Title:	Confined Water in Amyloid-Competent Oligomers of the Prion Protein
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Abstract:	Conformational switching of the prion protein into the abnormal form involves the formation of (obligatory) molten-oligomers that mature into ordered amyloid fibrils. The role of water in directing the course of amyloid formation remains poorly understood. Here, we show that the mobility of the water molecules within the on-pathway oligomers is highly retarded. The water relaxation time within the oligomers was estimated to be ≈1 ns which is about three orders of magnitude slower than the bulk water and resembles the characteristics of (trapped) nano-confined water. We propose that the coalescence of these obligatory oligomers containing trapped water is entropically favored because of the release of ordered water molecules in the bulk milieu and results in the sequestration of favorable inter-chain amyloid contacts via nucleated conformational conversion. The dynamic role of water in protein aggregation will have much broader implications in a variety of protein misfolding diseases.
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