Osmotic Pressure Calculations Reveal the Need for Reparameterization of CHARMM Forcefield Carbonate Parameters

Balarama Sridhar Dwadasi[1], Kazi Shudipto Amin[1], Hristina R Zhekova[1], D Peter Tieleman[1], Dennis R Salahub[2] and Sergei Yu Noskov[1]

[1]CMS – Centre for Molecular Simulation and Department of Biological Sciences, University of Calgary, AB, Email: balaramasridhar.dwad@ucalgary.ca
[2]Department of Chemistry, CMS – Centre for Molecular Simulation, IQST – Institute for Quantum Science and Technology, Quantum Alberta, University of Calgary, AB

Carbonate and bicarbonate ions play a key role in pH maintenance in the human body. The SLC4 family of proteins regulates the transport of these ions across the cell membrane. These secondary transporter systems are at the core of anion homeostasis in living cells, moving selectively a range of substrates including carbonate and bicarbonate ions. Molecular simulation studies of these systems and their substrates can reveal important details of their transport and selectivity. The CHARMM forcefield has been extensively used in the study of similar membrane proteins. Currently, CGENFF provides CHARMM-compatible forcefield parameters for carbonate and bicarbonate. However, these parameters have not been extensively validated and their quality is unclear. Therefore, we tested the available parameters by performing Molecular Dynamics simulations for the sodium salts of carbonate and bicarbonate at different concentrations in aqueous solution to obtain osmotic pressures. Semi-permeable membranes were simulated by applying restraint forces on the ionic species only. The resulting trajectories were analysed to compute osmotic pressure in each of the systems. The results show that the osmotic pressures obtained from simulations of bicarbonate in solution agree with the available experimental observations. However, a higher rate of ion aggregation was seen in the carbonate solutions resulting in underestimation of the osmotic pressure across the range of concentrations studied. Therefore, reparameterization of the forcefield parameters of the carbonate ions is essential for accurate simulations of their transport.