Propensities of Asn-Gly heptapeptides to form β-turn structures: a Molecular Dynamics simulation approach

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Abstract

Both Molecular Mechanics (MM) and Quantum Mechanics (QM) calculations play an important role in describing the behaviour and structure of molecules. Each method individually is based on different physical theories and encompasses certain criteria. In this work, we focused on the accuracy of Molecular Dynamics simulations and their ability to approach systems from QM calculations. More specifically, three Molecular Dynamics (MD) simulations of 5 μs each in explicit water solvent were carried out for three Asn-Gly heptapeptides, in order to study their folding and dynamics. Previous data, based on QM calculations and the DFT methods from Kang & Yoo [1], have shown that these peptides adopt β-turn structures in aqueous solution, with type I' β-turn being the most preferred motif.

Methods

- The heptapeptides considered were Ac-Ala-Ala-**Asn-Gly**-Ala-Ala-NHMe (hp_{NG}-1), Ac-Leu-Val-**Asn-Gly**-Gln-Tyr-NHMe (hp_{NG}-2) and Ac-Phe-Val-**Asn-Gly**-Leu-Phe-NHMe (hp_{NG}-3).
- All simulations were performed with the NAMD software using the AMBER 99SB-STAR-ILDN force field and the TIP3P water model. The adaptive tempering method was also implemented. Each simulation resulted in ~5,000,000 frames.
- The trajectories were analysed using *Carma* [3] and the structural analyses were made with the *promotif* [4] program. All 3D models were created using *PyMOL* [5].
- We focused only on each peptide's four-residue central part, which presents a relatively more stable behaviour.

Introduction

β-Turns are structural motifs defined by four consecutive residues (*i* to *i*+3) and are classified into nine distinct types based on the backbone torsion angles φ,ψ of residues *i*+1 and *i*+2 [2]. ***Fig. 1*** illustrates the regions of Ramachandran plot occupied by residues *i*+1 and *i*+2 depending on their φ and ψ dihedral angle values.

Here, we studied the propensities of three Asn-Gly heptapeptides to form β-turn structures using MM calculations, and compared our results with the ones from QM calculations that performed with the same heptapeptides. Previous studies have shown that the Asn-Gly sequence is highly conserved and forms a type I' β-turn despite the absence of any strong side-chain to side-chain or side-chain to backbone interactions to stabilize it. However, hydration analysis of MD simulations has suggested that solvent-mediated interactions between the Asn side-chain and the peptide backbone play a role in the stabilization of type I' β-turns in water [1].

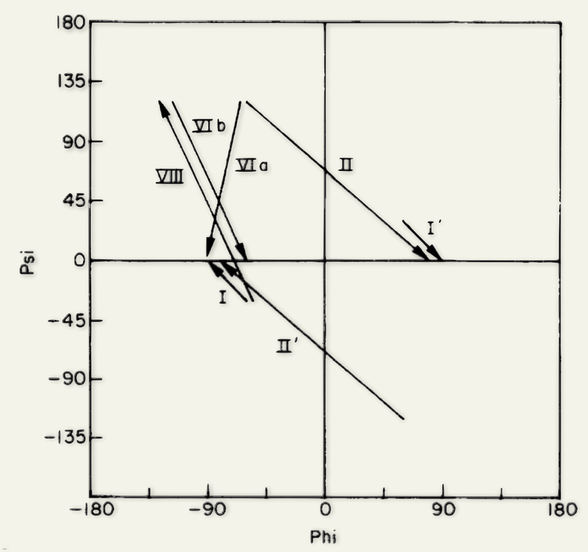

Fig. 1 *Schematic diagram showing a Ramachandran plot of classic β-turn types.*

Results

- The dPCA analysis produced approximately 15 clusters for each heptapeptide, indicating that there is no funnel-like gradient leading to a native state.
- For **hp_{NG}-1**, out of 1746788 frames allocated by *Carma* to clusters, 758688 frames (43.4%) were assigned by *promotif* to β-turn structures. Of these, the most highly populated was **type IV β-turn** with a total of 469604 frames (61.9%). For **hp_{NG}-2**, out of 1840843 frames allocated by *Carma* to clusters, 920820 frames (50.0%) were assigned by *promotif* to β-turn structures. **Type I β-turn** was the most populated with a total of 687809 frames (74.7%). Finally for **hp_{NG}-3**, out of 1596176 frames allocated by *Carma* to clusters, 1053088 frames (66.0%) were assigned by *promotif* to β-turn structures, with the most populated being **type I β-turn** with a total of 398377 frames (37.8%). The above analysis refers to the full-frame trajectories, with the temperature ranging between 280 K and 480 K.
- ***Figs. 2-4*** illustrate 500 superimposed structures from the most populated cluster of each heptapeptide, showing only the four-residue central part.
- Frames that were assigned by *promotif* to Asn-Gly β-turns correspond only to a minority of the trajectories. Only one cluster in each heptapeptide contains Asn-Gly β-turns, with their populations being less than 5% in each case.

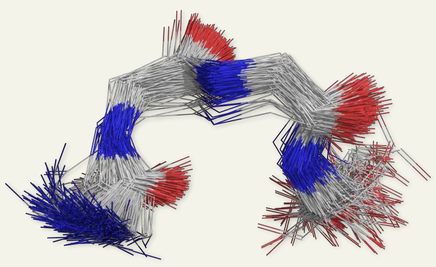

Fig. 2 *hp_{NG}-1 cluster No. 1 (11.80%) Ala-Asn βIV turn*

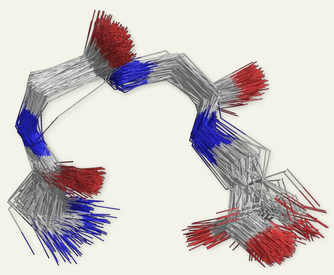

Fig. 3 *hp_{NG}-2 cluster No. 1 (20.10%) Gly-Gln βI turn*

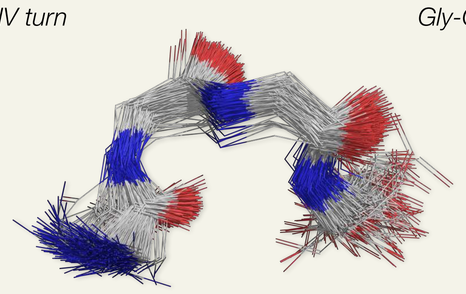

Fig. 4 *hp_{NG}-3 cluster No. 1 (20.66%) Val-Asn βI turn*

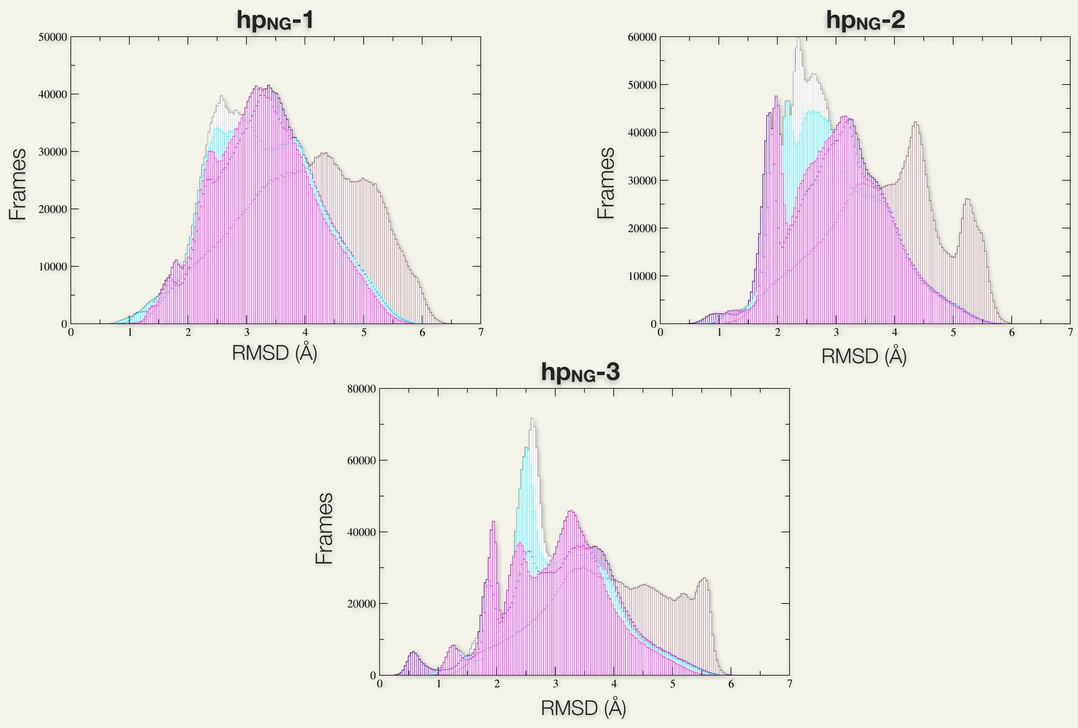

Fig. 5 *RMSD distribution in the trajectories using the ab initio models as reference structures. Different colours correspond to the different reference structures βI, βI', βII, βII' and extended conformation.*

- Frames corresponding to more stable conformations, in temperatures less than 360 K (about 1/3 of the trajectory in each case), were examined to find similarity with the *ab initio* models (***Fig. 5***). Selecting an overall cutoff of 2.2 Å for every case, the RMSD analysis indicated that βII turns have a higher probability distribution than other turn types for hp_{NG}-1. For hp_{NG}-2 and hp_{NG}-3, the probability distribution is higher for βI' and βII' turns, respectively.

Conclusions

- The results do not agree with the QM calculations.
- The heptapeptides suffer from severe kinetic frustration, however their four-residue central part appears to be more stable.
- There is a general tendency towards the formation of β-turn structures.
- For hp_{NG}-1 the most preferred structure is βIV turn motif, and hp_{NG}-2 and hp_{NG}-3 show a strong preference for βI motif. The preference in positions *i*+1 and *i*+2 in β-turns varies among the four central residues in each heptapeptide, with the Asn-Gly segment preferring these positions in negligible proportions in relation to the whole trajectories.
- The comparison with the *ab initio* models revealed similarity only for hp_{NG}-2, where type I' β turn has the highest probability.
- Such difference between our MD analyses and the *ab initio* models may attributed to simulations' parameters or to the differences of each method.

References

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