On-line monitoring of Grignard reactions

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Grignard reagents

Francois Auguste Victor Grignard (1871-1935)

Grignard found that magnesium reacts with alkyl and aryl halides to form organomagnesium compounds.

The Nobel Prize in Chemistry 1912

Grignard reagents

organomagnesium compounds

$$R - Mg - X$$

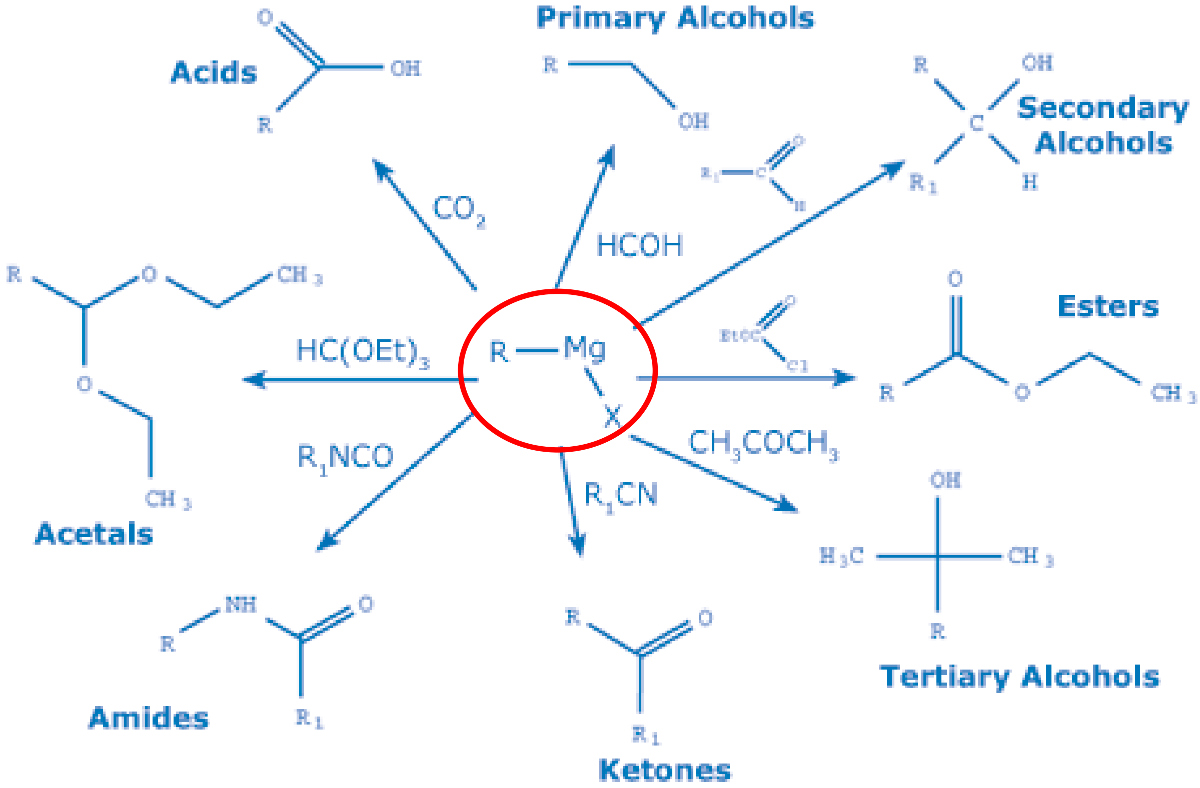
R: - alkyl residue
- aryl residue

X: halogen (Cl, Br, J)

Use of Grignard reagents

High reactivity of Grignard reagents $\Rightarrow$ intermediates for organic syntheses

fine chemistry, pharmaceutical industry, cosmetics industry



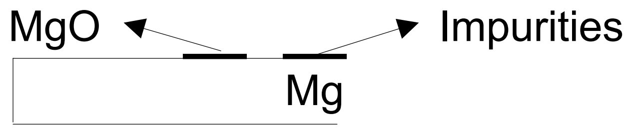
Reaction mechanism

Detailed reaction mechanism still unknown !

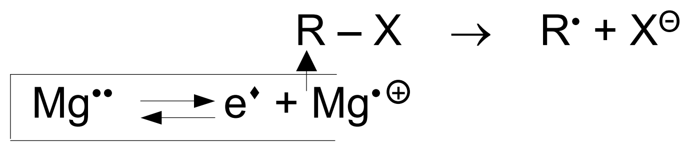
$$\underset{\text{organic halide}}{R-X} \quad + \quad \underset{\text{solid magnesium}}{Mg(s)} \quad \xrightarrow{Ether} \quad \underset{\text{Grignard reagent}}{R-Mg-X} \qquad \Delta H_R = \text{-}200\ldots\text{-}350\ kJ/mol$$

Assumed mechanism (simplified):

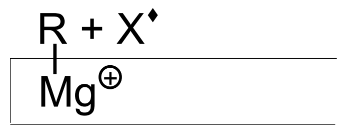
1. Mg activation by mass transfer



2. Electron transfer Mg $\rightarrow$ R



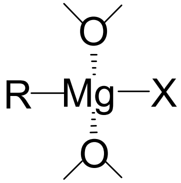
3. Bonding R – Mg



4. Dissolution and Grignard formation

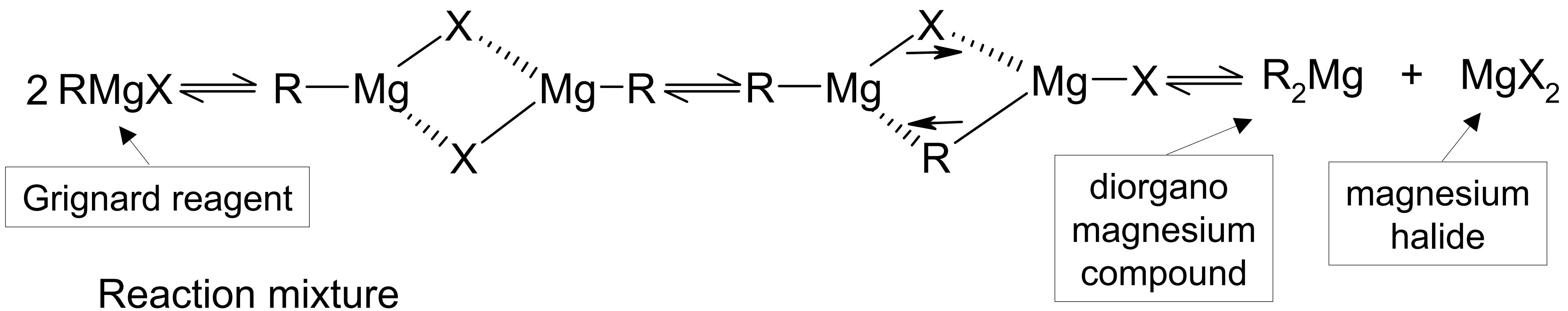
$R\text{ - }Mg^{\oplus} + X^{\bullet} \rightarrow R - Mg\text{ - }X$

5. Stabilisation of Grignard by solvent

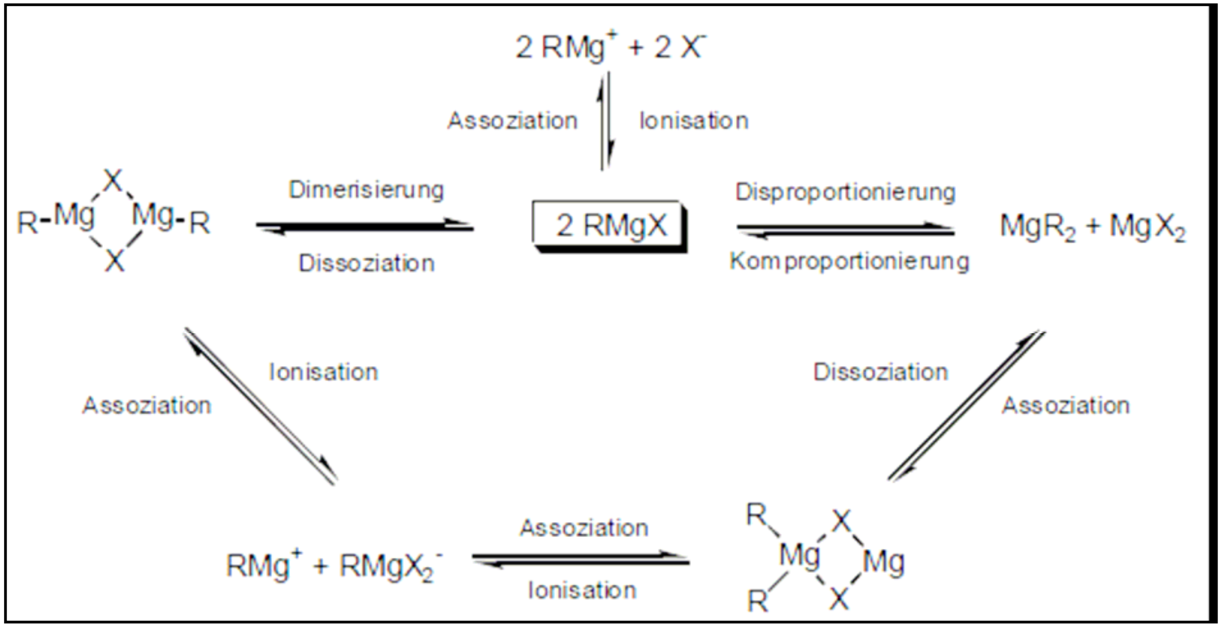


Schlenk equilibrium

Simplified mechanism



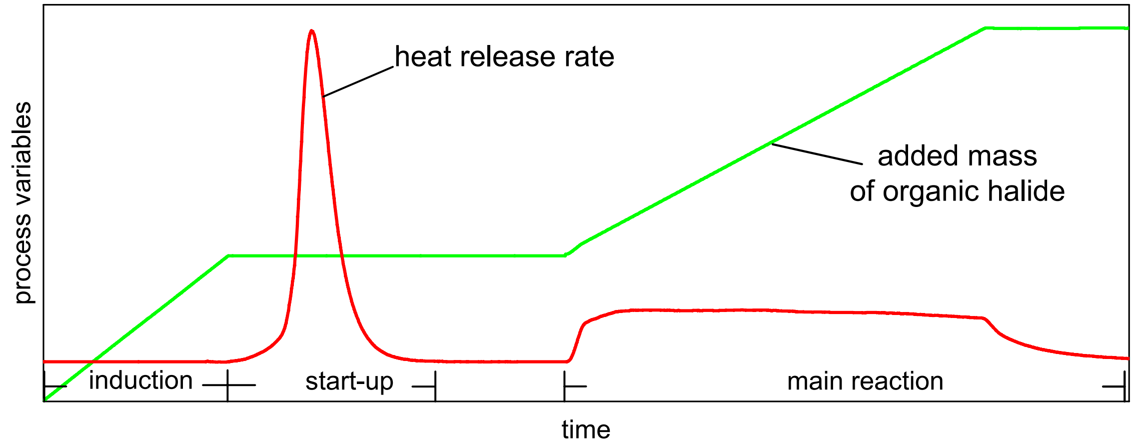
Reaction mixture



Process behaviour

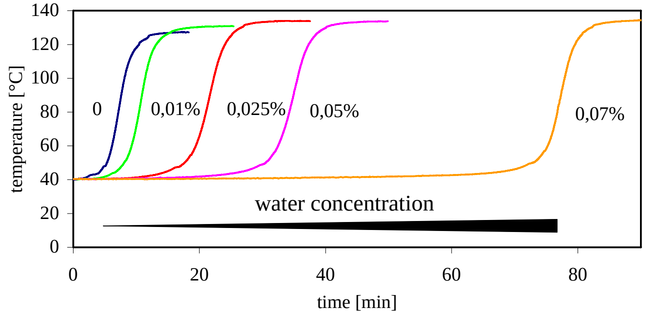
Complex reaction mechanism results in specific process behaviour

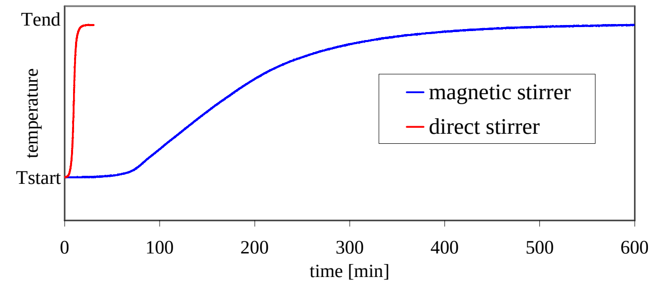
Thermal process course



No industrially applicable kinetics available !

kinetics = f { concentration, temperature, solvent, solvent purity, educt purity, mixing intensity, geometry





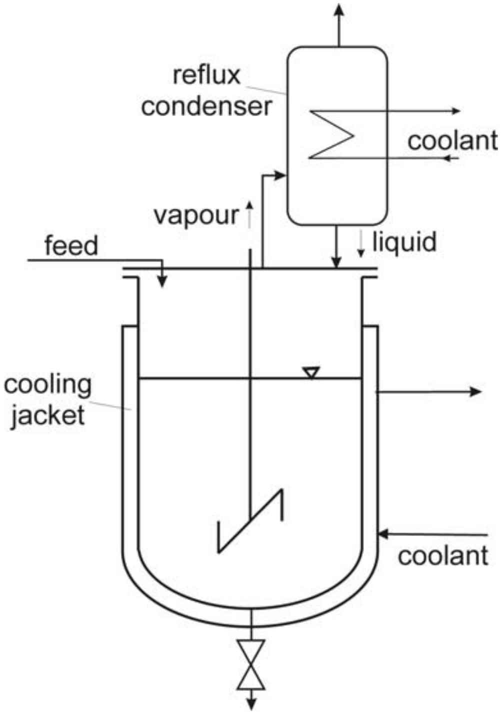
Common process control

Hazard potentials:

- strong exothermic reaction
- high reactivity of Grignard reagents (i.e. with impurities)
- start-up behaviour of the process (induction time, auto-catalysis)

Industrial process and apparatus:

- stirred tank reactor
- reflux cooling system
- boiling temperature
- semi-batch process (dosage of organic halide)
- start and main reaction separated



Common process control

Pros and cons of an open vessel system

Pros:
- no pressurised vessel
- second cooling system to quench exothermic peaks

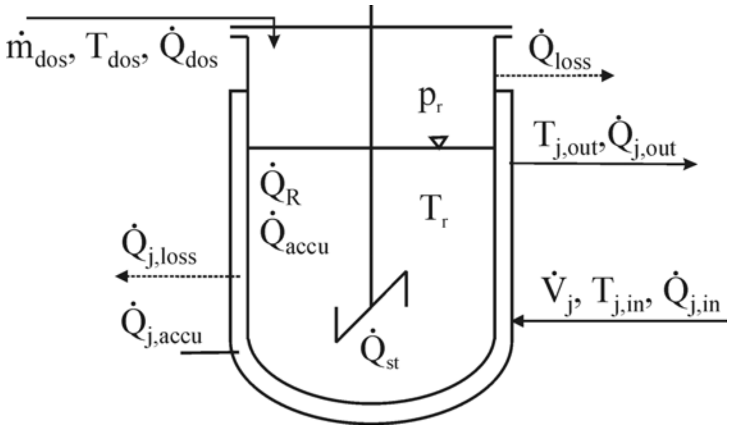
Cons:
- reaction stop and/ or to undesired exothermic side reactions due to impurity intrusion (e.g. air moisture due to solvent hygroscopicity)
- increased risk of hazardous substance emissions
- second cooling system required (Malfunctions increase the hazard potential of the process.)
- undesired reactions inside the cooler in case of reflux cooler coil leakage
- reaction temperature limited by the boiling point of the solvent
- complicated detection of reaction start or stop

Aim:
- modification of process control
- development of industrially applicable methods for an objective detection of the reaction start and for on-line detection of educt accumulation

On-line monitoring approach

On-line monitoring of concentration courses using heat flow/ mass flow balances

Precondition: pressurised stirred tank reactor !



heat balance:

$$\dot{Q}_R = \Delta\dot{Q}_j + \dot{Q}_{accu} - \dot{Q}_{st} - \dot{Q}_{dos} + \dot{Q}_{j,accu} + \dot{Q}_{loss} + \dot{Q}_{j,loss}$$

calculation of the heat balance terms:

$$\Delta\dot{Q}_j = \dot{Q}_{j,out} - \dot{Q}_{j,in} = \rho_{j,in}\dot{V}_j\left(c_{p,j,out}T_{j,out} - c_{p,j,in}T_{j,in}\right)$$

$$\dot{Q}_{accu} = \left(m_R\, c_{p,R} + C_{p,app}\right)\frac{dT_R}{dt}$$

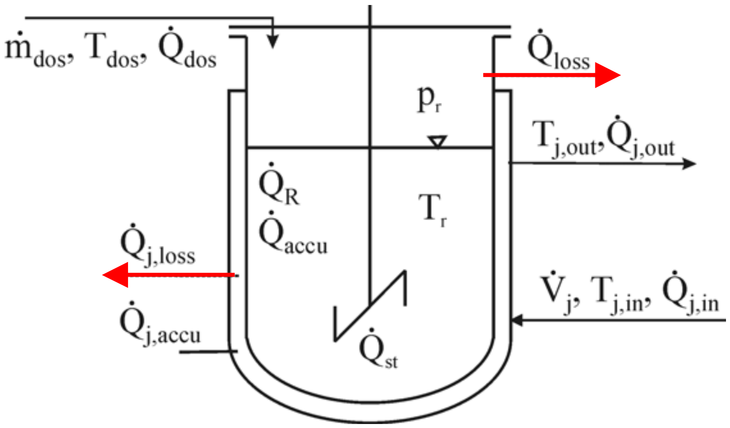
$$\dot{Q}_{dos} = \dot{m}_{dos}\, c_{p,dos}\left(T_{dos} - T_R\right)$$

$$\dot{Q}_{j,accu} = \left(V_j\, \rho_j\, c_{p,j} + C_{p,j,app}\right)\frac{dT_j}{dt}$$

$$\dot{Q}_{st} = f\left(Re, Geometry\right)$$

$$\rho, c_p, \eta = f\left(T, c\right) \qquad C_{p,app} = f\left(\frac{dT}{dt}\right)$$

On-line monitoring approach



consideration of heat losses

- ~~empirical correlations~~ ~~Q_{loss} = f(Re, Nu, Pr…)~~
- non-reactive experiment at target plant
- adaptive terms (MoSys approach)

instantaneous reaction (no educt accumulation):

$$\dot{Q}_{inst} = (-\Delta H_R)\frac{\dot{m}_{dos}}{M_{dos}}$$

heat difference to the balance result:

$$\Delta Q_{R,accu} = \int_{t_{start}}^{t} \left(\dot{Q}_{inst} - \dot{Q}_R\right) dt'$$

amount of accumulated educt:

$$n_{R,accu} = -\frac{\Delta Q_{R,accu}}{\Delta H_R}$$

calculation of concentration profiles by mass balances

Test of the method

Test reaction

$$R-Br \quad + \quad Mg(s) \xrightarrow{THF} R-Mg-Br$$

bromobenzene derivative — magnesium — organomagnesium bromide

Reaction enthalpy

ΔH_R = -(307±5) kJ/mol

RC1/HP60 measurements (closed system)

Process control

- miniplant: ALR 10 L pressurised stirred tank reactor
- isoperibolic temperature regime ($T_{j,in}$ = const.)
- semi-batch: dosage of the bromobenzene derivative
- recipe according to an industrial process

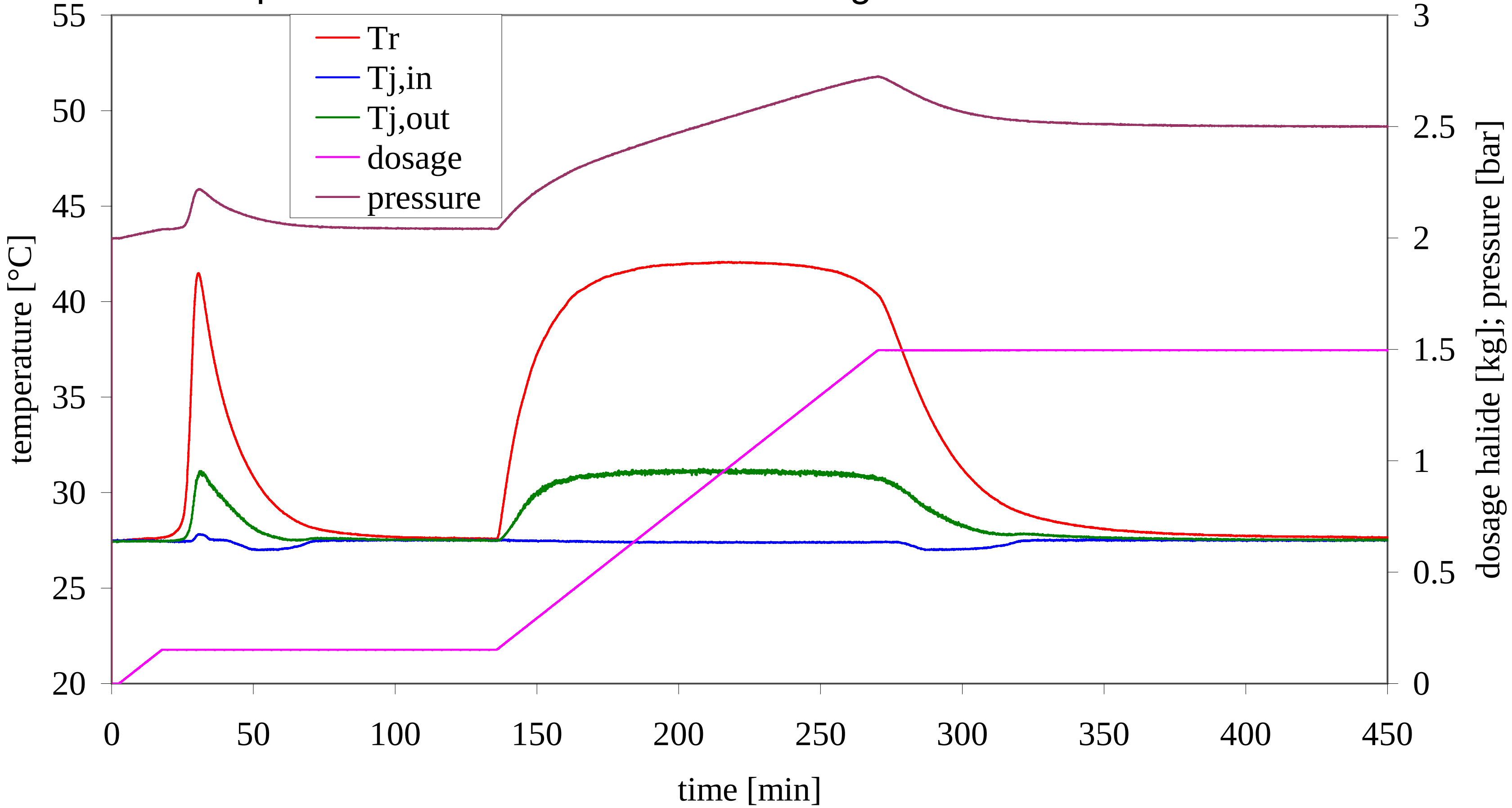
Validation of the results

in-situ FTIR spectroscopy

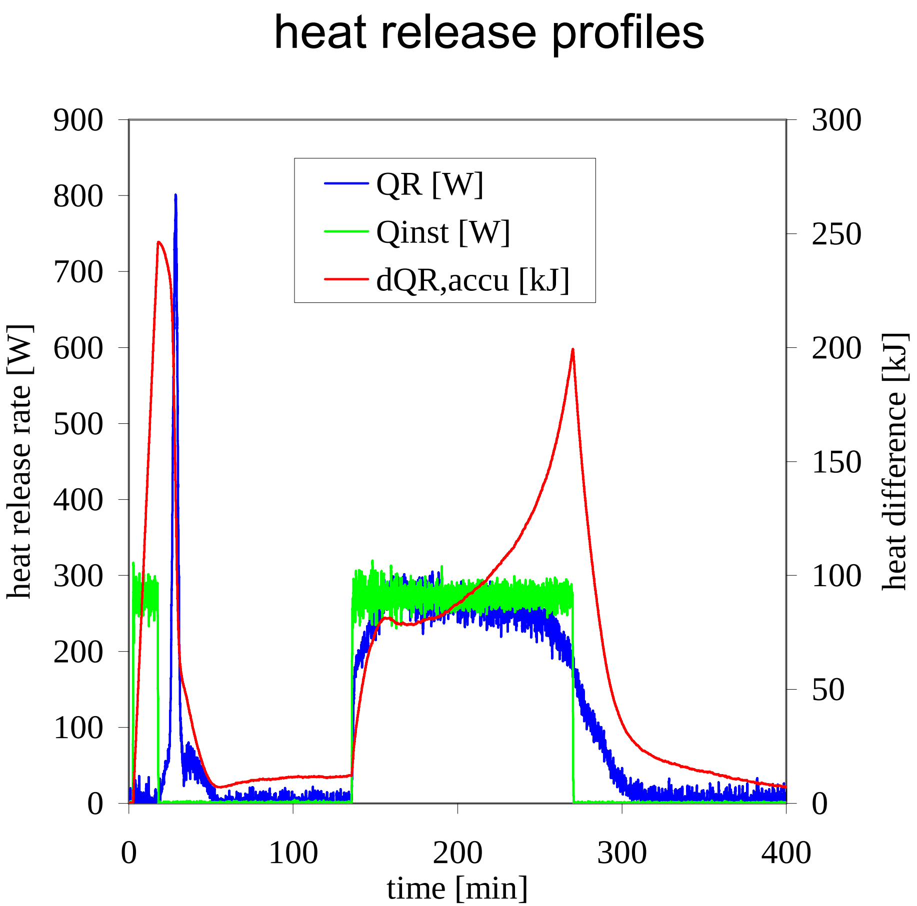
Test results

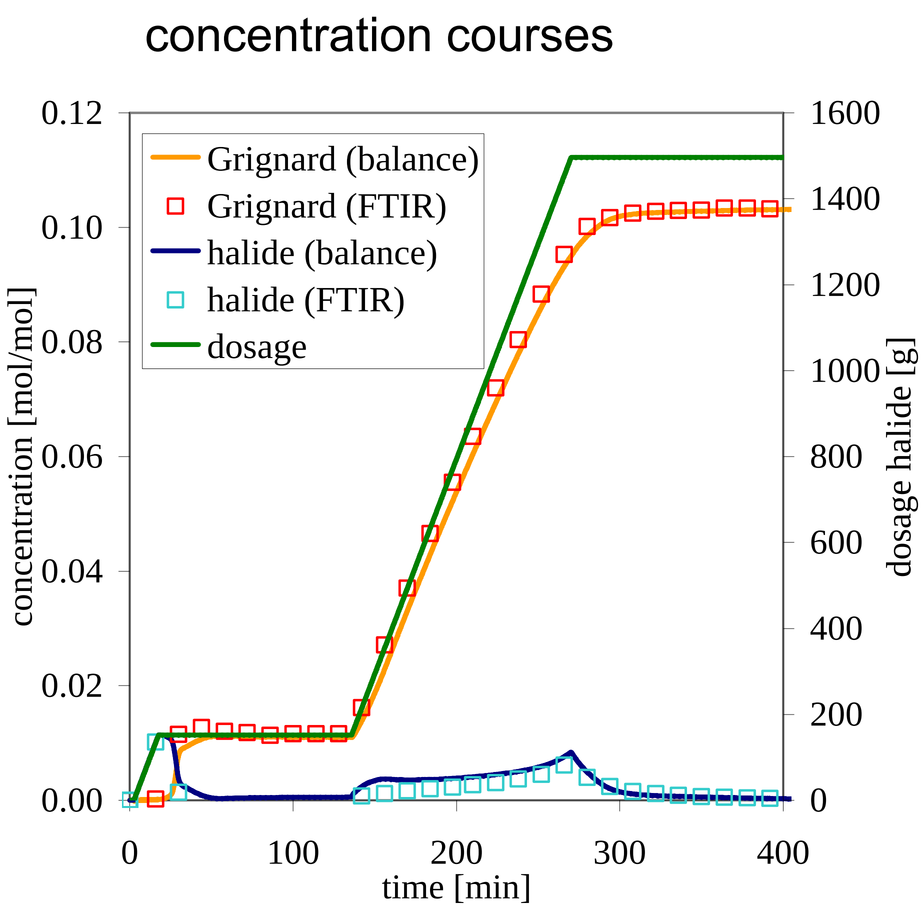
profiles of process variables during a Grignard reaction in the 10 L STR

- $T_{j,in}$ = 27°C
- separated start and main reaction stage



Test results





good match between monitoring results and FTIR measurements
⇒ heat/ mass balancing method suitable for on-line monitoring of Grignard reactions

Improvement of the method

- non-stop semi-batch mode with continuous dosage of organic halide would improve process efficiency (space time yield)
- application of advanced control strategies $\Rightarrow$ safety-oriented full automatic control

On-line estimation of safety-relevant parameters

$\Rightarrow$ on-line worst case calculations

assumptions:

- adiabatic runaway $\Rightarrow$ $\dot{Q}_R = \dot{Q}_{accu}$
- temperature and pressure rise up to the complete consumption of the accumulated reactants

maximum adiabatic temperature:

$$T_{ad,max} = T_r + \frac{\Delta Q_{R,accu}}{m_r \, c_{p,r}}$$

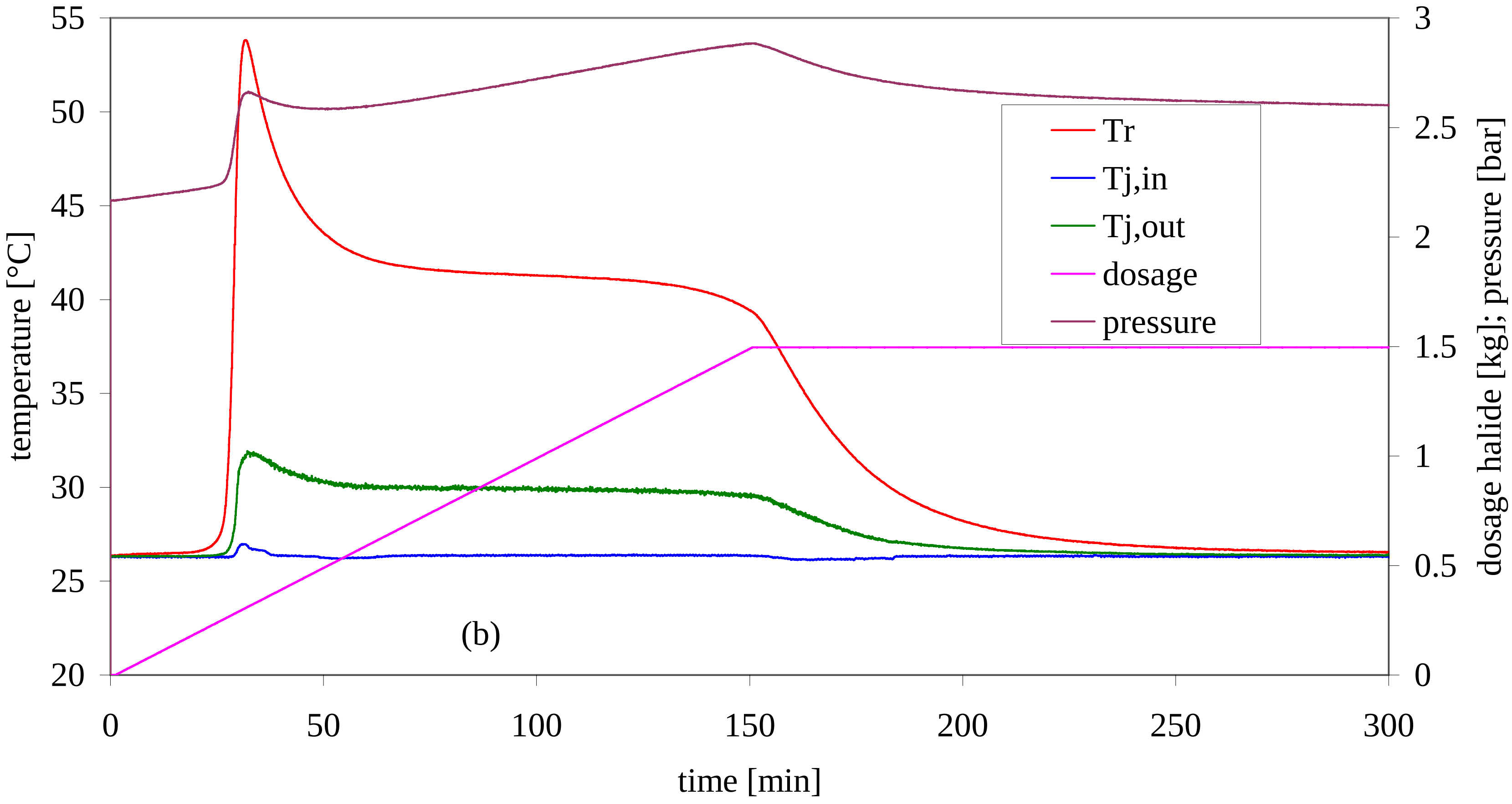
maximum adiabatic pressure:

$$p_{ad,max} = \left[p_v\left(T_{ad,max}\right) - p_v\left(T_r\right)\right] + p_r \frac{T_{ad,max} + 273\,K}{T_r + 273\,K}$$

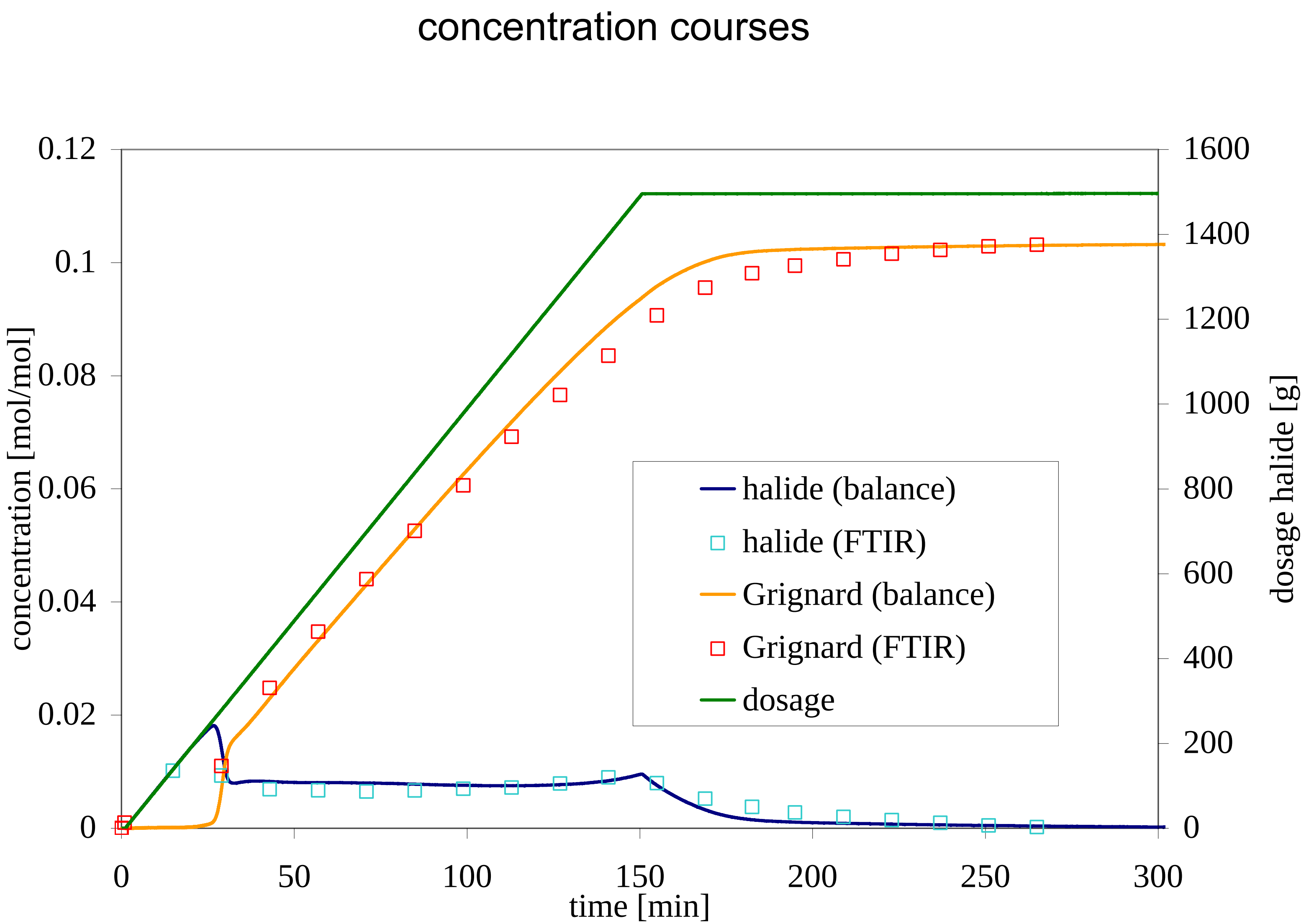
Test results

profiles of process variables during a Grignard reaction in the 10 L STR

- $T_{j,in}$ = 27°C
- non-stop semi-batch mode (continuous dosage of organic halide)

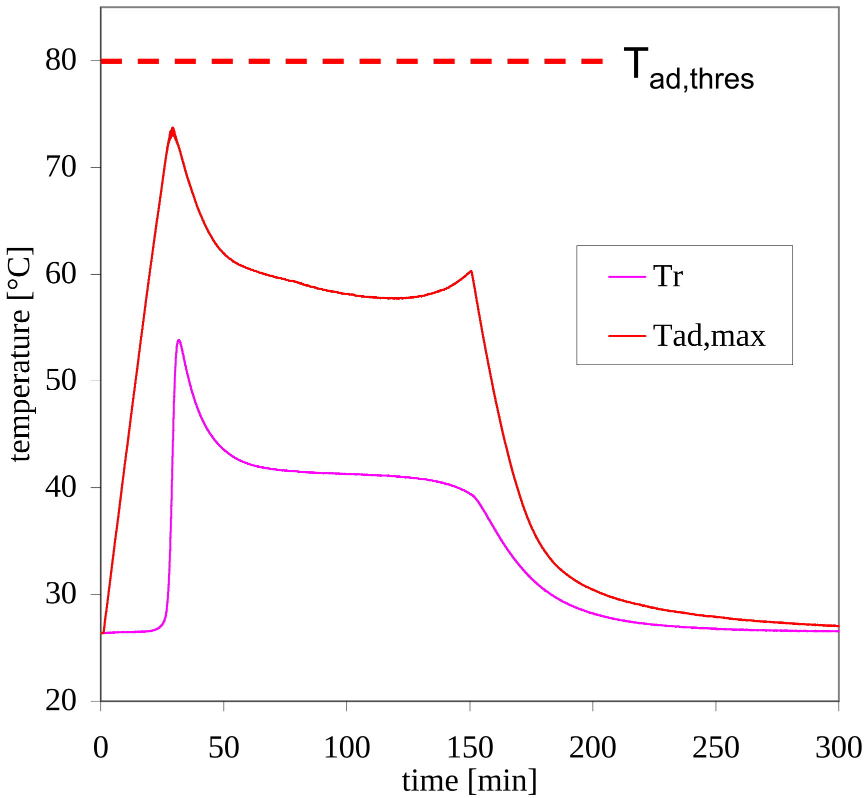


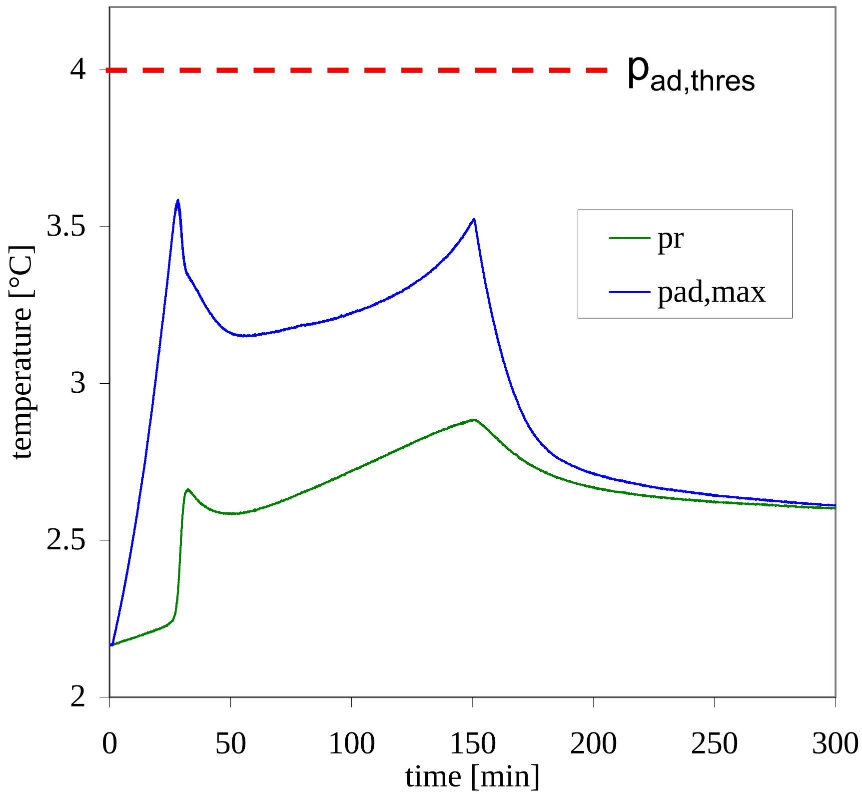
Test results



Test results

profiles of safety-relevant parameters

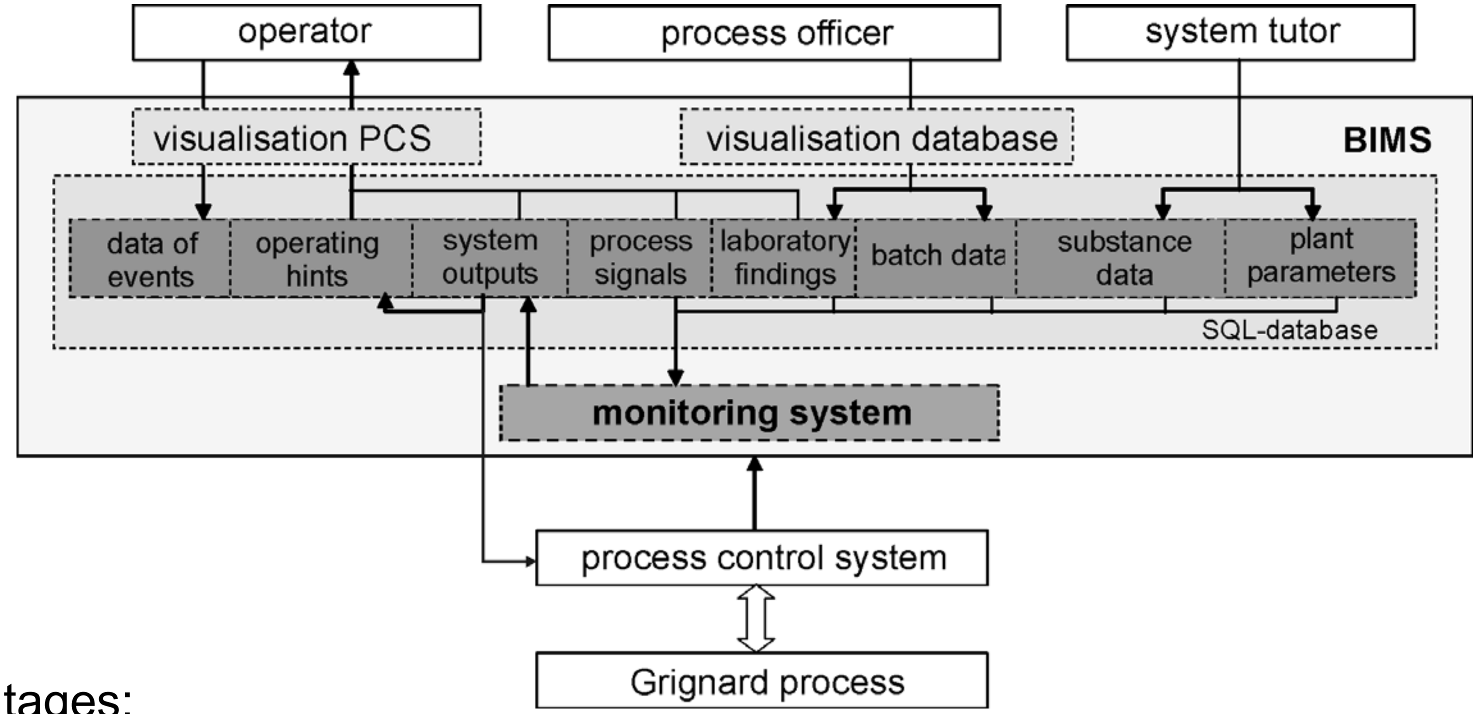




application of safety-oriented monitoring strategies by on-line comparison of $T_{ad,max}$ and $p_{ad,max}$ with pre-defined thresholds

Application at an industrial plant

the monitoring system as an integral part of a batch information system (BIMS)



Advantages:

- batch-wise data storage together with process signals, laboratory findings, plant and substance parameters
- traceability of complex batch processes (e.g. hazardous operating state, batch with bad product quality)
- optimisation of chemical batch processes by evaluation of archived data

Comparison of detection methods for Grignard processes

method	start-up detection	quanti-tative monitoring	pros	cons
primary process signals (p_R, T_R)	+	-	easy to use cost-efficient	dependent on process control misinterpretations possible
measurement of reflux flow rate	+	-	easy to use	applicable only to open systems additional sensor required
on-line FTIR-spectroscopy (qualitative)	+	-	independent of process control	high investment cost high operating costs local measurement
on-line FTIR-spectroscopy (quantitative)	+	+	independent of process control	high investment cost high operating costs high calibration effort local measurement
balance-based monitoring	+	+	cost-efficient virtually independent of process control (pressurized vessel recommended)	advanced knowledge of process and plant parameters required

Summary

- pressurised vessel process control of Grignard reactions has a number of advantages compared to the use of an open system

  ⇒ use of balance-based on-line monitoring methods
- the on-line monitoring approach is capable to detect the reaction start as well as concentration courses of educts and products with sufficient accuracy
- quantitative on-line monitoring opens up new perspectives regarding safety control strategies for Grignard processes

  ⇒ the next step: use of the safety-relevant on-line data as reference values for full-automated dosage control
- modification of process mode (non-stop dosage) leads to an improvement of process efficiency

  ⇒ time saving compared to common process mode ~25% !
- on-line monitoring systems as integral part of PIMS/BIMS provide the basis for further process optimisation