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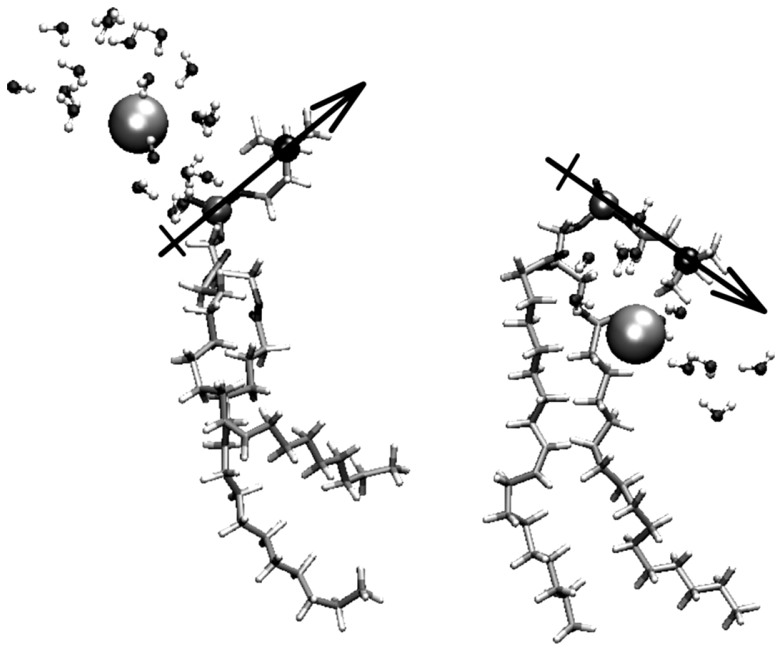

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Understanding the Hofmeister Effect in Interactions between Chaotropic Anions and Lipid Bilayers: Molecular Dynamics Simulations

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Large chaotropic anions induce complex interfacial interactions as a result of their propensity to disrupt water structure. For example, they increase efficiency in separation processes such as liquid chromatography[1,2] and induce swelling of poly(acrylamide) gels.[3] Several large anions are known pollutants and have been shown to affect protein structure,[4] as well as binding of peptides to membranes.[5] Additionally, there is a wealth of physiological[6] as well as both experimental and theoretical[7−10] biophysical data regarding their interactions with the lipid bilayer. Despite growing interest in these anions and the related Hofmeister effect, there is yet no detailed atomic-level model that can explain the data regarding bilayers.

For bilayers with neutral PC (phosphatidylcholine) headgroups, chaotropic anions affect conformational fluctuations of the headgroups, with the magnitude of this effect paralleling a Hofmeister series:[9] $NO_3^- < I^- < SCN^- < ClO_4^-$. Recently, the influence of this same series of anions on the dipole potential of DMPC (dimyristoylphosphatidylcholine) vesicles was studied using voltage sensitive dyes.[10] This study correlates the Gibbs solvation free energy of anions with changes in dipole potential and suggests that the chaotropic anions may penetrate more deeply into the bilayer interior than do the nonchaotropic anions.

Molecular dynamics (MD) simulations provide fundamental atomic-level descriptions and, as such, are capable of explaining macroscopic experimental results.[11,12] For many years, MD simulations were unable to address the questions raised by data on salt effects due to limitations in the empirical force fields. However, recent improvements to the force fields, through inclusion of the Ewald[13] summation technique for calculation of long-range electrostatic interactions, have opened the door to investigation of the salt−bilayer interactions.

To understand the Hofmeister series effect in the context of anion−bilayer interactions, we performed two all-atom MD simulations of fluid phase (L_α) POPC (palmitoyloleoylphosphatidylcholine) bilayers solvated by 1 M salt. The simulations are designed to isolate the role of anion size from shape and polarizability. The first simulation is of NaCl, while the second used altered anions whose effective van der Waals (vdW) radius was increased by 37.5% relative to chloride. Hence, the large anions, like Cl^-, are modeled as vdW spheres with a centrally located point charge. Thermochemical radii have been estimated for multi-atomic anions,[14] and we used these radii to rationally estimate the radial expansion of chloride. While one could choose to parametrize anions based on experimental solvation data alone, the effort here is to isolate the role of size and maintain as straightforward an analysis as possible. A recent parallel study of water structure and the Hofmeister effect applied computational Monte Carlo simulations using a nonpolarizable force field.[15] That study suggests that ionic charge density, a direct function of ionic radius, leads to tighter water binding for small ions.

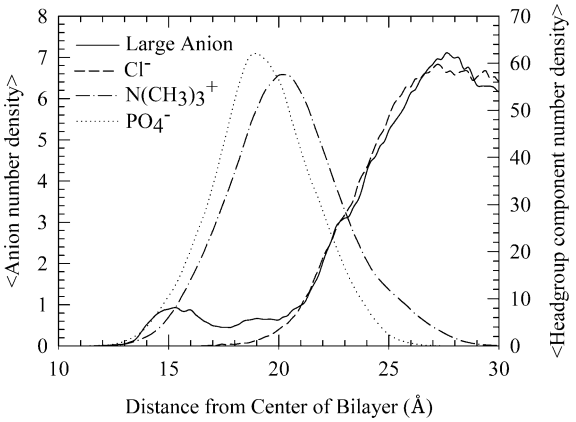

Figure 1. Trajectory-averaged number density profiles for the anions from both simulations, overlaying that of the headgroup phosphate and choline groups.

Simulations were performed using CHARMM version 26,[16] parameter set 27,[17,18] with the TIP3P water model.[19] The parametrization of the Na^+ and Cl^- ions was based upon comparison with solvation free energy data and quantum mechanical calculations.[20] Periodic boundary conditions were used with a constant number of atoms (N), temperature (T = 298 K), lateral area (A/lipid = 64 Å^2), and normal pressure (P_N = 1 atm) to generate NAP_NT ensembles. Bilayers consisted of 72 lipid molecules solvated by 3107 water molecules and a total of 120 ions. An initial salt-free POPC structure, provided by the Feller group,[12] was run for 5 ns for relaxation of the headgroups and chains. Ions were then added, followed by minimization and equilibration, and then 5 ns of dynamics. The last configuration was used as the starting point for both 5 ns simulations presented here. For the larger anion simulation, after enlargement of the anions, the system was allowed to relax through another set of minimization and equilibration before the production dynamics. Electrostatics were calculated using particle mesh Ewald.[13]

The central result from the simulations is that the large anions penetrate more deeply into the bilayer interior than do the Cl^- anions. Figure 1 plots trajectory averaged number density distributions for both anion types, along with the headgroup phosphate and choline groups for reference. In the case of Cl^-, the figure shows penetration to within 17.5 Å from the bilayer center. Na^+ ions penetrate 2−3 Å more deeply in both simulations (data not shown).[21] Strikingly, the figure shows that the larger anions penetrate even more deeply than the Na^+ ions, to within 12.5 Å of the bilayer center. Unlike Cl^- and Na^+, then, the larger anions are energetically stable in a hydrophobic environment, supporting the experimental observations regarding dipole potential.[10] In a series

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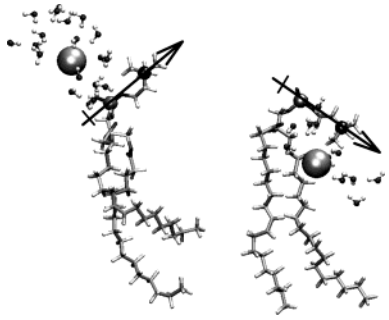

Figure 2. Snapshots of the deep anionic penetration into the bilayer interface which occurs only in the large anion simulations. Only those waters within the first minimum of the bulk anion $g(r)$, as described in the text, are shown. The snapshots are separated in time by 3 ns.

of NaCl/POPC simulations totaling 20 ns (not reported here), there were no instances of Cl^- penetration deeper than 17.5 Å, suggesting that the behavior is robust and not artifactual. While sampling of ions is limited by their small number, the penetration of the large anions is dynamic, with instances of anions stably trapped for several nanoseconds, as well as cases of more short-lived anionic capture (followed by release back into the bulk aqueous phase).

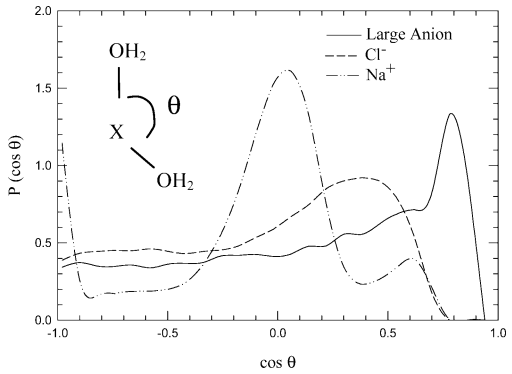

Figure 3. Hydration shell geometry, defined by the probability distributions of θ, the angle formed by water oxygen−anion−water oxygen as described in the text, for ions in the bulk aqueous phase.

Figure 2 illustrates the dynamic capture of a large anion. The headgroup dipole of this lipid, initially pointing out toward the aqueous phase, inverts as it shepherds the anion into the more hydrophobic interfacial region. The trajectory-averaged angle made by the PN-dipole vector from the bilayer normal across all lipids is calculated to be 81.5°, but for the lipid shown in Figure 2, the trajectory-averaged angle is 119.5°. Such a reorientation agrees well with the suggestion of Seelig and co-workers[22] and may underlie the changes seen in headgroup fluctuations.[9] The change in headgroup tilt stabilizes the electrostatic interaction between the negatively charged anion and the headgroup dipole.

We hypothesize that the large anions may impose too costly an entropic penalty on water to recruit well-structured hydration shells, thus increasing the likelihood of partitioning of the anion into the hydrophobic bilayer interior. In the bulk aqueous phase, the larger anions have an average water coordination number of 30.2 in the first hydration shell, defined by the position of the first minimum in the water-oxygen/anion radial distribution function (data not shown). This is in contrast to a bulk aqueous phase coordination number of 9.9 for Cl^- and 6.7 for Na^+. As the large anion passes from the bulk phase into the deep interfacial region, the water coordination number decreases to between 10 and 13. To begin to understand this water shedding, Figure 3 plots the probability distribution of oxygen−ion−oxygen angles (θ) within the first hydration shell for ions in the bulk aqueous phase. There is a clear geometric arrangement of waters around the Na^+ ions, with the peak at $\theta = 90°$ being consistent with a stable octahedral arrangement (as has been seen previously[23,24]). The water arrangement around the Cl^- ions is less well-defined than that of Na^+. Significantly, the structure around the large anion is even less well-defined, with a peak at approximately $\theta = 36°$ corresponding to an unstructured, dispersed hydration shell. Presumably, this "loose" hydration shell is more easily shed than that of Cl^-, facilitating the partitioning behavior.

Recent improvements to all-atom molecular dynamics force fields have, for the first time, allowed a detailed understanding of interactions between chaotropic anions and lipid bilayers. It has been demonstrated here that, unlike Cl^-, large chaotropic anions penetrate deeply into the interfacial region of the lipid bilayer. The simulations show that anion size alone can lead to this behavior. Larger anions are more hydrophobic and hence prefer the bilayer interior, explained by a less-structured hydration shell. Electrostatic interactions between the penetrating anion and headgroup lead to a change in the headgroup tilt. The implications of such structural rearrangements are far-reaching, as they impact upon critical interfacial phenomena.

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