MODELLING INTERMOLECULAR INTERACTIONS OF IBUPROFEN IN AQUEOUS HYDROTROPIC SOLUTIONS USING MD SIMULATIONS

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Poor solubility of candidate drug molecules in water is one of the most common obstacles in drug design, thus requiring methods to improve *in vitro* solubility[1]. The application of hydrotropy is one such method – mixtures of water and hydrotropes may improve drug molecule solubility by orders of magnitude[2]. Although hydrotropes are already seeing application, the hydrotropic effect itself has yet to be fully explained – there are currently three hypothesized mechanisms: self-aggregation, chaotropic effects, and the formation of low stoichiometry complexes[3]. Gaining insight into the working mechanism requires an investigation of changes within the first solvation layer of target drug molecules. In this work we investigate the hydrotropic effect of the ionic liquid cholinium salicylate on the model drug molecule ibuprofen. It has been shown in the literature that cholinium salicylate – an analog compound to the anti-inflammatory drug aspirin – is capable of increasing the solubility of ibuprofen in water by up to 6000-fold[4]. The investigation of the changes within the first solvation layer of ibuprofen is achieved via molecular dynamics (MD) simulations.

Initial geometries of ibuprofen, cholinium and salicylate molecules were constructed and optimized by using Gaussian[5], point charges and force field parametrization were acquired via the RESP method[6]. MD simulations were conducted using the AMBER MD packet[7]. The TIP4P-Ew water model was used for the water molecules and the General Amber Force Field (GAFF) was used for the remaining molecules[8]. In total – 7 simulation boxes were created: one reference system of ibuprofen in pure water; three systems containing 3%, 5%, and 7% molar fractions of sodium salicylate; and three 3%, 5%, and 7% systems of cholinium salicylate. MD simulations were conducted in two principal steps – equilibration and production phases. Equilibration was achieved by the minimization of potential energy, followed by a short 1 ns simulation in the NVT ensemble, at least 100 ns in the NPT ensemble (until equilibrium density is achieved), and 50 ns in the NVT ensemble before proceeding to the production run of 100 ns in the NVT ensemble. The resulting trajectories were analyzed using radial distribution functions which were integrated to obtain coordination numbers. Coordination numbers provide information about the first solvation layer of ibuprofen across systems of varying hydrotrope concentrations.

The trajectory analysis shows that the hydrotropic effect of cholinium salicylate is largely determined by the ejection of water molecules from the immediate surroundings of ibuprofen's aromatic ring, whereas the protection of the aliphatic chain of ibuprofen from interactions with water is not a determining factor. Furthermore, it was shown that salicylate ions maintain a significant distance from the aromatic ring of ibuprofen, which was contrary to prior expectations.

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