MOLECULAR DYNAMICS OF STAPLED PEPTIDES

Villavicencio, B.¹; Ligabue-Braun, R.¹; Verli, H.¹

¹ Grupo de Bioinformática Estrutural, Centro de Biotecnologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Peptides are promising for drug development research due to their reduced size, their ability to traverse membranes, and a reasonable contact surface for interacting with target proteins. However, without its complete proteic framework, a peptide’s secondary structure can be easily destabilized, allowing the loss of its biologically relevant conformation. In α-helices, a strategy to address this issue is the addition of a molecular staple linking one or more turns of the helix through an all-hydrocarbon bridge. While experimental studies yielded good results both in vitro and in vivo, predictive models are still scarce. One of such models is molecular dynamics, which renders information about conformational changes in the system, while reducing research costs and allowing a better understanding of stapled peptides and their potential use. In order to allow their application in protein engineering, we parameterized and simulated both stapled and unstapled peptides, starting as either helices or linear molecules with the potential to acquire defined structures. We evaluated staples of 6 or 8 carbons with different configurations (R-S). All simulations were carried out with the GROMOS54a7 force field in the Gromacs simulation suite. Results indicate that, while unstapled peptides tend to lose their helical form, stapled peptides tend to remain helical. In the case of initially linear peptides, the trend is to become helical. The type of staple used seems to influence the degree of helical content acquired. These alterations in secondary structure content seem to agree with experimental circular dichroism results. Our results are useful not only for allowing the implementation of simulation protocols for stapled peptides, but also for describing with a high level of confidence the conformational behaviour of such peptides at the atomic scale. Further simulations with different force fields are being performed in order to obtain a broader comparison landscape for these peptide modifications.

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