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Technical Notes

Safety Improvements of a Grignard Reaction by Controlling the Reactant Feed Rate by On-line Concentration Monitoring Using NIR

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Abstract:

Grignard reactions are often highly exothermic and are performed near to or at the boiling point of the solvent. Therefore, a detection of the initiation of the reaction based on temperature measurements is in many cases difficult in the industrial environment. A delayed initiation of the reaction can lead to an unsafe situation (overpressure in the reactor system). This paper describes the automated monitoring of the reactant feed rate to avoid any excessive reactant accumulation. The concentrations of the substances are determined on-line using NIR spectroscopy, and these data are used to control the feeding pump. The equipment used for this purpose is the same type as that used in production plants. Therefore, the transfer of this technology to a manufacturing plant is facilitated. The automation of chemical processes leads to safety improvement, increase of the plant efficiency, and reduction of the operating costs.

Introduction

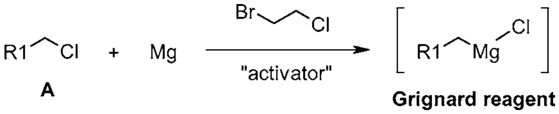
In Grignard reactions, an alkyl- or aryl halide and magnesium metal react in an ether to form an organomagnesium halide (RMgX). This so-called Grignard reaction is an easy way to form various compounds (e.g., tetrazoles for the pharmaceutical industry).

This kind of reaction is often highly exothermic and is performed near to or at the boiling point of the solvent. Therefore, the detection of the initiation of the reaction based on temperature measurements is, in many cases, difficult in the industrial environment. A delayed initiation of a Grignard reaction can lead to an unsafe situation; therefore, the aim of this paper is to show that the degree of accumulation determined by using NIR can be used in the ongoing plant process directly for feed control.

Safety Aspects of the Process

The investigated reaction is described in Scheme 1. The compound A reacts with magnesium to form a Grignard reagent (bromochloroethane is used as an activator).

Scheme 1. **Synthesis of the Grignard Reagent**



During the development of the process, it was observed that the initiation of the reaction was often delayed. In the case of a slow initiation of the formation of the Grignard reagent (or if the reaction drops off), the compound A will be accumulated. If this is followed by a sudden increase of the reaction rate, a significant solvent quantity will be evaporated within a short time period which can lead to a vigorous boiling and to flooding in the vapor tube with risks of overpressure and explosion.

To avoid this unsafe situation, the concentrations of the accumulated compound A and of the formed Grignard reagent must be monitored during the progress of the reaction. A thermal detection of the reaction initiation is difficult because the process is performed at reflux. Thus, only the increase of the solvent flow in the condenser can be measured, but the determination of the temperature difference of the cooling medium between the inlet and the outlet of the condenser is often not accurate enough to guarantee safe reaction conditions.

A previous study has shown that the concentrations of compound A and of the formed Grignard reagent can be monitored on-line with a good accuracy using NIR spectroscopy.[1]

The alternative traditional off-line HPLC analysis requires the presence of laboratory technicians and leads to delays due to the time necessary to perform the analyses. These are serious disadvantages for a high-volume production plant. Therefore, on-line measurement of the concentrations leads to a significant saving of time and also guarantees a high level of safety in the process. Moreover, the control of the reactant feed rate can only be automatically performed by using on-line concentration monitoring.

In comparison with the process described in the earlier study, the concentration of the reaction mixture was increased

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(1) Wiss, J.; Länzlinger, M.; Wermuth, M. *Org. Process Res. Dev.* **2005**, *9*, 365−371.

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Table 1. **Cross Validation of the Models Used for the Monitoring of the Grignard Reagent Formation**

	frequency range	data preprocessing	number of factors	RMSEE [mass %]	RMSECV [mass %]	R^2
cmpd A	4597 − 5581 and 6067 − 9014 cm^{-1}	first derivation and vector normalization	6	0.328	0.347	97.32
Grignard	7536 − 9503 cm^{-1}	first derivation and vector normalization	6	0.269	0.291	99.86

by about 35%. Therefore, the chemometric models used for the evaluation of the NIR data were adapted.

Experimental Procedures

The experiments were performed with a Mettler-Toledo RC1 reaction calorimeter equipped with a 0.9l glass reactor, a four-bladed glass anchor stirrer, a heated steel/Teflon-cover, glass inserts, and a condenser. Magnesium turnings and THF were charged into the dry reactor, and the reaction mixture was heated up to 66 °C (boiling temperature of the solvent). Then, bromochloroethane was added in small portions to start the reaction. After the reaction initiation (detected by measuring the heat release rate with the calorimeter), a solution containing the compound A, bromochloroethane, and THF was added within 2 h. Afterwards, the reaction mixture was stirred during 3 h at the same temperature.

On-line Monitoring of the Reaction Using NIR

A Matrix F NIR spectrometer (Bruker Optics) equipped with a Zafiro transmission immersion probe (Solvias) with an optical path length of 5 mm and a sapphire window (body in stainless steel) was used for the concentration measurements. The experimental conditions were the following: resolution, 8 cm^{-1}, and number of scans, 200. A fine Teflon grating was installed around the probe slot to reduce the spectral noise caused by the magnesium turnings agitated in the reactor (mesh 0.5 mm).

The chemometric models are calibration functions used for the analysis of unknown samples. These models based on a PLS algorithm (partial least-squares regression method[2]) were optimized using results of several hundreds of analyses performed during the campaigns in the pilot and production plants. The frequency ranges used for the PLS regression, the data used in preprocessing, the number of factors, RMSEE (root-mean-square error of estimation), RMSECV (root-mean-square error of cross validation), and R^2 (determination coefficient) are summarized in Table 1. RMSECV was plotted as function of the rank to determine the optimum number of factors (the curve goes through a minimum for the optimal rank).

The results of the cross validation are shown in Figure 1 for compound A and in Figure 2 for the Grignard reagent.

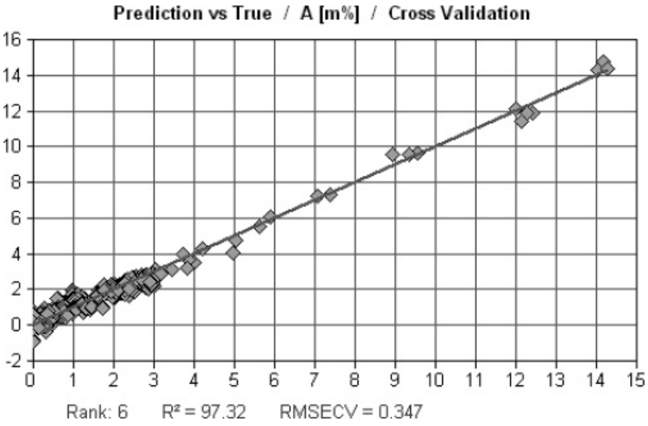

Figure 1. **Results of the cross validation for the determination of the concentration of the compound A.**

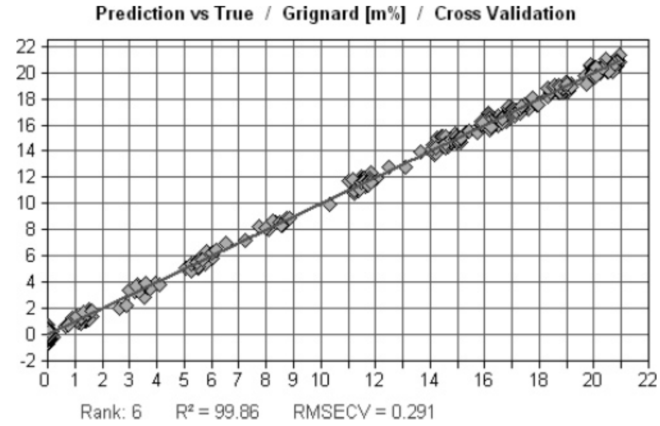

Figure 2. **Results of the cross validation for the determination of the concentration of the Grignard reagent.**

The formation of the Grignard reagent as well as the concentration of compound A (indicator of the accumulation) can be monitored in real time. A maximum admissible compound A concentration of 5% was determined during the risk analysis of the process. For this reaction, the mean deviation between NIR and reference HPLC analysis (3σ) is about 1% (abs.) for compound A and about 0.9% (abs.) for the Grignard reagent (probability of 99.5% that the deviation is below 3σ). This accuracy is sufficient for detecting the initiation of the Grignard formation reaction by means of on-line NIR monitoring. The dangerous accumulation of compound A can thus be avoided. Moreover, the progress of the reaction can be followed in real time.

Control of the Reactant Feed Rate

A significant improvement of this on-line monitoring of the concentrations is to control the feed rate of the solution of compound A as a function of the chemical accumulation.

If the accumulation curve a in Figure 3 is considered as a function of the time, it can be seen that the condition

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(2) Kessler, R. W. *Prozessanalytik*; Wiley-VCH: Weinheim, 2006; p 117.

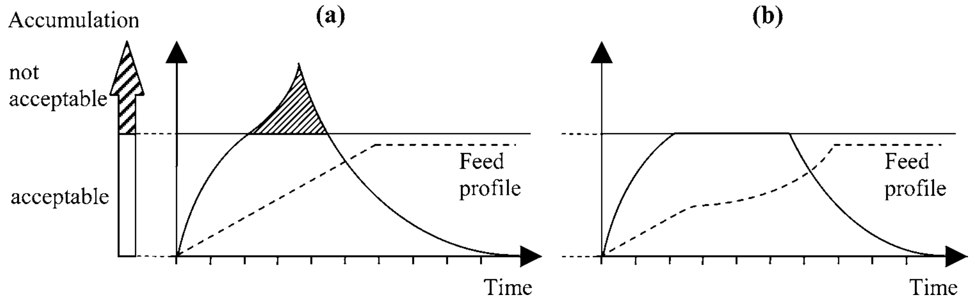

Figure 3. **Feed as a function of accumulation. (a) Method with unacceptable reactant accumulation. (b) Method with feed as a function of the reactant accumulation.**

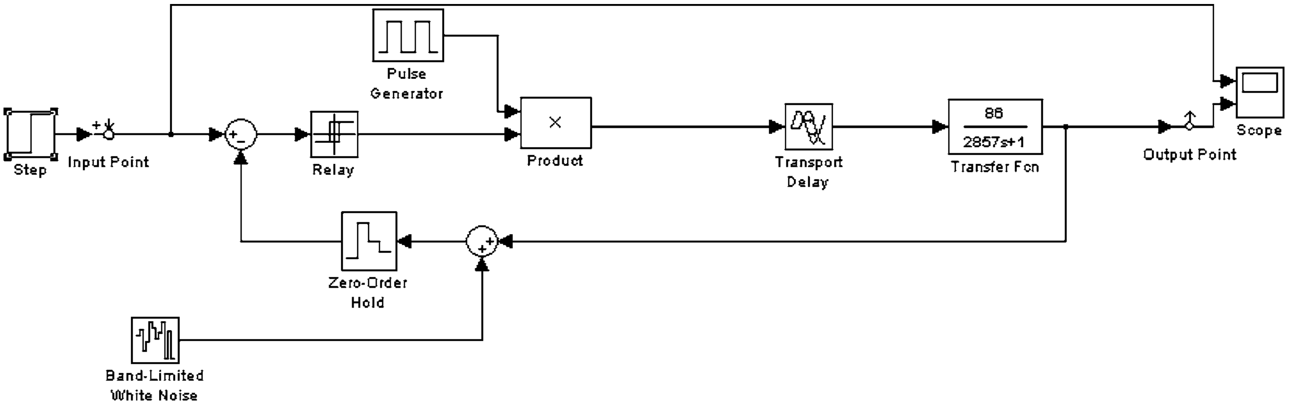

Figure 4. **Simulink model of a two-step regulation with switching hysteresis.**

assessed as critical holds during a certain period of time[3] of the process (shaded areas). Before and after this phase the process is not considered critical from a reactant accumulation point of view. In the process alternative of curve b, the observed reactant accumulation is fed back to the feed-controlling program, which reduces the feed after attainment of the acceptable degree of accumulation so that, from this point on, the added quantity of reagent corresponds exactly to the actual amount consumed by the reaction, i.e., the degree of accumulation remains constant. Once the degree of accumulation becomes less than the acceptable value at a later instant, the feed rate is increased.

The aim of this paper is to show that the degree of accumulation determined using NIR can be used in the ongoing process directly for feed control. The system should be able to monitor the concentration of A and adjust the feeding rate in such a manner that an excessive accumulation of this compound cannot occur.

The working model was designed in accordance with the GAMP-4 guidelines[4] to allow an easy and efficient technology transfer to the future production plant. The following duties were further specified:

(i) realize an interface between the spectrometer and the control system (Siemens S-7 PLC - *P*rogrammable *L*ogic *C*ontroller - with Profibus);

(ii) design, realize, and validate a software module to control the system with the Siemens S-7;

(iii) find a suitable actuator (pump) and a way to control it;

(iv) realize and start up a laboratory testing device (the working model).

For the design of the closed-loop control, the reaction was simulated using Matlab and Simulink, which are software packages for modeling, simulating, and analyzing dynamic systems.[5] Using the concentration profiles of the several compounds (determined by HPLC) a kinetics model of the Grignard reaction was established. A two-step controller with switching hysteresis was chosen for the system although several types of controllers have been examined. Figure 4 shows the graphical model of the system used for the simulation of the two-step controller.

The advantages of this type of regulator are the following:

(a) easy adjustment;

(b) easy to understand and to document (reduces the probability of errors and reduces the qualification effort);

(c) robustness against signal noise;

(d) a qualifiable functional test can be performed within a short time.

On the other hand, some drawbacks must be considered:

(a) Stable oscillations of the signal are possible in case of an inappropriate configuration (rare).

(b) For outliers with too-low concentrations, the regulation will activate the pump to dose more reagent up to the next measured value (in other words during a sampling period). Nevertheless, due to the high measurement frequency of the NIR spectroscope, this delay can be kept very short.

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(3) *Thermal Process Safety*; ESCIS (Expert Commission for Safety in the Swiss Chemical Industry): Basel, Switzerland, 1993; Booklet 8, pp 26−27.

(4) *GAMP-4*, The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems in Pharmaceutical Manufacture. ISPE (International Society for Pharmaceutical Engineering), 2001.

(5) Matlab and Simulink are registred trademarks of The MathWorks Inc., Natick, Massachusetts (U.S.A.).

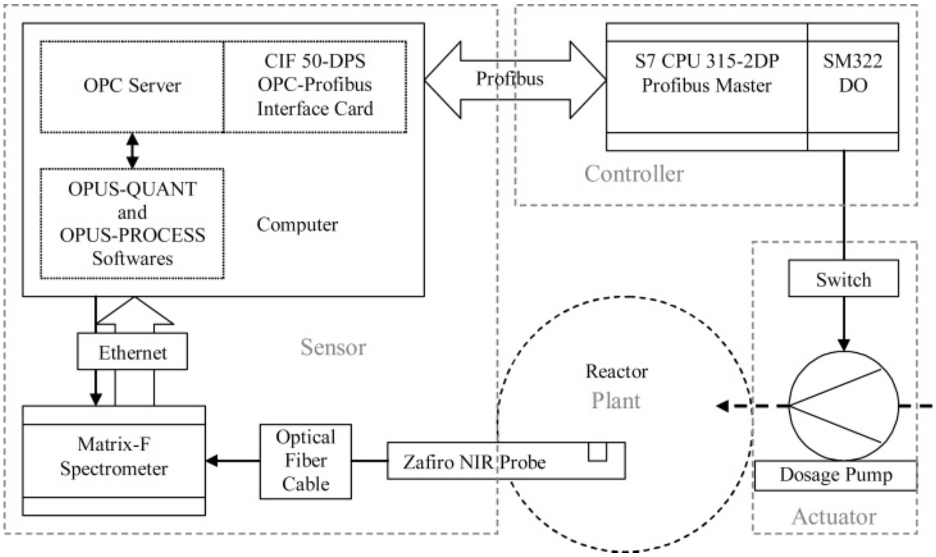
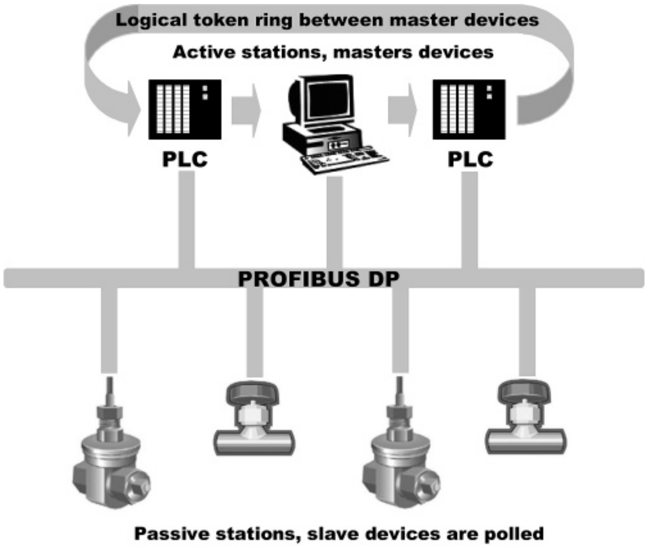


Figure 5. **System structure.**



* PLC: Programmable Logic Controller

Figure 6. **Structure of a Profibus with active masters and passive slaves.**

(c) The output signal has a certain wave-like form due to the hysteresis.

The system can be reduced to the sensor unit, the controller, the actuator, and the plant (see Figure 5):

- The sensor unit: the NIR probe is connected to the spectrometer using an optical fiber cable. This spectrometer communicates with the evaluation computer of the spectrometer via an Ethernet RJ45 cable. A Profibus interface card (Hilscher CIF 50-DPS) was installed in the computer to send the concentration values generated by the on-line evaluation software (Bruker OPUS Quant and OPUS Process) to the Siemens controller.

The Profibus network is built on a master/slave communication principle.[6] A central controller, the fieldbus master (here the Siemens S7), cyclically reads information from the field devices, the fieldbus slaves (the interface card in the evaluation computer), and writes, if necessary, output values to them. In a Profibus DP network high-speed transmission rates of up to 12 Mbaud are possible in industrial applications. The reason for using this system is that the Profibus is widely used in production plants in the pharmaceutical industry (the structure of a Profibus is shown in Figure 6).

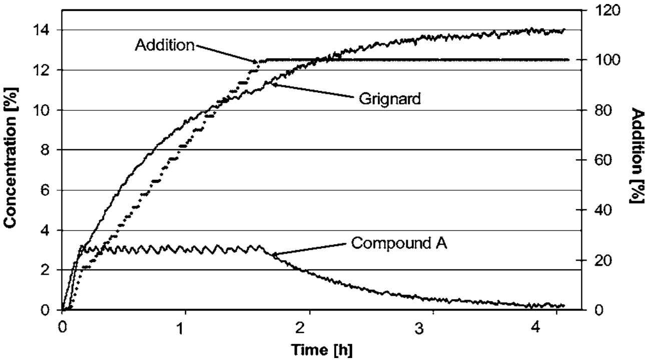


Figure 7. **Concentration of the added substance A and of the formed Grignard reagent, addition profile (set value 3%, hysteresis 14%).**

- The controller: a standard Siemens Simatic S7-300 PLC unit which is from the same type as are commonly used in production plants. The regulation software was written using the STEP7 programming environment from Siemens.
- The actuator: a potential free switch (Comat C3-A 30) is used to control the feeding pump (Prominent Gamma/4) by impulses.
- The plant is the above-mentioned Mettler-Toledo RC1 reaction calorimeter equipped with a 0.9l glass reactor.

The advantages of the presented system for use in an industrial environment are the following:

The spectrometer, the computer, and the controller can be installed in a non-explosion-safe zone; the only connection to the potentially explosive atmosphere in the surrounding area of the reactor is established by the optical fibers for the probe and the low-energy Profibus cables. This allows the use of cheaper, standard-issue components. The pump and

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(6) *PROFIBUS Technology and Applications*, System Description. Profibus User Organization: Karlsruhe, Germany, October 2002.

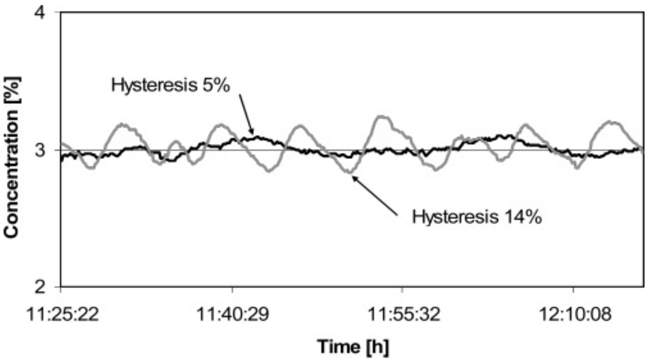

Figure 8. **Comparison of the oscillations of the values of the concentration of the added substance A with a hysteresis of 5% and 14%.**

the NIR probe are certified and can be used in a potentially explosive atmosphere. This safety precaution has also been used during the testing runs on the working model.

Experimental Results

Figure 7 shows the concentration of the added substance A and of the formed Grignard reagent. A set value of 3% was specified (with a hysteresis of 14% of this set value). The experiments show that the reaction can be performed with this highly automated system in a safe manner. A decrease of the hysteresis leads to a reduction of the oscillations of the signal (see Figure 8 with a hysteresis of 5% of the set value).

Conclusion

In addition to the improvements due to the on-line determination of the critical chemical concentrations using NIR spectrometry, this paper shows how to automatically control the feed rate of a reagent to ensure safe conditions. The equipment used for this purpose is from the same type as that in production plants. Therefore, the transfer of this technology to a manufacturing plant is facilitated.

This work was performed with a safety-critical Grignard reaction, but the methods used can also be implemented for other chemical processes. The automation of such processes leads not only to a risk reduction but also to an efficiency increase of the plant (optimization of the reactant addition time) and a reduction in operating expenses (due to the elimination of traditional analyses).

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