Graduate School Event

Thesis Defense: Exploring protein dynamics using specific labeling approaches for solid-state MAS NMR

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Characterizing protein dynamics at the atomic level is essential for our understanding of biological mechanisms. Whether it is to facilitate metabolite transport, catalyze reactions, transmit signals, or regulate metabolism – proteins are constantly in motion and sample multiple conformational states to fulfill their function. Nuclear magnetic resonance (NMR) spectroscopy is particularly well suited to elucidate the dynamics of biomolecules on their complex free-energy landscape. In particular, solid-state magic-angle spinning (MAS) NMR enables the study of large molecular assemblies, protein crystals, or insoluble proteins at atomic resolution without an inherent molecular size limitation. MAS NMR experiments to probe protein dynamics are extremely versatile and sensitive to motional timescales from picoseconds to seconds. Over the past decades, technological advances, developments in experimental design, and new isotope-labeling approaches have further expanded the possibilities of this technique and significantly improved the accuracy of the determined motional parameters.Functionally important sites of proteins often contain aromatic residues. Their side-chain motions have therefore long served as valuable indicators of mechanistically relevant dynamics in NMR studies. In this thesis, site-specifically labeled aromatic residues act as sensitive reporters for MAS NMR studies of protein dynamics. The first part addresses how different environments impact side-chain motion by probing ring flips of phenylalanines and tyrosines in crystalline proteins and amyloid fibrils. It provides important insights for the analysis of dynamics obtained in non-native protein environments and emphasizes the complex factors that determine the timescale of internal dynamics. In the second part, the focus shifts towards methodological questions regarding the investigation of protein dynamics by 19F MAS NMR. The fluorine nucleus exhibits promising characteristics for NMR studies but also presents significant challenges, which is why the full methodological potential of 19F MAS NMR has not been fully realized yet. This work demonstrates that paramagnetic doping can considerably reduce the measurement time and improve the sensitivity of fluorinated samples. Finally, 19F MAS NMR is evaluated as a tool for studying protein side-chain dynamics on the example of tryptophans. The results illustrate the challenges in analyzing such experiments and lay the foundation for further development of 19F MAS NMR relaxation studies.Taken together, this thesis highlights the potential of combining specific isotope labeling, MAS

NMR, and complementary methods such as crystallography and computational simulations to elucidate internal protein dynamics. The further development of such integrative approaches will be crucial to improving our understanding of complex mechanisms and protein function.

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Central Bldg / O1 / Mondi 2a (I01.O1.008)

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