Supporting material

The native contact energy function $U(r_{ij}, r_{ij}^0, \varepsilon, \varepsilon_{db}, \varepsilon_{ssm})$

As in references\textsuperscript{1,2}, the form of the native contact energy function, $U(r_{ij}, r_{ij}^0, \varepsilon, \varepsilon_{db}, \varepsilon_{ssm})$, is given by

\[
U(r_{ij}, r_{ij}^0, \varepsilon, \varepsilon_{db}, \varepsilon_{ssm}) = \begin{cases} \\
\varepsilon Z(r_{ij})[Z(r_{ij}) - 2] & \text{for } r_{ij} < r_{ij}^0 \\
CY(r_{ij})^2[Y(r_{ij})^2/2 - (r_{db} - r_{ij}^0)^2s]/2s + \varepsilon_{db} & \text{for } r_{ij}^0 \leq r < r_{db} \\
-BY(r_{ij}) - h_1/[Y(r_{ij})^m + h_2] & \text{for } r_{ij} \geq r_{db}
\end{cases}
\]

where

\[
Z(r_{ij}) = (r_{ij}^0/r_{ij})^k,
\]
\[
Y(r_{ij}) = (r_{ij} - r_{db})^2,
\]
\[
C = 4s(\varepsilon + \varepsilon_{db})/(r_{db} - r_{ij}^0)^4s,
\]
\[
B = m\varepsilon_{ssm}(r_{ssm} - r_{db})^2(m-1),
\]
\[
h_1 = (1 - 1/m)(r_{ssm} - r_{db})^2/(\varepsilon_{ssm}/\varepsilon_{db} + 1),
\]
\[
h_2 = (m - 1)(r_{ssm} - r_{db})^{2m}/(\varepsilon_{db}/\varepsilon_{ssm} + 1).
\]

Here, $r_{ssm} = r_{ij}^0 + 3\text{Å}$, which followed from the consideration that 3Å is approximately equal to the diameter of a water molecule, and $r_{db} = (r_{ssm} + r_{ij}^0)/2$. The parameters $k$, $m$, and $s$ are taken to be $k = 6$, $m = 3$, and $s = 2$.

The method for introducing the experimental zero-denaturant condition

As in previous studies\textsuperscript{3,4}, the zero-denaturant condition is introduced by matching the simulation folding stability with the experimental folding stability under zero-denaturant condition. At any $\varepsilon/k_BT$, the simulation folding stability $\Delta G/k_BT$ is given by

\[
\Delta G/k_BT = -\ln[P(Q > Q_F)/P(Q < Q_U)]
\]

where the threshold $Q$ values $Q_F$ and $Q_U$ are chosen to provide physically reasonable demarcations for the folded and unfolded states; $P(Q > Q_F)$ and $P(Q < Q_U)$ are, respectively, normalized conformation population for $Q > Q_F$ and $Q < Q_U$. The experimental folding stability under zero-denaturant condition can also be transformed into $\Delta G/k_BT$ (dimensionless). In the calculation of experimental folding stability $\Delta G/k_BT$, it should be noted that the $\Delta G$ is measured by experiment and the temperature $T$ is the experimental absolute temperature. When the simulation folding stability $\Delta G/k_BT$ at certain $\varepsilon/k_BT$ is comparable to the experimental folding stability under zero-denaturant condition, it is considered as zero-denaturant condition.

Supporting Figures
Fig. S1. Nonnative contact numbers (black lines, left scale) and nonnative interactions (red lines, right scale) as functions of fraction number of native contact $Q$ by the $db + MJh\theta$ model under zero-denaturant conditions for the wildtype (a) and the mutant (b). The approximate range of $Q$ values for the conformations constituting the transiently trapped intermediate in $db + MJh\theta$ model is highlighted by vertical gray shaded band.

Fig. S2. Contact probability maps near transition state $0.58 < Q < 0.68$ under zero-denaturant conditions for Fyn SH3 domain (a) and A39V/N53P/V55L Fyn SH3 domain (b). In (a) and in (b), (upper left) nonnative contact probability map, (lower right) native contact probability map.

Fig. S3. Model chevron plots by the $db$ model and the $db + MJh\theta$ model for the wildtype (a) and the mutant (b). The $\Delta G/k_BT$ values corresponding to the experimental stability under zero-denaturant conditions are marked by vertical dashed lines. Fitted curves are merely guides for eye.

References