

In situ Analytics for Hydrogenation Reactions

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Abstract: The state of the art in industrial process analysis is illustrated with two examples. Process optimization with the help of infrared and Raman spectroscopy was carried out for the hydrogenation of 1-chloro-2-nitrobenzene. Process control helped to avoid the formation of side products in the hydrogenation of a hydrazone.

Keywords: *In situ* monitoring · Process optimization · Reaction control · Reaction kinetics

1. Introduction

Catalytic hydrogenations are transformations with considerable industrial importance. Common processes include the hydrogenation of olefins, aromatics and various unsaturated compounds, and the catalytic reduction of nitro groups to the corresponding amino compounds. Enantioselective hydrogenations are an attractive way to introduce chiral centers [1]. As for other reactions performed under high pressure, it is difficult to obtain timely information about the progress of the reaction. Sampling is a time-consuming procedure and labile intermediates tend to get lost, certainly when standard analytical techniques like NMR spectroscopy or liquid chromatography are used. This can make it impossible to obtain accurate information about the thermal safety of the reaction mixture. In this context, we see two main areas of appli-

cations for *in situ* analytics: process optimization in development departments and process control in the chemical production.

2. Process Optimization

Our vision is that process optimization done with the help of *in situ* analytics will result in a better understanding of the chemistry. Qualitative analysis will give information on the reaction pathway and quantitative analysis will result in a description of the chemical kinetics, of the thermodynamics and of the mass transport. The goal of *in situ* analytics is to obtain the concentration profiles of all relevant components in the reaction mixture.

Conventional analytical methods like NMR and liquid chromatography show good selectivity and resolution. As a consequence, only a small calibration effort is necessary. On the other hand, *in situ* measurements are not possible with these methods. This leads to a loss of information and to long analysis times. Direct *in situ* measurements with optical methods like infrared (IR) and Raman spectroscopy are often able to detect labile intermediates.

In order to obtain the concentrations of the components in function of time, the raw spectra have to be analyzed. Analysis of band heights provides quick insights, but only in rare cases does this allow a quantitative description of the concentration profiles. The reason lies in the fact that signals of different chemical

species overlap strongly in optical spectra and call for an elaborate analysis of the raw data: Deconvolution is needed. Very precise soft modeling methods are available where many samples of varying composition (spanning the complete parameter space that needs to be covered in the future) are measured consecutively both with optical spectroscopy and with an accurate reference method. In this way, the optical method is calibrated using 20–100 samples. After such extensive calibration work, the optical method is ready for use with typical analysis times of less than one minute.

Clearly, this is not an acceptable procedure for research and development laboratories. In such an environment, time for calibration must be reduced to a minimum. As a consequence, model-free methods, like self-modeling curve resolution (SMCR) [2][3], can be applied. They make use of the basic structure of the data which can be described by the Beer-Lambert law where the effects of individual molecules are considered to be linearly additive. The difficulty of this approach lies in the fact that there are more than 1000 parameters to be adjusted in order to find the one and only correct answer: the true concentration profile of all components in the reaction mixture. Additional help comes from the fact that spectra and concentrations are positive and concentration profiles are considered to be unimodal, *i.e.* not oscillating. SMCR has made considerable progress in the last few years. Whereas in the early days results strongly depended both on the spectral region selected in the raw

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data and on the type of data (Raman vs. IR), today's methods are much more robust.

Example: Hydrogenation of 1-Chloro-2-nitrobenzene

The example shown here is the hydrogenation of 1-chloro-2-nitrobenzene to form 2-chloro-aniline [4] (Scheme). The starting material was introduced with 9% concentration in methanol and the reaction was carried out under 1.1 bar of hydrogen with a Pt/charcoal catalyst. The reaction was monitored with IR and Raman spectroscopy simultaneously. Each data set (Raman, IR) was analyzed twice: once using the full spectrum and once using only half of the spectrum. Clearly, all four analyses must result in the same concentration profiles for reactant, intermediate, and product. Unfortunately, the SMCR algorithms did not provide us with unique results. Depending on the algorithm used, results vary significantly (Fig. 1): The estimate for the initial relative concentration of 1-chloro-2-nitro-

benzene varied from 8–65% when the older algorithm was used (Fig. 1a). The more recent SMCR algorithm yielded much better results (Fig. 1b): The initial relative concentration for the starting material was estimated to vary from 98–105%. As a matter of fact, pure starting material was used and initially neither intermediate nor product was present. Similarly, product concentration after 110 min was estimated by the older algorithm to lie between 60% and 80% (Fig. 1a), by the recent SMCR algorithm to lie between 98% and 103%, whereas we know that after 110 min all starting material was fully converted to product.

A more robust analysis is possible if more prior knowledge is used by the data analyst. The chemist is an excellent resource: he knows the chemistry that is run and often it is straightforward to describe the chemistry using a set of chemical equations. They form the basis for the kinetic equations used in the hard model. The advantage of this approach is that the number of free parameters is reduced

dramatically from over 1000 to less than ten. In addition, measures of quality can be developed that describe the performance of the data analysis. In the example shown here, the advantage of a hard model is obvious. Fig. 1c illustrates that all four data sets produce the same result within a few percent.

In Fig. 2 raw data points at three vibrational energies are plotted together with the calculated curves using the hard model. The quality of the fit can be judged from the even distribution of data points around the solid lines. After subtracting the fitted result from the raw data, only unstructured noise remains, see right hand side of Fig. 2. In other words, there are no systematic discrepancies between data and model.

With an analytical tool like this at hand, process optimization will become faster. The chemist, faced with the goal to reduce the amount of intermediate, can try several strategies and will obtain immediate results when using *in situ* analytics. Fig. 3 demonstrates a successful cata-

Scheme. Reaction scheme for the hydrogenation of nitro-aryl compounds. When 1-chloro-2-nitrobenzene is converted to chloro-aniline, considerable amounts of hydroxylamine accumulate, unless a co-vanadate catalyst is used.

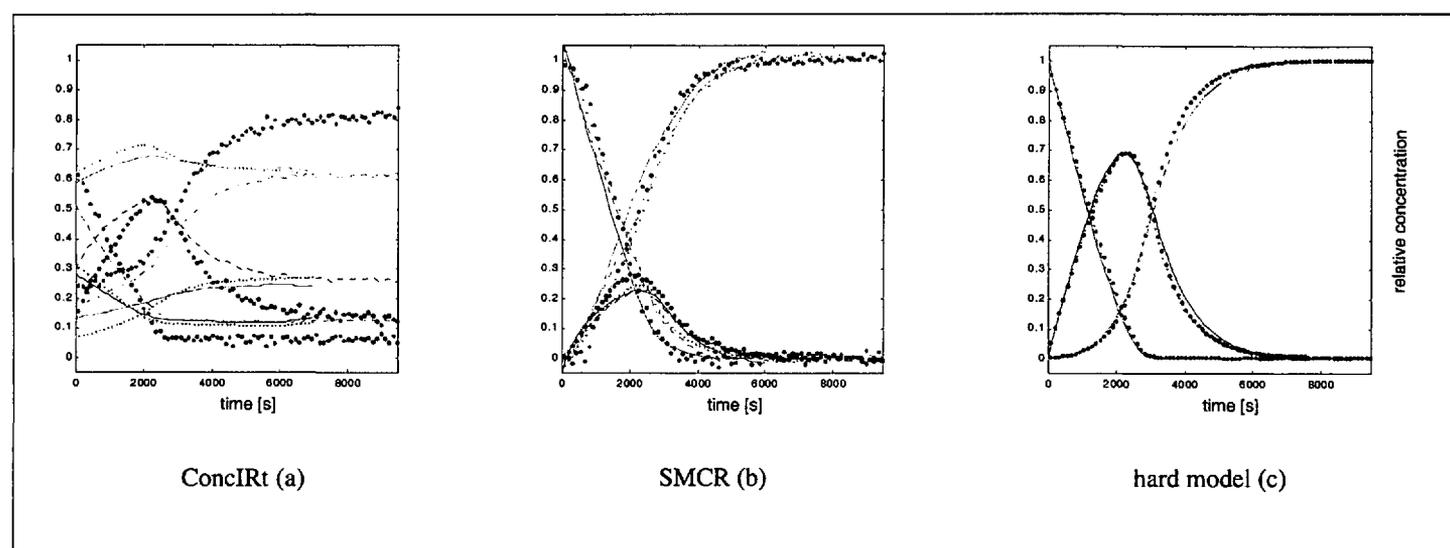
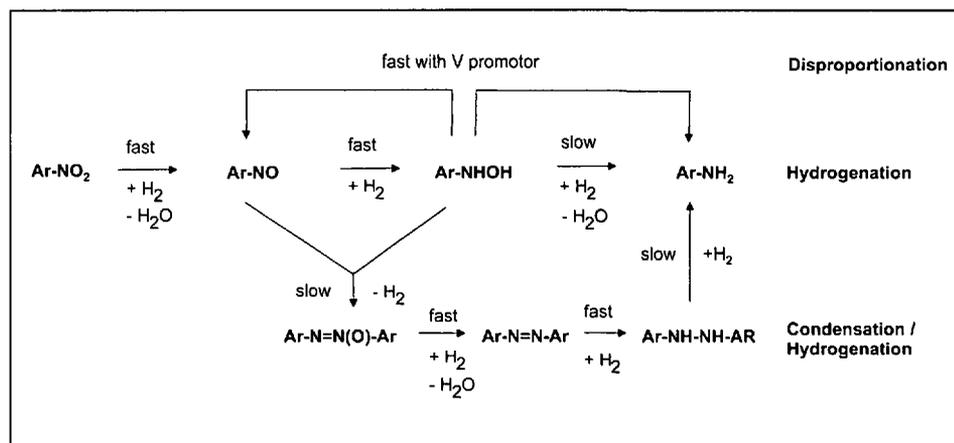


Fig. 1. Four sets of raw data from one run of the hydrogenation of 1-chloro-2-nitrobenzene are analyzed using three different algorithms: ConcIRT (a), SMCR (b) and hard model (c).

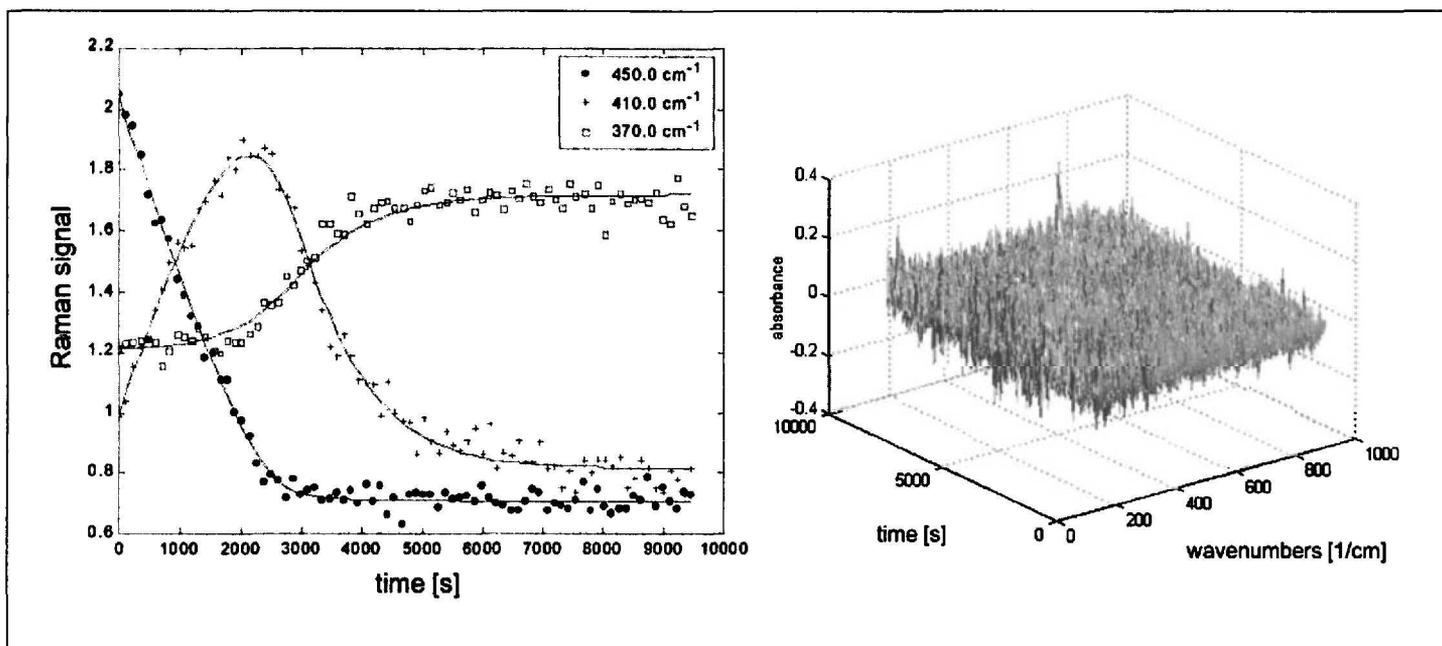


Fig. 2. The quality of the fit is illustrated: On the left hand side, the calculated Raman signals (solid lines) are plotted with the data at three vibrational energies. On the right hand side, the residual (the signal that cannot be explained by the model) is shown.

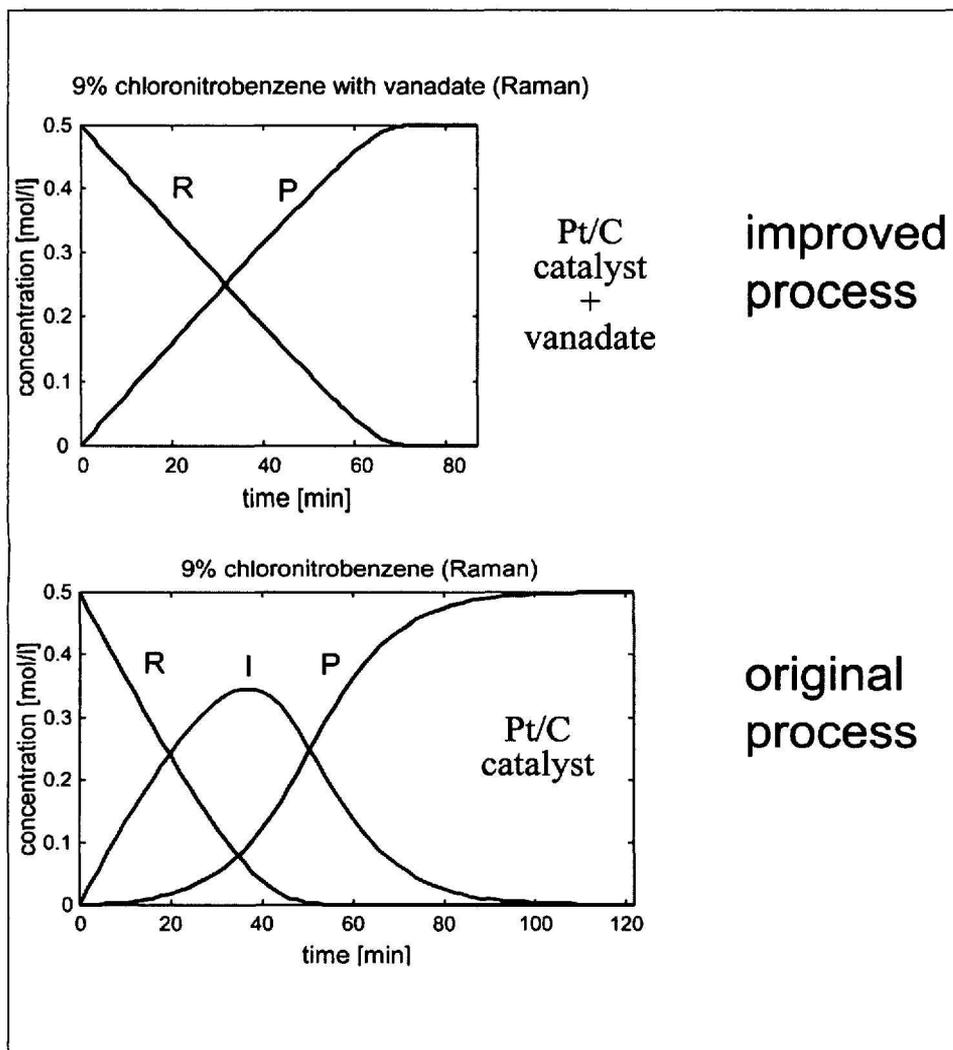


Fig. 3. Comparison of the optimized process with the original process; concentration profiles of reactant (R), intermediate (I) and product (P).

lyst optimization. The improved process resulted from the addition of a vanadate promoter to the reaction mixture. Not only was there no visible accumulation of the intermediate (hydroxylamine) but a reduced cycle time as well.

3. Process Control

Even after extensive process optimization has been performed, there are hydrogenation processes that need some kind of analysis while the process is operated. Many hydrogenation processes tend to generate more side product(s) after a certain time because the desired product is reduced further. Formation of side products has serious consequences for the profitability of the process: the addition of a purification step may be required and yield is reduced. A simple measurement for the progress of the reaction is monitoring of hydrogen consumption. On a technical scale, however, this is often not accurate enough. Since hydrogenation changes the degree of saturation, electronic absorption can be used to monitor the course of the reaction and here ultraviolet (UV) spectroscopy is the method of choice. Since UV absorptions tend to be very strong, highly diluted samples or very small optical path lengths must be used. The latter is achieved using the attenuated total reflection (ATR) technique. Light is sent

through a sapphire prism which is in contact with the reaction medium. Total internal reflections keep the light inside the sapphire while an evanescent wave escapes the sapphire and probes the reaction medium. The evanescent wave is attenuated in the process and carries information about the concentration of the components present in the reaction. An additional advantage of the ATR technique is the low sensitivity of the optical measurement to the presence of highly absorbing solid particles, like charcoal.

Example: Hydrogenation of a Hydrazone

Reduction of a substituted hydrazone to the corresponding hydrazine is a process that is prone to over-hydrogenation. Because the reaction is run under hydrogen pressure, taking samples (for off-line analysis) from the reaction mixture is not an option. During a feasibility study, the process was run in a laboratory reactor equipped with a fiberoptic UV spectrometer. Pure reactants, products, and side products in the desired solvent were

With the calibration at hand, the spectrometer calculates conversion directly from the spectra. Fig. 4 shows a comparison of two measures for the conversion to hydrazine. The solid line represents hydrogen consumption, which is initially fast then slows but does not stop completely. This makes it very difficult to accurately determine the endpoint of the reaction. In the initial phase the UV spectra determine the same conversion. After consumption of all hydrazone, the UV absorption does not change any further because the hydrazine and the over-hydrogenated species have very similar absorptions. Therefore, the end of the intended reaction can be determined accurately.

The advantage of the spectroscopic method is obvious: the hydrogenation can be stopped at full hydrazone conversion and no side product is generated.

Received: July 13, 2001

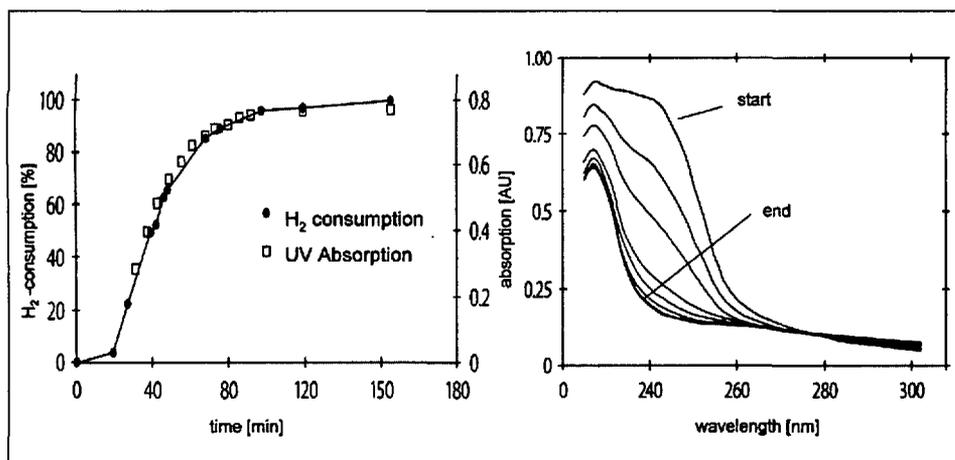


Fig. 4. Left: The hydrogenation is monitored by two methods, hydrogen consumption and UV-absorption. Right: The UV-absorption spectra change with the progress of the reaction.

measured separately with an ATR probe in order to see how well UV spectroscopy can discriminate the compounds. As a next step, a quantitative calibration was made using samples of known composition. This step is necessary since the compounds do not have isolated absorption peaks and the spectra need deconvolution.

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