Title: Ion-Protein Interactions
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**Abstract:** Conventional molecular dynamics simulations in combination with advanced methods of analyses were used to improve the understanding of the interaction between ions and proteins in salt solutions. Thus systems of diverse complexity and size were investigated, starting with simple (and molecular) salt solutions with small fragments that mimic the various functional groups of amino acids such as N-methylacetamide representing the peptide bond or alkylated ammonium cations.

Continuing with individual positively charged amino acids (arginine, histidine, lysine) a strong binding interaction with small fluoride anion that is significantly weakened for larger halides ($Cl^-$, $Br^-$, $I^-$) was described. This observation was extended by detecting the strong sensitivity of fluoride to charge distribution on ammonium, lysine side chain, and the N-terminal of glycine while sensitivity of iodide was found to be low. Later it was shown that the attractive side chain-side chain interactions are significant for short positively charged peptide fragments in polyarginine and dihistidine, while they are not present at all in case of polylysine.

Considering the qualitative difference in the origin of ion-specific interactions, electrophoretic mobility measurements (for mono- and tetra- amino acids) were employed in tandem with MD simulations. The ion-specific arginine-sulphate and arginine-guanidinium interactions were proved, both pronounced as the specific decrease or increase in electrophoretic mobility in contrast to observations for lysine, chloride anion, and sodium cation.

Cation-specific interaction was found, both experimentally and computationally, to be responsible for specific affecting of the enzymatic activity of HIV-1 protease and LinB enzyme from dehalogenase family. In both cases the general salting out effect was experimentally observed (pronounced as the increase of the enzymatic activity). Finally, the denaturant-specific unfolding pathway of TrpCage minipeptide was identified by comparing the denaturation process in urea and guanidinium chloride solution. In all the studies the aim was to shed more light on complex behaviour caused by ion-specific effects such as ordering in Hofmeister series, speeding up the enzymatic activity, preferential interactions with functional groups or the osmolyte specific denaturation pathways.

**Keywords:** molecular dynamics, proteins, denaturation, salts, osmolytes.