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Decoupling Multiple Potentially Runaway Reactions using Calorimetry: Acid Catalyzed Esterifications Case Study

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The application of reaction calorimetry to fast and exothermic processes is a cornerstone in process safety analysis, especially when potentially runaway phenomena can be triggered by uncontrolled temperature rise. Peltier-cell calorimeters allow for accurate measurement of heat flow signals during semi-batch or batch experiments. However, in systems involving multiple consecutive or parallel reactions, the measured overall heat flow is a convolution of different contributions, complicating the interpretation of calorimetric data. This work addresses the challenge of decoupling heat flow signals to determine the reaction enthalpies of individual consecutive steps and to extract basic kinetic information. The acid-catalysed esterification of propionic anhydride with isopropanol was investigated as a case study. The process involves three exothermic reactions of comparable magnitude, whose simultaneous occurrence can hinder quantitative analysis. A systematic calorimetric approach was developed, combining experimental runs under isothermal conditions at different temperatures, calibration tests, mixing enthalpy determination, and signal deconvolution. The results demonstrate that, despite limitations, it is feasible to derive reliable estimates of reaction enthalpies and to infer kinetic behaviour directly from Peltier calorimetry. The methodology is discussed in the context of process safety and productivity optimization, with emphasis on the importance of complementary techniques, such as NMR, to validate calorimetric findings.

1. Introduction

Process safety represents a critical aspect in chemical engineering, particularly in relation to the risk of runaway reactions, the explosibility of dusts, and the flammability of both liquids and powders. In this context, the availability of reliable mathematical models or well-established experimental protocols is essential to properly assess the hazardous properties of substances involved in industrial processes (Copelli et al., 2016, Scotton et al., 2020).
Runaway phenomena in chemical reactors have been extensively investigated in the last decades (Casson et al., 2016; Copelli et al., 2017). A runaway reaction occurs whenever the rate of heat generation surpasses the capacity of the system to remove heat fluxes, causing a sharp temperature increase and a subsequent self-accelerating reaction rate. This thermal explosion scenario is particularly relevant for exothermic reactions with short characteristic times, such as acid-catalysed esterifications, where minor deviations in operating conditions can lead to an uncontrolled behaviour. Esterification reactions between anhydrides and alcohols catalysed by sulfuric acid find a plethora of applications in cosmetic, food and pharmaceutical technology (Hoff and Eisenacher, 2025). Also, it is well known that their thermal behaviour is often hard to be interpreted (Qiang et al., 2022).
Reaction calorimetry represents one of the most powerful techniques to study the thermal behaviour of reactive systems under controlled laboratory conditions (Widell and Karlsson, 2006; He et al., 2025). Calorimetric tests can provide direct measurement of heat flow exchanged between the reactor contents and its surroundings, allowing estimation of reaction enthalpies, reaction rates, and potential hazards. In particular, modern calorimeters based on Peltier-cell technology (e.g. EasyMax 102™, OptiMax™, Mettler Toledo) have gained widespread use in both academia and industry due to their accuracy, flexibility, and ease of use.

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Despite their strengths, these instruments present intrinsic limitations when dealing with multi-step reactions (Yao et al., 2022). The overall heat flux signal recorded during an experiment is the sum of the contributions from all chemical and physical processes occurring in the system: main reaction, side reactions, mixing, dilution, and even secondary hydrolysis. Consequently, when several exothermic reactions occur simultaneously, it becomes challenging to uncouple the specific contributions and to assign enthalpy values to each individual reaction. The aim of this work is to explore the possibility of using a pure calorimetric approach to decouple overlapping heat flow contributions in consecutive reactions, and thereby to estimate reaction enthalpies and extract basic kinetic parameters. The case study selected is the esterification of propionic anhydride with isopropanol catalysed by sulfuric acid, a reaction scheme involving three consecutive exothermic steps. This system represents a paradigmatic example of the challenges posed to calorimetric interpretation: fast kinetics, significant exothermicity, and the presence of side reactions triggered by water contamination.

2. Methodology

2.1 Case Study: Esterification of Propionic Anhydride

The esterification of propionic anhydride with isopropanol proceeds via three possible reactions, all catalyzed by sulfuric acid. The corresponding theoretical reaction enthalpies, estimated using CHETAH 10.0 software, are reported below (see also Figure 1).

1. Main esterification reaction
   Propionic anhydride (A) + Isopropanol (B) → 2-propyl propanoate (C) + Propionic acid (D)
   ΔH = –59.6 kJ/mol
2. Secondary esterification
   Propionic acid (D) + Isopropanol (B) ↔ 2-propyl propanoate (C) + Water (W)
   ΔH = –4.83 kJ/mol
3. Hydrolysis reaction
   Propionic anhydride (A) + Water (W) → 2 Propionic acid (D)
   ΔH = –58.16 kJ/mol

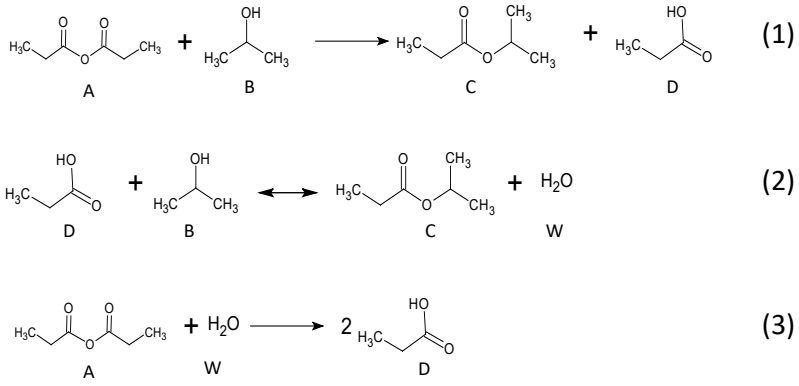

Figure 1: Stoichiometric sketch of the three main reactions involved.
The main reaction (1) is highly exothermic and essentially irreversible under the studied conditions, as is the hydrolysis (3). Reaction (2) is reversible and characterized by a low reaction enthalpy value.

2.2 Calorimetric Setup

All experiments were carried out using a Mettler Toledo EasyMax 102™ calorimeter, equipped with Peltier cells for precise isothermal control. The device provides direct heat flow data (q), reactor temperature (T), jacket temperature, and volume changes over time.
The calorimetric method relies on measuring the instantaneous heat flux exchanged between the reactor and the thermostatic jacket. By integrating the heat flow signal over time, the total enthalpy change associated with the reaction can be obtained.

2.3 Experimental Procedure

Three different recipes were used. The first recipe (Recipe n° 1) employed was the esterification of propionic anhydride with isopropanol and it was as follows:

- Propionic anhydride (> 99%, 39.7 g) – loaded as initial charge;

- Isopropanol (> 99.9%, 18.3 g) + concentrated sulfuric acid (98%, 0.315 g) – dosed over 20 minutes.

The second recipe (Recipe n° 2) used was for the esterification of propionic acid with isopropanol and it consisted of:

- Propionic acid (> 99%, 39.7 g) – loaded as initial charge;
- Isopropanol (> 99.9%, 18.3 g) + concentrated sulfuric acid (98%, 0.315 g) – dosed over 20 minutes.

Finally, the third recipe (Recipe n° 3) was setup to determine the reaction enthalpy of the propionic anhydride hydrolysis (Reaction (3)) and it consisted of:

- Propionic anhydride (> 99%, 39.7 g) – loaded as initial charge;
- Water (5.5 g) – dosed over minutes 10 minutes.

It is important to notice that for Reaction 2 a strong excess of propionic acid was used to measure the direct reaction enthalpy.

Three isothermal experiments per recipe were performed at 15, 25, and 35 °C. Moreover, an additional calibration test was conducted at 5 °C to evaluate the enthalpy of mixing between propionic anhydride and isopropanol because, at such a temperature, the system reactivity was observed to be negligible. Then, all raw calorimetric signals coming from experimental tests where propionic anhydride and isopropanol were used were corrected for the enthalpy of mixing determined from the calibration run at 5 °C. This step was essential to isolate the chemical contributions from the physical mixing processes. During each run where isopropanol and sulfuric acid were used as reactants, they were continuously dosed over 20 min into the anhydride-containing reactor. The calorimeter recorded the heat flow profile during dosing and subsequent equilibration (post reaction time).

2.4 Data Analysis and Decoupling Strategy

To attempt decoupling all the overlapping heat contributions during the different syntheses, the following approach was adopted.

- **Step 1**: Carry out syntheses using Recipe n° 2 and Recipe n° 3 to determine their reaction enthalpies (in fact, such reactions gave a final stable system) by integration of their heat flow signals at each temperature.
- **Step 2**: Comparison with theoretical enthalpies. Experimental enthalpy values were compared with CHETAH-calculated reaction enthalpies to assess completeness and to identify missing contributions.
- **Step 3**: Carry out syntheses using Recipe n° 1 to determine their “apparent” reaction enthalpies by integration of their heat flow signals at each temperature. The aim of this step is to assess whether Reaction (2, both + and -) and/or Reaction (3) can alter the measure of the reaction enthalpy.
- **Step 4**: Peak analysis. The timing and magnitude of heat flux peaks were examined to assess safety concern due to reactants accumulation.
- **Step 5**: Decoupling. NMR analyses of the final mixture coming from Step 3 coupled with the reaction enthalpies from Step 1 were used to confirm product distribution and to verify which reactions had actually occurred.

3. Results and Discussion

3.1 Preliminary enthalpies and validation (Step 1 and 2)

Table 1 summarizes the results coming from Step 1 and Step 2, as described in paragraph 2.4. As it is possible to observe, the mixing enthalpy of isopropanol and propionic anhydride was moderately endothermic; while reactions occurring using Recipe n° 2 and n° 3 were exothermic, the first one very low (because the reaction was affected by equilibrium conditions, the only reason for observing only the exothermic direct reaction was because an excess of propionic acid was used) and the second quite high.

Table 1: Comparison of reaction enthalpies for recipes n° 2 and 3 and the mixing between isopropanol and propionic anhydride at 5 °C.

Recipe	Enthalpy @ 25 °C (Experimental) [kJ/mol]	Enthalpy @ 35 °C (Experimental) [kJ/mol]	Enthalpy @ 25 °C (CHETAH 10.0) [kJ/mol]
N° 2	-4.57	-4.35	-4.83
N° 3	-54.6	-56.3	-58.16
Mixing @5°C	4.296		Not available

Experimental reaction enthalpies measured using the Mettler Toledo EasyMax 102™ calorimeter were found to be in a good agreement with the theoretical maximum values predicted using CHETAH 10.0 software (which is based on the Benson's group contribution method). This means that the experimental apparatus used, and its setup is reliable.

3.2 Heat Flow Profiles and Reaction Enthalpies (Step 3 and 4)

Figure 2 reports the calorimetric heat flow signals obtained at 15 (a), 25 (b), and 35 °C (c), respectively, for the synthesis performed using Recipe n° 1. Such a recipe is critical because, theoretically, all the three reactions could be involved according to the operating conditions and the dosing time used.

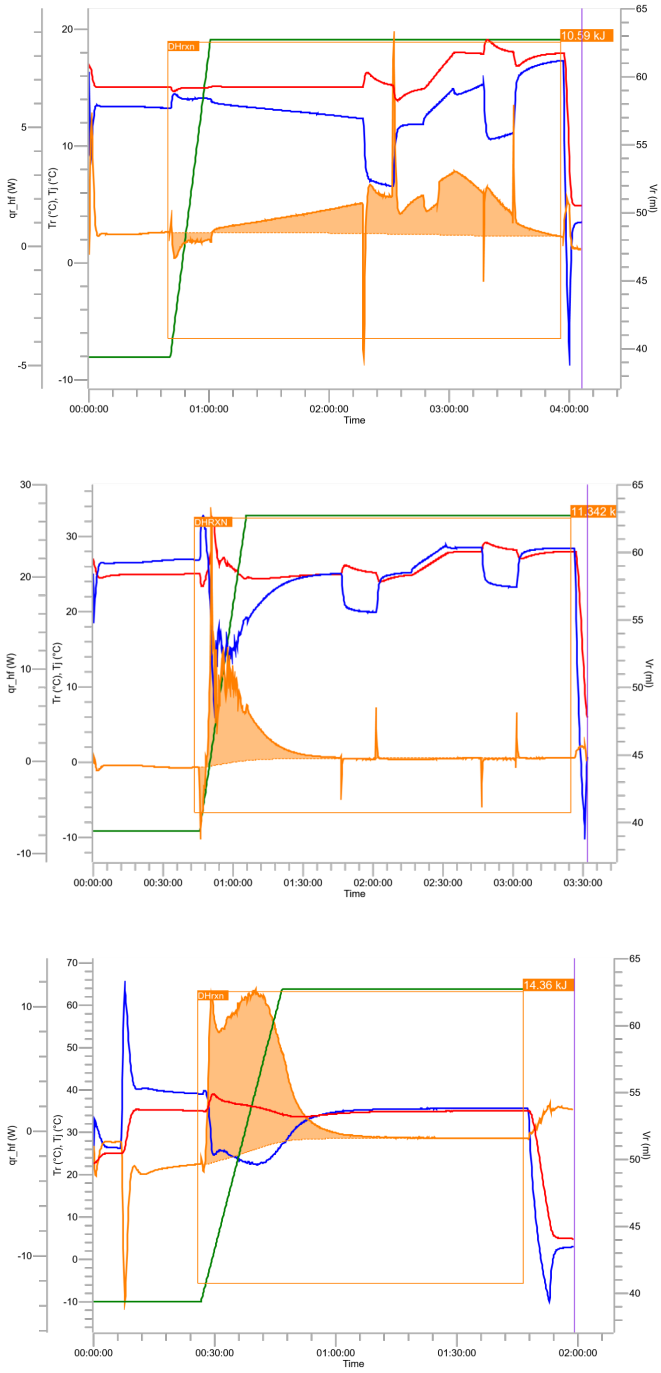

Figure 2: Heat fluxes (orange), reactor temperature (red), jacket temperature (blue) and real volume (green) for recipe n° 1 carried out at: a) 15 °C; b) 25 °C; c) 35 °C.

At low temperature (15 °C), the maximum heat flux was delayed, occurring over one hour after dosing was completed (and during calibration operations, where a 3 °C temperature increase step was used for determining the specific heat capacity of the final reacting mixture). This indicates that the system behaved as a batch reactor, with reaction occurring after the accumulation of all reactants. Temperature control is always optimal, and no safety concerns seemed to arise during the synthesis.
At higher temperatures (25 °C and 35 °C), the peak heat flux occurred within the dosing period, reflecting faster kinetics and stronger overlap between feed addition and reaction. The intensity of the peak decreased with increasing temperature, suggesting more controlled and distributed heat release.
Experimental reaction enthalpies (obtained by direct integration of the three heat fluxes reported in Figure 2) are summarized in Table 2. It is possible to observe that, at all tested temperatures, the experimental reaction enthalpies for Recipe n° 1 were lower than theoretical predictions for a complete conversion of Reaction (1).
The systematic underestimation of all the reaction enthalpies could be attributed to both incomplete conversion of Reaction (1) (because of the presence of the other two reactions), the presence of water as contaminants (which could therefore trigger Reaction (3)), and the masking effect of mixing enthalpy (between isopropanol and propionic anhydride). In fact, calibration at 5 °C yielded an enthalpy of mixing of about +4.3 kJ/mol (endothermic effect), which further confirmed the need for correction to correct understand the calorimetric data coming from a synthesis using Recipe n° 1.

Table 2: Apparent reaction enthalpies and peak fluxes for recipe n° 1 at different temperatures.

Temperature [°C]	Apparent Enthalpy Experimental [kJ/mol]	Peak Flux Experimental during reaction time (and dosing) [W/kg]	Enthalpy (CHETAH 10.0) [kJ/mol]
15	-36.14	142.1 (14.57)	-59.6
25	-42.10	615.4 (615.4)	-59.5
35	-47.30	304.0 (304.0)	-59.4

3.3 Decoupling of Reactions (Step 5)

NMR analyses were carried out to qualitatively determine the presence of the substances involved in the synthesis of Recipe n° 1. The absence of propionic anhydride in all final mixtures, combined with traces of isopropanol (not quantified in this study but the amount of isopropanol diminished as the synthesis temperature increased), suggested that reaction (1) had occurred, while the other reactions, were negligible. Moreover, NMR results did not detect an excess of either propionyl propionate or propionic acid beyond the amounts expected from reaction (1). Therefore, the overall calorimetric enthalpy could be attributed primarily to the main esterification reaction, which was not complete at any investigated temperature. Such evidence was also supported by the fact that if Reaction (3) or (2-direct) had occurred, the registered apparent system enthalpy would have been major with respect to the theoretical value for Reaction (1) only. This supports the fact that both Reaction (3) and (2-direct) were negligible in all the tested conditions (except for minor water contamination before starting the syntheses). Table 3 reports the values of the corrected (by the mixing enthalpy) reaction enthalpies for all the Recipe n° 1 syntheses and the corresponding calorimetric conversions of Reaction (1) at the different tested temperatures.

Table 3: Reaction enthalpies and calorimetric conversions for Reaction 1 at different temperatures.

Temperature [°C]	Corrected Enthalpy Experimental [kJ/mol]	Calorimetric Conversion Reaction (1) [%]	NMR results
15	-40.44	68	No A, B traces
25	-46.40	78	No A, B traces
35	-51.60	87	No A, B traces

Although a quantitative kinetic modelling was beyond the scope of this work, qualitative insights can be obtained from calorimetric data. Particularly, the position and shape of the heat flow peaks revealed useful information; at 15 °C, the delayed peak indicates slow reaction kinetics relative to dosing, with conversion extending well beyond feed addition. Otherwise, at both 25 °C and 35 °C, heat flux peaks were all during the dosing period,

implying faster kinetics and a low degree of post-dosing reactants accumulation. The trend of decreasing peak intensity with increasing temperature points to a more distributed heat release, enhancing process safety. These observations highlight that calorimetry can provide basic kinetic information even without full mechanistic modelling, supporting process design and hazard assessment.

3.4 Implications for Process Safety

The ability to decouple heat contributions and to assess reaction kinetics as a function of the operating parameters is fundamental for a safe scale-up. For fast, exothermic esterifications, operating at higher temperatures within the studied range improved both conversion and safety margin, by aligning reaction rate with dosing profile and avoiding large post-dosing peaks. Nevertheless, this study also underscores the limitations of a purely calorimetric approach. Without complementary analytical techniques, misinterpretations of the calorimetric data can arise, particularly when consecutive reactions can overlap. The integration of calorimetry with other analytical techniques (e.g. NMR, FTIR, GC, etc..) is always strongly recommended to confirm the effective selectivity with respect to the desired product and to avoid underestimating potential hazards (e.g. the presence of an exothermic unwanted reaction).

4. Conclusions

This work investigated the feasibility of using Peltier-cell reaction calorimeters to decouple heat flow signals in systems involving either consecutive or parallel exothermic reactions. The esterification of propionic anhydride with isopropanol was selected as a case study, characterized by fast kinetics and multiple possible pathways. The main conclusions that can be drawn by this work were that: a) it is possible to identify and assign calorimetric heat flow signals to specific reactions by combining calorimetric data (with proper calibration) and NMR analysis; b) correcting for mixing enthalpy is essential to avoid underestimating reaction enthalpies; c) despite limitations, Peltier-cell calorimetry provides valuable insights into both enthalpy and kinetics of fast complex reaction systems; d) higher operating temperatures (25–35 °C) improved both conversion and process safety, reducing delayed peak fluxes; e) a pure calorimetric approach can be reliable for process characterization, provided that appropriate precautions are taken, and complementary techniques are employed. The methodology developed within this work represents a promising route to extract thermochemical and kinetic information directly from calorimetric data, supporting safer and more efficient scale-up of fast, exothermic processes.

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