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Title:	Stepwise unfolding of human β2-microglobulin into a disordered amyloidogenic precursor at low pH
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Abstract:	Amyloid fibril formation by human β2-microglobulin (β2m) is associated with dialysis-related amyloidosis. In order to understand the mechanism of protein misfolding, it is important to characterize the nature and properties of various intermediates formed during protein unfolding. In this work, we studied the effect of pH change on the unfolding of β2m using a range of spectroscopic readouts. In order to investigate the local structural changes, we created single tryptophan (W60 and W95) mutants of β2m. The equilibrium results suggested that in the acid-unfolded state of β2m at pH 2.5, the W60 residue attains non-native local structure whereas the W95 residue becomes more exposed. Our stopped-flow kinetic data revealed that β2m undergoes unfolding in a stepwise manner. Initial unfolding of β2m involves non-uniform protein expansion with the unpacking of tertiary structure and significant core solvation while maintaining a native-like structure around residue W95. The resolved-phase of unfolding exhibits a timescale of ~500 ms that describes the transition from the native-like swollen intermediate to an acid-induced disordered state. Taken together, our results demonstrate that β2m has a complex pH-induced unfolding mechanism yielding a disordered amyloidogenic precursor comprising both exposed and buried segments.
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