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Solvation Effect on the Conformations of Alanine Dipeptide: Integral Equation Approach

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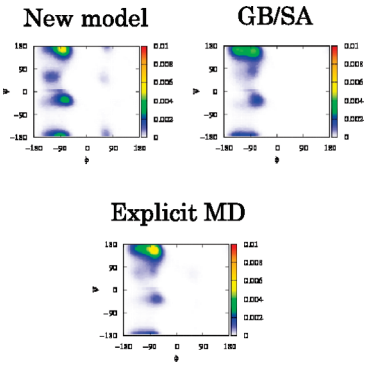
ABSTRACT We present an implicit solvent model based on the extended reference interaction site model (XRISM) integral equation theory, which is a molecular theory of solvation. The solvation free energy is composed of additive potentials of mean force (PMF) of various functional groups. The XRISM theory is applied to determine the PMF of each group in water and NaBr electrolyte solutions. The method has been coupled to Brownian dynamics (BD) and is illustrated here on alanine dipeptide. The results of the method are compared with those obtained by explicit water simulations and other popular implicit solvent models for detailed discussion. The comparison of our model with other methods indicates that the intramolecular correlation and the solvation structure influence the stability of the P_{II} and α_R conformers. The results of NaBr electrolyte solutions show that the concentration of electrolyte also has a substantial effect on the favored conformations.

SECTION Biophysical Chemistry



Molecular dynamics (MD) simulation has been a powerful tool to study the structure, dynamics, and function of proteins in atomic detail. However, the accessible time scales of typical MD simulations are up to hundreds of nanoseconds. A major computational burden comes from the treatment of solvent molecules, which constitute a large part of the system. For this reason, Brownian dynamics (BD) simulation with implicit solvation models has been used for the longer simulation[1] of biological systems. Recent progress[2] has enhanced the possibility of BD simulation as an alternative to explicit simulation. In general, the result of BD simulation is sensitive to the choice of the implicit solvation model. A successful implicit solvation model with high accuracy, versatility, and low computational cost is, therefore, an important key to successful BD simulation. Because the potential of mean force (PMF) includes the static solvation effect, which is deeply related to the hydration structure around a macromolecule, the solvation term of PMF should be treated carefully. The solvation term of the PMF for N-particle interaction $W^{sol}(\mathbf{R}^N)$ can be decomposed into single-body, pairwise, and nonpairwise terms

$$W^{solv}(\mathbf{R}^N) = \sum_i \Delta\mu_i + \sum_{i\neq j} \Delta W^{(2)}(\mathbf{R}_i, \mathbf{R}_j) + \sum_{i\neq j\neq k} \Delta W^{(3)}(\mathbf{R}_i, \mathbf{R}_j, \mathbf{R}_k) + \ldots + \Delta W^{(N)}(\mathbf{R}_1, \mathbf{R}_2, \ldots, \mathbf{R}_N) \quad (1)$$

where $\Delta\mu_i$ is the excess chemical potential of ith particle, $\Delta W^{(i)}$ corresponds to the ith-order term, $\mathbf{R}^N = (\mathbf{R}_1, \mathbf{R}_2, \ldots, \mathbf{R}_N)$, and $\mathbf{R}_i$ is the ith atom coordinate of a macromolecule. The sophisticated calculation of eq 1 leads to the establishment of the accurate implicit solvation model. The generalized Born and surface area (GB/SA) model[3] is the most commonly used implicit solvation model. To reduce the computational cost, the surface area approximation is applied to the nonpairwise contribution. Recent studies of the MD simulation indicate that the triplet term in eq 1 can be described qualitatively by molecular surface area.[4,5] The reference interaction site model (RISM) is a versatile method for calculating the PMF in terms of the solute−solute radial distribution function (RDF).[6] In this approach, the properties of the hydration structure, which are not considered in the GB/SA model, can refine the PMF in terms of the microscopic theory. Henceforward, superscripts "u" and "v" denote the solute and solvent species, respectively. According to the RISM theory, W^{solv} can be expressed as follows[6]

$$W^{solv}(\mathbf{R}^N) = \sum_i \Delta\mu_i - k_B T \sum_{i\neq j} [t_{ij}^{uu}(r_{ij}) + b_{ij}(r_{ij})] \quad (2)$$

where k_BT is the Boltzmann constant times the absolute temperature, $r_{ij} = |\mathbf{R}_j - \mathbf{R}_i|$, $t_{ij}^{uu}(r) = h_{ij}^{uu}(r) - c_{ij}^{uu}(r)$, $h_{ij}^{uu}(r)$ and $c_{ij}^{uu}(r)$ are the site−site total and direct pair correlation function, respectively, and b_{ij} is the bridge function. Pioneering simulation based on eq 2 was carried out by Pettitt and Karplus,[6] and the conformation of alanine dipeptide in water was discussed in their article. They solved the extended RISM

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(XRISM) equations for a monatomic solute at infinite dilution to obtain $t_{ij}^{uu}(r)$

$$\mathbf{h}^{vv}(r) = \omega^{vv} * \mathbf{c}^{vv} * \chi^{vv}(r) \quad (3)$$

$$\mathbf{h}^{uv}(r) = \mathbf{c}^{uv} * \chi^{vv}(r) \quad (4)$$

$$\mathbf{h}^{uu}(r) = \mathbf{c}^{uu}(r) + \mathbf{c}^{uv} * \rho_v \mathbf{h}^{vu}(r) \quad (5)$$

where the asterisk denotes the convolution integral, ρ_v is the density of pure solvent, $\chi_{ij}^{vv}(r) = \omega_{ij}^{vv}(r) + \rho_v h_{ij}^{vv}(r)$ is the site−site density pair correlation function, and $\omega_{ij}(r) = \delta(r - l_{ij})/4\pi r^2$ (where l_{ij} is the distance between sites i and j) is the intramolecular correlation function. The hypernetted chain (HNC) closure was employed as the second equation that relates $h_{ij}^{uu}(r)$ and $c_{ij}^{uu}(r)$, and the bridge function was neglected in their article. From the viewpoint of the liquid state theory, all nonpairwise terms in eq 1 are renormalized into the bridge function by integrating the multibody correlation functions. Whether the bridge function is considered is, therefore, the central problem for the accuracy of the RISM theory. Recently, the promising bridge function in which the four-body correlations are projected has been proposed by Perkyns et al.[7] By employing this bridge function, the theoretical deficiency might be filled up. A more direct and accurate manner is the RISM calculation with an individual peptide at each time step. If a solute molecule is small, the calculation of the RISM at every integration step is comparably expensive. In contrast, for a giant molecule that has more than 100 000 atoms, the RISM calculation with individual molecular configuration has to handle the 100 000 × 100 000 matrix of the intramolecular correlation function. Therefore, the computational cost is not comparabe but far more expensive. To make matters worse, the convergence of the RISM calculation at each step would be very poor because of the large anisotropy of a macromolecule. This is the reason why the three-dimensional RISM (3DRISM) theory is widely used for a giant molecular system.[8] However, the coupling of the 3DRISM with MD (3DRISM/MD), which is proposed by Miyata and Hirata,[9] is not a promising approach. Who would want to use the slower and far more expensive "implicit" solvation model rather than the explicit water MD? Additionally, their approach does not include the dynamic properties of the solvent such as viscosity. Most people, therefore, would prefer the explicit water MD to the 3DRISM/MD. For these reasons, we extend the approximation of Pettitt and Karplus to the class of groups.

Here, to extract the multibody correlation without correcting the bridge function, we apply the classes of atoms or groups that are defined by Ooi and coworkers[10] to eq 2, namely, (I) aliphatic groups, (II) aromatic groups, (III) hydroxyl groups, (IV) amide and amine groups, (V) carboxyl and carbonyl groups, and (VI) sulfur atoms and thiol groups. For group molecules at infinite dilution, the corresponding eqs 4 and 5 can be expressed as follows

$$\mathbf{h}^{uv}(r) = \omega^{uu} * \mathbf{c}^{uv} * \chi^{vv}(r) \quad (6)$$

$$\mathbf{h}^{uu}(r) = \omega^{uu} * \mathbf{c}^{uu} * \omega^{uu}(r) + \omega^{uu} * \mathbf{c}^{uv} * \rho \mathbf{h}^{vu}(r) \quad (7)$$

In eqs 6 and 7, the multibody correlations are approximated as the product of ω^{uu} and $\mathbf{c}^{uu}$ at the level of Kirkwood superposition approximation. Representation of alanine dipeptide

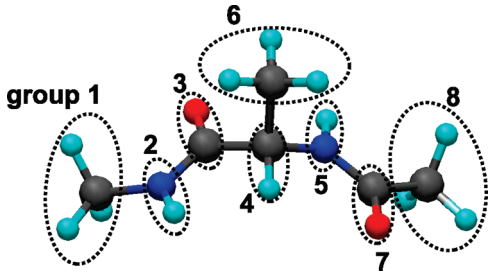

Figure 1. Representation of alanine dipeptide with groups.

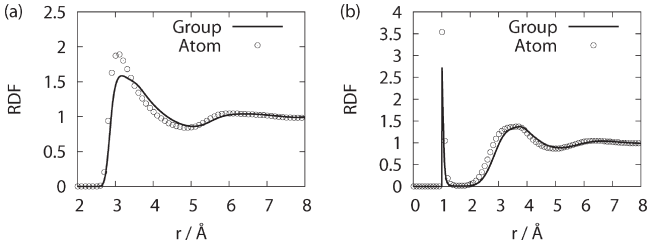

Figure 2. Radial distribution functions (a) between carbon atom of CH_3 group and water oxygen and (b) between carbon atom of CH_3 group and water hydrogen. The solid and circle lines denote the XRISM/KH result for isolated CH_3 group molecule and carbon atom of CH_3 group in water, respectively.

Table 1. Excess Chemical Potential $\Delta\mu$ (kilocalories per mole) of Isolated Groups of Alanine Dipeptide in Water

group	$\Delta\mu$ [kcal/mol]
CH_3 (group 1)	10.562
NH (group 2)	−9.083
CO (group 3)	−4.819
CH (group 4)	7.595
NH (group 5)	−9.083
CH_3 (group 6)	11.655
CO (group 7)	−4.819
CH_3 (group 8)	11.681

with the above definitions is shown in Figure 1. The XRISM equations are complemented with the Kovalenko−Hirata (KH) closure for effective convergence of the calculation.[11] The theoretical framework and analytical expression of $\Delta\mu_i$ for KH closure can be found elsewhere. The XRISM/KH results of $\Delta\mu$ for isolated groups of alanine dipeptide in water (T = 298K, ρ = 0.03334 Å^{-3}) are listed in Table 1. The positive values of $\Delta\mu$ for CH_3 and CH groups indicate that the hydrophobicity of aliphatic groups in water is reproduced thanks to the multibody correlations of eq 6. RDF between the carbon atom of CH_3 and water atoms is plotted in Figure 2. The solid and circle lines are the result of eqs 4 and 6, respectively. As is clearly seen, the oxygen distribution of our model is slightly lower than that of the monatomic model because of the steric effect of CH_3. The Ramachandran plots of aqueous alanine dipeptide, which are calculated from the BD with the above-mentioned implicit solvation models and explicit water MD, are shown in Figure 3. The fractions of P_{II} and α_R are listed in Table 2. The result of our model shows the stability of the P_{II} ($-105° \le \phi \le -65°$, $140° \le \psi \le 180°$) conformers, which is

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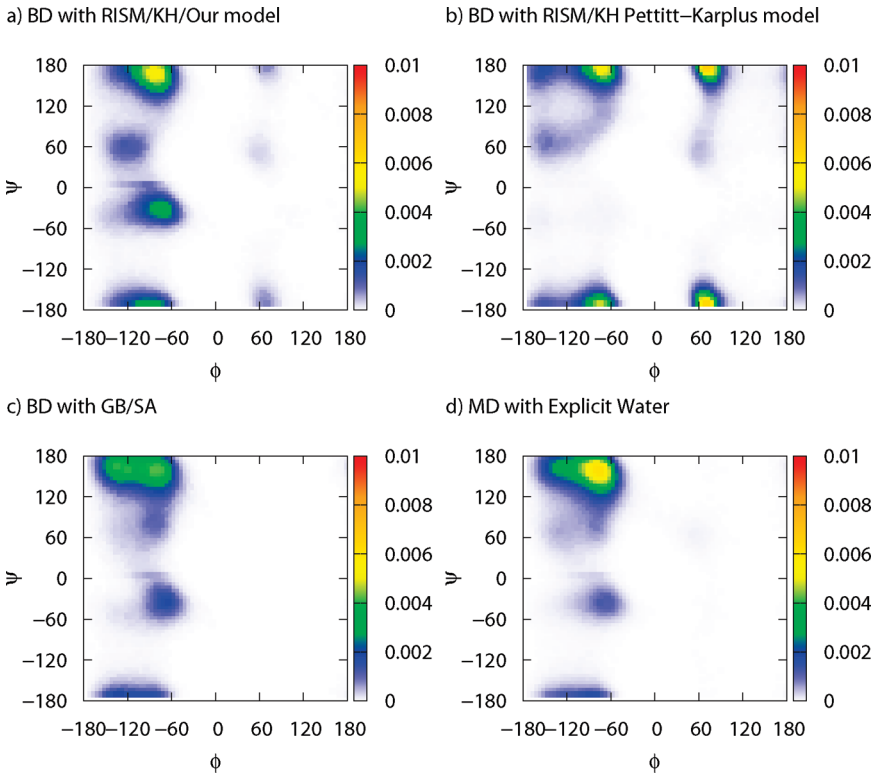

Figure 3. Ramachandran plot of aqueous alanine dipeptide calculated from (a) Brownian dynamics (BD) with XRISM/KH our model, (b) BD with XRISM/KH Pettitt−Karplus model, (c) BD with GB/SA, and (d) molecular dynamics (MD) with explicit water.

Table 2. Fraction of Conformers and CPU Time Ratio

method	P_{II} [%]	α_R [%]	CPU time ratio
our model	22.12	10.62	4.38×10^{-5}
Pettitt and Karplus	17.58	0.29	4.38×10^{-5}
GB/SA	18.75	6.37	5.03×10^{-5}
explicit MD	26.18	4.52	1

in good agreement with MD results. Other models are somewhat less satisfactory. The improvement of monatomic model is, therefore, achieved by the renormalization of the multibody correlation in eqs 6 and 7. The result of GB/SA model agrees with the MD result, except for the P_{II} conformer. From this result, the changes of the solvation structure are deeply related to the P_{II} conformer. However, our model produces a less broadened population around the P_{II} conformer and overestimates the population of α_R ($-100° \le \phi \le -60°$, $-70° \psi \le -30°$) conformer in contrast with the GB/SA model. Because they are not also observed in Figure 3b, these conformers are sensitive to the approximations of the XRISM theory. The computational cost of each model is also listed in Table 2. The CPU time of the explicit MD is normalized.

Salt effects on the conformation of biomolecules have been an important problem because the function of protein is deeply related to the salt concentrations in technological as well as physiological settings. To demonstrate the applicability of our model, we briefly discuss the salt effect on the conformation map of alanine dipeptide. By applying eq 3 to an electrolyte mixture, we can easily include the salt effect in the PMF. The PMFs between the amide carbonyl oxygens at each mole concentration with our model are plotted on the l.h.s of Figure 4. The Ramachandran plots are also shown on the r.h.s of these Figures. From the results of PMFs, it appears possible that at high Na^+ concentration a Na^+ ion may tend to coordinate the two amide carbonyl oxygens, favoring the P_{II} conformer. This result indicates that the PMF between sodium ion and the amide carbonyl oxygen overcomes the repulsive interaction between oxygens (Figure 5). To improve our approach, we will apply the dielectric consistent RISM (DRISM)[12−14] to our model and report on it in an upcoming article.

METHOD

OPLS-AA force field parameters[15−21] and the TIP3P model[22] are employed for potentials of alanine dipeptide and water, respectively. The first-order Ermak and McCammon algorithm[1] is implemented in BD simulations

$$d\mathbf{R}_i = \frac{D_i}{k_B T}\mathbf{F}_i\, dt + \sqrt{2D_i\, dt}\,\mathbf{X}_i \tag{8}$$

where dt is a time step, D_i is the diffusion coefficient of atom i, and $\mathbf{X}_i$ is a random noise vector obtained from a standard normal distribution. The diffusion coefficients of individual atoms are assigned according to

$$D_i = \frac{k_B T}{6\pi\eta(\sigma_i + 1.4\ \text{Å})} \tag{9}$$

where σ_i is the van der Waals radius and η is the solvent viscosity: the experimental values of η for pure water and

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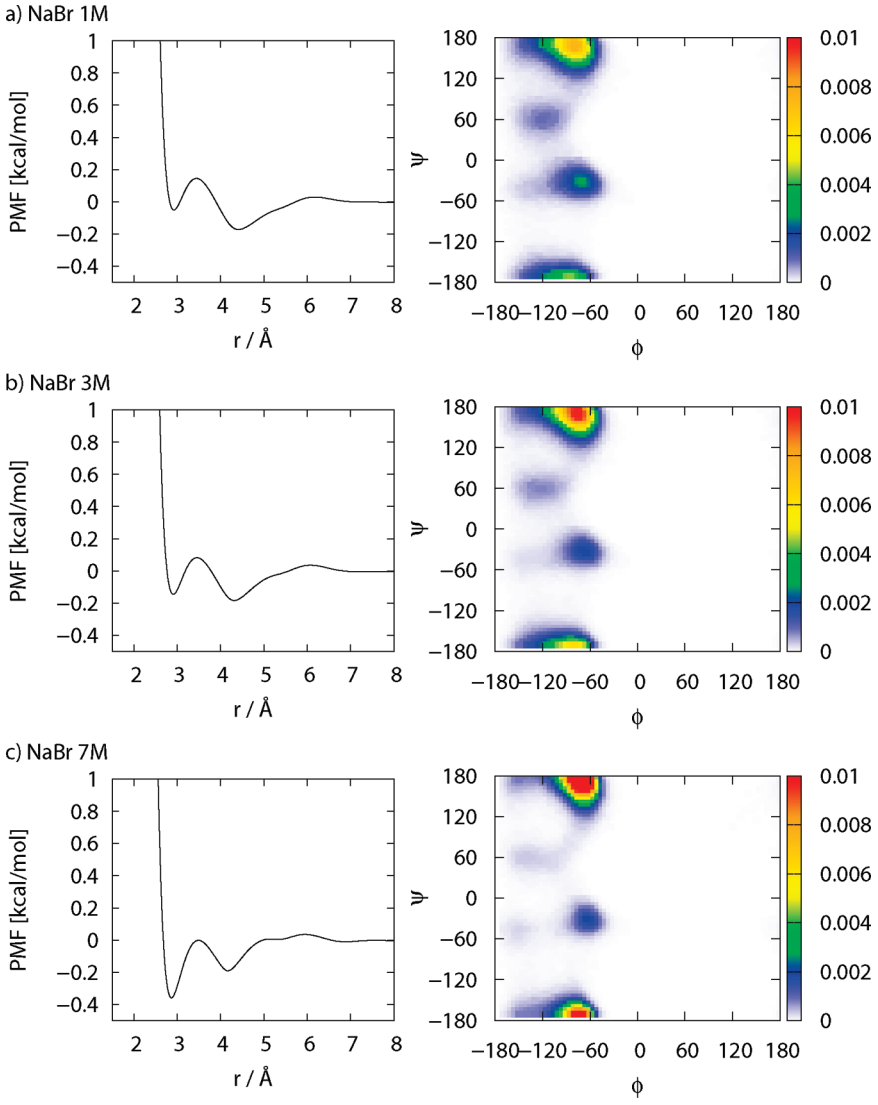

Figure 4. Left column: PMFs between the amide carbonyl carbons of (a) 1, (b) 3, and (c) 7 M NaBr electrolyte solutions. Right column: Ramachandran plot of alanine dipeptide of (a) 1, (b) 3, and (c) 7 M NaBr electrolyte solutions.

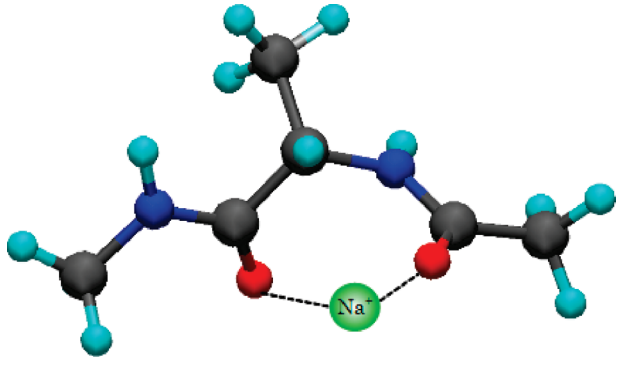

Figure 5. Schematic view of the stabilized P_{II} conformer by sodium ion.

NaBr solution are employed.[23] Time steps of BD simulations are set to 10 fs, and trajectories of 300 ns are generated. We obtained the result of explicit-water MD simulation by carrying out the *NVT* ensemble simulation including 491 water molecules. The time step of MD simulation is set to 2 fs, and trajectories of 100 ns are generated. The potential parameters and thermal conditions used for all simulation are unified. As was reported,[24] the Ramachandran plot of alanine dipeptide strongly depends on the force field parameters.

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