Solvent-Driven Dynamical Cross-Overs in Amyloid-Beta Fibrils

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Introduction

Amyloid–β (Aβ) peptide is the major component of plaques found in Alzheimer's disease patients. Our previous studies demonstrated that the core of the fibrils is highly dynamic with motions persisting down to low temperatures.[1,2] Using deuterium NMR measurements we conducted further experiments focusing on the aromatic side chain of F19 located inside the core as well as on M35 side-chain pointing into water-accessible cavity. Changes in the dominance of motional modes with temperature can be viewed as the dynamical cross-over, which was the subject of this study for the two key side-chains of Aβ.

Experimental

We have utilized static deuterium line shape measurements as well as measurements of T_{1Z} (Zeeman) and T_{1Q} (Quadrupolar order) relaxation times and performed measurements We have used the 750 MHz magnet at the College of William and Mary as well as the 600 and 400 MHz magnets at NHMFL equipped with low-E static probes.

Results and Discussion

The M35 site is shown to undergo a solvent-dependent dynamical transition, in which slower amplitude diffusive motions of the methyl axes are activated at high temperatures, while fast methyl jumps dominate at low temperatures. The transition is suppressed in both the dry fibrils and the FMOC-Met amino acid.[2,3] For the aromatic side-chain of F19 the dynamics are dominated by small-angle fluctuations at low temperatures and by π-flips of the aromatic ring at high temperatures (Fig. 1). The cross-over temperature is more than 43 degrees lower for the hydrated state of the fibrils compared to the dry state, indicating that interactions with water facilitate π-flips. Further, cross-over temperatures are shown to be very sensitive to polymorphic states of the fibrils.[4]

Conclusions

Dynamical cross-overs were observed in two key side-chains of Aβ fibrils. They are strongly modulated by hydration and show dependence on the polymorphic state. The results underline the complexity of dynamical modes in the fibrils.

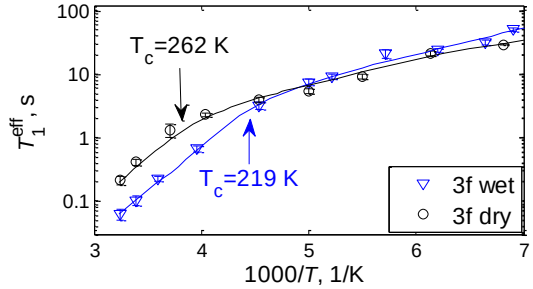

Fig. 1. ^{2}H Longitudinal relaxation times (at 17.6 T) as a function of inverse temperature for the deuterated ring of F19 in the 3-fold polymorph of Aβ.[7] The arrows indicate the cross-over temperatures at which the dominant relaxation mechanism changes.

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References

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