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Operando monitoring of mechanisms and deactivation of molecular catalysts

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Observing and understanding the phenomena associated with the reaction mechanisms and catalyst deactivation in molecular catalysis is a very challenging task in green chemistry. This knowledge is crucial for applying and scaling catalyzed reactions as well as preventing misproduction at a very early point. Over the years, experimental arrangements have evolved towards analysis of catalysts and reaction products in the so-called *operando* setups. This contribution reflects on the potential of *operando* studies to elucidate reaction and deactivation mechanisms in homogeneous catalysis as well as the outstanding opportunities that arise from the application of *operando* experimental setups. Such setups mostly rely on spectroscopic analysis, optionally coupled with chromatographic techniques that monitor the reaction system. This in turn means that not only the evolution of the reaction substrates and products can be monitored, but also changes of the molecular catalyst species that may affect the catalytic performance. Therefore, this review focusses on techniques to monitor the catalyst under real conditions. In this review, different spectroscopic techniques relevant for monitoring molecular transition metal catalysts in solution are covered, followed by numerical methods used in the chemometrics literature to undertake the challenge of untangling the complex raw signals and allocating them to individual chemical species. Finally, two exemplary case studies of industrially relevant chemical reactions are presented, namely the hydroformylation and the asymmetric hydrogenation. These examples illustrate the significance of the application of both the experimental setups as well as data processing and signal resolution to have an insight into the deactivation of catalytic systems. The *operando* approach shows high potential for the increased use in future research to develop stable and more selective catalysts which can be applied in greener processes.

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1. Introduction

Unravelling the mysteries of chemical reaction mechanisms and the deactivation of the catalytic species involved therein is a topic that has attracted the interest of industrial practice and research in catalysis.¹ It is of paramount importance to understand catalytic cycles and how catalysts become inactive throughout the chemical reaction on a molecular level. In this way, researchers will be able to develop catalyst species or process designs that show optimal performance in terms of activity and selectivity as well as stability when applied in processes with adequate operating conditions. To detect a deviation on the molecular catalyst level can prevent misproduction and make the process greener and safer.

Concerning these types of studies, the classic approach is to analyze the reaction kinetics and product mixtures *ex situ* in order to draw conclusions on the evolution of chemical reactions and deactivation mechanisms. The goal is to detect compounds associated with a deactivation process, such as a deactivated catalyst species.² Although this strategy is limited to trace species which are stable at *ex situ* measuring conditions, very important knowledge can be gained.^{3–6} *In situ* methods have been applied for several decades, allowing to perform spectroscopic measurements of the catalyst in a model setup or reactor under idealized and controlled conditions, such as an inert atmosphere. Later came the evolution to *operando* techniques, a term coined by Bañares and his collaborators.^{7,8} These feature the characterization of the used catalyst as well as the simultaneous detection and quantification of the substrates, intermediates and products of the reaction by real-time analytical techniques. *Operando* analytical methods run within the real operating reaction medium and conditions, thereby reducing sampling delay and avoiding air contacting, thus allowing the detection of unstable reaction intermediates that otherwise would deteriorate upon sample withdrawal and work

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up for analysis. In this way, a much more insightful relationship between the state of the catalyst, the reaction kinetics and the overall catalytic performance can be established.⁹

An ideal workflow of the *operando* analysis of catalytic chemical reaction starts by using an *operando* experimental setup featuring spectroscopic analytical methods to understand the events inside a catalytic process with many unknown elements. Depending on the complexity of the retrieved data, more or less complex data processing curve resolution techniques could be performed to identify individual chemical species. Such multivariate curve resolution methods can lead to the establishment of more accurate mechanisms by isolating the signals and identifying more species. Finally, with all the knowledge derived from this experimental arrangement and data analysis, catalytic and deactivation mechanisms can be elucidated.⁵

Different articles have illustrated that the analysis of reaction mechanisms and deactivation of the catalytic species is mainly performed by spectroscopic techniques. These may vary significantly depending on the type of catalysts being investigated. Wachs *et al.* have portrayed a thorough historical background on *operando* spectroscopic techniques with its prime focus on heterogeneous catalysis.⁹ More recently, a perspective article has described *in situ* and *operando* techniques applied for the characterization of single atom catalysts supported on heterogeneous materials.¹⁰ For heterogeneous catalysts, methods highlighting chemical and structural changes of the solid materials are of special relevance. Furthermore, recent work has used *operando* setups to conduct kinetic and mechanistic studies of molecular catalysts supported on solid materials.¹¹ All these reviews show that the understanding of deactivation of active catalytic sites can lead to longer life time of the catalyst alongside stable selectivity.

In molecular transition metal catalysis,^{12–14} thus far research discussion has focused mostly on mechanistic studies, leaving the study of deactivation phenomena somewhat unattended, particularly under relevant reaction conditions.⁵ Molecular catalysis features milder reaction conditions and unique selectivity and reactivity in comparison to heterogeneous catalysis. The lack of *operando* studies of molecular catalysis can be seen in literature searches: searching the term “*operando* spectroscopy” together with “catalyst deactivation”, “catalyst degradation”, “catalyst decomposition” or “catalyst inhibition” in SciFinder® gives in total seven results which can be assigned to the field of homogeneous catalysis. In contrast, 116 references on heterogeneous catalysis and 39 on electrocatalysis can be found with the same search items. These results, without claiming completeness, clearly show an underrepresentation of molecular catalysis. Studies in this particular field of catalysis remain very challenging due to the sensitivity of the spectroscopic methods in relation to the usually very low concentration of the catalytic species. These studies would be of great importance in industrially established reactions like the hydroformylation of olefins,¹⁵ asymmetric hydrogenations,¹⁶ telomerizations¹⁷ or carbonylations.¹⁸

Anyhow, regardless of the type of catalysts to which the aforementioned spectroscopic techniques are applied, the complexity of the signals suggests that often times advanced mathematical techniques can provide a powerful tool towards a proper interpretation of the results. For this reason, several studies in the chemometrics literature have used different numerical approaches to face the challenging resolution of curves and its ascription to each individual chemical species involved.^{19–21}

This review focusses on techniques which provide information of the catalyst species on a molecular level during a reaction. Emphasis is placed on metal organic compounds used as catalyst, even though most of these methods can also be applied to monitor organo-, photo- or electrocatalyzed reactions if the catalyst is in solution. The main focus and motivation of the article is to find direct proof of catalytic reaction and deactivation mechanisms.

Therefore, this work first describes the relevant *operando* spectroscopic techniques applicable to molecular catalysis, including their features and application in mechanistic studies. Then, an overview of numeric methods for multivariate curve resolution for the interpretation of the spectroscopic signal is presented. Last, reaction mechanisms and catalytic deactivation are explained in relation with *operando* studies for two exemplary case studies of well-established reactions in industry, namely hydroformylation and asymmetric hydrogenation. Overall, this review intends to highlight the importance of *operando* techniques and data treatment to shed light on the correct interpretation of homogeneously catalyzed reactions and especially their deactivation.

2. *Operando* techniques for molecular catalysis

In this section *operando* techniques that have been used for the study of molecular organometallic catalysts in solution, namely nuclear magnetic resonance, electron paramagnetic resonance, infrared spectroscopy, Raman spectroscopy, ultraviolet-visible spectroscopy, X-ray absorption spectroscopy and electrospray ionization mass spectrometry will be summarized. The use of a particular technique depends on the nature of the catalyst, the composition of the reaction medium, the characteristics of the analytical instruments, and of course the ease of device setting-up. The features of each technique and its application in kinetic and mechanistic *operando* studies will be discussed as well. Besides, chromatography techniques, such as online GC or HPLC are useful tools to quantify the conversion, selectivity, and kinetic study, which indirectly reflects the catalyst activity but will not be discussed here.

2.1. *Operando* analytical techniques

Nuclear magnetic resonance spectroscopy (NMR), one of the most widely applied spectroscopic techniques in chemical research, provides detailed information about molecular structure as well as dynamic processes and allows the direct obser-



vation of chemical reactions.²² Jagadeesh and coworkers have investigated the reductive amination of carbonyl compounds to a variety of primary amines with a $[\text{RuCl}_2(\text{PPh}_3)_3]$ catalyst. With the help of *in situ* ^1H and ^{31}P NMR spectroscopy, an appropriate reaction mechanism was proposed, clarifying the formed ruthenium hydride species to be the active catalytic species.²³ In addition to the most common ^1H NMR, multi-nuclear spectra supply more information for catalytic intermediates during reaction processing. Especially for transition metal catalyzed reactions, ^{13}C NMR (for metal carbonyls, metal carbenes), ^{31}P NMR (for phosphine ligands) and ^{19}F NMR (for fluorine catalysts) are very useful approaches to observe the coordination mode and to identify the active intermediates, which eventually improves the understanding of the catalytic cycle.^{24–26}

Many molecular reactions, such as hydrogenation and hydroformylation, require high gas pressures. High pressure NMR technology has been performed for over 60 years.²⁷ Limited by the volume of the NMR tube, *in situ* static NMR often lacks mixing, which might lead to inaccurate kinetic data for reactions involving gases.²⁸ High pressure flow NMR cells were developed to improve the mass transfer. There are two typical designs. The first design keeps a constant stream of gas bubbles through the solution in the NMR tube.^{29,30} In order to reduce the degradation of spectral resolution caused by the gas bubbles, the gas flow has to be adjusted to a moderate rate and gas circulation has to be stopped during the excitation and acquisition periods. More recently, Dušan's group has developed a pure-shift method by removing all heteronuclear and homonuclear couplings of the selected signal, which can improve in the signal-to-noise (S/N) ratio remarkably. This method was then applied to monitor inhomogeneous reaction with gas sparging, and the singlets can be improved 8-fold in S/N.³¹ The other type of design continuously circulates the reaction solution from the reactor to the NMR probe. The liquid flow rate has to be optimized to allow enough residence time for sample magnetization and acquisition. A correction factor is necessary to quantify the integral data at flow conditions vs. static conditions.³² Recently, Hintermair's group reported a study using *operando* flow NMR spectroscopy to monitor the Rh/PPh_3 catalyzed hydroformylation of 1-hexene with multi-nuclear ^1H and $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy.³³ The reaction mixture was infused from high pressure vessels (up to 20 bar) to a high field NMR with a flow rate of 4 mL min^{-1} (about 30 s delay). To obtain quantitative data, correction factors of different species (reactant, catalyst and product) in the mixture were calculated with varied concentrations. The flow NMR setup allowed to monitor all the species and the corrected NMR data showed good agreement with the GC results, which makes it a promising method for further study of other catalytic hydroformylation systems.

High-field NMR instruments provide high sensitivity and large chemical-shift dispersion. However, large size and high cost prevent its wide application for *operando* studies. Instead, compact NMR spectrometers are an economic and operable alternative for real-time analysis on workbench.^{34–36} Danieli

et al. reported a study on the hydrogenation of acetophenone with isopropanol catalyzed by iridium complexes in flow conditions in a low field NMR with 60 MHz. They considered that the field homogeneity and the kinetic rate could be studied as a function of the catalyst concentration and good agreement was found with the results obtained by gas chromatography.³⁷ Compact NMR spectrometers have become an important analytical tool for both quality control and process monitoring. However, low sensitivity for reaction intermediate monitoring limits its application for chemical analysis. It is to be expected that the accuracy of compact NMR will be improved by device developments such as increasing magnetic field strengths and increasing line shape specifications.³⁴

Electron paramagnetic resonance (EPR) is a magnetic resonance technique similar to NMR, but instead of measuring the nuclear transitions, it detects the transitions of unpaired electrons in an applied magnetic field. *In situ* EPR is widely used for studying transient radical-pairs in photo-excited systems, for instance for monitoring the primary photochemistry in reaction centers of photosystems I and II.^{38,39} Besides, it is a good tool for the characterization of catalysts involving paramagnetic centers, *e.g.* iridium, iron and chromium coordinated by N-heterocyclic carbene (NHC) or phosphine ligands.^{40,41} Brückner's group investigated photocatalyzed water reduction using iridium and iron complex catalysts.⁴² *In situ* EPR enabled to monitor the paramagnetic radical intermediates. Coupled with Raman and IR spectroscopy, two detailed catalytic cycles were proposed. In this study, the reaction was carried out in a typical EPR tubing. The relaxation properties of transition metals are highly sensitive to temperature, which further influences the signal intensity of paramagnetic species.⁴³ Hence *operando* EPR is preferably carried out under harsh conditions, for instance the above cases were measured below 200 K. However, Brückner *et al.* were able to perform *operando* EPR measurements of Cr in ethylene tetramerization at $40\text{ }^\circ\text{C}$ and up to 14 bar ethylene pressure.⁴⁴ These results gave hints to a deactivation pathway forming Cr (I) species.

Infrared spectroscopy (IR), concerns the study of molecular structure and properties from their vibrational transitions induced by infrared light. Compared to NMR, IR has a faster time scale and is more sensitive. Especially in the case where the catalytic species is a transition metal carbonyl complex, the strong CO vibrations provide an excellent analytical tool for studying intermediate species.¹² Typical catalytic carbonylation reactions include alkene hydroformylation, methanol carbonylation and methoxycarbonylation, which employ high pressure and high temperature.^{45–48} In order to increase the concentration of gases in solution for faster reaction rates or beneficial shifts in chemical equilibria, high-pressure IR spectroscopic techniques have been developed.

Two main sampling setups are in common use: (1) transmission and (2) attenuated total reflectance (ATR). Varied types of high-pressure transmission IR cells have been devel-



oped to facilitate real reaction conditions for *operando* studies.⁴⁹ Due to the limited mechanical strength of the observation windows and optimum pathlength for different compounds, the volume of high-pressure transmission IR cells is usually relatively small. Hence, one type of design consists of an extra variable pathlength view-cell connected to an autoclave through which the reaction mixture is circulated. As the reaction is carried out in a big vessel, this design avoids the mass transfer issue but has to consider the delay time. A second type is a high-pressure vessel with two IR transparent windows wherein the reaction occurs. This realizes *in situ* testing but lacks mixing and pathlength variation. To minimize the delay time and mixing problem, van Leeuwen's group has developed a high-pressure IR autoclave with integrated IR cell and reaction vessel (50 cm³) *via* two connected chambers. A turbine rotor was employed to stir and circulate the reaction mixture from reaction vessel to IR cell in 33 ms at the quickest. This cell has been used to investigate the kinetics of CO ligand exchange between the rhodium complex and H₂, which proved to be a key step in hydroformylation catalysis.⁵⁰

Different from the transmission IR, attenuated total reflection infrared spectroscopy (ATR-IR) measures the optical absorption of evanescent waves at the interface between a sample and a transparent sensing element rather than through a very thin sample. The ATR setup can be mounted onto a benchtop instrument or implemented in an immersion probe, which is easier and more flexible than transmission IR setups.^{51,52} It is already commercially available in systems such as ReactIR⁵³ and Arcoptix FTIR-FC.⁵⁴ The evanescent wave of infrared radiation has a limited penetration depth which is larger in the case of longer wavelengths, causing a sensitivity change of the ATR spectrum in the different range of wavelengths. This is the main difference between ATR and transmission IR and also the reason for the low sensitivity of ATR spectra in short wavelength regions, which has been proved by our group in the study of the hydroformylation of 1-dodecene. It compared the ability of transmission and ATR IR setups for monitoring the active catalyst species in batch and continuous flow reactions. In the latter, transmission IR enables the detection of organometallic intermediates at a ppm level while ATR cannot.⁵⁵ In conclusion, both transmission and ATR IR are adequate tools for *operando* study, and the individual choice certainly depends on the specific process constraints and the required specificity.

Raman spectroscopy is IR complimentary, as it can access IR inactive vibrations since Raman active vibrations cause a polarizability change, differing from IR active vibrations which change the dipole moment of a molecule.⁵⁶ As a scattering technique, Raman signals are weaker than the ones obtained from IR spectroscopy. However, Raman spectra are generally sharp with rare overlapping, which is convenient for spectral analysis. Since water is a weak Raman scatterer, Raman spectroscopy is ideal for monitoring aqueous phase reactions. One application of *operando* Raman spectroscopy in aqueous phase was performed by Haumann *et al.*, investigating ruthenium catalyzed methanol dehydrogenation.⁵⁷ The reaction inter-

mediate formate was detectable by Raman spectroscopy, which further proved the postulated mechanism.

UV-vis spectroscopy produces comparatively sensitive spectra, which can show the d-d* and charge transfer transitions of transition metal complexes and the formation of organic molecules *via* their n-p* or p-p* transitions.^{58,59} Due to the limited structural information UV-vis can provide mainly qualitative data. However, for those compounds having UV-vis chromophores, it is still a useful tool for supplementing information gained from other spectroscopic techniques. Schaub and coworkers investigated the chromium catalyzed dehydroperoxidation of cyclohexyl hydroperoxide to cyclohexanone, using *in situ* UV-vis spectroscopy to monitor the intermediate alkylperoxochromium(vi) complex formation and decomposition. Coupled with NMR spectroscopy and DFT calculations, a promising mechanism was proposed.⁵⁹

X-ray absorption spectroscopy (XAS), measuring the energy-dependent fine structure of the X-ray absorption coefficient near the absorption edge of a particular element, is a powerful tool for probing the average local electronic and geometric structures of catalysts in the working state.^{60,61} It is widely used in heterogeneous *operando* studies, however, only few cases have been presented on molecular catalysis *in situ* analysis.⁶²⁻⁶⁶ Among one of the first *in situ* XAS studies is a study on the bromobenzene homocoupling with a [Ni(cod)(bpy)] by Tanaka's group.⁶⁷ Using time-resolved XANES and EXAFS analysis they were able to monitor the reactant [Ni(cod)(bpy)], the intermediate [Ni(bpy)(Ph)Br(DMF)₂] and the subproduct [Ni(bpy)Br₂(DMF)₂]. Recently, Bäckvall's group published a work of *operando* XAS to study the activation of a ruthenium racemization catalyst.⁶⁸ X-ray absorption spectroscopy enabled the inspection of the stereostructure coordination environment around ruthenium during activation, as well as the proposed acyl intermediate and the activated alkoxide complexes for different molecular ruthenium catalysts, providing a valuable foundation for efforts to further catalyst development. Since XAS analysis requires structural models which hinder it to discriminate elements from the same periodic row, a combination with other structural and analytical techniques, such as NMR, can make it more effective.⁶⁹

Electrospray ionization mass spectrometry (ESI-MS) is a soft ionization technique applicable particularly for solutions containing charged species, which yields little fragmentation products and proves to be an excellent tool for analyzing organometallic complexes.^{70,71} Compared to standard spectroscopy, it is relatively simple to analyze reaction mixtures applying ESI-MS, as each species in solution usually can be identified by a single peak in the mass spectrum. Therefore, this technique has been widely used to investigate the mechanisms of several classic and organocatalyzed reactions.⁷²⁻⁷⁵ In 2007, Santos *et al.* were able to detect three catalytically involved species of the Stille reaction *via* direct infusion ESI-MS, characterizing most of the major intermediates in the cycle for the first time.⁷⁶ The same group reviewed the application of real-time ESI-MS analysis on the mechanistic study of Morita-Baylis-Hillman (MBH) reactions.⁷⁷ Some neutral



intermediates were expected to be in equilibrium with their protonated or cationized forms in methanolic solutions, and could therefore be detected and analyzed *via* ESI-MS. After testing several different catalysts, a dual mechanism was observed by online ESI-MS. Additionally, ionic liquids acting as additives as well as (thio)urea working as organocatalyst were monitored.

The typical way of continuous infusion of reaction mixture into a mass spectrometer is by using syringe pumps or HPCL pumps. In order to realize *in situ* conditions, instead of applying a pump, McIndoe *et al.* have connected the reaction vessel directly to a mass spectrometer *via* PEEK tubing. By slightly pressurizing the reactor, the reaction mixture was infused into the instrument. This simplified technique has been used for the kinetic study of the rhodium catalyzed hydrogenation of a charge-tagged alkyne, and the experimental data showed great agreement with numerical modeling.⁷⁸

Chen combined *in situ* chemical synthesis and gas-phase ion molecular reaction in a tandem ESI-MS.⁷⁹ This technique can achieve reaction, "purification", and analysis in a single device, which makes it an extremely fast method for the assessment of catalytic activity relative to conventional studies. Reactions such as olefin metathesis and Ziegler Natta polymerization were screened using this setup. The results of the *in situ* study showed good agreement with the analysis of the separately conducted synthesis, which demonstrated that this technique is an effective and reliable method.

However, the use of ESI-MS for accurate quantification of a species has its limitations because numerous minor variations can affect the ionization efficiency of different compounds.⁸⁰ Accurate ESI-MS quantification can only be achieved *via* repeatable sample preparation methods that provide reliable recoveries, for example the use of internal standards.⁸¹

2.2. Combination of multiple techniques

Multiple *operando* and *in situ* techniques applied to investigate the catalytic system from different perspectives allow us to bring all the information together and gain a detailed understanding of the catalyst performance. In Fig. 1, two examples are presented to show the currently available techniques for *operando* and *in situ* analysis of molecular catalysts.

Example A shows the investigation on the impact of different activators (MMAO and AlR_3) on the *in situ* formation of the depicted chromium complex and its performance in ethylene oligomerization to 1-octene.⁸² After mixing the chromium precursor ($\text{Cr}(\text{acac})_3$) **1**, ligand (PNP) **2** and activator (MMAO or AlR_3), *operando* EPR immediately detected the reduction of EPR active Cr^{III} to EPR silent Cr^{II} , which indicates the formation of the active species $(\text{PNP})\text{Cr}^{\text{II}}(\text{CH}_3)_2$ **3**. However, when using AlR_3 activators, Cr^{I} species were also observed along with a reduced consumption of ethylene and low selectivity for 1-octene. Raising the bulkiness of the alkyl

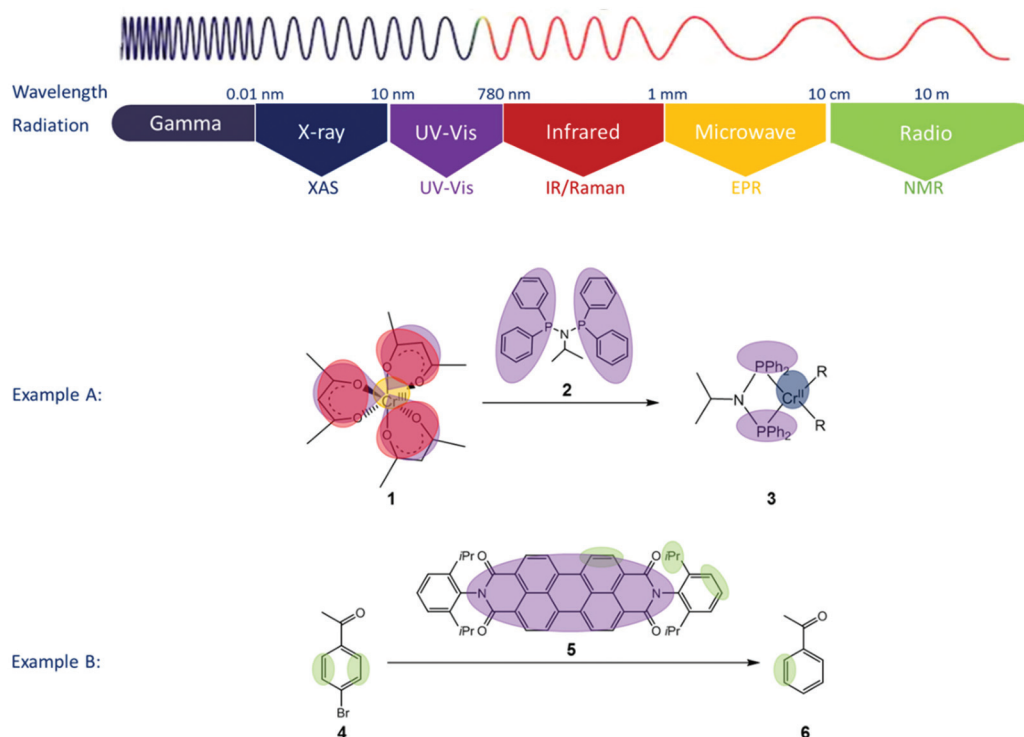


Fig. 1 Examples for the application of multiple *operando* and *in situ* techniques. A: Investigation of the influence of activators on the performance of a chromium complex in ethylene oligomerization;⁸² B: exploration on the photoreduction of aryl halides.⁵⁸ Chemical bonds and atoms are colored corresponding to the detecting spectroscopic technique listed in the leading entry.



could promote the reduction to Cr^{I} . However, the ethylene consumption with AlEt_3 and $\text{Al}^{\text{I}}\text{Bu}_3$ was the same and slightly higher with AlOEt_3 . In order to elucidate the reasons for the decreased activity, *in situ* UV-vis, ATR-IR and XAS analysis were applied. Firstly, with $\text{Al}^{\text{I}}\text{Bu}_3$, the $[\text{acac}]^-$ ligand, which could facilitate further reduction of Cr^{II} to Cr^{I} , was detected using UV-vis spectroscopy, consistent with the *operando* EPR results. The ATR-IR results showed that in the case of AlR_3 activators, a ligand exchange between $\text{Cr}(\text{acac})_3$ **1** and the activator takes place followed by the formation of $\text{Al}(\text{acac})_3$ rather than the active Cr^{II} species, which was also observed by UV-vis. From the XAS results, it is evident that only with MMAO a bidentate coordination by two phosphorous atoms was observed, while with AlR_3 the larger alkyl groups partially hindered the complete coordination of the PNP ligand **2** to the chromium center. Hence, with the help of *operando* EPR and *in situ* UV-vis, ATR-IR and XAS spectroscopy, the low conversion when using the AlR_3 activator is found to be partially due to the formation of Cr^{I} instead of the active Cr^{II} species. However, the main influence on the chromium complex performance in this reaction system was proved to be the mode of PNP coordination rather than the Cr^{I} content.

It seems clear that approaches which integrate multiple techniques together can provide a more complete picture of the reaction system.⁸³ Two or more techniques are applied simultaneously to supplement or contrast each other, improving the quality of the obtained information. Gschwind's group developed a novel fully automated setup that skillfully integrated illumination with *operando* NMR and UV-vis spectroscopy, which enables the simultaneous and time-resolved detection of paramagnetic and diamagnetic species.⁵⁸ This setup was applied for the study of the photoreduction of aryl halides **4** with PDI **5** as photocatalyst (Example B, Fig. 1). During the illumination, *operando* UV-vis spectroscopy enabled the detection of PDI and the stable $\text{PDI}^{\cdot-}$ radical, while the proton NMR signals of the PDI core vanished completely. Therefore, the UV-vis data provided time-resolved information about the photocatalyst that was invisible to NMR spectroscopy. In the meantime, the *operando* NMR spectra supplied full quantitative and structural insight into the diamagnetic reactant and product **6**.

In general, the selection of *operando* techniques is determined by the nature of the targeted species, reaction conditions and other specific issues caused by the particular reaction. Therefore, it is crucial to investigate the catalyst, reactants and reaction conditions by the optional techniques considered in advance. The most common technique for reaction monitoring is NMR, which can be applied under high pressure, but it is not applicable for paramagnetic species. Instead, EPR spectroscopy can only detect species with unpaired electrons. Raman and IR spectroscopy provide complementary information about the vibrational state of molecules, in particular when metal complexes are participating in catalytic reactions. UV-vis spectroscopy gives limited information about the molecular structure, but for those com-

pounds having UV-vis chromophores, it is still a useful tool for supplementing information for other spectroscopy. XAS spectroscopy enables to inspect the stereo-structure coordination environment around a working state, but low sensitivity and discriminating elements from the same periodic row limit its information content. ESI-MS, which transfers ions directly from the solution to the gas phase with efficiency and gentleness, can provide proper snapshots of the ion composition of the reaction solutions. Repeatable sample preparation is required for reliable ESI-MS result.

2.3. *Operando* techniques for monitoring molecular homogeneous electrocatalysis

With the rising relevance of the chemical conversion of renewable energy, the field of homogeneous electrocatalysis is increasingly gaining in importance, especially with regard to the activation of small molecules such as CO_2 , N_2 , O_2 and H_2O . Special analytical techniques are available to investigate electrocatalytic systems. They are tailored to the specific features of these reactions, such as the central role of electron transfer processes or the fact that electrocatalytic events mostly occur within a reaction diffusion layer at the vicinity of the electrode rather than in the bulk. The most relevant methods are shortly introduced below. For interested readers, recent reviews^{84–90} give a detailed overview about the potential of the application of these techniques in the *in situ/operando* context to help understand catalytic mechanisms and deactivation processes.

Analytical voltammetries, among which cyclic voltammetry (CV) is the most popular, can be applied to investigate mechanistic aspects of catalytic systems involving electron transfer reactions. The energy needed to oxidize or reduce a molecule is measured by recording the current passing through an electrolyte containing the analyte as a function of an applied potential. Even though no direct structural information can be obtained from CV measurements, the resulting voltammograms provide information namely about the redox nature of the catalytic species, reaction kinetics regarding chemical and electrochemical (electron transfers) steps or catalyst deactivation.^{84,85,87,90}

The field of *operando* **spectroelectrochemistry (SEC)**^{84–90} involves the utilization of the spectroscopic tools described above, often in specific setups adapted to the needs of electrocatalytic reactions. The most widespread are IR and UV-vis, as they are easily accessible in most laboratories. The development of dedicated cells and beamline setups have also made Raman, fluorescence, EPR, NMR and XAS available. A special technique within the SEC analysis of molecular catalyst is the application of sum-frequency generation (SFG), where two lasers operating at different frequencies generate a beam in a nonlinear optical interaction of the involved photons. It is extremely sensitive to molecular orientations near an electrode surface and therefore a particularly informative method.⁸⁹ Transient absorption spectroscopy (TAS), where a the formation of an excited state is generated by a flash of light, trig-



gering for example an electron or proton transfer, can detect short-lived intermediates and resolve reaction kinetics on pico-second scales.⁸⁷

3. Mathematical methods for signal resolution in spectroscopy

Whilst providing great insights into the behavior of chemical systems, *operando* spectroscopic measurements retrieve responses of challenging interpretation. The overlapping of signals characteristic of spectroscopy requires chemometric approaches for the resolution of the signals and allocation to individual chemical species. Several authors have tackled the challenge of processing the entangled sets of data obtained from measurements, for which a number of advanced numerical approaches have been proposed.

In general, multivariate curve resolution (MCR) analysis is based on the following matrix expression:

$$D = CS^T + E \quad (1)$$

where D contains the experimental spectra, C the pure concentration profiles and S^T the pure spectral profiles. E is an error matrix including the deviations not explained by the resolved components. It is worthwhile mentioning that in the case of the signals generated in spectroscopic methods, the underlying analytical model for eqn (1) is formally bilinear accounting for pure signal contributions (the Beer–Lambert law). Whilst bilinear models can also describe well chromatographic and other analytical measurements like electrochemical data, they are widely applied to spectral data sets.^{20,91} To solve eqn (1), the chemometrics literature has developed curve resolution methods based on whether there is a specification of the profile shapes within the signals or not. Table 1 presents a number of selected methods commonly used.

A method is referred to as soft-model if there is no constraint to the profile shape. These models describe processes empirically without prior knowledge of the underlying phenomena, which avoids errors derived from wrong assumptions. Conversely, the drawback is the intensity and rotational ambiguity of the profiles, which becomes relevant when different chemical species show similar profiles.^{91,101}

In non-iterative soft models, the sequential structure of concentration profiles is obtained combining subsets of information from the global and local ranks. Such subsets correspond to certain concentration windows or regions of the original data matrix with particular properties, such as the presence or absence of chemical species in the systems.^{19,20} Examples of these models include window factor analysis (WFA),⁹² subwindow factor analysis (SFA)⁹³ or heuristic evolving latent projections (HELP).⁹⁴ However, the use of these algorithms is currently in decline owing to the difficulty of setting the concentration or spectral windows in multicomponent datasets and non-sequential orders or with unstructured concentration directions.^{19,20}

For their part, iterative approaches optimize initial estimates of concentration values or the corresponding spectra imposing a series of constraints until a convergence tolerance is reached. Typically, these models are referred to as multivariate curve resolution-alternating least squares (MCR-ALS).^{20,102} Among them are key set factor analysis (KSFA),⁹⁵ simple-to-use interactive self-modelling mixture analysis (SIMPLISMA)⁹⁶ or interactive principal component analysis (IPCA).⁹⁷ They are preferred to non-iterative for not requiring a structured concentration direction and, more significantly, the fact that the implementation of constraints can be made in the optimization process. These constraints can contain chemical or mathematical information, such as non-negativity of profiles, unimodality, closure of mass-balances, correspondence of species, calibrations, *etc.* In turn, this means that soft iterative models open the door to the application of hybrid soft-hard models, particularly MCR-ALS.^{20,101} This is the case of the work by Cruz *et al.*, who developed a MCR-ALS method with multiple hard constraints to elucidate kinetic parameters of the homogeneously catalyzed Heck reaction between iodobenzene and *n*-butyl acrylate catalyzed by Pd-based complexes measuring FTIR spectra.¹⁰³

Despite the overall good performance of the methods addressed above, there are drawbacks to spectral resolution. These include the weak signals displayed by minor species, the presence of components with a high degree of spectral overlap and the possible non-linearity of the spectra. A different approach named band-target entropy minimization (BTEM) was developed to face these issues, with implementation in *in situ* spectroscopic investigations.^{98,104,105} BTEM is based on the subsequent reconstruction of pure component spectra by singular value decomposition of the original data set according to eqn (2):

$$D = U\Sigma V^T \quad (2)$$

U and V^T are matrices containing the left and right singular vectors of the data and Σ is a diagonal matrix of singular values. The right singular vectors are searched for interesting spectral features, whose relevant spectral channels are named band targets (BTs). For each BT, the algorithm finds a linear combination of the selected vectors that satisfy minimum entropy, and non-negativity of the spectra.⁹⁹ BTEM has the additional advantage of not requiring initial estimates of the number of species present, which helps the elucidation of complex reaction mechanisms.^{21,105}

Recently, a comparison between MCR-ALS and BTEM was published, where the authors implement the use of these techniques separately and jointly to mass and UV-Vis spectra as well as Raman images. The conclusion reached is that the two methods performed well in all cases, although MCR-ALS performed better for UV-vis spectra and was more robust to noise. On the other hand, BTEM led to more accurate profiles in Raman and mass spectra data sets as well as being better at reducing the rotational ambiguity of data.⁹⁹ BTEM had previously been compared to MCR techniques to obtain the pure



Table 1 Summary of selected algorithms used for the resolution of concentration signals from different spectroscopic measurements

| Classification | Method | Description | Application example | | Ref. |
|-------------------------------|---|--|--|---|---------------|
| | | | Description | Analytical techniques | |
| Soft-model/non-iterative | Window factor analysis (WFA) | The concentration profiles are obtained from the original data set and the window at concentration equals zero. This way, a vector with the spectral variation of the component of interest is calculated and, combining with the original data set, the concentration profile can be determined. | Resolution of 7 bismuth species in flow injection experiments | UV-vis | 92 |
| Soft-model/non-iterative | Subwindow factor analysis (SFA) | The method retrieves the pure response profile of each component using the knowledge of the concentration windows. The pure component spectra of each species are calculated as the intersection of two subspaces with only that compound in common. | Resolution of 4 components of a polyaromatic mixture | HPLC-DAD | 93 |
| Soft-model/non-iterative | Heuristic evolving latent projections (HELP) | It starts finding a selective concentration region for the component to be resolved. Such region provides directly the component spectrum and the concentration profile is recovered from this selective region as well as the zero-concentration window. The algorithm then recovers concentration profiles one at a time by subtraction of the contribution of the resolved compound. | Resolution of mixtures of drug isomers | HPLC-DAD | 94 |
| Soft model/iterative approach | Key set factor analysis (KSFA) | The strategy is to properly select pure wavelength columns applying principal component analysis (PCA) on the set of mixture spectra. A column of normalized PC values is obtained dividing the spectra by the length of the PCs at a wavelength value. This procedure emphasizes the purest wavelengths, from which the compounds can be determined in subsequent order. The main issue is dealing with spectral noise, since regions of low absorbances may yield large random signals. The processing of the original spectra does not use PCA. The user must select a pure wavelength and an average spectrum is calculated from the mixture spectra. The difference between the average and each of the mixture spectra determines a standard deviation. Then, in subsequent iterations, pure spectra for the pure wavelengths are resolved depending on the magnitude of the standard deviation. As in KSFA, the main difficulty is setting a correct noise level, which affects resolution. | Effect of solvent in ^1H NMR shifts of substituted methanes; retention indices for a set of ethers in different stationary phases; resolution of mass spectra of mixtures of aromatic compounds | NMR, GC, HPLC, mass spectrometry | 95 |
| Soft model/iterative approach | Simple-to-use interactive self-modelling mixture analysis (SIMPLISMA) | Developed from a combination of KSFA and SIMPLISMA to determine the pure wavelengths and predict the components. This method gives a good estimate of background noise and improves the signal to noise ratio. However, for minor components, spectral predictions are improvable. | Elucidation of the reaction mechanism for the synthesis of 4-amino-3,5-dimethyl pyrazole | ATR-FTIR | 96 |
| Soft model/iterative approach | Interactive principal component analysis (IPCA) | It is based on singular value decomposition obtaining the resolved curves sequentially until no additional spectra can be retrieved. The method searches for spectral patterns with the least information entropy. An initial estimate of the observable species is not a prerequisite, it does not rely on the concept of pure wavelength and it can resolve minor species in the analyzed system. | Esterification of 2-propanol and acetic anhydride; analysis and mixture of gases in natural gas | FTIR (mid IR data and near IR) | 97 |
| Soft model/iterative approach | Band target entropy minimization (BTEM) | | Monitoring hydroformylation reactions with organometallics (Rh-based); spectral resolution of mixtures of highly overlapping organics; analysis of Raman images of kidney calculi | FTIR, mass spectrometry and Raman imaging | 21, 98 and 99 |



Table 1 (Contd.)

| Classification | Method | Application example | | Ref. |
|----------------|--------------------------------------|---|-----------------------------|------|
| | | Description | Analytical techniques | |
| Hard model | Complemental hard modeling (CHM) | It is an IHM method whose starting point is an incomplete nonlinear model to which additional peak functions are complemented rather than having a difference spectrum calculated. After each complementing step, both the partial model and all complementary peaks are regressed at the same time with a non-linear least squares fitting. This enables the incomplete model to interact with the unknown pure component model throughout the process and a correct allocation of the unknown spectrum to the mixture spectrum. | FTIR and Raman spectroscopy | 100 |
| Hard model | Hard modeling factor analysis (HMFA) | It can identify all pure spectra in a completely unknown mixture from a limited set of mixed spectra. The method first estimates peak functions, but requires the presence of a distinctive peak for every component, even if it overlaps with the spectra of other components. Advantageously, HMFA does not require initial guesses for concentration profiles or pure spectra. | FTIR and Raman spectroscopy | 100 |

FTIR spectra in a mixture of six organic compounds. In this case, BTEM outperformed SIMPLISMA and IPCA not only in the ease of use (not requiring initial estimates), but also because the latter two methods resolved spectra including negative values for certain components.¹⁰⁶ Nevertheless, there are few pieces of work that compare data sets of similar nature with these numerical methods, which makes it difficult to establish a much desirable direct relationship or identification between the suitable algorithms to be used depending on the spectroscopic technique used.

MCR methods often provide non-unique solutions. This in turn means that many authors have accepted the output of these algorithms without pondering over the actual significance of the results and whether there could be a range of other possible results. Characterizing an area of feasible solutions (AFS) for 2-component systems is relatively simple, but for systems comprising more components this calculation becomes far more complicated. For 3-component systems, different algorithms based on the variation of the area of polygons have been applied, including Borgen plots, the triangle-boundary-enclosure algorithm or the polygon-inflation methods.^{107,108} For 4-component mixtures the sliced-triangle-boundary-enclosure and the polyhedron-inflation algorithms have been reported.^{107,108} Finally, for higher number of components, the so-called ray casting method has been proposed.¹⁰⁹ In this context, it is relevant to highlight the work by Sawall, Neymeyr and collaborators, who have implemented methods into the software FACPAC.¹⁰⁷

Contrary to soft models, hard models rely on physico-chemical constraints, thereby retrieving parameters with fundamental significance. These methods provide very insightful results if the proposed model is plausible, such as equilibrium or kinetic rate constants. On the other hand, their main weakness is precisely that prior knowledge of the chemical system is expected; otherwise, data regression can evolve into cumbersome trial and error. An additional disadvantage of these models is that they cannot be applied with unmodelled noise or spectral artifacts like a baseline drift.^{19,101}

Marquardt *et al.* developed significant work on hard models, first introducing what they called indirect hard modeling (IHM). This consisted of a nonlinear spectral model, using the Voigt functions to describe the convolution of peaks, and a linear calibration to predict the concentration from pure component weights. IHM allows accounting for nonlinear effects such as peak variations or spectral shifts.¹¹⁰ Within the IHM methods, they developed complemental hard modeling (CHM), especially indicated to obtain a single unidentified pure component spectrum in a mixture where the rest of the components is known. Additionally, hard modeling factor analysis (HMFA) has been proposed. In this method, all pure component spectra can be deduced from unordered data with correlated concentration profiles if there is at least one peak per component that does not occur in any other pure component spectrum (although this distinctive peak can be highly overlapped with others).¹⁰⁰



4. Cases of *operando* deactivation studies in hydroformylation and asymmetric hydrogenation

Operando spectroscopic techniques, optionally assisted by mathematical deconvolution of the complex spectral data, have been applied to various molecularly catalyzed reactions. As an example, the aerobic oxidation of alcohols can be mentioned. Multi-technique *operando* studies by the groups of Stahl on the Pd-catalyzed¹¹¹ and Brückner on the Cu-catalyzed aerobic oxidation^{112–114} have contributed significantly to a deeper mechanistic understanding of the reaction.¹⁴ Other reactions that are relevant in industrial application and for the transformation towards a sustainable chemical economy, like hydroformylation and asymmetric hydrogenation, were likewise subjected to extensive studies, also to investigate deactivation mechanisms. In this section a comprehensive description of the previously described *operando* spectroscopic techniques used to unravel deactivation mechanisms in hydroformylation and asymmetric hydrogenation are given.

A lot of knowledge about deactivation processes in these two reactions has been gained from experiments using classic *ex situ* analysis. The systematic variation of reaction conditions, the use of distinct substituents¹¹⁵ or isotope labelling studies^{116,117} are helpful tools to deepen the insights gained from this strategy.

Kinetic investigations of deactivation reactions can be performed in the same manner, taking samples during the reaction or repeating the same experiment with different reaction times.¹¹⁵ Another possibility is the measurement of uptake of a specific gas, e.g. O₂¹¹⁸ or H₂.^{119–121} The observation of colour changes during the reaction has also been used to draw conclusions about the time of formation of inactive species.^{115,119}

In contrast, the *in situ* and *operando* technologies described above allow for direct spectroscopic measurements while catalyst species are forming or decomposing and therefore provide particularly realistic insights to reaction and deactivation mechanisms of molecular catalysts.^{7,8} Generally, these measurements can be conducted by connecting a suitable analytical device to a reactor¹²² or by the performance of chemical reactions directly in measuring cells such as NMR tubes.^{123,124} Some relevant practical applications are presented in the following sections.

4.1. Rh-Catalyzed hydroformylation

The hydroformylation of olefins (see Fig. 2) is one of the most prominent examples for molecularly catalyzed reactions, yielding more than 10 million tons of aliphatic aldehydes per year. Phosphine modified Rh catalysts allow for high activities as well as selectivities and operate under mild reaction conditions. Other features of the reaction, such as high atom efficiency, availability of efficient recycling concepts, applicability to the conversion of sustainable resources and the suitability to combine a hydroformylation step with other reactions in a tandem catalysis to form tailor-made value products,

make hydroformylation a highly interesting field of modern research with regard to sustainable chemistry.⁶

Deactivation processes in hydroformylation reactions have been extensively reviewed.^{3–6,125} It is noticeable that even in very recent publications on the topic,⁶ the majority of cited works are from the years before 1990 and result from *ex situ* analytical investigations.

The main focus of most *operando* spectroscopic studies in hydroformylation catalysis has been on the investigation of mechanistic and kinetic aspects. Some authors^{126–128} also describe the observation of deactivation processes. The use of *operando* technology for the targeted investigation of deactivation mechanisms in hydroformylation catalysis is, however, rare. Appropriate examples highlighting the potential of such studies are illustrated below. A graphic summary of most discussed deactivation products and their role in the catalytic hydroformylation cycle (species **8** to **10**) can be found in Fig. 3. Infrared spectroscopy – being especially powerful when it comes to monitoring metal carbonyls – is the most frequently applied technology, but there are also examples for the use of NMR spectroscopy.

One of the first studies using *in situ* spectroscopy to investigate hydroformylation catalysts was published in 1968 by the group of Wilkinson.¹²² They were able to identify species formed from RhH(CO)(PPh₃)₃ that are only stable under CO atmosphere by connecting an IR cell to an autoclave containing stoichiometric concentrations of the catalyst under atmospheric CO and/or H₂ pressure. Among these species was a carbonyl-bridged dimeric Rh carbonyl phosphine species, the so-called “yellow dimer” (**11**).¹²⁹ The formation of this species was reversible upon the addition of H₂.

Moser placed a cylindrical internal reflection (CIR) crystal into a stainless-steel autoclave, allowing for measurements directly in the reactor.¹³⁰ He was able to observe the formation of an inactive dimer **12** under 1-hexene hydroformylation conditions leading to deactivation of the system.¹²⁶ Moderately high catalyst concentrations of 0.01 M rhodium were applied in this setup. The formation of inactive dimers and clusters has also been observed by other groups^{106,131,132} using *operando* transmission infrared spectroscopy.

Kiss and Horvath combined high-pressure IR and NMR spectroscopy to study a Rh catalyst system modified with the tripodal triphos ligand (CH₃C(CH₂PPh₂)₃). At typical hydroformylation conditions, they showed a reversible dissociation of one phosphine arm of the tripodal ligand in RhH(CO)[η³-CH₃C(CH₂PPh₂)₃] (**7a**) to form RhH(CO)₂[η²-CH₃C(CH₂PPh₂)₃] (**7b**) under high pressure of CO. This process can lead to a loss of n:iso selectivity in triphos-modified hydroformylation catalysis.¹³³

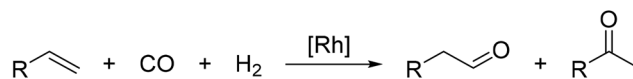


Fig. 2 Rh-Catalyzed Hydroformylation of a terminal olefin.



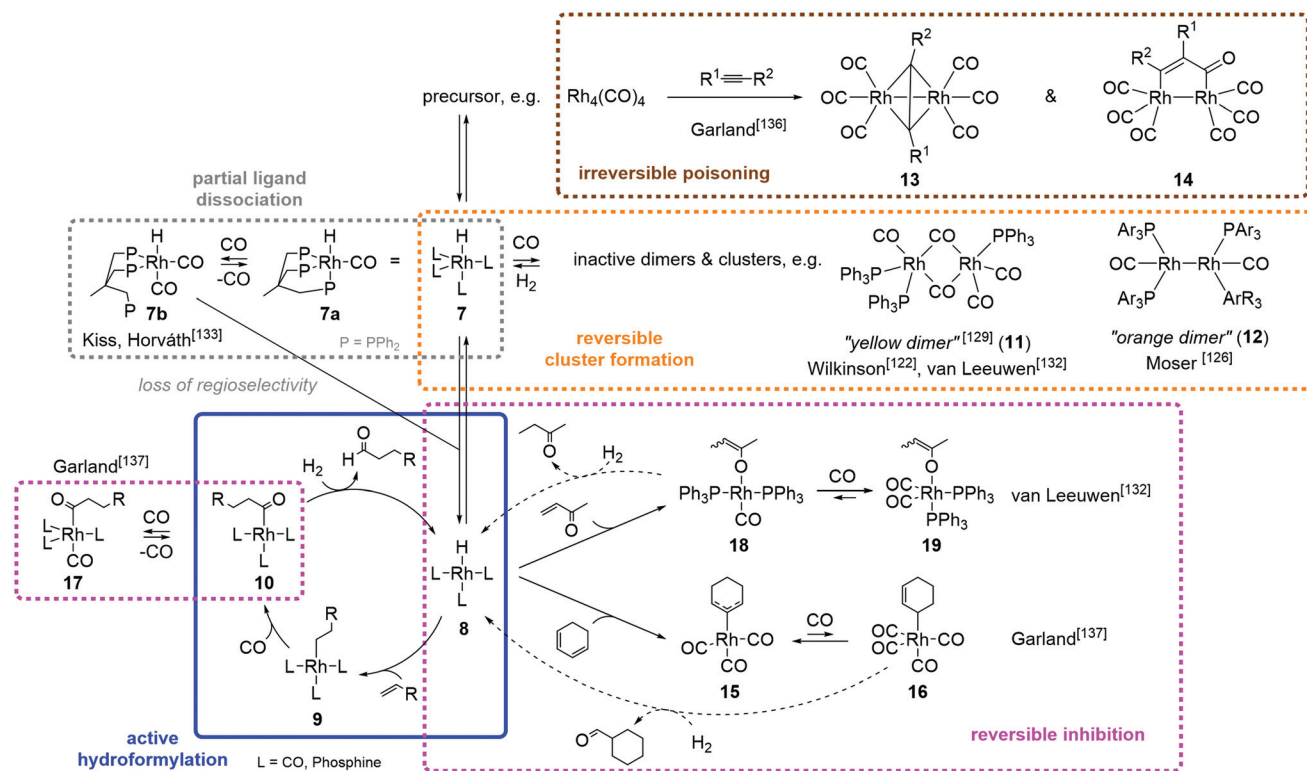


Fig. 3 Examples of deactivated catalyst species and their formation pathways in the Rh catalyzed alkene hydroformylation observed by *operando*/in situ spectroscopic methods. The ligand L can be CO or different phosphines, in different ratios for every compound and varying for each system.

The group of Garland has greatly contributed to demonstrate the power of chemometrics in the field of *operando* spectroscopic monitoring of molecular catalyst by the development of the BTEM algorithm (*cf.* Section 3) and also the provision of illustrative application examples thereof.^{105,134,135} With regard to catalyst deactivation, the group investigated the influence of alkynes¹³⁶ and dienes¹³⁷ on the unmodified $\text{Rh}_4(\text{CO})_{12}$ hydroformylation catalyst. Being more reactive towards the catalyst, these typical alkene feedstock impurities block the catalytic activity for alkene hydroformylation. In a first study,¹³⁶ $\text{Rh}_4(\text{CO})_{12}$ was reacted with 20 structurally varying terminal and internal alkynes under CO pressure. The forming catalyst species were monitored by connecting a high-pressure infrared transmission cell to the autoclave. The deconvolution of multicomponent spectra was achieved using Gauss–Lorentz areas as basic functions. It showed only two repeating absorbance patterns for the different alkynes, which were assigned to the dinuclear complexes **13** and **14** where R^1 and R^2 represent the substituents of the respective alkyne. Both complexes showed high stability in the presence of H_2 gas, so that the catalyst deactivation can be interpreted as irreversible poisoning.¹³⁶

In a similar work, $\text{Rh}_4(\text{CO})_{12}$ was exposed to a series of conjugated dienes both in non-competitive situations and as impurities under *cis*-oct-4-ene hydroformylation conditions. Spectral deconvolution was carried out using a precursor version of BTEM, suggesting the presence of at least three

mononuclear species which do not occur in the hydroformylation of uncontaminated alkenes. The authors suggested to assign them to an η^3 -allyl rhodium tricarbonyl species **15**, a σ -allyl rhodium tetracarbonyl species **16** and an acyl rhodium tetracarbonyl species $\text{R}'\text{CORh}(\text{CO})_4$ (**17**, R' = alkenyl and/or formylalkyl).¹³⁷

The group of van Leeuwen has developed a special autoclave to conduct *operando* transmission infrared spectroscopic measurements of fast catalytic reactions.⁴⁷ In 2003, the group used this cell to investigate the deactivation of a $\text{Rh}(\text{acac})(\text{CO})_2/\text{PPh}_3$ hydroformylation catalyst system by alkynes, dienes (Fig. 4) and, in particular, enones.¹³² Just like alkynes and dienes, enones have a higher affinity to the rhodium catalyst than olefins, blocking its active hydroformylation sites. In phosphine modified catalyst systems, the aforementioned compounds undergo slow hydroformylation themselves, so that the catalyst deactivation is only temporary; it is reactivated as soon the impurity has been completely converted. Besides the formation of the inactive “yellow dimer”¹²² mentioned earlier, the formation of an inactive carboalkoxyrhodium species **19** formed from the reaction of $\text{RhH}(\text{PPh}_3)_2(\text{CO})$ (**8**) with 3-buten-2-one could be shown.

Supplementary *in situ* ^1H , ^{13}C and ^{31}P NMR experiments conducted at low temperatures (80 °C to 20 °C) allowed for the identification of several intermediates of the deactivation process, also assisted by the simulation of spectra.¹³²



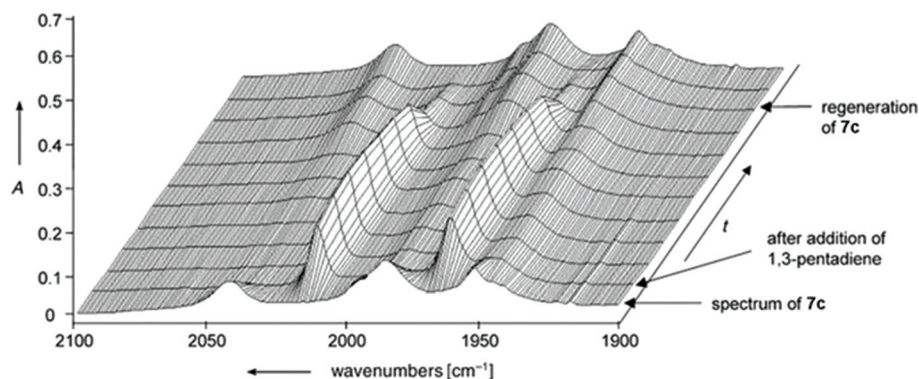


Fig. 4 Reversible inhibition of hydroformylation catalyst $\text{RhH}(\text{CO})_2(\text{PPh}_3)_2$ (**7c**) in the presence of 1,3-pentadiene monitored by *operando* HP-IR.¹³² Reproduced with permission from John Wiley & Sons, Ltd.¹³⁸

The monitoring of catalyst deactivation in continuous flow was realized by our own group.⁵⁵ A comparative study of different setups implementing both high pressure transmission and attenuated total reflection (ATR) IR spectroscopy in a batch setup and a continuously operated miniplant was presented. All four resulting setups were tested under authentic reaction conditions for the hydroformylation of 1-dodecene with a Rh/BiPhePhos catalyst. A special challenge in the continuous setup proved to be the realization of a very precise dosing strategy which is necessary for the spectral deconvolution *via* BTEM (*cf.* Section 3). While the sensitivity of the ATR-IR probe turned out not to be sensitive enough to monitor catalyst in the continuous setup, a spectral estimate for a metal organic species was detected with the other three setups. The comparison with simulated spectra obtained from DFT calculations suggested that it is actually caused by two or more metal organic phosphine species. The decay of these species can be connected with the simultaneous loss of regioselectivity of the hydroformylation reaction on the continuously operated miniplant, as can be seen in Fig. 5.

An illustrative example demonstrating the potential to enhance catalyst performance by in-depth understanding of the system's deactivation pathways and corresponding rational adaption was provided by the group of Börner. Phosphites represent a particularly active class of ligands in the *n*-regio-selective hydroformylation. Unfortunately, they are prone to hydrolysis by nucleophilic cleavage of the P–O bond. To study the hydrolysis reactions of hybrid bidentate phosphite ligand **21** (Fig. 6), *in situ* NMR spectroscopy was performed directly in an NMR tube under elevated temperatures. The acylphosphite unit (red) of the ligand proved very sensitive towards water, while the phenolphosphite part (blue) is more stable. The detailed understanding of the hydrolysis pathway of **21** allowed for a rational modification of the backbone of the acyl unit, giving a ligand **22** of much higher hydrolysis stability.¹²⁴ In a separate study, the group investigated the effect of substitution patterns on the reactivity and hydrolysis stability, showing the stabilizing effect of substituents in *ortho*-position, especially *tert*-butyl substituents.¹⁴⁰ An additional surprising discovery was that the coordination to rhodium seemed to stabilize

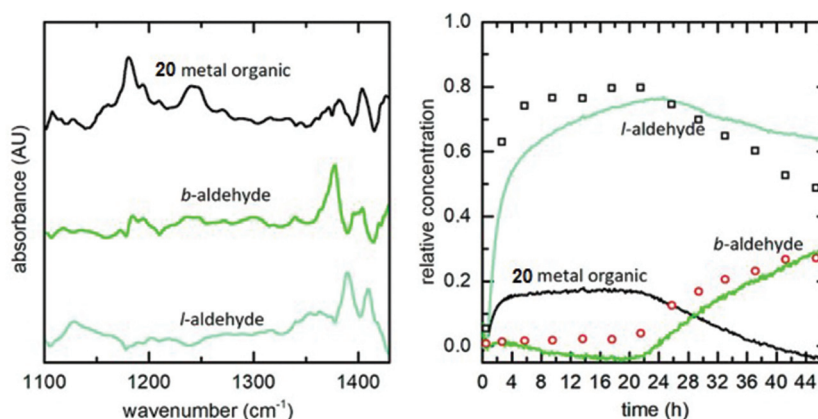


Fig. 5 Single component spectral estimates for the hydroformylation of 1-dodecene catalyzed by Rh/BiPhePhos monitored by *operando* high pressure transmission IR spectroscopy (left) and corresponding concentration profiles (right). The decline in regioselectivity occurs simultaneously with the loss of metal organic species **20**.⁵⁵ Reproduced and adapted with permission from the American Chemical Society.¹³⁹



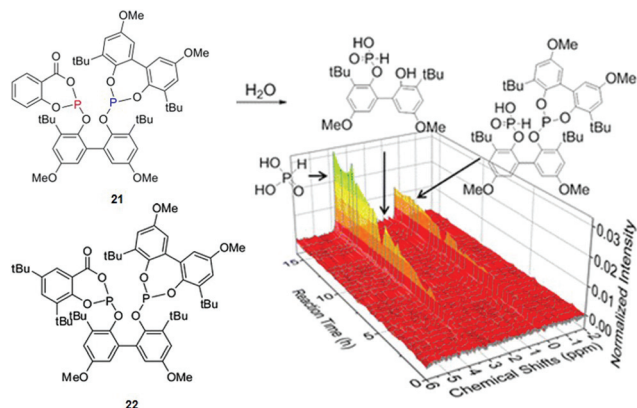


Fig. 6 *In situ* ^{31}P NMR spectra of the hydrolysis of 21 (100 equiv. of water, 120 °C) in the tetravalent oxide phosphorus (PV) region (left) and structure of modified and more stable ligand 22 (right).¹²⁴ Reproduced and adapted with permission from the American Chemical Society.¹⁴¹

monodentate ligands, while bidentate ligands such as 22 were destabilized towards hydrolysis.¹²⁴

4.2. Asymmetric hydrogenation

The asymmetric hydrogenation of C=C, C=O and C=N bonds is considered the most relevant enantioselective reaction,¹⁴² awarded with a Nobel prize for Knowles¹⁴³ and Noyori¹⁴⁴ in 2001. Instead, the use of catalysis for asymmetric hydrogenation has made it possible to form chiral compounds through its inherent atom efficiency without creating waste. The high enantioselectivity further reduces the need of complex separation processes for racemic mixtures contributing to the sustainable nature of such processes.¹⁴⁵

The first highly enantioselective catalysts used for the hydrogenation of C=C bonds were cationic rhodium complexes containing chiral chelating diphosphine ligands, such as Diop (2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenyl-

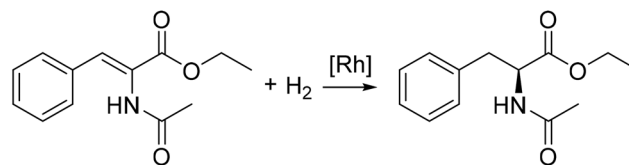


Fig. 7 Asymmetric hydrogenation of ethyl-(*Z*)- α -acetamidocinnamate to the amino acid derivative *N*-acetyl-(*S*)-phenylalanine ethyl ester.

phosphino)butane).¹⁴⁶ The mechanism of this reaction was deeply investigated in the late 1970's and early 1980's by Brown^{147–152} and Halpern^{153–155} using dehydroamino acids or esters as substrates.

In 1980 Halpern found that the main product of the hydrogenation of ethyl-(*Z*)- α -acetamidocinnamate with [Rh (chiraphos)][BF₄] is *N*-acetyl-(*R*)-phenylalanine ethyl ester even though the major complex occurring in the reaction would yield *N*-acetyl-(*S*)-phenylalanine ethyl ester (Fig. 7). Later, Halpern and Landis studied the kinetics of the hydrogenation of methyl-(*Z*)- α -acetamidocinnamate using dipamp as ligand to discover the origin of the enantioselectivity. Besides classic *ex situ* measurements, they performed reactions in NMR tubes to measure the equilibrium of the diastereomers and to monitor the hydrogenation reaction of the substrate adduct. A stopped-flow UV-vis apparatus helped determining the association rates of the substrates and measurement of the H_2 gas uptake under constant pressure was used for the determination of the catalytic hydrogenation rates. It was found that the reactivity of the diastereomers towards hydrogen is the origin of the enantioselectivity.¹⁵⁵

Besides mechanistic investigations, overcoming catalyst deactivation was a major issue early on in the development of asymmetric hydrogenation reactions. Examples are the use of iridium as catalyst metal¹¹⁹ or the realization of the technical production of the herbicide (*S*)-metolachlor, which is nowadays the most important enantioselective process with a capacity of 10 000 tons per year.²

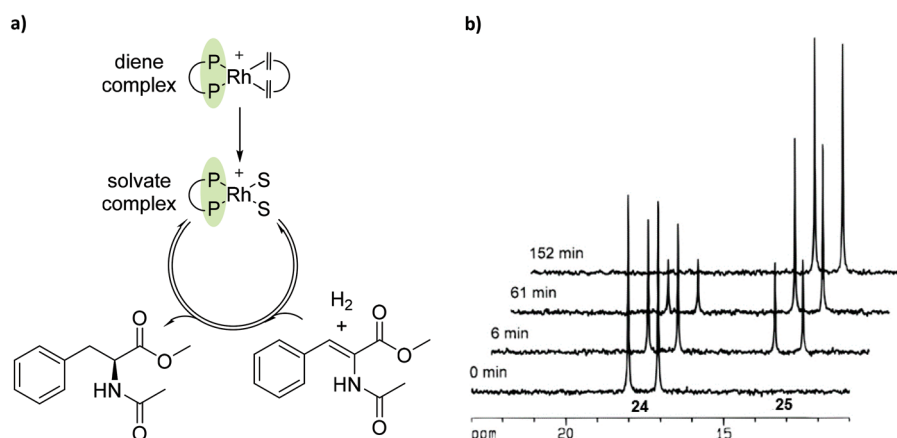


Fig. 8 Formation of the solvate complex which serves as starting point in the asymmetric hydrogenation and which was studied by Heller *et al.* (a). ^{31}P NMR spectra of the complexes 24 and 25 which are formed consecutively (b).¹⁵⁶ Reproduced and adapted by permission from John Wiley & Sons, Ltd.¹⁵⁸



Known deactivation mechanisms have been recapped in review literature.^{4,5} Next to classic *ex situ* investigations, measuring kinetics by monitoring gas uptake has helped to identify inhibition and deactivation processes.^{119,121} In particular, Heller *et al.* monitored the hydrogen uptake to investigate the induction period needed for the activation of catalyst precursors. In asymmetric hydrogenations precursors are commonly stabilized by diolefins like norbornadiene and cyclooctadiene. In a catalytic reaction with *in situ* formation of the active species, these diolefins need to be hydrogenated to form the active species. By monitoring the gas uptake in a reaction it was found that this induction period not only takes longer

than assumed but also that it differs for the stabilizing diolefin used.^{121,156}

In order to further examine these findings Heller *et al.* performed a Rh-catalyzed hydrogenation of a cyclooctadiene and norbornadiene mixture with a diop ligand *in situ* in an NMR cell designed for monitoring gas-liquid reactions. In this cell, constant bubbling of the reaction mixture with hydrogen is ensured without disturbance of the NMR signal by cutting a PTFE inlet pipe directly above the measurement region. Alternating ¹H and ³¹P measurements were conducted to monitor both the formation of the monoalkenes and the complexes present. They showed that norbornadiene complexes

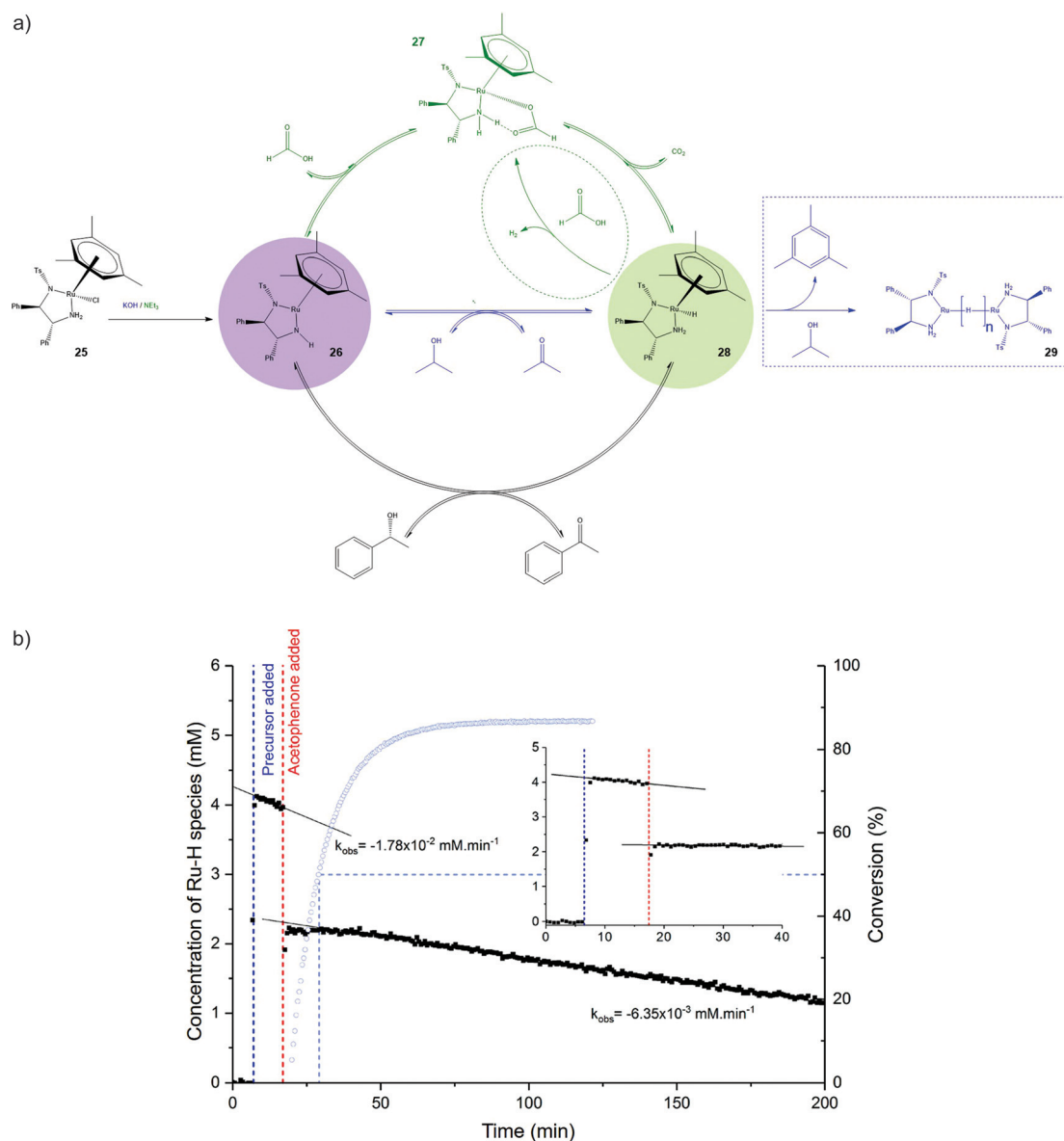


Fig. 9 (a) Catalytic cycle of the asymmetric transfer hydrogenation of acetophenone with isopropanol (blue) and formic acid (green) as H-donor including the proposed deactivation pathways (dashed), (b) concentration of in-cycle Ru-H species (28) (black) and conversion (blue) over time. The colored circles refer to the colour code introduced in Fig. 1.^{159,162} Reproduced and adapted with permission from the American Chemical Society.¹⁶³



(24) are formed first and afterwards, after hydrogenation of norbornadiene, the cyclooctadiene complexes (25) emerge (Fig. 8).¹²³ In a subsequent study Heller *et al.* used the same set-up to investigate the effect in the asymmetric hydrogenation of prochiral olefins using five-membered diphosphine Rh-catalysts. With this type of catalyst the difference in reactivity can be up to three orders of magnitude due to very slow hydrogenation of cyclooctadiene.¹⁵⁷ This difference has to be considered in the evaluation of catalyst activity of different catalysts since differences in TOFs might be caused by longer induction periods, not lower activity.

The studies by the group of Heller show how measurements of the gas uptake and conducting reactions in specifically designed NMR cells contributed to a deeper understanding of the nature of catalyst activation. Meanwhile, another *operando* study regarding the deactivation of Noyori's [(mesitylene)((*R,R*)-TsDPEN)-RuCl] catalyst (25) in the asymmetric transfer hydrogenation of acetophenone with isopropanol (Fig. 9a, blue) can serve as an example for the use of ¹H NMR and selective excitation techniques.¹⁵⁹ The Noyori type catalyst has many advantages, among them a high enantioselectivity at high reaction rates, and can be used with a variety of substances and auxiliary bases. It is, however, also known for deactivation.^{5,160}

For this reason, Hintermair and coworkers used an established FlowNMR *operando* setup³² for the investigation of transfer hydrogenation of acetophenone with this catalyst.¹⁵⁹ Starting point of the investigation was a Variable Time Normalization Analysis (VTNA)¹⁶¹ on catalyst concentration which showed deviations in a range between 50% conversion and equilibrium conversion, indicating catalyst deactivation at this part of the reaction. In order to gain insight into the deactivation mechanism, Hintermair *et al.* used a selective excitation method to monitor the concentration of the known in-cycle Ru-H species 28. By these means, its signal was amplified by >1000 times while allowing quantitative evaluation by linking the receiver gain to the integral of the hydride.

Following the course of the reaction by normal ¹H NMR measurements while tracking the amount of species 28 showed a decline in its concentration before addition of acetophenone and again a smaller decay when 50% conversion were reached (Fig. 9b), which corresponds to the results of the VTNA. The decay before addition of substrate indicates deactivation occurring from 28.

Conducting the hydrogenation reaction in deuterated solvents a liberation of mesitylene could be observed. As the rate of formation of free mesitylene corresponds to the decline of concentration of the Ru-H species and the chemical shifts and *T*₁ values of the deactivation product are in accordance with hydride-bridged dimers, Hintermair *et al.* propose that the formation of hydride-bridged dimers (29) by loss of mesitylene ligand is a major deactivation process of Noyori's type catalysts (Fig. 9a).

While this shows the power of a flow NMR setup in combination with signal enhancement techniques for *operando* studies, a consecutive work by the same group can be used as

a practical example of the use of multiple complementing techniques.¹⁶²

The authors investigated the same reaction but using formic acid as H-donor instead of isopropanol. The flow NMR setup from the previous study was expanded by a HPLC, a UV-vis spectrometer and a gas phase mass-spectrometer installed on the reactor. These techniques made a complete monitoring of the reactants possible. The gas phase mass spectrometer allowed tracking of the formation of CO₂ and H₂, the HPLC was used for measuring the enantiomeric excess, ¹H NMR for the determination of conversion, dissolved H₂¹⁶⁴ and again the Ru-H species 28. UV-vis spectroscopy allowed tracking of the intermediate 26 by a characteristic absorbance band.¹⁶²

The authors found a continuous formation of H₂ throughout the reaction and figured out that the formate species 27 is the major, stable intermediate in the reaction with formic acid as species 26 and 28 make up less than 2% and maximum 40% respectively of the total catalyst amount. Using this information about the catalytic species in the reaction system Hintermair *et al.* report that three reactions compete from species 28: a re-insertion of CO₂ forming species 27, hydrogen transfer to form the desired product and protonation to H₂, which consumes the substrate formic acid and is thus a side reaction lowering the reaction performance.¹⁶²

5. Conclusions and outlook

In this review, key techniques have been summarized to study molecular catalyst under reaction conditions in an *operando* approach in order to develop green processes. Spectroscopic methods like NMR, IR, EPR, Raman, UV-Vis or ESI-MS can individually give access to specific structural data that is important to gain information on the low concentrated molecular catalyst in a reaction system. To harvest the full information out of the spectroscopic data, different mathematical tools were introduced and compared. Most of them were used to give mechanistic insights of catalytic systems but can also be applied to give information on deactivation mechanisms also in continuously operated systems. These mathematical models differ mostly on initial constraints and therefore hard modelling methods need more prior knowledge of the system.

In two cases, the state of the art of *operando* studies in the investigation of deactivation in hydroformylation and asymmetric hydrogenation were summarized. In hydroformylation, mostly IR and NMR studies have been published to show resting states and dormant species. Also poisoning effects for the molecular rhodium catalyst have been investigated under reaction conditions. Deactivation processes have been described for the hydroformylation in a miniplant setup. The asymmetric hydrogenation was studied in detail by NMR techniques to detect the activation and deactivation of the molecular catalyst by tracing ligand structures.

These examples show the importance and potential of these studies to describe apart from the ideal catalytic cycle also the fate of the molecular catalyst under reaction con-



ditions. The activity and the lifetime of a catalyst is crucial for scaling and applicability in a process. Also, the design of more stable catalysts due to the *operando* data is a rare exercise in the molecular catalysis community. This technique will contribute to design sustainable processes by allowing to apply stable and selective molecular catalyst at mild reaction conditions.

The data of *operando* experiments highly depend on finding the best analytical method to detect the catalyst features at real reaction conditions. A challenge, in addition to high temperatures and pressures, is the usually low catalyst concentration that causes relatively small signals in comparison to substrates, products, solvents *etc.* Therefore, mathematical tools are handy to detect even traces by assigning single component spectra if needed.

In the future, the merging of the broad variety of spectroscopic techniques has to be applied to provide a deeper insight into the molecular catalyst at work. This data will show deactivation mechanisms that are at the moment only theory or are unknown. If these combined data are fed to algorithms, new insights can be gained and stable catalyst systems can be designed in the future. The development of data formats for *operando* data and wide while cheap availability of spectroscopic techniques play an important role to push these techniques into the production field. Also the ever improving processing of these vast data amounts makes it more attractive for the industry to work and learn from this approach.

Conflicts of interest

There are no conflicts to declare.

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