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Scale-Up of a Vilsmeier Formylation Reaction: Use of HEL Auto-MATE and Simulation Techniques for Rapid and Safe Transfer to Pilot Plant from Laboratory

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Abstract:

The application of reaction calorimetry and process modelling to allow for the rapid and safe scale-up of a Vilsmeier formylation reaction to the pilot plant will be described. This transformation was a key step in the preparation of the backbone amide linker (the so-called "BAL" handle) for solid-phase chemistry. In particular, use was made of Auto-MATE equipment from Hazard Evaluation Laboratories (HEL) and "Reaction Simulator" software to derive a thermokinetic model which allowed us to simulate heat-flow data on-scale. The model was then refined using a HEL SIMULAR 1-L calorimeter, and a direct comparison of the data showed there to be a 20% error in the enthalpy data gathered from the smaller Auto-MATE. The use of a preformed Vilsmeier reagent and dichloromethane as a reaction solvent gave a "square-wave" profile typical of a feed-controlled reaction. These conditions were successfully scaled to a 50-L pilot-plant vessel.

Introduction

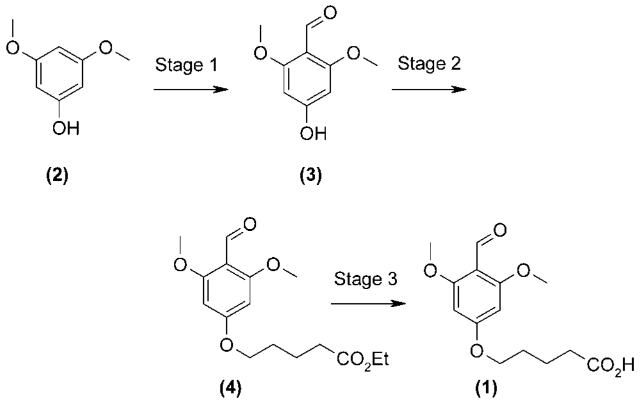
The so-called "BAL" (backbone amide linker) handle **(1)** is a useful reagent for solid-phase chemistry and is widely used within Roche both locally and globally. Small laboratory batches had previously been synthesised within our department using the literature procedure[1] involving a hazardous Vilsmeier reaction as the first stage. With a requirement for larger amounts it was felt that to scale the synthesis to our pilot plant some modifications were required.

In this report we discuss the use of the HEL Auto-MATE reaction calorimeter and reaction simulation software to rapidly address the problems we envisaged in the scale-up of Stage 1 (Scheme 1) to a 50-L pilot-plant vessel.

Discussion

General Overview. Our objective was to transfer this chemistry from the laboratory to the pilot plant in an expedient and safe manner. The volume requirements for this material were likely to be very low, and we anticipated the preparation of only one or two batches. Our primary goal to make use of reaction calorimetry, in particular the HEL Auto-MATE and an "in-house" software package[2] for delineating safe conditions for the pilot plant.

Scheme 1



In looking to scale up the process rapidly we focused on the ease of isolation of **3** from the crude mixture of aldehydes generated in the Vilsmeier reaction and its separation by recrystallisation.

Derivation of a Solvent-Based Procedure. In seeking to control the heat of reaction we felt that a solvent-based procedure would be advantageous over the neat process described in the literature. Using Auto-MATE we simultaneously evaluated four reaction protocols under isothermal conditions at −5 °C (Table 1).

Run 1 provided us with an evaluation of the neat literature conditions and as expected showed heat accumulation. The mixture also became quite viscous and stirred with difficulty. In run 2 we explored the use of *N*,*N*-dimethylformamide as

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[§] The initial spike in the power profile was an artifact due to imperfect PID loop response.

(1) Albericio, F.; Kneib-Cordonier, N.; Biancalana, S.; Gera, L.; Masada, R. I.; Hudson, D.; Baranay, G. *J. Org. Chem*. **1990**, *55*, 3730.

(2) The reactor model dynamically recalculates the overall heat-transfer coefficient *U* through evaluation of reactor outside (h_o) and inside (h_i) film coefficients coupled to a knowledge of the reactor thermal conductivity (k/l). In addition a correction term U_{corr} is included to account for other extraneous factors (e.g., fouling). U_{corr} is in turn evaluated from a simple heating or cooling curve collected in the target reactor. The program maintains a database of reactor properties, heat transfer fluid properties and solvent properties. The major process solvent is generally chosen to model the process; however, for mixed-solvent systems Wilson plots may be needed to select the most appropriate solvent for modelling. The reaction model can include up to five consecutive reactions with 26 independent chemical species. Reactions are modelled using a standard power law protocol. The powers correspond to the molecularity of the fundamental reaction steps in the model. This is clearly distinct from the empirical order of reaction, which generally relates to the rate-determining step (rds) of the mechanism. The powers can be user-defined so that multistep processes can, when appropriate, be truncated into one reaction. In this case the powers would usually correspond to the rds for the truncated reaction sequence. For more information about Reaction Simulator Software contact Dr. Mark B. Mitchell by e-mail at Mark.Mitchell@Pfizer.com.

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Table 1: **First Auto-MATE experiment assessing solvent effect**

run	vessel contents	addition mixture	comments
1	ArOH/$POCl_3$	DMF	accumulation, viscous and unstirrable
2	ArOH/DMF	POCl3	accumulation, viscous and unstirrable
3	ArOH/$POCl_3$/DCM	DMF in DCM	accumulative, controlable and stirrable
4	ArOH/$POCl_3$/ trifluorotoluene	DMF in trifluorotoluene	accumulative and a two-phase mixture

reaction solvent, while run 3 used dichloromethane and finally run 4 used α,α,α-trifluorotolune, proposed as a useful alternative to DCM. No other solvents were considered at this stage. From this study we felt that only DCM was suitable as a candidate solvent for further scale-up. Under the conditions evaluated in Table 1 we observed that the exotherm was accumulative and not completely feed-controlled as desired. It should be noted that the above experiment involved the formation of the Vilsmeier intermediate reagent “in situ”. We next sought to evaluate the use of preformed reagent and the effects of temperature.

Refinement of the Dichloromethane Process. From this experiment it was clear that the preferred conditions for scale-up involved the use of preformed Vilsmeier reagent (Table 2, run 3). From the “square wave” form of the power trace[2] (Figure 1) it was clear that the reaction of the Vilsmeier reagent with the phenol was fast and proceeded in an essentially feed-controlled manner. By way of contrast the rate of formation of the Vilsmeier reagent must be slow compared to the addition rate to account for the induction and accumulation observed when using “in situ” generated reagent. The use of Auto-MATE allowed us to screen reaction conditions and to select those most suitable for scale-up in only seven experiments.

We now wished to use the data generated from the Auto-MATE experiments to simulate temperature profiles on scale-up using “Reaction Simulator” software. This, we hoped, would further refine the process and generate useful information for a HAZOP.

Reaction Modelling and Simulation. The objective for reaction modelling was to derive kinetic data for the crucial first stage (Vilsmeier reaction) of the process, as obtained through fitting of empirical calorimetric profiles to a proposed reaction model. Armed with both the kinetic and thermal data, it would be possible to simulate the thermal behaviour of the process upon scale-up to a pilot-plant reactor.

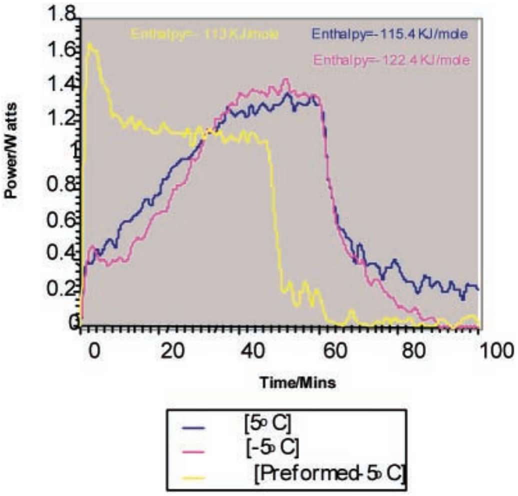


Figure 1. **Comparisons of calorimetric power profiles.**

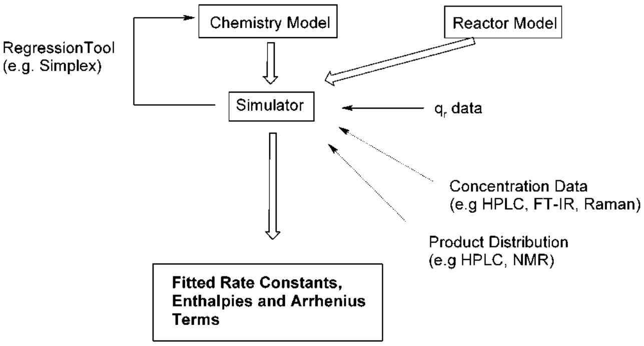
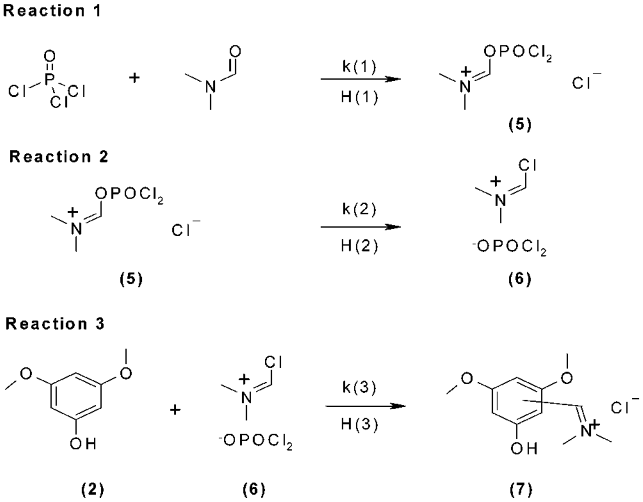


Figure 2. **Process of kinetic data extraction.**

Scheme 2



It is generally accepted that the mechanism of Vilsmeier formylation proceeds through the intermediacy[3,4] of chloroiminium ion **(6)**, which acts as the electrophile in the aromatic substitution process rather than the initially formed phosphorylated species **(5)** (Scheme 2).

Kinetic data was extracted from the power data by use of an in-house software package “Reaction Simulator”. The process of kinetic data extraction is illustrated in Figure 2, and effectively involves the systematic variation of trial enthalpy and rate constant values to minimise the deviation between the empirical and simulated power trace (q_r). Note in this example only q_r will be used in the so-called objective function fitting; however, the process could also be performed with, or in combination with, product distribution

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(3) When many potential mechanisms exist each, should be modelled in turn to see which fits the data best (see ref 10, for example). In this case the mechanism of Vilsmeier formation is well accepted to proceed through the indicated pathway. It was not deemed necessary to model other potential routes, a decision which seems justified in the light of the comparable activation data found from this work when compared to the literature (ref 7).

(4) Jugie, G.; Smith, J. A. S. *J. Chem. Soc., Perkin Trans. II* **1975**, 925.

Table 2: **Temperature dependence and effect of preforming the Vilsmeier reagent**

run	temp °C	vessel contents	addition mixture	comments
1	−5	ArOH/$POCl_3$/DCM	DMF/DCM	peak heat output at end of feed; exotherm accumulates; ΔH = −122 kJ/mol
2	5	ArOH/$POCl_3$/DCM	DMF/DCM	peak heat output at end of feed; exotherm accumulates; ΔH = −115 kJ/mol
3	−5	ArOH/DCM	DMF/$POCl_3$/DCM	constant heat output;. feed-controlled; ΔH = −113 kJ/mol

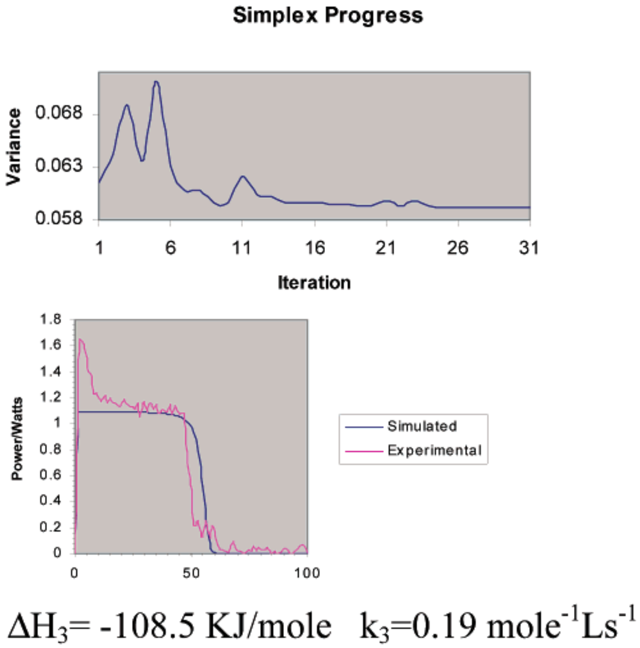

Figure 3. **Simplex regression and comparison of experimental and simulated power profiles for Reaction 3.**

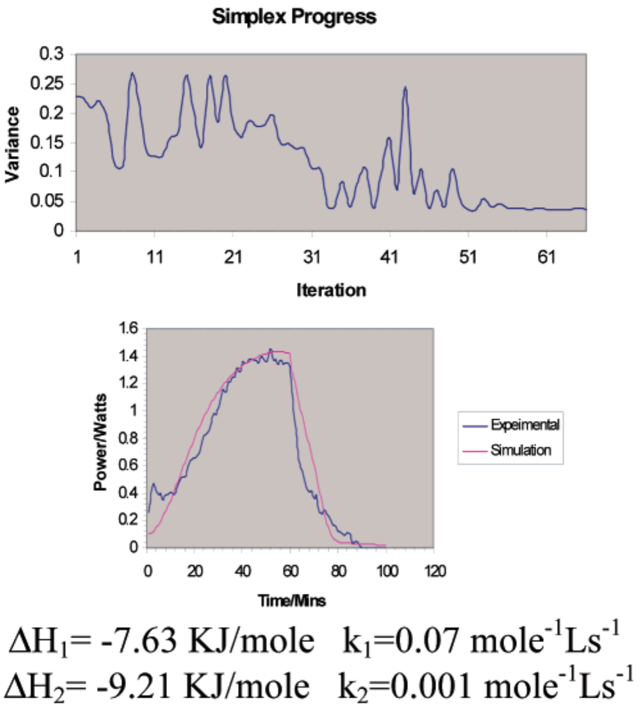

Figure 4. **Simplex regression and comparison of experimental and simulated power profiles for in situ at −5 °C allowing derivation of enthapies for reactions 1 and 2 (ΔH_1 and ΔH_2).**

and concentration data. For more complex chemistry models the use of a multidata objective function is essential. This approach to data extraction is also used in commercial simulation packages such as Batchcad[5] and ProSim.[6] For the case of “Reaction Simulator” the objective function was optimised using a modified simplex algorithm.

The thermo-kinetic data for reaction 3 (Scheme 1) was initially extracted, by simplex regression of initial trial data against the power data for the preformed Vilsmeier reaction (Figure 1, yellow trace). Both k_3 and ΔH_3 were variable in the simplex, and the simplex progress, optimized values, and fit comparisons are illustrated in Figure 3.

The process was now repeated for the *in situ* example at −5 °C, keeping the above values for ΔH_3 and k_3 constant, and allowing k_1, k_2, ΔH_1, and ΔH_2 to be variable in the regression. The results are depicted in Figure 4.

Finally, the analysis was performed for the *in situ* example at 5 °C, holding the obtained enthalpy values ΔH_1, ΔH_2, and ΔH_3 constant, whilst allowing k_1, k_2, and k_3 to be variable. The outcome can be found in Figure 5.

Approximate rate constants were now available for all three steps in the reaction, and since rate constant data was available at two temperature points, the Arrhenius terms could be calculated using a standard logarithmic plot. This would clearly only give a rough idea of the temperature dependence since only two data points were available. Activation enthalpy and entropy values could also be obtained from an Eyring plot. The derived parameters are presented in Table 3.

Using the rate data we were able to show significant temperature dependence for the formation of the Vilsmeier reagent. At low temperatures (below 15 °C) there is significant accumulation. An increase in reaction temperature results in an increase in rate of reaction, and at 25 °C the process is essentially feed-controlled as illustrated in Figure 6.

Figure 7 illustrates that the rate-determining step for lower temperatures is clearly that for the chloride displacement reaction. The activation enthalpy and entropy for this rate-limiting step (Table 1, reaction 2) is comparable to that previously reported[7] by use of a spectroscopic method to follow the overall reaction kinetics $\Delta H^{\ddagger} = 66$ kJ mol^{-1}, $\Delta S^{\ddagger} = -128$ J K^{-1} mol^{-1})

Most importantly though an approximate rate constant[8] for reaction 3 (k_3 = 0.23 mol^{-1} L sec^{-1}) was derived, and

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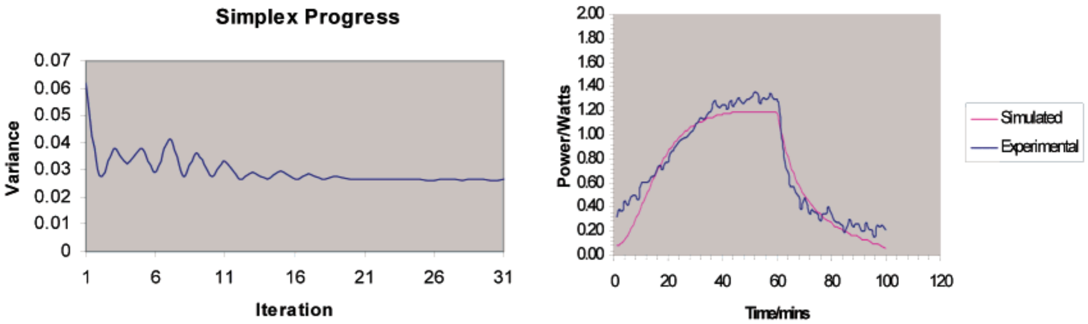
(5) BATCHCAD is a registered trademark of GSE Systems Inc., U.S.A.

(6) ProSim is a registered trademark of ProSim S.A., France.

(7) Alunni, S.; Linda, P.; Marino, G.; Santini, S.; Savelli, G. *J. Chem. Soc., Perkin Trans. II* **1972**, 2070.

(8) It has been commented that rate constants exceeding 0.1 mol^{-1} L s^{-1} reflect feed-controlled reactions and, as such, should be more accurately described as in excess of the limiting value where heat output rate becomes dominated by factors other than kinetics. Whilst we agree in part with this view, it is well established from the literature that rate constants significantly greater than this can be derived using mathematical regression methods (see ref 10).



k_1=0.076 mole^{-1}Ls^{-1} k_2=0.0023 mole^{-1}Ls^{-1} k_3=0.23 mole^{-1}Ls^{-1}

Figure 5. **Simplex regression and comparison of experimental and simulated power profiles for in situ at 5 °C, allowing derivation all three rate constants (k_1, k_2, and k_3).**

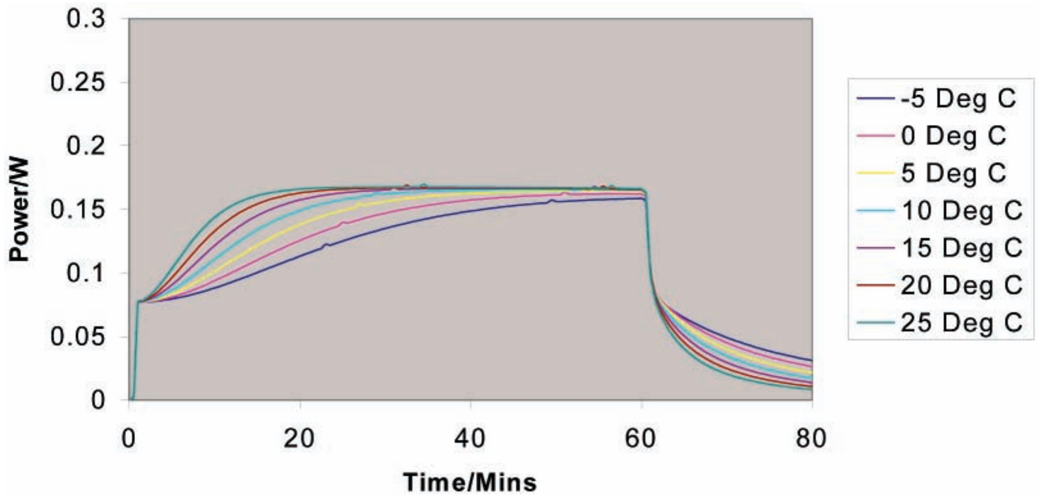


Figure 6. **Simulated power profiles of formation of Vilsmeier reagent at different temperatures.**

Table 3: **Arrhenius terms and activation ethalpies and entropies**

reaction	A mol^{-1} L s^{-1}	E_a kJ mol^{-1}	$\Delta H^{\ddagger}$ kJ mol^{-1}	$\Delta S^{\ddagger}$ J K^{-1} mol^{-1}
1	0.9179	5.74	3.39	−288
2	4.09×10^7	54.55	52.20	−142
3	38.49	11.83	9.48	−257

this would allow us to model the heat flow of this reaction on-scale.

Calorimetric Studies in SIMULAR and Pilot Plant Simulation. Having chosen to scale the route involving preformation of the Vilsmeier reagent we wanted to characterise the process in our 1l SIMULAR calorimeter. We wished to primarily compare the quality of calorimetric data obtained from our well established SIMULAR system with data obtained from the small-scale Auto-MATE. The manufacturers (HEL) themselves acknowledge that Auto-MATE is less accurate than SIMULAR and do not recommend transfer of a process purely on the basis of Auto-MATE data.[9]

The data for reaction of the preformed Vilsmeier reagent with the phenol is presented in Figure 8.

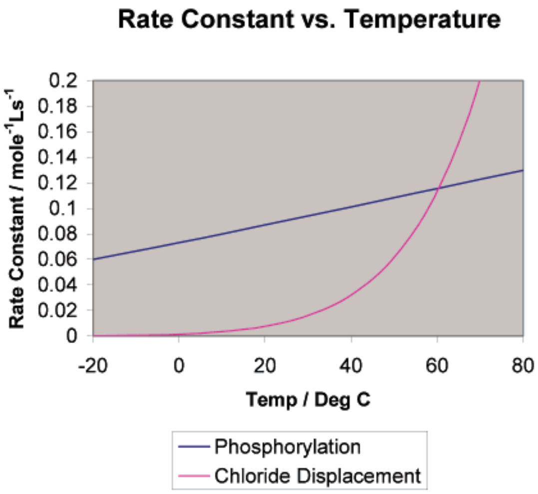


Figure 7. **Temperature dependence of rate of phosphorylation and chloride displacement.**

There was a difference between Auto-MATE and SIMULAR collected data. For reaction of Vilsmeier reagent with the phenol Auto-MATE appears to have over-estimated the reaction enthalpy (−113 kJ/mol vs −93 kJ/mol) by around 20%, although the reaction profile was the expected "square wave" form. The reaction was simulated as before, and these data are also presented in Figure 8.

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(9) Simms, C.; Singh, J. *Org. Process Res. Dev.* **2000**, *4*, 554.

(10) Bollyn, M.; Van den Bergh, A.; Wright, A. *Chem.-Anlagen Verfahren* **1996**, *29*, 95.

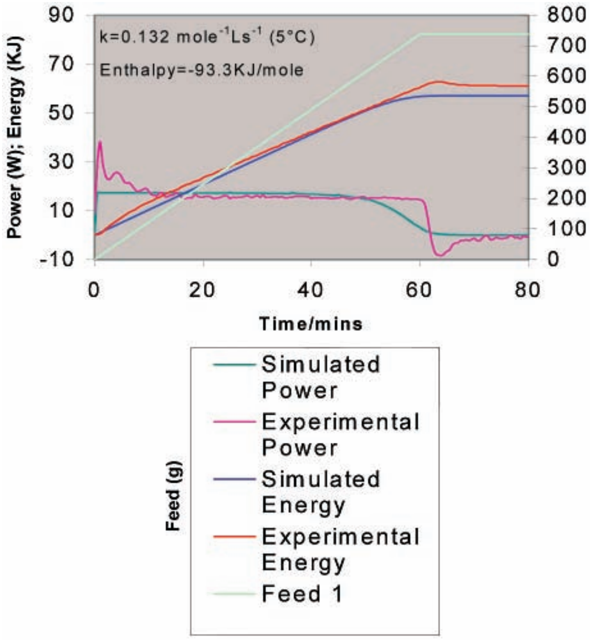

Figure 8. **SIMULAR experimental and simulated power and energy profiles.**

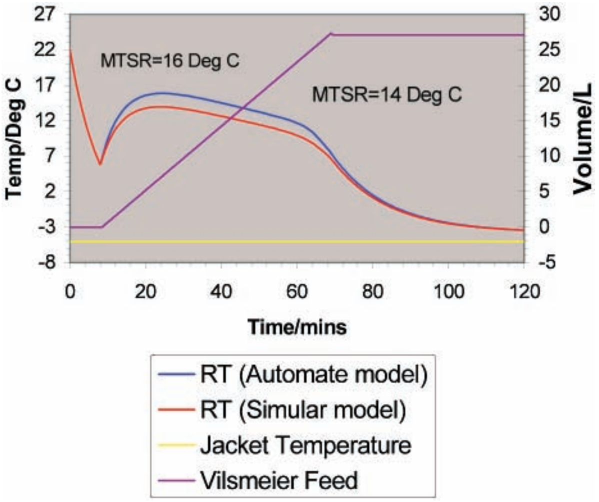

Figure 9. **Comparison of Auto-MATE and SIMULAR simulated Vilsmeier reaction data under isoperiobolic conditions in 50-L Pfaudler vessel.**

With data available from both the Auto-MATE and SIMULAR models for the Vilsmeier reaction we were able to predict thermal behaviour of the process in a 50-L Pfaudler glass-lined steel reactor. The "reaction simulator" enabled us to generate a range of temperature and addition profiles, but for brevity only that which was chosen following a HAZOP discussion is shown.

The reaction would be performed under isoperibolic (constant jacket temperature) conditions, and hence the simulations were also performed for an isoperibolic reaction. Figure 9 illustrates the difference between the Auto-MATE and SIMULAR-based models.

The maximum temperature of synthetic reaction (MTSR) is overestimated in the Auto-MATE model by approximately 2 °C. This discrepancy can be traced back to the 20% error in the ΔH value for the addition of Vilsmeier reagent to the phenol, when performed under power-compensation mode, in Auto-MATE in comparison to that for SIMULAR.

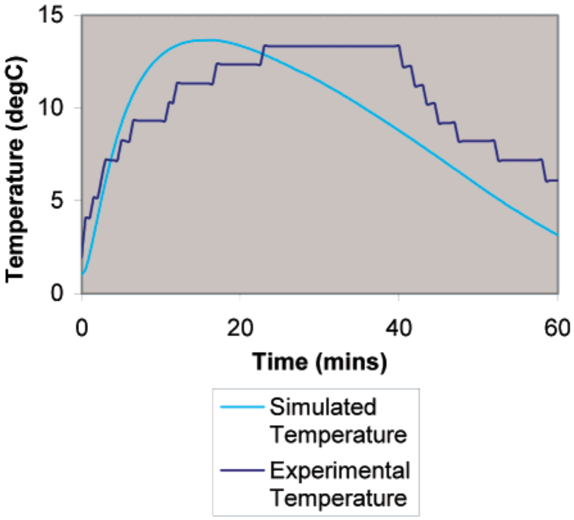

Figure 10. **Comparison of real and simulated temperature profiles from Vilsmeier reaction in a 50-L pilot-plant vessel.**

With the data generated we felt confident enough to safely scale the process to our 50-L pilot-plant vessel. Once the Vilsmeier reagent had been preformed in a separate vessel, it was added to a solution of 3,5-dimethoxyphenol in dichloromethane over approximately 45 min under isoperibolic conditions. The temperature profile was taken from the vessel chart recorder and compared to that predicted using the SIMULAR model data (Figure 10).

The MTSR for both the experimental and simulated data was around 14 °C, and in that respect the data seemed to fit very well. The temperature profiles, although, did not appear to fit as well, with a slight skew of the experimental data away from the simulated data. This was probably due to the nature of the manually controlled feed on the pilot-plant vessel, making it difficult to get precise control over the addition rate. "Reaction Simulator" assumed a constant addition rate.

Conclusions

HEL Auto-MATE allowed us to rapidly screen reaction conditions and to successfully select a suitable solvent. Thermokinetic data was obtained from three parallel Auto-MATE experiments. The so-obtained data allowed us to derive rate constants for each step in the mechanism, and these were then used to approximately simulate temperature profiles and addition regimes on-scale for both the preformation of Vilsmeier reagent and its subsequent reaction with 3,5-dimethoxyphenol in DCM. The model derived for the reaction was then refined in one SIMULAR experiment, and a 20% error in the enthalpy calculation in Auto-MATE was observed. This error did impact the extracted kinetic data; however, it did not significantly affect the thermal modelling of the process since the isoperibolic MTSR value differed at most by only 2 °C. The process was successfully scaled to a 50-L Pfaudler pilot-plant vessel, and the observed experimental temperature profile showed a good correlation with the final computer-simulated model.

Experimental Section

Preparation of 4-Formyl-3,5-dimethoxyphenol (3). 3,5-Dimethoxyphenol **(2)** (4.86 kg) was charged to a 50-L glass-lined vessel followed by dichloromethane (10.0 L). The resulting endotherm lowered the reactor temperature to around 4 °C. The solution was then stirred at ca. 5 °C for about 3 h.

To a separate 50-L glass-lined vessel was charged phosphorus oxychloride (7.24 kg) followed by dichloromethane (10.0 L). The solution was cooled to ca. 10 °C, and a solution of DMF (2.69 L) in dichloromethane (10.0 L) was added over 45 min, maintaining the reactor temperature between 9 and 16 °C. When the addition was complete, the mixture was allowed to stir for 30 min.

The Vilsmeier solution was then added gradually to the phenol solution over 40 min, maintaining the reactor temperature between 1 and 15° C. The reaction mixture was allowed to stir for 1.5 h at 5 °C before being quenched by running slowly into precooled R.O. Water (50 L) in a glass-lined 250-L vessel over 35 min. The reactor temperature was kept between 5 and 17 °C. Dichloromethane (20 L) was added, and the layers were separated. The upper aqueous layer was then re-extracted with dichloromethane (25 L). The upper aqueous layer was neutralized with 50% aqueous potassium hydroxide (13.5 L) to pH 6, and the resultant slurry was filtered through a "Nutsche" pressure filter. The filter cake was washed with water (3 × 5.0 L). The damp cake was dried in a vacuum oven at 40 °C, to constant weight (53 h) furnishing 4.92 kg of product. NMR analysis revealed the material to contain ca. 60% desired para isomer.

This isomer mixture was charged to a 50-L glass-lined vessel followed by addition of ethanol (39.0 L). The stirred mixture was then heated to reflux and allowed to cool naturally overnight. The suspension was cooled to ca. 10 °C and filtered. The filter cake was washed with cold ethanol (2 × 4.9 L) and dried to constant weight (24 h) in a vacuum oven at 30 °C, to give 2.72 kg product.

NMR showed that the material still contained ca. 7% unwanted ortho isomer.

The crude product was slurried in ethanol (10.0 L) in a 20-L flask for 2 h and filtered. The filter cake was washed with ethanol and dried in vacuo overnight to give 4-formyl-3,5-dimethoxyphenol (1.81 kg) as a white solid.

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