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Side-Chain Ordering in Homopolymers

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In order to study the relation between backbone and side-chain ordering in proteins, we have performed multicanonical simulations of five amino acid homopolymers. Glu10, Gln10, Asp10, Asn10, and Lys10 were selected to cover a wide variety of possible interactions between the side chains. All polymers undergo helix-coil transitions. We found that peptides with long side chains that are capable of hydrogen bonding, i.e. Glu10 and Gln10, exhibit a second transition at lower temperatures connected with side-chain ordering. This occurs in gas phase as well as in solvent. However, in polymers with short side chains capable of hydrogen bonding, i.e. Asp10 and Asn10, side-chain ordering takes place over a wide temperature range and exhibits no phase transition-like character. Again, these results are qualitatively independent of the environment. Side chain ordering in Lys10, whose side groups are long and polar, also takes place over a wide temperature range and exhibits no phase transition-like character in both environments.

1 Introduction

In the last two decades, energy landscape and folding funnel paradigms[1] have led to an emerging understanding of the protein folding process. However, these concepts describe only the general characteristics of folding. Many details still remain poorly understood. One aspect is the role of side-chain ordering in the folding process. Since amino acids are distinguished by the side chains, the study of side-chain ordering can help us understand the protein folding problem. Using the multicanonical Monte Carlo method[2,3], we have studied the side-chain ordering of five homopolymers Glu_{10}, Gln_{10}, Asp_{10}, Asn_{10}, and Lys_{10}[4,5]. It is found that, besides the helix-coil transition, a side-chain ordering transition is taking place for particular polypeptides only. The de-coupling of side-chain and backbone ordering transitions is independent of the environment.

2 Methods

We used the ECEPP/3 force field[6] as implemented in the program package SMMP[7]. Here the intramolecular interactions are approximated by a sum consisting of electrostatic energy, a Lennard-Jones term, a hydrogen-bonding term and a torsional energy term. The protein-solvent interactions are approximated by a solvent accessible surface term[8].

The above defined energy function leads to a landscape that is characterized by a multitude of minima separated by high barriers. In order to enhance sampling we rely on the multicanonical approach[2,3]. Here, configurations are weighted with a term $w_{MU}(E)$ determined iteratively such that the resulting histogram obeys

$$P_{MU}(E) \propto n(E) w_{MU}(E) \approx const\ , \tag{1}$$

where $n(E)$ is the spectral density of the system.

3 Results and Discussions

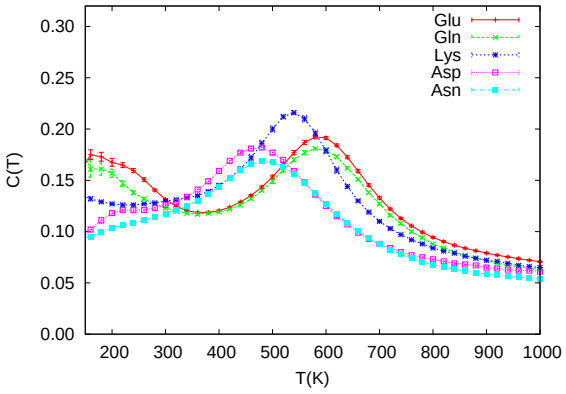

Figure 1. Specific heat $C(T)$ as function of temperature T for the five homopolymers in gas phase. This figure is taken from Ref. 5.

We first studied the molecules in gas phase. Fig. 1 displays the specific heat per molecule for the five polymers as a function of temperature. In each case one observes a peak at a temperature T_1 in the range $450\ K$ to $600\ K$. The individual peak temperatures T_1 and other properties are listed in Table 1. These peaks correspond to the helix-coil phase transitions which separate a high temperature region where the backbone has no ordering from a region where temperatures are low enough to allow the formation of an α-helix[4,5].

The transition temperatures are largest for Glu_{10} and Gln_{10}, and lowest for Asn_{10} and Asp_{10}, with the individual values being very close to each other in each block. The ordering of the transition temperature can be understood from the particular energetic and entropic contributions of the various side chains[5].

Interestingly, a second peak in the specific heat is observed for Glu_{10} and Gln_{10}. The peak temperatures T_2 are around $170\ K$ (see table 1). This second peak is related to the side-chain ordering in the form of hydrogen bonding between side groups[4,5].

Asn_{10} and Asp_{10}, whose side chains are only one CH_2-group shorter than those of Glu_{10} and Gln_{10}, show no second peak in the specific heat. The reason for this remarkably different behavior is the apparent existence of a threshold length for the side chains. If these chains are not long enough, the number of degrees of freedom is simply too small to allow for the fluctuations observed for Glu_{10} and Gln_{10}. Consequently, the ordering of the side chains in Asn_{10} and Asp_{10} does not have a transition-like character but is spread out over a wide range of temperatures. Side-chain ordering behavior for Lys_{10} is similar to Asn_{10} and Asp_{10}. Since its side groups can participate only in weak hydrogen bonds, they act neutrally at the helix-coil transition and finally order themselves by wrapping around the helical cylinder[5].

The structural features in the low-temperature phase found here correspond to early results from theoretical investigations on the ground state structure of such homopolymers in vacuum, performed by H. Scheraga's group, see e.g. Ref. 9.

Table 1. Properties of the helix-coil transitions observed for the five homopolymers: Transition temperatures T_1 and T_2, half width ΔT, and the specific heat per molecule at the transition temperatures, $C(T_1)$ and $C(T_2)$. The number in parenthesis is the uncertainty in the last digit. The data are taken from Ref. 5.

	vacuum			solvent		
	T_1[K]	ΔT[a]K]	$C(T_1)$ [b]	T_1[K]	ΔT[a]K]	$C(T_1)$ [b]
Glu_{10}	587(14)	161	0.193(2)	477(7)	88	0.296(3)
Gln_{10}	584(14)	163	0.181(1)	484(8)	97	0.268(3)
Lys_{10}	538(8)	151	0.216(2)	447(10)	98	0.266(3)
Asn_{10}	485(19)	193	0.169(2)	424(9)	105	0.249(4)
Asp_{10}	471(19)	170	0.182(2)	415(6)	82	0.300(3)
	T_2[K]	ΔT[c]K]	$C(T_2)$ [b]	T_2[K]	ΔT[c]K]	$C(T_2)$ [b]
Glu_{10}	166(16)	203	0.176(4)	111(10)	166	0.152(2)
Gln_{10}	181(23)	187	0.161(6)	120(17)	146	0.133(3)

[a]Determined at $C = [C(T_1) + C(T_{min})]/2$, with T_{min} from either $C'(T_{min}) = 0$ or $C''(T_{min}) = 0$.
[b]Unit is Kcal/mol.
[c]Determined at $C = [C(T_2) + C(T_{min})]/2$, with T_{min} from $C'(T_{min}) = 0$.

So far, we have focused on the molecules in gas phase. However, in nature proteins are usually solvated, and their function often depends on the solvent environment. For this reason we have extended our investigation to that of solvated homopolymers.

As in the case of gas phase simulations we observed for all five molecules a helix-coil transition indicated by peaks in the specific heat, see Fig. 2, their properties also being listed in Table 1. As can be seen clearly, the width of these peaks is much narrower, and their height is larger than in gas phase, indicating a sharper transition.

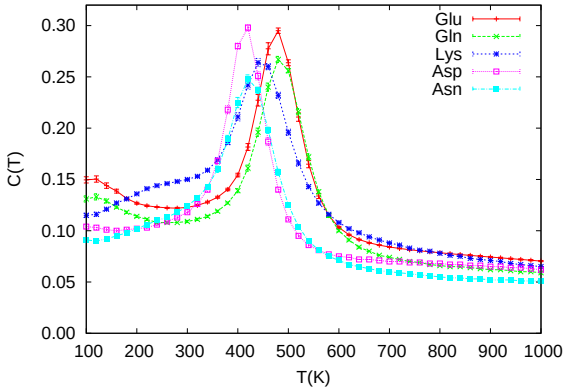

Figure 2. Specific heat $C(T)$ as function of temperature T for the five solvated homopolymers. The figure is taken from Ref. 5.

All transition temperatures are shifted to lower values. The reason is the competition between the formation of backbone hydrogen bonds that stabilize the α-helix, and interac-

tion between the peptide and the solvent in the coil phase. While in vacuum the transition to the coil phase is driven solely by entropy, here also the peptide-solvent interaction favors the coil phase. These effects collaborate so that the transition takes place at a lower temperature and becomes sharper. However, the relative ordering of the transition temperatures among the polymers remains practically the same as in the gas phase.

Interestingly, again a second peak in the specific heat is observed for Glu_{10} and Gln_{10}, the exact properties also being listed in Table 1. However, here the reason for such a behavior is not the formation of hydrogen bonds among the side chains, because the total number of hydrogen bonds is limited to those that stabilize the helix backbone. A closer inspection shows that this second peak in the specific heat of Glu_{10} is mainly due to fluctuations in the solvent energy[4]. For Gln_{10}, it is the interplay of fluctuations in solvent energy with the fluctuations in ECEPP/3 energy that causes the second peak[5].

No such second peaks in the specific heat can be observed for Asn_{10} and Asp_{10}. Their fluctuations in solvent energy are cancelled by the strong anti-correlations between solvent energy fluctuations and ECEPP/3 energy fluctuations for these two peptides. For similar reasons Lys_{10} also does not exhibit particular features with respect to side-chain ordering. As before in gas phase, its side-chain ordering does not have a transition-like character but is spread out over a wide range of temperatures.

Detailed reports of this work are available in Refs. 4 and 5.

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