ONLINE MONITORING OF GRIGNARD REACTIONS

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1. Introduction

Metal-organic compounds like Grignard reagents are of vital importance as an initial stage of numerous organic syntheses in the fine-chemical and pharmaceutical industries. Reactions between organic halides and solid magnesium in an ethereal solution comprise one of the most common methods to prepare Grignard reagents. Due to the spontaneous heat release during the delayed autocatalytic initiation of these strongly exothermic reactions and the high reactivity of the Grignard compounds, the formation reactions of Grignard reagents (herein after referred to as Grignard reactions) possess considerable hazard potentials [1]. Primary sources of hazards can be attributed to a long delayed reaction start due to traces of impurities after the accumulation of a high amount of the organic halide or to undesired exothermic consecutive 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 accumulation of the organic halide during the process.

Industrial Grignard processes are normally carried out in stirred tank reactors, equipped with a reflux system at the boiling point of the reaction mixture to ensure removal of the spontaneous heat release. This process control complicates an objective detection of the reaction start-up and increases the risk of intrusions of impurities into the reactor. A few methods for online concentration measurements using FTIR and NIR spectroscopy have been developed [2, 3]. However, such methods and the appropriate devices require high investments and operating costs and, especially in case of quantitative measurements, huge calibration efforts. The process control of Grignard reactions in pressurized vessels without reflux system opens up new perspectives towards the estimation of concentration courses and safety relevant parameters using heat and mass balance-based online monitoring systems.

2. Laboratory investigations

The following reaction between bromobenzene derivative and magnesium in a THF solution was used as a model Grignard formation process to develop and test the online monitoring approach:

\[
\text{THF} 
\begin{array}{ccc}
\text{R - Br} & + & \text{Mg(s)} \\
\text{bromobenzene derivative} & & \text{magnesium} \\
(\text{organic halide}) & & \text{organomagnesium bromide} \\
& & \text{(Grignard reagent)}
\end{array}
\]

It is of vital importance for the application of heat balance-based monitoring systems to the reactive processes to know the exact reaction enthalpy. 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. Experiments, carried out in the isothermal operating mode, gave a reaction enthalpy of \(\Delta H_r = -(307\pm5) \text{ kJ/mol}\) independent of the reaction temperature in the 25 °C to 120 °C temperature range. The enthalpies were calculated for the main reaction stage to ensure maximum accuracy and reproducibility.

The Grignard reaction experiments have been carried out in a miniplant consisting of a 10 liters STR and a jacket cooling system to test the monitoring system. In accordance to indu-
trial applications, an isoperibolic process mode was used for the experiments. The organic halide concentrations were measured in-situ using the FTIR spectrometer ReactIR1000 for validation purposes. Two sets of experiments acted as test runs for the monitoring approach:

a) common process mode:
   separate start and main reaction stage by interruption of the dosage  
b) improved process mode:
   non-stop semi-batch mode with continuous dosage to demonstrate the efficiency improvement capabilities of an online monitoring system

Typical profiles of process variables of the experiments according to set (a) and (b) are depicted in Fig. 1.

![Fig. 1: Process variables of Grignard reactions (process mode (a) and (b))](image)

Additional non-reactive experiments were carried out to estimate plant parameters like the heat capacities of the vessel and the cooling jacket as well as the heat loss coefficients of the apparatus.

3. Working principle of the monitoring system

The heat and mass balance model is part and parcel of the online calculation algorithm. By solving a set of dynamic heat / mass balances in real time, the concentrations of the reacting species can be monitored. On the basis of these results, the courses of safety relevant data like adiabatic temperature and pressure rises can be estimated. Fig. 2 illustrates the heat and mass flows in the stirred tank reactor during the Grignard reaction.

![Fig. 2: Heat and mass flows during the Grignard reaction](image)
The reactor heat balance is given by:

$$\dot{Q}_R = \Delta \dot{Q}_j + \dot{Q}_{accu} - \dot{Q}_{st} - \dot{Q}_{dos} + \dot{Q}_{j,accu} + \dot{Q}_{loss} + \dot{Q}_{j,loss}$$  \hspace{1cm} (1)$$

The main portion of the heat release rate $\dot{Q}_R$, generated by the exothermic reaction, can be eliminated from the reactor content by the jacket cooling system. The resulting heat flux difference $\Delta \dot{Q}_j$ can be calculated as follows:

$$\Delta \dot{Q}_j = \dot{Q}_{j,\text{out}} - \dot{Q}_{j,\text{in}} = \rho_{j,\text{in}} V_j \left( c_{p,j,\text{out}} T_{j,\text{out}} - c_{p,j,\text{in}} T_{j,\text{in}} \right)$$  \hspace{1cm} (2)$$

Particularly during the initiation reaction, a good portion of the reaction heat is accumulated in the reaction mixture, the vessel and the cooling jacket. The resulting heat fluxes are considered by the $\dot{Q}_{accu}$ and $\dot{Q}_{j,accu}$ terms respectively.

$$\dot{Q}_{accu} = \left( m_{r} c_{p,r} + C_{p,\text{app}} \right) \frac{dT_{r}}{dt}$$  \hspace{1cm} (3)$$

$$\dot{Q}_{j,accu} = \left( V_{j} \rho_{j} c_{p,j} + C_{p,j,\text{app}} \right) \frac{dT_{j}}{dt}$$  \hspace{1cm} (4)$$

The calculation of the heat flux caused by the dissipation energy of the stirrer $\dot{Q}_{st}$ is based on common NEWTON number correlations [4]. Especially, if the reactor temperature $T_r$ differs from the temperature of the dosed halide $T_{dos}$, the cooling or heating of the reactor mixture by the dosed liquid has to be considered. The corresponding heat flux $\dot{Q}_{dos}$ is calculated as follows:

$$\dot{Q}_{dos} = \dot{m}_{dos} c_{p,dos} \left( T_{dos} - T_{r} \right)$$  \hspace{1cm} (5)$$

The heat losses through the top of the reactor $\dot{Q}_{loss}$ and the cooling jacket $\dot{Q}_{j,loss}$ can be considered by experimental assessment of the heat flux coefficients at the target plant. Probably, more appropriate approach in order to consider the difficult to model heat losses and heat bridges at industrial plants would be the addition of correction terms to the heat balance. These terms include adaptive parameters, which can be determined by a neural network adaptation algorithm described in detail in [5]. However, a set of process signals of at least one batch at normal operating conditions is necessary in order to adapt the monitoring system to the target plant.

Assuming an instantaneous reaction according to the dosage of the organic halide $\dot{m}_{dos}$ (no accumulation of the halide), the heat release rate $\dot{Q}_{inst}$ can be calculated on the basis of the reaction enthalpy $\Delta H_R$ according to the following equation:

$$\dot{Q}_{inst} = (\cdot \Delta H_R) \frac{\dot{m}_{dos}}{M_{dos}}$$  \hspace{1cm} (6)$$

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

$$
\Delta Q_{R,\text{accu}} = \int_{t_{\text{start}}}^{t} (\dot{Q}_{\text{inst}} - \dot{Q}_{R}) \, dt' \\
n_{R,\text{accu}} = \frac{\Delta Q_{R,\text{accu}}}{-\Delta H_{R}}
$$

(7) (8)

Since the pre-filled and dosed amounts of reactants and solvents are known, the concentration profiles of the organic halide and the Grignard reagent during the process can be computed simply by application of appropriate mass balances.

In addition to the online monitoring of substance amounts and concentrations, the heat and mass balance approach opens up new opportunities in safety oriented process control strategies as well as process automation using online computing of safety-relevant parameters. The approach provides an estimation of the hazard potential caused by the reactivity of the halide accumulated in the reaction mixture. Assuming an adiabatic behavior as a worst case, the maximum temperature profile $T_{\text{ad,max}}$ can be estimated according to the following equation:

$$
T_{\text{ad,max}} = T_{r} + \frac{\Delta Q_{R,\text{accu}}}{m_{r} c_{p,r} p_{r}}
$$

(9)

The maximum reactor pressure profile $p_{\text{ad,max}}$ is primarily a result from the rise of the vapor pressure $p_{v}$ of the reaction mixture and secondarily from the expansion of the gas phase above the liquid surface. To simplify the calculations, the gas phase can be assumed to have the properties of an ideal gas.

$$
p_{\text{ad,max}} = \left[ p_{v}(T_{\text{ad,max}}) - p_{v}(T_{r}) \right] + p_{r} \frac{T_{\text{ad,max}} + 273K}{T_{r} + 273K}
$$

(10)

An objective evaluation of the process state is feasible at any time by comparing the time dependent courses of $T_{\text{ad,max}}$ and $p_{\text{ad,max}}$ with predefined by means of design parameters of the industrial plant and the initial response pressure of the safety valve respectively, thresholds.

4. Test results

After developing the approach by means of calorimetric experiments in the RC1 calorimeter, the monitoring system was tested at process conditions using results from two sets of experiments at 10 liters scale (see chapter 2).

As an example for the functionality of the method, selected results of Grignard reactions at common process mode (a) are displayed in Fig. 3 and Fig. 4. Fig. 3 shows the profiles of the heat release rate according to the heat balance $\dot{Q}_{R}$, the heat release rate of an assumed instantaneous reaction $\dot{Q}_{\text{inst}}$ and the integral value of the difference $\Delta Q_{R,\text{accu}}$ as a measure for the accumulated halide. The resulting concentration courses of the organic halide and the Grignard reagent are diagrammed in Fig. 4. The molar concentrations are calculated with respect to the total reaction mixture without consideration of the solid magnesium in order to be able to compare the results with related online FTIR measurements. Especially for the concentration profile of the organic halide accumulated during the process, the results of the monitoring system exhibit a good agreement with the FTIR measurements.
The highest amounts of organic halide occur after the dosage before the reaction starts and at the end of the main reaction stage. The accumulation rise at the end of the main reaction stage is caused by the decrease of the reaction rate due to the lack of magnesium.

Whenever a balance-based online 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 full automated process control strategies. To demonstrate the capabilities of the safety-oriented online monitoring, a set of experiments in non-stop semi-batch mode were carried out. Fig. 5 shows the concentration courses in comparison to FTIR measurements. Again, the results of the monitoring system are in good agreement with the related FTIR measurements.

By means of an online estimation of the safety-relevant parameters $T_{ad,max}$ and $p_{ad,max}$ according to Fig. 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 pre-defined thresh-
olds, the dosage of the organic halide can be interrupted by the process control system. Furthermore, the online data of $T_{\text{ad, max}}$ and $p_{\text{ad, max}}$ can be used as reference values for a full-automated dosage control of the halide.

5. Summary

The objective detection of the initiation reaction as well as of reactant accumulations during the process is of vital importance for the safety oriented process control of Grignard reactions. To establish industrially applicable methods for an objective online detection of the reaction start-up and for the accumulation of the organic halide during the process, miniplant studies of a special Grignard reaction using a 10 liters pressurized stirred tank reactor were carried out. Operating in closed systems opens up new opportunities with respect of the use of online monitoring systems. On the basis of the experimental results, a heat / mass balance-based online monitoring approach has been developed which is capable of providing the operator with additional information on the process state particularly for the accumulation of the organic halide. Additionally, the online estimation of the safety-relevant parameters, like adiabatic temperatures and pressures, enables application of advanced control strategies up to the point of a safety-oriented full automatic control of Grignard reactions. In the same time, such systems can contribute to improved process efficiency by increasing the space-time yield as well as to an improvement of the inherent process safety.

Nomenclature

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Br</td>
<td>bromine</td>
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<tr>
<td>FTIR</td>
<td>Fourier transform infrared</td>
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References