Conformational study of methionine-enkephalin and its unnatural analogue using molecular dynamics

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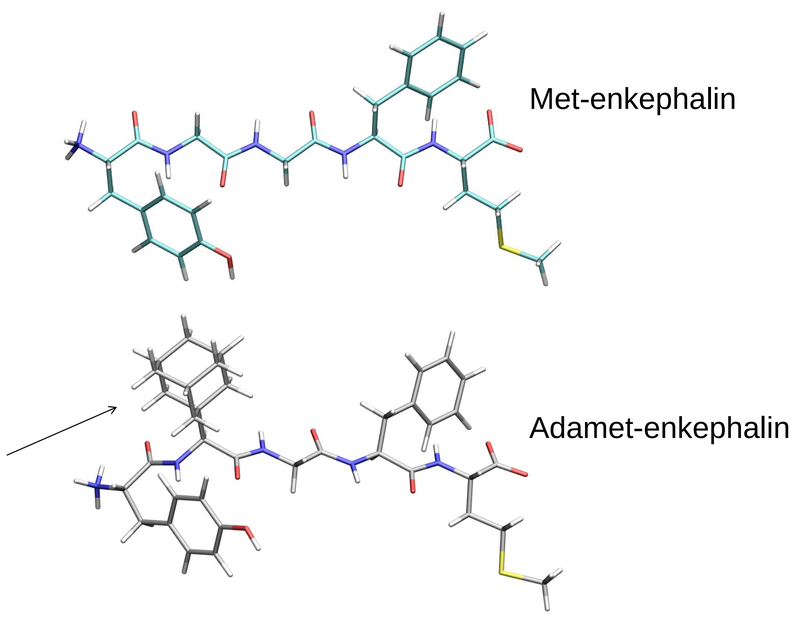
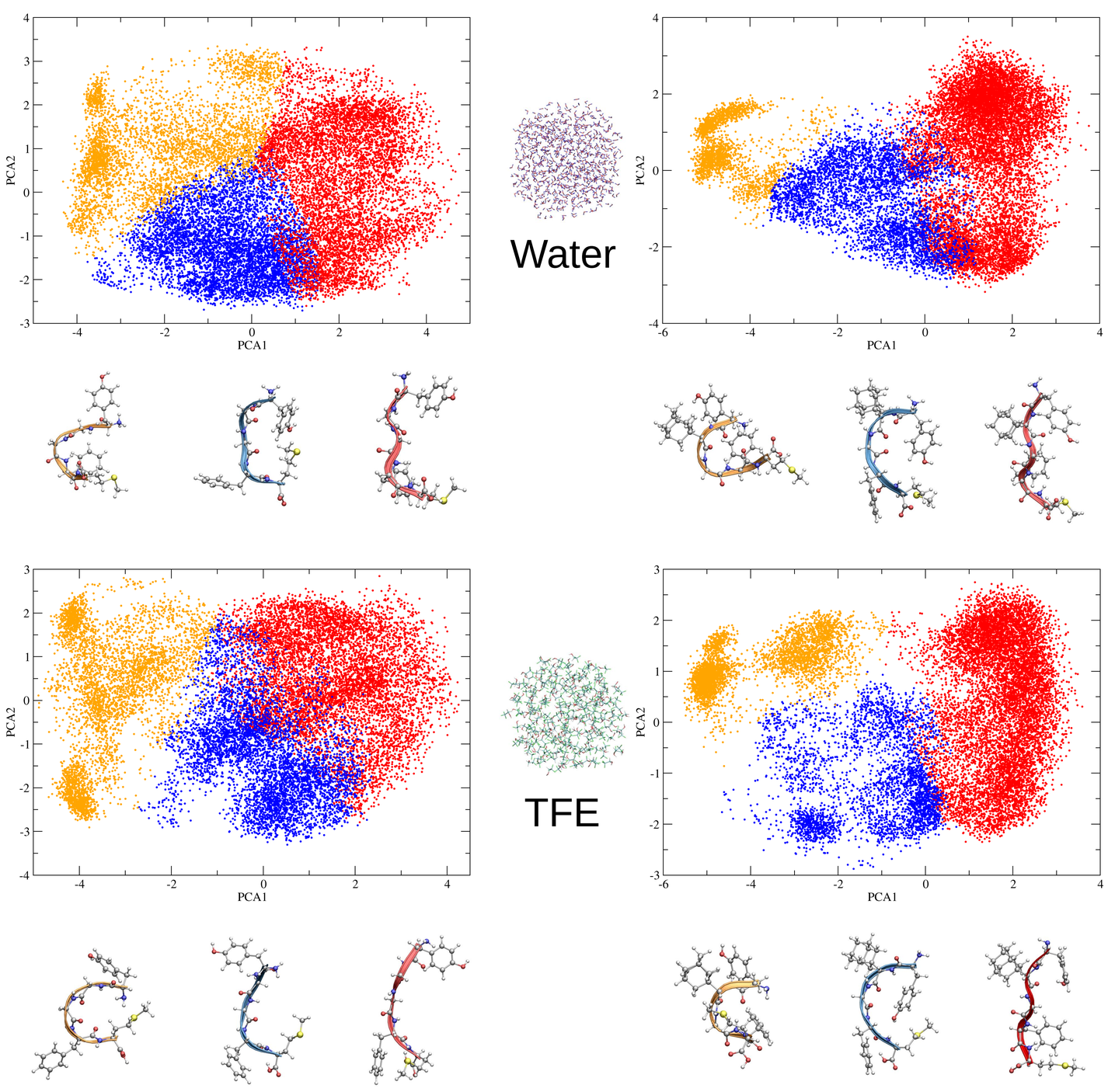
Introduction

Met-enkephalin (Tyr-Gly-Gly-Phe-Met) is a pentapeptide that belongs to a group of opioid peptides and acts as an inhibitor of tumor-cells in a receptor-mediated fashion. This effect is even more pronounced when an unnatural analogue of Met-enkephalin, Adamet-enkephalin, which contains an adamantane group, was employed. Previous studies [1] indicate that the solution conformation of the peptides affects their biological activity.



Met-enkephalin

Adamet-enkephalin



Principal component analysis (PCA) and clustering (k-mean algorithm) [3] were used in order to compare the data obtained from the REMD simulations. Only α-C atoms of the peptides were used in both methods.

The plots above show the projections of the members of each cluster (color coded) on the phase space spanned by the first two principal components. The depicted structures correspond to the conformations closest to the centroid of each cluster.

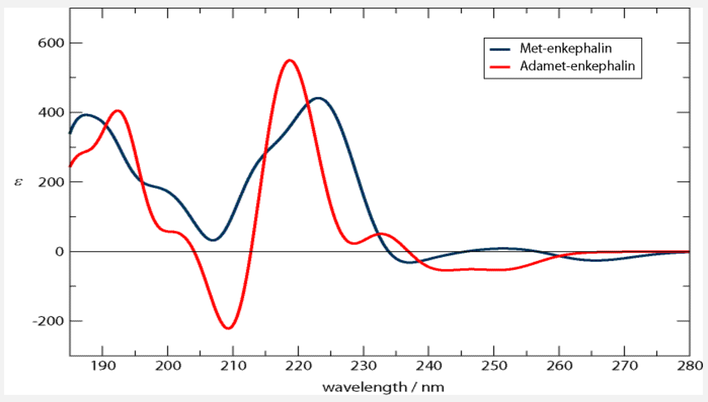
Methods

The conformational spaces of the peptides were generated by the replica exchange molecular dynamics (REMD) technique. 16 replicas were prepared and simulated for a total of 160 ns. The trifluoroethanol (TFE) and water solvents were included explicitly. The target temperatures of the replicas ranged from 275 K to 420 K. All simulations were performed using the AMBER 9 [2] .

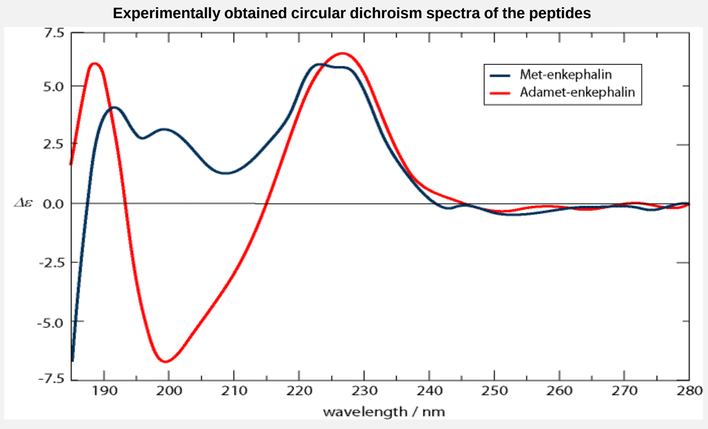
Circular dichroism

Circular dichroism spectra of the peptides simulated in TFE were calculated using time dependent density functional theory with the ONIOM (B3LYP/6-31G(d) : AMBER) method [4]. The peptides were treated quantum-mechanically whereas the solvents were treated classically.

Theoretically calculated circular dichroism spectra of the peptides



Experimentally obtained circular dichroism spectra of the peptides



The calculated spectra were obtained as a weighted average of the individual spectra of representative structures, which were themselves convoluted with Gaussian functions of width 0.2 eV. The initial agreement between experiment and theory appears promising.

References

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[2] D. A. Case et al., (2006), AMBER 9, UCSF, San Francisco
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[4] M. J. Frisch et al., (2009) Gaussian 09; Gaussian, Inc., Wallingford