Modeling Peptides in Aqueous Ionic Liquid Mixtures: a QM/MD Study of Structural and NMR Properties

Žyginta Murnikova[1], Kęstutis Aidas[1]
[1]Institute of Chemical Physics, Faculty of Physics, Vilnius University, Lithuania,
zyginta.murnikova@ff.vu.lt

Ionic liquids (ILs) have been known as "green" and biocompatible solvents for quite some time and are widely used as solvents in chemistry, electrolytes in batteries, drug carriers in pharmaceuticals, and so on [1]. Because of many possible combinations of a desired cation and anion pairs, they are called "designer" solvents, allowing the tunability of various properties. Some of ionic liquids' possible biological uses include changing catalytic activity of enzymes, stabilizing or destabilizing various proteins, as well as making them permeate more easily through membranes [1]. The nature of ILs and proteins' interactions varies and is difficult to evaluate because of the size and complexity of large protein structures. So, smaller peptides are often used as a model system to discover how different ILs interact with said peptides and change their structure in the aqueous solution. The most suitable method for recognizing intermolecular interactions is nuclear magnetic resonance (NMR) spectroscopy as atoms', especially hydrogen, chemical shift is very sensitive to changes of central molecule's close environment. While experimental NMR provides insight into changes in the vicinity of the molecule, computational methods can aid in identifying what specific interactions are deciding the changes in proton chemical shift.

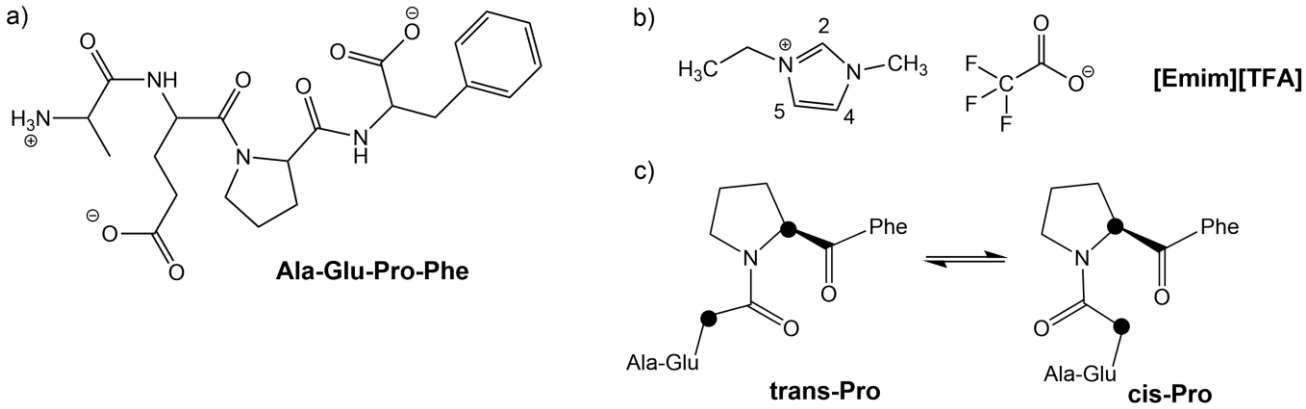

Figure 1. Structural formulas of a) peptide Ala-Glu-Pro-Phe, b) ethyl-3-methylimidazolium trifluoroacetate, c) *trans/cis* isomeric forms of AEPF

In this work an Ala-Glu-Pro-Phe tetrapeptide (AEPF) was investigated using molecular dynamics (MD) simulations and quantum mechanics/molecular mechanics (QM/MM) calculations, while in an aqueous environment and in IL/water mixture. This peptide exists in two different isomers due to proline amino acid – *cis* or *trans* and is often used as a substrate for investigating peptidyl-prolyl *cis-trans* isomerase Pin1 [2]. An ionic liquid consisting of a popular imidazolium cation and trifluoroacetic acid – ethyl-3-methylimidazolium trifluoroacetate ([Emim][TFA]) was chosen as the solvent for this investigation.

MD simulation data revealed some structural changes in the peptide's structure itself, thus resulting in 4 different possible structures being evaluated for *cis*- and *trans*- conformers.

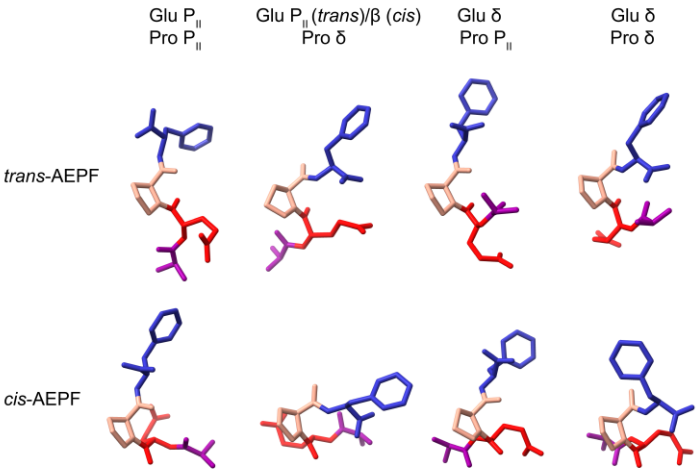

Figure 2. Representative structures of conformers of *trans*- and *cis*-AEPF tetrapeptide observed in aqueous and aqueous [EMim][TFA] solution. The Ala, Glu, Pro and Phe residues are colored in magenta, red, pink and blue, respectively.

Coordination numbers of water and IL ions around the peptide were calculated to evaluate the constituents of the peptide's first solvation shell. Chemical shift differences of all peptide conformers' hydrogen atoms were calculated using QM/MM methods and compared to experimental results [3]. This allowed us to evaluate the different interactions taking place in peptide/IL/water systems.

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