Attractive interaction between macroanions mediated by multivalent cations in biological fluids

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ABSTRACT

Attractive interaction between macroanions mediated by divalent cations is studied using an Ornstein–Zernike equation with hypernetted-chain closure. The calculated results indicate that the divalent cations mediate the strong attraction and that this attractive force is much stronger than that mediated by monovalent cations. In this article, we shed light on effects of the co-existing of monovalent cations because the attractive interaction mediated by multivalent cations is observed in various biological fluids that also contain monovalent cations. When the system also contains monovalent cations, they suppress the attraction mediated by the divalent cations. However, the attraction remains and the reentrant behavior of attraction appears due to the exchange of attraction-mediating divalent cations for monovalent cations if the charge of the macroanions is sufficiently large.

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1. Introduction

Strong effective attraction between like-charged macroions is often observed in biological systems, such as in the assembly of G-actins [1–11]. Many such biological systems exhibit reentrant behaviors. For example, acidic proteins are negatively charged and the effective interaction between them changes from repulsive to attractive interaction if multivalent cations are added to the system; the proteins aggregate with each other. This attraction mysteriously disappears when more multivalent cations are added. Similar reentrant behaviors have been observed with the coil–globule transition of DNA [4–9].

Various theoretical studies on the attractive interactions caused by countercharged ions have been reported [12–34]. After the pioneering works of Oosawa [12] and of Manning [13], this attraction has been studied on the basis of molecular picture. The molecular picture of the attraction was shown using an integral equation theory in 1980 [16] and some studies by integral equation theories with molecular picture were carried out [17,18,25,26,28,33,34]. Molecular simulation studies also showed this attraction [19–24,27]. These theoretical studies confirmed the existence of the attraction between like charged particles mediated by counter ions, and Wu and coworkers suggested that DLVO theory [35,36] and Sogami–Ise theory [37] fail to describe this attractions [22,23].

Akiyama and Sakata studied the effective interaction between two like-charged macroions immersed in an electrolyte solution using an Ornstein–Zernike equation with hypernetted-chain closure (HNC-OZ theory), because of the difficulty of adequate simulations for the electrolyte concentration dependence. Conditions under which the Coulomb interaction was greater than the thermal energy were examined. Some calculated results [16,23] have shown non-monotonic behaviors on the electrolyte concentration dependence. In our previous results, the reentrant behavior [33,34] clearly appeared in dependence of interaction on the concentration of counter charged ion. Although the cations of the electrolyte solution were monovalent, they mediated the attractive interaction. It was because the charges of the macroanions were sufficiently large.

In the previous studies [33,34], the calculated results were basically consistent with the experimental results, with the exception of cation charges. It follows that calculated results are reasonable to discuss the related behaviors in biological systems. Experimental results have indicated that strong attraction is induced when multivalent cations are added. For example, ions such as Y^{3+}, and Fe^{3+} effectively induce attractions between various acidic proteins. For the assembly of ATP-bounded G-actins, the structural analyses indicated that the attractions between G-actins were mediated by Mg^{2+} ions [38]. Therefore, in the present study, we confirm that multivalent cations mediate the strong attractive interactions. We also examine the effects of co-existing monovalent cations, because in vivo systems contain so many monovalent cations such as Na^+. Ringer's solution, which is an artificial physiological solution, contains 151 mM monovalent cations and 3.0 mM

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divalent cations. The present study could be important to understand a degenerative cartilage disease [39].

2. Model

We calculated the effective interaction, i.e. the potential of mean force, between two macroanions immersed in an electrolyte solution. The system contained only two macroanions. So, we studied a dilute limit for the macroanions. The electrolyte solution consisted of solvent molecules, monovalent cations, divalent cations, and monovalent anions. The solvent molecules were modeled as hard spheres with a diameter equal to that of water, $\sigma_S = 2.8$ Å, where subscript S denoted the solvent molecule. Charged hard spheres were adopted as ions. The diameter of the macroanions was $\sigma_M = 6 \times 2.8$ Å $= 16.8$ Å and the charge was Q_M, where subscript M denoted the macroanion. The sizes of other ions were the same as that of solvent molecule.

The potential of mean force between macroanions depends on the number density of ions ρ_i, $i = C_1, C_2, A$, where a monovalent cation, a divalent cation, and a monovalent anion are denoted as C_1, C_2, and A, respectively. We examined the dependence of the potential of mean force on the density of cations ρ_{C_i} under electroneutrality conditions ($\rho_{C_1} + 2\rho_{C_2} - \rho_A = 0$). In this study, the total packing fraction was maintained at 0.383, which is the packing fraction of water. The temperature was set to 298 K.

3. Method

The Ornstein–Zernike (OZ) equation

$$h_{ij}(\mathbf{r}_{12}) = c_{ij}(\mathbf{r}_{12}) + \sum_{l=S,C_1,C_2,A} \rho_l \int c_{il}(\mathbf{r}_{13}) h_{lj}(\mathbf{r}_{23}) d\mathbf{r}_3 \tag{1}$$

coupled with the hypernetted-chain (HNC) closure

$$h_{ij}(r) = exp\left[\frac{-u_{ij}(r)}{k_B T} + h_{ij}(r) - c_{ij}(r)\right] - 1 \tag{2}$$

is solved to obtain the correlation functions. Here, $\mathbf{r}_{ij}$ ($i, j = 1, 2, 3$) is the vector separation between $\mathbf{r_i}$ and $\mathbf{r_j}$. $c_{ij}(\mathbf{r})$, $h_{ij}(\mathbf{r})$, $g_{ij}(r)$, $u_{ij}(r)$ are the direct correlation function, the total correlation function, the radial distribution function, and direct pair potential between particles i and j ($i, j, l = S, C_1, C_2, A, M$), respectively. There is a relation $g_{ij}(r) = h_{ij}(r) + 1$. ρ_i is the number density of i. k_B is the Boltzmann constant, and T is temperature.

The effective interactions are obtained on the basis of the correlation functions. The details of the calculations have been described elsewhere [33,34,40–46]. The potential of mean force between macroanions $\Phi(r)$ is obtained as

$$\begin{aligned}\Phi(\mathbf{r}_{12}) &= -k_B T \ln[h_{MM}(\mathbf{r}_{12}) + 1] \\ &= u_{MM}(\mathbf{r}_{12}) - k_B T \sum_{l=S,C_1,C_2,A} \rho_l \int c_{Ml}(\mathbf{r}_{13}) h_{lM}(\mathbf{r}_{23}) d\mathbf{r}_3,\end{aligned} \tag{3}$$

where $u_{MM}(\mathbf{r})$ is the pair potential between macroanions. We discuss the dimerization free energy of macroanions, ϵ, which is the stability of the contact dimer formed from macroanions: i.e., ϵ is defined as

$$\epsilon = \Phi(\sigma_M). \tag{4}$$

Because the counter charged small ions were found to mediate the attraction between like-charged macroions in our previous study, the estimation of the number of mediators, N_i appears to be an important parameter. N_i is defined as

$$N_i = \iiint_A \rho_i g_{M_1,M_2;i}^{(3D)}(x,y,z) dx dy dz, \tag{5}$$

where $g_{M_1,M_2;i}^{(3D)}(x,y,z)$ is the three-dimensional (3D) reduced density profile of particle i ($i = C_1, C_2$), in the case where the pair of macroanions is located at $(x,y,z) = (-8.4,0,0)$ and $(8.4,0,0)$, respectively. Here M_1 and M_2 denote two macroanions. The surface between the macroanions is equal to 0 Å ($r = \sigma_M$). The 3D profile $g_{M_1,M_2;i}^{(3D)}(x,y,z)$ was calculated using a typical radial–symmetrical distribution function with a Kirkwood superposition approximation [47]. This approximation is given by the following equation:

$$g_{M_1,M_2;i}^{(3D)}(x,y,z) \sim g_{M_1;i}(x,y,z) \cdot g_{M_2;i}(x,y,z), \tag{6}$$

where $g_{M_j;i}(x,y,z)$ ($j = 1,2$) is the 3D reduced density distribution of cations i near the j-th macroanion. This 3D distribution $g_{M_j;i}(x,y,z)$ is calculated using the radial distribution function, $g_{Mi}(r)$, consistent with the radial–symmetrical HNC-OZ theory.

A schematic diagram of volume A for the integral is shown in Fig. 1. R_{1st} is defined as the distance r at the first minimum of $g_{MC_2}(r)$ (Fig. 1(a), (b)). The inner and outer surfaces of the first coordination shell are defined by spheres with radii $(\sigma_M + \sigma_{C_2})/2$ and R_{1st}, respectively. Thus, the first coordination shell is the region between the dotted and dashed lines in Fig. 1(c). Volume A is defined as the overlap region of two first coordination shells generated by the contact macroanions M_1 and M_2. It is represented by the black region in Fig. 1(d).

4. Results & discussions

Fig. 2 shows the dependence of the dimerization free energy of macroanions on cation concentration. When the charge of the macroanion is $-6\,e$, the half-valent and monovalent cations cannot mediate the effective attraction between macroanions. However, the dimer becomes more stable, as the charge of the cation increases. A stable dimer appears when the cation charge is greater than 1.5 e. Although the macroanions repel each other in a dilute electrolyte solution (approximately 1×10^{-6} M), a strong effective attraction between the macroions appears at medium concentration (approximately 1×10^{-3} M for $+1.5\,e$ cations, approximately 1×10^{-4} M for $+2\,e$ cations). The contact dimer of the macroanions only becomes stable at such medium concentrations. The stability (~10 k_BT for $+1.5\,e$ cations and ~90 k_BT for $+2\,e$ cations) is much greater than the thermal energy. However, this attraction disappears at higher electrolyte concentrations. Therefore, the system exhibits the reentrant behavior.

Wu et al. also studied the attraction between like-charged colloidal spheres in electrolyte solutions [22,23]. Those were molecular simulation studies, and the concentration of electrolyte c_s is about 0.1 M. In their calculation, $c_s = 0.5$ M, the monovalent counter charged ions did not mediate the attraction between like-charged colloidal spheres, and the divalent counter charged ions mediated the attraction [22]. Our results calculated by using the integral equation theory can be compared to their simulation data. In our results, the attraction mediated by cations does not appear in the solution whose cation concentration is about 0.5 M, even if the counter charged cations are divalent. Because our model has solvent particles, most of the weak attraction at 0.5 M in Fig. 2 is arising from the translational motion of solvent molecules [48–54]. The concentration 0.5 M is too high if it corresponds to the strong attraction mediated by counter charged ions in our model (See Fig. 2). Those results look like a qualitative difference. However, $-6\,e$ and $-10\,e$ are examined as the charge of macroanion in our calculation and the charge of macroion for the simulation, $-20\,e$, is much larger than them. As the charge of macroanion becomes larger, the attraction increases. Because the size of macroions ($\sigma = 20$ Å) in the simulation is similar to the size of our model ($\sigma = 16.8$ Å), the above difference in the effective attraction could be reasonable. To clarify this problem we will examine the calculation on the basis of similar model in our future study.