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# Reaction calorimetry in continuous flow mode. A new approach for the thermal characterization of high energetic and fast reactions

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ABSTRACT: A new method for the calorimetric characterization of high-energetic, fast reactions in flow mode was developed. The use of an engineered flow reactor in combination with a process modelling software allowed the deconvolution of the reaction enthalpy from space-resolved temperature profiles. The new procedure was verified in a comparison with a conventional batch calorimeter and subsequently implemented for the thermal characterization of an organolithium flow process. The information collected for this reaction successfully supported a scale-up to the pilot plant. Overall, the new approach resulted to be superior when compared with established procedures, enabling the generation of precise calorimetric data in an accurate scale-down flow device.

KEYWORDS: continuous reaction calorimetry, continuous manufacturing, organolithium chemistry, scale-up concept, flow chemistry

### **INTRODUCTION**

Fast and high energetic synthetic transformations represent one of the most successful area of application of flow chemistry technologies.<sup>1</sup> Continuous approaches allow chemicals to be fast mixed under superior temperature control and instable intermediates to be instantly produced and selectively transformed. As a result, those processes that need cryogenic temperature and long dosing time in semi-batch, could be performed in continuous mode at milder temperatures with residence times of few seconds and overall higher efficiency and quality.<sup>2</sup> The archetype sequence of this class of reactions is represented by the lithiation of aryl halides by means of organolithium reagents followed by a quench with electrophiles.<sup>3</sup> While the halogen-lithium exchange is a fast, highly exothermic transformation that necessitates a careful heat management, the lithiated

intermediate is unstable and prone to react with any electrophile present in the reaction pot. As a consequence, the long dosing time of the organo-lithium reagent in a batch reactor translates into a lower overall quality when compared with a flow process at the same temperature.

Despite the great progresses done in the field of continuous manufacturing with established flow processes implemented at a commercial scale,<sup>4</sup> the direct thermochemical characterization of flow reactions still require some efforts to develop equipment and procedures alternative to classical batch calorimetry. The use of batch equipment for the calorimetric analysis of fast, energetic flow processes often comes with accuracy concerns, particularly when dealing with unstable intermediates that dictate long dosing time in semi-batch mode. The reaction parameters optimized in flow need to be adapted in order to control the reaction exotherm and achieve the desired process performance and product quality. As a result, the thermodynamic data generated are often not fully representative of real scenarios with consequences on the overall process understanding. A precise calorimetric characterisation represents indeed a key milestone towards a smooth and safe scaleup of processes.<sup>5</sup> Beyond the safety aspects related to the thermal stability of the reaction components, the characterization of thermochemical behaviour of chemical transformations is instrumental to develop accurate kinetic models that assist process chemists and engineers towards the design and the implementation of the most appropriate processes and reactors settings. The thermodynamic data generated in lab are utilized to define the opportune plant capacities and to test and eventually adapt operations and plant specifications by simulating process failure or other undesired events. Accordingly, the development of direct flow calorimeters able to faithfully reproduce the flow process performance at scale is an area of great interest.<sup>6</sup> Recently, a coil flow reactor integrated into a commercial calorimeter vessel was proven to be an effective setting for the enthalpy determination of a series of high energetic reactions.<sup>6a</sup> The same year, Kockmann et

*al.* reported the development and implementation of a plate-type microreactor equipped with Seebeck elements. The versatile flow device tested with neutralisation reactions enabled the accurate real time recording of spatially and temporally resolved heat profiles.<sup>6b</sup> While the use of miniaturized Seebeck elements as heat-flux sensors was also the choice of the Fraunhofer ICT to develop a commercially available flow calorimeter,<sup>6c</sup> the infrared thermography was utilized by Romano *et al.* to estimate in real time the enthalpy of a microfluidic acid-base reactions.<sup>6d</sup>

In the present work we present a new meso-flow calorimeter which utilizes an axial NiCr-Ni probe (thermocouple) for the detection of the reaction inner temperature profile. The heat balance calorimeter concept is based on the integration of a Fluitec 10xT jacketed tube reactor (JTR)<sup>7</sup> with a process modelling software that relies on the axial temperature data for the computation of the thermal energy and heat transfer in the heat balance equation. The Fluitec reactor and hardware represent a scale-down of a continuous pilot plant, accurately reproducing the hydro- and thermodynamic features of the chemistry at scale and providing similar chemical and mechanical resistance. The set-up can be implemented for the thermal characterisation of a variety of flow reactors avoiding microchannels which may be prone to clogging. All together, these features facilitate the generation of precise and representative thermochemical and kinetic data instrumental for a reliable process development, design and integration at scale.

### **MATERIALS AND METHODS**

The JTR was purchased from Fluitec and it is constituted by a jacketed tube (l = 51 cm, i.d. = 7.8 mm,  $V_{hyd} = 17$  mL) equipped with static mixers (CSE-X/6)<sup>7b</sup> and a NiCr-Ni probe (diameter = 1.6 mm) for the measurement of inner temperature at 10 different points along the pipe length (Figure

1). The temperature sensors are connected to the Graphtec midi Logger software for the real time visualization and recording of the reaction temperatures at steady state conditions.



**Figure 1.** Stainless steel Fluitec jacketed tube reactor with 10xNiCr-Ni temperature sensors (JTR). A) Injector with two inlet pipes equipped with temperature probes (HiTec Zang Pt100, class B,  $\pm$  0.3 °C). B) Stainless steel CSE-X/6 static mixers with support for T1-10 temperature probe (NiCr-Ni, class 1,  $\pm$  1.5 °C). C) Details of static mixing elements (CSE-X/6) and temperature probes. D) Jacketed tubular house (M16 connection for cooling system).

The JTR was insulated with an Armacell tubolite pipe (polyethylene foam, 58 mm o.d x 18 mm i.d.). The temperature of the two inlets were controlled using two separate coils (Swagelok PFA tubes 5 mm i.d. x 8 mm o.d.) equipped with PTFE helical static mixer elements (provided by ESSKA.de) immersed in a Huber circulator bath. The inlet tubes were insulated with Aeroflex insulation pipes (48 mm o.d. x 10 mm i.d.) and the temperature of the inner streams were accurately measured by two dedicated probes (HiTec Zang Pt100; class B,  $\pm$  0.3 °C) installed right before entering the reactor (T0<sub>A</sub> and T0<sub>B</sub>, Figure 2). The chemicals were pumped using two hermetic inert pumps (HNP Mikrosysteme, series mzr-7255) interfaced with digital mass flow meters

(Bronkhorst, M14 mini CORI-FLOW) for the accurate mass flow control of the chemicals (Figure 3). The heat transfer fluid (Huber, DW-Therm M90.200.02) was refrigerated with an Huber Unistat 510. The cooling media hoses were equipped with a flowmeter (Endress + Hauser Proline Promass F300) and temperature sensors (HiTec Zang Pt100; class B,  $\pm$  0.3 °C) to control the cooler flow rate and the inner/outer jacket temperatures (Tj<sub>in</sub> and Tj<sub>out</sub>) respectively (Figure 2, 3).



**Figure 2.** A) View of the insulated JTR with position of temperature sensors (HiTec Zang Pt100; class B,  $\pm 0.3$  °C). B) Details of the injection system.



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**Figure 3.** Unit for reaction calorimetry in continuous flow mode. A) Chemicals flow controllers including HNP pumps, Bronkhorst Coriolis flow meters and Wika pressure sensors. B) Graphtec midi Logger GL240 for inner temperature profile visualization. C) Endress + Hauser flow meter for cooling media control.

The estimation of the reaction enthalpy was enabled by the iterative computing of the heat balance equation (Figure 4) using DynoChem, a software for chemical process simulation, optimisation and model parameter fittings.<sup>8a</sup> The flow calorimeter is simulated with a plug flow reactor (PFR) model in DynoChem which solves the corresponding PFR mass balance, as well as the heat balance equation described in Figure 4.<sup>8b</sup>

**Figure 4.** Description of the heat balance equation consisting of 1) fluids physical parameters as density, volume and heat capacity ( $\rho$ , V, Cp) and variation of temperature over time; 2) reactor and operation components, i.e. heat transfer coefficient (U), heat transfer area (A) and temperature difference between jacket and reactor ( $\Delta$ T); 3) reaction heat ( $Q_R$ ) embracing the reaction enthalpy  $\Delta$ H and the reaction rate (r). The rate equation is expressed as a second order reaction with respect to the reactants [A] and [B]. The values of the rate constant ( $k_0$ ) and the activation energy ( $E_A$ ) are defined a priori in order to model a fast reaction, i.e. mixing limited.

The deconvolution of the  $\Delta H$  from the energy balance requires the specific heat capacity (Cp) and the heat transfer coefficient (U, in W m<sup>-2</sup> K<sup>-1</sup>) values of all components to be carefully estimated. The Cp can be either based on literature data or retrieved in databases. In this work, Cp values at

various temperatures were calculated by using the DIPPR database embedded in the DynoChem utility.<sup>8c,d</sup> The heat transfer coefficient U was extrapolated in the calibration phase suppressing the reaction heat component  $(Q_R)$  of the energy balance equation (Figure 4). Indeed, by pumping inert solvents at T0<sub>A</sub> and T0<sub>B</sub> higher than T<sub>in</sub>, the DynoChem fitting of the inner temperatures allowed the determination of the U value depending on all the hardware components and on the operating conditions (e.g. flow rate, viscosity, heat conductivity of process and cooling media). In a second phase, the chemical process was run and the in-process temperatures recorded. For the  $\Delta H$ deconvolution, the DynoChem model included  $Q_R$  in the heat balance equation (Figure 4). The reactant stream temperatures  $T0_A$  and  $T0_B$  were set to be equal to  $Tj_{in}$ . Considering the focus on very fast transformations, the reaction was assumed to be mixing controlled (mass transfer limited) and the process completed after full mixing. The rate constant  $k_0$  (1'000 L/mol s) was defined a *priori* to ensure a simulated reaction time much smaller than the mixing time. The activation energy ( $E_A$ ) was set according to literature data (52 kJ/mol)<sup>9</sup> and the model was confirmed to be not sensitive to E<sub>A</sub> when the kinetic rate constant was sufficiently high. The energy associated with the solvents mixing was not considered resonably high to have an impact on the quality of the data and was not deconvoluted in the energy balance equation neither in the calibration nor in the  $\Delta H$ estimation phases. All the chemicals and solvents were purchased from Aldrich and all the flow experiments were performed at a total flow rate of circa 88 mL/min. This translated in a total fluid velocity of 4.45 cm/sec and a residence time of 12 sec. According to correlations available in literature for similar geometries,<sup>10</sup> it was calculated that mixing was completed (assuming a coefficient of variation of 0.05) at a length of approximately 51 mm, corresponding to a mixing time of about 1.2 sec. Considering the fluid velocity, the first inner temperature at T1 was measured after 0.36 sec while the 9 remaining values (T2-T10) were read each 1.15 sec. T1 located in close

proximity of the entrance point of the inlet streams and before the reaction completion (complete mixing) was achieved. In this zone, the energy released by the reaction and the relative temperatures strongly depend on the fluids behavior. These details prompt us to consider the data measured at T1 potentially spurious and not relevant for the computation of the energy balance equation. T1 was excluded from the experimental data sets and the temperature profile during mixing was simulated in DynoChem using  $TO_A$ ,  $TO_B$ , volumetric flow rates, Cp, densities, heat transfer and reaction enthalpy (when applicable).

In the initial exploratory phase, it was found that the accurate fitting of the experimental temperature data points entailed the modelling of three distinct heat transfer zones: the mixer (U1), the initial reaction section (U2) and the final residence time zone (U3) (Figure 5). This requirement was explained considering two specific features related to the position of the probes  $T0_A$  and  $T0_B$  and to the construction of the M16 connections for the cooling media respectively.



**Figure 5.** Representation of the JTR with details on the temperature sensors locations and the heat transfer zones U1, U2 and U3. Technical drawing used with friendly permission from Fluitec mixing + reaction solutions AG.

1)  $T0_A$  and  $T0_B$  were not detected exactly at the entry point of the reactor and the stainless steel connections to the JTR entrance were in contact with the reactor jacket (Figure 6, A). Consequently, when the inlet streams had higher temperatures than the cooling media ( $T0_A$  and 

 $TO_B > Tj_{in}$ ), the reactants entered the JTR at a lower temperature than the one measured at  $TO_A$  and  $TO_{\rm B}$  due to cooling in the inlet pipes. The DynoChem model was not adjusted for such a detailed geometry thus leading to an over-estimation of the cooling capacity in the mixer zone. 2) The M16 connection for the inlet of the heat transfer fluid was perpendicular to the flow reactor and located between T1 and T2. Although the cooling media was pumped at the maximum possible flow rate, we envisaged that the stream's turbulence at the entrance of the jacket evolved into a laminar behavior while flowing towards the exit port. This hypothesis matched with the observed cooling capacity trend and was confirmed in two ways. First, the entrance length of the jacket was evaluated using a correlation suggested for a concentric annular tube (i.e. tube-in-tube reactor).<sup>11</sup> The resulting length for developing laminar conditions was found to be 149 mm, which corresponded to the distance from the jacket inlet (between T1 and T2) until the interval between T4 and T5 (Figure 5). This first finding was integrated with the calculation of the heat transfer coefficient in the jacket side  $(h_{outside})$  as a function of the length for a concentric annular tube (Figure 6, B).<sup>12</sup> The result showed that the initial turbulence offered significantly higher heat transfer rates at the entrance of the tube until about 150 mm. The curve then flattens to reach the minimum level in the fully established laminar conditions. According to these data, the U2 zone was extended until the laminar flow was fully developed (hydrodynamic and thermal), while U3 was considered as the zone with the lowest heat transfer coefficient and laminar conditions in the jacket (Re  $\sim$  1100) (Figure 5). The model complexity could have been reduced (i.e. constant U value along the entire reactor) positioning  $TO_A$  and  $TO_B$  closer to the JTR injector along with a different jacket construction or higher cooling fluid flow rates. Beyond the technical challenges related to the commissioning of all modifications needed, it could be anticipated that none of the above remodeling would have been critical to accomplish the final goal.



**Figure 6.** A) Visual description of the heat flow from the inlet tubes to the cooling jacket (conduction through metallic parts). B) Turbulent-to-laminar transition of the cooling media and decrease of jacket-side heat transfer coefficient  $h_{\text{outside}}$  (W m<sup>-2</sup> K<sup>-1</sup>) over the length of a concentric annular tube, based on VDI Wärmeatlas.<sup>12</sup> Technical drawing used with friendly permission from Fluitec mixing + reaction solutions AG.

Starting with the hardware modeling and the customisation of a PFR multi-section DynoChem model,<sup>8e</sup> the initial focus of this study was to prove the effectiveness of the new approach. This was accomplished by characterising a benchmark transformation, thus comparing the thermodynamic data from the flow calorimeter with those obtained by using standard batch equipment. Specifically, the deprotonation of ethanol (EtOH) with hexyllithium (HexLi) was selected as model reaction. Among other reasons such as the ultrafast kinetic and mixing limited feature, the main driver to this choice was the opportunity to avoid the formation of any reactive or unstable intermediates thus to obtain unequivocal calorimetric data in batch as in flow. After the verification phase, the new methodology was applied to a real-case scenario where the thermodynamic data generated with the flow calorimeter supported the piloting of a fast, energetic process at multi-kilogram scale.

### **RESULTS AND DISCUSSION**

### 1. Verification of the method

The benchmark reaction of choice was the quench of a 0.5 M EtOH solution in tetrahydrofuran (THF) pumped at 73 mL/min against a commercial solution of HexLi 2.5 M in hexane pumped at 15 mL/min (1.05 equivalents) (Scheme 1).



**Scheme 1.** Schematic representation of the flow set-up used for the calorimetric characterization of the benchmark reaction.

The U parameters estimation, instrumental to calculate the  $\Delta$ H of the process, was performed by flowing a solution of EtOH in THF against pure hexane. In the effort to simulate the most suitable temperature profiles, the pre-cooler chillers were adjusted to target similar temperatures at T2 to those obtained when HexLi replaced the pure hexane. As we planned to fix all jacket temperatures at -25 °C, we had foreseen, based on the adiabatic temperature increase, to reach around 15 °C at T2. To cover a wider temperature range for a better estimation of the U values, the experiments for the equipment calibration were performed at three different temperatures, specifically targeting 20 °C, 15 °C and 10 °C at T2. To do this, the inlet streams (T0<sub>A</sub> and T0<sub>B</sub>) were adjusted at 56 °C, 47 °C and 38 °C respectively. The higher inlet temperature was dictated by the cooling in the mixer

zone before the second temperature measurement point T2. The temperatures were recorded each 2 sec and the values recorded at the thermal steady state are reported in Table 1. The fitting of the experimental temperature profiles in Table 1 returned the U values for the three heat transfer zones (Table 2). The fitting was run individually for each temperature set point (Figure 7 and Table 2, entries 1-3) and with all the data at once (Table 2, entry 4).

**Table 1.** Experimental temperature profiles obtained processing EtOH 0.5 M in THF against hexane with T2 ranging between 10 °C and 20 °C. All temperatures are reported in °C.

Entry	Tj <sub>in</sub>	Tj <sub>out</sub>	$TO_A$	$TO_B$	<u>T2</u>	ТЗ	Τ4	<i>T5</i>	Т6	Τ7	Τ8	Т9	<i>T10</i>
1	-26.16	-25.3	38.54	37.11	<u>10.0</u>	-1.5	-7.7	-11.6	-13.9	-15.5	-16.6	-17.6	-18.4
2	-26.11	-25.0	47.23	45.42	<u>14.8</u>	1.3	-5.7	-9.8	-12.3	-14.2	-15.3	-16.4	-17.3
3	-26.17	-25.0	56.0	53.75	<u>20.0</u>	4.7	-3.1	-7.8	-10.6	-12.8	-14.0	-15.2	-16.3



**Figure 7.** DynoChem fittings of the temperature profiles reported in Table 1, A) entry 1, B) entry 2, C) entry 3.

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Table 2. U values obtained from the fitting of the temperature	profiles reported in Table 1.
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Entry	T2 (°C)	$U1 \ (W \ m^{-2} \ K^{-1})$	$U2 (W m^{-2} K^{-1})$	$U3 (W m^{-2} K^{-1})$
1	10.0	1125	647	280
2	14.8	1147	681	270
3	20.0	1153	688	280
4	10 to 20	1088	690	270

With U values in hand, we proceeded to the  $\Delta$ H determination of the EtOH quench with HexLi. As depicted in Scheme 1, the two streams of substrate and base were both precooled to target -25 °C at T0<sub>A</sub> and T0<sub>B</sub>. After 5 min run (time to steady state) at -25 °C Tj, the inner temperature data were recorded. The experiment for the determination of the reaction enthalpy was performed in triplicate and the temperature profiles recorded (Table 3). By fitting the temperature datasets reported in Table 3 with DynoChem (Figure 8), the  $\Delta$ H of the reaction was determined (Table 4). The three experiments yielded very similar results when fitted all together (Table 4, entry 4) or individually (Table 4, entries 1-3).

**Table 3.** Temperature data obtained processing EtOH (0.5 M in THF) against HexLi (2.5 M in hexane). All temperatures are reported in °C.

Entry	Tj <sub>in</sub>	Tj <sub>out</sub>	$TO_A$	$TO_B$	T2	<i>T3</i>	Τ4	<i>T5</i>	Т6	Τ7	<i>T8</i>	<i>T9</i>	<i>T10</i>
1	-26.37	-25.5	-25.81	-26.42	13.0	0.9	-6.0	-10.2	-12.7	-14.6	-15.8	-16.9	-17.9
2	-26.49	-25.6	-26.06	-26.45	13.0	0.9	-6.1	-10.3	-12.8	-14.6	-15.8	-16.9	-17.8
3	-26.17	-25.3	-26.22	-26.47	13.0	0.8	-6.1	-10.3	-12.8	-14.6	-15.8	-16.9	-17.8



**Figure 8.** DynoChem fitting of the temperature datasets reported in Table 3, entry 1 using U data reported in Table 2, entry 4. For the  $\Delta$ H determination, T0<sub>A</sub> and T0<sub>B</sub> were equal to Tj and the reaction heat released during mixing brought forth a temperature peak.

**Table 4.**  $\Delta$ H values obtained from the fitting of temperature data reported in Table 3. For all the fittings, the U values used are those reported in Table 2 entry 4.

Entry	$\Delta H (kJ mol^{-1})$	Confidence interval <sup>c</sup>
$I^a$	-209.43	±0.3%
$2^a$	-210.92	±0.5%
3 <sup>a</sup>	-208.98	±1.1%
$4^b$	-210.14	±0.0%

<sup>*a*</sup>Data obtained from the individual fitting of the corresponding temperature profiles reported in Table 3. <sup>*b*</sup>Single fitting including all the temperature profiles reported in Table 3 together. <sup>*c*</sup>Confidence level 95%.

As mentioned above, the value of the heat transfer coefficient U1 obtained from the calibration runs (Table 2) is over-estimated due to the heat transfer from inlet tubes to the cooling jacket (Figure 6, A). In order to quantify the consecutive error on the  $\Delta H$  determination, two additional

fittings were run considering two different settings for U1 (Table 5 entries 2, 3): 1) the average between the values of U1 and U2 and 2) the fitted U2 as in Table 2 entry 4. The corresponding  $\Delta$ H are summarized in Table 5. The average enthalpy corresponded to -198 kJ/mol with a difference of +/- 6% when compared with the scenarios using highest and lowest U1. This data shows that the variation of U1 in the broad range of 690-1080 W m<sup>-2</sup> K<sup>-1</sup> in the first, short reactor section (mixer zone), does not translate into a meaningful difference of the fitted  $\Delta$ H value. The uncertainty about the U1 value is therefore not a critical limitation for the proposed flow calorimetry method.

**Table 5.**  $\Delta$ H data obtained by fitting the temperature profiles reported in Table 3 using different heat transfer coefficient U1.

Entry	$U1 (W m^{-2} K^{-1})$	$\Delta H (kJ mol^{-1})$	Confidence interval <sup>a</sup>	Comment
1	1088	-210	±0.0%	Value fitted for U1 as in Table 2 entry 4 (highest possible value)
2	890	-198	±0.0%	Average between fitted U1 and U2 values
3	690	-187	±0.0%	Value fitted for U1= U2 as in Table 2 entry 4 (lowest possible value)

<sup>*a*</sup>Confidence level 95%.

To test the accuracy of the approach, the same reaction was performed at identical conditions with the same quality of reagents using a standard batch calorimeter. As mentioned before, the quenching of diluted HexLi with a solution of EtOH does not produce any unstable intermediate or side reactions allowing the unequivocal extrapolation of the neat energy release also in semi-batch modality. A Mettler Toledo's RC1 was used as batch calorimeter.<sup>13</sup> After the standard experiment programming and calibration, a commercial HexLi solution (2.5 M in hexane, 120 mL, 1.05 equivalents) was dosed over 30 min into a solution of EtOH 0.5 M in THF (570 mL) cooled at -25 °C under inert atmosphere. The integration of the heat trend (pink line, Figure 9) gave a  $\Delta$ H

equal to -206 kJ/mol. When compared with the average  $\Delta$ H of -198 kJ/mol obtained using the JTR, the difference of 4% indicates the high accuracy and reliability of the new flow calorimeter.



**Figure 9.** Temperature and heat profiles for the calorimetric characterization of the benchmark reaction with the Mettler Toledo RC1.

## 2. Calorimetric characterization of the 3-chloro-bromobenzene lithiation and pilot plant scale-up.

As previously mentioned, the halogen-lithium exchange generate highly reactive and unstable intermediate that, if not selectively and promptly quenched, could react at the electron-poor centre of any species present in the reaction mixture. Beyond other side reactions whose relevance is substrate specific, common by-products derive from the proton-lithium exchange promoted by the presence of any protic sources and from the coupling with the alkyl halide generated from the

halogen-lithium exchange (Scheme 2). While the proton quench can be effectively suppressed by removing any traces of water in the initial substrate solution,<sup>14</sup> the second side reaction can be limited only by the fast generation and electrophilic quench of the lithiated intermediate. Indeed, in this pathway the second halide substitution is considered the rate-limiting step (Scheme 2 C). When the calorimetric assessment of this type of transformation is performed in batch, the contribution of the energy released by the undesired reactions could lead to significant overestimation of the  $\Delta$ H, which is very conservative, but might lead to unrealistically high requirements or set of controls in the plant.





**Scheme 2.** Chemical scheme of the A) main reaction (lithiation) and side reactions such as B) proton quench (des-bromination) and C) alkyl halide coupling (Wurtz coupling).

In line with this and following the method described above, the new flow calorimeter was implemented to characterise the lithiation of the 3-chloro-bromobenzene (1). The data obtained were utilized for the safe and accurate process transfer into a pilot plant. Considering the halogen-lithium exchange as an overall milder transformation than the benchmark reaction, we expected initial temperatures at T2 ranging from 0 °C to -10 °C. Accordingly, the U value was determined aiming at having -10 °C, -5 °C and 0 °C at T2. For the generation of the temperature profiles 19

reported in Table 6, MeTHF was pumped at 74 mL/min and mixed with pure hexane flowing at 14 mL/min. Both streams were maintained at *circa* 0 °C, 10 °C and 20 °C before entering the JTR while the jacket temperature was set at -25 °C. To estimate the heat transfer coefficient, the experimental inner temperature profiles were entered into the DynoChem model and fitted individually (Figure 10 and Table 7, entries 1-3) and all together (Table 7, entry 4).

**Table 6.** Experimental temperature profiles obtained processing MeTHF against hexane with T2 ranging from *circa* -10 to 0°C. All temperatures are reported in °C.

Entry	Tj <sub>in</sub>	Tj <sub>out</sub>	TOA	$TO_B$	T2	ТЗ	<i>T4</i>	Τ5	Тб	Τ7	Τ8	Т9	<i>T10</i>
1	-26.62	-26.2	0.51	1.18	-11.3	-15.9	-18.4	-20.1	-21.0	-21.8	-22.2	-22.6	-22.9
2	-26.35	-25.9	10.21	10.12	-5.2	-11.7	-15.3	-17.6	-18.9	-19.9	-20.5	-21.1	-21.6
3	-26.34	-25.7	19.94	19.43	-0.2	-8.3	-12.7	-15.5	-17.1	-18.4	-19.2	-20.0	-20.6



**Figure 10.** DynoChem fittings of the temperature profiles reported in Table 6, A) entry 1, B) entry 2, C) entry 3.

Entry	T2 (°C)	$U1 \ (W \ m^{-2} \ K^{-1})$	$U2 (W m^{-2} K^{-1})$	$U3 (W m^{-2} K^{-1})$
1	-10	1166	605	255
2	-5	1120	640	277
3	0	1182	645	288
4	-10 to 0	1160	636	288

Table 7. U values obtained from the fitting of the temperature profiles reported in Table 6.

After having defined the U values, the  $\Delta$ H for the selected chemical transformation was determined. In particular, a solution of the 3-chloro-bromobenzene (1) 0.5 M in MeTHF was mixed with 1.05 equivalents of HexLi 2.5 M in hexane with a total flow rate of 88 mL/min. The feeds and the jacket oil were pre-cooled to target -25 °C at T0<sub>A</sub>, T0<sub>B</sub> and Tj<sub>in</sub> (Scheme 3).



Scheme 3. Schematic representation of the flow set-up used in the calorimetric characterization of the bromobenzene 1 lithiation.

In order to minimise the energetic contribution of the undesired proton quench and following the procedure we recently published,<sup>14</sup> the aryl bromide **1** feed was treated with an appropriate amount of *i*PrMgCl to chemically deactivate any acidic protons already present either in the solvent or in the starting material. To control the reaction performance and quality, the product solution was

quenched with iodine to selectively derivatize the lithiated intermediate into a more stable species that can be then easily analysed by quantitative HPLC. The product quality of 98 % based on HPLC spectra confirmed the negligible energy contribution released by side reactions. The temperature profiles obtained at steady state (Figure 11 and Table 8) translated in a  $\Delta$ H of -93 kJ/mol +/- 6%. The average, lowest and the highest enthalpy values were determined depending on the heat transfer coefficient U1 (Table 9), according to the method described above for the benchmark reaction (see Table 5). The DynoChem fitting of the scenario with U1 equal to 898 W m<sup>-2</sup> K<sup>-1</sup> is depicted in Figure 12.



Figure 11. Temperature profile visualization with the Graphtec midi Logger software

 Table 8. Temperature profile obtained at steady state processing 1 (0.5 M in MeTHF) against

 HexLi (2.5 M in hexane). All temperatures are reported in °C.

Tj <sub>in</sub>	Tj <sub>out</sub>	$TO_A$	$TO_B$	T2	Т3	Τ4	Τ5	Тб	Τ7	Τ8	Т9	<i>T10</i>
-25.6	-25.2	-25.5	-26.4	-7.2	-12.4	-15.4	-17.5	-18.6	-19.5	-20.1	-20.7	-21.2

**Table 9.** Results of  $\Delta H$  fitting for the lithiation of bromobenzene 1, depending on the value used for the heat transfer coefficient U1.

E	Entry	$U1 (W m^{-2} K^{-1})$	$\Delta H (kJ mol^{-1})$	Confidence interval <sup>a</sup>	Comment
	1	1160	-98.45	±0.1%	Value fitted with U1 as in Table 7, entry 4 (highest possible value)
	2	898	-93.23	±0.1%	Average between fitted U1 and U2 values
	3	636	-86.56	±0.1%	Value fitted for U1= U2 as in Table 7, entry 4 (lowest possible value)
	C* 1	1 1050/			

<sup>a</sup>Confidence level 95%.



**Figure 12.** DynoChem fitting for  $\Delta$ H of the lithiation of bromobenzene 1 based on the reaction temperature profile reported in Table 8 with a heat transfer coefficient U1 as in Table 9, entry 2.

To highlight the benefits of the new calorimetric method described above, the classical pathway for the safety characterization of flow reactions in batch mode was followed. The experimental flow procedure was adapted to a semi-batch strategy and two consecutive tests were performed into a Mettler Toledo's RC1 equipped with 1 L vessel. The first was executed dosing the solution of HexLi (2.5 M in hexane) in 30 min into a -60 °C cooled 3-chloro-bromobenzene (1) solution (0.5 M in MeTHF). Considering the very poor yield obtained (67% HPLC yield after quench with 4 equiv. of I<sub>2</sub> 0.5 M in MeTHF), a second experiment was run, cooling the aryl bromide 1 solution down to -70 °C and dosing the HexLi in 1 hour. The latter experiment resulted into 73% HPLC

yield. While the first test produced a  $\Delta H = -167$  kJ mol<sup>-1</sup>, the same reaction performed using the second conditions released less of additional heat from secondary reactions and generated a  $\Delta H = -120$  kJ mol<sup>-1</sup> (Figure 13). Both values are significantly above the flow calorimetric estimation (80% and 29% respectively) which can also be understood as the very short residence time in the flow setup further reduced the fraction of heat released by secondary reactions. These data showcase the challenges in minimizing side products formation in this specific reaction and the effectiveness of the flow calorimeter which enabled a more accurate determination of the thermodynamic process parameter through a faithful and detailed reproduction of the optimized flow process.



**Figure 13.** Reaction calorimetry in batch: A) Addition of HexLi at -60 °C in 30 min; B) Addition of HexLi at -70 °C in 1 hour.

With the most representative  $\Delta H$  value in hand, it was possible to assess the process scalability aligning the cooling capacity of the plant with the energy demand of the chemistry. This allowed to define a suitable reactor set-up and temperature levels for safety alarms. The lithiation of the 3-chloro-bromobenzene (1) was scaled-up to the pilot plant with a total flow rate of 500 mL/min (scale factor 6x from lab experiment). The jacketed tube reactor selected for pilot production scale (Fluitec Contiplant PILOT) was of very similar design to the laboratory equipment. Residence time and cooling time were chosen as scale-up criteria ensuring a mixing time at least as short as in the laboratory experiments. The main parameters of both setups are compared in Table 10.

Table 10. Comparison between laboratory and pilot plant conditions

	Laboratory (Fluitec JTR)	Pilot plant (Fluitec Contiplant PILOT)
Internal diameter [mm]	7.8	6.0
Mixer type	CSE-X/6 (X-type mixer)	CSE-X/4-W (helical mixer with X-type mixing zone)
Cross section [mm <sup>2</sup> ]	33 (void fraction = 0.70 due to static mixer)	22 (void fraction = 0.80 due to static mixer)
Length / diameter ratio [-]	65	250
Residence time [sec]	12	12
Linear velocity [cm/sec]	4.45	36.8
<i>Reynolds number</i> [-] (based on empty tube diameter)	295	1879
Mixing time [s]	About 1 s	About 0.1 s
Characteristic cooling time [s]	About 7 s	About 5 s

During the pilot production, the mass flow plus the supply and return temperatures (T3 and T4, Figure 14) of the cooling medium (Therminol D12) were measured. The specific heat capacity Cp was taken from the temperature dependent data sheet as provided by the supplier of the cooling medium and interpolated according to the actual supply and return temperatures. During the start-

up phase, the solvents were pumped at the process flow rates and the cooling was applied (Figure 14, A). The first pump was then switched from solvent to the 3-chloro-bromobenzene (1) solution (0.5 M in MeTHF, Figure 14, B). With the switch of the second pump from solvent to HexLi solution (2.5 M in hexane), the onset of the heat release was observed on the internal temperature probes T1 and T2 and on the return temperature T4 of the cooling medium (Figure 14, C).



**Figure 14.** Temperature and heat release trends displayed online in the process control system (PCS). T1 and T2 are subsequent internal temperature probes for visualization of start and stop of heat release by reaction (thermocouple type K, ROTH+CO.AG). T3 and T4 are the supply and the return temperatures of the cooling medium (resistance thermometer Pt100 class A, ROTH+CO.AG). The lower picture shows the online value of the heat released in the relevant reactor section (inverted sign).

At steady-state conditions, the process control system (PCS) indicated online an average heat intake into the cooling medium of 647 W in the reactor section. This value also includes losses by radiation via the reactor and additional cooling capacity as required to cool down further the thermal mass of the inlet streams. In order to deconvolute the heat of reaction from the other

contributions, the cooling capacity as recorded just before switching the second pump from solvent to HexLi (228 W transferred to cooling medium) was subtracted from the steady-state value. This results in a heat of reaction of -419 W corresponding to a  $\Delta$ H of -95 kJ mol<sup>-1</sup>. This value deviates from the average flow calorimetric lab value by only 2% and lies within the precision range of +/-6% that was estimated above. In Table 11, all experimentally measured  $\Delta$ H are compared and highlight the value and accuracy of the flow calorimetry approach. Hence the proposed method could be considered as superior when applied in the thermodynamic characterization of fast, energetic transformations especially if heat contributions from secondary reactions can be captured or excluded similarly to the desired process. The set-up can be potentially evolved integrating more JTRs in sequence or installing classical PFA coil reactors before or after the JTR. This would enable the full characterisation of any type of flow reaction cascades which involve the formation of unstable intermediates.

Table 11. Comparison of results for enthalpy of reaction

Setup	$\Delta H(kJmol^{-1})$	Relative deviation from $\Delta H$ determined with the Fluitec JTR
Fluitec JTR	-93 (+/- 6%)	NA
Fluitec Contiplant PILOT	-95	2%
RC1 @ -60 °C, 30 min dosing	-167	80%
RC1 @ -70 °C, 60 min dosing	-120	29%

### CONCLUSIONS

A new meso-flow calorimeter was tested and successfully implemented. It relies on a jacketed tube reactor that allows to generate in-line, space-resolved temperature profiles. The modelling of the flow reactor as well as the deconvolution of the reaction enthalpy through the fitting of the

temperature data were performed in DynoChem. The project was focused on the characterisation of fast energetic chemical reactions and was carried out in two phases. In the first phase, the equipment and procedures were verified with a benchmark reaction between EtOH and HexLi. The thermodynamic data obtained in flow were compared with those obtained with a traditional batch calorimeter. The scope to obtain unequivocal data in batch as in flow was fully met by selecting a benchmark reaction which did not produce unstable intermediates. In the second phase, the verified approach was applied for the characterisation and scale-up of the 3-chlorobromobenzene (1) lithiation. The data obtained showcased the effectiveness of the new approach, accurately measuring the reaction enthalpy and facilitating the scale-up of the process to the pilot plant while avoiding unnecessary process control measures. The JTR was confirmed to be a superior alternative to existing batch devices and will be utilised in our laboratory to complement the safety and thermochemical assessments of all the fast and energetic flow transformations we might investigate in the future.

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### ABBREVIATIONS

 $\Delta$ H reaction enthalpy [kJ mol<sup>-1</sup>]; U overall heat transfer coefficient [W m<sup>-2</sup> K<sup>-1</sup>]; Q<sub>R</sub> reaction heat [W]; A heat transfer area [m<sup>2</sup>]; Cp specific heat capacity [kJ kg<sup>-1</sup> K<sup>-1</sup>];  $\rho$  density [kg m<sup>-3</sup>]; E<sub>A</sub> activation energy [kJ mol<sup>-1</sup>]; k<sub>0</sub> rate constant, second order [L mol<sup>-1</sup> s<sup>-1</sup>]; r reaction rate [mol L<sup>-1</sup> s<sup>-1</sup>]; T temperature [K]; h<sub>outside</sub> jacket-side heat transfer coefficient [W m<sup>-2</sup> K<sup>-1</sup>]; 1 length [m]; i.d. inner diameter [m]; o.d. outer diameter [m]; V<sub>hyd</sub> volume based on hydraulic diameter [m<sup>3</sup>]; V volume [m<sup>3</sup>].

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