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Thermochemical Scale-Up of a Mesylation Reaction

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Abstract:
The scale-up of the synthesis of a very expensive key pharmaceutical intermediate requires a very accurate knowledge of the overall heat-transfer coefficient of the plant reactors. Those data allow the optimization of the safety, quality, and yield of the process. Starting from the accurate and reliable measurements determined by reaction calorimetry, the overall heat-transfer coefficient of the plant reactor can be evaluated, and the reaction performance can be simulated with a computer program. Here is reported an example of a reaction successfully scaled up to 1500-fold with excellent yield and high product quality.

Introduction

The purpose of this work is to determine the conditions for an efficient scale-up of a process for the synthesis of a very expensive key pharmaceutical intermediate obtained by the addition of mesyl chloride (**B**) into a mixture containing an alcohol (**A**), to give the corresponding mesylate (**C**) as shown in Figure 1.

The calorimetric study shows that the reaction is safe, but the lack of rigorous control of the reaction time (the fastest possible, not more than 60 min) and of the temperature (−18 to −10 °C), causes a drop of the yield and the formation of a certain number of impurities in the isolated product. For this reason it is necessary to determine if the plant reactor in which the reaction will be performed is able to remove the heat evolved by the reaction, respecting the critical parameters defined in the lab experiments.

Calorimetric Principles

The calorimetric principles of a heat flow reaction calorimeter have been described in detail elsewhere;[1−4] here are briefly described only the few points needed for the present discussion.

In general, heat flow calorimetry is accomplished by way of an energy balance around the reaction calorimeter and the heat transfer in an agitated vessel having an external jacket follows the relationship:

$$Q_{\mathrm{flow}} = UA(\mathrm{Tr} - \mathrm{Tj})$$

where (Tr − Tj) is the temperature gradient between the reaction mixture and the jacket temperature, U is the overall heat-transfer coefficient, and A is the heat exchange area, i.e., the area of the reactor wall wetted by the liquid phase, which also may depend on the stirring speed.

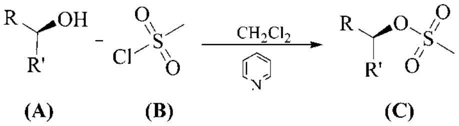

Figure 1. **Reaction scheme.**

Lab reaction calorimetric investigations allow the determination of the heat production rate (W/kg), the enthalpy of the reaction (J/kg), and the specific heat of the reaction mass. These mass-related values are independent of the scale of the reactor; in fact they are the same in the lab as in the plant, when the reaction path is the same. In both laboratory- and large-scale reactors the cooling power can be calculated according to equation:

$$Q_{\mathrm{cool}} = Q_{\mathrm{flow}} = UA(\mathrm{Tr} - \mathrm{Tj})$$

The overall heat-transfer coefficient is normally unknown because of the lack of data on the complex reaction mixtures. In general it is function of three fundamental contributions[5−8]

$$\frac{1}{U} = \frac{1}{\mathrm{hr}} + \frac{1}{\mathrm{hw}} + \frac{1}{\mathrm{hj}} \qquad (1)$$

hr is the heat-transfer coefficient between the reaction mixture and the inner wall of the reactor. It is due to the reaction and depends on the physical properties of the reaction mass (mainly its viscosity), temperature, shape of agitator, and stirring speed. Under the same hydrodynamic conditions this coefficient should be identical in the lab as well as in the plant reactor and can be calculated by the Wilson method.[8]

hw is the heat-transfer coefficient through the reactor wall. It depends mainly on the temperature.

hj is the heat-transfer coefficient between the wall of the reactor and the jacket. It depends on the physical properties of the liquid in the jacket (mainly its viscosity), temperature and flow.

The last two coefficients can be grouped into a resistance term Φ(Tr) that depends only on the temperature if the rate of circulation of the cooling medium is constant.

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(2) Landau, R. N.; Blackmond, D. G. *Chem Eng. Prog.* **1994**, *November*, 43−48.
(3) Landau, R. N., Ed. Special Issue: Reaction Calorimetry. *Thermochim. Acta* **1996**, *289*, 101−378.
(4) Regenass, W. *RC User Forum USA* 1996, US1996.25. (This paper can be freely downloaded from http://www.rxeforum.com.)
(5) Ackley, E. J. *Chem. Eng.* **1960**, *22*, 133−140.
(6) Bondy, F.; Lippa, S. *Chem. Eng.* **1983**, *4*, 62−71.
(7) Dream, R. F. *Chem. Eng.* **1999**, *1*, 90−96.
(8) Choudhury, S.; Utiger, L.; Riesen, R. *Mettler Toledo Publication 00724218*; Mettler Toledo: Columbus, OH. (This paper can be freely downloaded from http://www.rxeforum.com.)

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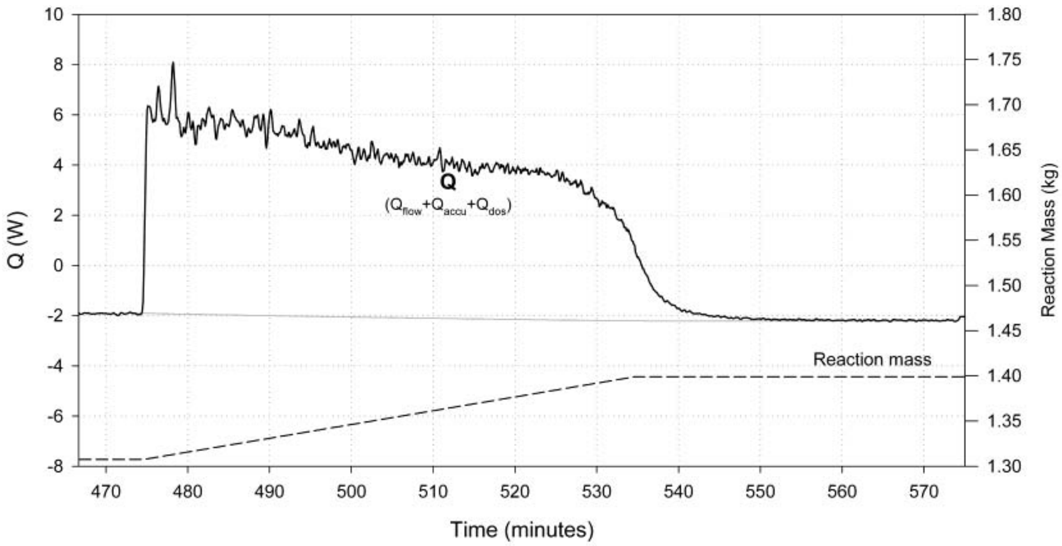

Figure 2. **Thermochemical profile of the reaction run with RC1.**

$$\Phi(\mathrm{Tr}) = \frac{1}{\mathrm{hw}} + \frac{1}{\mathrm{hj}} \qquad (2)$$

Equation 1 can be rewritten to give

$$\Phi(\mathrm{Tr}) = \frac{1}{U} - \frac{1}{\mathrm{hr}} \qquad (3)$$

This last equation is the basis for a more detailed discussion on the estimation of the overall heat-transfer coefficient of the plant reactor that will follow later in this paper.

The Reaction Calorimeter RC1

The Mettler Toledo RC1 reaction calorimeter,[9] through controlled temperature ramping and the calibration heater, can be used to release a known amount of thermal energy for a fixed period of time into the reactor to determine the product of the overall heat-transfer coefficient and the exchange area (*UA*), and the heat capacity of the reaction mixture. The data obtained with the RC1 can be applied to the plant reactors previously calibrated by heating and cooling solutions with known thermal properties.

Experimental Section

Experimental Apparatus. Reaction experiments were performed using a Mettler Toledo RC1 reaction calorimeter, equipped with a 2-L (AP01) jacketed glass vessel, an anchor agitator, a temperature sensor, and the glass calibration probe.

Raw materials. All reagents were obtained from commercial sources and used in the plant as well as in the RC1.

Procedure. The AP01 vessel was charged with the reagent **A** (135 mmol), then dissolved in methylene chloride and pyridine (154 mmol). The stirrer speed was set at 100 rpm. The mass was cooled at −17 °C. After the temperature has been stabilized, a calibration and a temperature ramp to −12 °C have been performed to determine the *UA* and the heat capacity. Then the mesyl chloride (154 mmol) dissolved in methylene chloride (73.9 g) was added in 60 min. At the end of the reaction, additional determinations of *UA* and heat capacity of the reaction mixture were performed ($^{MXR}U_{RC1} = 135$ W·K^{-1}·m^{-2} − $^{MXR}Cp_{RC1} = 1179$ J·kg^{-1}·K^{-1}).

The reaction is exothermic and the heat of reaction is 177.37 kJ/mol of reagent **A** ($Q = Q_{accu} + Q_{flow} + Q_{dos}$), corresponding to a theoretical adiabatic temperature rise of 14.5 °C (i.e., the temperature rise expected if no heat is dispersed). The accumulated ΔH_{accu} during all the reaction time is close to zero, i.e., the mesyl chloride is consumed with the same rate of addition (Figure 2). This reaction has been performed at different temperatures in the range −18 to −12 °C, and the thermochemical profile did not change.

Due to the kinetic independence of the temperature, the scale-up to the plant reactor will need to verify the capacity of the reactor and the services to remove the heat generated respecting the time and temperature limits determined in the lab experiments taking into account that the minimum temperature of the cooling fluid in the plant is about −20 °C.

Mathematical Modeling of the Reaction System

First of all a reliable mathematical model of the reaction has to be developed on the basis of the reaction calorimetric data, and then the model can be scaled up to the plant reactor.

As there is no accumulation of reagents (the reaction is almost feed-controlled) and the heat profile of the reaction is independent of the temperature of the reaction mass, it is possible to correlate the released heat with the fraction of the reagent added.

For this reason a mathematical relation to express the conversion as a function of the dosed reagent has been found.

To determine this relation the calorimetric conversion versus the fraction of the dosed reagent has been plotted. The experimental data has been fit with a parabolic curve (Figure 3). It is worth noting that there are two distinct contributions to the heat profile. The first one is due to the heat of reaction that is almost constant during all the addition. The second one is the heat of solvation of the pyridinium

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(9) Stoessel, F. *Mettler Toledo Publication 00724474*; Mettler Toledo: Columbus, OH. (This paper can be freely downloaded from http://www.rxeforum.com.)

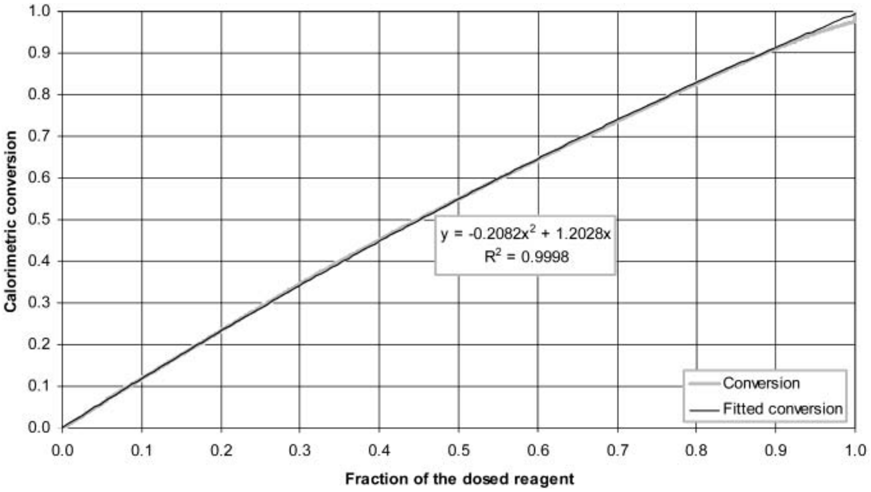

Figure 3. **Conversion vs dosing.**

chloride formed during the reaction. This contribution is not constant with respect to the dosing because it depends mainly on the concentration of the product itself and slightly decreases during the reaction. For this reason the parabolic fitting of the calorimetric conversion does not imply a complex reaction but only visualizes two distinct contributions.

The regression analysis that fits the data gives the following equation as:

$$\alpha = f(\text{dos}) = -0.2082 \cdot \text{dos}^2 + 1.2028 \cdot \text{dos}$$

where $\alpha = f(\text{dos})$ is the calorimetric conversion and dos is the fraction of reagent already added to the reaction mass.

The heat $\Delta H_{\text{partial}}$ released from the beginning of the process to a certain dosed fraction is equal to:

$$\Delta H_{\text{partial}} = f(\text{dos}) \cdot \Delta H_{\text{rxn}} = \alpha \cdot \Delta H_{\text{rxn}}$$

where ΔH_{rxn} is the heat of reaction as determined by reaction calorimeter RC1.

The instantaneous heat of reaction (W_{rxn}) is equal to:

$$W_{\text{rxn}} = \frac{\mathrm{d}\Delta H_{\text{partial}}}{\mathrm{d}t}$$

The quantity of heat removed through the reactor jacket (W_{flow}) is equal to

$$W_{\text{flow}} = UA(\text{Tr} - \text{Tj})$$

where U is the overall heat exchange coefficient at time t, Tr and Tj are the temperatures of the reaction mixture and of the reactor jacket at time t, and A is is the heat exchange area.

The heat due to the dosage of the mesyl chloride, kept at a certain temperature, (W_{dos}) into the reaction system kept at a different temperature is equal to:

$$W_{\text{dos}} = \frac{\mathrm{d}m_{\text{r}}}{\mathrm{d}t}\text{Cp}_{\text{reag}}(T_{\text{reag}} - \text{Tr})$$

where m_{r} is the reaction mass at time t; Cp_{reag} and T_{reag} are the specific heat and the temperature of the reagent, respectively.

In RC1 isothermal mode, the reactor jacket temperature Tj at time t is adjusted by a proportional controller which action can be described by the following equation:

$$\text{Tj} = \text{Tr}_{\text{setpoint}} + (\text{Tr}_{\text{setpoint}} - \text{Tr})P_{\text{control}}$$

where $\text{Tr}_{\text{setpoint}}$ is the working temperature and P_{control} is the proportional factor.

To model a more real response of Tj it is possible to consider a systematic delay of about 15 s.

The reaction mass temperature will be:

$$\frac{\mathrm{dTr}}{\mathrm{d}t} = \frac{W_{\text{rxn}} - W_{\text{flow}} + W_{\text{dos}}}{m_{\text{r}}\text{Cp}_{\text{r}}}$$

$$\text{Tr} = T_{\text{start}} + \int_{t_0}^{t} \frac{\mathrm{dTr}}{\mathrm{d}t}\mathrm{d}t$$

where Cp_{r} is the specific heat of the reaction mass at time t and T_{start} is the temperature of the system at time t_0 (see Table 1). For a numerical solution of the described model the “Berkely Madonna v.8.0.1” software can be used.[10,11]

Running the model the thermochemical profile has been obtained as shown in Figure 4.

Figure 5 shows the very good correlation between the simulated reaction and the RC1 run.

Due to the good correlation between the real and simulated temperatures, the same model used for RC1 can be applied to a plant reactor. The only unknown parameter needed to scale-up this model is the overall heat-transfer coefficient of the plant reactor. This coefficient can be determined in various ways:[7,12] when it is possible to measure precisely the flow of the fluid in the reactor jacket, it can be calculated from the mass and energy balance between the

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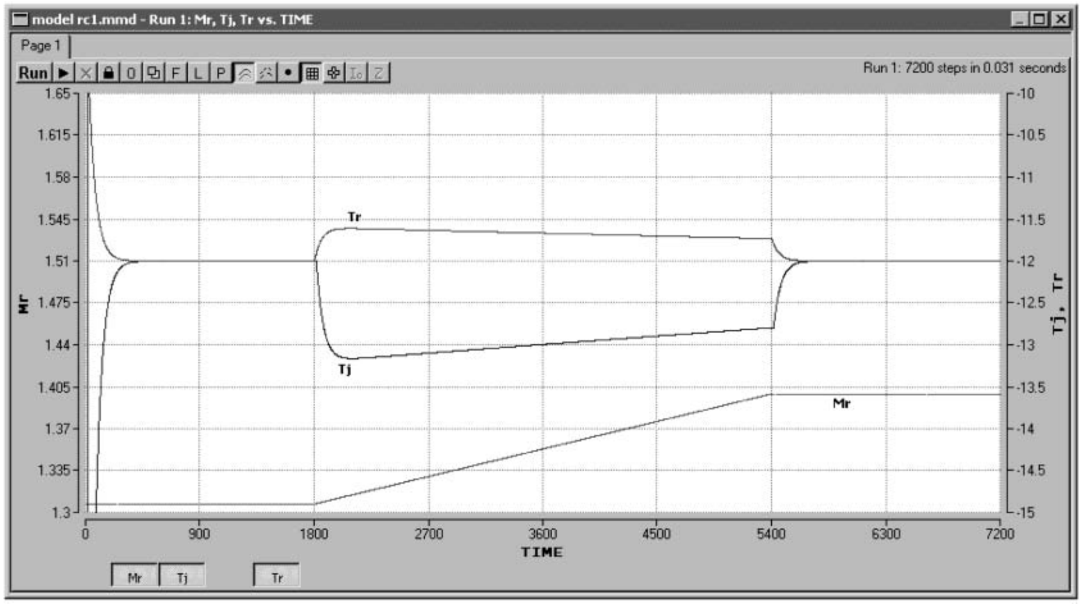
(10) This package compared with other software is very easy to implement and use, and its price is very cheap. It is possible to download a demo version from http://www.berkeleymadonna.com.

(11) Ingham, J.; Dunn, I. J.; Heinzle, E.; Přenosil, J. E. *Chemical Engineering Dynamics*, 2nd ed.; Wiley-VCH: Weinheim, 2000.

(12) Kumpinsky, E. *Thermochim. Acta* **1996**, *289*, 351−366.

Table 1. **Starting data for the model of the RC1 reactor**

StartTime	0	sec	start of simulation
StopTime	7200	sec	end of simulation
DosStart	1800	sec	time when the dosing starts
DosDuration	3600	sec	dosing time
ΔH_{rxn}	23945	J	heat of Reaction
Cp_{i}	1177	$\mathrm{J{\cdot}kg^{-1}{\cdot}K^{-1}}$	specific heat of the reaction mass at starting time
Cp_{f}	1179	$\mathrm{J{\cdot}kg^{-1}{\cdot}K^{-1}}$	specific heat of the reaction mass at end time
m_{i}	1.307	kg	reaction mass at time 0
m_{dos}	0.092	kg	weight of the dosed reagent
A_{i}	0.0424	$\mathrm{m^2}$	initial wetted surface
A_{f}	0.0448	$\mathrm{m^2}$	final wetted surface
U	135	$\mathrm{W{\cdot}K^{-1}{\cdot}m^{-2}}$	overall heat-transfer coefficient for the mxr in RC1 ($^{\mathrm{MXR}}U_{\mathrm{RC1}}$)
P_{control}	4		proportional control factor (the same used in the RC1 experiment)
T_{setpoint}	−12	°C	operational setpoint
T_{start}	−10	°C	initial temperature
Cp_{reag}	1350	$\mathrm{J{\cdot}kg^{-1}{\cdot}K^{-1}}$	specific heat of the dosed reagent
T_{reag}	21.4	°C	temperature of dosed reagent



Run 1: 7200 steps in 0.031 seconds

Figure 4. **Simulation of the reaction run on RC1.**

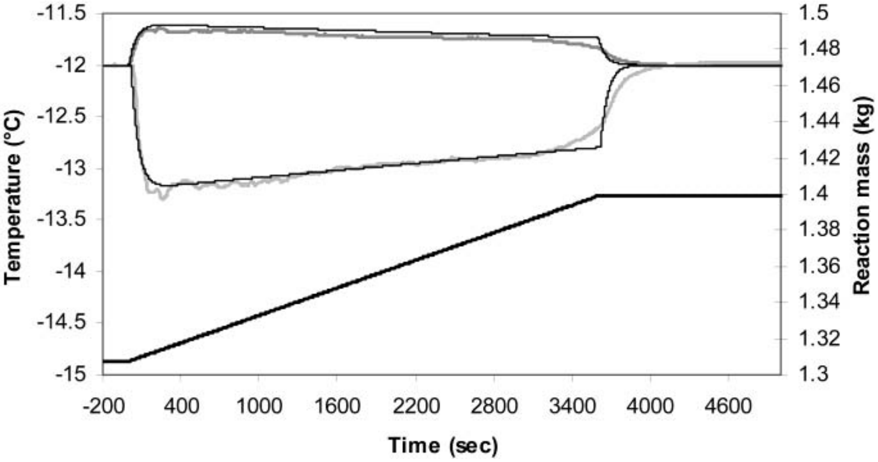


Figure 5. **Real (gray) and simulated (black) temperature profiles for RC1 reactor.**

fluid in the jacket and the content of the reactor. When it is impossible to get accurate measurements of those parameters, a simplified method can be used. The simplify method does not need any measure of the flow in the reactor jacket, but only its temperature.

Method for the Determination of the Overall Heat-Transfer Coefficient in a Plant Reactor

The experiment is conduced dosing a liquid (kept at room temperature) into an empty reactor, where the stirrer is on and the jacket is held at a constant different temperature

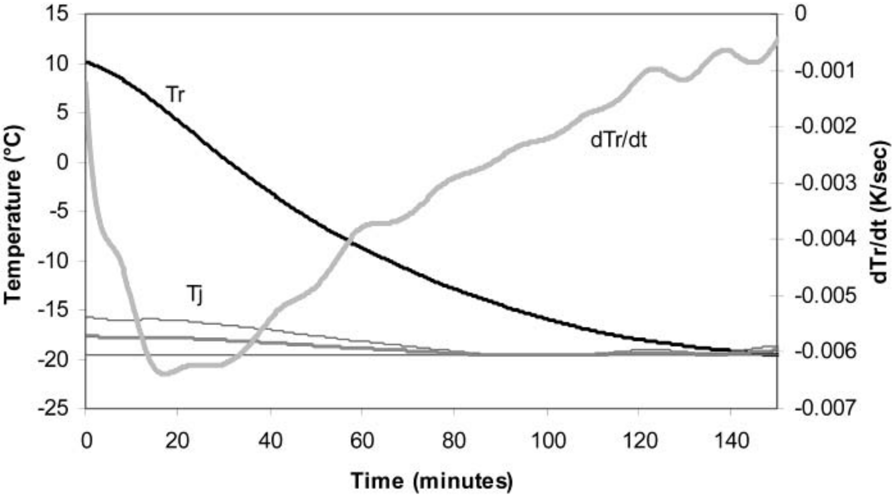


Figure 6. **Cooling of a warm liquid added to an undercooled reactor.**

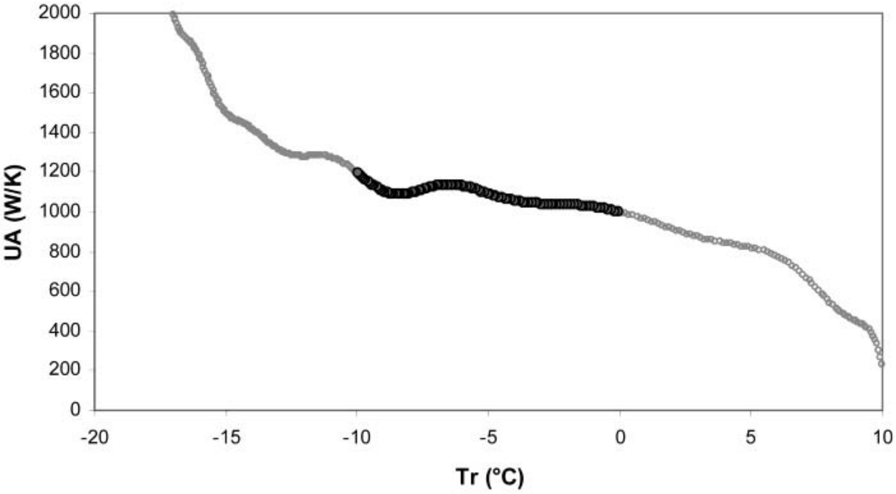


Figure 7. **UA vs temperature of the reaction mass.**

during all the experiment. The thermal profile is shown in Figure 6 (the acquisition time starts when all the liquid has been charged into the reactor).

The heat flow through the reactor wall (Q_{flow}) is:

$$Q_{\text{flow}} = UA(\text{Tj} - \text{Tr})$$

and the heat transferred from the liquid (Q_{accu}) is:

$$Q_{\text{accu}} = m\text{Cp}\frac{\text{dTr}}{\text{d}t}$$

where m is the mass of the liquid contained in the reactor and Cp its specific heat. If the heat due to the stirring is not taken into account (it is negligible for low-viscosity systems) and if it is assumed that the variation of the temperature in the reactor is due only to the heat flowing through the jacket, then:

$$Q_{\text{accu}} = Q_{\text{flow}}$$

$$m\text{Cp}\frac{\text{dTr}}{\text{d}t} = UA(\text{Tj} - \text{Tr})$$

$$UA = \frac{\text{mCp}\frac{\text{dTr}}{\text{d}t}}{\text{Tj} - \text{Tr}} \qquad (4)$$

The only unknown parameter is the heat-transfer coefficient U. As the flow of the cooling fluid in the jacket is not very fast, the thermal gradient between the inlet and the outlet fluid cannot be ignored, and the jacket temperature has to be approximated with its average value. The value UA is calculated and plotted versus the temperature of the reaction mass.[13] In Figure 7 can be recognized a quasi-linear zone where an average value for UA at the working temperature range can be estimated.

To validate this alternative method for the determination of the overall heat-transfer coefficient, the RC1 reaction calorimeter will be used to compare the results with the ones obtained using the standard calibrations.

Experimental Determination of the Overall Heat-Transfer Coefficient

Overall Heat-Transfer Coefficient of AP01 RC1 Reactor Containing Methylene Chloride. The jacket temperature of the empty RC1-AP01 reactor has been set at −12 °C; the stirrer speed at 100 rpm (anchor stirrer). When the jacket temperature was stabilized, 1160 g of methylene chloride ($d = 1.318$ g/mL, Cp 1190 J·kg^{-1}·K^{-1}, temperature 22 °C)

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[13] By applying a smoothing function the plot is made more readable—software packages such as MS-Excel or SigmaPlot are well suited for this transform.

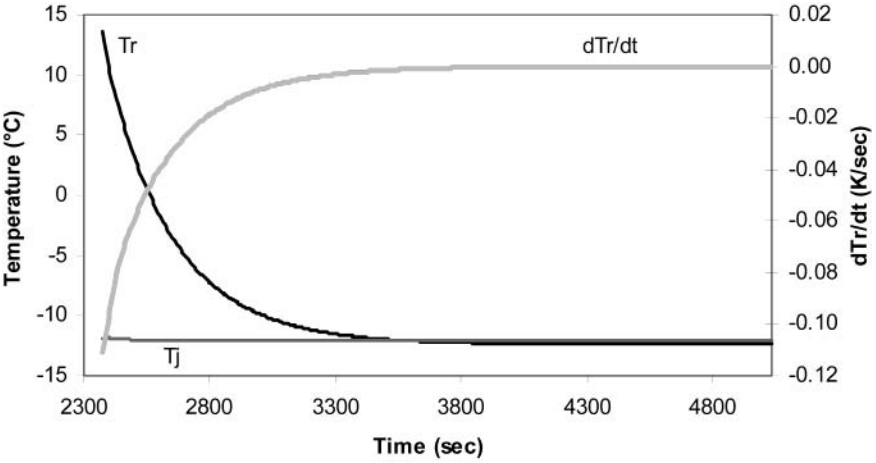

Figure 8. **Cooling of the methylene chloride in RC1-AP01 reactor.**

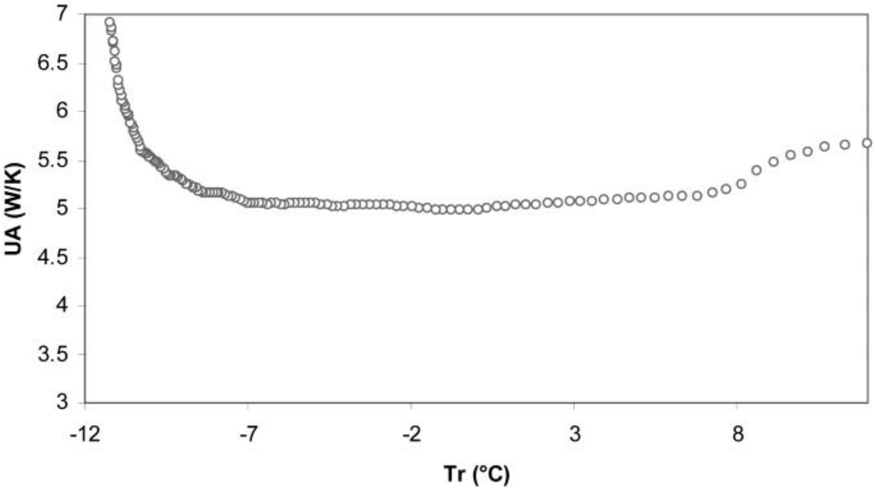

Figure 9. ***UA*** **calculated for methylene chloride in RC1-AP01 reactor.**

were added into the reactor, as fast as possible. Figure 8 shows the profile of the cooling curve.

The overall heat-transfer coefficient is calculated according to eq 4 and *UA* versus the temperature, Tr, can be plotted. The *UA* is calculated as the average of values obtained between +6 and −6 °C (Figure 9). To verify this calculation method three RC1 standard calibrations have been performed, using the calibration heater, with the solvent already present in the reactor at three different temperatures.

The same procedure has been repeated using 735.3 g of toluene ($d = 0.865$ g/mL, Cp 1710 J·kg^{-1}·K^{-1}, temperature 22 °C). The results of these determinations are summarized in Table 2.

Table 2. ***UA*** **determinations in RC1-AP01 reactor**

UA proposed method	UA standard RC1 calibration	
UA (W/K)	Tr (°C)	*UA* (W/K)
	methylene chloride	
	−12	4.817
5.036	−7	4.965
	0	5.187
	toluene	
	−12	4.452
4.839	−7	4.602
	0	4.738

Overall Heat-Transfer Coefficient of Reactor n°R9011/01 Containing Toluene[14]

The 3000-L stainless steel reactor n°R9011/01 is equipped with anchor and baffles. The reactor jacket has been cooled at −20 °C, the stirrer was set at 80% of the maximum speed (38 rpm). After stabilizing the system for 30 min, 1495 kg of toluene, held at room temperature (21 °C), was charged into the reactor as soon as possible (15 min). The cooling curve is shown in Figure 10 (the acquisition time starts when all the toluene has been charged into the reactor).

The overall heat-transfer coefficient can be calculated according to eq 4; then, *UA* versus the temperature, Tr, can be plotted. In the calculation the specific heat of pure toluene is increased by 5% to take into account the specific heat of all the inserts (stirrer, baffles, etc.).

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(14) The determination of the overall heat-transfer coefficient has been done with toluene instead of the solvent used in the reaction (methylene chloride). This is due to economic reasons. In fact the mesylation reaction requires a water content in methylene chloride lower than 50 ppm, and if we were to use methylene chloride we should throw away a few thousand kilograms of it since it will not meet the required specification after this experiment; at the same we were not able to recycle it in another process because this was only the one run at that time.

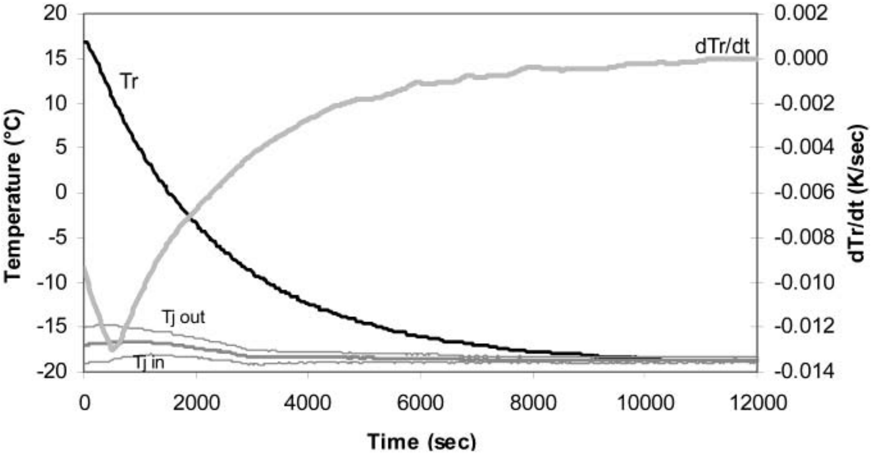

Figure 10. **Cooling of toluene in the plant reactor.**

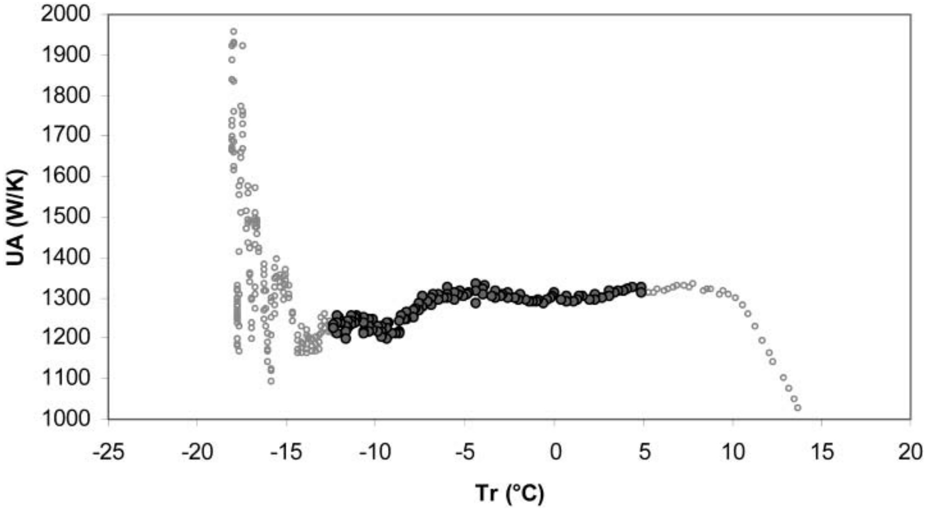

Figure 11. ***U*A vs temperature for toluene in the plant reactor.**

UA is calculated as the average of values obtained between −13 and +5 °C. (1272.9 W/K: Figure 11).

Since the wetted area of the reactor is 5.765 m^2, the overall heat-transfer coefficient for plant reactor (${}^{\text{toluene}}U_{\text{plant}}$) n°R9011/01, determined with toluene, is equal to 221 $W{\cdot}K^{-1}{\cdot}m^{-2}$.

Estimation of the Overall Heat-Transfer Coefficient of the Plant Reactor for the Reaction Mixture

Having determined the overall heat-transfer coefficient for plant reactor using toluene, now this coefficient has to be estimated for the real reaction mixture.

From the literature[8,15] it is known that the heat-transfer coefficient due to the reaction film depends on the stirring speed and temperature. This dependence is described as:

$$\frac{1}{\text{hr}} = \beta\left(\frac{N}{N_0}\right)^{-2/3} \tag{5}$$

where N is the stirrer speed, N_0 is a reference speed, and β is the slope in Wilson relation. Combination of eqs 2 and 5 leads to the equation of a straight line.

$$\frac{1}{U} = \Phi(\text{Tr}) + \beta\left(\frac{N}{N_0}\right)^{-2/3} \tag{6}$$

The Wilson method applied on the RC1 reactor allows the determination of the parameters in eq 6 by performing several isothermal calibrations at different stirring speeds. As shown in Figure 12 the reciprocal values of U isothermally determined at −12 °C for toluene are plotted versus the term $N/N_0{}^{-2/3}$ (in this example $N_0 = 50$ rpm, but the final result is anyhow independent from this reference value).

Applying a linear regression to the experimental values $\Phi(\text{Tr})$ can be obtain as the intercept and β as the slope. From eq 5 we have:

$$\frac{1}{{}^{\text{toluene}}\text{hr}_{\text{RC1}}} = \beta\left(\frac{N}{N_0}\right)^{-2/3} = 2.565 \times 10^{-3}\ \text{W}^{-1}{\cdot}\text{K}{\cdot}\text{m}^2$$

$${}^{\text{toluene}}\text{hr}_{\text{RC1}} = 390\ \text{W}{\cdot}\text{K}^{-1}{\cdot}\text{m}^{-2}$$

Since $\Phi(\text{Tr})$ depends only on the temperature and on the rate of circulation and it does not depend on the content of the reactor, the term ${}^{\text{MXR}}\text{hr}_{\text{RC1}}$ for the real reaction mixture can be calculated by standard RC1calibrations. (${}^{\text{toluene}}U_{\text{RC1}} = 122\ \text{W}{\cdot}\text{K}^{-1}{\cdot}\text{m}^{-2}$; ${}^{\text{MXR}}U_{\text{RC1}} = 135\ \text{W}{\cdot}\text{K}^{-1}{\cdot}\text{m}^{-2}$) using the same volume and agitation speed (see eq 3).

$${}^{\text{toluene}}\Phi(\text{Tr})_{\text{RC1}} = {}^{\text{MXR}}\Phi(\text{Tr})_{\text{RC1}}$$

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(15) Uhl, V. W.; Voznick, H. P. *Chem. Eng. Prog.* **1960**, *56*, 72−77.

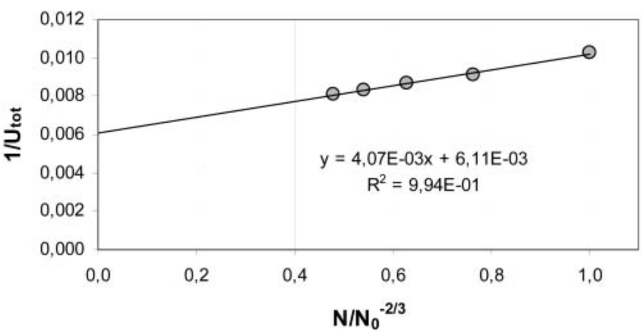

Figure 12. **Wilson plot for toluene.**

$$\frac{1}{^{\text{toluene}}U_{\text{RC1}}} - \frac{1}{^{\text{toluene}}\text{hr}_{\text{RC1}}} = \frac{1}{^{\text{MXR}}U_{\text{RC1}}} - \frac{1}{^{\text{MXR}}\text{hr}_{\text{RC1}}}$$

$$^{\text{MXR}}\text{hr}_{\text{RC1}} = 563\ \text{W}\cdot\text{K}^{-1}\cdot\text{m}^{-2}$$

To be able to scale-up the reaction, Φ(Tr) for the plant reactor has to be known. As described by Choudhury,[8] when the geometry of plant reactor is similar to the that of the lab reactor, as it is in this case, the hr for the plant reactor can be correlated to the hr determined in the lab with the following expression

$$^{\text{toluene}}\text{hr}_{\text{plant}} = {}^{\text{toluene}}\text{hr}_{\text{lab}}\left(\frac{D_{\text{plant}}}{D_{\text{RC1}}}\right)^{1/3}\left(\frac{N_{\text{plant}}}{N_{\text{RC1}}}\right)^{2/3}\left(\frac{\mu}{\mu_{\text{w}}}\right)^{0.14}$$

$$^{\text{toluene}}\text{hr}_{\text{plant}} = 503\ \text{W}\cdot\text{K}^{-1}\cdot\text{m}^{-2}$$

where D_{plant} is the diameter of plant reactor (1.8 m), D_{RC1} is the diameter of the RC1 reactor (0.115 m for the AP01 reactor), N_{plant} is the stirrer speed for the plant reactor (38 rpm) used in the experimental determination of U and N_{RC1} is the stirrer speed of RC1 (100 rpm) during the determination of U for the toluene, μ/μ_{w} is a viscosity correction term where μ is the viscosity at the temperature of the reaction mass and μ_{w} is the viscosity of reactor contents at the wall surface temperature. When a liquid is cooled, the correction term will be smaller than 1, and the worst case is when the wall temperature is equal to the jacket temperature. In our case, for a content temperature of −12 °C and a jacket temperature of −18 °C, the viscosity ratio for toluene[16] is 0.931. The Φ(Tr) for the plant reactor can now be calculated as the difference between the reciprocal values of $^{\text{toluene}}U_{\text{plant}}$ (221 $\text{W}\cdot\text{K}^{-1}\cdot\text{m}^{-2}$—as experimentally determined) and $^{\text{toluene}}\text{hr}_{\text{plant}}$ (see eq 3).

$$\Phi(\text{Tr})_{\text{plant}} = \frac{1}{^{\text{toluene}}U_{\text{plant}}} - \frac{1}{^{\text{toluene}}\text{hr}_{\text{plant}}} = 2.54 \times 10^{-3}\ \text{W}^{-1}\cdot\text{K}^{1}\cdot\text{m}^{2}$$

The $^{\text{MXR}}\text{hr}_{\text{plant}}$ for the reaction mixture in the plant can be calculated as the product of $^{\text{toluene}}\text{hr}_{\text{plant}}$ (503 $\text{W}\cdot\text{K}^{-1}\cdot\text{m}^{-2}$) and a ratio of the reaction mixture $^{\text{MXR}}\text{hr}_{\text{RC1}}$ (563 $\text{W}\cdot\text{K}^{-1}\cdot\text{m}^{-2}$) and the toluene $^{\text{toluene}}\text{hr}_{\text{RC1}}$ (390 $\text{W}\cdot\text{K}^{-1}\cdot\text{m}^{-2}$) both determined with the RC1.

$$^{\text{MXR}}\text{hr}_{\text{plant}} = {}^{\text{toluene}}\text{hr}_{\text{plant}}\frac{^{\text{MXR}}\text{hr}_{\text{RC1}}}{^{\text{toluene}}\text{hr}_{\text{RC1}}}$$

$$^{\text{MXR}}\text{hr}_{\text{plant}} = 727\ \text{W}\cdot\text{K}^{-1}\cdot\text{m}^{-2}$$

During the industrial process the stirring speed will be held at the maximum value (47 rpm) instead of 38 rpm used in the determination of the overall heat-transfer coefficient with toluene. This variation does not affect the Φ(Tr) factor of the plant reactor but only the $^{\text{MXR}}\text{hr}_{\text{plant}}$ coefficient that must be corrected.

$$^{\text{MXR}}\text{hr}_{\text{plant corr}} = {}^{\text{MXR}}\text{hr}_{\text{plant}}\left(\frac{N_{\text{process}}}{N_{\text{plant}}}\right)^{2/3}$$

$$^{\text{MXR}}\text{hr}_{\text{plant corr}} = 851\ \text{W}\cdot\text{K}^{-1}\cdot\text{m}^{-2}$$

where N_{process} is the stirrer speed (47 rpm) used in the process and N_{plant} is the stirrer speed (38 rpm) used in the calibration procedure. Thus, the overall heat-transfer coefficient can be calculated as (see eq 3)

$$\frac{1}{^{\text{MXR}}U_{\text{plant}}} = \frac{1}{^{\text{MXR}}\text{hr}_{\text{plant corr}}} + \Phi(\text{Tr})_{\text{plant}}$$

$$^{\text{MXR}}U_{\text{plant}} = \frac{^{\text{MXR}}\text{hr}_{\text{plant corr}}}{1 + \Phi(\text{Tr})_{\text{plant}}} = 269\ \text{W}\cdot\text{K}^{-1}\cdot\text{m}^{-2}$$

Scale-Up of the Reaction into the Plant Reactor

Since the overall heat-transfer coefficient of the plant reactor has been estimated, it is now possible to implement the model developed on RC1 scaling up all the values to the industrial batch size.

In Table 3 are reported the initial data used to run the model.

The specific heat of the reaction mass is increased by 5% to take into account the thermal inertia of the various inserts. The temperature of the reactor jacket is limited to the value of −18.7 °C since this is the value observed on the industrial reactor.

Figure 13 shows the simulated thermal profile. The maximum temperature reached during the simulation is −11.2 °C.

According to the simulation, the reaction can be run safely in the reactor n°R9011/01 without exceeding the prefixed value of −10 °C. The mesylation reaction has finally been performed into the 3000-L reactor, and the maximum temperature reached has been −11.5 °C (Figure 14).

Conclusions

The use of RC1 reaction calorimeter associated with some computer modelling allowed the determination the overall heat-transfer coefficient in a plant reactor. This is a good approach for a safe scale-up of a production process. When experimental and simulated thermal profiles for the reaction studied are compared, a good agreement is shown. This means that the assumptions used to create the model were correct.

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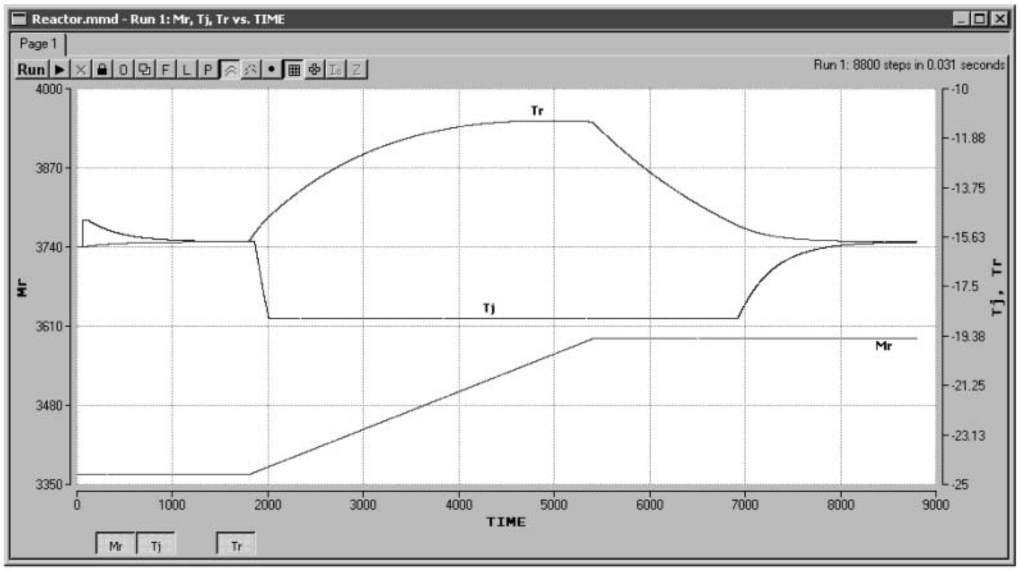
(16) Lide, D. R. *Handbook of Chemistry and Physics*, 75th ed.; CRC Press: New York, 1995.

Table 3. **Initial data for the model for the plant reactor**

StartTime	0	s	start of simulation
StopTime	8800	s	end of simulation
DosStart	1800	s	time when the dosing starts
DosDuration	3600	s	dosing time
ΔH_{rxn}	$58 \cdot 10^6$	J	heat of reaction
$\mathrm{Cp_i}$	1236	$\mathrm{J \cdot kg^{-1} \cdot K^{-1}}$	specific heat of the reaction mass at starting time
$\mathrm{Cp_f}$	1238	$\mathrm{J \cdot kg^{-1} \cdot K^{-1}}$	specific heat of the reaction mass at end time
m_{i}	3366	kg	reaction mass at time 0
m_{dos}	223	kg	weight of the dosed reagent
A_{i}	7.755	$\mathrm{m^2}$	initial wetted surface
A_{f}	8.127	$\mathrm{m^2}$	final wetted surface
U	269	$\mathrm{W \cdot K^{-1} \cdot m^{-2}}$	overall heat-transfer coefficient (${}^{\mathrm{MXR}}U_{\mathrm{plant}}$)
P_{control}	5		proportional control factor
T_{setpoint}	−15.8	°C	operational setpoint
T_{start}	−16	°C	initial temperature
$\mathrm{Cp_{reag}}$	1350	$\mathrm{J \cdot kg^{-1} \cdot K^{-1}}$	specific heat of the dosed reagent
T_{reag}	21.4	°C	temperature of dosed reagent
$\mathrm{Tj_{lowest}}$	−18.7	°C	lowest jacket temperature



Reactor.mmd - Run 1: Mr, Tj, Tr vs. TIME

Run 1: 8800 steps in 0.031 seconds

Figure 13. **Simulation of the reaction run on industrial reactor.**

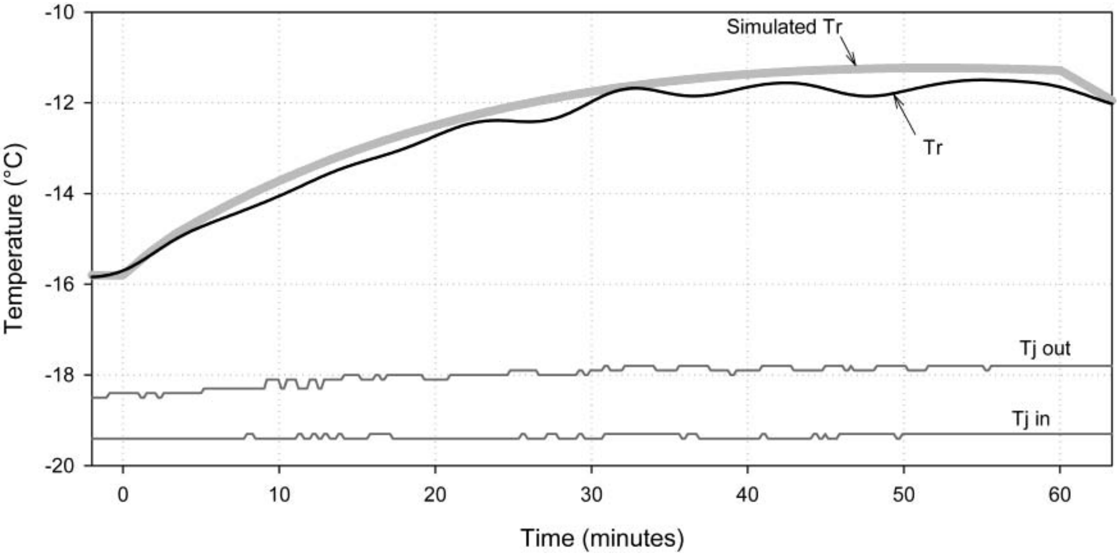


Figure 14. **Temperature profile of the process run into the plant reactor. (The temperature of the reaction mass is slightly irregular because of the nonuniform addition of the reagent).**

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Appendix

“Berkeley Madonna” Mathematical Model for RC1.

```
METHOD EULER
STARTTIME=0
STOPTIME=7200
dt=1
;- - - - - - - - - - - - - - - - - - - - - -
;- - - RAMP generator - - -
;- - - - - - - - - - - - - - - - - - - - - -
DosDuration = 3600
DosStart=1800
INIT ramp=0
ramp′=IF (TIME>=DosStart and ramp<1) THEN 1/DosDuration ELSE 0
;- - - - - - - - - - - - - - - - - - - -
;- - - Qrxn′ = Wrxn - - -
;- - - - - - - - - - - - - - - - - - - -
DHrxn=23945
Qr=(-0.2082*ramp∧2+1.2028*ramp)*DHrxn
INIT Qrxn=0
Qrxn′=(Qr-DELAY(Qr,dt,0))/dt
;- - - - - - - - - - -
;- - - Cpr - - -
;- - - - - - - - - - -
CPi=1177
CPf=1179
CPr=CPi+(CPf-CPi)*ramp
;- - - - - - - - - -
;- - - Mr - - -
;- - - - - - - - - -
Mi=1.307
Mdos=0.092
Mr=Mi+((Mdos+Mi)-Mi)*ramp
;- - - - - - - - - -
;- - - UA - - -
;- - - - - - - - - -
Ai=0.0424
Af=0.0448
U=135
UA=(Ai+(Af-Ai)*ramp)*U
;- - - - - - - - - -
;- - - Tj - - -
;- - - - - - - - - -
PControl=4
TrSet=-12
Tjset=(TrSet-Tr)*PControl+TrSet
Tj=DELAY(TjSet,15,0)
LIMIT Tj >=-40
LIMIT Tj <=140
Wflow=(Tr-Tj)*UA
;- - - - - - - - - - - -
;- - - Wdos - - -
;- - - - - - - - - - - -
Cpreag=1350
Treag=21.4
INIT dos=0
dos’=(Mr-DELAY(Mr,dt,Mi))/dt
Wdos=dos'*Cpreag*(Treag-Tr)
;- - - - - - - - - -
;- - - Tr - - -
;- - - - - - - - - -
INIT Tr=-10
Tr′=(Qrxn′-Wflow+Wdos)/(Mr*CPr)
;- - - - - - END - - - - - - -
DISPLAY Tr,Tj,Mr,Qrxn,Qr,dos
```

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