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Side-Chain Ordering in PolyGlutamic Acid

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We report results from multicanonical simulations of Poly-Glutamic acid chains of length 10 residues. A decoupling of backbone and side chain ordering is observed in its folding process. While the details of the two transitions vary between the peptide in gas phase and in an implicit solvent, our results indicate that side chain ordering occurs only after the backbone topology is completely formed, independent of the particular environment.

1 Introduction

The folding of proteins involves several structural transitions, such as α-helix or β-sheet formation, and the ordering of side chains. The role of these transitions and their order are still only poorly understood. Computer experiments offer one way to study these questions but are often hampered by poor convergence of the simulations[1]. We used multicanonical sampling[2] to study the role of side chain ordering. A homopolymer, Poly-Glutamic acid, was used because its long side chains can interact through hydrogen bonds. In both gas phase and solvent we observed a two-step process starting with a coordinated helix-formation and collapse of the molecule. At much lower temperatures side chain ordering takes place. The two-step process itself is independent on the specific environment, indicating the de-coupling of backbone and side-chain ordering could be a common characteristic of protein folding. A more thorough discussion of the results presented here can be found in Ref.[3]

2 Methods

Our investigations rely on simulations of Glu_{10} with the ECEPP/3 force field[5] as implemented in the 2005 version of the program package SMMP[4,7]. The interactions between the atoms within the homopolymer chain are approximated by a sum consisting of electrostatic energy, Lennard-Jones, hydrogen-bonding, and torsion energy terms.

In order to enhance sampling we rely on the multicanonical approach[2] as described in Ref[4]. Configurations are weighted with an iteratively determined term $w_{MU}(E)$ such that the probability distribution is approximately constant. Multicanonical simulations of 5×10^6 sweeps were performed both in vacuum and in an implicit solvent[8]. The thermodynamic averages of any quantity $< O >$ are obtained by re-weighting[9]:

$$< O > (T) = \frac{\int dx\ O(x) e^{-E(x)/k_B T} / w_{MU}[E(x)]}{\int dx\ e^{-E(x)/k_B T} / w_{MU}[E(x)]} \tag{1}$$

where x counts the configurations of the system.

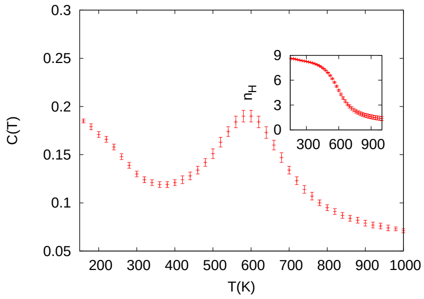

Figure 1. Specific heat $C(T)$ as a function of temperature T for Glu$_{10}$ in gas phase as obtained from a multicanonical simulation with 5×10^6 sweeps. The inlay shows the average number of helical residues $< n_H > (T)$.

3 Results and Discussions

In the vacuum simulation, two peaks are observed in the specific heat plot (Fig. 1) indicating two transitions. The first peak at $T_1 = 590$ K corresponds to a helicity change (see the inlay to Fig. 1) that separates a high temperature region where the backbone has no ordering from a region where temperatures are low enough to allow the formation of backbone hydrogen bonds and subsequent growth of an α-helix.

In Fig. 2 we display the average number n^S_{hb} of side-chain and n^B_{hb} of backbone hydrogen bonds as function of temperature. The change in the number of side-chain hydrogen bonds and the fluctuations in this figure at $T_2 = 164$ clearly show that the corresponding peak in the specific heat indicates indeed a second transition. In the low temperature phase the side chains nestle along the cylinder formed by the helix and are stabilized by the side chain hydrogen bonds (not shown here). Such a structure was already described in Ref.[10].

We have also extended our investigation to that of solvated Glu$_{10}$. Again, we observe two peaks in the specific heat (see Fig. 3). The peak at the higher temperature, $T_1 = 477$ K, marks again the collapse and subsequent formation of an α-helix (see the inlay of Fig. 3). But the transition temperature is 113 K lower than in the gas phase. Also, the peak in the

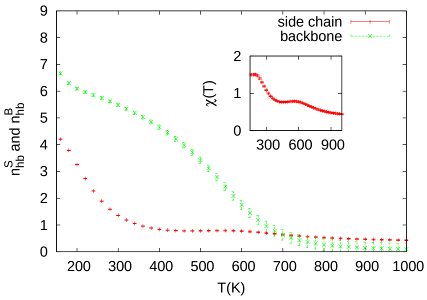

Figure 2. Average number of side chain hydrogen bonds $< n^S_{hb} > (T)$ and backbone hydrogen bonds $< n^B_{hb} > (T)$ as functions of temperature T for Glu$_{10}$ in gas phase as obtained from a multicanonical simulation with 5×10^6 sweeps. The inlay shows the fluctuation $\chi(T)$ in the number of side chain hydrogen bonds.

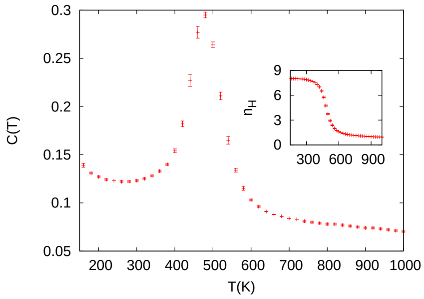

Figure 3. Specific heat $C(T)$ as function of temperature T for solvated Glu$_{10}$ as obtained from a multicanonical simulation with 5×10^6 sweeps. The inlay shows the average number of helical residues $< n_H > (T)$

specific heat is higher and narrower, indicating a sharper, more well-defined transition.

The second peak in the specific heat that is observed in Fig. 3 at the lower temperature $T_2 = 111$ K is more narrow and smaller than the corresponding one for the molecule in gas phase. As with the coil-helix transition temperature T_1, this transition is also shifted to lower temperatures in the solvent, albeit by the smaller amount of 53 K.

As in the case of of Glu$_{10}$ in gas phase, the side chains are ordered at temperatures below T_2. However, in contrast to the gas phase, the mechanism of side chain ordering is different in water. In Fig. 4, although no pronounced decrease in the solvation energy can be seen around T_2, the $fluctuations$ of the solvation energy show a pronounced increase. The increase of the solvent energy fluctuations continues to lower temperatures, while the fluctuations of the internal energy show a plateau and decrease below T_2. The peak in the specific heat around T_2 is due to increasing anti-correlations below T_2. In the low temperature phase the side chains order themselves by extending into the solvent (not shown here), in contrast to the gas phase behavior.

Hence, while the structure of the solvated molecule also evolves in a two-step process, the mechanism that leads to the side chain ordering is different from the gas phase. There

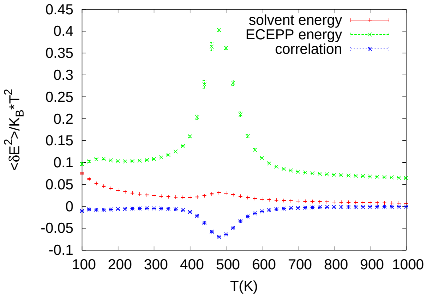

Figure 4. Fluctuations of the solvation energy $< \delta E^2_{solv} > (T)$ and intra-molecular energy $< \delta E^2_{ECEPP/3} > (T)$ for solvated Glu$_{10}$ as obtained from a multicanonical simulation with 5×10^6 sweeps. In addition, the cross-correlation $< \delta E_{solv} \delta E_{ECEPP/3} > (T)$ is shown. Note that $\delta E = E- < E >$.

the ordering of side chains was due to formation of hydrogen bonds between the side chain. In solvent, however, the polar side chains interact directly with the surrounding water that screens them from forming hydrogen bonds among each other. Our results indicate that the de-coupling of backbone and side-chain ordering does not depend on the details of the environment. Hence, it is reasonable to assume that this could be a common characteristic in protein folding.

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