

Mechanism of Tau R3 Aggregation and Inhibition Revealed by NMR-based Chemical Kinetics

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Protein misfolding diseases are becoming increasingly prevalent with the increase in life expectancy and lifestyle changes over the last century, and constitute a health challenge at a global level. Macroscopic protein deposits of amyloids are associated with diseases such as Alzheimer's (tau and β -amyloid) and Parkinson's (α -synuclein). The mechanisms of protein aggregation are poorly understood, and such knowledge would enable the rational design of therapeutics for these diseases. Several key chemical processes have been proposed; chemical kinetics approaches can be applied to test such models, but are limited by the information content and reproducibility of the data. A recently developed nuclear magnetic resonance spectroscopy (NMR) assay is the basis for a numerical integration method to quantify the kinetics of aggregation. This is a label-free method that can account explicitly for the effects of drugs and molecular chaperones. The work presented here extends this method by automating the model building, selection and testing routine, and provides a mechanistic model for the aggregation of the biomedically relevant R3 fragment of tau and its inhibition by a non-natural amino-acid compound.