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Technical Notes

Improvement of Process Safety and Efficiency of Grignard Reactions by Real-Time Monitoring

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Abstract:

Grignard reactions possess considerable hazard potentials due to the spontaneous heat release during the initiation of these strongly exothermic reactions and the high reactivity of the Grignard compounds. To establish an industrially applicable method for an objective real-time detection of the reaction start-up and for the accumulation of the organic halide during the process, a heat/mass balance-based real-time monitoring approach was developed and tested by miniplant experiments. In addition to the concentration profiles provided by the approach, the real-time estimation of the safety-relevant parameters, such as adiabatic temperature rises and corresponding pressures, enables application of advanced control strategies up to the point of a safety-oriented, fully automated control of Grignard reactions. At the same time, such systems can contribute to improved process efficiency by increasing the space-time yield as well as enhancing the inherent safety of the process.

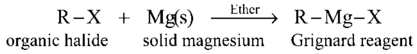
Introduction

Metal–organic compounds such as Grignard reagents are of vital importance as an initial stage of numerous organic syntheses in the fine-chemical and pharmaceutical industries. In general, there are two methods to prepare Grignard reagents: (i) reactions between organic halides and solid magnesium,[1] and (ii) halogen–magnesium exchange reactions.[2]

Due to their high reactivities, Grignard reagents possess significant hazard potentials which can lead to thermal instabilities of the reaction mixture. Such instabilities might occur as a result of reactions between the reaction mixture and any remaining magnesium[3] as well as due to interactions between byproducts of the halogen–magnesium exchange reactions with the Grignard reagents.[4] The risks of thermal instabilities are higher if the reactants are enriched in the mixture (i.e., by an improper evaporation rate of the solvent).[3,4]

Still, the most common method to prepare Grignard reagents is reactions between organic halides and solid magnesium in an ethereal solution according to the following simplified reaction equation:

Scheme 1. **Formation of a Grignard reagent**



$$\underset{\text{organic halide}}{R-X} + \underset{\text{solid magnesium}}{Mg(s)} \xrightarrow{\text{Ether}} \underset{\text{Grignard reagent}}{R-Mg-X}$$

To initiate the formation of the Grignard reagent, active centers have to be formed on the magnesium surface. After some induction time, the Grignard reaction seems to go autocatalytically. When a critical amount of the Grignard reagent is formed, new active centers are exposed, and subsequently the rate of reaction increases exponentially. The initiation reaction is only stopped when one of the reactants is consumed. After this initiation period, the reaction can be controlled in a classical semibatch manner by dosing the appropriate amount of organic halide. The thermal process behavior of a typical Grignard reaction is shown in Figure 1. Due to the spontaneous heat release during the initiation of these strongly exothermic reactions, Grignard reactions possess considerable hazard potentials.[5] The primary sources of hazards can sometimes be attributed to an additionally delayed reaction start due to traces

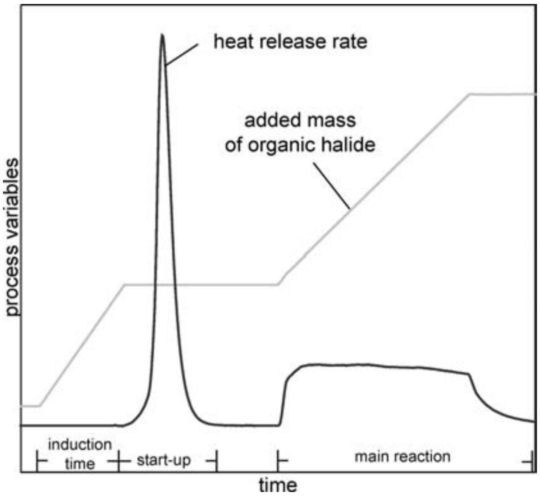


Figure 1. **Heat-release rate during a Grignard reaction.**

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(1) Richey, H. G. *Grignard Reagents: New Developments*; John Wiley & Sons: New York, 2000.

(2) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

(3) Leazer, J. L.; Cvetovich, R.; Tsay, F.-R.; Dolling, U.; Vickery, T.; Bachert, D. *J. Org. Chem.* **2003**, *68*, 3695.

(4) Reeves, J. T.; Sarvestani, M.; Song, J. J.; Tan, Z.; Nummy, L. J.; Lee, H.; Yee, N. K.; Senanayake, C. H. *Org. Process Res. Dev.* **2006**, *10*, 1258.

(5) Yue, M.-H.; Sharkey, J. J.; Leung, J. C. *J. Loss Prev. Process Ind.* **1994**, *7*, 413.

10.1021/op700012g CCC: $37.00

of impurities after the accumulation of a high amount of the organic halide or to undesired exothermic reactions of the Grignard reagent with such impurities. Therefore, it is of vital importance to establish industrially applicable methods for an objective detection of the reaction start-up and determination of the accumulation of the organic halide during the process.

An industrial Grignard process is normally carried out in a stirred-tank reactor at the boiling point of the reaction mixture, equipped with a reflux system to dissipate the heat release during the reaction. Such process control complicates objective detection of the reaction start-up. A relatively simple method (but with the disadvantage of being qualitative) to detect the reaction start is to dose the halide at the reactor temperature slightly below the boiling temperature. In this case, the reaction start-up will lead to a temperature rise; however, misinterpretations are possible due to alternating coolant and/or dosing temperatures as well as due to mixing enthalpies. Furthermore, process control in reactors containing reflux condensers increases the risk of intrusions of impurities into the reflux system (e.g., air moisture due to the hygroscopicity of the solvent or coolant due to leakage of the reflux cooler coil) as well as the risk of emissions of hazardous substances. Moreover, the risk of an improper high evaporation rate is present if the process is carried out at boiling conditions. Few methods for online concentration measurements using FTIR and NIR have been developed.[6,7] Such online measurements provide quantitative information on educt accumulations irrespective of the process control. However, spectroscopic methods and the appropriate devices require high investment and operating costs and, especially in the case of quantitative measurements in nonisothermal systems, lots of calibration efforts. The process control of Grignard reactions in pressurized vessels without reflux systems opens up new perspectives for the estimation of concentration courses and safety-relevant parameters using heat and mass balance-based real-time monitoring systems.

Laboratory Investigations

The following reaction between bromobenzene derivative and magnesium in a THF solution was used as a model process to develop and test the real-time monitoring method:

Scheme 2. **Test reaction**

$$\underset{\text{bromobenzene derivative}}{\mathrm{R-Br}} \quad + \quad \underset{\text{magnesium}}{\mathrm{Mg(s)}} \xrightarrow{\mathrm{THF}} \underset{\text{organomagnesium bromide}}{\mathrm{R-Mg-Br}}$$

The knowledge of the exact reaction enthalpy is of crucial importance for the application of heat balance-based monitoring systems to reactive processes. Since calorimetric measurements under reflux conditions produce higher errors than in closed systems, the reaction enthalpies were measured using the high-pressure RC1e/HP60 calorimeter equipped with a FTIR spectrometer (ReactIR1000). Experiments, carried out at isothermal operating mode, gave reaction enthalpy of $\Delta H_r = -(307 \pm 5)$ kJ/mol independent of the reaction temperature in the 25–120 °C temperature range. Neither the spectra nor the thermal process behavior indicated significant influences of the temperature on the product quality caused by side reactions and/or decompositions within that temperature range. During the measurements, a higher variance for reaction enthalpies obtained from the initiation reaction stage was observed. Therefore, the molar enthalpies were calculated for the main reaction stages with respect to the dosed amount of the bromobenzene derivative during the main reaction in order to ensure maximum accuracy and reproducibility of the results.

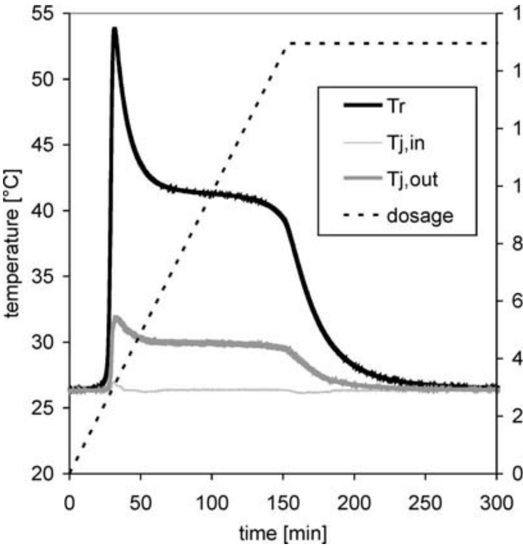

Figure 2. **Process variables of the investigated Grignard reaction for the improved process mode.**

The Grignard reaction experiments have been carried out in a miniplant consisting of a 10-L STR and a jacket cooling system to test the monitoring system. An isoperibolic process mode (constant jacket inlet temperature $T_{j,in}$) was used for the experiments in accordance with common industrial applications. The organic halide concentrations were measured in situ, using a FTIR spectrometer ReactIR1000 for validation purposes. Two sets of experiments acted as test runs for the monitoring method: (a) common process mode: separate start and main reaction stage by interruption of the dosage (see Figure 1) and (b) improved process mode: nonstop semibatch mode with continuous dosage to demonstrate the efficiency-improvement capabilities of a real-time monitoring system.

Typical profiles of the process variables of an experiment according to set (b) at $T_{j,in} = 27$ °C are depicted in Figure 2, as an example. To agree with industrial applications, no specially dried THF was used for the Grignard reactions. Thus, induction times of 20–30 min were observed for all experiments. Additional nonreactive experiments were carried out to estimate certain plant parameters such as the heat capacities of the vessel and the cooling jacket as well as the heat loss coefficients of the apparatus.

Working Principle of the Monitoring System

When a balance-based monitoring approach is used, it is strongly recommended that the process be carried out in a pressurized vessel because balancing under reflux conditions produces higher errors than in closed systems due to the additional heat losses and the evaluation of the heat of the reflux.

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(6) Am Ende, D. J.; Clifford, P. J.; DeAntonis, D. M.; SantaMaria, C.; Brenek, S. J. *Org. Process Res. Dev.* **1999**, *3*, 319.

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

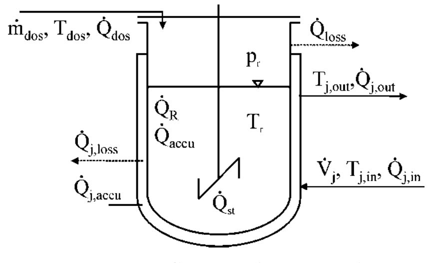

Figure 3. **Heat and mass flow during a semibatch process.**

Further error sources can be caused by irregular boiling conditions due to the nonoptimised difference between the temperature of the reaction mixture and that of the coolant.[8] The heat and mass balance model is the essential part of the real-time calculation algorithm. In the case of simple reaction schemes as assumed in Scheme 1, the concentrations of the reacting species can be monitored by solving a set of dynamic heat/mass balances in real time. On the basis of these results, the courses of safety-relevant data such as the adiabatic temperature increase and the appropriate reactor pressure can be estimated. Figure 3 illustrates the heat and mass flow in the stirred-tank reactor during a semibatch process typically employed to carry out Grignard reactions.

The reactor heat balance can be written as

$$\dot{Q}_{\mathrm{R}} = \Delta\dot{Q}_{\mathrm{j}} + \dot{Q}_{\mathrm{accu}} - \dot{Q}_{\mathrm{st}} - \dot{Q}_{\mathrm{dos}} + \dot{Q}_{\mathrm{j,accu}} + \dot{Q}_{\mathrm{loss}} + \dot{Q}_{\mathrm{j,loss}} \tag{1}$$

The main portion of the heat release rate $\dot{Q}_{\mathrm{R}}$, generated by the exothermic reaction, is removed by the jacket cooling system. The resulting heat flux difference $\Delta\dot{Q}_j$ can be calculated as

$$\Delta\dot{Q}_{\mathrm{j}} = \dot{Q}_{\mathrm{j,out}} - \dot{Q}_{\mathrm{j,in}} = \rho_{\mathrm{j,in}}\dot{V}_{\mathrm{j}}(c_{\mathrm{p,j,out}}T_{\mathrm{j,out}} - c_{\mathrm{p,j,in}}T_{\mathrm{j,in}}) \tag{2}$$

where $T_{\mathrm{j,in}}$ is the coolant temperature at the jacket inlet, $T_{\mathrm{j,out}}$ is the coolant temperature at the jacket outlet, $\rho_{\mathrm{j,in}}$ is the density of the coolant at $T_{\mathrm{j,in}}$, $\dot{V}_{\mathrm{j}}$ is the coolant flow rate, $c_{\mathrm{p,j,in}}$ is the specific heat capacity of the coolant at $T_{\mathrm{j,in}}$, and $c_{\mathrm{p,j,out}}$ is the specific heat capacity of the coolant at $T_{\mathrm{j,out}}$.

Particularly during the initiation reaction, the greatest part of the reaction heat is accumulated in the reaction mixture, the vessel, and the cooling jacket. The resulting heat fluxes are expressed by the $\dot{Q}_{\mathrm{accu}}$ and $\dot{Q}_{\mathrm{j,accu}}$ terms respectively:

$$\dot{Q}_{\mathrm{accu}} = (m_{\mathrm{R}}c_{\mathrm{p,R}} + C_{\mathrm{p,app}})\frac{\mathrm{d}T_{\mathrm{R}}}{\mathrm{d}t} \tag{3}$$

$$\dot{Q}_{\mathrm{j,accu}} = (V_{\mathrm{j}}\rho_{\mathrm{j}}c_{\mathrm{p,j}} + C_{\mathrm{p,j,app}})\frac{\mathrm{d}T_{\mathrm{j}}}{\mathrm{d}t} \tag{4}$$

where m_{R} is the mass of the reaction mixture, $c_{\mathrm{p,R}}$ is the specific heat capacity of the reaction mixture, $C_{\mathrm{p,app}}$ is the heat capacity of the vessel (excluding the cooling jacket), T_{R} is the reactor temperature; V_{j} is the volume of the cooling jacket, ρ_{j} is the density of the coolant, $c_{\mathrm{p,j}}$ is the specific heat capacity of the coolant, and $C_{\mathrm{p,j,app}}$ is the heat capacity of the cooling jacket.

The calculation of the heat flux caused by the dissipation energy of the stirrer $\dot{Q}_{\mathrm{st}}$ was estimated as a function of the stirrer speed n_{St} by the common NEWTON number correlations.[9] Especially if the reactor temperature T_{R} differs from the temperature of the dosed halide T_{dos}, the cooling or heating effect of the reactor mixture by the dosed liquid has to be considered. The corresponding heat flux $\dot{Q}_{\mathrm{dos}}$ can be calculated, depending on the mass flow of the halide m_{dos} and its specific heat capacity $c_{\mathrm{p,dos}}$, as:

$$\dot{Q}_{\mathrm{dos}} = \dot{m}_{\mathrm{dos}}c_{\mathrm{p,dos}}(T_{\mathrm{dos}} - T_{\mathrm{R}}) \tag{5}$$

The heat losses through the lid of the reactor Q_{loss} and the cooling jacket $\dot{Q}_{j,\mathrm{loss}}$ were considered by experimental determination of the heat flux coefficients at the target plant. Probably a more appropriate approach in order to consider the difficulty to model heat losses and heat bridges at industrial plants would be the addition of correction terms to the heat balance. These terms may also include adaptive parameters. However, a process signals set of one batch at normal operating conditions is enough to adapt the monitoring system to the target plant. During the adaptation process, adaptive parameters, introduced as additional coefficients in eq 2 as well as in the heat loss equations, can be adjusted using a neural network approach. An adaptive real-time monitoring system, originally developed for hydrogenation reactions and tested at STR volumes up to 4 m^3 during several production campaigns, is described by Hessel et al.[10]

Assuming an instantaneous reaction according to the dosage of the organic halide m_{dos} (no accumulation of the halide), the heat release rate Q_{inst} can be calculated on the basis of the molar reaction enthalpy ΔH_{R} and the molar mass of the halide M_{dos} according to the following equation:

$$\dot{Q}_{\mathrm{inst}} = (-\Delta H_{\mathrm{R}})\frac{\dot{m}_{\mathrm{dos}}}{M_{\mathrm{dos}}} \tag{6}$$

In the case of reactant accumulation in the reaction mixture, a difference of the instantaneous heat release rate $\dot{Q}_{\mathrm{inst}}$ and the heat flow $\dot{Q}_{\mathrm{R}}$ according to the heat balance occurs. The integral value of this difference $\Delta Q_{\mathrm{R,accu}}$ from the reaction start time t_{start} to the actual time t is a measure of the accumulated amount of the dosed halide $n_{\mathrm{R,accu}}$.

$$\Delta Q_{\mathrm{R,accu}} = \int_{t_{\mathrm{start}}}^{t}(\dot{Q}_{\mathrm{inst}} - \dot{Q}_{\mathrm{R}})\mathrm{d}t' \tag{7}$$

$$n_{\mathrm{R,accu}} = -\frac{\Delta Q_{\mathrm{R,accu}}}{\Delta H_{\mathrm{R}}} \tag{8}$$

Since the charged and dosed amounts of reactants and solvents are known, the concentration profiles of the organic halide and

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(8) Wiss, J.; Stoessel, F.; Kille, G. *Chimia* **1990**, *44*, 401.

(9) Dickey, D. S.; Bittorf, K. J.; Ramsey, C. J.; Johnson, K. E. *Chem. Eng. Prog.* **2004**, *100*, 21.

(10) Hessel, G.; Kryk, H.; Schmitt, W.; Seiler, T.; Weiss, F.-P. *Wiss.-Tech. Ber.-Forschungszent. Rossendorf* **2001**, *318*, 74.

the Grignard reagent during the process can be computed simply by application of appropriate mass balances.

In addition to the real-time monitoring of substance amounts and concentrations, the heat and mass balance approach opens new opportunities in safety-oriented process control strategies as well as in process automation using real-time computing of safety-relevant parameters. The approach provides an estimation of the hazard potential due to the reactivity of the organic halide accumulated in the reaction mixture. Assuming an adiabatic behavior as the worst case, the maximum temperature of the synthesis reaction (MTSR)[11] in the case of a runaway can be estimated as a time-dependent function according to the following equation:

$$\mathrm{MTSR} = T_{\mathrm{R}} + \frac{\Delta Q_{\mathrm{R,accu}}}{m_{\mathrm{R}} c_{\mathrm{p,R}}} \qquad (9)$$

The corresponding maximum reactor pressure profile p_{MTSR} primarily results from the rise of vapor pressure p_{v} of the reaction mixture and secondarily from the expansion of the gas phase above the liquid surface.

$$p_{\mathrm{MTSR}} = [p_{\mathrm{v}}(\mathrm{MTSR}) - p_{\mathrm{v}}(T_{\mathrm{R}})] + p_{\mathrm{R}} \frac{\mathrm{MTSR}[K]}{T_{R}[K]} \qquad (10)$$

An objective evaluation of the process state is feasible at any time by comparing the time-dependent courses of MTSR and p_{MTSR} with thresholds predefined by means of design parameters of the industrial plant and the initial response pressure of the safety valve. Additionally, it is important to ensure that the MTSR threshold is set below the temperature of decomposition and/or that of undesired side reactions.

Test Results

The monitoring system was tested at process conditions using results from two sets of experiments at 10-L scale. Selected results of Grignard reactions at common process mode (a) are displayed in Figure 4 as an example for the functionality of the method. The molar concentrations were calculated with respect to the total reaction mixture without consideration of the solid magnesium in order to be able to compare the results with the related online FTIR measurements. The results of the monitoring system exhibit a good agreement with the FTIR data. The highest amount of organic halide is observed before the initiation and at the end of the main reaction stage. The accumulation rise is caused by the decrease of the reaction rate due to the lack of magnesium at the end of the main reaction.

When a balance-based real-time monitoring method is used to trace the accumulation of the dosed organic halide, it is no longer necessary to interrupt the process after dosing the halide amount sufficient to start the reaction. Continuous dosage over the whole reaction period leads to an improvement of the space-time yield and opens up new opportunities regarding fully automated process control strategies. To demonstrate the capabilities of real-time monitoring in this regard, a set of experiments in nonstop semibatch mode were carried out. Figure 5 shows the corresponding concentration courses compared to the ones obtained by FTIR measurements for an experiment at isoperibolic process mode ($T_{\mathrm{j,in}} = 27$ °C). Once again, the results of the monitoring system are in a good agreement with the related FTIR measurements.

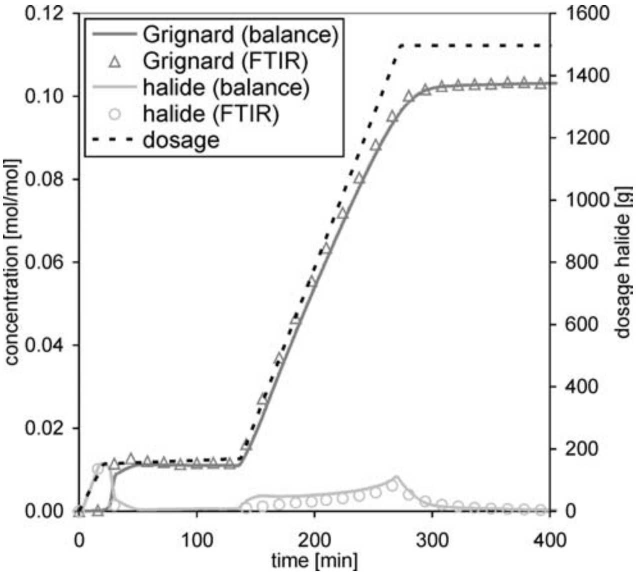

Figure 4. **Concentration profiles during a Grignard reaction at common process mode.**

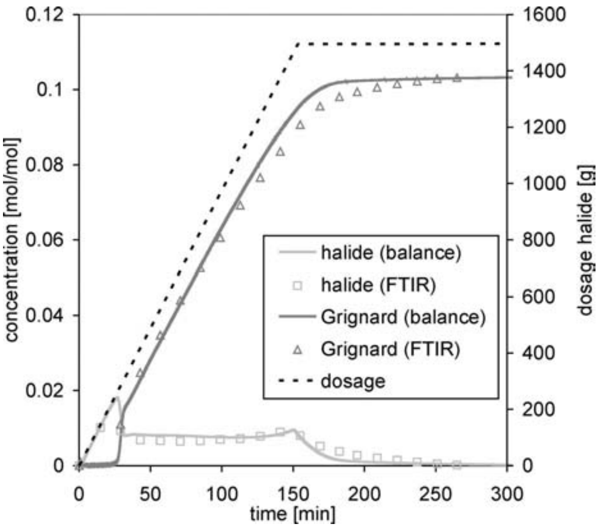

Figure 5. **Concentration profiles during a Grignard reaction at improved process mode.**

By means of a real-time estimation of the safety-relevant parameters MTSR and p_{MTSR} according to Figure 6, the hazard potential due to the reactivity of the accumulated halide can be evaluated at any time during the process. If one of the parameters exceeds the predefined limits, the dosage of the organic halide can be interrupted by the process control system. This may happen in the case of a much delayed reaction initiation due to impurities as well as in the event of a drop-off of the reaction rate caused by lack of magnesium or insufficient mass transfer. As an outlook, the real-time data of MTSR and p_{MTSR} could be used as a reference value for a fully automated

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(11) Lerena, P.; Wehner, W.; Weber, H.; Stoessel, F. *Thermochim. Acta* **1996**, *289*, 127.

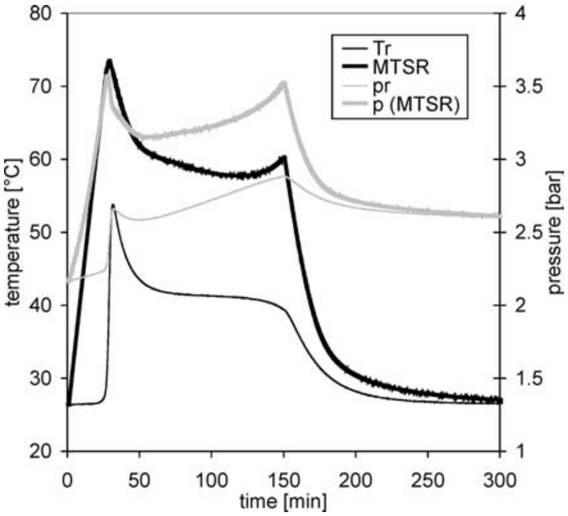

Figure 6. **Profiles of the safety-relevant parameters MTSR and p_{MTSR}.**

dosage control of the halide. A similar approach was demonstrated on the basis of online NIR measurements by Wiss et al.[12]

Application at the Industrial Process

Before the balance-based monitoring system can be used at industrial scale, some preconditions have to be fulfilled. A set of plant and process parameters, such as heat capacities of the plant and reaction enthalpies as well as substance data (i.e., densities, specific heat capacities), are to be estimated by appropriate experiments and/or calculations. The MTSR and p_{MTSR} thresholds should be predefined by considering the following factors of influence:

- start-up behavior of the particular Grignard reaction (investigation by reaction calorimetry)
- thermal stability of the reaction mixture depending on the reaction progress[13]
- vapor pressure of the substances
- if an existing reactor should be used (i.e., multipurpose plants): maximum permissible working pressure and temperature as well as initial response pressure of the safety valve.

It is recommended to set the MTSR threshold lower than the limit ascertained by the above methods to have the opportunity to induce the reaction start-up by increasing the reactor temperature. Further possibilities to force the reaction start are enhancement of the mass transfer by increasing the stirrer speed, addition of a small portion of Grignard reagent from a previous batch or addition of drying and/or reducing agents.[14] In all of these cases, the monitoring approach preserves its functionality. The choice of the process mode (separated start and main reaction stage or continuous dosage) should be made on the basis of the start-up behavior and the thermal stability of the reaction mass.

To apply the balance-based monitoring system to an industrial plant, minimum requirements regarding the process instrumentation have to be fulfilled. The measuring points of a reactor, adapted to use the real-time monitoring system, are shown in Figure 7. To ensure the highest possible accuracy, the sensors should be calibrated at regular intervals. Furthermore, the vessel should be insulated to keep the heat losses as low as possible. When a pressurized vessel is used, it must be equipped with a safety valve or a rupture disk.

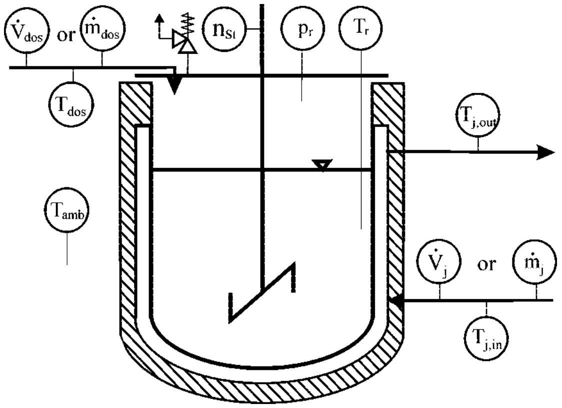

Figure 7. **Measuring points required for the use of the monitoring system.**

In general, the monitoring system can be used at industrial plants either as a stand-alone system or as an integral part of a complex batch information management system (BIMS). Although the latter is a more complicated monitoring method, it has the following advantages:

- The data generated by the monitoring system can be stored and archived batch-wise, together with the process signals, laboratory findings, and plant and substance parameters.
- The demand for traceability (e.g., hazardous operating state, batch with poor product quality) of complex batch processes can be fulfilled.
- The evaluation of the archived data allows to optimize chemical batch processes (e.g., yield, quality) and to repeat them with high product quality.

An example scheme of a BIMS with the embedded real-time monitoring system is shown in Figure 8 where the reactor is controlled by a process control system (PCS). The process data obtained by the PCS are stored together with the output data of the real-time monitoring system as well as the input data such as substance and plant parameters in a shared SQL database. In addition to the estimation of concentration profiles and the safety-relevant parameters, the outputs of the monitoring system can be used to provide the operators with operating hints in case of undesired process states (i.e., high concentration of organic halide). All the data can be displayed for the current batch as well as for previous batches at the operator screens in the control station. The working principle of such a system is described in detail by Hessel et al.[10]

Summary

The objective detection of the initiation reaction as well as of reactant accumulations during the process is of crucial importance for the safety-oriented process control of Grignard reactions. To establish industrially applicable methods for an objective real-time detection of the reaction start-up and for the accumulation of the organic halide during the process, miniplant

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(12) Wiss, J.; Ermini, G. *Org. Process Res. Dev.* **2006**, *10*, 1282.

(13) Stoessel, F. Safety Aspects of Grignard Reactions. Scale-Up of Chemical Processes, 6th International Conference, Dublin, November 1–4, 2004.

(14) Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 906.

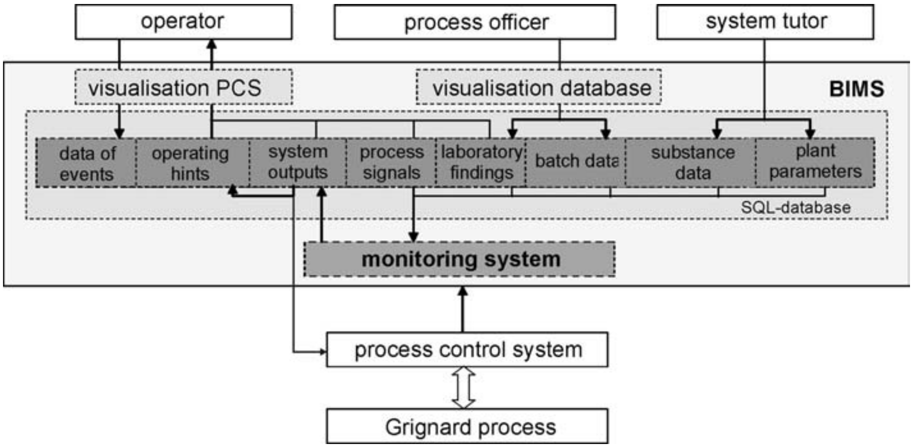

Figure 8. **Data and information flow in a BIMS.**

studies of a specific Grignard reaction using a 10-L pressurized stirred-tank reactor were carried out. Operating in pressurized systems opens up opportunities to use balance-based real-time monitoring systems. On the basis of the experimental results, a heat/mass balance-based real-time monitoring approach, which is capable of providing the operator with additional information on the process state (particularly for the accumulation of the organic halide), has been developed. The concentration profiles obtained from the monitoring system exhibit good agreement with the related in situ FTIR measurements. Additionally, the real-time estimation of the safety-relevant parameters, such as the courses of MTSRs and the corresponding maximum reactor pressure profiles, enables application of advanced control strategies up to the point of a safety-oriented, fully automatic control of the Grignard reactions. At the same time, such systems can contribute to improved process efficiency since the space-time yield can be increased by avoiding the dosage interruption between start and main reaction stages. A further increase of the space-time yield could be achieved by dynamic adjustment of the dosing rate with respect to the MTSR and pressure thresholds. Moreover, the real-time calculations of the safety-relevant parameters can be conducive to improving the inherent process safety. If the real-time monitoring approach were to be integrated into a complex batch information management system, the additional data could contribute to the enhancement of the process knowledge as a basis for continuative process optimization.

Supporting Information Available

Details of the FTIR Measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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