



**Grignard-reagent formation in
Multi-product facilities – not an easy
task!**

**A fascinating synthesis tool in laboratory.
Unfortunately, it is difficult to transfer
into the large-scale production.**

Editor

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Grignard-reagents are challenging synthesis tools for Multi-product chemistry. They enable the manufacture of economically interesting chemicals. Grignard-reagents are made by transformation of organic halides with metallic magnesium in heterogeneous reaction systems –mostly under reflux conditions. Their processes are highly exothermic and sometimes difficult to get started. Some result in large halide accumulations and therefore carry a high risk of runaway reactions.

In general, chemical production processes should be designed in a way that they can safely be carried out in the Multi-product facilities. On the one hand, the development of safe chemical processes requires a good process knowledge. On the other hand, the experimental skill that is used for this task reflects the accumulated experience of the synthetic chemists but not on that of chemical engineering. This is a lack because only for known hazards is it possible to develop safe chemical reaction steps. Especially for highly exothermic chemical reactions, it is essential to know their behaviour over the whole course of reactions.

The transformation of organic halides with metallic magnesium follows various macro-kinetic mechanisms. Some halides react mass transport-limited. In this cases, the reaction rates depend on the measurable concentration of the organic halide in reaction-media, on undefined and unmeasurable physical characteristics of the magnesium surface and on the speed of agitation of reaction-mass. Other halides do not react mass transport-limited. Then, the reaction rates depend not only on the mentioned parameters, but also on polarity of reaction-medium, which changes with reaction-progress. For these Grignard-reagent formations, it is more difficult to develop safe production processes.

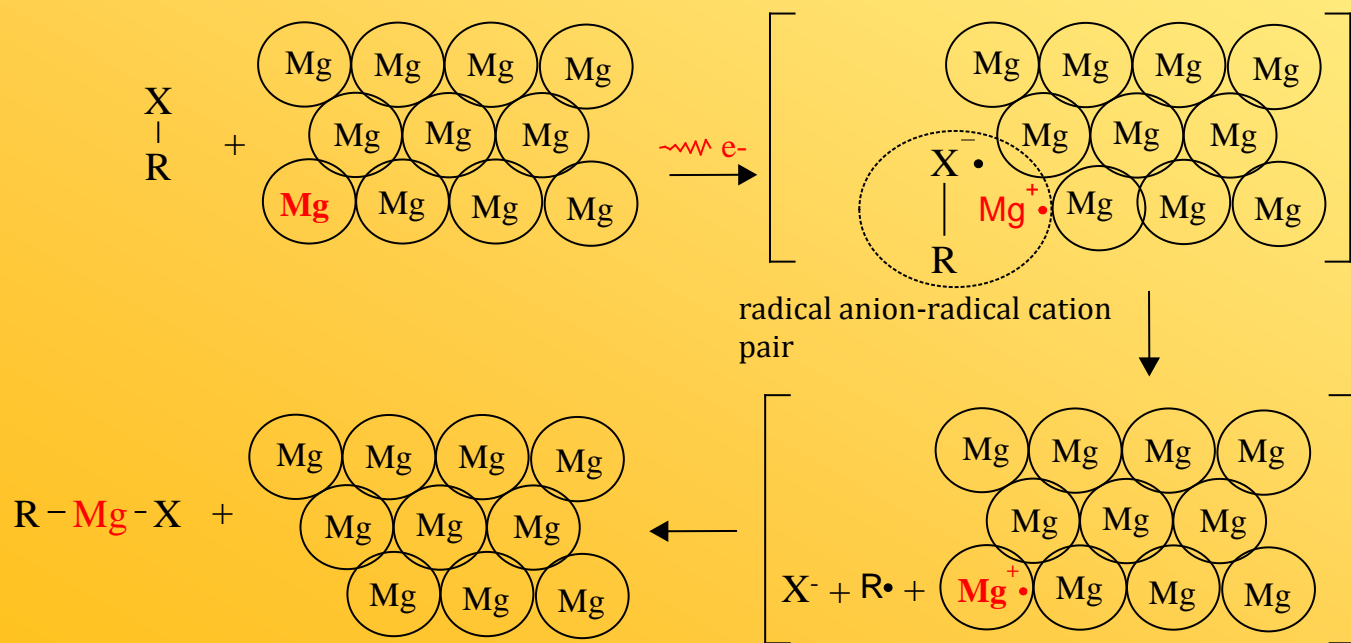
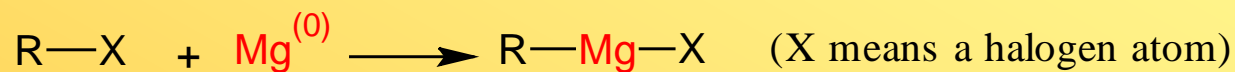
Today, Multi-product chemistry is interested in using organic chlorides for the Grignard-reagent formations, as they are cheaper than the organic bromides. However, for organic chlorides is the development of safe chemical reaction processes very tricky.

This publication illustrates the safety-relevant features of Grignard-reagent formations. It shows the influencing parameters, with which safe Grignard-reagent formation processes can be developed. With a case study –based on reaction-calorimetric methods– the process development effort is outlined, which is necessary in order to transfer a laboratory process into a Multi-product plant.

What can we learn from literature in order to develop safe Grignard-reagent formation processes?

The question how in an organic halide the magnesium atom is inserted between the carbon-halogen bonds is a subject that is still not fully understood. Simply formulated, the formation of Grignard-reagent is as follows:

It seems that all the processes involved in the Grignard-reagent formation run on the surface of magnesium.



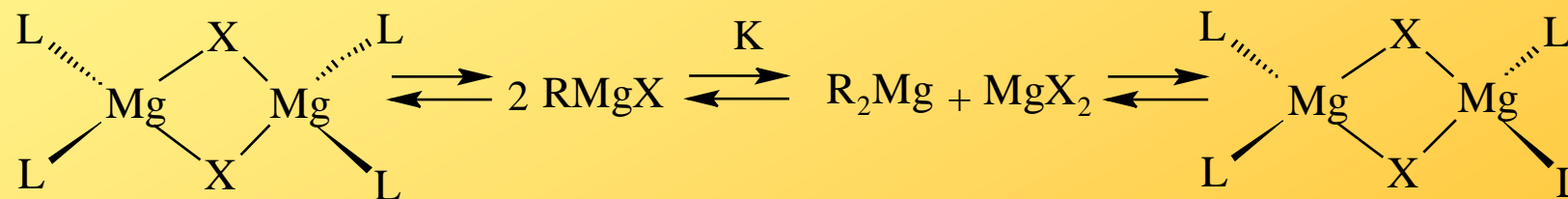
A brief summary of the knowledge of the involved processes is given below. [1]:

First, the halide adsorbs on the magnesium surface. Then, the rate-determining step takes place, the electron transfer from the magnesium surface into the σ^* anti-bonding orbital of the carbon-halogen bond, which forms a tight **radical anion-radical cation pair** as transition state or as an intermediate (schematically sketched in figure 1).

Figure 1

Following, free radicals are generated –either by a concerted electron transfer bond breaking or by the dissociation of a tight radical anion-radical cation pair– in order to produce loose radical pairs that are adsorbed on the magnesium surface. The amount of the latter depends on the strength of the carbon-halogen bond. The weaker the bond –or, the other way round, the lower the reduction potential– the greater the amount of loose radical pairs. In other words, in the mechanism proposed, the amount of these pairs would be predicted to increase in going from C-Cl, to C-Br, to C-I, and from sp^2 , to sp^3 .

The Grignard-reagent molecule exists in an equilibrium with other species the «Schlenk equilibrium» (simplified in figure 2).



L = donor solvent molecules (ether, THF)
 K = equilibrium constant (K= 0,2 für EtMgBr)

Figure 2

A stoichiometric mixture of MgX_2 und R_2Mg in ethers behaves chemically like a conventionally produced Grignard-reagent.

The influences of solvents, concentrations and the nature of R on the structure of the Grignard-reagent are various. (figure 3):

- In tetrahydrofuran (THF) the structure of R-MgX is in a wide range of concentrations monomeric as $R-MgX \cdot (THF)_2$.
- In higher concentrations, dimeric and oligomeric species are formed (figure 3). This transformation splits off THF molecules.

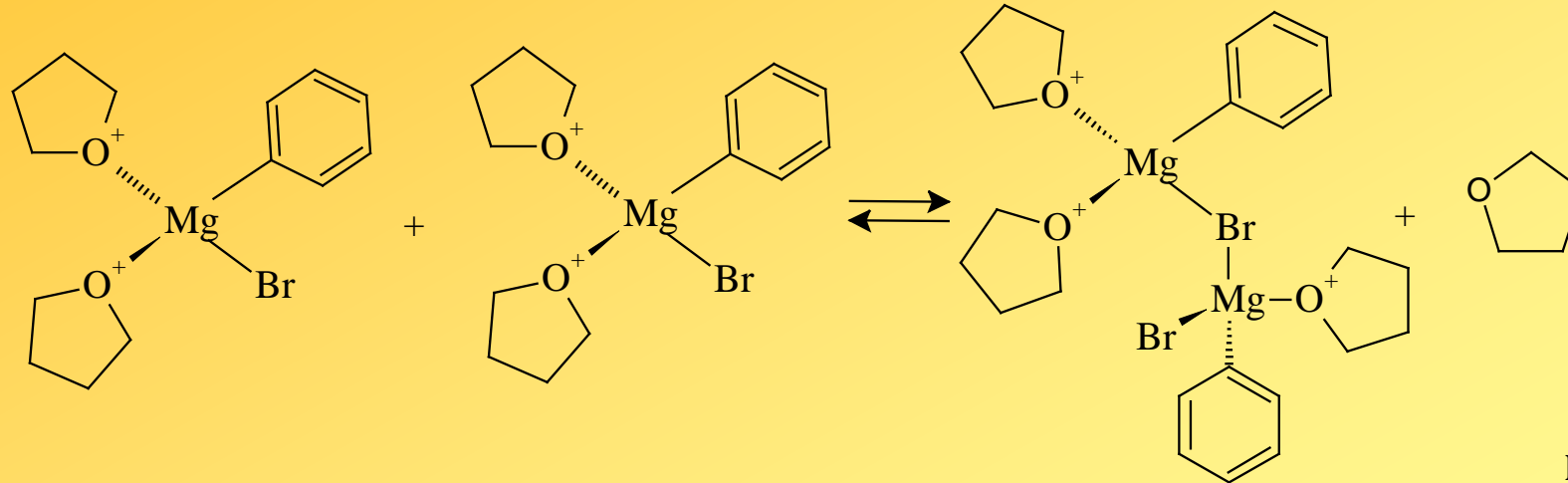


Figure 3

The formulated mechanism is not only of academic interest –it can be safety-relevant. It may lead to a sudden release of solvent, because of the fast changing boiling temperature of the reaction mass. That is caused by the instantaneous boiling point decrease (see figure 13). In the large-scale production, this behaviour may lead to a froth over of the reaction mass.

Macro kinetic aspects of Grignard-reagent formation

In the seventies of the last century, scientists tried to define the rate-determining step for the formation of Grignard-reagents [2]. By using the constant-surface technique, they have measured the rate of decrease of organic halides in contact with a large mass of magnesium in the reaction media. This technique has allowed to carry out the experiments without significant changes of the magnesium surface; other parameters of the reaction mass such as temperature, stirring, polarity and viscosity were variable. With these experiments many interesting discoveries were made. Its knowledge helps to develop safe Grignard-reagent steps. Such as, the rates of reaction of cyclopentyl bromide and cyclopentyl chloride with magnesium are proportional to the exposed surface area of the metallic magnesium. Or else, cyclopentyl bromide reacts mass transport-limited, but not so cyclopentyl chloride. See the following discussion.

First, the comparison of the rates of reaction of cyclopentyl bromide and of cyclopentyl chloride with magnesium in solvents of different viscosities have shown that on the one hand the relative rates of reaction of cyclopentyl bromide with magnesium in different solvents were proportional to the inverse of the solvent viscosity, on the other hand the reaction of cyclopentyl chloride was insensitive to the solvent viscosity but 102 times slower [3].

Second, the comparative study for cyclopentyl bromide and cyclopentyl chloride have shown that the rate of reaction of cyclopentyl bromide is dependent from the stirring rate. However, not so the rate of reaction of cyclopentyl chloride. It can be expected that the increase in the stirring rate decreases the thickness of the boundary layer at the magnesium. For a transport-limited chemical reaction, this would increase the rate with which the halide reaches the metal surface and the speed of reaction should be higher. Hence, it can be stated that cyclopentyl bromide reacts transport-limited but not so cyclopentyl chloride.

Third, the measured energy of activation for the chemical reaction of cyclopentyl bromide in diethyl ether with magnesium is low ($E_a = 9.4$ kJ/mol). As is known, the free energy of activation for diffusion of low molecular weight compounds in solvents of low viscosity is small (about 8 to 20 kJ/mol). This indicates that not the activation energy of the

chemical reaction was measured but that of the mass transport. It signifies that the chemical reaction in question is transport-limited. The activation energy for the isolated chemical reaction is significantly higher. For example, the activation energy for ethyl chloride is about 124 kJ/mol.

Further important characteristics are

- The rate of reactions of neopentyl bromide and of aryl bromides are mass transport-limited in tetrahydrofuran and more polar solvents but not in diethyl ether and less polar solvents. Among other organic bromides, they provide examples of reactions whose rate can be adjusted from non-transport-limited to transport-limited by small changes in reaction medium.
- The rate of reaction of aryl iodides reacts transport limited, even in diethyl ether.
- Aryl chlorides react not mass transport-limited over a broad region of reaction-media's polarities. Chlorobenzene reacts with magnesium in diethyl ether 10^4 times slower than bromobenzene.

What is transport-limited –and why knowledge of macro-mechanism is so vital for process development?

The Grignard-reagent formation is a heterogeneous chemical reaction system. In the reaction system, the halide is diluted in a solvent and the magnesium will be whirled up by rapidly stirring the reaction mass. Even with very good stirring, the liquid cannot be stirred up to the magnesium surface. Between the liquid and the magnesium surface there is a film-layer in which the liquid will not be mechanically moved. For the chemical reaction, the molecules must move by diffusion through this film to the surface of the magnesium. This requires a certain time (figure 4). Therefore, the speed of reaction depends on the speed of diffusion of organic halide molecules through the film layer and on the speed of reaction of the halide with magnesium.

speed of formation = speed of diffusion + speed of reaction

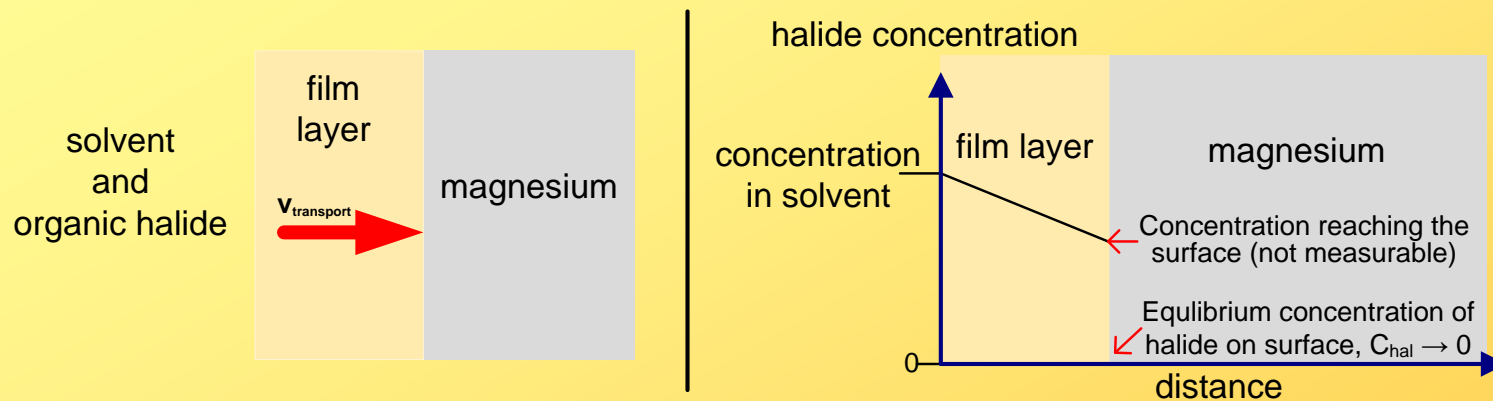


Figure 4

If the reaction rate of the organic halide with magnesium is much faster than the diffusion rate, the rate of diffusion becomes limiting; the overall speed of reaction is «transport-limited». Therefore, the maximum rate of reaction of dissolved halide and magnesium is reached, when the transport limitation reduces the halide concentration to zero at the magnesium surface.

Visualising the kind of macroscopic reaction mechanism

The influence of reaction-media's dielectric constant on the reaction rates of halides with magnesium can be visualised by comparing their reaction rates with that of a suitable organic halide. The conversion of cyclopentyl bromide with magnesium is very fast and transport-limited in the whole range of the measured media's dielectric constant and therefore suitable for this purpose. Forming the quotients of the corresponding reaction rates with that of cyclopentyl bromide provides a measure that separates the speed of reactions of different halides.

$$\text{relative rate} = \frac{\text{measured speed}}{\text{speed of cyclopentyl bromide}}$$

The method allows on the one hand comparing the reactivity of different halides and on the other hand to reveal their macroscopic mechanism. Figure 5 shows the comparison of the reaction courses of cyclohexyl bromide, neopentyl bromide and cyclopentyl chloride. By analysing the relative reaction rates, interesting statements can be made. Such as, the

- relative rate of reaction of cyclohexyl bromide is nearly insensitive to the polarity of reaction-media but it differs by the factor of 0.9 of that of cyclopentyl bromide.
- relative reaction rates of neopentyl bromide and cyclopentyl chloride are sensitive to solvent polarity. However, that of neopentyl bromide is much more sensitive to the dielectric constant (ϵ) of the reaction mass. A change from $\epsilon \cong 3$ to $\epsilon \cong 6$ increases it drastically. Above $\epsilon \cong 12$, the chemical reaction also becomes transport limited.
- relative rate of reaction of cyclopentyl chloride is less sensitive to solvent polarity than that of neopentyl bromide. A change from $\epsilon \cong 3$ to $\epsilon \cong 36$ approximately doubled it (figure 5).
- course of relative rate of reactions of neopentyl bromide and bromobenzene –and presumably that of the other organic bromides, which react in dimethyl ether at a rate less than transport-controlled– are remarkable.

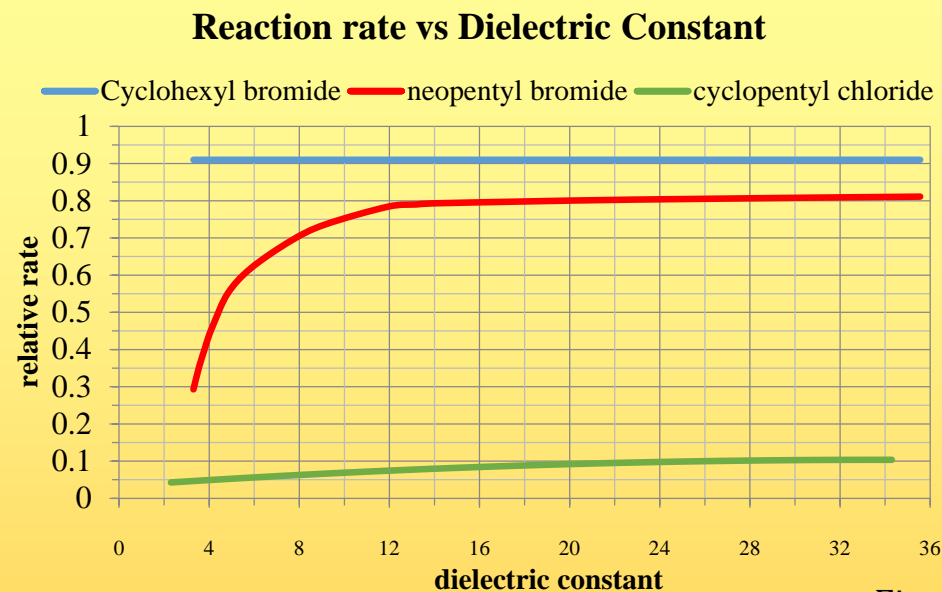


Figure 5

- They provide examples of reactions whose rate can be adjusted from non-transport-limited to transport-limited by small changes in reaction-media.

Based on the following reaction rate equation we will try to bring some order to the described reaction behaviours.

$$-\frac{d(R - X)}{dt} = \alpha_g * S_{Mg} * [R - X]^n$$

In this equation, α_g characterises the behaviour of chemical reaction. However, α_g is not only temperature dependent, rather it is a function with two dependencies; on the temperature and –sometimes to a big extent– on the polarity of reaction-mass, it means; $\alpha_g = f(T, polarity)$. And S_{Mg} takes into account all the magnesium surface characteristics that influence the reaction rate.

Fully transport-limited Grignard-reagent formation: The speed of reaction is independent on the polarity of reaction-mass. Hence

- $\alpha_g = f(T, mixing)$; α_g is constant at isothermal conditions and at constant mixing. It is not much temperature dependent. Because the speed of transport of halide through the film is not as much temperature dependent as a chemical reaction.
- $S_{Mg} = f(t)$; The value of S_{Mg} decreases during the Grignard-reagent formation.

Partly transport-limited Grignard-reagent formation: The speed of reaction is dependent on the polarity of reaction-mass up to a certain value of the dielectric constant. After that, the speed of reaction is independent on the polarity of it. Hence

- $\alpha_g = f(T, polarity)$: This is so up to a certain dielectric constant of reaction-mass. After that $\alpha_g = f(T, mixing)$, α_g is constant at isothermal conditions and constant mixing.
- $S_{Mg} = f(t)$: S_{Mg} decreases during the Grignard-reagent formation.

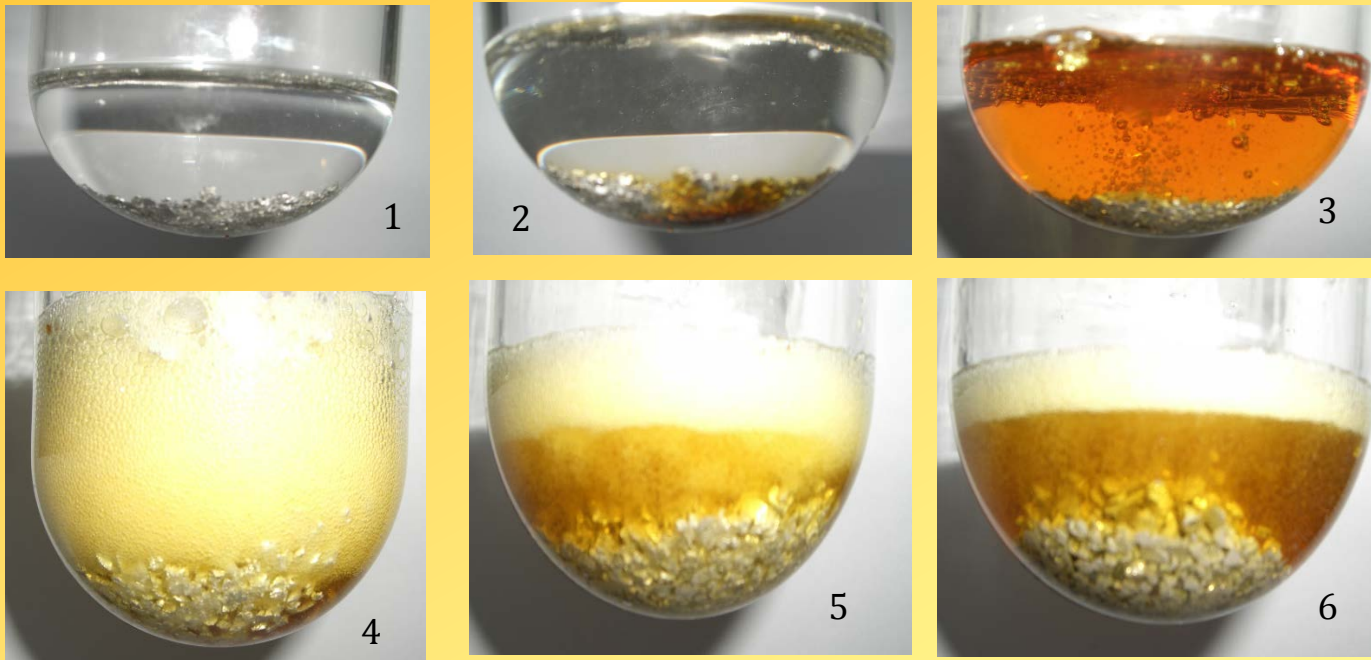
Not transport-limited Grignard-reagent formation: The speed of reaction is dependent on the polarity of reaction-mass.

- $\alpha_g = f(T, \text{polarity})$, over the whole Grignard-reagent formation. It shows a temperature dependency in the order of ordinary chemical reactions.
- $S_{Mg} = f(t)$; S_{Mg} decreases during the Grignard-reagent formation.

Facts –fundamental for development of safe Grignard-reagent formation steps

- The conversions of organic halides with magnesium to Grignard-reagents run by different macroscopic mechanisms. Consequently, to develop a safe reaction step, it is crucial to understand the appropriate macroscopic mechanism.
- The polarity of reaction-medium –measured by its dielectric constant– depends on the concentration of Grignard-reagent. Its dielectric constant increases during the course of Grignard-reagent formation.
- Some Grignard-reagent formations run transport-limited over the whole concentration range. Hence, the halide concentration, the quality of stirring and the reaction temperature determine the speed of reaction. In this case, the speed of reaction can be controlled by the speed of halide dosing. That means that it must be tailored to the reactor coolant-capacity.
- Others accelerate up to a specific Grignard-reagent concentration. After this concentration –a certain dielectric constant– is reached, the reaction rate depends only on the available halide; despite increasing polarity. Consequently, during the acceleration phase unreacted organic halide accumulates in the reaction-mass. That is dangerous for process safety, because this may lead in a runaway reaction. The tolerable amount of halide accumulation must be adjusted to the reactor's cooling capacity. The dosing step must be tailored to the used reactor system by process development. Safe process conditions are closely linked with the used reactor system. The chemical reaction-step is not inherently safe.

- Again others, accelerate over the whole concentration range. If the acceleration is large in relation to polarity of the chemical reaction system, then, the Grignard-reagent formation step is difficult to run in large-scale production. Because for large-scale production, the influence of a doubling of the reaction speed is significant for process safety. No matter whether the heat of reaction is removed via the reactor wall or via the reflux system.
- Figure 6 visualizes the behaviour of a reaction mass of Grignard-reagent formation due to its acceleration that was caused by halide accumulation. Picture 1 shows magnesium in solvent with halide; picture 2 the starting procedure with iodine; pictures 3 the slow reacting phase and picture four the very fast reacting phase. Figure 8 shows such a behaviour of the reaction mass with a very fast increasing heat flow curve. Finally, the pictures five and six show the decreasing reaction speed due to lowering halide accumulation.



The volume of reaction undergoes a large expansion because the speed with which vapour breaks through the liquid surface is limited. The reaction mass swells and forms a foam, see pictures 4, 5, and 6 in figure 6. It is easy to imagine that such a behaviour of Grignard-reagent formation cannot be controlled in a large-scale reactor of a Multi-product plant. The accumulation is too large.

Figure 6

Features of Grignard-reagent formation –some insights by reaction calorimetric experiments

Influencing parameters –important for developing safe Grignard-reagent formation steps

In this chapter, heat-flow curves of selected experiments will be discussed with respect to the influencing parameters, such as polarity, concentration, surface-mass relation of magnesium and temperature. Because of its exothermicity, the course of Grignard-reagent formation can be visualised by reaction calorimetric experiments. The chosen experiments should give answer to questions, like...

- What is the influence of the concentration of Grignard-reagent on the dielectric constant of reaction media?
- What is the influence of the polarity on the course of the Grignard-reagent formation of an aryl chloride in tetrahydrofuran?
- What is the different in the Grignard-reagent formation between aryl bromide and the corresponding aryl chloride?
- What is the influence of the surface area of magnesium on the rate of reaction?
- What is the temperature dependence of a not mass transport-limited Grignard-reagent formation?

Dielectric constant and concentration of Grignard-reagent

Figure 7 shows the dielectric constants of ethyl magnesium bromide in diethyl ether in relation of the concentration of Grignard-reagent from literature ^[4]. This fact is important to consider because the increasing concentration of Grignard-reagent –resulting from the ongoing chemical reaction– rises the polarity of reaction-medium. This, in turn, accelerates the reaction rate of some Grignard-reagent formations.

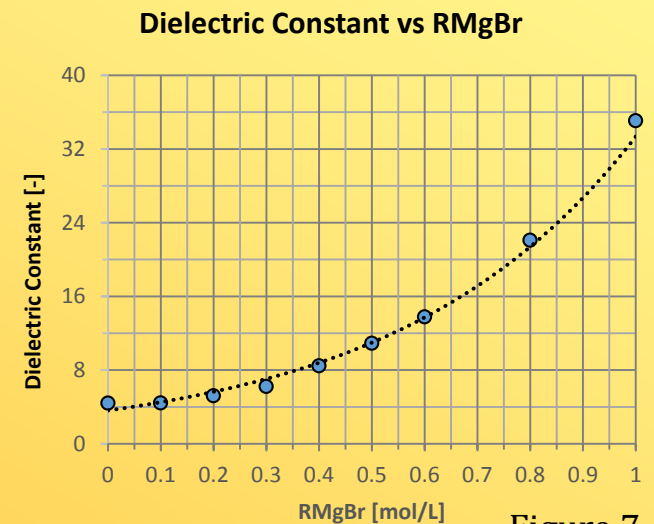


Figure 7

Influence of reaction-medium polarity on process safety Aryl chlorides react not transport-limited. It means their reaction rates will increase during the course of conversion (see brown red curve in figure 5). The influence of the polarity of reaction-medium on reaction-rate is shown by the transformation of an aryl chloride with magnesium in tetrahydrofuran by two experiment types:

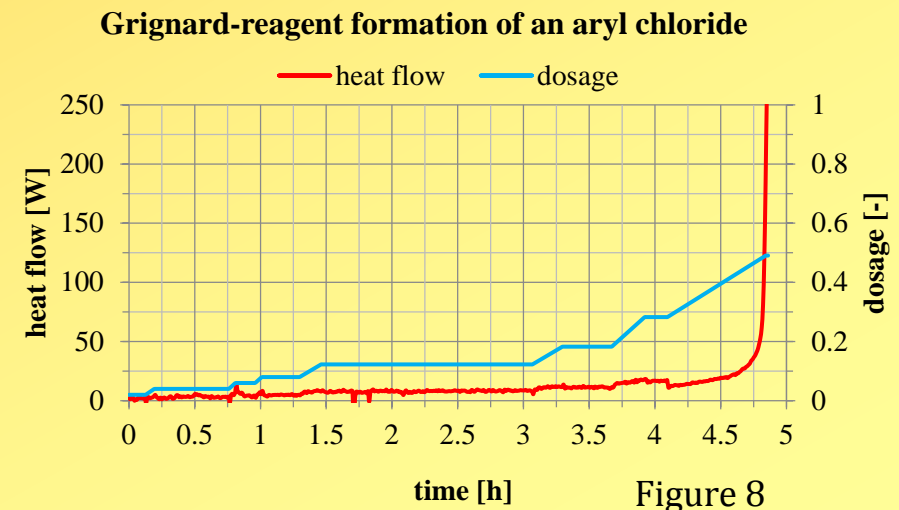
First, the Grignard-reagent formation was started conventionally with iodine. Then, aryl chloride was added to the reaction mass in arbitrary intervals.

Second, before the Grignard formation was initiated, some Grignard-reagent was added to the pre reaction mass in order to get a higher dielectric constant of reaction-medium.

Figure 8 shows an experiment of the first type. The starting concentration of magnesium was 3.75 mol/kg. Before starting the halide dosage, the magnesium surface was initiated with iodine. The slowly growing signal has shown that the conversion of halide had started. The heat flow increased steadily during several hours. Then, after quite a long induction time –when about 50 % of aryl chloride had been dosed– occurred a sudden runaway reaction.

At that moment, most of the aryl chloride was accumulated in the reaction mass. It is obviously, that such a behaviour cannot be controlled on production scale (see also picture 4 in figure 6).

Figure 9 shows an experiment of the second type. The Grignard-reagent formation of the same aryl chloride was run in a starting reaction medium with a higher dielectric constant. Aryl magnesium chloride was added to the pre-reaction mass in order to achieve its polarity (see figure 7).



The Grignard-reagent formation was started with iodine. The starting concentration of magnesium in tetrahydrofuran was 3.75 mol/L and the added amount of aryl magnesium chloride was 0.7 mol/L. The so achieved dielectric constant of the starting reaction-mass was in the order of 18 (see figure 7).

The red curve shows the heat flow, the blue the dosage, the black the conversion of heat and the brown the temperature. With the start of dosing of aryl chloride the heat flow starts immediately. After stop of dosing the heat flow slows down to zero within about 2.5 hours. The maximum accumulation of heat was at the end of dosing. Its value was approx. 15 %. Such a Grignard-reagent formation is easy to control on production scale. However, the crux is that somewhere some amount of Grignard-reagent has to be produced in order to run the first batch in the Multi-product facility. These two experiments demonstrate the enormous impact of polarity on the reaction rate of the Grignard-reagent formation.

Figure 10 shows the Grignard-reagent formation with the homologous aryl bromide in tetrahydrofuran. As usual, the Grignard-reagent formation was initiated with iodine (first peak). With start of dosing of aryl bromide (blue curve), the heat flow starts immediately (red curve). The heat flow stops very fast with interrupt of dosing. After restart of dosing, the heat flow rises to the same level as before. At end of dosing, the heat flow sinks to zero within few minutes. Such a reaction profile of Grignard-reagent formation is desirable and is easy to control on a large scale (see page 20).

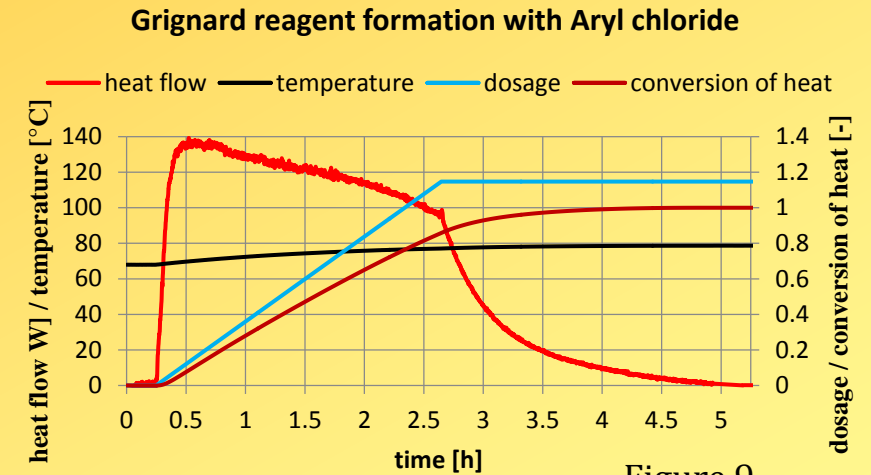


Figure 9

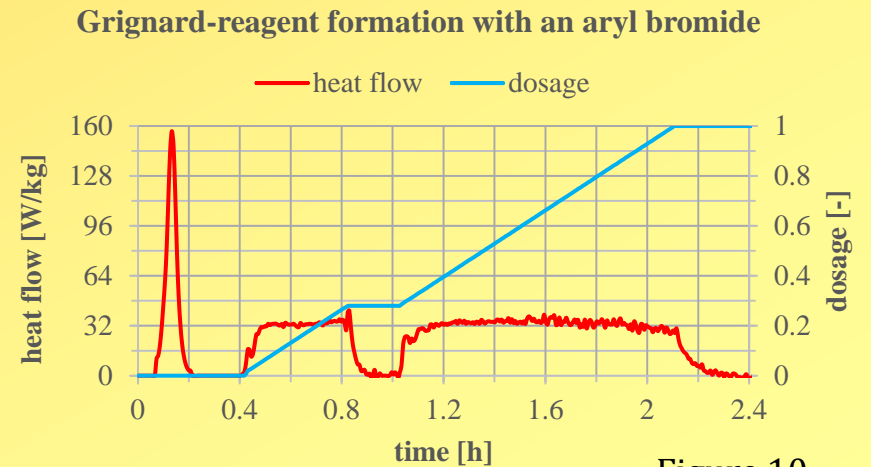


Figure 10

What effect has the magnesium surface area on the rate of reaction of an aryl chloride? Figure 11 compares heat flow curves of two reaction calorimetric experiments with two different qualities of magnesium. Magnesium concentration and aryl chloride concentration in tetrahydrofuran as well as the starting and dosing procedures was the same. The green curve shows the heat flow of the experiment with the widely used magnesium turnings and the red curve the one with magnesium powder. The comparison of the heat-flow profiles shows clearly how strong the type of magnesium influences the speed of Grignard-reagent formation.

Discussion of some experiments regarding to Grignard-reagent formation from aryl chlorides: Figure 12 shows an experiment in which a mixture of aryl chloride and aryl bromide was used. The aim was to examine whether the presence of the faster reacting aryl bromide increases the reaction rate of the aryl chloride. The starting concentration of magnesium was 7.75 mol/kg. After reaction start, the mixture of aryl halides was dosed in an arbitrary manner.

- During the dosing of the first part of the halide mixture, there was a spontaneous temporarily increase of the heat flow.
- After that peak, the heat flow increases slowly, reaches a maximum and decreases steadily.

Grignard-reagent formation of an aryl chloride with different surface areas of magnesium

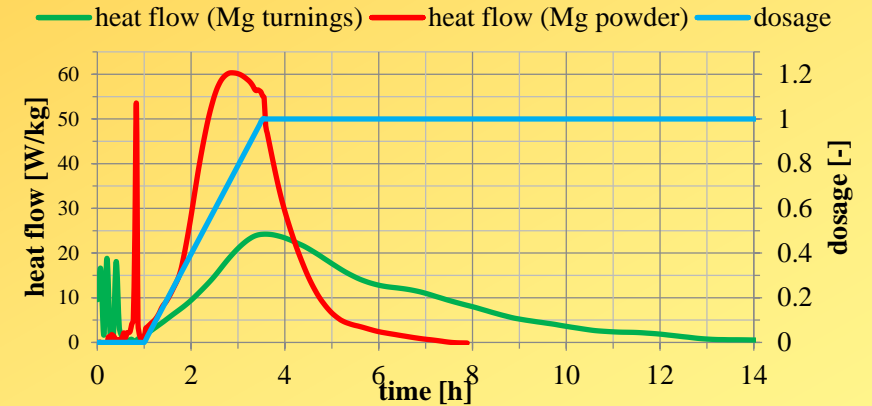


Figure 11

Grignard-reagent formation with a mixture of 83% aryl chloride and 17% aryl bromide

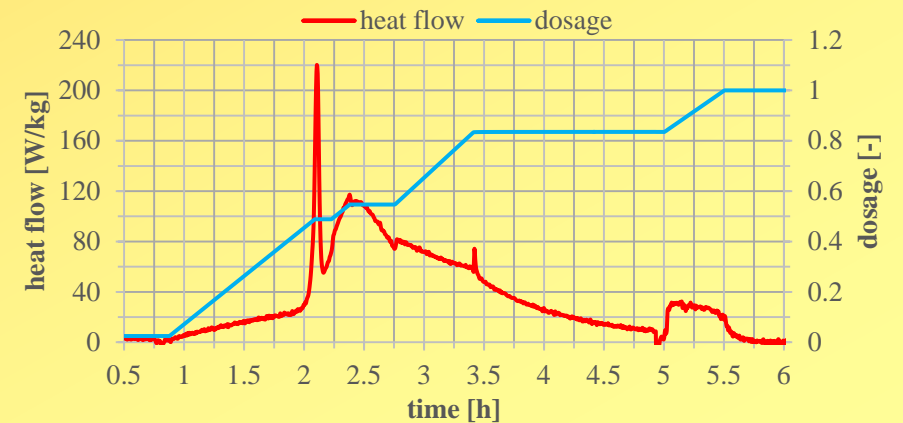


Figure 12

Mixtures of halides, in which the individual halides have different reaction mechanisms, result in an uncontrolled course of reaction.

Figure 13 shows a reaction calorimetric experiment using an aryl chloride. The Grignard-reagent formation was initiated with aryl bromide (0.06 mol/kg). The starting concentration on magnesium turnings in tetrahydrofuran was 2.64 mol/kg.

The Grignard-reagent formation accelerates very slowly (red curve). The experiment accumulates about 30 % of aryl chloride during the dosing procedure (green curve).

In a set of experiments, the aryl chlorides were transformed in reaction masses that led to higher concentrations of Grignard-reagents. The aim of the experiments was, on the one hand to reach at an earlier time high polarities of the reaction masses, and on the other hand, to perform the Grignard-reagent formations at significantly higher temperatures in order to get higher reaction speeds. Figure 14 shows the reaction course of such an experiment in tetrahydrofuran. The chemical reaction was initiated with a trace of iodine. The starting concentration of magnesium was 8.73 mol/kg. At the end of reaction the reaction mass contains only 2.65 mol of tetrahydrofuran per mole of Grignard-reagent.

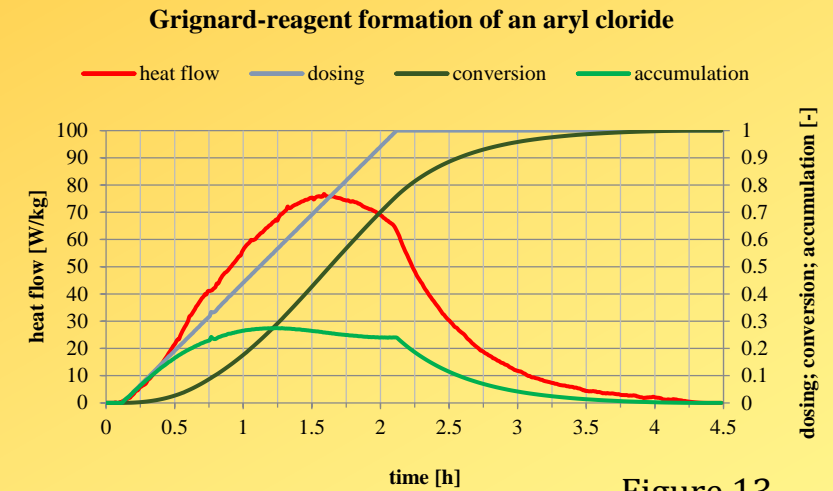


Figure 13

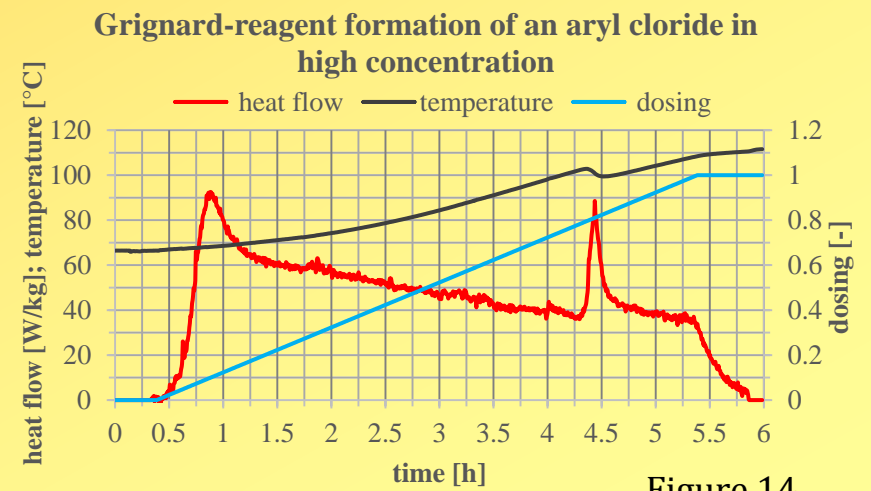


Figure 14

Because of this high concentrated reaction mass is the temperature rise during course of the Grignard-reagent formation remarkable (see violet curve in figure 14). This rise in temperature influences the speed of reaction positively so that the accumulation of the aryl chloride remains on a small level. Grignard-reagent formations, which are not transport limited, are easier to develop for closed reactor systems, because their reaction speeds are temperature dependent (see page 26). Because in closed reactors, higher temperatures are possible without to use reaction masses that have such high concentrations of Grignard-reagents. Very interesting in this experiment is the spontaneous rise in heat flow at the time when approximately 80 % of the aryl chloride were dosed (red curve figure 14). This increase in heat flow results in a lowering of temperature (violet curve). At this point, the reaction mass contains approximately three moles of tetrahydrofuran per mole of Grignard-reagent. After that, this ratio becomes smaller and tetrahydrofuran is spontaneously set free, presumably by dimerization of the monomers $R-MgX \cdot (THF)_2$ (see discussion on page 6, figure 3).

Developing safe Grignard-reagent formation processes for Multi-product plants –a case study

General remarks In Multi-product plants, Grignard-reagent formations can be carried out in open systems under boiling conditions or in closed systems. No matter which system is chosen, the Grignard-reagent formation in the Multi-product plant must be controllable at any time. Measures must be defined, which allow to control whether the chemical reaction has started and as well, whether conversion runs as planned. During the whole operation, it must be assured that there is no heat accumulation, which the reactor system is not able to remove at a process deviation.

Note: The danger of water entry into the reaction is not discussed in this context. This danger is especially given if a glass condenser is installed on top of reactor.

Grignard-reagent formation carried out under boiling conditions

Introductory remarks By evaporation of solvent, much heat can be removed from the reaction mass. By refluxing, more heat can be dissipated than through the reactor wall. However, under boiling conditions the heat removal is limited by interactions of chemical reaction and reactor system as well as of solvent and solvent vapour. Beside the knowledge of the heat of reaction and of the thermal stability of the reaction mass, the following issues must also be investigated.

- What is the maximum allowable rate of evaporation of solvent so that its backflow not floods the vapour pipe?
- How big is the swelling of the reaction mass at the maximum allowable rate of solvent evaporation?
- How easy do the vapour bubbles break through the liquid-surface? There is a danger of foam formation, see figure 6.
- What is the speed with which the flow-back of the condensed solvent is remixed into the reaction mass?

How is the system controlled? Under boiling conditions, the heat of reaction of the Grignard-reagent formation will immediately be consumed by the evaporation of solvent. This means that the amount of the evaporated solvent is proportional to the released heat. Because of that, a good control system is to measure the flow-back of the condensed solvent in relation to time (figure 15).

In order to decide, whether a Grignard-reagent formation can be performed in a given Multi-product facility, the following investigations must be carried out.

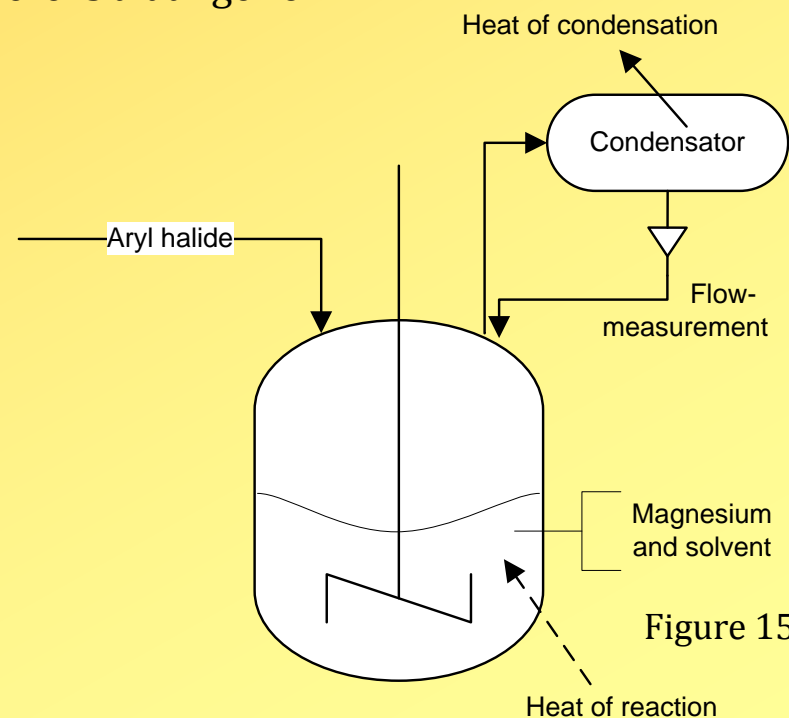


Figure 15

What information must be provided for the safety assessment?

- Necessary are data such as heat of reaction, power of heat and the heat accumulation in relation to the halide dosage.
- Definition of safe normal operating conditions, such as starting procedure and the dosing time with respect to the reaction rate and the accumulation of the halide.
- Defining the necessary safety measures for the reactor system, in order to control the planned operating conditions.
- Assessing the starting procedure for the Grignard-formation and the dosing procedure for the halide. The question should be answered whether the distillation system is able to control the boiling of solvent. The condenser of the used reactor should be able to dissipate at least twice of the maximum power of reaction heat.
- Assessments, whether the cross-section of the vapour pipe can control the boiling of the reaction mass as well as the reactor volume the associated swelling.

Thermal data: The heat of evaporation at boiling temperature is 413 kJ/kg. The heat of reaction is 468 kJ/mol. Due to the reaction calorimetric investigation, the Grignard-reagent formation follows a transport-limited mechanism.

Main features of the planned Grignard-reagent formation step

- Reactor: 6300 L steel reactor with propeller stirrer and distillation system
- Starting reaction volume: 1350 L (halide concentration $0.13 \frac{\text{mol}}{\text{L}}$)
- Magnesium load: 233.4 kg (9600 mol)
- Reaction medium: Tetrahydrofuran
- Dosing mass: 2685 kg tetrahydrofuran containing 8000 mol of aryl halide
- Planned dosing time: 5 hours
- Planned end reaction mass: 5478 kg

Are the planned process conditions controllable by the reactor system?

Maximum rate of solvent boiling: The rate of reaction of an organic halide with metallic magnesium depends on the measurable concentration of the organic halide in solution and on –presently undefined and unmeasurable– physical characteristics of the magnesium surface.



By a transport controlled mechanism, the maximum rate of reaction of the dissolved halide and magnesium is reached when the diffusion limitation reduces the halide concentration to zero at the magnesium surface (figure 4). At the highest rate, the chemical reaction shows a first order dependence on the halide concentration and a linear dependence on the Mg surface area [5]. Hence, the rate of conversion of diluted organic halide with magnesium is given by the equation (II). This rate is proportional to the speed of heat formation and therefore measurable by reaction calorimetric experiments.

$$r = - \frac{d(\text{Ar}-\text{X})}{dt} = k_g * S_{\text{Mg}} * [\text{Ar} - \text{X}] \sim \frac{dQ_R}{dt} \quad (\text{II})$$

(The term S_{Mg} takes into account all the magnesium surface characteristics that influence this rate.)

After the start of the reaction, the product $k_g * S_{\text{Mg}}$ (equation II) is nearly constant. To make it accessible to the calorimetry we define the value φ_i .

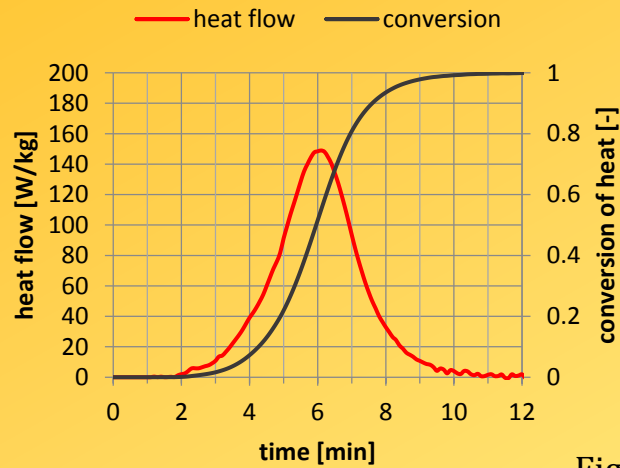
$$\varphi_i = k_g * S_{\text{Mg}} \approx \text{konst} \quad / \quad \varphi_i = k_{\text{Mg}} * A_{\text{Mg}} * [\text{Mg}] \approx \text{konst} \quad (\text{III})$$

The index (i) means that the value of φ depends on a particular type of magnesium with a defined concentration. The term k_{Mg} is a rate constant with the dimension [m/s]. The term A_{Mg} is based on a magnesium type; it has two meanings, the amount and the surface of magnesium, its dimension is $(\text{mol}/\text{m}^3) * (\text{m}^2/\text{mol}) = [1/\text{m}]$. The dimension of φ_i is [1/s].

Consequently, the heat release is given by $\frac{dQ_R}{dt} = \varphi_i * [\text{Ar} - \text{X}] * \Delta H_{\text{R,start}} * V_i \quad (\text{IV})$

Calculation of φ_i -Value: This was calculated by using equation (II) and reaction calorimetric experiments in which the magnesium concentration was much larger than the halide concentration. The conversion of heat is nearly constant over a broad range (see figure 16). From the regression analysis of the values of conversion of in relation to time –in the range of the conversion of heat from 0.75 to 0.15– the value of φ_i has been calculated as 0.00478 [1/s].

Starting of the Grignard-reagent formation
concentration of R-X : 0.13 mol/L



Regression analysis
 $\ln\{1\text{-conversion of heat}\}$ versus time

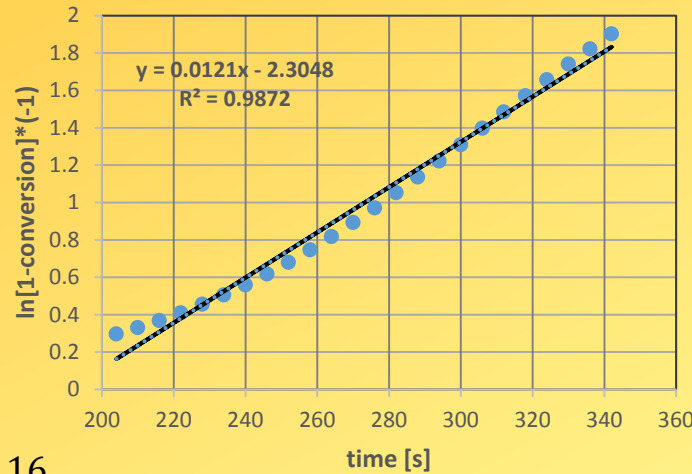


Figure 16

The good correlation of the regression analysis of the logarithmic values of conversion in relation to time proves the assumption of first order dependence of reaction rate on the aryl bromide concentration in presence of a big excess of magnesium.

Estimation of the speed of THF evaporation: The heat release at the start of Grignard-reagent formation is calculated by the equation V:

$$\frac{dQ_R}{dt} = \varphi_i * [R - X]_{\text{start}} * \Delta H_{R,\text{start}} * V_i = 0.00478 * \frac{1}{s} * 0.13 * \frac{\text{mol}}{L} * 1350 * L * 468 * \text{kJ} = 392.6 \text{ kW} \quad (\text{V})$$

Then the speed of THF evaporation is calculated by the equation VI:

$$\frac{d(\text{mol}_{\text{THF}})}{dt} = \varphi_i * [R - X]_{\text{tot},i} * V_i * \frac{Q_R}{\Delta H_{V,\text{THF}}} = 0.00478 * \frac{1}{s} * 0.13 * \frac{\text{mol}}{L} * 1350 * L * \frac{468 * \frac{\text{kJ}}{\text{mol}}}{29.8 * \frac{\text{kJ}}{\text{mol}}} = 13.17 * \frac{\text{mol}}{s} \quad (\text{VI})$$

Needed vapour tube at the start of Grignard-reagent formation: The critical cross-section area of the vapour tube is a function of the heat release and the latent heat of evaporation.

$$\phi[m^2] = F \left\{ \frac{dQ_R}{dt}, \Delta H_v \right\} \quad (\text{VII})$$

On the base of the measured heat release, the needed cross section area can be calculated by the Wiss-correlation [6]. Due to this correlation, the maximum allowable heat release rate for a vapour tube-cross section is given as follows:

$$\frac{dQ_R}{dt} = (4.52 * \Delta H_v + 3.37 * 10^6) * \phi - (49.51 * 10^{-6} * \Delta H_v + 77.15) \quad (\text{VIII})$$

The conversion of the equation (VIII) yields the relation for the cross section:

$$\phi[m^2] = \frac{\frac{dQ_R}{dt} + (49.51 * 10^{-6} * \Delta H_v + 77.15)}{4.52 * \Delta H_v + 3'370'000} \quad (\text{IX})$$

The **first** term is much larger than the **second**, so the equation is simplified to:

$$\phi[m^2] \approx \frac{\frac{dQ_R}{dt}}{4.52 * \Delta H_v + 3'370'000} = \frac{392600}{4.52 * 413'000 + 3'370'000} = 0.075 \text{ m}^2 \quad (\text{X})$$

For the start of the Grignard-reagent formation with the above defined process conditions, the critical diameter of vapour tube is calculated as 0.31 m (figure 17).

The swelling of the reaction mass due to boiling is more difficult to judge. The correlation from Jacques Wiss et al [6] could be used but it requires the knowledge of the surface tension of the reaction mass, which changes during conversion. The reaction calorimetric experiments showed that for the planned dosing time the production size is too large in order to control the thermal expansion and the swelling of the reaction mass.

Speed of tetrahydrofuran evaporation using the planned dosing time: Figure 18 shows the reaction calorimetric

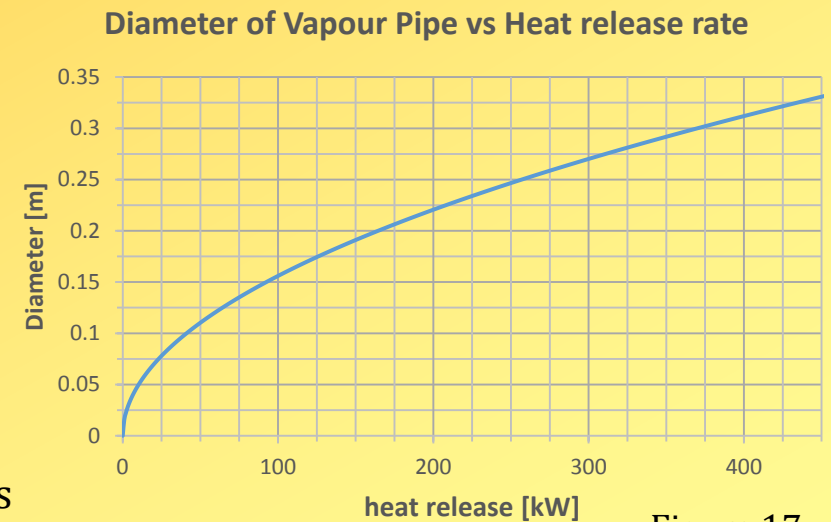


Figure 17

experiment of the Grignard-reagent formation step with the planned normal operating conditions. The red curve shows the heat flow, the blue curve the dosage and the brown curve the conversion of heat. With the dosing time of five hours, the maximum heat flow is about 39 W/kg_{RM}. For the planned batch size, the maximum power of heat is about 220 kW. This value is smaller than that for the starting reaction.

For safety reasons the following conditions must be held:

Vapour tube cross section: If for the start reaction the cross section of the vapour tube of the planned reactor is smaller than 0.31 m, the Grignard-formation step must be redesigned.

In order to perform the dosing of the halide safely, the reactor must be equipped with a vapour tube that has the cross section of at least 0.24 m. If not, the reaction step must be redesigned.

Swelling of reaction mass. The allowable dosing time for the halide have to be adjusted or the reaction mass volume should be reduced.

Piloting of a Grignard-reagent formation with an aryl chloride –an example: Figure 19 illustrates a pilot production of a Grignard-reagent formation with an aryl chloride. The procedure was similar to that what the figure 14 shows. For the pilot production, 85 kg magnesium were used.

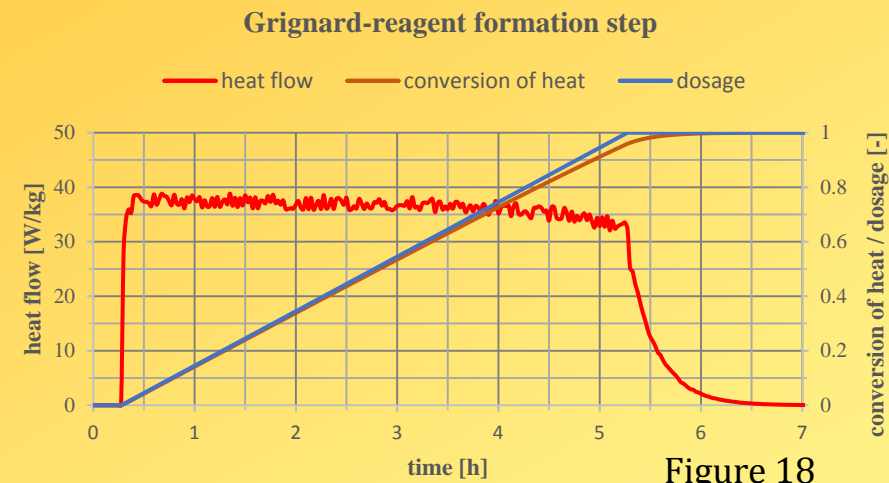


Figure 18

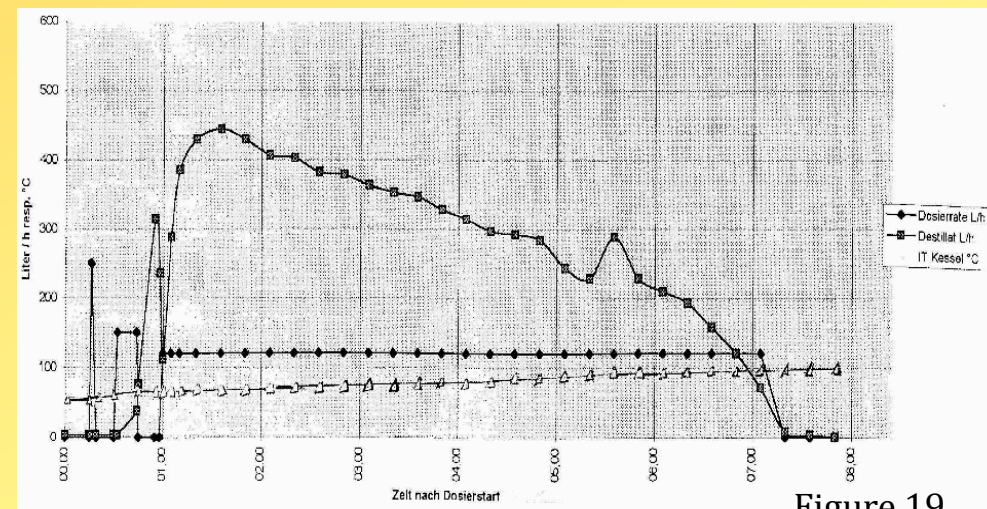


Figure 19

Legend to figure 18: The curve with the quadratic marks shows the flow back of solvent that corresponds to the heat flow, the curve with the rhombic marks the halide dosage and the one with the triangles the temperature of the reaction mass.

The progress of the Grignard-reagent formation was controlled by measuring the flow-back of the condensed solvent (figure 15). This flow-back was compared with the calculated flow-back in relation to the dosage of the aryl chloride. By comparing figures 14 and 18, it is interesting to discern, that the spontaneous peak that have appeared in the heat flow curve during the dosing step could be measured too.

Grignard-reagent formation carried out in closed system –some arguments

Because in a closed system even small accumulations of halide can lead to considerable temperature and pressure increase, a precise control of the reaction course and of the dosage of halide is necessary. A suitable means to control the reaction course is the heat balance. At any process time, the values for the dosed amount of halide, the amount of reacted halide and the accumulated amount of halide must be known. From these values, the worst case pressure rise in the reactor for the whole process time must be calculated.

Performing the Grignard-reagent formation in a closed system is challenging but very interesting for halides, which react with magnesium not transport-limited. Because in this case the reaction rate can be influenced by the temperature. The reason is that the temperature dependence of diffusion in liquids is much smaller than that of the chemical reaction.

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The previous text has shown that for the development of safe Grignard-reagent formation steps a good process knowledge is crucial. This is true not only for this type of chemical reaction, but for all chemical reaction types.

Often one is not aware that –for Multi-product plants– the necessary safety planning effort has to be carried out with every new chemical process, which will be performed in it. For reason that the real cause for most accidents of chemical process steps is the insufficient process knowledge. This is still strongly underestimated by the Multi-product chemistry as well as by the authorities. Likewise underestimated is what an enormous economic potential a good process knowledge has. In as much...

- it helps to accelerate the process of implementing a Custom Synthesis into a Multi-product plant.
- it is very expensive to make changes on the production plant or to do extra development work, which not have been considered in the contract.

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[Part 2a: Visualising the Dangers](#) / [Part 2b: Case study, Methodology](#)

In preparation are the subsequent lectures. The problem areas of the heat generation and heat removal, of the accumulated heat and the avoidance of it as well as of the decomposable reacting and distillation masses.



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