results include the temperature-density(pressure) dependence of translational diffusion coefficients *D* and orientational relaxation times τ for acetonitrile in water, methanol in water and methanol in acetonitrile, all in the limit of infinite dilution. Calculations are performed over the range of temperatures and densities employing the SPC/E model for water and optimized site-site potentials for acetonitrile and methanol. The theory is able to reproduce qualitatively all main features of temperature and density dependences of *D* and τ observed in real and computer experiments. In particular, anomalous behavior, *i.e.* the increase in mobility with density, is observed for *D* and τ of methanol in water, while acetonitrile in water and methanol in acetonitrile do not show deviations from the ordinary behavior. The variety exhibited by the different solute-solvent systems in the density dependence of the mobility is interpreted in terms of the two competing origins of friction, which interplay with each other as density increases: the collisional and dielectric frictions which, respectively increase and decrease with increasing density.

I-N-2 Theoretical Study on the Dynamic Properties of Compressed Water and Water-Hydrophobic Solute Mixtures

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The dynamic properties, including shear viscosity, self-diffusion coefficient, dielectric relaxation time and single-molecular reorientational relaxation time, of neat compressed water and model water-hydrophobic solute mixtures are calculated theoretically from the intermolecular interaction potentials. The reference interaction-site model integral equation theory is used to obtain the equilibrium structure of the liquid, which in turn is used as the input of the numerical calculation by the mode-coupling theory for molecular liquids based on the interaction-site model. For neat compressed water, the theory reproduced the increase in the molecular mobility with applying pressure qualitatively. The reorientational mobility is more enhanced by pressure than the translational one, which is in harmony with experiments. The retardation of the motion of water in the aqueous solution of hydrophobic solutes is also obtained by the theory. In a model system in which the electrostatic interaction between the solute and solvent is continuously varied, the mobility of solvent water has a maximum as the function of the hydrophobicity of the solute. This theoretical trend is in harmony with the transition from positive, *via* negative, to hydrophobic hydration regimes experimentally observed.

I-N-3 Solvation Dynamics in Water Investigated by RISM/Mode-Coupling Theory

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[*J. Mol. Liq.* **119**, 63 (2005)]

The reference interaction site model (RISM) theory combined with the generalized Langevin/mode-coupling theory (MCT) is applied to the investigation of solvation dynamics in water. The dynamic response function Ss(t) which measures the energy relaxation of the system is calculated with different model solutes. The RISM-MCT framework recently presented by Yamaguchi and coworkers [*J. Chem. Phys.* **117**, 2216 (2002); *Mol. Phys.* **101**, 1211 (2003)] is shown to be applicable well to the realistic description of solvation dynamics. Ss(t) initially relaxes with a Gaussian decay followed by an overdamping oscillation with the time period of 30 fs. As the multiplicity of the solute pole is increased, the magnitude of the Ss(t) damping becomes smaller and relaxation gets slower.

I-O 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-O-1 A Molecular Theory of Liquid Interfaces

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[*Phys. Chem. Chem. Phys.* **7**, 1785 (2005)]

We propose a site-site generalization of the Lovett-Mow-Buff-Wertheim integro-differential equation for the one-particle density distributions to polyatomic fluids. The method provides microscopic description of liquid interfaces of molecular fluids and solutions. It uses the inhomogeneous site-site direct correlation function of molecular fluid consistently constructed by nonlinear interpolation between the homogeneous ones. The site-site correlations of the coexisting bulk phases are obtained from the reference interaction site model (RISM) integral equation with our closure approximation. For illustration, we calculated the structure of the planar liquid-vapor as well as liquid-liquid interfaces of n-hexane and methanol at ambient conditions.