

A Modern Solvation Theory: Quantum Chemistry and Statistical Chemistry

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This perspective highlights recent developments in the field of statistical mechanics for molecular liquids, *i.e.* the integral equation (IE) theory, especially focusing on hybrid approaches incorporating quantum chemistry and IE theory. The electronic structure of solvated molecules is characterized, followed by recent developments and applications. The latter include for some specific systems: evaluation of acidity, basicity, pH and pKa, chemical equilibrium and molecular structure, chemical reactions, ionization and electron transfer reactions, as well as excited states and their free energy.

1 Introduction

Chemical solutions play important roles in a wide range of systems, many of which are the subject of present-day research. As just a few examples, chemical solutions are studied using a new experimental technique employed in physical chemistry, they are utilized in numerous practical manners in synthetic chemistry, and they appear ubiquitously in biological systems. Despite the fundamental roles played by solutions in numerous fields, however, the formulation of theoretical treatments of chemical processes in solution systems remains a great challenge. The two most prominent approaches to treating solution systems are the so-called ‘implicit’ approaches, employing dielectric continuum models (for example, the polarizable continuum model (PCM)), and the ‘explicit’ approaches, employing molecular simulations (for example, molecular dynamics (MD) simulations). Recently, a third type of treatment has been the topic of a great deal of study, the integral equation (IE) theory. This can be regarded as a kind of intermediate treatment between the implicit and explicit treatments.

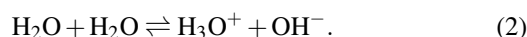
Let us start to consider the pH of neutral water, which is 7 at room temperature. This can be attributed to the fact that $K_w = 1.0 \times 10^{-14}$, where K_w is the ionic product (self-ionization constant) of water. The self-ionization of water accounts for its *amphoteric* nature. Based on the standard treatment, K_w can be expressed in terms of the free energy difference (ΔG°), which is approximately 19 kcal/mol,¹ as

$$\Delta G^\circ = -RT \ln K_w. \quad (1)$$

The self-ionization of water is described by the following

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equilibrium process:



The energy difference of this process is computed using the standard *ab initio* quantum chemical method. Under the rigid-rotor and harmonic approximations, the energy difference is estimated to be approximately 255 kcal/mol at CCSD(T) level.² The discrepancy between 19 kcal/mol and 255 kcal/mol can, of course, be attributed to the solvation effect. Actually, a QM/MM simulation has yielded a very reliable free energy difference.³ It should be noted that cluster models have also been used to obtain ΔG . However, because such models treat systems consisting of ~ 10 molecules, which is too small to observe bulk behavior, the resulting ΔG differs from those obtained from QM/MM simulations. We wish to emphasize the presence of the temperature, T , in Eq. (1) and its resulting role in the process described by Eq. (2). Let us now consider what happens if T is changed. It has been found experimentally that K_w exhibits a temperature dependence, changing monotonically from $\text{p}K_w = -\log K_w = 14.0$ at 298 K to $\text{p}K_w = 12.3$ at 373 K.⁴ Thus, the temperature dependence of the free energy difference is determined by the competing contributions of K_w and T .

From the above considerations, we come to understand two important points. First, because Eq. (2) represents a simple chemical reaction including O–H bond formation and breaking, quantum chemistry is necessary to understand this process. Second, quantum chemistry alone is insufficient to obtain a complete description, because the solvation effect is also important. To describe the solvation effect requires a statistical mechanical treatment of the molecular system. Hence, a unified approach combining quantum chemistry and statistical mechanics is essential for describing solution systems. In a standard quantum chemical method, the only consid-

eration given to T is through the primitive approximations mentioned above. However, in reality, such an approach that largely ignores the macroscopic description is fundamentally lacking. To obtain a complete description of solution system, both macroscopic quantities, most importantly the temperature, which controls the nature of the statistical ensemble of particles, and microscopic phenomena, in particular, the hydrogen bonding and its network, must be considered. Of course, the actual nature of such systems is very complex, but to obtain a proper description, all microscopic phenomena, such as chemical bond formation, should be modeled in such a way that properly takes into account macroscopic quantities, including the temperature.

There exist several computational and theoretical approaches for treating solution systems. Dielectric continuum models, such as PCM,^{5,6} constitute the most widely used and well-established approaches. Molecular simulations, particularly MD simulations, represent another powerful technique for treating molecular ensemble systems. A third approach, IE theory for liquids,⁷ may be regarded as an alternative to these two. Instead of providing a description in terms of the motion of individual molecules, IE theory provides a probabilistic description in terms of the distribution function, which represents the probability of finding a particle (atom or molecule) at a specific position, as predicted by statistical mechanics. Figure 1 displays radial distribution functions (RDFs) of liquid

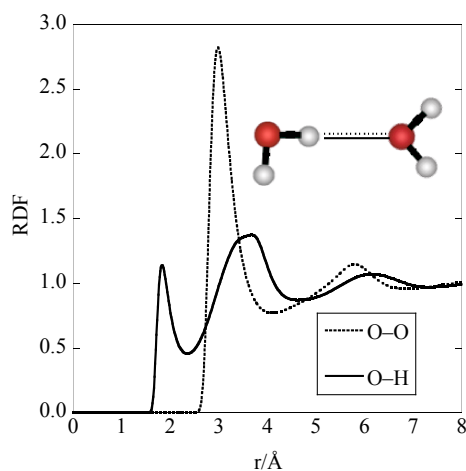


Fig. 1 Radial distribution function of liquid water computed using IE theory.

water. Such functions are typical predictions of IE theory. The function $g(r)$ represents the probability of finding a particle (atom) belonging to another molecule at a specific distance of separation, r , from a reference molecule. Let us focus on the oxygen atom of a specific water molecule. Because all of the water molecules are densely packed in the system, the nearest oxygen atom belonging to another water molecule should be

found at a distance of approximately 3Å from the reference oxygen atom. The first peak of the O-O (dashed) curve corresponds to the direct contact of water molecules. The distinct peak of the O-H (solid) curve appearing at approximately 1.8Å corresponds to the hydrogen bond formed between the oxygen and hydrogen atoms. Note that the covalent binding near 1Å observed in scattering experiments does not exist because only intermolecular interaction is treated in this frame work. The widths of these peaks are, of course, determined by the fluctuations. In the MD approach, this function is obtained by following the time evolution of the particles; a histogram is calculated from a long trajectory by counting the numbers of particles falling into small intervals at each inter-particle distance. By contrast, this function is obtained directly in IE theory; the value of the function is computed for a set of distances between particles $\{r_i|i = 1, 2, \dots, N\}$ on the basis of statistical mechanics.⁸

We now give a brief summary of the features of IE theory. (1) The theory provides a method to derive thermodynamic ensembles and is free from statistical error, or, the so-called sampling problem. In principle, it can treat systems with an infinite number of solvent molecules; no simulation box is required. (2) Because it is expressed in terms of algebraic equations, the computational cost is significantly smaller than in the case of the standard molecular simulation method. This inherent simplicity may allow for the analytic investigation of solution systems. (3) Both the inputs and outputs of the computation are the same as those of simulations. In practice, the computational results obtained from these methods are essentially the same in general. In the rare cases that there are inconsistencies, they are usually due to the approximations used in IE theory or insufficient sampling in the simulation.

In the present article, we focus on a hybrid approach to the treatment of molecular liquids that incorporates statistical mechanics through IE theory and quantum chemistry through various high-level methods. In contrast to other commonly used hybrid approaches, such as PCM^{5,6} and QM/MM,⁹ the IE hybrid approach yields information regarding the microscopic features of solvation, like hydrogen bonding, together with quantum chemical and thermodynamic properties. It is also noteworthy that because of its aforementioned inherent simplicity (2), IE theory can be readily combined with high-level quantum chemical methods, which are generally computationally demanding.

2 IE theory for molecular liquids

2.1 RISM theory

Among the numerous forms of IE theory, in this section we consider the theory applied to molecular liquids, *i.e.*, liquids consisting of polyatomic molecules. The theory for atomic

liquids (simple liquids) dating back to the monumental work by Ornstein and Zernike in 1914 will not be treated. Because it is impossible to fully explain the IE theory, only a brief outline of the theory is presented here, while the physical background is mostly omitted for the sake of conciseness. For readers who are unfamiliar with molecular liquid theory, more detailed explanations can be found in several textbooks^{7,10} and reviews.^{11,12}

The reference interaction site model (RISM), which is also referred to as the site-site Ornstein-Zernike (SSOZ) equation, plays a central role in the field of the statistical mechanics of molecular liquid systems. The theory was originally developed by Chandler and Andersen,¹³ and subsequently it was extended to treat the electrostatic interaction term (XRISM).¹⁴ The theory consists of the following equation:

$$\mathbf{p}\mathbf{h}\mathbf{p} = \mathbf{\omega} * \mathbf{c} * \mathbf{\omega} + \mathbf{\omega} * \mathbf{c} * \mathbf{p}\mathbf{h}\mathbf{p}. \quad (3)$$

Here, ‘*’ denotes a convolution integral, \mathbf{p} is the particle number density, and $\mathbf{\omega}$ is the intramolecular correlation function defining the molecular geometry. In this equation, all functions take the form of $n \times n$ matrices, where n is the number of interaction sites in the solvent molecule, which corresponds to individual atoms or groups of atoms, such as the methyl group (often called ‘united atoms’). For example, the water molecule consists of three atoms, and thus in this case, all of the functions are represented by 3×3 matrices. In the case of $\mathbf{\omega}$, each row (and/or column) corresponds to one of the atoms:

$$\mathbf{\omega} = \begin{pmatrix} \delta(r) & \omega_{\text{OH}}(r) & \omega_{\text{OH}}(r) \\ \omega_{\text{OH}}(r) & \delta(r) & \omega_{\text{HH}}(r) \\ \omega_{\text{OH}}(r) & \omega_{\text{HH}}(r) & \delta(r) \end{pmatrix}, \quad (4)$$

where the (α, γ) th element is proportional to the probability for finding the α th and γ th particles separated by a distance r . The off-diagonal elements are given by

$$\omega_{\text{OH}}(r) = \frac{1}{4\pi l_{\text{OH}}^2} \delta(r - l_{\text{OH}}) \text{ and } \omega_{\text{HH}}(r) = \frac{1}{4\pi l_{\text{HH}}^2} \delta(r - l_{\text{HH}}).$$

These are obtained with the assumption that the distance between the atoms is fixed at a specific value, l_{OH} or l_{HH} ; l_{OH} is covalent bond length between oxygen and hydrogen ($\sim 1.0\text{\AA}$) and l_{HH} is the distance between two hydrogen atoms ($\sim 1.6\text{\AA}$). Hence, the molecular geometry is defined by the function $\mathbf{\omega}$.

In Eq. (3), \mathbf{h} and \mathbf{c} are the total and direct correlation functions, respectively. The elements of \mathbf{h} are related to the RDF between sites α and γ in a simple manner:

$$h_{\alpha\gamma}(r) = g_{\alpha\gamma}(r) - 1. \quad (5)$$

The quantity $g_{\alpha\gamma}(r)$ is what we would like to compute. Because \mathbf{c} in Eq. (3) is also unknown, an additional relation,

called the ‘closure,’ is needed to close this equation. One standard formula used for this purpose is the hyper-netted chain (HNC) closure, given by

$$\begin{aligned} c_{\alpha\gamma}(r) &= \exp[-\beta u_{\alpha\gamma}(r) + t_{\alpha s}(r)] - t_{\alpha\gamma}(r) - 1, \\ t_{\alpha\gamma}(r) &= h_{\alpha\gamma}(r) - c_{\alpha\gamma}(r), \end{aligned} \quad (6)$$

where $u_{\alpha\gamma}(r)$ represents the interaction between sites α and γ , and $\beta = 1/k_{\text{B}}T$. The Kovalenko-Hirata (KH) closure,¹⁵ given by

$$\begin{aligned} h_{\alpha s}(r) &= \begin{cases} \exp[d_{\alpha\gamma}(r)] - 1 & \text{for } d_{\alpha\gamma}(r) \leq 0 \\ d_{\alpha\gamma}(r) & \text{for } d_{\alpha\gamma}(r) > 0 \end{cases} \\ d_{\alpha\gamma}(r) &= -\beta u_{\alpha\gamma}(r) + t_{\alpha\gamma}(r), \end{aligned} \quad (7)$$

is also widely used. Because Eq. (3) is conveniently treated in reciprocal space, the closure equation is generally coupled to it with the aid of the Fourier transformation. The quantities \mathbf{h} and \mathbf{c} are obtained as the solution of these simultaneous equations. Note that the thermodynamic state of the system (represented by T , ρ , etc.) is assumed to be defined in these equations. Equation (3) is applicable not only to neat liquid systems, but to any kind of solution system, including mixture solvents, electrolytes, etc. An infinitely dilute solution can be described by taking the infinitesimal limit of the solute density ($\rho_{\text{u}} \rightarrow 0$).¹⁶ The theory is also capable of describing solute-solvent systems.

2.2 Three-dimensional theory

Although the RISM expresses all of the correlation functions, including the distribution $g_{\alpha\gamma}(r)$, as functions of the distance between interaction sites, r , a three-dimensional (3D) representation is more intuitive and readily understandable. There are several methods for constructing three-dimensional representations of the information contained in the inherently one-dimensional representation provided by the RISM and other methods.¹⁷⁻²¹ The computation of the spatial distribution function (SDF),

$$H_{\alpha}(\mathbf{k}) = \sum_{\gamma} c_{\gamma} * [\omega_{\gamma\alpha}^{\text{V}} + \rho h_{\gamma\alpha}^{\text{V}}], \quad (8)$$

in 3D space is the most direct of these.^{15,22-28} The so-called 3D-RISM is a promising method to evaluate solvation structure in three-dimensional space. It is particularly suited to the treatment of systems containing biomolecules. This point warrants some comments. The water in a biosystem can be separated into parts classified as ‘surface’ and ‘bound,’ according to whether they are surrounded by other water molecules (outside) or by biomolecules, such as proteins (inside). Some protein molecules contain bound water molecules inside their structure, and these water molecules play an essential role in

the protein's function. Because the sampling of the interaction between the protein and water molecules must be carried out over an extensive free energy hypersurface, which usually requires great computational time, it is not easy to compute the distribution using a MD simulation. In particular, it is unfeasible to properly treat water confined in a protein cavity or cleft with the standard MD simulation method, because the trapping of water molecules is a rather rare event, perhaps because of the large conformational fluctuations of the protein or its folding. If a simulation that perfectly sampled the entire configuration space of water molecules could be carried out, the distribution would be correctly obtained. However, in practice, a specific number of molecules must be positioned within each cavity by hand at the start of the simulation, because the water distribution inside a cavity throughout a simulation strongly depends on the initial conditions. By contrast, in the 3D-RISM theory, the SDF is computed without any such *ad hoc* preparations. In principle, this computation does not depend on the initial conditions, because it is carried out through an integration over the entire configuration space. If states in which water is contained within a cavity are thermodynamically stable, then the number of microscopic configurations corresponding to such states will be large, and the distribution function for the molecule obtained from the calculation will reflect this. Electrolytes provide another good example demonstrating the advantage of IE theory, in which careful sampling is usually required in simulations because of the strong Coulombic interaction in the system.²⁹

Starting from pioneering works, such as the molecular Ornstein-Zernike (MOZ) theory³⁰ and reduction to three dimensions of the six-dimensional MOZ equation,²⁸ efforts are still being made to develop an efficient approach. For instance, Griebel and Jager proposed the BGY3dM model, based on the Born-Green-Yvon equation. This model yields 3D SDF.³¹ An efficient algorithm for solving the MOZ equation that utilizes a modified direct inversion of the iterative subspace (DIIS)³² has also been reported.³³ Yokogawa *et al.* proposed an efficient approach to computing 3D SDF called the multicenter-molecular OZ (MC-MOZ) theory.³⁴ The procedure employed in this theory does not require the use of a 3D fast Fourier transformation (3D FFT).³⁵ Because the MC-MOZ theory does not require use of a 3D FFT, numerical computations employing this theory can be highly parallelized, and this allows them to be carried in much shorter times than those of the 3D-RISM theory.³⁶

2.3 Free energy, excess chemical potential

Once **h** and **c** are obtained using the 1D procedure or the 3D procedure, the solvation free energy is readily computed.^{37,38} In the case of an infinitely dilute solution with HNC closure,

the following formula has been derived:

$$\Delta\mu = -\frac{\rho}{\beta} \sum_{\alpha s} \int d\mathbf{r} \left[c_{\alpha s}(\mathbf{r}) - \frac{1}{2} h_{\alpha s}^2(\mathbf{r}) + \frac{1}{2} h_{\alpha s}(\mathbf{r}) c_{\alpha s}(\mathbf{r}) \right]. \quad (9)$$

Here, ρ is the solvent density, and α and s indicate the interaction sites in the solute and solvent molecules, respectively. Unlike in the molecular simulation approach, in the IE theory, a closed formula for the solvation free energy can be obtained. This is one of the greatest advantages of IE theory. Any other thermodynamic quantity can also be derived on the basis of this formula.

Despite its many advantages, IE theory has the disadvantage that the accuracy of its numerical results is sometimes insufficient, due to the approximations employed in the theory. A systematic improvement can be made by utilizing the bridge function. The contribution by Kast and Kloss³⁹ in this regard is crucial to understanding the excess chemical potential, especially in the mathematical context of KH closure. The partial wave theory⁴⁰ serves as the bridge between the RISM and other, more rigorous IE theories.^{41,42} Dielectrically consistent bridge corrections were examined to improve the accuracy of dielectric properties.⁴³ Although the treatment does not follow from a formal and rigorous derivation of the bridge function, several attempts to rigorize it are on-going. One such attempt employed the repulsive bridge correction (RBC).⁴⁴⁻⁵⁰ Further empirical correction methods and combinational approaches have also been proposed to improve the accuracy of the numerical results.⁵¹⁻⁵³

2.4 Other theories

In addition to neat liquid systems, the range of applicability of IE theory has expanded to include a variety of molecular systems. Kovalenko *et al.* proposed a replica RISM theory to treat microporous materials⁵⁴ and a molecular theory for liquid-liquid interfaces.⁵⁵ The molecular theory for these systems seems to be rather limited, though there are many studies concerning simple liquid systems consisting of simple (spherical) atoms. Contrastingly, solid-liquid interfaces have been extensively studied for polyatomic systems. Akiyama *et al.* utilized a polymer RISM theory to describe an atomic wall, and they studied the solvation structure of water at an electrode-solution interface.⁵⁶ The 3D-RISM was applied to compute the distribution of liquid water in the vicinity of a Lennard-Jones surface.^{23,57} A singlet-RISM, in which a solid is treated as an atomic site of infinite radius, is another efficient approach.⁵⁸ A 2D-RISM has recently been developed in which the solvation structure near the interface is described with a two-dimensional density distribution along two directions, one perpendicular to the interface and the other parallel to it.⁵⁹

The internal structure of a molecule and its flexibility are also important subjects in IE theory. A chain molecule has numerous conformations, and the equilibrium of such a molecule has been studied for many years.^{60,61} A simplified intramolecular correlation function is employed in the PRISM approach,⁶³ and Munakata *et al.* proposed an equation to determine this function based on density functional theory.⁶² Several new approaches have also been reported.^{64–67}

Finally, we briefly comment on solvation dynamics. The original RISM and other IE theories are basically theories of the equilibrium state. However, the dynamical behavior of systems can be expressed in terms of the time evolution of variables in Liouville space.¹⁰ The site-site Smoluchowski-Vlasov (SSSV) equation proposed by Hirata in 1992 is an example of a theory that employs such an approach.⁶⁸ Also, the surrogate Hamiltonian description is useful for analyzing the molecular response of a solvent to a sudden change in the system.⁶⁹ Mode-coupling theory has also been utilized to describe dynamical processes on the basis of the interaction-site representation.⁷⁰ These methods have been further extended to treat many types of chemical processes, including the solvation dynamics of a benzonitrile excited state in polar solvents,⁷¹ dynamics near solid-liquid interfaces,⁷² and a generalization of the SSSV equation.⁷³

In the RISM and other IE theories, the treatment of many-body problems in molecular systems is based mainly on classical mechanics. The validity of this treatment is due to the fact that the thermal energies of such systems are generally small compared to the energies involved in chemical bonds. In other words, the two types of interactions in such systems – intramolecular and intermolecular – are of very different strengths, and thus the collisions characterizing the latter can be treated without considering the former. Of course, this simplifies the problem considerably. For simple liquids (*i.e.*, those whose intermolecular interactions are isotropic), the problem is indeed readily treated. However, for (polyatomic) molecular liquids, the situation is more difficult to treat both analytically and numerically, and the results for such liquids are still quite limited. This anisotropy exhibited by the molecules in non-simple liquids makes their treatment complicated but, at the same time, interesting.

3 Hybrid methods of IE theory and quantum chemistry

3.1 RISM-SCF: the first generation

The RISM is regarded as an alternative to MD simulations. Similarly to the QM/MM method, the RISM-SCF is a hybrid method consisting of the RISM and quantum chemical computations. This theory was developed in the research group of Late Prof. Shigeki Kato at Kyoto University. As the first

step in its development,⁷⁴ the solvated Fock matrix was introduced in a rather intuitive manner. Soon after, this operator was rederived on the basis of a variational principle.⁷⁵

In the original procedure, the electrostatic potential at a solute site is expressed as a mean field by making use of the total correlation function $h_{\alpha s}(r)$:

$$F_i^{\text{solv}} = F_i - f_i \sum_{\alpha} V_{\alpha} b_{\alpha}, \quad V_{\alpha} = \rho \sum_s q_s \int_0^{\infty} 4\pi r^2 \frac{h_{\alpha s}(r)}{r} dr. \quad (10)$$

Here, b_{α} is a proper population operator. Solving for this modified Fock operator, the solvated electronic structure is obtained. Partial charges of the solute molecule are then assigned by applying a least-square fitting technique to the electrostatic potential (ESP). These partial charges are utilized to solve the RISM equation. The newly obtained $h_{\alpha s}(r)$ is then used to rederive the Fock operator. This procedure is repeated until convergence of the RISM-SCF is realized. Hence, the electronic structure of a solute in solution and the solvation distribution around the solute are determined in a self-consistent manner.

In the latter treatment,⁷⁵ the total energy of the solution system is defined as

$$\mathcal{A} = E_{\text{solute}} + \Delta\mu, \quad (11)$$

where E_{solute} is the total energy of the solute molecule described by standard *ab initio* molecular orbital theory. The quantity $\Delta\mu$ is defined in Eq. (9). The energy \mathcal{A} is a function of the molecular orbital coefficient, v_{ri} , the CI coefficient, C_I , and the correlation functions in RISM theory, $h_{\alpha s}$, $c_{\alpha s}$ and $t_{\alpha s}$. Imposing the constraints of the orthonormality of v_{ri} and C_I , the following function is defined:

$$\mathcal{L} = \mathcal{A}[\mathbf{c}, \mathbf{h}, \mathbf{t}, \mathbf{v}, \mathbf{C}] - E \left(\sum_I C_I^2 - 1 \right) - \sum_{im} \varepsilon_{im} (S_{im} - \delta_{im}). \quad (12)$$

Then, using a variational principle with respect to all the functions, a set of equations describing a solution system is obtained with the aid of the variational nature of the HNC formula.³⁸ It is thus seen that the RISM-SCF consists of two major theories, the *ab initio* molecular orbital (MO) theory and the RISM. It is also noteworthy that this variational treatment enables us to derive an analytical expression of the energy gradient with respect to the nuclear coordinates, which is crucial for computing the stationary point on the free energy surface corresponding to the equilibrium geometry or the transition state geometry. The RISM-SCF method can be regarded as an alternative to QM/MM, because both provide information regarding the microscopic solvation structure, such as hydrogen bonding.

3.2 RISM-SCF-SEDD: the second generation

Although the original version of RISM-SCF was successfully applied to a wide range of chemical phenomena in the solution phase, it is sometimes difficult to realize numerical convergence in the SCF process.⁷⁶ This drawback is mainly attributable to the procedure of determining the partial charge assigned to the atom in the solute molecule. This results from the well-known, ill-posed nature of the ESP charge fitting procedure,⁷⁷ and the difficulty becomes greater when a buried atom exists in the system. Another drawback of the original RISM-SCF concerns the grid points that are necessary to perform the fitting. It has been found that the computed values of the partial charges depend slightly on the choice of the set of these points.

Yokogawa *et al.* laid the groundwork for the second generation of the theory.⁷⁸ One of the main advantages of this improved form of the theory is its explicit treatment of the spatial electron density distribution (SEDD). By utilizing the auxiliary basis sets (ABSs) at each atom, following the procedure proposed by Gill *et al.*,⁷⁹ this treatment makes it possible to obtain a more accurate description of the Coulombic interaction.⁷⁸ The electron density $\rho(\mathbf{r})$ in this theory is represented by

$$\rho(\mathbf{r}) = \sum_i^{N_{\text{ABS}}} d_i f_i(\mathbf{r}), \quad (13)$$

where N_{ABS} is the number of ABSs, d_i are the expansion coefficients, and $f_i(\mathbf{r})$ are the ABSs, expressed as Gaussian functions, whose exponents are taken from the employed basis sets. The electrostatic potential in this method is given by

$$V_i = \rho \sum_s q_s C_i \left(\frac{\pi}{\zeta_i} \right)^{\frac{3}{2}} \int_0^\infty 4\pi r^2 \frac{\text{erf}(\sqrt{\zeta_i} r)}{r} h_{\alpha s}(r) dr, \quad (14)$$

where i indexes the ABSs centered on the atom α ($i \in \alpha$), and ζ_i is the exponent of the Gaussian function taken from that of the basis sets employed in the *ab initio* MO computations. Owing to this treatment, RISM-SCF-SEDD does not require a set of grid points, which can be regarded as artificial parameters in the original RISM-SCF method. Furthermore, the new method is numerically much more robust than the original method, even if a buried site exists in the solute molecule. Consequently, RISM-SCF-SEDD significantly extends the realm of applicability of the hybrid method. In fact, it is unfeasible to realize convergence of the iterated hybrid procedure described above without using the SEDD method for many chemical systems. Computations for chemical processes in electrolytes, ionic liquids, and organic solvents can be realized only after the development of the appropriate RISM-SCF-SEDD theory.

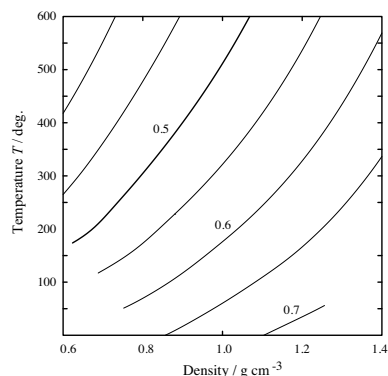


Fig. 2 Change of dipole moment (Debye unit) with respect to the value of an isolated water molecule. Reprinted with permission from Hirofumi Sato and Fumio Hirata, *J. Chem. Phys.*, **111**, 8545 (1999). Copyright 1999, American Institute of Physics.

3.3 Hybrid methods employing other integral equation theories

Several other hybrid methods incorporating IE theory and quantum chemical methods have been proposed. The hybrid method of MOZ and *ab initio* MO theory (MOZ-SCF) was developed by Yoshida *et al.* and applied to water and formaldehyde in aqueous solution.⁸⁰ Later, the energy gradient technique was also implemented.⁸¹ The 3D-RISM was first combined with the Kohn-Sham density functional theory (KS-DFT).⁸² The resulting method was applied to study solvation effects on conformational equilibria, tautomerization energies, and activation barriers⁸³ through the implementation of the Amsterdam Density Functional (ADF) package with analytical gradients.⁸⁴ The hybridization with *ab initio* molecular orbital theory was also carried out around the same time (3D-RISM-SCF).⁸⁵ That was followed by the improvement of the algorithm used the solute–solvent electrostatic interaction.^{86,87} Du and Wei independently developed a hybrid method based on 3d-RISM-HNC and demonstrated the computation by studying a system consisting of an N-methyl amine molecule in aqueous solution.⁸⁸ A similar approach was proposed by Kloss *et al.*, and it was applied to investigate the free energy difference for the gauche-trans equilibrium and to pK_a shift calculations.⁸⁹ A further combination, that of 3D-RISM and QM/MM, was proposed for large, biomolecular systems in solution.⁹⁰ The role of solvent in the intercalation of proflavine with DNA was elucidated through application of this approach.

All of the aforementioned methods are similar to the QM/MM method, in which a quantum chemical system is immersed in an environment described by classical mechanics. Contrastingly, Car-Parrinello method provides a quantum mechanical description of the whole system. Although

a DFT based MD study reveals that the melting point of water computed with PBE or BLYP functional is up to 400 K,⁹¹ it is another prominent approach to treating solution systems. Another combination of QM and RISM allows for the treatment of neat liquids without any empirical parameters.⁹² This *ab initio* method was applied to analyze the liquid structures and electronic and thermodynamic properties of liquid water over a wide range of temperatures and densities.⁹³ Figure 2 plots the change of molecular dipole moment as a function of temperature (T) and density (ρ). At room T and standard ρ , the dipole moment is increased by 0.7 D from that of an isolated water molecule. This is consistent with the experimental knowledge that the dipole moments in the gas phase and liquid phase are about 1.8 and 2.5 Debye, respectively. In addition, the computational result at high T and low ρ shows good agreement with an analysis of NMR chemical shift.⁹⁴

Finally, we comment on improvements in the description of intermolecular interactions. Although the electrostatic contribution dominates the solute–solvent interaction in many molecular systems, other contributions, such as the dispersion interaction and Pauli repulsion, are also important, especially in the description of short-range interactions. Because the solute–solvent interaction is fundamentally quantum mechanical and non-local in nature, a treatment based on first principles is difficult to construct. For this reason, empirical interactions, such as the Lennard-Jones potential, are widely adopted. Several attempts have been made to systemize the treatment of the interaction by utilizing spectral representation⁹⁵ and perturbation theory.⁹⁶ Detailed studies of dispersion and repulsive interactions have also been reported.⁹⁷ Furthermore, charge migration between solute and solvent molecules and inhomogeneity or non-uniform nature of solvation are other examples that need to be incorporated later on in the near future.

3.4 Electronic structure of solvated molecules

3.4.1 Characterization of the electronic structure

In the solution phase, a solvent generates a strong electrostatic field experienced by the solute, especially in polar solvent systems. A direct indication of the strength of this field is provided by the experimental ionization potential of the solvated molecule, which often significantly differs from that in the gas phase. Further information is provided by the mean field given in Eq. (10), which is generally on the order of a few eV. Because of the influence of the solvent, the electronic structure of the solvated molecule differs considerably from that in isolation. There are a variety of methods to characterize the electronic wave function and its distortion caused by the solvation. Partial charges, like that used in Mulliken population analysis, assigned to each atom of the molecule and the bond order index are representative of the quantities used to characterize

the electronic structure. In general, the electronic structure of a solvated molecule is distorted (polarized) with respect to that in the isolated state. The energy difference between the solute in the isolated state (E_{isolated}) and that in the solvent (E_{solute}) is a measure of the solvation effect:

$$E_{\text{reorg}} = E_{\text{solute}} - E_{\text{isolated}} = \langle \Psi | H | \Psi \rangle - \langle \Psi_0 | H | \Psi_0 \rangle, \quad (15)$$

where H is the electronic Hamiltonian of the (isolated) solute molecule, and $|\Psi\rangle$ and $|\Psi_0\rangle$ are the total electronic wave functions in solution and in the isolated states, respectively. Hence, the total energy shown in Eq. (11) can be rewritten as follows:

$$\mathcal{A} = E_{\text{isolated}} + E_{\text{reorg}} + \Delta\mu. \quad (16)$$

The energy E_{reorg} is not negligible for the description of chemical phenomena. The change in the solvation energy due to the polarization is nearly proportional to E_{reorg} . This reveals that the linear response regime provides a good description of the solvation process.⁹⁸ Several analyses in this regard employing RISM-SCF, RISM-SCF-SEDD and other hybrid methods have been reported.

The orbital energy, ϵ , of a one-electron wave function is directly related to the ionization potential, and it represents another useful measure to examine the solvation effect. Actually, the value of ϵ computed using the RISM-SCF or the PCM is usually shifted from that in the isolated state, due to the solute–solvent interaction. Although the shift $\Delta\epsilon$ appears to be rather complicated at first glance, it can be approximately accounted for by the following simple equation:⁹⁹

$$\Delta\epsilon = \frac{(2D+1)(n^2+2)}{6(2D+n^2)} E^{UV}. \quad (17)$$

Here, D is the dielectric constant of the solvent, n is the refractive index of the solute molecule, and E^{UV} is the solute–solvent electrostatic interaction assigned to each orbital. The quantity $\Delta\epsilon$ corresponds to the spectral shift of the ionization potential. It is noted that both RISM-SCF and PCM yield results that are consistent with Eq. (17). Investigation of the orbital-free embedding potential approach has been reported in application to solvatochromic shifts.¹⁰⁰

It may be possible to obtain a more visual representation of the distortion of the electronic structure by focusing on the nature of the chemical bonds. A method to evaluate the weights of the resonance structures based on orbital localization and a second quantized expression enables one to analyze the computed wave function,¹⁰¹

$$A^-B^+ : \sum_{\mu \in A} \sum_{\nu \in A} \langle \phi_i | \chi_{\nu}^{\sigma_1^+} \chi_{\mu}^{\sigma_2^+} \phi_{\nu}^{\sigma_2^-} \phi_{\mu}^{\sigma_1^-} | \phi_i \rangle, \quad (18)$$

$$A-B : 2 \sum_{\mu \in A} \sum_{\nu \in B} \langle \phi_i | \chi_{\nu}^{\sigma_1^+} \chi_{\mu}^{\sigma_2^+} \phi_{\nu}^{\sigma_2^-} \phi_{\mu}^{\sigma_1^-} | \phi_i \rangle, \quad (19)$$

$$A^+B^- : \sum_{\mu \in B} \sum_{\nu \in B} \langle \phi_i | \chi_{\nu}^{\sigma_1^+} \chi_{\mu}^{\sigma_2^+} \phi_{\nu}^{\sigma_2^-} \phi_{\mu}^{\sigma_1^-} | \phi_i \rangle, \quad (20)$$

Table 1 Characterization of chemical bonds in the isolated state and in aqueous solution

| No. | structure | basis set I | | basis set II | |
|-----|-----------|-------------|---------|--------------|---------|
| | | isolated | aqueous | isolated | aqueous |
| 1 | | 18.2 | 15.3 | 18.1 | 15.2 |
| 2 | | 41.0 | 42.4 | 41.2 | 42.3 |
| 3 | | 8.6 | 5.8 | 8.2 | 5.5 |
| 4 | | 22.0 | 28.7 | 23.1 | 29.6 |
| 5 | | 9.8 | 8.1 | 9.5 | 7.9 |
| 6 | | 0.9 | 0.5 | 0.9 | 0.5 |
| 7 | | 0.4 | 0.1 | 0.1 | 0.0 |

The standard Hartree-Fock and RISM-SCF-SEDD method were used to compute the weight of each resonance structure (shown in %). I and II are standard double zeta (DZV) and triple zeta plus polarization (TZP) basis sets, respectively.

where χ_{μ}^{+} and ϕ_{ν}^{-} are, respectively, the creation and annihilation operators related to the biorthogonal atomic orbital basis functions, μ and ν . As shown in Table 1, the electronic structure is distorted by the solvation, and the contribution from a covalent bond is generally decreased.

NMR chemical shielding is regarded to be a good probe of the wave function. This effect was derived within the framework of RISM-SCF.¹⁰² However, further investigation is necessary, especially with regard to short-range interactions. The representation of the interaction may be improved through utilization of recently developed techniques^{95–97} or by direct inclusion of the influence of nearest-neighbor solvent molecules in the quantum-mechanical description.¹⁰³

3.4.2 Relationship to other hybrid methods

The PCM developed by the Pisa group⁵ is certainly the most commonly used approach for computing the electronic structure of solvated molecules, and its applications are innumerable. It has been well established that this method provides

reliable results for many chemical phenomenon under the condition that there is no significant contribution from any local interaction, such as hydrogen bonding. A comparison of the RISM-SCF and the PCM was made for a typical S_N2 reaction of methyl chloride and chloride anions in aqueous solution.¹⁰⁴ Interestingly, these two methods yield very similar energy profiles: The energy profiles computed with the RISM-SCF and the PCM look very similar (Please refer Figure 1 of the reference¹⁰⁴). The barrier heights are respectively 23.5 and 22.7 kcal/mol, though the energy components differ slightly. The height is also very close to that of the pioneering work by the Jorgensen group, in which Monte Carlo and *ab initio* MO computations are combined.¹⁰⁵ The close similarity between these results is probably due to the fact that the reaction can essentially be characterized as a charge shift, in which the long-range electrostatic field generated by the bulk solvent is dominant. The conformational equilibrium of 1,2-dichloroethane in aqueous solution was also examined for comparison.¹⁰⁶

An important alternative to the PCM and the RISM-SCF is the QM/MM method. Several efficient and related approaches based on QM/MM method have been proposed including averaged solvent electrostatic potential/molecular dynamics (ASEP/MD),¹⁰⁷ real space grid QM/MM,^{108,109} quantum mechanical charge field molecular dynamics (QMCF-MD) and so on.¹¹⁰ Compared to biological systems, for example those containing enzymes, the number of applications to solution phases may be relatively small, but the obtained data from QM/MM and RISM-SCF are very similar in many chemical systems as described below.

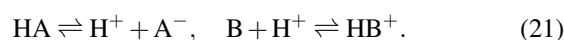
At present, application of the 3D-RISM-KH theory is facilitated by the computational packages ADF and AMBER.⁸⁴ The number of applications will almost certainly increase due to the popularity of the available computational packages. In any case, additional detailed studies are needed to further our understanding of solution systems.

4 Recent developments and applications

The hybrid methods discussed above have been applied to a variety of chemical processes over the past few decades. The discussion given in the present section is confined to the hybrid methods incorporating quantum chemistry and IE theory. For further discussion of IE theory, the RISM and the 3D-RISM, refer to Refs.^{7,10, 11,12} and¹¹¹.

4.1 Acidity, basicity, pH and pK_a

Acidity and basicity are the most fundamental properties of a molecule in solution:



In both cases, the free energy difference in the solution phase is the quantity that determines the equilibrium. Computation of pK_a based on hybrid method is very challenging.^{3,112} Kawata *et al.* reported RISM-SCF computations applied to the irregular order in the basicity of substituted methylamines¹¹³ and the acidities of haloacetic acids.¹¹⁴ The classical problem of the acid strength of hydrogen halides (HX, where X=F, Cl, Br, I) in aqueous solution has also been studied.¹¹⁵ The characteristic behavior of hydrogen fluoride as a weak acid was explained in terms of the enhanced stability of the non-dissociated form of the molecule in aqueous solution due to the double hydrogen bonding.

As described in the introduction, the theoretical evaluation of the ion product of water and its logarithm (K_w and pK_w) is usually very difficult, because it requires highly accurate treatments of both the electronic and liquid structures, as well as their coupling. The RISM-SCF was applied in a series of works¹¹⁶ to elucidate the molecular origin of temperature and density dependences of pK_w over wide ranges. The results obtained in those works are consistent with the experimental results. The behavior of pK_w is ascribed mainly to the difference in the solvation free energy for the equilibrium shown in Eq. (2), because E_{isolated} appearing in Eq. (16), which corresponds to the reaction-energy difference, depends on neither the temperature nor density. It is also noted that the contribution from E_{reorg} is crucial for properly evaluating the behavior of pK_w . Here, the contribution from hydroxide (OH^-) is entirely different from that of the other species, and this gives rise to the observed behavior of pK_w .

The relation between pK_w and the free energy difference ΔG° given in Eq. (1) is representative of the general case. In general, we have

$$\Delta G = -RT \ln K_a, \quad (22)$$

where K_a is the acid dissociation constant for an arbitrary molecule, and ΔG is the relevant free energy. The most widely employed method to evaluate ΔG utilizes a dielectric continuum model with $\epsilon = 80$. It is noted, however, that an aqueous solution should be considered in a different way. In the standard approach, the pH of an aqueous solution is determined by the concentration of the acidic (basic) species. Hence, the effect of the ionic strength in the system is entirely ignored in conventional theoretical models. In the RISM, the number density is employed to define the concentration of the species in the system (see Eq. (3)). For this reason, it is not necessary to count explicitly the particle numbers in the target system. Hence, an aqueous solution with the desired pH can be theoretically realized by controlling the density of the proton species.¹¹⁷ It has been found that the effect of the ionic strength is insignificant for moderate values of the pH, but it is important for $\text{pH} < 2$. This suggests that the widely employed conventional pK_a prediction using the evaluation of the free

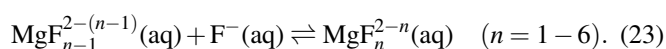
energy in pure water, *i.e.* $\epsilon = 80$, is safely applicable in most cases. The hydrogen-bonding solvation structure is also significantly affected only in the low pH region.

4.2 Chemical equilibrium and molecular structure

Solvation often affects chemical equilibrium. The syn-/anti-conformational equilibrium of acetic acid in aqueous solution¹¹⁸ is a previously studied example. The free energy difference between the two conformers computed using the RISM-SCF method is 1.7 kcal/mol, which is close to the result 1.1 ± 0.3 kcal/mol obtained from the QM/MM computations based on AM1 carried out by Gao *et al.*, while it is consistent with the experimentally obtained estimate of 1–2 kcal/mole.¹¹⁹ Another prototypical system of this kind consists of formamide and formic acid,¹²⁰ which interconvert through a tautomerization. Ishida *et al.* carried out RISM-SCF computations of the energy difference in various solvents, including carbon tetrachloride (CCl_4), carbon disulfide (CS_2), dimethyl ether (DME), tetrahydrofuran (THF), acetonitrile (CH_3CN), and dimethyl sulfoxide (DMSO).¹²¹ The keto-enol tautomerization of acetylacetone is interesting, because the equilibrium is governed by the surrounding solvent. While the enol form is stable in the gas phase and in non-polar solvent, the keto form is dominative in a polar environment. This trend is nicely described by the RISM-SCF method,¹²² though Schlund *et al.* pointed out the importance of the basis sets in this system.¹²³ The tautomeric equilibrium of 2-pyridone and 2-hydroxypyridine is another typical example. In this case a significant contribution to the solvation free energy from hydrogen bonding was found, especially those at the nitrogen and oxygen atoms.¹²⁴

Quantum chemistry has contributed greatly to the elucidation of molecular structure. In the present context, it has provided the results discussed in the following. Because the electrostatic field generated by the environment can be strong, the molecular geometry is often altered by solvation. For example, Ishida, Rosky and Castner reported that the structure of urea in aqueous solution is closer to that of the gas phase than a planar crystal structure.¹²⁵ The change in molecular structure can be directly observed in spectroscopy experiments. For example, the molecular properties of the triiodide ion (I_3^-) in polar liquids have been studied with many experimental techniques, and there is strong evidence that the nominal $D_{\infty h}$ symmetry of the ground-state structure can be broken. In fact, the computed free energy surface in aqueous solution is very flat with respect to nuclear motion. This indicates that there is a large probability for the appearance of structures with lower symmetry.¹²⁶ A similar symmetry lowering was reported for a system of carbonate and nitrate anions in aqueous solution investigated using QM/MM method¹²⁷, RISM-SCF-SEDD method¹²⁸ and QMCF-MD.¹²⁹ The RISM-SCF-SEDD

and QMCF-MD computations show that the structure of the nitrate anion retains planarity in both gas and solution phases. By contrast, symmetry breaking involving loss of planarity occurs for a system consisting of carbonate anions in an aqueous solution from D_{3h} to C_{3v} (or lower). This is consistent with the results of experiments measuring IR and Raman spectra. It is noteworthy that the symmetry breaking of a molecule in the solution phase is closely related to the coupling between the electronic structure of the molecule and the environment. In this context, a hybrid method is necessary to explore the possibility of symmetry breaking. In addition, the accurate evaluation of the solvation free energy and/or its analytical energy gradient with respect to the nuclear coordinates is needed to specify the location of the minimum of the energy surface with small statistical error. In a recent study, several possible species of magnesium fluoride were examined in aqueous solution,¹³⁰ considering the transitions



Because the free energy difference governs the stability among these hydrated species, a reliable evaluation of the energy with uniform accuracy for all n is required. Interestingly, the running coordination numbers of solvent water molecule are fully consistent with the number of vacant site of fluoride ligands (Please refer Figure 6 in the original paper¹³⁰). Moreover, the mole fraction of the system in an actual system is determined not only by the stability but also by the concentrations of the species. Recent QMCF-MD study also reported that the first hydration shell of Mg^{2+} is hexa-coordinated.¹³¹

4.3 Chemical reactions

Chemical reactions are obviously one of the most important classes of phenomena studied in chemistry. Almost all experiments in the field of synthetic chemistry utilize the solution phase, and the effect of the solvation often governs the reactivity and the selectivity of the product. Needless to say, quantum chemistry is also necessary to describe such systems, because bond formation and breaking is the phenomenon of primary interest. The $\text{S}_{\text{N}}2$ reaction is a typical example. In addition to the aforementioned symmetric reaction, Menshutkin-type reactions in the solution phase have been thoroughly studied:



The pioneering QM/MM simulation carried out by Gao *et al.* clearly demonstrates the importance of the solvation,¹³² especially in the product state of the reaction. This is a typical feature of chemical reactions in the solution phase: The bond breaking itself is usually endothermic, but the instability is compensated for by the stabilization due to solvation. A computation performed for the same reaction using a more

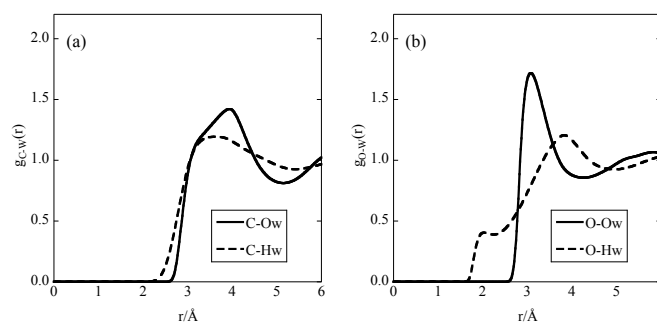
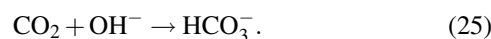


Fig. 3 RDFs between CO_2 atomic sites, carbon and oxygen, and solvent water. Solid and dashed lines refer to the water oxygen and hydrogen, respectively.

sophisticated model (RISM-SCF coupled with MP2) yielded essentially the same results.¹³³ This reaction was further studied from the point of view of reaction dynamics based on the solution reaction path Hamiltonian through evaluation of the transmission coefficient.¹³⁴ A drastic change in the reaction profile was also found in the following ubiquitous process by means of RISM-SCF-SEDD:¹³⁵



Leung *et al.* computed the free energy difference on the basis of the simulation using Vienna ab initio simulation package (VASP) corrected with a MP2 calculation.¹³⁶ Their result and RISM-SCF-SEDD study provide qualitatively equivalent results. Different from the $\text{S}_{\text{N}}2$ reaction, the charge-separation does not occur, but the solvation affects the stabilization of reactant and product in a delicate manner. As a consequence, the reaction profile in the solution phase is very different from that in an isolated system: the great stabilization of the product (more than 40 kcal/mol) is significantly reduced. The energy change of the reaction computed by RISM-SCF-SEDD is -16 kcal/mol, which is close to the result by Leung *et al.* (-12.5 kcal/mol). The barrier heights in aqueous solution phase with RISM-SCF-SEDD and theirs are respectively 6.1 kcal/mol and 7.1 kcal/mol.

Figure 3 shows RDFs computed by RISM-SCF-SEDD method.¹³⁷ Although a small peak corresponding to hydrogen bonding is clearly observed in RDF between CO_2 oxygen and water hydrogen ($\sim 2\text{Å}$), all the functions closely resemble their results shown in Figure 2 of the reference¹³⁶. QMCF-MD study also reports a broad peak of C-O_w with a maximum at 4.0 Å¹³⁸ CO_2 is a simple molecule, but it has rich chemistry. For example, its solubility is larger than that of CO, though CO_2 is larger in size and has no dipole moment.¹³⁹ Other chemical processes in the solution phase have also been elucidated at the molecular level, including CO_2 capture by amine in aqueous solution,¹⁴⁰ proton-coupled electron transfer of the phenoxyl/phenol couple,¹⁴¹ and Grignard reagents in

ether solvent.¹⁴² For this process, the reaction with acetone was found to proceed through the linear dimeric reaction path using the free energy gradient technique of RISM-MP2.

One of the several distinct advantages of the RISM-SCF methods is their capability of treating systems with a wide range of solvent and thermodynamic conditions, including a wide range of temperatures. Also, as mentioned several times above, they provide a computationally efficient means to reliably evaluate the free energy. This allows one to perform computations for larger systems, such as transition metal complexes, using a high-level theory.

One example of a system in which the first of these advantages is exploited is the Diels-Alder reaction in the subcritical state.¹⁴³ Because the temperature and density (corresponding to the pressure) of the system can be readily controlled through the input parameter appearing in Eq. (3) and the closure equation, the effect of the thermodynamic conditions on the reaction profile can be directly calculated. In the cycloaddition of cyclopentadiene with methyl vinyl ketone, *endo/exo* selectivity was computed on the basis of the free energy difference. The results are qualitatively consistent with the experimentally observed selectivity. This method also enables one to study chemical reactions in room temperature ionic liquids (RTIL). In general, the strong electrostatic interaction of solvent molecules in RTILs makes it difficult to properly describe the solvation with molecular simulations, such as molecular dynamics simulations. Although QM/MM simulations based on semi-empirical quantum chemical computations have been carried out,¹⁴⁴ *ab initio* computations have not yet been performed, because of the difficulty in the sampling. The application of the RISM to a RTIL system was first done by Bruzzone *et al.*¹⁴⁵ and by Malvaldi *et al.*¹⁴⁶ Later, the hybrid RISM-SCF-SEDD method was applied to a Diels-Alder reaction at CCSD(T) level,¹⁴⁷ and the same reaction was subsequently investigated using KS-DFT/3D-RISM-KH theory by Chiappe *et al.*^{148,149} The RISM-SCF-SEDD method was also applied to the S_N2 reaction of a methyl *p*-nitrobenzenesulfonate molecule and a chloride anion in [mmim][PF₆].¹⁵⁰

Concerning the second advantage mentioned above, computations for transition metal complexes are distinctive examples of the applications of the theory. Although DFT allows one to treat a wide variety of catalytic reactions with transition metal complexes, consideration of the solvation effect is still limited. Owing to the development of the RISM-SCF-SEDD method, convergence of the self-consistent treatment is remarkably improved. This has made possible computations for many chemical systems, including the complex formation of [RuCp]⁺ and coronene in dichloromethane solvent¹⁵¹ and the oxidative addition of methyl iodide to a Pt(II) complex in nitromethane solvent.¹⁵² In the latter case, a dissociated iodide anion is stabilized by the solvation, and the reaction profile is

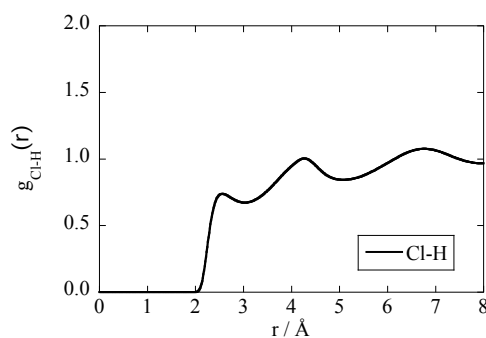
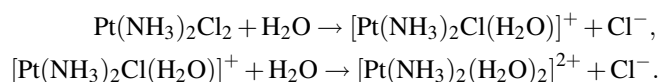


Fig. 4 RDF between chloride of *cis*-Pt(NH₃)₂Cl₂ and solvent hydrogen.

significantly different from that in an isolated system. Another example is the aquation reaction of *cis*-platin complex, which is a well-known anti-tumor drug.¹⁵³ In this reaction, the injected reagent loses a chloride anion, and this is followed by a second aquation reaction:



The same reaction has been studied using a variety of methods. In particular, the solvation structure is extensively reported. Table 2 lists the first peak position of RDFs of Pt(NH₃)₂Cl₂ in aqueous solution, showing that the peak positions of RDFs are very similar to each other. Figure 4 is RDF between chloride and solvent oxygen computed by RISM-SCF-SEDD, which looks very similar to that obtained by FMO(3)-MP2-MD method.¹⁵⁴ The energy profile computed with RISM-SCF-SEDD in aqueous solution is drastically changed from that in the gas phase (Please refer Figure 3 of the reference¹⁵³). The stabilization due to solvation is enhanced as the total charge of the Pt complex is increased through the reaction. Unfortunately, the computed free energy change of the reaction has not been reported except for this study. Note that the energy computations were performed at CCSD(T) level, combined with the solvation effect.¹⁵³ Car-Parrinello study on an analogue, oxaliplatin, in aqueous solution was also reported.¹⁵⁸

Table 2 The first peak position of RDFs of *cis*-Pt(NH₃)₂Cl₂ (Å)

| | Pt-O _w | H-O _w | Cl-H _w |
|------------------------------|-------------------|------------------|-------------------|
| RISM-SCF-SEDD ¹⁵³ | 4.04 | 1.89/1.97 | 2.57 |
| FMO(3)-MP2-MD ¹⁵⁴ | 4.02 | 1.96 | 2.45 |
| CPMD ¹⁵⁵ | – | 1.9 | 2.5 |
| classical MD ¹⁵⁶ | 4.2 | 1.8 | 2.6 |
| Monte Carlo ¹⁵⁷ | 4.45 | 1.95 | 2.65 |

4.4 Ionization and electron transfer reactions

In the field of quantum chemistry, it is usually possible to explicitly treat all of the atomic coordinates in a system. This is because there exists a one-to-one correspondence between the geometrical structure of all the molecules and the potential energy, which is useful to characterize the system. Contrastingly, the concept of the free energy is necessary to describe a solution system. In this case, because there are infinitely many configurations (geometrical structures) with virtually the same potential energies, the correspondence used in quantum chemistry is no longer valid. In general, the evaluation of the free energy is a very time-consuming task. Thermodynamic integration and free energy perturbation techniques have been established in the field of classical molecular simulations, and they have been widely utilized in conjunction with the QM/MM method. In particular, a new powerful strategy called the energy representation method has been proposed by Matubayasi *et al.*,¹⁵⁹ which was combined with QM/MM method (QM/MM-ER).¹⁶⁰ The method is applied to a wide range of chemical phenomena in aqueous solution.¹⁶¹ The Sprik group is working vigorously to address the problem of the redox reaction based on DFT based MD.¹⁶²

As mentioned in Section 2, the RISM method and other IE theories are capable of yielding analytic expressions for the free energy. The same is true in the case of hybrid-type IE theories. In solute–solvent systems, a set of spatially-fixed nuclear coordinates sufficient to describe the critical structure of the solute molecule under consideration is introduced so as to facilitate evaluation of the (solvation) free energy hypersurface as a function of these coordinates. In this way, an infinite number of degrees of freedom are reduced to a small number of coordinates. Although the original RISM applies only to the equilibrium state, Chong *et al.* proposed a procedure to extend it in order to treat the nonequilibrium free energy surface arising from solvent fluctuations.¹⁶³ On the basis of this treatment, a Marcus-type free energy profile along the reaction coordinate was evaluated for a system consisting of *N,N*-dimethylaniline in an acetonitrile solvent and 1,4-dimethoxybenzene using information obtained from the RISM-SCF method.¹⁶⁴ The computed solvent reorganization energy, λ , was compared with experimental results. This method was also applied to hexaammineruthenium (II, III) in aqueous solution.¹⁶⁵ The electronic and spin structures of the dinuclear transition metal complexes ($[\text{Fe}_2\text{S}_2(\text{SCH}_3)_4]^{2-/3-}$) in a DMSO solvent were derived by Higashi *et al.*¹⁶⁶ The redox potential was investigated on the basis of a high-level computation, multi-reference second-order Møller-Plesset perturbation (MRMP) theory coupled with RISM-SCF. Yoshida *et al.* extended the procedure to evaluate the adiabatic free energy profile and applied it to 1,3-dinitrobenzene radical anions in acetonitrile and methanol sol-

vents.¹⁶⁷ They also derived the temperature dependence of the free energy profile as well as the electronic coupling strength.

The ionization energy was compared with that derived from the dielectric continuum model by Iida *et al.*¹⁶⁸ They also compared the spectral widths of the ionization potential in the solution phase predicted by the two theories. All of these studies treat systems that are nearly static, and hence they study thermodynamic features of nonequilibrium solvation. Such phenomena can be essentially understood within the framework of Marcus theory. Recent work by Aono *et al.* aspires to treat the dynamic aspects of solvation beyond such a scope.¹⁶⁹

4.5 Excited states and exploring their free energy surfaces

The capability of performing computations of electronic excited states of a solvated molecule is another important issue. $n \rightarrow \pi^*$ transition was analyzed based on QM/MM method¹⁷⁰ and ASEP/MD method.¹⁷¹ Recently, non-adiabatic excited state dynamics was treated with QM/MM method,¹⁷² and hydrated Li was studied by QMCF-MD method.¹⁷³ RISM-SCF has been widely applied to a variety of solution systems. For instance, the absorption properties of (2,2,6,6-Tetramethylpiperidine-1-yl)oxyl (TEMPO) were derived with a combination of TD-DFT and RISM-SCF-SEDD theory.¹⁷⁴ More importantly, its combined use with high-level quantum chemical methods, such as complete active space (CAS) SCF and multi-configurational quasi-degenerate perturbation theory (MCQDPT) has been reported. Both the ground and excited states of a betaine dye molecule in a polar solvent were investigated.¹⁷⁵ Excited-state proton transfer of 1-[(dimethylamino)methyl]-2-naphthol¹⁷⁶ and intramolecular charge-transfer state formation of 4-(*N,N*-dimethylamino)benzonitrile,¹⁷⁷ both in acetonitrile solution, were investigated using the RISM-SCF method combined with the CASSCF method. The dynamical correlation effect was then taken into account through a perturbative treatment applied to this zeroth-order electronic Hamiltonian. In the latter work, Minezawa *et al.* considered the consistency of the HNC excess chemical potential, $\Delta\mu^{\text{HNC}}$, and the solute electronic energy at the perturbation level within the framework of the site-potential description.¹⁷⁷

One of the unique applications of the present method is the computation of the density dependence of the absorption spectra of *p*-aminobenzonitrile. In a recent experimental study of the electronic absorption spectra of this molecule in supercritical and subcritical water, it was observed that the peak position exhibits a minimum in the specific density.¹⁷⁸ With a combination of MCQDPT and RISM-SCF-SEDD theory, the

low excited states were computed over a wide range of densities. The results suggest that the turnover is due to the difference in the sensitivity to the solvent for the two states.¹⁷⁹ We emphasize that the nature of the RISM allows its application to a wide range of thermodynamic conditions with uniform accuracy, and because of its computational efficiency, it is well-suited to combination with high-level quantum chemical methods, which generally are quite computationally intensive.

As discussed in the previous section, the nonequilibrium solvation free energy describing solvent fluctuations offers a convenient point of view to explore the hyper-free-energy space of many chemical processes. The linear-response free energy method,^{180,181} based on the Gaussian fluctuation model,^{182,183} is a particular realization of this treatment. That method has been combined with the RISM-SCF theory and applied to elucidate the conical intersections in solution phase. The method was applied to ethylene and CH_2NH_2^+ ,¹⁸⁰ 9H-Adenine,¹⁸⁴ and the absorption and fluorescence spectra of coumarin-151 in polar solvents.¹⁸⁵ A related method to locate the minimum energy conical intersection coupled with the dynamical correlation has also been constructed¹⁸⁶ through utilization of the local equilibrium property.¹⁸⁷ A direct QM/MM analog of such a mean-field theory was recently formulated on the basis of variational and perturbative frameworks,¹⁸⁸ and electronic polarization of the solvent was also treated.¹⁸⁹

5 Concluding remarks

This perspective summarizes hybrid methods incorporating IE theory and quantum chemical methods. After briefly outlining the IE theory for molecular systems, we explained the theoretical framework of the hybrid method. As repeatedly emphasized, a unified point of view in which quantum chemistry and statistical mechanics are both used is essential to properly understand solution systems. A theory consisting of one without the other is often insufficient to adequately describe the chemical behavior of systems under study.

IE theory is regarded as an alternative to molecular simulation methods, such as MD, but it offers a different approach to the treatment of solution systems. Because of its inherent simplicity, it allows for the analytical treatment of solution systems. In addition, it is computationally much more efficient than standard molecular simulation methods. However, approximations are introduced in the derivation of the IE theory. For this reason, it lacks precision in some cases. This leads us to conclude that these two approaches should be utilized together in a complementary manner.

In practice, the availability of programs that facilitate the application of IE theory and improvements of their algorithms are crucial for the popularization of IE theory. The author

is confident that such obstacles will be overcome in the very near future. More importantly, the development of molecular theory based on statistical mechanics is a challenging problem, and there remain many undiscovered topics to investigate. The more chemists become aware of this situation, the more rapidly we can deepen our understanding of ubiquitous solution systems.

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