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Mis-folding and self-association: opportunities for alternative modes of self-recognition during the folding of TIM barrel proteins[1]

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The $(\beta\alpha)8$ or TIM barrel motif is one of the most common in biology, represented in all three super-kingdoms of life. Detailed thermodynamic and kinetic analysis of the folding reactions of three members of the TIM barrel family of proteins reveal a common propensity to mis-fold to an off-pathway intermediate in less than a few milliseconds. The unfolding of this stopped-flow burst-phase intermediate controls access to an on-pathway intermediate that is highly-populated at moderate denaturant concentrations. Curiously, the equilibrium intermediate for two of the three nominally monomeric proteins spontaneously adopts a dimeric form; the native state of the third also dimerizes at micromolar concentrations. The early mis-folding reactions may reflect the rapid access to non-native folds enabled by the simple, repetitive $\beta\alpha$ topology of this motif. The propensity of stable forms, either intermediate or native, to form dimers may reflect a segment-swapping mechanism enabled by the modular folding of these single structural domain proteins. Off-pathway intermediates and non-native dimers serve as examples of important, alternative intra- or inter-molecular self-recognition events.

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