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Weak chemical interactions in catalysis probed by solid-state NMR spectroscopy

The functionality and performance of catalysts in chemical reactions as well as in biological enzymatic processes are strongly interconnected with the initial catalyst conformation as well as the dynamics and transient structures of the catalyst-substrate complex during the catalytic cycle. Weak chemical interactions spanning the entire range of non-covalent interactions (NCIs) – including hydrogen bonds, dispersion interactions, π-π stackings or halogen bonds – guide catalyst-substrate interactions and thus influence the catalysts' performance, efficiency and selectivity (for a recent review article see ref. [1]). Therefore, for understanding catalytic processes at the molecular level, spectroscopic techniques often in concert with high-level quantum-chemical calculations are essential to detect and quantify the role of NCIs in these processes enabling the further optimization and fine-tuning of the performance of the catalysts. Solid-state Nuclear Magnetic Resonance (NMR) is a powerful tool for probing these NCIs during catalytic processes offering multiple experimental observables to address different questions (for our recent review article see ref. [2]). Samples suitable for solid-state NMR cover a broad range – from solid powders to protein sediments and gels. High resolution NMR spectra in the solid state are obtained by the magic-angle spinning (MAS) NMR experiment, in which an NMR rotor (usually made of ZrO_2) containing the sample is spun around an axis that is inclined by the "magic angle" of 54.74° with respect to the external magnetic field direction [3-4]. This allows to fully average anisotropic interactions such as the magnetic shielding anisotropy or through-space dipolar couplings if the MAS frequency is chosen sufficiently fast enough and thus enhances spectral resolution. Proton nuclear spins, which are often engaged in NCIs, are typically influenced by strong homonuclear proton-proton dipolar couplings. At the same time, their isotropic chemical shift value is highly sensitive towards the chemical and electronic environment and for instance serves as a strong indicator for hydrogen-bond formation detected by characteristic high-frequency shifted ^{1}H NMR resonances. To enable the extraction of this kind of information from proton-detected solid-state NMR spectra, fast MAS frequencies exceeding 100 kHz are required for efficiently averaging the proton dipolar coupling network.

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Further NMR observables besides isotropic chemical shift values reporting on NCIs are the temperature dependence of the isotropic chemical shift, the chemical shift anisotropy or isotropic *J*-coupling constants [2]. In addition, dipolar interactions contain information on internuclear distances and thus reveal spatial proximities within non-covalently bound molecular fragments. As mentioned above, these interactions are typically averaged by MAS, but can be "recoupled" by certain pulse sequences (such as the famous Rotational Echo Double Resonance – REDOR – sequence [5]) allowing for accurate distance measurements in solids and insight into molecular dynamics. In case of ^{1}H or ^{19}F nuclear spins with large gyromagnetic ratios, homonuclear distances up to around 15 Å can be accessed often using double-quantum based dipolar recoupling schemes [6]. These pulse sequences together with multidimensional correlation experiments (e.g., ^{1}H-^{1}H, ^{13}C-^{1}H or ^{13}C-^{13}C) and further tailored experiments serve as key ingredients for the design of a solid-state NMR toolbox enabling the detection and quantification of NCIs.

Probing NCIs by solid-state NMR: The example of a cation-π interaction.

The group is currently focussing on establishing such a solid-state NMR toolbox that is subsequently applied to various examples from biological and chemical catalysis research. In that vein, specific NCIs are studied initially in suitable model compounds, such as lanthanide-π-containers as molecular platforms able to entrap different small molecules [8], to further explore the sensitivity of solid-state NMR observables on weak chemical interactions. One example that we recently studied is a calix[4]arene lanthanum(III) complex (Figure 1a) that contains a non-covalently bound guanidinium cation trapped in the calixarene cavity by cation-π interactions [7]. Specific isotope labelling of the guanidinium cation (^{13}C and ^{15}N) enabled an unambiguous identification of its heteronuclear NMR resonances. Starting from these resonance assignments, the guanidinium cation ^{1}H chemical shift values were identified by 2D correlation NMR experiments (^{13}C-^{1}H and ^{15}N-^{1}H). These protons indeed display a significant lower chemical shift value as found for free guanidinium cations in reference compounds, which is attributed to ring-current effects caused by the cation-π interaction between the aromatic calixarene units and the guanidinium cation. Interestingly, only single ^{1}H and ^{15}N guanidinium cation resonances were observed in the MAS spectra close to room temperature even though multiple ones were expected. Temperature-dependent ^{1}H-^{15}N cross polarisation (CP-) MAS NMR spectra revealed the influence of motional dynamics

averaging the different atomic positions, as at low temperatures the expected two ^{15}N resonances in a 2:1 integral ratio have been detected (Figure 1b). The dynamic properties were further characterized by several solid-state NMR experiments, including ^{13}C-^{15}N REDOR. The therein measured ^{13}C-^{15}N dipolar coupling constant is significantly reduced in comparison to the rigid limit, as it is modulated by the internal motion of the guanidinium cation. Temperature-dependent longitudinal ^{13}C and ^{15}N relaxation times allowed an estimation of motional correlation times assuming a simple three-site jump model considering only dipolar contributions as relaxation pathways pointing to a guanidinium cation rotation along its C_3-symmetry axis. Possible rotations along the C_2-axes were discarded based on Density Functional Theory (DFT) calculations of potential energy curves (Figure 1c). Molecular Dynamics (MD) simulations indeed revealed that the guest molecule undergoes only a rotation along its internal C_3-axis indicated by discrete 120° jumps with a motional correlation time in the range of nanoseconds as concluded from the NMR relaxation time analysis. In conclusion, the cation-π interaction serves as a bearing for the rotation, and the confined space of the calixarene cavity provides sterical hindrance suppressing further possible motions. This paves the way for controlling molecular rotations by chemical design principles. Moreover, these results exemplary show the power of solid-state NMR combined with additional computational techniques to fully characterize the underlying NCIs and the dynamic features in such host-guest complexes.

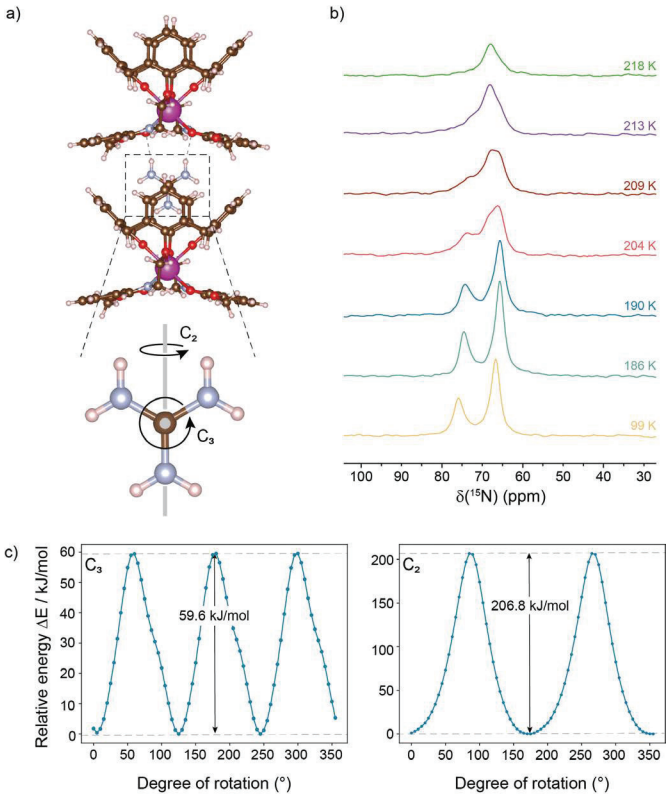

Fig. 1: a) Dimer of the studied calix[4]arene lanthanum(III) complex and possible local rotation axes (C_2 and C_3) of the guanidium cation. The colour coding is white = hydrogen, brown = carbon, blue = nitrogen, red = oxygen and pink = lanthanum. b) Temperature dependent ^{1}H-^{15}N cross polarization (CP)-MAS NMR spectra. c) Potential energy curves for the rotation of the guanidinium cation along the local C_2 and C_3 axes determined by DFT single point energy calculations (r^2SCAN-3c/ def2-mTZVPP) with the maximum energy difference indicated as the energy barrier for the rotation. The figure has been reproduced from ref. [7].

Enzymatic catalysis: The example of ATP hydrolysis.

The concerted interplay of multiple NCIs enables highly selective and efficient enzymatic catalysis. In the past years, the group has studied the role of NCIs in enzymatic catalysis for various proteins involved in DNA replication, such as the bacterial DnaB helicase from *Helicobacter pylori* or the archaeal primase from the plasmid pRN1 (for selected references see [9-11]). The central objective was to gain mechanistic insights in DNA unwinding or primer formation by identifying the key NCIs driving the reaction and rendering it highly selective. Of special interest is to unravel the coupling of ATP hydrolysis with biological functioning in ATP-driven motor proteins. Here, nucleotides are recognized specifically within the active pocket of ATPases via a network of NCIs, which can be identified by solid-state NMR. While real-time reaction monitoring is typically not possible due to high reaction rates, the ATP hydrolysis can be slowed down (or even fully suppressed) for NMR-spectroscopic investigations by using stable ATP-analogues, often considered as “non-hydrolysable” (Figure 2a) [12]. Recently, we presented a nucleotide-detected solid-state NMR approach which allowed probing the nucleotide conformations and dynamics during ATP hydrolysis. As a model protein, we used the dimeric P-loop ATPase SmsC responsible for the biogenesis of Fe-S clusters [13]. By detecting the phosphorus-31 nuclear spins of the nucleotide, NMR benefits from the high sensitivity of this nucleus (100% natural abundance and high gyromagnetic ratio), its large chemical shift dispersion and the often sizeable chemical shift anisotropies that provide insight into molecular dynamics. At the same time, the costly and time-consuming ^{13}C, ^{15}N isotope labelling of the protein can be avoided. Our study on SmsC revealed that the ATP-mimics bind with different degrees of conformational heterogeneity to the enzyme as concluded from the ^{1}H-^{31}P CP-MAS NMR spectra (Figure 2b). Computational modelling allowed us to track these binding phenomena back to the role of a hydrogen bond between SmsC and the terminal phosphate group of the nucleotides responsible for guiding the binding of the nucleotide within the binding pocket. Further ^{31}P-^{31}P homonuclear dipolar recoupling experiments allowed us to probe molecular dynamics of the SmsC-substrate complexes, pinpointing to a higher molecular mobility for the ATP and transition-state ATP-analogues compared to the post-hydrolytic mimics. In addition, the sedimented protein still hydrolyses various ATP mimics (such as AMP-PNP or even ADP) on a time scale of several days enabling us to perform real-time NMR spectroscopic investigations to study the corresponding reaction mechanisms and kinetics. In that vein, the SmsC-catalysed hydrolysis of AMPPNP in solution was compared to the one in the solid-state, which interestingly revealed differences in the corresponding reaction products (Figure 2c). We next aim to incorporate additional NMR-active isotopes, such as ^{19}F, in the ATP mimics that will expand the applications of nucleotide-detected solid-state NMR spectroscopy in probing NCIs in various protein-ligand complexes.

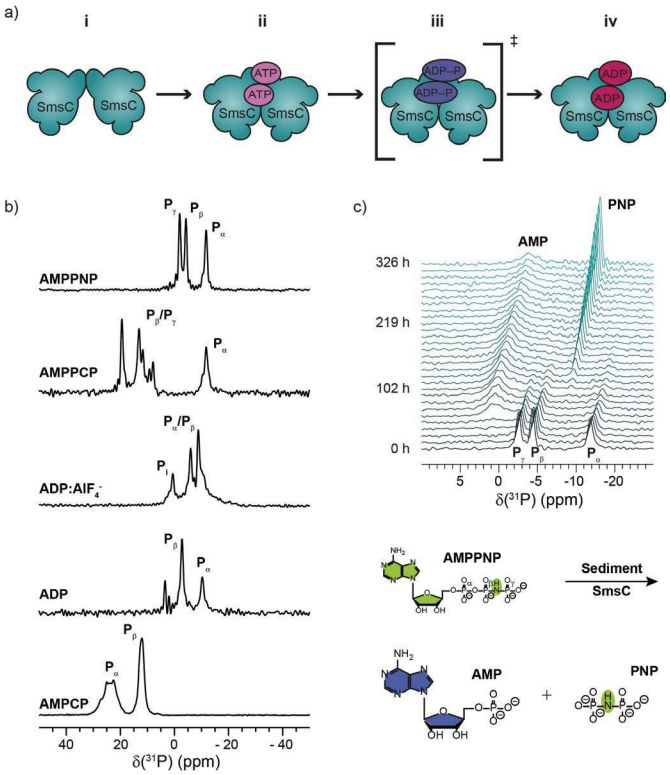

Fig. 2: a) Different stages of ATP hydrolysis in the dimeric P-loop ATPase SmsC. b) Structural heterogeneity of the bound ATP-mimics could be observed for AMPPCP and AMPCP for which multiple different ^{31}P resonances were found for the individual phosphate groups in the ^{1}H-^{31}P CP-MAS spectra instead of only a single set of resonances as observed for AMPPNP, ADP:AlF$_4^-$ as transition-state mimic and ADP. c) Real-time ^{1}H-^{31}P CP-MAS NMR spectra of the SmsC-AMPPNP complex indicating the hydrolysis of AMPPNP as shown in the chemical reaction during a time range of about two weeks. The figure has been reproduced from ref. [13].

Immobilized catalysts employing the supported ionic liquid phase concept.

Solid-state NMR spectroscopy and the NCI toolbox are the ideal analytical tools to achieve atomic-level structural and dynamic information on catalysts immobilized on solid molecularly modified support materials and to shed light on the role of weak chemical interactions in catalysis. Supported ionic liquid phases (SILPs), in which ionic liquids (ILs) are covalently grafted on silica surfaces, have been identified as an extremely versatile platform to immobilize catalytically active metal nanoparticles (NPs) enabling the unique control of catalytic activities and selectivities in hydrogenation and hydrogenolysis reactions (for a selected review article see [14]). Additionally, such catalysts are often considered as “adaptive”, e.g., they are able to switch their catalytic performances reversibly in presence of external stimuli [15]. Such multicomponent, highly disordered catalysts are ideal targets for characterization by multinuclear solid-state NMR spectroscopy. The chemisorption of the IL on the silica support materials can be proven by ^{29}Si MAS NMR, as the ^{29}Si chemical shift values for silica atoms of the ILs covalently bound to the silica surface are indicative for the number of C–Si–O^{surface} groups (T_n nomenclature with n being the number of C–Si–O^{surface} groups). Doing so, the successful immobilization of palladium *N*-heterocyclic carbene (NHC) complexes on a silica support has been demonstrated. Such complexes have been used in combination with ruthenium NPs for the synthesis of *E*-chalcones (Figure 3a) [16]. Structural and dynamic properties of the IL molecular modifiers in these systems are further probed by ^{13}C, ^{15}N, ^{19}F and ^{31}P solid-state NMR spectra, in most cases recorded under CP conditions to boost the signal-to-noise ratio by transferring polarization from the more abundant ^{1}H nuclei. The spectroscopic investigation of the NPs themselves has been shown for materials bearing RuP (Ru$_x$P$_{100-x}$) NPs by recording static ^{31}P NMR spectra using the Wideband Uniform Smooth Truncation-Carr-Purcell Meiboom-Gill (WURST-CPMG) scheme [17]. Significantly high-frequency shifted ^{31}P NMR resonances caused by Knight shift effects indicate the formation of Ru$_x$P$_{100-x}$ species (Figure 3b) [18]. Such immobilised RuP NPs have been used for the selective hydrogenation of heteroarenes and solid-state NMR allowed to access the integrity of the catalyst after catalysis [19]. Solid-state NMR can also be applied to probe molecular interactions and NCIs between species that are adsorbed on the SILP material and the ILs. A recent study has reported the CO_2-triggered adaptive hydrogenation of ketones [20] that has been linked to the reversible formation of formic acid species stabilized on the SILP surface. Solid-state NMR was applied to answer the questions (i) whether formic acid indeed shows various degrees of immobilization on different silica surfaces explaining the observed adaptive control of hydrogenation reactions by changing the feed gas to H_2/CO_2 and (ii) whether specific molecular interactions between formic acid and the ILs can be identified [21]. For such purposes, four representative SILP materials have been impregnated with ^{13}C-isotope labelled

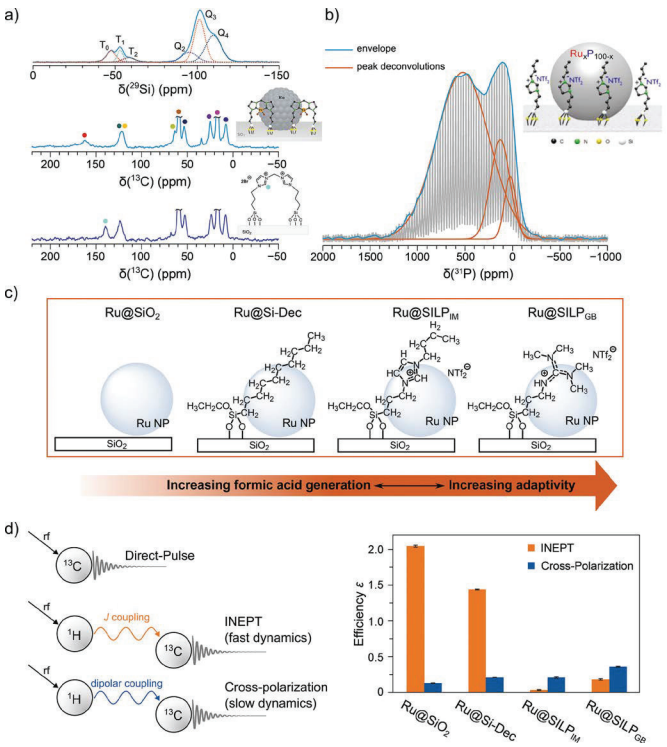

Fig. 3: a) ^{1}H-^{29}Si and ^{1}H-^{13}C CP solid-state NMR spectra of a [Pd-NHC] complex grafted on Ru@SiO$_2$ (top and middle), as well as ^{1}H-^{13}C CP spectrum of the grafted NHC in the absence of Pd^{2+} (bottom) (taken from ref. [16]). b) ^{31}P WURST-CPMG spectrum of Ru$_{50}$P$_{50}$@SILP reproduced from ref. [19]. c) Chemical structures of catalyst materials for which the immobilization of formic acid has been studied. d) Schematic drawing of used excitation and polarization transfer schemes (left) and polarization transfer efficiencies (ε) of CP and INEPT polarization transfers determined from the ratios between the integrals of the formic acid signal in the INEPT or CP spectra and the DP spectra (taken from ref. [21]).

formic acid (Figure 3c). Proton transverse relaxation times as well as the efficiency of polarization transfer techniques (CP vs. Insensitive Nuclei Enhanced by Polarization Transfer, INEPT), both being sensitive to molecular motion, have been explored to monitor differences in the degree of formic acid immobilization dependent on the SILP material used (Figure 3d). And indeed, the increase in formic acid stability on certain SILP materials can be correlated with the previously observed CO_2-triggered reaction selectivities. ^{1}H-^{1}H 2D correlation NMR-spectra recorded at fast MAS frequencies further identified spatial proximities between formic acid and the cationic ILs hinting at weak chemical interactions between such entities. In subsequent work, we are using homonuclear dipolar-recoupling experiments to probe spatial ordering effects in such SILP-based catalysts, e.g., by accessing the distribution of molecular modifiers on the support as well as identifying possible interactions between the NPs and molecular modifiers.

Outlook

Studying the role and importance of weak chemical interactions in catalysis is still in its infancy and finding overarching trends between biological and chemical catalysis remains a hallmark of catalysis research. The detection and quantification of NCIs by spectroscopy supplemented by quantum-chemical calculations will be crucial to shed further light on this highly important research questions. This requires both, novel and sensitive spectroscopic approaches in detecting NCIs as well as advances in the precise calculation of spectroscopic observables. We believe that NMR spectroscopy will be central in this research endeavour and thus aim at expanding our solid-state NMR toolbox for such purposes in the next future.

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