# Supplementary Text S1 for the article:
# The Dominant Folding Route Minimizes Backbone Distortion in SH3

by H. Lammert, J. K. Noel and J. N. Onuchic

We study the free energy landscape $\Delta F(Q, Q_{\text{path}})$ determined from our simulations and the underlying energy and entropy contributions $\Delta U(Q, Q_{\text{path}})$ and $T\Delta S(Q, Q_{\text{path}})$. The full contributions $\Delta U(Q, Q_{\text{path}})$ and $+T\Delta S(Q, Q_{\text{path}})$ are plotted in Fig. S1. Both plots are dominated by the gradient along the reaction coordinate $Q$, which describes the overall progress of the folding reaction. Any structure in the direction of $Q_{\text{path}}$, which describes the folding mechanism, is obscured. In order to reveal the superimposed structure that is shaping the folding mechanism we remove the global gradients along $Q$. In Eqn. 6 we define a function $f(Q)$ that contains the common portion of $\Delta U$ and $T\Delta S$ that is canceled in their subtraction to form $\Delta F$. The complete information about the mechanism is contained in the residuals $\delta U(Q, Q_{\text{path}}) = \Delta U(Q, Q_{\text{path}}) - f(Q)$ and $T\delta S(Q, Q_{\text{path}}) = T\Delta S(Q, Q_{\text{path}}) - f(Q)$. $f(Q)$ is obtained from a fit to $\Delta U$ and $T\Delta S$.

Although the dominant contribution to the potential is contact energy, and $Q$ is simply the number of formed contacts, the observed $Q$-dependence of the energy is not linear. The energy and entropy terms possess enough curvature to necessitate the use of a quadratic function $f(Q) = a_2Q^2 + a_1Q + a_0$.

In order to obtain a fair estimate of the common component of energy and entropy we fit $f(Q)$ to both $\Delta U$ and $T\Delta S$ together. For a least-squares fit this is equivalent to fitting to the average of both terms, $(1/2)[\Delta U + T\Delta S]$.

All points on both the surfaces $\Delta U(Q, Q_{\text{path}})$ and $T\Delta S(Q, Q_{\text{path}})$ enter equally into the fit. This is different from a fit to the one-dimensional functions $\Delta U_{1\text{D}}(Q)$ and $T\Delta S_{1\text{D}}(Q)$ that could be obtained as components of the one-dimensional free energy profile $\Delta F_{1\text{D}}(Q)$, where points at different $Q_{\text{path}}$ enter with different thermodynamic weights. Instead it corresponds to a fit to the direct averages along $Q_{\text{path}}$, which give a beter description of the overal shape of the two-dimensional surfaces, i.e. $\overline{\Delta U(Q)} = (1/N)\sum_{i=1}^{N} \Delta U(Q, Q_{\text{path},i})$ for the energy.

The one-dimensional functions $\overline{\Delta U(Q)}$ and $\overline{T\Delta S(Q)}$ for the original, unperturbed model are shown in Fig. S2 together with their average and with the fitted quadratic function $f(Q)$.