1. Introduction

Today’s Research and Development world demands faster results to be able to deliver more products on time. Automation techniques coupled with in-situ analytics offer the ability to obtain physical and chemical information at the same time. Rapid process development is achieved by incorporating automation tools and instrumentation expertise into traditional organic chemistry. Furthermore the processes can be maximized if they are used in hand with statistical design and screening.

In this study, we focused on the formation of an Imine. The goal was to investigate the progress of the reaction as well as the endpoint. The work consisted of four batch experiments to gather initial information on the reaction. At a later stage four semi-batch experiments were performed.

The reaction was monitored by:
- The temperatures of the reaction mass and jacket (Tr-Tj)
- Mid-IR signal
- Heat of the Reaction (Qr)
- Thermal Conversion

2. Reaction

The reaction studied is an imine formation in methanol (Schiff base).

Recipe:
- Ramp Isobutylamine in methanol to desired temperature
- Add Benzaldehyde

Variables:
- Temperature (20 °C or 40 °C)
- Dosing time (5 min) or batch reaction

Table 1

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Quality</th>
<th>Mol</th>
<th>Ratio</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzaldehyde</td>
<td>99.5+ %</td>
<td>10 mmol</td>
<td>1</td>
<td>10.44 g</td>
</tr>
<tr>
<td>Isobutylamine</td>
<td>99%</td>
<td>10 mmol</td>
<td>1</td>
<td>7.36 g</td>
</tr>
<tr>
<td>Methanol</td>
<td>99.93%</td>
<td></td>
<td></td>
<td>15 mL</td>
</tr>
</tbody>
</table>

For the batch reactions 10 mL were added in one shot using a pipette while the semi-batch ones were done automatically using a dispenser box.
Investigation of an Imine Formation
Small Scale Using Screening Calorimetry

3. Apparatus
Figure 1 – The MultiMax™ multiple reactor system is designed for process screening, optimization and safety studies. It delivers precise and reproducible control of critical reaction variables such as temperature, stirrer speed, etc. and automation of routine procedures such as dosing, pH measurement, and pH control. The high quality of the temperature control and measurements allows getting valuable reaction and process information such as reaction initiation, reaction end-point, and thermal data.

The MultiMaxIR™ is a multiple automated lab reactor with in-situ Mid Infrared Technology. The system uses a MultiMax™ reactor box RB 04x50; part of the MultiMax™ family; which consists of four 50ml tank style vessels with independent control and built-in infrared sampling technology. The reactor box is coupled to an optical docking station with an automated light conduit and a ReactIR system.

4. Considerations
4.1. Calorimetry
Figure 2 – Reaction Calorimetry measures the instantaneous heat generated by a given reaction. The measured heat is related to the reaction rate (kinetics), which makes rate the primary measured parameter of calorimetry. By contrast, conventional techniques such as FTIR, NMR and chromatographic methods yield concentration as a function of time. Calorimetry is a complementary method that provides thermal information. This makes calorimetry an ideal complementary analytical method.

4.2. Reaction Enthalpy
Figure 3 – Reaction Enthalpy ($\Delta H_r$) by definition is the integral of heat generated ($Q_r$) minus a baseline ($Q_b$), over the time of the reaction. A suitable baseline means that under the same experimental conditions there is no heat generated.

4.3. Thermal conversion
Figure 4 & 5 – The thermal conversion is the curve that describes the partial integral related to the total heat of reaction. It is displayed in function of time and varies between 0 and 100%.
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5. Experiments – Screening Calorimetry in MultiMax™

Figure 6 – In order to make the thermal information quantifiable, we performed screening calorimetry at the reaction temperature, by activating a calibration heater inside the reactor. This heater is connected to the MultiMax™ by the Universal Control Box. The calibration steps are performed before and after the reaction takes place, allowing us to determine the calibration factors necessary for the calorimetric calculations.

Figure 7 – Once the experiment with the corresponding calorimetry steps was completed, the trends of the calibration heater (Qc), the reaction mass (mr) and the temperature difference between the reaction mass and the jacket temperature (Tr - Tj) were displayed. Subsequently, the results such as heat flow and thermal conversion were evaluated.

Figure 8 – After evaluating the calibration factors, we selected the heat terms that were involved in the heat of reaction such as heat flow (Q_flow), heat accumulated (Q_acc), and heat due to dosings (Q_dos). We observed the numeric values for the start and end time of the reaction, and the selected baseline type. The specific heat of the reaction mass (cp) and the temperature of the material dosed (T_dos) are presented too.

Figure 9 – Once the corresponding selections were made in the dialogue box for heat integration, the software calculated the enthalpy of the respective reactions and displayed them together with the start and end times of the integration ranges.

Figure 10 – Shows the graphical representation of the evaluated heat flow curve (Qr) together with the calibration signal and the mass balance.

Figure 8 – MultiMax™ dialogue box for heat integration

Figure 9 – MultiMax™ results box for the screening calorimetry method

Figure 10 – Graphical display for the heat of the reaction (Qr)
6. Results

6.1. Graphical Analysis

Figure 11 – By using the experimental approach described in the previous section, we determined the thermal conversion and end point for the given reaction.

6.2 Batch Reaction Results

Table 2 – After performing the analysis it was possible to tabulate the results with the reaction temperature and mixing speed. The results showed that the reaction proceeded fast, but it was difficult to determine whether the reaction rate was limited by mixing or temperature, or both.

Fig 11

Thermal conversion with mass and heat of reaction

Table 2
Batch results

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Stirrer speed</th>
<th>Time to reaction completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 °C</td>
<td>1000 rpm</td>
<td>7 min</td>
</tr>
<tr>
<td>20 °C</td>
<td>200 rpm</td>
<td>7.5 min</td>
</tr>
<tr>
<td>40 °C</td>
<td>1000 rpm</td>
<td>5 min</td>
</tr>
<tr>
<td>40 °C</td>
<td>200 rpm</td>
<td>5.5 min</td>
</tr>
</tbody>
</table>

Table 3
Semi-batch results

*No significant difference between 71.6 and 68.5%*

6.3 Semi-batch Reaction Results

Table 3 – Similarly to the data analysis for batch reactions, we performed the analysis for the semi-batch ones. In this case we focused on the thermal conversion after dosing was completed and tabulated it with the reaction temperature and mixing speed.

We observed that at 20 °C the results were the same independently of the mixing speed. When the reaction was performed at 40 °C the thermal conversion was identical. These results excluded mixing as the cause for rate limitation and identified the reaction temperature as a rate limiting factor.

6.4 Enthalpy Results

Tables 4 & 5 summarize the enthalpies calculated for the eight experiments performed. In average, the result was 3.98 kJ; the individual results spread within ±20% of what we expected for a screening calorimetry experiment.

Table 4 & 5

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Stirrer speed</th>
<th>Enthalpy</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 °C</td>
<td>1000 rpm</td>
<td>3.78 kJ</td>
</tr>
<tr>
<td>20 °C</td>
<td>200 rpm</td>
<td>3.58 kJ</td>
</tr>
<tr>
<td>40 °C</td>
<td>1000 rpm</td>
<td>4.44 kJ</td>
</tr>
<tr>
<td>40 °C</td>
<td>200 rpm</td>
<td>3.62 kJ</td>
</tr>
</tbody>
</table>

Table 5
Batch enthalpy results

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Stirrer speed</th>
<th>Enthalpy</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 °C</td>
<td>1000 rpm</td>
<td>4.38 kJ</td>
</tr>
<tr>
<td>20 °C</td>
<td>200 rpm</td>
<td>4.34 kJ</td>
</tr>
<tr>
<td>40 °C</td>
<td>1000 rpm</td>
<td>3.65 kJ</td>
</tr>
<tr>
<td>40 °C</td>
<td>200 rpm</td>
<td>4.10 kJ</td>
</tr>
</tbody>
</table>
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6.5 Validation of the Information
Figure 12 & 13 – In order to validate the thermal information, we utilized Mid-IR data as a complementary measurement. The measurement was performed with a MultiMaxIR™. It scans all reactor vessels simultaneously while the reaction is performed. The Mid-Infrared profiles can be presented together with the MultiMax™ data in the same trend graph which allows us to compare them directly with the heat flow trends.

Figure 12
Mid-IR progress of the reaction using MultiMaxIR™

Figure 13 shows that the thermal as well as the chemical conversions are in agreement.

Figure 13
Comparison of the chemical and thermal conversions

7. Conclusions
- Reaction calorimetry allows the determination of thermal conversion.
- Thermal conversion can be used as an in-situ analytical technique that allows to study:
  - Factors that have an impact on the reaction rate such as:
    - Mixing
    - Reaction temperature
  - Addition rate
  - Concentration
    - Reagent/substrate accumulation during a reaction
    - Reaction dynamics and kinetics studies
    - Troubleshoot scale up issues
  - With only a few experiments we gained a better understanding of the imine formation and identified the driving factors of the process. Temperature was identified as the decisive factor whereas mixing only plays a secondary role.

Using MultiMax™ calorimetry and ReactIR™ as analytical tools increased the speed of development, but also supported the validation of the results assuring its correctness and integrity.