Title:	Dynamics and dimension of an amyloidogenic disordered state of human β2-microglobulin
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Abstract:	Human β2-microglobulin (β2m) aggregation is implicated in dialysis-related amyloidosis. Previously, it has been shown that β2m adopts an ensemble of partially unfolded states at low pH. Here we provide detailed structural and dynamical insights into the acid unfolded and yet compact state of β2m at pH 2.5 using a host of fluorescence spectroscopic tools. These tools allowed us to investigate protein conformational dynamics at low micromolar protein concentrations in an amyloid-forming condition. Our equilibrium fluorescence data in combination with circular dichroism data provide support in favor of progressive structural dissolution of β2m with lowering pH. The acid unfolded intermediate at pH 2.5 has high 8-anilinonaphthalene, 1-sulfonic acid (ANS)-binding affinity and is devoid of significant secondary structural elements. Using fluorescence lifetime measurements, we have been able to monitor the conformational transition during the pH transition from the native to the compact disordered state. Additionally, using time-resolved fluorescence anisotropy measurements, we have been able to distinguish this compact disordered state from the canonical denatured state of the protein by identifying unique dynamic signatures pertaining to the segmental chain mobility. Taken together, our results demonstrate that β2m at pH 2.5 adopts a compact noncanonical unfolded state resembling a collapsed premolten globule state. Additionally, our stopped-flow fluorescence kinetics results provide mechanistic insights into the formation of a compact disordered state from the native form.
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