Assisted Peptide Folding by Surface Pattern Recognition

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Supplement

Definition of percent of helical dihedral angle $X_\alpha$

For a peptide consisting of 35 residues, the total number of dihedral angles is 32. However, the maximal number of helical torsion angles that could be present in the perfect helix-coil-helix is only 26 because torsion angles in the turn regions (3 residues long) were excluded. Therefore, in our analysis, 26 helical torsion angles correspond to $X_\alpha = 26/26 = 100\%$ (i.e. not $26/32 = 81.25\%$). In other words, $X_\alpha$ does not reflect the absolute value of the helical content. Instead, it is a measure of the relative helix content present for a given state with respect to a perfect helix-coil-helix. It is also important to point out that $X_\alpha$ (the percent of helical dihedral angles) calculated here does not directly translate into the standard definition of helical content.

Surface induced stabilization of an intrinsically stable $\beta$-hairpin

For comparison, we also explored the behavior of a stable peptide (with $\beta$-sheet secondary structure) in the vicinity of patterned and uniform surfaces. Like the helix-coil-helix, the $\beta$-hairpin peptide model in our study is half of a larger 4-stranded $\beta$-barrel. However, unlike the helix-coil-helix, the $\beta$-hairpin folds spontaneously in the bulk. The folding temperature of the 2-stranded $\beta$-hairpin near a surface is indicated by the position of the peak in the heat-capacity curves shown in (Supplement material Figure S6). When two peaks are present, the left-most peak corresponds to the folding temperature and the peak to the right corresponds to the release of the peptide from the surface. For this peptide to fold, attraction between the two $\beta$-strands must overcome the loss of conformational entropy of the unfolded state. This unfolded entropy is considerably reduced when the two strands are confined to a 2-dimensional surface. Thus, in agreement with theory (53), we observed that the stability of the $\beta$-hairpin is increased in the presence of a uniformly attractive, smooth surface (Supplement material Figure S6, $h=0.2\ldots h=1.0$).

However, we found that the stability of our $\beta$-hairpin model can be further enhanced by a patterned surface (Supplement material Figure S6, dashed line, left peak). The patterned surface used here is a 2x12 rectangle of hydrophobic beads (similar to the 2x9 pattern used to stabilize the helix-coil-helix), and it resembles the pattern of hydrophobic beads from the other half of the original 4-strand $\beta$-barrel molecule before it was truncated. Unlike the uniformly attractive smooth surface, which rewards the two strands for lying anywhere in the surface plane, the patterned surface only rewards the two strands when they are in contact with each other, as they would be in the 4-stranded barrel.
Fig. S1 Four-body torsion angle forces between 4 successive beads in the chain ($\phi$) of type B or L. Two deep minima are located at 60° and 180°, corresponding to $\alpha$-helix and $\beta$-strand conformations. A parameter ($\delta$) controls the depth of each minima, which can be used to bias the relative stability of $\alpha$-helical or $\beta$-strand conformations. A value of $\delta=65^o$ weakly favors $\alpha$-helices, and a value of $\delta=55^o$ weakly favors $\beta$-strands. (This bias is roughly similar in magnitude to the bias that would result from a peptide containing amino acids with high or low $\alpha$-helix propensity, respectively.) When $\delta=60^o$, both $\alpha$ and $\beta$ conformations are equally favored. Dihedral angles involving one or more beads of type N are nearly unconstrained, allowing the chain to be very flexible in the turn regions.
**Fig. S2**

Kinetics for the helix-coil-helix construct in the bulk: This plot shows the conformations visited by the helix-coil-helix monomer in the bulk during a short constant-temperature simulation. Structures from this simulation were divided into clusters (see below). The vertical axis corresponds to the RMSD between the structure of the molecule at a particular time, and the representative structure for the cluster to which it belongs (shown above using “N” and “C” to distinguish the two termini). Time is expressed on the horizontal axis in units of $\tau_D = \sigma^2/6D$. ($\tau_D$ is the time necessary for an amino acid to travel a distance of $\sigma$ by diffusion, which is on the order of $10^2$ ps. $\sigma$ is the distance between consecutive amino acids, and lies in the range 3.8-5.5 Angstroms. $D$ is the diffusion constant, $k_BT/\zeta m$.) This simulation was carried out using Langevin dynamics at temperature $T=0.3\epsilon/k_B$, using a velocity damping rate $\zeta = 1.0 \tau^{-1}$ (where $\tau$ is the square root of ($m\sigma^2/\epsilon$), $m$ is the mass of a typical amino acid, approximately 110 Da and $\epsilon$, the hydrophobic bonding energy, is explained in the methods section of the main text). Clustering was performed using the “kclust” algorithm from the MMTSB toolset (67), using a RMSD radius of $1.8\sigma$. (Clusters returned by the program whose centroids differed by less than $1.8\sigma$ were merged. Data from the first 10000 $\tau_D$ of the simulation was discarded.)

For comparison, here we show the kinetic behavior of the helix-coil-helix construct in contact with the patterned surface consisting of two 1x9 stripes (shown in figure 4, main text, top right-hand corner). The horizontal and vertical axes are explained in detail in the caption for figure S2. This figure demonstrates that the peptide has minimal ability to move on this surface, when compared to the bulk. All of the conformations sampled during this simulation were classified as equivalent, when clustered according to the same method used in figure S3. However, we were able to detect more subtle conformational changes using more sensitive clustering criteria (radius $0.9\sigma$). Even then, the two alternate clusters (blue and green) are sparsely populated. Simulation conditions were identical to those described in the caption for Figure S2.
Fig. S4 To illustrate if a continuous surface behave like a surface made from explicit beads, we show free energy maps for the helical peptide on explicit homogeneous surfaces made from identical beads. These beads have \(1/r^6\) attractive interactions with the hydrophobic (B) beads in the protein which are 40% (top) and 50% (bottom) as strong as the intra-molecular attraction between “B” beads within the protein, respectively. The X-axis is the radius of gyration (in units of \(\sigma\)), and the Y-axis represents the percent of helical dihedral angles, \(X_\alpha\). At 40% attraction, the surface does not stabilize the 2-helix conformation of the helical peptide. (This free energy basin corresponds to unfolded molten globule states. See main text.) The two-helix conformation is not stabilized until the surface attraction is 50% as strong (as the attraction between type B beads). This behavior is similar to the behavior of the peptide in the vicinity of a continuous surface with hydrophobic fractions \(h=40\%\) and 50\%, respectively. (See figure 3, main text.)
Fig. S5 The helix-coil-helix structures observed on the explicit surfaces are different from the ones obtained on the continuous surface. The differences in the packing of their hydrophobic beads (yellow color) are illustrated in the side view snapshots. On some explicit surfaces (including the alternating stripes, 1 x 9 & 1 x 9, and 2 x 9), the packing between the two helices resembles that found in the larger 4-helix bundle, where the yellow beads are facing each other, in addition to facing the hydrophobic beads on the surface (Left). On the continuous surface, the packing is more relaxed and the hydrophobic beads in the model exclusively face the surface instead of facing each other (Right).
Fig. S6 Heat-capacity, as a function of temperature, for the β-hairpin in the bulk, and in the presence of various attractive continuous surfaces, as well as a patterned surface consisting of a 2 x 12 rectangle of hydrophobic (B) beads (see results section). The folding temperature of the β-hairpin is indicated by the location of the peaks. When two peaks are present, the lower temperature peak (left peak) corresponds to the folding temperature. The higher temperature corresponds to adsorption/desorption from the surface.