Linear peptide-based anion receptors in water

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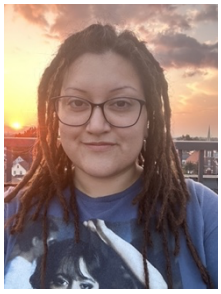

Abstract: In nature's biological systems, proteins can bind anions in aqueous solution by forming hydrogen bonds with charge-neutral motifs. Amino acids are the fascinating building blocks of all proteins, and they have huge potential for the design of simpler peptide-based supramolecular constructs. With inspiration from protein structures in the biological world there is a limitless potential of designing sophisticated functional supramolecular materials based on the 20 natural amino acid building blocks. A commonality shared between multiple transmembrane proteins that inspire this research area is that they contain hydrogen-bond donating (side chain and backbone) amino acid residues that envelop a bound anion in a solvent-shielding microenvironment with low polarity. This has steered anion recognition in water towards semi-synthetic cyclic pseudo-peptides that are only loosely related to natural peptides. This departure from peptide designs loses the context of understanding emergence of selectivity in biology, and it also limits the versatility of bio-application. There are many synthetic anion receptors that show good selective binding in organic solvents yet there is a shortage of anion receptors that work well in water. In aqueous solutions, both substrates are heavily solvated. Here lies the challenge with the energetic costs of disturbing the anion solvation sphere. To accommodate a linear scaffold, incorporating glycine residues will provide the flexibility necessary for induced fit to occur along with backbone binding NH moieties. To encourage the conformational dynamics involved with induced fit, aromatic side chain amino acid residues are to be integrated in pairs to exploit the π-π self-stacking intramolecular interactions. Serine is a good contender for providing hydrogen bonds from both the backbone and the side chain. I will begin my investigations by exploring the effects of the aromatic side chains. Coarse-grained MARTINI simulations are applied to get an insight into the potential stability of the conformational dynamics of the complex more quickly than an atomistic simulation. The generic sequences that have been simulated with ATP are illustrated (figure 1). I use simple solid-phase peptide synthesis to procure the suitable peptides for the study and do further conformational analysis through experimental and computational techniques. I plan to utilize each peptide for anion binding assays. Various spectroscopic techniques like Nuclear Magnetic Resonance, Circular Dichroism, Spectrofluorimetry, and Microcalorimetry can be used in titration assays with the peptide and anion of interest. Furthermore, utilizing the knowledge attained in experiments regarding peptide sequence and conformational preference and their role in anion recognition, I aim to achieve selective binding of ATP and GTP using minimalist peptide sequences. To further compare my sequences with phosphate binding proteins in nature, I plan to do PDB mining of the phosphate binding protein crystal structures and understand the nature of interactions responsible for selective binding.

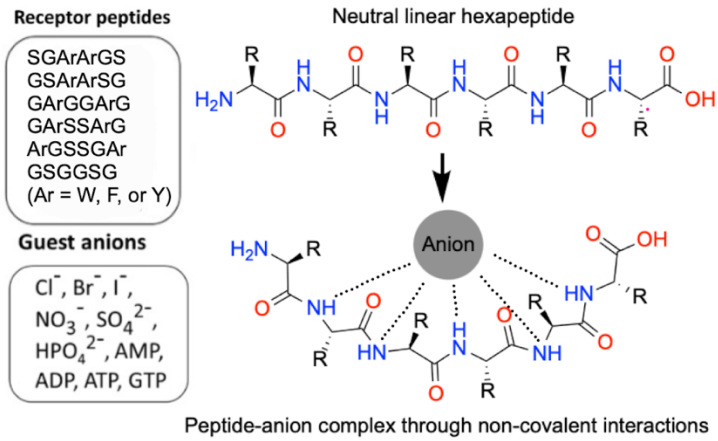

Figure 1: General overview of concept