I^- Effects on the Helical Stability of a 21 Residue Alanine Based Peptide

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Introduction:

It has long been known that protein conformation and activity are greatly impacted by the presence of ions in aqueous solution. The mechanisms behind these impacts are still poorly understood. Investigations into protein stability in general have focused mainly on alpha-helix stability and how it is affected by the presence of ions within solutions. Currently, the fundamental principals explaining alpha-helix stability in salt solutions are still being debated. Alanine peptides form particularly stable alpha helices. Alanine peptides have experimentally been studied in detail as they reveal information about the characteristics of a peptide that create alpha helix stability.[1]

Ions have the ability to stabilize or destabilize alpha-helices according to their placement in the Hofmeister series:

Anions: $H_2PO_4^- > SO_4^{2-} > F^- > Cl^- > Br^- > NO_3^- > I^- > ClO_4^- > SCN^-$

Cations: $Mg^{2+} > Li^+ > Na^+ \sim K^+ > NH_4^+$

Placement within the Hofmeister series is based on the ability to precipitate proteins from solution, salting-out. Ions on the left side of the series tend to salt-out proteins while

those on the right salt-in proteins increasing their solubility.[2] It is thought that the salting-out and salting-in effects of these ions is caused by entropic changes in the protein's salvation shell. These entropic changes are believed to ultimately be a result of ions altering the structure of water's hydrogen bonding network. Chaotropes, large low-charge ions, disrupt water's hydrogen bonding structure while kosmotropes, small or highly charged ions, impose higher order within water's hydrogen bonding network.[3,4]

As it is impossible to physically observe the actual interactions between salt molecules and the atoms that compose an alpha-helix, computational methods are being used to simulate these interactions. Molecular dynamic (MD) simulations of the interactions between proteins and ions provide detailed insight into the fundamental principals responsible for stability characteristics of alpha-helices in salt solutions.

Expected Results:

It is hypothesized that the I^- anion will destabilize the alpha-helical structure of the alanine based peptide. I^- is a strong denaturant that salts in the peptide group and interacts more strongly with the unfolded form of the protein.[5]

Methods:

The interactions between an alanine based peptide and 0.2M I^- will be investigated through molecular dynamic simulations using the AMBER 10, sander, xleap, and VMD. The system to be studied is the 21 residue alanine peptide: $AAAAA(AAARA)_3$ where A represents the amino acid alanine and R represents the amino acid arginine. Simulations are to be preformed using the AMBER 10 with a

modified version of the AMBER-99 forcefield, ffSB99. This force field has improved φ/ψ parameters that more accurately represent alanine peptides.[6]

A cubic water box will be constructed containing the alanine peptide in a 60 buffer. This box will have a initial volume of 3736355.423$Å^3$ and be composed of approximately 105646 water molecules, 403 I^- molecules, and 400 Na^+ molecules to ensure a neutral charge. The water model to be used is the TIP3P and the parameters for I^- to be used are $R^{min}/2$=2.860 and ε= 0.0536816 as they have been previously determined as optimal by In Suk Joung at al.[7] The simulation data will then be analyzed to determine the reasons for alpha helix stabilization/destabilization. These simulations will be used to determine if Debye screening, ion-pairing, electrostatics, or water activity mechanisms are the cause responsible for the effects of I^- of helix stability.

Goals:

The Goal of this molecular dynamics simulation is to understand the physical mechanisms governing the role ions play in protein stability as observed by experimental techniques such as ultraviolet resonance Ramen spectroscopy and circular dichroism spectroscopy. The data collected can then be compared to other ions in the Hofmeister series to seen if the results correlate to the iodine ions location within the series.

References:

[1] Martin Shollz J., York E. J., Stewart J.M., Baldwin R. L. *J. Am. Chem. Soc*., **1991**, 113 (13), 5102-5104.

[2] Hofmeister, F. 1888, *Zur Lehre von der Wirkung der Salze.* Arch. Exp. Pathol. Pha, Vol. 24, Solv, Vol. 56, pp. 196-202.

[3] *Water and proteins. II. The location and dynamics of water in protein systems and its relation totheir stability and properties.* Edsall, J.T. and McKenzie, H. s.l. : 153-183, 1983, Adv. Biophys., Vol. 16, pp.153-183.

[4] Conway, B.E. *Ionic hydration in chemistry and biophysics.* Amsterdam : Elsevier, 1981.

[5] Baldwin, R.L. *Biophysical Journal*, **1996,** 71, 2056-2063.

[6] Hornak, V. et al. 2006, *Comparison of multiple amber force fields and development of improve backbone parameters.* Prot. Struct. Function and Bioinf., Vol. 65, p. 712.

[7] Joung I. S., Cheatham T. E. III. *J. Phys. Chem B.,* **2008**, 112 (30), 9020-9041.