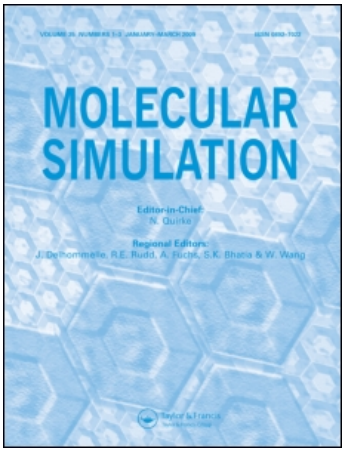

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A molecular dynamics study of the pentacyclo-undecane (PCU) cage polypeptides of the type Ac-3Ala-Cage-3Ala-NHMe

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A molecular dynamics study of the pentacyclo-undecane (PCU) cage polypeptides of the type Ac-3Ala-Cage-3Ala-NHMe

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An extensive exploration of the conformational space of the seven-residue peptide sequences, Ac-Ala-Ala-Ala-Cage-Ala-Ala-Ala-NHMe and the model peptide Ac-Ala-Ala-Ala-Ala-Ala-Ala-Ala-NHMe, was carried out using single trajectories of molecular dynamics (MD) in the solution phase using the periodic boundary conditions. Our MD studies revealed that the majority of the motifs of the PCU cage peptide exist as type I–III β-turns along with their mirror conformations, viz. type I′–III′ β-turns. This peptide sequence adopted a U-shaped backbone, with alpha-helical characteristics. The results reported here provide further evidence that the PCU cage amino acid exhibits C_{7eq}, C_{7aq}, α_R and α_L conformations in aqueous solution.

Keywords: Unnatural amino acids; Pentacyclo-undecane cage dipeptide; Conformational analysis; AMBER; Reverse-turn characteristics; β-Turns

1. Introduction

Polycyclic cage compounds are well studied [1–3] with the potential of inducing some interesting bioactivity to peptides. The cage amino compounds are known to exhibit a range of bioactive characteristics that could enhance the activity of the novel bioactive pentacyclo-undecane (PCU) cage amino compounds. In particular, the rigid cage structures in some PCU amino compounds are known to induce receptor site specificity in areas such as antibacterial activity, anabolic action and analgesic activity [4–10]. Previous theoretical studies [11–14] in our laboratory suggested that the PCU cage monopeptide (**1**) has a strong tendency to promote β-turn characteristics [15] (figure 1).

These studies also indicated that the PCU cage peptide sequences are effective at stabilizing the trans-conformer of the amide bonds between residues (i + 1) and (i + 2) which satisfy the criteria for reverse-turns. The inclusion of the intervening three-residues (-Ala-Cage-Ala-) would not only increase the peptide chain length, but also display distinct conformational preferences, and hence provide additional information about the conformational characteristics of PCU cage peptides in general.

The aim of the present study is to broaden our understanding of the general folding characteristics of the longer chain PCU cage polypeptides. Thus, the question posed in this study is not whether a β-turn will occur, but which type of β-turn will occur. The outcome of this study could significantly enhance our understanding of the concept of β-turn-mediated peptide folding of PCU cage polypeptides.

2. Computational methodology

The molecular dynamics (MD) trajectories were carried out within the framework of molecular mechanics, using the all-atom parm94 force field parameters from AMBER 5.0 [16,17]. The PCU cage residue was built using the PREP module of AMBER from the parm94 force field parameters described in an earlier study [11]. Extended conformations of the seven-residue peptide sequences were used in the initial conformation of the system. The system was minimized using 10,000 steps of steepest descent, followed by a subsequent energy minimization using the conjugate gradient algorithm until a convergence of the gradient norm was lower than 0.001 kcal mol^{-1} $Å^{-1}$.

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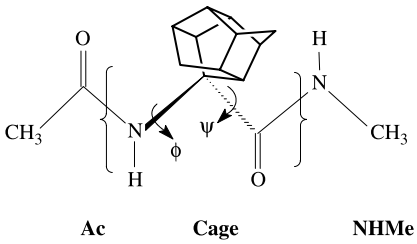

Figure 1. Pentacyclo-undecane cage monopeptide.

The molecule was placed into a rectangular box of $30 \times 25 \times 20\,\text{Å}^3$ within TIP3P water molecules [18]. The energy minimization of this new system was completed when a convergence criteria of $0.001\,\text{kcal mol}^{-1}\,\text{Å}^{-1}$ was fulfilled. Thereafter, periodic boundary conditions were introduced and the structure was allowed to equilibrate for 200 ps at a temperature of 300 K and at elevated temperatures up to 900 K, with pressure set to 1 bar. SHAKE was used on bonds involving hydrogen atoms with a time-step of 2 fs. After the first equilibration phase, the particle mesh Ewald (PME) [19] method was applied with a grid spacing of approximately 1 Å. The tolerance for evaluating the direct sum was set to 10^{-5} and a cutoff of 8 Å was used to evaluate non-bonded interactions. The equilibration phase involved a single dynamic trajectory run for 1600 ps under these conditions. The CARNAL module of AMBER 5.0 was used to calculate the backbone torsion angles. The procedure involved using CARNAL twice. In the first step, the average structure was calculated over the entire MD trajectory. In the second step, the root mean displacement (RMSD) between the average structure and the MD trajectory was calculated [16].

3. Results and discussion

For the initial equilibration period, the system temperature was gradually increased from 0 K to the working temperature of 300 K, which was subsequently maintained for the duration of the entire MD simulation. Analysis of the thermodynamic profiles revealed that the equilibration was stable. The RMSD of each atom for the starting as well as the average structures is depicted in figure 2. The starting structure varies between 0.5 and 2.5 Å, whereas the average structure RMSD values vary between 0 and 1.5 Å.

The conformational profile of Ala in figure 3 shows clustering around torsion angles of $\pm 180°$ associated with the C_5 extended structure or the β-sheet conformations, while the restricted conformational profile of the PCU cage residue is characterized by the C_{7ax} structures, consistent with our previous studies [11–14].

The plots presented in figure 4 suggest that major fluctuations in the backbone torsion angles along the MD trajectories are in accordance with the corresponding conformational profile displayed in the Ramachandran

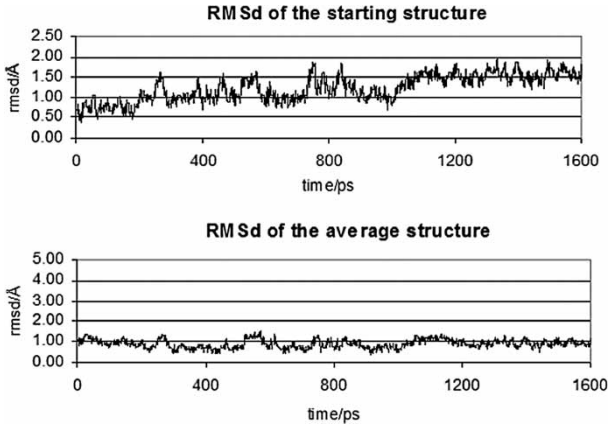

Figure 2. Observed trends in RMSD for the cage peptides obtained from MD.

plots in figure 3. The graphs indicate that the backbone torsion angles of the PCU cage in the (i + 3) position remain relatively fixed during the MD simulation, with ϕ_3 near $-60°$ and ψ_3 varying from 60 to 120°. However in the case of Ala, a differential feature of these plots is in the distribution of the (ϕ_3, ψ_3) torsion angles from about 400 to 450 ps was observed. Clustering around this region is clearly visible in the Ramachandran plots shown in the third panel of figure 3. This is a significant result since it reflects geometrical effects (fluctuations and movement) during the course of the MD trajectory. The significance of the negative ϕ value of $-60°$ for Ala3 shown in figure 4, reflects the intrinsic steric effects of the methyl side-chain, imposed by the C^α chiral centre on the carbonyl oxygen.

Figure 5 shows the low energy conformation obtained from a preliminary investigation of MD studies on Ac-Ala-Ala-Ala-Ala-Ala-Ala-Ala-Ala-NHMe and Ac-Ala-Ala-Ala-Cage-Ala-Ala-Ala-NHMe. The replacement of alanine by the PCU cage residue in the (i + 3) position has a marked influence on the overall pattern of the ψ backbone torsion angles. About 50% of the conformations have ψ backbone torsion angles ranging from $-20°$ to 20°. On the other hand, the two distinct regions for the ϕ backbone torsion angles ranging from -160 to $-120°$ and -80 to $-50°$ are observed. The stability of the PCU segment is the result of large steric hindrance and is in agreement with our previous results [11–14]. The predominance of two different types of β-turns [20,21], viz. type I and a 3_{10} α-helix conformation are observed in residues 2/3, 3/4, 4/5 and 5/6. Thus the inclusion of the PCU cage residue in the (i + 3) position has the tendency to cause the chain to fold into β-turns or α-helices in positions (i + 1)–(i + 6).

The graphical results in figure 6 clearly highlight the preference of the reverse-turn characteristics exhibited by the PCU cage residues over the Ala residues. A sharp increase in the percentage conformations adopting reverse-turn characteristics is observed in the case of seven-residue PCU cage peptides compared with the corresponding Ala residues. In addition, the plots also reveal that the PCU cage residues are much more effective at inducing reverse-turn characteristics.

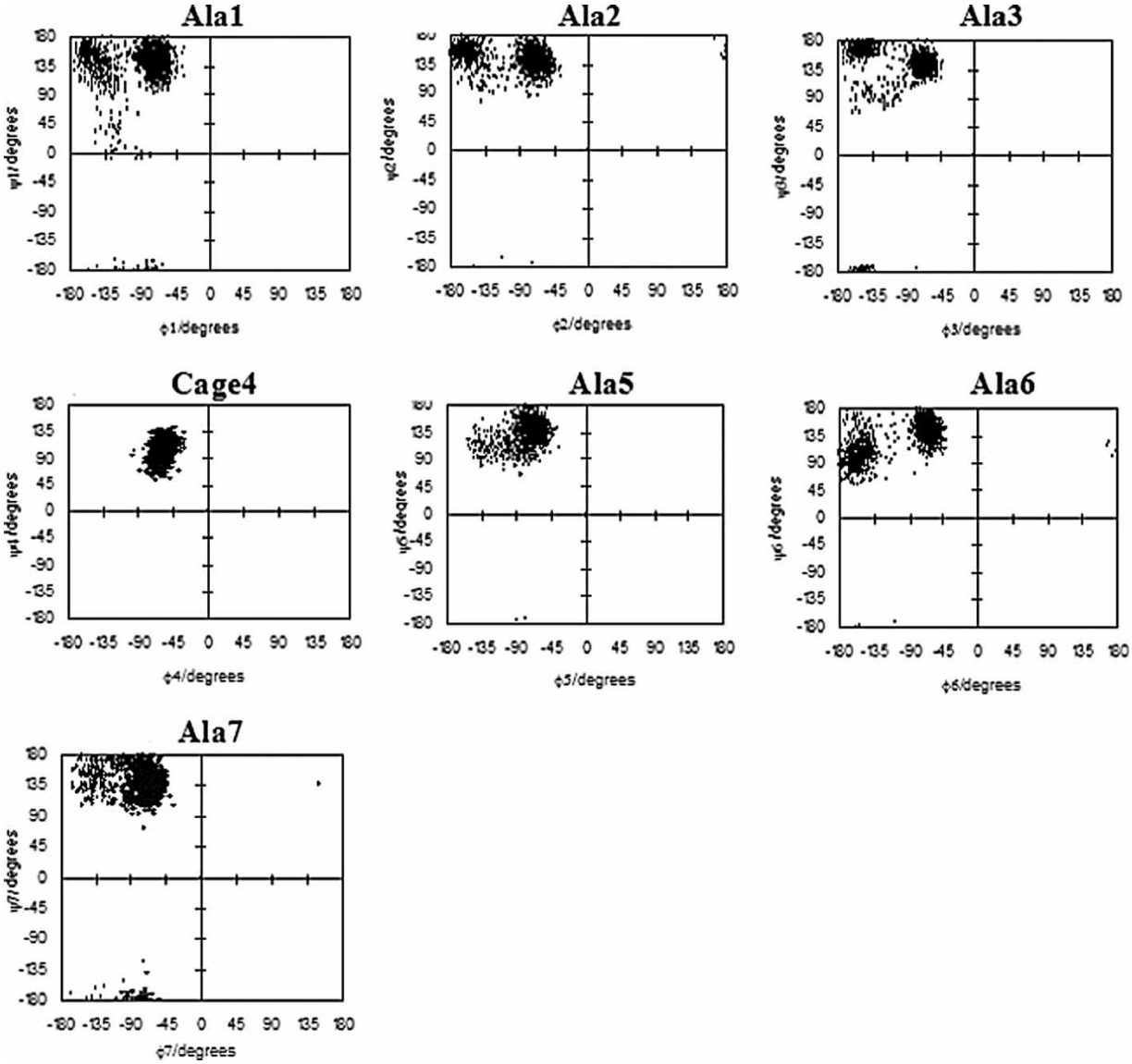

Figure 3. Ramachandran plots for MD trajectories at 300 K.

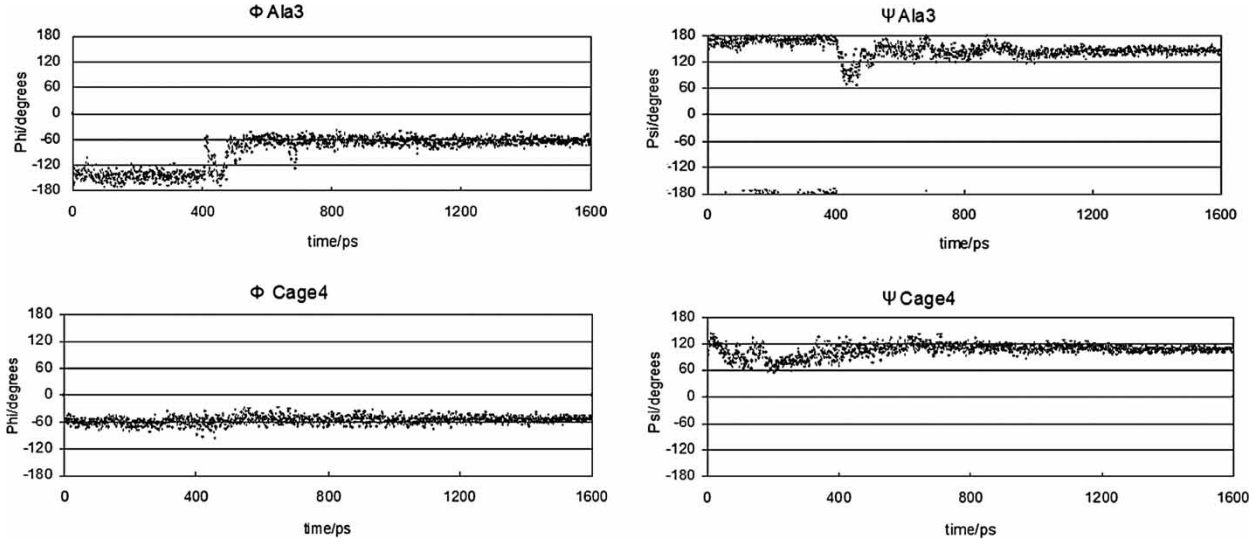

Figure 4. The backbone torsion angles for MD trajectories.

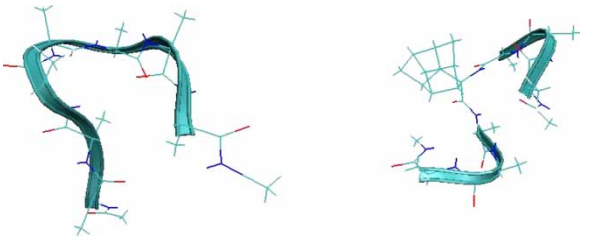

Figure 5. Low energy conformation for Ac-7Ala-NHMe and Ac-3Ala-Cage-3Ala-NHMe.

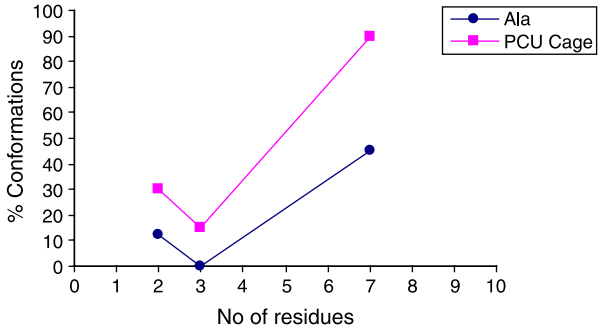

Figure 6. Comparison of the percentage conformations of Ala and PCU cage peptides satisfying all three criteria for reverse-turn (β-turn) characteristics.

4. Conclusions

The fundamental goal of this study was to examine the structural roles of β-turns in cage polypeptides of the type, Ac-Ala-Ala-Ala-Cage-Ala-Ala-Ala-Ala-NHMe. The replacement of the hydrogen atom as well as the methyl groups at the C^{α} position produces severe restrictions on the conformational freedom in contrast to Ala peptides. These results suggest that 300 K is not adequate for studying the conformational profile of the PCU cage residue as the conformations are trapped in a local minimum. On the other hand, the MD trajectories at 900 K revealed a complete exploration of the peptide landscape containing analogues of the PCU cage peptides. The results confirmed the preference for the PCU cage peptide to adopt bent structures, which further support the tendency of this peptide to form C_5 extended conformation, 3_{10}-helical and α-helix conformations. Specifically the PCU cage residue has a tendency to fold into β-turns or α-helices in positions $(i + 1), (i + 2), (i + 3), (i + 4)$ and $(i + 5)$. This means that in the case of the seven-residue peptide analogues, the system of three-residues (-Ala-Cage-Ala-) may be taken as a "block," and such blocks (of three-residues) may then serve as excellent places for folding back in a polypeptide chain, as predicted before [14].

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