

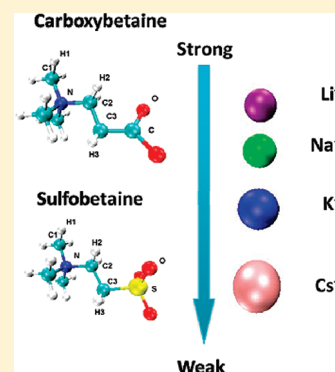
# Molecular Dynamics Simulation Study of Ion Interactions with Zwitterions

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Supporting Information

**ABSTRACT:** Using molecular dynamics simulations, we investigated the associations between two zwitterions (carboxybetaine and sulfobetaine) and four types of cations ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cs}^+$ ) in aqueous solutions. We studied the number and lifetime of various zwitterion–cation associations and observed that both carboxybetaine and sulfobetaine have the same order of association number and lifetime:  $\text{Li}^+ > \text{Na}^+ > \text{K}^+ > \text{Cs}^+$ . Simulation results showed that the association variation as a function of cation types for these two zwitterions is significantly different. The effect of anion type on the order was also investigated by varying the type of anions from  $\text{Cl}^-$  to  $\text{Br}^-$  and  $\text{F}^-$ . In order to further investigate zwitterion–cation association, we simulated the systems either with one type of zwitterion and two types of cations or with one type of cation and both carboxybetaine and sulfobetaine presented. This allowed direct competition between the solutes, and the observed association number and lifetime validated the order. Simulation results further demonstrated that, although CB associates stronger with  $\text{Li}^+$  and  $\text{Na}^+$  than SB, the latter is associated preferentially by  $\text{K}^+$  and  $\text{Cs}^+$ .



## I. INTRODUCTION

Biocompatible materials with high resistance to nonspecific protein adsorption are critical for many applications.<sup>1–3</sup> Recently, zwitterionic materials such as poly(carboxybetaine methacrylate) (polyCBMA) and poly(sulfobetaine methacrylate) (polySBMA) are receiving considerable attention because they present excellent nonfouling properties even in undiluted blood serum and plasma.<sup>3</sup> Significant efforts have been devoted to the application of these materials to a wide range of applications, such as drug delivery carriers, marine coatings, and medical devices.<sup>4–7</sup>

The microscopic interaction between substances is determinant to the macroscopic performance of a material. The rational design and application of novel biomaterials require a fundamental understanding of interactions among zwitterions themselves and their interactions with the surroundings. Our previous studies have shown that zwitterionic carboxybetaine and sulfobetaine have different hydration characteristics, although they both present a strong hydration overall.<sup>8</sup> Ions are ubiquitous in biological and industrial systems. For instance, ions such as  $\text{Na}^+$  and  $\text{K}^+$  exist both in the cellular and extracellular environments. Similarly, marine environments have a high concentration of ions. These ions can affect the properties of zwitterionic materials profoundly because zwitterionic materials consist of highly charged groups.<sup>3</sup> For instance, it is found that zwitterionic polymers have antipolyelectrolyte properties. Adding more salts increases the solubility of the polymers.<sup>9–11</sup> A thorough understanding of zwitterion–ion interactions is thus crucial to the application of zwitterionic materials in complex media.

Ionic effects on various properties of materials have been studied theoretically and experimentally for more than one hundred years. Experimental observations led to the Hofmeister

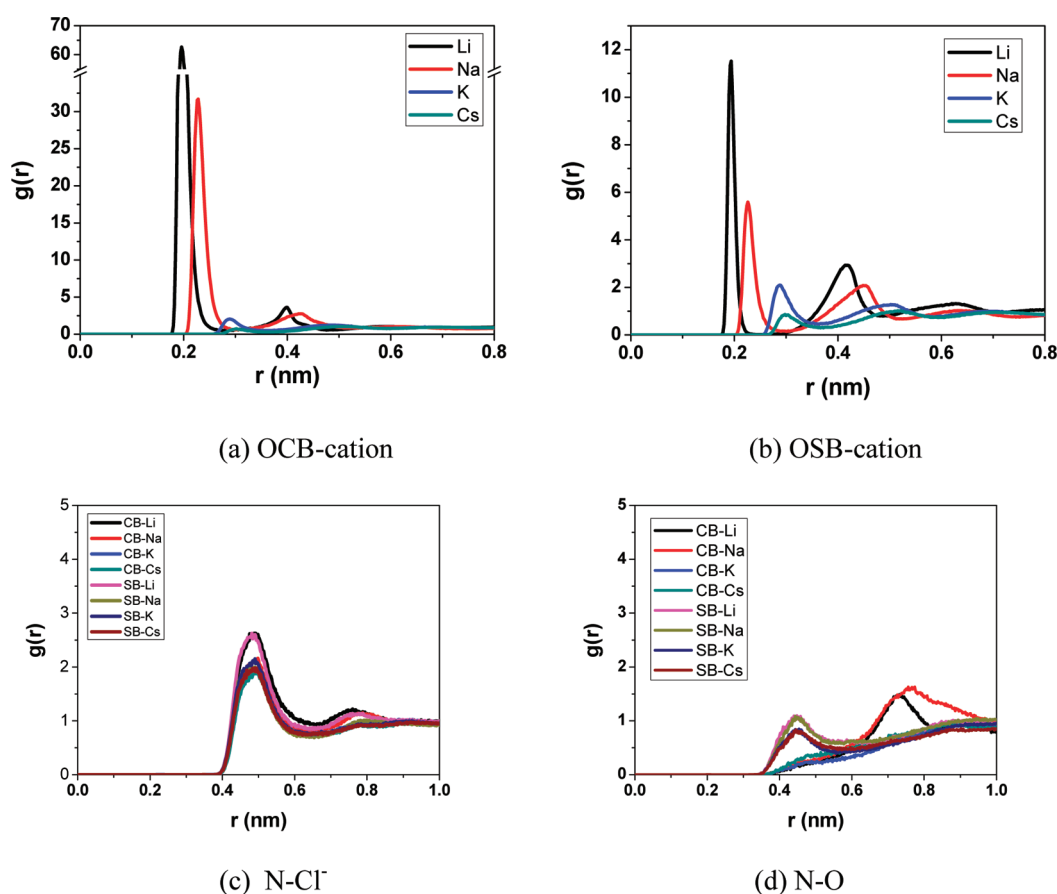
series,<sup>12</sup> which ranks ions into a series according to their ability to salt in or salt out proteins. The classical view considers ions such as  $\text{Li}^+$  and  $\text{Na}^+$  as water structuring, resulting in water more ordered than neat water. This type of ions is viewed as strong ion. Another type of ions, such as  $\text{K}^+$  and  $\text{Cs}^+$ , is suggested to make water structure less ordered than neat water, partially due to their large size and hydrophobic character.<sup>13–15</sup> This type of ions is considered as weak ion. Recently, Collin<sup>16</sup> proposed a “like–likes–like” theory to explain the relationship between the strong and weak ions. This theory explains the preferential association between different types of inorganic ions quite well. In this theory, strong cations prefer to associate with strong anions and vice versa for weak ions. Using this “like–likes–like” theory, Jungwirth and his colleagues<sup>17</sup> studied the associations between the organic anions such as  $\text{CH}_3\text{COO}^-$  and  $\text{CH}_3\text{SO}_3^-$  with inorganic monovalent cations using molecular simulations. In their studies, they suggested that  $\text{CH}_3\text{COO}^-$  prefers to associate with  $\text{Na}^+$ , whereas  $\text{CH}_3\text{SO}_3^-$  favors association with  $\text{K}^+$  based on the difference in their results of association free energy. Hess et al.<sup>18</sup> also found an order of increasing binding affinity with carboxylate ions from their molecular simulation study of specific ion binding to a protein. The order they found is  $\text{Li}^+ > \text{Na}^+ > \text{K}^+$ . These studies serve as a good point for the fundamental understanding of zwitterion–ion associations.

Zwitterions, however, have their own features which make them distinguished from other molecules. One feature is in their

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**Figure 1.** Radial distribution functions (RDFs) of zwitterions and ions. (a) The RDFs between the oxygen atoms of CB and cations (OCB-cation), (b) the RDFs between the oxygen atoms of SB and cations (OSB-cation), (c) the RDFs between the nitrogen atoms of zwitterions and  $\text{Cl}^-$  (N- $\text{Cl}^-$ ), and (d) the RDFs between the nitrogen and oxygen atoms of zwitterions (N-O).

structure. For example, although carboxybetaine has the same negatively charged group ( $\text{COO}^-$ ) as acetone, zwitterionic carboxybetaine has a large positively charged group (quaternary amine) which affects the nearby charged groups. Association competition is another studied aspect. A zwitterion itself is a neutral solute with two opposite highly charged groups. This means that there are at least one type of anion and one type of cation in solvent, which causes competitive association between the different charged groups of zwitterion and ions.

It should be noted that several recent researches suggested that there is still a lot of unrevealed aspects about the ionic effect.<sup>15,19</sup> For instance, Lund et al.<sup>20</sup> showed that the weak anions such as  $\text{I}^-$  will prefer to bind near the hydrophobic surface groups instead of the positively charged surface groups. It also showed that the weak ions will prefer to approach the air–liquid interface and not stay in the bulk solution as predicted by the theory of classical electrolyte solution.<sup>21,22</sup> The recent simulations carried out by Zangi<sup>23</sup> also proposed that both strong and weak ions decrease water structure, instead of the conventional concept that strong ions increase water structure, whereas weak ions decrease water structure. These new findings provide strong justification for studying zwitterion–ion association at the molecular level.

In this work, we carried out a series of simulation studies of zwitterionic carboxybetaine (CB) and sulfobetaine (SB) in various electrolyte solutions. The goals of these simulations are to identify zwitterion–ion associations and rank association

strengths between various ions and these two zwitterions. We selected four cations ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cs}^+$ ) in this study. The former two ( $\text{Li}^+$  and  $\text{Na}^+$ ) are strong ions and the latter two ( $\text{K}^+$  and  $\text{Cs}^+$ ) are weak ones. Since our previous simulations<sup>8</sup> have shown the hydration difference of CB and SB, it is interesting to explore further whether there is any difference in ionic association for these two zwitterions, especially for their competitive association. The rest of the paper is organized into three parts. Section II is the description of simulation models and details used in this work. Section III presents simulation results and discussions. Conclusions are given in section IV.

## II. SIMULATION DETAILS

In every simulation system, a periodic box (initial size:  $3.58 \times 3.58 \times 3.58$  nm) containing 10 zwitterionic molecules, 50 cations, 50 anions, and 1300 water molecules was built. The simulation system was created in the following steps: at the first step, the zwitterionic molecules were placed randomly in the simulation box using packmol.<sup>24</sup> Next, 10 zwitterionic molecules were solvated in a water box containing 1400 water molecules. Finally, 100 water molecules were selected randomly in the simulation system and replaced by 50 cations and 50 anions. The final simulation system contains 10 zwitterion molecules, 50 cations, 50 anions, and 1300 water molecules.

The potential energy of intermolecular interactions is calculated as a combination of Lennard–Jones (L-J) 12–6 potential

and Coulombic potential, as shown in eq 1

$$U(r_{ij}) = 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{r_{ij}} \quad (1)$$

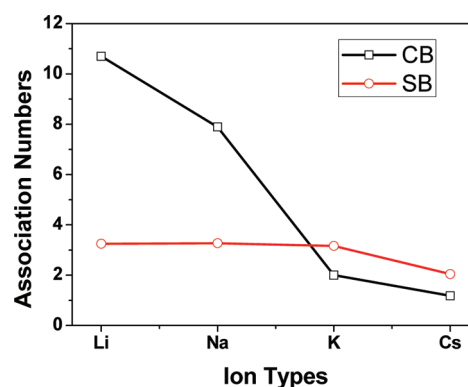
where  $r_{ij}$  is the distance between atoms  $i$  and  $j$ ,  $q_i$  is the partial charge assigned to atom  $i$ , and  $\epsilon_{ij}$  and  $\sigma_{ij}$  are energy and size parameters obtained by Lorentz–Berthelot combining rules, where  $\sigma_{ij} = (\sigma_i + \sigma_j)/2$  and  $\epsilon_{ij} = (\epsilon_i \epsilon_j)^{1/2}$ . The force field parameters for zwitterions were the same as those in our previous work.<sup>8</sup> The ion was treated as a single Lennard-Jones site and the force field parameters from the work of Aqvist were used.<sup>25</sup> The SPC/E water model<sup>26</sup> was used because of its good replication of the dipole moment, dielectric constant, and diffusion properties of water molecules. Table S1 lists the force field parameters for all of the ions and atoms used in this study.

Molecular dynamics (MD) simulations were performed using Gromacs (version 4.5.3)<sup>27</sup> in an isobaric–isothermal ensemble (NPT). After energy minimization and a 1.0 ns MD run with an integral step of 1.0 fs for equilibrium, another 5.0 ns run was carried out with the integral step of 1.0 fs for data collection. The coordinates were saved every 0.1 ps. Long-range electrostatic interactions were computed with the particle mesh Ewald method<sup>28</sup> with periodic boundary conditions in all three dimensions. The short-range van der Waals (VDW) interactions were calculated with a cutoff distance of 1.1 nm. The system was maintained at 298 K (0.1 ps time constant) and 100.0 kPa with the Berendsen algorithm<sup>29</sup> (with a compressibility of  $4.5 \times 10^{-5}$  bar<sup>-1</sup> and a 1 ps time constant). Intramolecular bonds of zwitterionic molecules and water molecules were kept constrained with the LINCS algorithm.<sup>30</sup>

### III. RESULTS AND DISCUSSION

**III.1. Radial Distribution Functions.** The first property studied is the radial distribution functions (RDFs) between zwitterion and ions, and within zwitterions themselves. We focused on three types of RDFs: (a) between the oxygen atoms of zwitterion and the cation in solution, (b) between the nitrogen atoms of zwitterion and the anion in solution, and (c) between the oxygen atoms and the nitrogen atoms of the zwitterions. The purpose of investigating these three RDFs is to explore the association among zwitterion, cation, and anion in these three-component systems and the possible self-assembly of zwitterions themselves. Figure 1 shows the RDFs of zwitterions and ions, and Figure S1 shows the representative snapshots of CB–Na<sup>+</sup> and SB–Na<sup>+</sup> associations.

Previous simulations have shown that hydration of the quaternary ammine of both CB and SB is nearly identical,<sup>8</sup> and the betaine will not form stable association. From Figure 1c, we can observe that the peak location of the RDFs of N–Cl<sup>-</sup> is identical, and Figure 1d shows that there is no significant peak for O–N RDFs, indicating that there is no stable association between the zwitterion themselves. The main difference occurs around the negatively charged sites. As shown in Figure 1, panels a and b, the peak locations for Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, and Cs<sup>+</sup> are 0.20, 0.23, 0.30, and 0.3 nm, respectively. For CB, the peak height decreases following the order Li<sup>+</sup> > Na<sup>+</sup> > K<sup>+</sup> > Cs<sup>+</sup>. This observation of CB based on RDF is consistent with those simulation results of Hess et al.<sup>18</sup> that cation affinity to carboxylate anion follows the order: Li<sup>+</sup> > Na<sup>+</sup> > K<sup>+</sup>. The same order was observed for SB, as shown in Figure 1b.



**Figure 2.** Zwitterion–cation association numbers (ANs) for various cations in the presence of Cl<sup>-</sup> as the anion.

This order correlated well with the decreasing order of the ion VDW radius size. Our previous simulation study has shown that the oxygen atoms of these two zwitterions have high partial charge.<sup>8</sup> The ion with smaller size has a higher charge density and probably causes stronger zwitterion–cation association.

However, the magnitude of peak height change for OSB–cation RDFs is significantly smaller than that for CB, indicating that the variation of SB–cation association is less than that of the CB–cation association. Comparing the corresponding RDFs for CB and SB in Figure 1, we found that the peak heights of Li<sup>+</sup> and Na<sup>+</sup> RDFs for CB are much higher than the corresponding ones for SB. This implies that CB associates with these two relative smaller cations stronger than SB, probably because the oxygen atoms of CB have partial charges higher than those of SB.<sup>8</sup> The height difference for the K<sup>+</sup> and Cs<sup>+</sup> RDFs between these two zwitterions is not significant. From the analysis of the RDFs, it is hard to conclude whether SB associates with two cations stronger than CB or not. Thus, further analysis about the association number and lifetime is needed.

**III.2. Association Numbers.** In order to investigate the zwitterion–cation association more in details, we obtained the association numbers (ANs) by counting the amount of cations whose distance from the oxygen atoms of zwitterions is less than the first minimum of the corresponding RDFs. Figure 2 shows the results of ANs for CB and SB as a function of cation type. It is found that the ANs for CB are 10.70 with Li<sup>+</sup>, 7.89 with Na<sup>+</sup>, 2.00 with K<sup>+</sup>, and 1.18 with Cs<sup>+</sup>, decreasing in the following order: Li<sup>+</sup> > Na<sup>+</sup> > K<sup>+</sup> > Cs<sup>+</sup>, in a very good agreement with that observed for RDFs. The variation of ANs for SB with various cations is much less significant than that for CB. As shown in Figure 2, the ANs for SB with Li<sup>+</sup> (3.25), Na<sup>+</sup> (3.27), and K<sup>+</sup> (3.16) are quite similar. Even for the Cs<sup>+</sup> case in which we observed the most reduction, the decrease is only 37% relative to the SB–Li<sup>+</sup> AN. This is insignificant compared to the dramatic decrease of AN from CB–Li<sup>+</sup> to CB–Cs<sup>+</sup> case, which has a nearly 90% drop.

The different variations of ANs for CB and SB result in a cross over point. As shown in Figure 2, for Li<sup>+</sup> and Na<sup>+</sup>, the ANs of CB are obviously larger than the corresponding ones for SB. However, for two weak cations, K<sup>+</sup> and Cs<sup>+</sup>, the ANs for SB turn out to be larger than those for CB. In other words, CB can associate more with two strong cations (Li<sup>+</sup> and Na<sup>+</sup>) than SB, whereas the latter can associate more with two weak cations (K<sup>+</sup> and Cs<sup>+</sup>) than CB. However, it should be noted that both CB and SB associate with the strong cations more than the weak ones, as

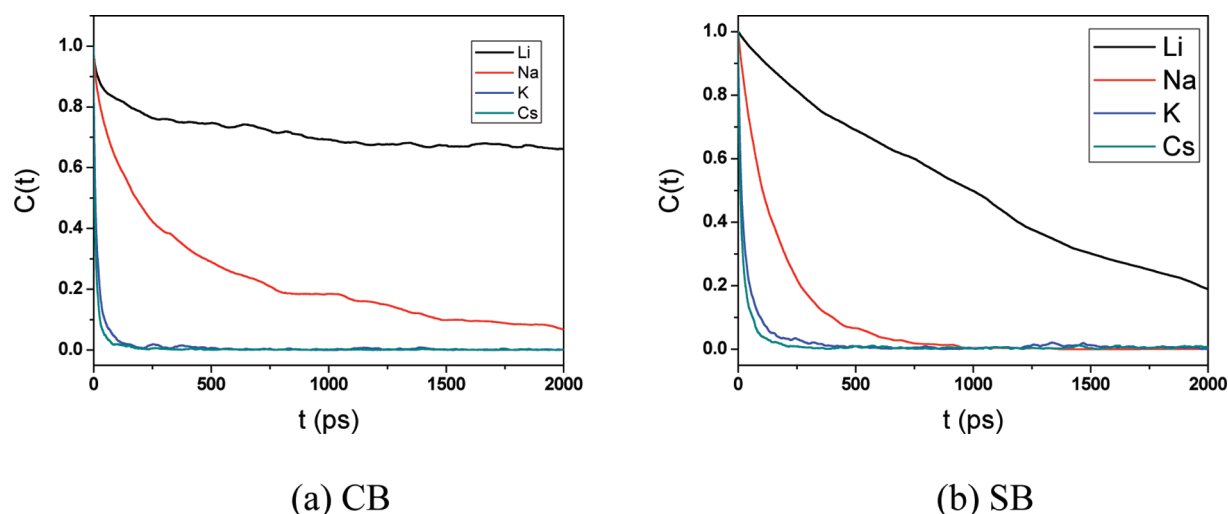


Figure 3. Residence curves of zwitterions–cation associations for (a) CB and (b) SB.

indicated by the gradual decrease of individual AN curves in Figure 2.

**III.3. Association Lifetime.** Besides the AN, another important studied property is the lifetime of individual association. A longer lifetime indicates a more stable association. The association curve is defined as  $C(t) = \sum \delta_{i,t_0,t_1} / N_{t_0}$ , where  $N_{t_0}$  is the amount of association exists at  $t_0$ , and  $\delta_{i,t_0,t}$  is equal to 1 when the association  $i$  exists at  $t_0$  and  $t$ , otherwise 0, regardless whether the association forms or not during  $t_0$  to  $t$ . Figure 3, panels a and b, shows the  $C(t)$  curves for the CB and SB with  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cs}^+$ . From these two figures, we can see that, for both CB and SB cases, the decrease of  $C(t)$  curve follows the order:  $\text{Li}^+ < \text{Na}^+ < \text{K}^+ < \text{Cs}^+$ . This indicates that the association stability for both CB and SB with cations also obeys the same order that we found for ANs. Hence, for both CB and SB, their association with cations follows the order:  $\text{Li}^+ > \text{Na}^+ > \text{K}^+ > \text{Cs}^+$ .

To further analyze the association lifetime between CB and SB with various cations quantitatively, we fitted the curve with the single-exponential function  $C(t) = e^{-t/\tau}$  and obtained the association lifetime  $\tau$ . The integration is only done to  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cs}^+$ , not to  $\text{Li}^+$ , because tail for the  $\text{Li}^+$  curve still has a very high value even after 5 ns simulation. Table 1 lists the association lifetime  $\tau$  for CB and SB with association to  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cs}^+$ .

In Table 1, we can find that, with  $\text{Cl}^-$  as the anion,  $\tau$  for CB– $\text{Na}^+$  association is larger than the one for SB– $\text{Na}^+$ , whereas CB– $\text{K}^+$  and CB– $\text{Cs}^+$  associations are less than the corresponding ones of SB. From Figure 3 we can observe that the CB– $\text{Li}^+$  curve decreases significantly more slowly than the SB– $\text{Li}^+$  one. In the previous section, we have shown a switch in ANs for CB and SB. In this section we observed the same phenomenon for the association lifetime  $\tau$ . Thus both the AN and lifetime  $\tau$  show that CB associates more as well as stronger to the two strong cations ( $\text{Li}^+$  and  $\text{Na}^+$ ) than SB. SB associates more as well as stronger to the two weak cations ( $\text{K}^+$  and  $\text{Cs}^+$ ). In our previous simulation, we have shown the different hydration behavior of CB and SB.<sup>8</sup> The observed phenomenon here indicates that these two nonfouling materials also have different interactions with various salts, especially the different effect of  $\text{Na}^+$  and  $\text{K}^+$ .

**III.4. Effect of Anion.** In order to study the effect of anions, in addition to the anion above,  $\text{Cl}^-$ , we studied two more anions,  $\text{Br}^-$  and  $\text{F}^-$ . The simulation systems and protocol were the same

Table 1. Association Lifetime  $\tau$  for  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cs}^+$  with CB and SB with  $\text{Cl}^-$ ,  $\text{Br}^-$ , and  $\text{F}^-$  as the Anions

	$\tau$ (ps)		
	$\text{Na}^+$	$\text{K}^+$	$\text{Cs}^+$
CB– $\text{Cl}^-$	432.6	13.9	7.8
CB– $\text{F}^-$	468.5	13.6	6.9
CB– $\text{Br}^-$	473.1	13.0	6.3
SB– $\text{Cl}^-$	163.8	27.8	17.4
SB– $\text{F}^-$	208.5	28.0	18.8
SB– $\text{Br}^-$	67.5	26.7	15.9

as those with  $\text{Cl}^-$ . Figure 4 shows the ANs for CB and SB with the four cations studied along with the three different anions. It can be seen that with variation of the anion the ANs for zwitterion–cation association change quantitatively. However, the order of ANs is the same:  $\text{Li}^+ > \text{Na}^+ > \text{K}^+ > \text{Cs}^+$ . We similarly observed that the identity of the anion preserved the preferential association of CB with  $\text{Li}^+$  and  $\text{Na}^+$  and SB with  $\text{K}^+$  and  $\text{Cs}^+$ .

Table 1 shows the lifetime  $\tau$  for the association of  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Cs}^+$  with CB and SB when  $\text{Br}^-$  or  $\text{F}^-$  are present as the anion. The residence curves for CB– $\text{Li}^+$  and SB– $\text{Li}^+$  are shown in Figure S2 (a and b). We can observe from Table 1 that the change of anion types from  $\text{Cl}^-$  to either  $\text{Br}^-$  or  $\text{F}^-$  changes the lifetime quantitatively. However, this varying does not change the order  $\text{Li}^+ > \text{Na}^+ > \text{K}^+ > \text{Cs}^+$ . Comparing the lifetimes and residence curves of the corresponding association of CB and SB to the cations, we can also observe that, with  $\text{Br}^-$  and  $\text{F}^-$  as the anion, the CB associates longer to  $\text{Li}^+$  and  $\text{Na}^+$ , while the SB associates longer to  $\text{K}^+$  and  $\text{Cs}^+$ . This is consistent with the observations with  $\text{Cl}^-$ . The varying of anions does not change the order of association number and lifetime qualitatively, although it will change the typical AN and lifetime quantitatively.

**III.5. Competitive Associations.** To further verify the phenomena observed for the zwitterion–cation association, we studied two types of competitive associations. One is with one type of zwitterion and two types of cations (i.e., Competition of different cations). The other is with one type of cation with two zwitterions (i.e., Competition of different zwitterions). The



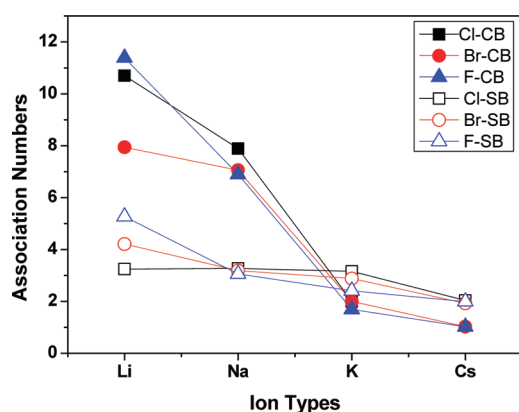


Figure 4. ANs of zwitterion—cation associations with various anions.

Table 2. ANs and Association Lifetime  $\tau$  for CB and SB with Various Cations in the System with One Type of Zwitterion and Two Types of Cations ( $\text{Cl}^-$  as the Anion)

	AN				$\tau$ (ps)			
	$\text{Li}^+$	$\text{Na}^+$	$\text{K}^+$	$\text{Cs}^+$	$\text{Li}^+$	$\text{Na}^+$	$\text{K}^+$	$\text{Cs}^+$
CB- $\text{Li}^+/\text{Na}^+$	6.06	2.67			495.2			
CB- $\text{Na}^+/\text{K}^+$		3.15	0.91		347.8	17.8		
CB- $\text{K}^+/\text{Cs}^+$			1.15	0.52			12.7	6.1
SB- $\text{Li}^+/\text{Na}^+$	2.27	1.99			292.7			
SB- $\text{Na}^+/\text{K}^+$		2.39	1.37		237.9	28.2		
SB- $\text{K}^+/\text{Cs}^+$			1.76	0.89			34.1	15.6

investigation of these two types of competitions will help to understand the preferential association of zwitterion and cation in a more direct way. As shown in the previous section, the anion type does not affect the association order qualitatively. Here, we chose  $\text{Cl}^-$  as the anion.

**III.5.1. Competition of Different Cations.** To investigate the preferential association order found based on single ion in a more direct way, we selected three cases:  $\text{Li}^+/\text{Na}^+$ ,  $\text{Na}^+/\text{K}^+$ , and  $\text{K}^+/\text{Cs}^+$ . This is able to directly elucidate which cation preferentially associates with the zwitterion. The simulation system used for this section is similar to what we described in section II. The major difference is that instead of having 50 cations of the same type, we now have two types of cations with 25 each. All of the other simulation details are the same as that described in section II.

Table 2 shows the ANs and lifetime of various cations when they are competing with other cations. Figure S2(c and d) shows residence curves of the association of  $\text{Li}^+$  and  $\text{Na}^+$  with respective zwitterions in the zwitterion- $\text{Li}^+/\text{Na}^+$  solvent. It can be seen that, for both CB and SB, the order for both AN and lifetime is still the same as we found in the previous section. Valchy et al.<sup>17</sup> investigated the associations of different cations with organic solutes, and they viewed  $\text{SO}_3^-$  as weak ion because their results showed that the association of a single  $\text{K}^+$  to  $\text{SO}_3^-$  is favored over that of single  $\text{Na}^+$  to  $\text{SO}_3^-$ . However, our simulations show that both CB and SB prefer to associate more with  $\text{Na}^+$  to  $\text{K}^+$ . This observation indicates that, if we rank the zwitterions, both of these two zwitterions are probably viewed as strong ones according to the “like-likes-like” theory,<sup>16</sup> although the CB is stronger than SB. However, a recent simulations carried out by Zangi showed that there is no disruption or

Table 3. ANs and Association Lifetime  $\tau$  for CB and SB in the System with One Type of Cation and Both CB and SB Presented ( $\text{Cl}^-$  as the Anion)

	AN		$\tau$ (ps)	
	CB	SB	CB	SB
$\text{Li}^+$	8.16	3.06		
$\text{Na}^+$	3.58	1.89	517.67	268.3
$\text{K}^+$	1.05	1.57	14.41	26.0
$\text{Cs}^+$	0.64	0.79	8.32	14.8

sudden change in the observed properties as we might think of the strong and weak ions.<sup>23</sup> This means more effort will be needed to have an insightful view of the ion effect and its ranking.

**III.5.2. Competition of Different Zwitterions.** In the previous section, we have shown that  $\text{Li}^+$  and  $\text{Na}^+$  associate with the CB stronger than with the SB, whereas  $\text{K}^+$  and  $\text{Cs}^+$  seem to associate preferentially with SB. To verify this phenomenon in more detail, we simulated the system with the same type of cation and both CB and SB presented. A typical simulation system used for this purpose has 5 CB and SB molecules distributed randomly in the simulation box. All of the other simulation details are exactly the same as described in section II.

Table 3 lists the ANs and the lifetimes of each type of cation with CB and SB when they are in the solvent. As shown in Table 3, we can observe directly that, for  $\text{Li}^+$  and  $\text{Na}^+$ , the ANs for CB are significantly larger than those for SB. As to  $\text{K}^+$  and  $\text{Cs}^+$ , the ANs for SB turn to be larger than those for CB. The same situation is observed for the lifetime. This observation demonstrates directly what we found in previous sections, namely that the  $\text{Li}^+$  and  $\text{Na}^+$  associate with the CB stronger than to SB, whereas  $\text{K}^+$  and  $\text{Cs}^+$  associate preferentially with SB.

## IV. CONCLUSIONS

In this work, we performed a series of MD simulations to investigate the association of two zwitterions, carboxybetaine and sulfobetaine, with four cations ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cs}^+$ ). We studied the radial distribution functions between the zwitterion and the ions and measured the association number per zwitterion and the lifetimes of these associations. Simulation results show that for both carboxybetaine and sulfobetaine the association number and lifetime follow the order:  $\text{Li}^+ > \text{Na}^+ > \text{K}^+ > \text{Cs}^+$ . This order is verified by simulations of competitive association of single zwitterion with two types of cations and simulations of varying anion types. Carboxybetaine prefers to associate more significantly with strong cations than weak ones, whereas sulfobetaine has a similar trend, but to a much lesser degree. This demonstrates that carboxybetaine is stronger than sulfobetaine. Consequently, the two strong cations ( $\text{Li}^+$  and  $\text{Na}^+$ ) associate more strongly with carboxybetaine than with sulfobetaine, whereas the two weak cations ( $\text{K}^+$  and  $\text{Cs}^+$ ) associate more strongly with sulfobetaine.

## ■ ASSOCIATED CONTENT

**S Supporting Information.** Force field parameters used in this work (Table S1), representative associations between zwitterions and cations (Figure S1), and residence curves of zwitterion—cation associations (Figure S2). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## ■ REFERENCES

- (1) Castner, D. G.; Ratner, B. D. *Surf. Sci.* **2002**, *500*, 28.
- (2) Iwasaki, Y.; Ishihara, K. *Anal. Bioanal. Chem.* **2005**, *381*, 534.
- (3) Jiang, S. Y.; Cao, Z. Q. *Adv. Mater.* **2010**, *22*, 920.
- (4) Cao, Z. Q.; Yu, Q. M.; Xue, H.; Cheng, G.; Jiang, S. Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 3771.
- (5) Zhang, L.; Xue, H.; Gao, C. L.; Carr, L.; Wang, J. N.; Chu, B. C.; Jiang, S. Y. *Biomaterials* **2010**, *31*, 6582.
- (6) Carr, L. R.; Xue, H.; Jiang, S. Y. *Biomaterials* **2011**, *32*, 961.
- (7) Yang, W.; Xue, H.; Carr, L. R.; Wang, J.; Jiang, S. Y. *Biosens. Bioelectron.* **2011**, *26*, 2454.
- (8) Shao, Q.; He, Y.; White, A. D.; Jiang, S. Y. *J. Phys. Chem. B* **2010**, *114*, 16625.
- (9) Georgiev, G. S.; Karnenska, E. B.; Vassileva, E. D.; Kamenova, I. P.; Georgieva, V. T.; Iliev, S. B.; Ivanov, I. A. *Biomacromolecules* **2006**, *7*, 1329.
- (10) Das, M.; Sanson, N.; Kumacheva, E. *Chem. Mater.* **2008**, *20*, 7157.
- (11) Kumar, R.; Fredrickson, G. H. *J. Chem. Phys.* **2009**, *131*, 104901.
- (12) Kunz, W.; Henle, J.; Ninham, B. W. *Curr. Opin. Colloid Interface Sci.* **2004**, *9*, 19.
- (13) Collins, K. D. *Biophys. J.* **1997**, *72*, 65.
- (14) Collins, K. D.; Neilson, G. W.; Enderby, J. E. *Biophys. Chem.* **2007**, *128*, 95.
- (15) Kunz, W. *Curr. Opin. Colloid Interface Sci.* **2010**, *15*, 34.
- (16) Collins, K. D. *Methods* **2004**, *34*, 300.
- (17) Vlachy, N.; Jagoda-Cwiklik, B.; Vacha, R.; Touraud, D.; Jungwirth, P.; Kunz, W. *Adv. Colloid Interface Sci.* **2009**, *146*, 42.
- (18) Hess, B.; van der Vegt, N. F. A. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 13296.
- (19) Tobias, D. J.; Hemminger, J. C. *Science* **2008**, *319*, 1197.
- (20) Lund, M.; Vrbka, L.; Jungwirth, P. *J. Am. Chem. Soc.* **2008**, *130*, 11582.
- (21) Vrbka, L.; Mucha, M.; Minofar, B.; Jungwirth, P.; Brown, E. C.; Tobias, D. J. *Curr. Opin. Colloid Interface Sci.* **2004**, *9*, 67.
- (22) Jungwirth, P.; Tobias, D. J. *Chem. Rev.* **2006**, *106*, 1259.
- (23) Zangi, R. *J. Phys. Chem. B* **2010**, *114*, 643.
- (24) Martinez, L.; Andrade, R.; Birgin, E. G.; Martinez, J. M. *J. Comput. Chem.* **2009**, *30*, 2157.
- (25) Aqvist, J. *J. Phys. Chem.* **1990**, *94*, 8021.
- (26) Berendsen, H. J. C.; Grigera, J. R.; Straatsma, T. P. *J. Phys. Chem.* **1987**, *91*, 6269.
- (27) Van der Spoel, D.; Lindahl, E.; Hess, B.; Groenhof, G.; Mark, A. E.; Berendsen, H. J. C. *J. Comput. Chem.* **2005**, *26*, 1701.
- (28) Essmann, U.; Perera, L.; Berkowitz, M. L.; Darden, T.; Lee, H.; Pedersen, L. G. *J. Chem. Phys.* **1995**, *103*, 8577.
- (29) Berendsen, H. J. C.; Postma, J. P. M.; Vangunsteren, W. F.; Dinola, A.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684.
- (30) Hess, B. *J. Chem. Theory Comput.* **2008**, *4*, 116.