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Molecular-Recognition Events probed by Solid-State NMR Spectroscopy

Molecular-recognition processes play a fundamental role in many disciplines of life and are essential in biology and chemistry. These events are driven by the cooperative interplay of noncovalent interactions (NCIs), such as for instance hydrogen bondings, dispersion or cation-π interactions. My group develops and applies Nuclear Magnetic Resonance (NMR) spectroscopy techniques to probe such weak chemical interactions in the solid state. This allows us to shed light on the atomic-level details of molecular recognition in rather diverse fields of biological and chemical sciences. In that vein, we currently focus with our collaboration partners on cellular organization by phase separation, mechanochemically-induced organic reactions and interactions of substrate molecules with catalytic surfaces (Figure 1). Our research themes require continuous further development of the solid-state NMR methodology in concert with computational modelling, for a recent example see ref. [1].

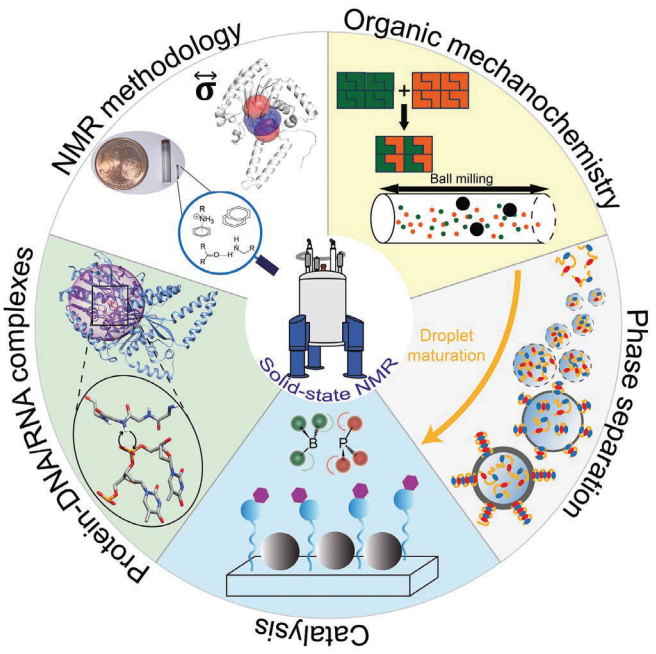

Fig. 1: Molecular-recognition events in biological and chemical sciences probed by solid-state NMR spectroscopy in our laboratory. Copyright: AK Wiegand

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Solid-state NMR spectroscopy has been developed into a well-established technique in materials sciences and biology allowing to access high-resolution structural and dynamic information. It particularly benefits from the fact that even disordered or amorphous materials escaping standard structure-elucidation tools can be investigated. The wealth of information encoded in NMR interactions enables among others to measure internuclear distances, to probe connectivity networks or to derive electron density information. Powdered solid samples typically yield broad and unresolved NMR spectra caused by anisotropic NMR interactions rendering the resonance frequencies orientation dependent. To improve spectral resolution for polycrystalline or amorphous solids, magic-angle spinning (MAS) has been introduced to reduce or even eliminate the effects of these anisotropic interactions on the NMR lineshape [2-3]. In a typical setup, cylindrical rotors made from ZrO_2 are spun rather fast (typically at rates of 10^4 to 10^5 s^{-1}) around an axis that is inclined with respect to the external magnetic field by the "magic angle", which is around 54.74°. A current line-of-research lies in the design of rotors with smaller and smaller outer diameters allowing to spin them with ever higher rotation frequencies (up to >170 kHz in 0.5 mm rotors [4]), which is essential for achieving high-resolution ^{1}H solid-state NMR spectra. Combining fast MAS with high static magnetic fields (such as the recently available 28.2 T magnets [5]) further improves spectral resolution as well as sensitivity [6-7] essential for detecting NCIs in solids.

As protons are at the centre of many NCIs, my group develops a set of dedicated ^{1}H solid-state NMR experiments enabling the detection and quantification of NCIs. We interpret our experimental results in feedback with quantum-chemical calculations on how NMR observables are influenced by NCIs. Our recent example comprises a hydrogen-π interaction in a lanthanide-calixarene complex, in which an isolated water molecule is fixed in the calixarene cavity of the complex [8]. ^{1}H-detected multidimensional spectra recorded at 100 kHz MAS enabled an unambiguous identification of the water molecule at quite atypical chemical-shift values around zero ppm. The sensitivity of the ^{1}H chemical-shift value on such a hydrogen-π interaction has been further studied by DFT calculations. We also probe hydrogen bonding in proteins and small organic molecules by measuring proton chemical-shift changes as a function of temperature [9-10]. The group is particularly interested in studying protein-nucleotide interactions; recent examples include motor proteins [10], an archaeal primase [11], and nucleotide-amyloid interactions [12].

Cellular organization by phase separation. A central molecular-recognition event we are focussing on is liquid-liquid phase separation and subsequent liquid-to-solid phase tran-

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sition of proteins linked with neurodegenerative diseases (e.g. RNA-binding proteins, see Figure 2). Real-time solid-state NMR allows us to monitor liquid-droplet maturation and to follow amyloid fibril formation [13]. Small peptide derivatives designed based on the "sticker-and-spacer" concept have been studied as model systems [14].

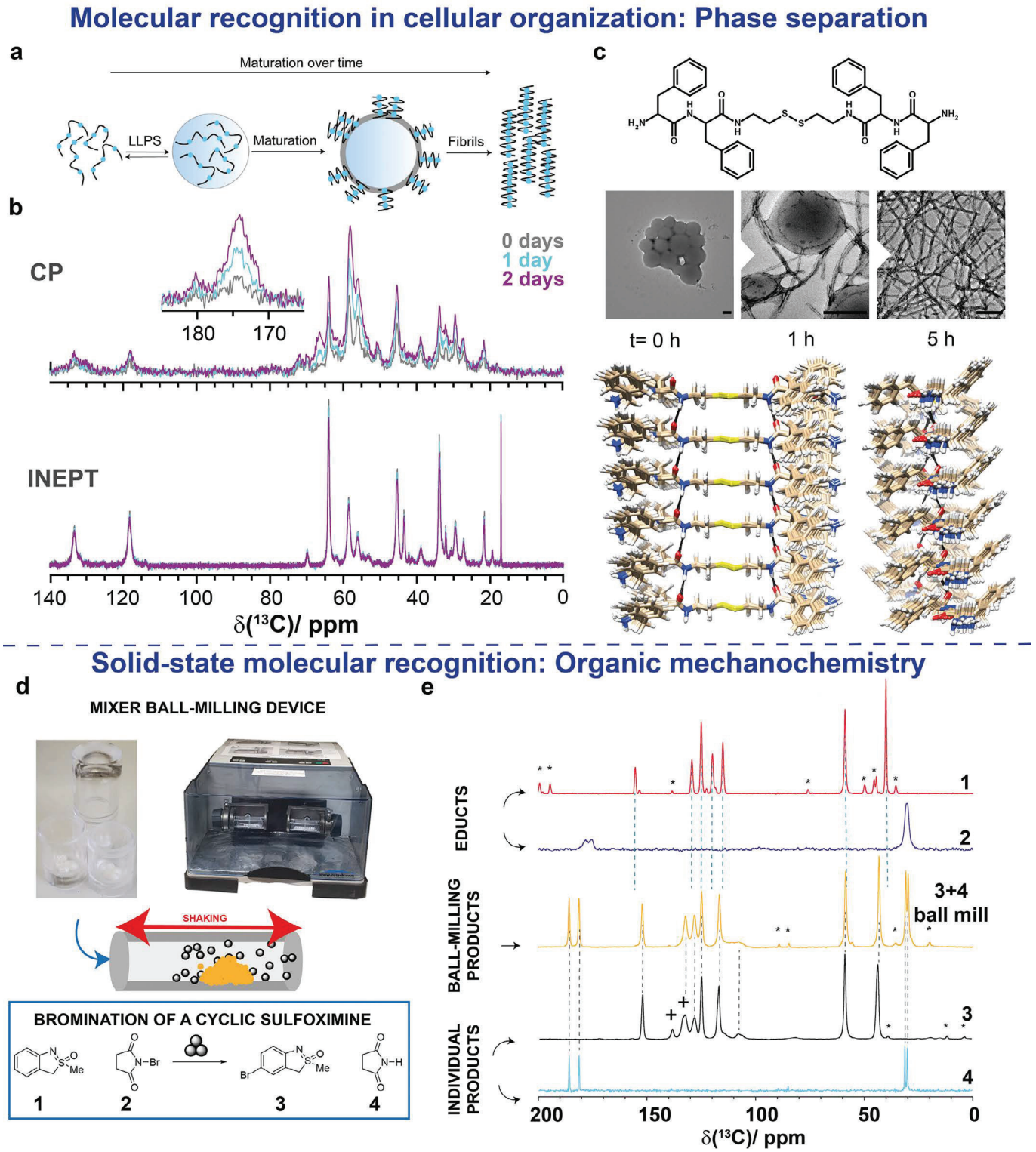

Fig. 2: Molecular recognition in cellular organization by biomolecular phase separation and in organic mechanochemistry investigated by solid-state NMR. **a)** Schematic illustration of the maturation of liquid droplets into solid fibrils (figure prepared by M. Sc. Ettore Bartalucci). **b)** Real-time solid-state NMR to follow fibril formation of the Fused in Sarcoma protein (immobilized species are detected in cross-polarization, CP, and mobile species in INEPT spectra, taken from ref. [13], copyright: Nature Portfolio). **c)** Liquid-to-solid phase transition of a small peptide derivative and fibril structure determination by solid-state NMR (taken from ref. [14], copyright: Wiley-VCH). **d)** The bromination of a cyclic sulfoximine in the mixer ball-milling device is studied by *ex-situ* solid-state NMR. A clean, regioselective and fast (<30 min) bromination is observed (for the NMR spectra see e, adapted from ref. [16], * indicates MAS sidebands and + an unknown isomeric product).

Organic mechanochemistry. Molecular recognition in mechanochemically-induced solid-state reactions is an important research topic studied in the group. Spectroscopic techniques are crucial for shedding light on the mechanisms of such reactions, and solid-state NMR offers a variety of opportunities in this research field [15]. The first reaction that we have studied was the mechanochemical bromination of a cyclic sulfoximine revealing the importance of disentangling the effects of mixing and pressure on product formation (Figure 2) [16]. We have currently extended our study to the mechanochemical racemic-phase formation of chiral organic molecules, as well as amino acids. The technique of resonant-acoustic mixing as an alternative tool is further explored in our laboratory [17].

Immobilized catalysts. We are studying immobilized catalysts, such as supported ionic liquid phases, with a focus on probing molecular interactions between substrate molecules and the catalyst surface. Furthermore, we try to shed light on ordering phenomena of immobilized catalysts and their effects on the catalytic activity.

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Thomas Wiegand was appointed in 2021 as a Heisenberg professor for magnetic resonance of complex materials and catalysts at RWTH Aachen University and as a research group leader at the Max Planck Institute for Chemical Energy Conversion. He has received his Dr. rer. nat. in physical chemistry at the University of Münster (supervisor Prof. Dr. Hellmut Eckert) and habilitated at ETH Zürich (mentor Prof. Dr. Beat H. Meier). His passion is the development and application of solid-state NMR techniques with a focus on the investigation of molecular-recognition events and underlying noncovalent interactions in biomolecular phase separation, heterogeneous catalysis and organic mechanochemistry.