

Free energy landscapes of metal ions at phospholipid membrane surfaces

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Abstract

Metal cations are ubiquitous components in biological environments and play an important role in regulating cellular functioning and membrane properties. Exploring the free-energy landscape of metal cations on phospholipid membrane surfaces is important for the understanding of chemical and biological processes in cellular environments. However, despite the significant progress in free-energy calculations, a comprehensive knowledge of the free-energy of metal cations on phospholipid membrane surfaces is still missing. This is due to the complexity of the membrane environments, making the application of the state-of-the-art sampling techniques a challenge.

By applying metadynamics simulations, we have performed systematic free-energy calculations of Na⁺, K⁺, Ca²⁺, and Mg²⁺ bound to phospholipid membrane surfaces for the first time. The free-energy landscapes unveil specific binding behaviors of metal cations on phospholipid membranes. Na⁺ and K⁺ are more likely to stay in the aqueous solution, and can easily bind to a few lipid oxygens by overcoming low free-energy barriers. Ca²⁺ is most stable when bound to four lipid oxygens of the membranes, rather than being hydrated in the aqueous solution. Mg²⁺ is tightly hydrated, and can hardly lose a hydration water and bind directly to the membranes. When bound to the membranes, the cations' most favorable total coordination numbers with water and lipid oxygens are the same as their corresponding hydration numbers in aqueous solution, indicating a competition between ion binding to water and lipids. The binding specificity of metal cations on membranes is then highly correlated with the hydration free-energy and the size of the hydration shell.

Our work provides a general methodology to explore the free-energy landscapes for ions at complex biological interfaces which can be extended to study other interactions of interest between ions and charged headgroups in colloidal chemistry and soft matter.