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Towards an Information-Rich Process Development. Part I: Interfacing Experimentation with Qualitative/Semiquantitative Modelling

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Abstract:

In today's competitive environment, the low-tonnage chemicals industry (fine and effect chemicals) is under increasing pressure to deliver more products to the market quicker and more cost effectively. Process development is a critical phase in bringing a fine chemical product from discovery to the market and requires the provision of an efficient framework for the capture of process knowledge and understanding. This is traditionally done by somewhat indirect means—either through building understanding in individuals or the construction of a mathematical or physical model of the process. Such approaches suffer from two defects: first they do not collect understanding in a form that is readily shared by all the technologists involved, and second they do not collect understanding early enough in design. For example, the data required for the detailed modelling of a process is often only available well after the process configuration is fixed and properties can be measured under relevant conditions. Considering a liquid biphase reaction system, this paper demonstrates the interaction of targeted experimentation and qualitative/semiquantitative reaction evaluation to allow capture, testing, and sharing of understanding much earlier in design. The resultant qualitative predictions are tested against experimental observations to identify aspects where the qualitative model needs refinement. Recommendations for using more rigorous process analysis tools to explain these so-called anomalous observations are thus made.

Introduction

Currently, laboratory experimentation is typically carried out in small stirred vessels that mimic the large-scale tank. The use of these often precludes particular strategies: for example, stirred tanks are not suited to short reaction times (typically less than minutes) as the time taken to feed reactants and withdraw products is usually much longer. Waiting until there is complete process knowledge before defining the most appropriate operating strategy is seldom an option, given the short process development time scales. Thus, the quality of process chemistry understanding is significantly degraded as a result of incomplete investigation of complex reactions at laboratory scale, under ever tighter deadlines for research and development work.[1] There is thus a gap between conventional chemical engineering methods, which assume known reaction kinetics and idealised reactor conditions, and development of a mathematical model which optimises some property of the reaction system. Unfortunately, these precise mathematical tools do not always contribute as much as is expected towards a full understanding of the tasks under study. This often restricts and prevents access to innovative and intensive processing options.

It is no paradox that less information-intensive methods of analysis often achieve more realistic results in cases where the system which is being modelled is very complex, and/or ill-known. The BRITEST project[2] has identified key decisions in process design and the associated minimum data requirements. These involve identification and manipulation of the relevant rate processes and consideration of the phases of matter that are (or could be) present. By use of qualitative and semiquantitative reasoning it is possible to produce a range of possible process options very early in design.[3] This is particularly useful in the low-tonnage chemicals sectors where process design is primarily an empirical activity. It also helps to deal rationally with the complex chemistry prevalent in those industries. Interfacing experimentation with qualitative/semiquantitative reasoning, the work reported herein seeks to develop a somewhat methodical approach to the development of fine chemicals processes. The approach relies on limited experimental data and qualitative reaction assessment tools to provide a fairly comprehensive understanding of the process chemistry and to identify potential sound processing options.

Reaction System

This study was intended to examine an industrially relevant biphase reaction system that exhibits some of the most common problems encountered in fine chemicals process development.[4] Biphasing emerged as an attractive strategy for enhancing the industrial acceptability of homogeneous catalysis with the successful implementation in 1984 of the aqueous biphasic oxo technology for the hydroform-

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[2] *B*est *R*oute *I*nnovative *T*echnology *E*valuation and *S*election *T*echniques. http://www.britest.co.uk/.

[3] (a) Sharratt, P. N.; Wall, K.; Borland, J. N. *Proceedings of the 6th World Congress of Chemical Engineering*, Melbourne, 23−27 September, 2001. (b) Sharratt, P. N.; Wall, K.; Borland, J. N. *J. Chem. Technol. Biotechnol.* **2003**, *78*, 156−160. (c) Walsh, J. *Proceedings of the Switching from Batch to Continuous Processing Conference*, London, 22−23 November, 2004.

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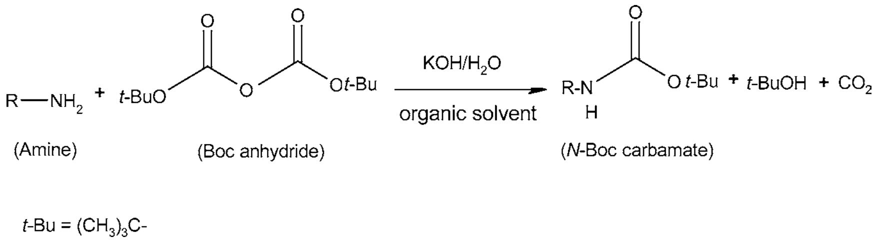

Figure 1. **Main synthetic scheme for the formation of *N*-Boc carbamate.**

ylation of propylene. In this process,[5] the reactants and products remain in the same phase, and the highly water-soluble catalyst (solubilised by using a water-soluble ligand) remains in the aqueous phase. The consequent easy separation of catalyst from product added a new dimension to catalysis that gives it a decided edge over its solid−liquid counterpart for many reactions.

The reaction considered is the Boc-protection of an amine group using potassium hydroxide as catalyst. In addition to its biphasic nature, various processing difficulties are associated with the reaction system, including heterogeneous catalysis, competing reactions, mixing, mass transfer and solubility limitations, ionic equilibria, solvent volatility, gas evolution, catalyst depletion, and heat evolution. The main reaction scheme is shown in Figure 1. Different chemical and physical properties of both the reagents and solvent lead to a range of competing phenomena that characterise the model reaction in solution. These affect both the kinetic and phase-partition properties. The selected reaction system illustrates common mechanistic features that can be seen in other industrially relevant reactions, thus making its study a model of physicochemical behaviours in industrial reactors. Industrial interest is on the synthesis of an *N*-Boc carbamate intermediate, where selectivity is known to be dependent on mixing efficiency and temperature profile.[6] A detailed consideration of the mechanistic aspects is given later.

Preliminary Qualitative Evaluation

The derivation of the qualitative approach is effected through the application of a certain minimum number of underlying axioms. These have been reviewed by Sharratt and co-workers[3b] and will not be reproduced here. The BRITEST tool kit[2] comprises tools in each of the following six areas: *project definition and evaluation*, *process structure analysis*, *duty definition and equipment selection*, *experimental planning*, *risk appraisal*, and *project definition statement*. While all of these tools are extremely useful and beneficial, the discussion in this paper will be limited to process structure analysis (PSA), which is considered as the first set of tools to be used in process design.[3] These support representation of the chemistry and the phases in which the process is carried out.

Reaction Map. The initial PSA technique involves developing a map of the chemical and physical transformations. This entails defining all the entities present and the various transformations they undergo. The purpose is to challenge the understanding of the underlying science and ensure any key gaps are closed prior to progression to process design. A vital design requirement is that the reaction map should be developed using the core competencies of chemists and process engineers involved in early process development. It should be noted that the reaction scheme typified by Figure 1 is an oversimplification of the reaction map, as it neither includes any undesired side transformations that may occur nor considers the behaviour of the catalyst. It will be shown later that Figure 1 alone does not explain the experimental observations and needs to be refined accordingly with the acquisition of detailed process chemistry understanding.

Driving Force Analysis. Driving force analysis (DFA) allows the recording of known or expected chemical pathway data in a compact and readily exploitable tabular form. These may be data on the reaction stoichiometry and some associated information about the reactions and other rate processes. This often involves the construction of a conceptual model of the transformations, specifically: (i) identifying the rate processes occurring (both desired and undesired), including chemical reactions, physical rate processes such as mass transfer, and instantaneous chemical equilibria, (ii) classifying these rate processes as desired (e.g., the main product-forming reactions) or undesired (e.g., impurity-forming reactions), (iii) identifying the time scale of each of the rate processes as an order of magnitude, (iv) identifying the factors which will influence the rate processes (e.g., temperature, pressure, pH, concentrations of reagents, etc.), and (v) identifying the effect each factor will have on every rate process occurring, in qualitative terms.

The DFA should allow for the identification of strategies to improve the outcome of the process in terms of yield and volume efficiency. The simplified DFA output for the "inaccurate" representation of the process chemistry (Figure 1) is given in Table 1. Representing an interim qualitative reaction model, this suggests that the most important variables affecting the rate of the synthesis reaction in the organic phase are the concentration of the reagents, temperature, and the intensity of mixing. These are obvious results of the exothermic and biphasic nature of the reaction system. To test the validity of Table 1 and thus confirm whether it is a reasonable model, the ensuing experimental activity was carried out.

Experimental Methods

Raw Materials. Analytical grade reagents were obtained from Sigma-Aldrich, UK, and used without further purification. Separate solutions of the organic reactants (i.e., Boc_2O and the amine) in 2-propanol (IPA) and potassium hydroxide in deionised water were prepared each time they were to be used in a reaction according to the procedure described by Tarbell and co-workers.[7]

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(5) Kuntz, E. G. *CHEMTECH* **1987**, September, 570−575.

(6) Brechtelsbauer, C.; Ricard, F. *Org. Process. Res. Dev.* **2001**, *5*, 646−651.

Table 1. **Simplified DFA table for the reaction scheme (Figure 1) based on data from the literature**

driving force	reaction rate[a] in organic phase	reaction rate[a] in aqueous phase
Reaction Component Concentrations		
R-NH_2	+	?
Boc_2O	+	?
KOH/H_2O	+	+
N-Boc carbamate	o	o
t-BuOH	o	o
CO_2	o	o
Reaction Conditions		
temperature	+	?
agitation intensity	+	+
heat of reaction	exo	exo?
reaction time	fast (mins)	?

[a] + = positive effect, o = no effect, ? = missing or uncertain information, exo = exothermic.

Liquid−Liquid Partition Equilibria. Liquid−liquid biphasic catalytic systems are relatively difficult to handle due to the introduction of additional complexities often resulting from their intrinsic multiphase nature[8] and the effect of the aqueous phase catalyst on the phase partitioning behaviour.[9] Another feature of the *methodical* approach is to assess the partitioning behaviour for the system under study, since it is necessary to get an indication of the dominant phase, and thus determine the phase speciation and the dependence of the partitioning behaviour on the strength of the aqueous catalyst. The later is readily quantified by the solute partition coefficient, *K* (see eq 1) for the ternary system.

$$K_i = \frac{C_{i(\mathrm{org})}}{C_{i(\mathrm{aq})}} \qquad (1)$$

Methods for estimating K_i vary from simple approaches to those that are highly complex and can be measured or calculated.[10] Experimental methods provide an estimate of the propensity of a solute to partition to the immiscible liquid phases. The *K*-values were measured using the well-known shake-flask method as follows. Known amounts of the organic solutes were added separately to an immiscible liquid mixture initially containing equal volumes (20 mL) of IPA (organic phase) and standard KOH solution (aqueous phase) in a measuring cylinder (100 mL capacity) at different conditions of temperature and electrolyte ionic strength. The mixtures were vigorously shaken before separation of the phases. After thermodynamic equilibrium was reached (approximately 2 h), samples from both liquid phases were analysed by GC (FID Varian CP-3800, 15 m VF-1, 0.25 mm i.d., 0.25 μm film thickness). Stepwise addition of solutes up to a maximum of 0.1 mol and equilibration provides the partition coefficient for the solute.

Kinetic Investigation. The kinetic experiments were carried out isothermally at atmospheric pressure in an HEL (Hazard Evaluation Laboratory) SIMULAR reaction calorimeter operating in power compensation mode.[11] The setup of the reactor and some commonly used features are shown schematically in Figure 2. In addition to the usual equipment setup, the upper end of the reflux condenser was fitted with flexible rubber tubing to vent any evolved gas and vaporised volatile components into a fume cupboard.

In a typical experimental run, the reactor vessel was initially loaded with predetermined quantities of KOH solution (∼200 mL), with the stirrer turned on. The system was then preheated over a 12-h period to ensure that thermodynamic equilibrium was reached prior to the reaction step. A standard mixture of the amine/Boc_2O/IPA (∼100 mL) was then dosed continuously through the metering pump at a constant interval (0.5−1 h), and the semibatch reaction was continued for 1 h to ensure complete conversion of the amine. For purely batch experiments the entire amine/Boc_2O/IPA feed was dosed manually. In an independent set of experiments reaction samples were withdrawn periodically to analyse the component concentrations in both liquid phases by GC. The experiments were designed to study the effects of five variables (see Table 2) on the reaction kinetics over ranges which permit mass transfer-free conditions.

Results and Analysis

Partition Isotherms. It is well-known that thermodynamic equilibrium in the case of ternary mixtures cannot be described properly for the full range of compositions by a constant partition factor, *K*. Where very dilute solutions are encountered, partition isotherms may be conveniently fitted with functions where *K* is derived as an empirical parameter.[10] However, in the case of the ternary system described here and for the range of concentrations used, Figure 3a shows the partition behaviour to be approximated by the linear relation described by eq 1. The measured partition coefficients show an increase in the concentration of the organics in the organic phase with electrolyte ionic strength, *I* (see Figure 3b). This equilibrium behaviour is referred to as the salting-out effect, and can be explained by the Debye−Huckel theory:[9] a defined volume element of the electrolyte-containing solution exhibits a polarisation potential in an ionic field, thereby increasing the dielectric strength of the solution. Assuming that the polarisation experienced by water is much larger than that of the nonelectrolyte, then near an ion the concentration of the latter is reduced. Integrated over the whole solution this corresponds to a decrease in solubility resulting in a salting-out. Salting-in will occur when an ion can polarise the nonelectrolyte solute more than the solvent.

Because a kinetic characterisation of the catalytic reaction would involve a range of temperatures, the effect of temperature on the partition coefficient was checked. The measured concentrations of the amine in the organic phase after thermodynamic equilibration at 30 wt % KOH provide data which conform to eq 1. This is well demonstrated in the parity diagram of Figure 4 in which the measured solute concentration in the organic layer is plotted against the

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(11) (a) Landau, R. N. *Thermochim. Acta* **1996**, *289*, 101−126. (b) Zogg, A.; Fischer, U.; Hungerbuhler, K. *Ind. Eng. Chem. Res.* **2003**, *42*, 767−776.

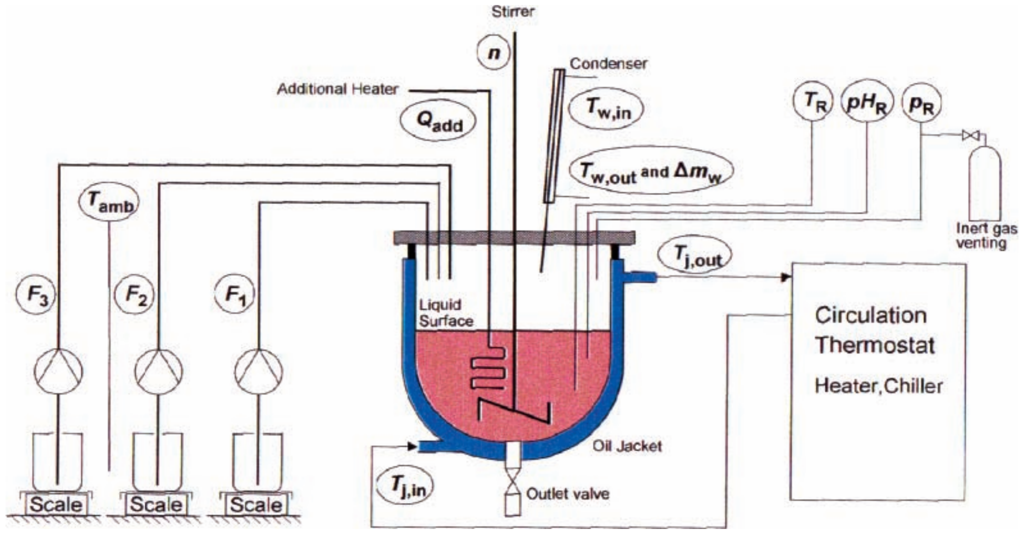
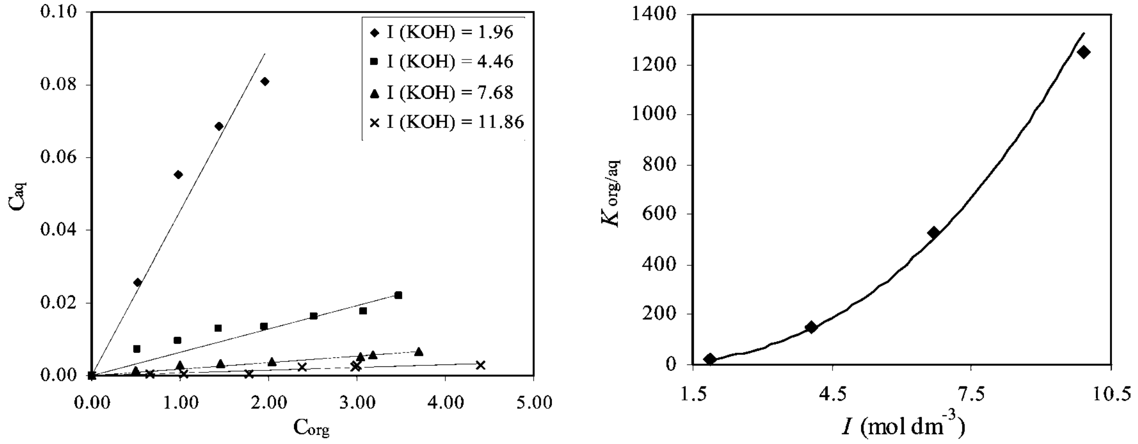


Figure 2. **Schematic diagram of the HEL SIMULAR reaction calorimeter.**



(a) (b)

Figure 3. **Partitioning behaviour of amine component in the biphase mixture at 20 °C: (a) Partition isotherms, (b) dependence of partition coefficients on electrolyte ionic strength (*I*).**

Table 2. **Range data for experimental variables in kinetic experiments**

experimental variable	range
agitator speed (*N*)	200−580 rpm
catalyst (i.e., $KOH_{(aq)}$) concentration	0.25−3.0 M
Boc_2O/amine feed molar ratio (*F*)	0.25−2.0
aqueous phase volume (V_{aq})	200−350 mL
temperature (*T*)	20−50 °C

concentration given by the linear approximation described by eq 2, derived from the two-phase steady-state mass balance of each component, *i*, where n_i is the molar quantity of the solute in the experiment and α is the liquid-phase volumetric ratio (V_{org}/V_{aq}). These results evidence the weak influence of temperature on the partition coefficients within the range of temperatures used. It should be noted that systematic differences (unexplained) in the concentration measurements as a function of temperature do exist.

$$C_{i,\mathrm{org}} = \frac{\alpha K_i n_i}{(1 + \alpha K_i) V_{\mathrm{org}}} \qquad (2)$$

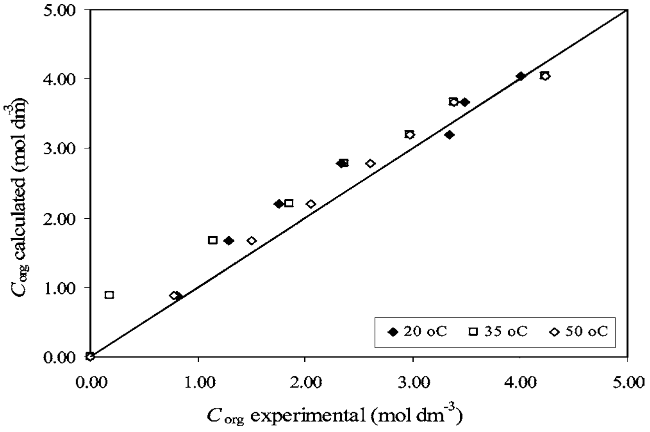


Figure 4. **Calculated (see eq 2) versus experimental organic phase amine equilibrium concentrations at different temperatures.**

Kinetic Effects. Figure 5 shows a typical isothermal calorimetry trace for the dosing of 100 mL of the organic phase (i.e., 1.0 M amine/1.5 M Boc_2O/IPA) solution at 2.5 g min^{-1} into 250 mL of 2.0 M KOH solution. In addition to providing important data regarding the magnitude of the heat

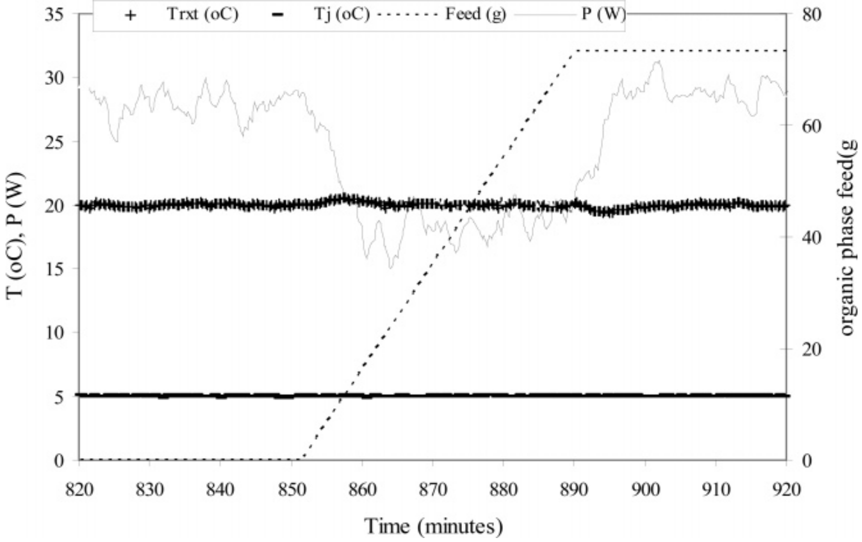
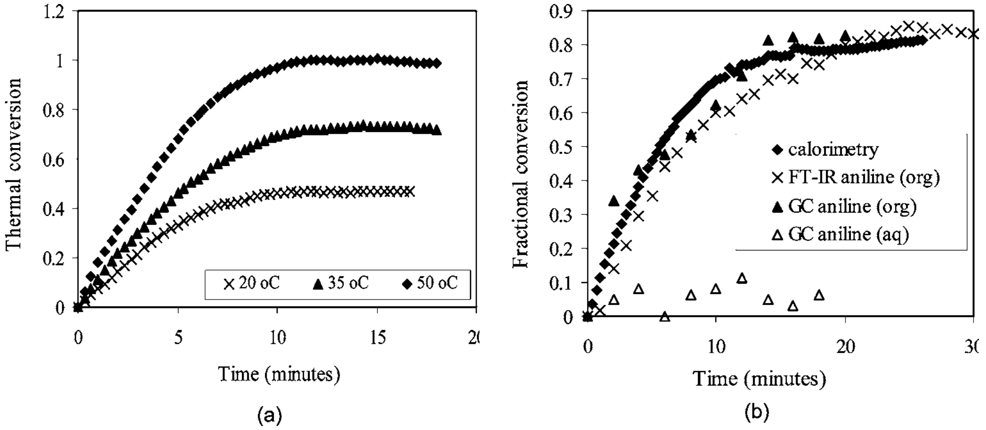


Figure 5. **Power compensation calorimetry of the Boc-protection reaction.**



(a)

(b)

Figure 6. **Sample conversion profiles ($C_{KOH} = 0.5$ M, $N = 550$ rpm, $F = 1.5$, $V_{aq} = 200$ mL): (a) overall heat output at different temperatures, (b) comparison of heat output data with GC amine data at 35 °C.**

release during the reaction, the shape of the heater power (P) profile provides useful information regarding the global kinetics. It should be noted that operation of the reaction calorimeter as an open system (with CO_2 venting) introduces an overall heat loss term, $\dot{Q}_{loss,overall}$ (unknown value) in the energy balance (see Appendix A), which constitutes a problem in quantifying the heat release data. Measured values for the heat tone would require adjustment before they could be used to estimate the heat of reaction. It can be observed from Figure 5 that on termination of the feed, the heater power quickly returns to a new baseline value. This is indicative of fast, (almost) feed-rate limited kinetics, in which the heat release profile is almost entirely determined by the feed rate of the second reactant. This information is especially important when the objective of process development is to scale up a reaction within the confines of an existing plant capacity.[12]

This is a typical liquid−liquid reaction involving simultaneous mass transfer and diffusion with chemical reaction. Knowledge of the intrinsic kinetic regime was considered to be the most essential element for analysis of the performance of the batch calorimetric reactor. As the heat flow rate is proportional to the reaction rate, monitoring this parameter over the course of the experiment gives a continuous measure of the reaction rate (see Appendix A). Figure 6a shows sample thermal conversion profiles at different temperatures. A comparison of the heat flow data with those obtained independently from GC and online FT-IR analyses of the amine component in both liquid phases for a typical experiment is given in Figure 6b. The good correlation between these data sets confirms that the thermal reaction progress data correlates with the formation of the desired *N*-Boc carbamate (see Figure 1), as the amine did not yield any byproducts. The kinetic effects (see Figure 7) were derived based on the initial rate of conversion (measured from the slopes of the conversion-time curves), since this is the condition that gives the maximum rate of reactant consumption.

1. Agitation Speed. Because mass transfer depends on the agitation of the batch reactor, the chemical regime was first checked in the vessel over a range of agitator speeds. The beginning of the "plateau region" indicates the transition between mass transfer limited by diffusion and mass transfer limited by chemical reaction. This should lead to the determination of the intrinsic kinetic parameters. Figure 7a

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(12) Simms, C.; Singh, J. *Org. Process Res. Dev.* **2000**, *4*, 554−562.

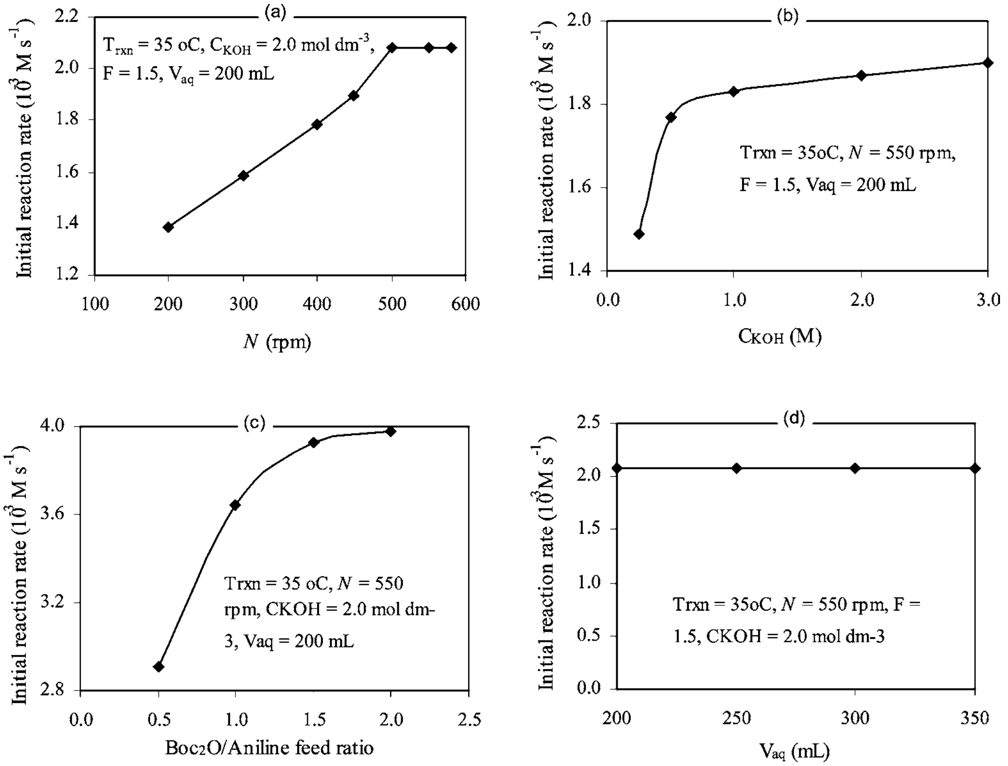

Figure 7. **Effects of the factors studied (see Table 2) for the Boc-protection reaction kinetics (reaction conditions included as inserts).**

shows that the initial reaction rate increases linearly with stirrer speed up to 500 rpm. This suggests that the availability of the reactive species to the catalyst increases as more effective agitation increases the rate of liquid−liquid mass transfer of the reactants. The attainment of the plateau region also suggests that the reaction occurs in one of the bulk liquid phases (i.e., either organic or aqueous). Hence, the chemical regime is reached for agitation speeds above 500 rpm. Consequently, all kinetic data were collected at an agitation speed of 550 rpm.

2. KOH Concentration. In the absence of external mass transfer resistance, the observed rate of reaction should, according to the initial model (see Figure 1), be directly proportional to the catalyst concentration based on the entire aqueous phase volume. Surprisingly, this is not the case as shown by Figure 7b. Although a general increase in reaction rate with KOH concentration is observed, it should be noted that at high catalyst concentrations (>0.25 mol dm^{-3}), the initial rate of reaction increases only gradually, but not proportionally,with KOH concentration. This may be due to solubility limitations of the organic reactants in the aqueous phase due to the salting-out effect (see Figure 3), with a corresponding reduction in their equilibrium concentrations in this phase.

3. Feed Molar Ratio. Knowledge of the appropriate reactant stoichiometry for this reaction was sought by studying the effect of the feed molar ratio based on the amount of the reactive Boc_2O species. As shown in Figure 7c, the initial reaction rate increases up to a feed molar ratio of 2.0. An increase in the concentration of Boc_2O results in a greater diffusion of this species to the aqueous phase. At feed molar ratios greater than 1.5, the reaction kinetics are not greatly changed, which suggests the possibility of a side reaction involving Boc_2O. An understanding of the various rate processes involved in this scheme will be given by the qualitative approach developed later.

4. Initial Aqueous Phase Volume. The volume ratio of organic to aqueous phases has been shown to greatly affect the kinetics of liquid−liquid reactions.[13] The majority of reported studies recommend using only enough water to dissolve or activate the catalyst. Figure 7d shows that the aqueous phase volume has no effect on the reaction kinetics insofar as the other conditions remain constant. This suggests that the reaction is likely to occur in the organic phase. For this study a minimum volume of 200 mL of the initial aqueous phase was just sufficient to totally submerge the additional power heater of the reaction calorimeter.

5. Temperature. As KOH concentration showed a significant influence on the reactant conversion and initial reaction rate, it was decided to study the temperature dependence of this parameter over a range of values of KOH concentration. In all cases the initial reaction rate increased with temperature. Figure 6a shows sample results at KOH concentrations of 2.0 mol dm^{-3}. It should be noted that correspondingly lower conversions were observed at low KOH concentrations (see Figure 6b for thermal conversion data at 35 °C). This thus provides further evidence that the reaction is limited by other processes at low catalyst concentrations. Other observations not shown here involve lower reactant conversions and product yields at high temperatures (>50 °C). This could also be explained by the loss of Boc_2O from the reaction at temperatures above its boiling point of 51.1 °C.

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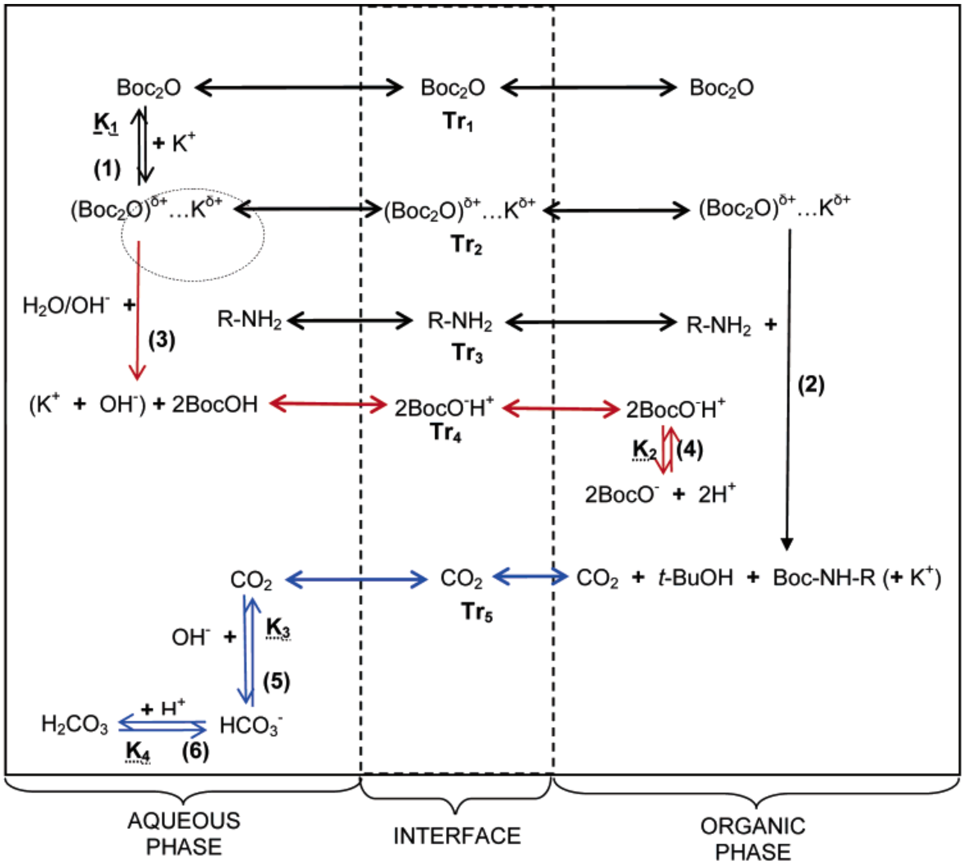
(13) Fan, W.; Tsai, R.-S.; Tayar, N. E.; Carrupt, P. A.; Testa, B.; Kier, L. B. *J. Am. Chem. Soc.* **1993**, *115*, 9632−9639.



Boc_2O:	Boc anhydride	$BocO^-$:	*tert*-butyl carbonate	HCO_3^-:	bicarbonate
$(Boc_2O)^{\delta+}\ldots K^{\delta+}$:	Boc anhydride/potassium transition complex	*t*-BocOH:	*tert*-butanol	H_2CO_3:	carbonic acid
Boc-NH-R:	*N*-Boc carbamate	NH_2-R:	amine		

Figure 8. **Generalised schematic representation of the reaction map for the model two-phase Boc-protection reaction (see text for explanation).**

Detailed Qualitative/Semiquantitative Modelling

The simplistic model of Figure 1/Table 1 cannot explain some of the observed kinetic effects. This strongly suggests the existence of a more complex reaction scheme. Taking into account these "odd" behaviours and building on from Table 1, this section focuses on the development of a detailed qualitative/semiquantitative model to provide a more comprehensive understanding of the process chemistry and to identify viable operating strategies for the reaction system.

Overall Reaction Network and Detailed DFA. To explain the observed kinetic effects, an extended reaction scheme was developed as shown in Figure 8. Some previous authors[14] have established a host of products under different reaction conditions and with different amines. Their analyses were, however, restricted to the main synthetic scheme, as the occurrence of side reactions consuming the reactive species and/or catalyst was not reported. It is worth noting that the isolable species shown in the reaction map were quantified directly by rigorous analytical techniques (involving GC−MS and simple acid−base titration) and indirectly by simple spreadsheet calculations to enable the accomplishment of a component mass balance analysis (see Appendix B).

With reference to Figure 8, the initial reactants, existing originally in the organic phase, transfer to the aqueous phase (Tr_1, Tr_3). While the amine is partially soluble in this phase, the hard Lewis acid cation, K^+ is complexed by an oxygen atom of Boc_2O in a preequilibrium (Reaction 1) and, thereby, converts the Boc group into a better nucleofuge. This is an example of elctrophile catalysis,[15] where coordination of the metal ion stabilises the developing negative charge on the oxygen atom in a transition state. The fate of the resulting $[(Boc_2O)^{\delta+}\cdots K^{\delta+}]$ complex may be two-fold:

(a) It proceeds through to the main synthetic scheme in the organic phase where it reacts with the amine by direct nucleophilic attack (Reaction 2) to yield the main *N*-Boc carbamate product, with subsequent decarboxylation and concomitant formation of *tert*-butyl alcohol. It should be noted that Reaction 2 may also occur in the aqueous phase/interface, but to a limited extent due to solubility limitations of the amine in this phase (see Figure 3).

(b) It engages in a relatively fast, parallel competitive hydrolysis in the aqueous phase to form two moles of *tert*-butyl carbonate (Reaction 3), which migrates to the organic phase. Subsequent deprotonation (Reaction 4) produces the

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(14) (a) Basel, Y.; Hassner, A. *Synthesis* **1997**, March, 309−311. (b) Basel, Y.; Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368−6380. (c) Rajesh, K. P.; Sharda, P. D.; Rajesh, K. U.; Mohan, K. D.; Pradeep, K. *Arkivok.* **2002**, 28−33.

Table 3. **Detailed DFA table for the biphase reaction system based on the qualitative approach**

	reaction rates in organic phase[a]						reaction rates in aqueous phase[a]						transfer processes across interface[a]				
driving force	1	2	3	4	5	6	1	2	3	4	5	6	Tr_1	Tr_2	Tr_3	Tr_4	Tr_5
Reaction Components																	
Boc_2O	+	?	o	o	o	o	+	?	o	o	o	o	+	o	o	o	o
KOH	?	o	o	o	o	o	o	+	o	+	o	o	+	+	+	+	+
$[Boc_2O)]^{\delta+}\cdots K^{\delta+}$	?	+	o	o	o	o	-	?	+	o	o	o	o	+	?	?	o
H_2O	o	o	o	o	o	o	o	o	+	o	o	o	o	o	o	o	o
$R\text{-}NH_2$	o	+	o	o	o	o	o	?	o	o	o	o	o	o	+	o	o
$BocO^-H^+$	o	o	o	+	o	o	o	o	o	?	o	o	o	o	o	+	o
$BocO^-$	o	o	o	-	-	o	o	o	o	o	o	o	o	o	o	+	o
CO_2	o	o	o	o	?	o	o	o	o	o	+	o	o	o	o	o	+
HCO_3^-	o	o	o	o	?	?	o	o	o	o	-	+	o	o	o	o	o
H_2CO_3	o	o	o	o	o	?	o	o	o	o	o	-	o	o	o	o	o
Reaction Conditions																	
T (rate)	o	+	o	+	o	o	o	?	+	o	o	o	o	o	o	o	o
T (equilibrium)	o	?	?	+	o	o	+	o	+	?	+	+	+	+	+	+	+
V_{aq}/V_{org}	o	o	o	o	o	o	o	o	o	o	o	o	?	?	?	?	?
agitation speed	o	+	?	+	o	o	+	?	+	?	+	+	+	+	+	+	+
pH	o	?	mod	?	o	high	?	mod	?	low	low	+	+	+	+	+	+
ionic strength	+	+	o	o	?	?	-	-	o	o	?	?	+	+	+	+	+
heat of reaction	?	exo	?	?	?	?	exo	exo	?	?	?	?	o	o	o	o	o
reaction time	?	min	min	?	?	?	vf	?	min	?	fast	fast	o	o	o	o	o
solvent polarity	high	mod	high	high	high	low	high	mod	high	mod	high	low	?	?	?	?	?

[a] + = positive effect, − = negative effect, o = no effect, ? = missing or uncertain info., exo = exothermic, min = minute, mod = moderate, inst = instantaneous, vf = very fast (see Figure 8 for details of the numbered reactions 1−6 and transfer processes Tr_1−Tr_5).

corresponding organic carbonate, which is in equilibrium with the protonated form.

In both cases the dissociated K^+ ion complexes to Boc_2O in the aqueous phase so as to repeat this catalytic cycle. The significance of the branch point (represented by a dotted oval) becomes apparent in reaction yield and selectivity considerations, and will be discussed later. A third reaction scheme within this network comprises the series of ionic equilibria (Reactions 6, 7) that may be initiated by the dissolution of CO_2 in the aqueous phase to form a weak acidic solution. Because of this the gaseous phase has been omitted in Figure 8, since very little gas is evolved to form a separate phase. It should be noted that, in addition to providing the active catalyst species (i.e., K^+ ion) for driving the main synthetic reaction, aqueous KOH neutralizes the evolved CO_2 gas and also maintains the alkalinity of the reaction mass. This prevents the amine from undergoing protonation by BocOH generated as a result of Boc_2O hydrolysis.

Table 3 gives a more complete representation of the main forces influencing the process chemistry. Compared to Table 1, it shows how each known or potential factor may influence any reaction process within a defined liquid phase, together with qualitative predictions as to issues regarding yields and selectivity of the product of choice.

Predictive Capability of the Qualitative Model. The validity of the qualitative approach was ascertained by comparing the model predictions with experimental evidence. Most of the key selected experimental observations are found to be explicitly explained by the model (see Table 4). However, certain attributes of the reaction system show behaviours that could not be explained by the model (see Table 5). A detailed characterisation of these anomalies would be helpful in generating further insights into the reaction network with regards to the detailed kinetic mechanism and site of the main synthetic reaction.

Inherent Processing Benefits

Product Selectivity. Figure 8 suggests that the initiation of Reaction 1 by mixing Boc_2O with catalytic amounts of aqueous KOH has the potential to generate all of the subsequent reactions. It would be possible to consider suppressing the parallel competitive Boc_2O hydrolysis scheme (Reactions 3, 4), thereby driving the transformation to almost 100% selectivity to the desired *N*-Boc carbamate product by taking a keen look at the branch point. Depicted by a dotted oval in Figure 8, this denotes the point where the ratio of the rates of the reaction pair in question determines the reaction outcome, referred here to the yield and selectivity of the desired product. It is evident from the data in the DFA (see Table 4) that:

- Reactions 3 and 4 could be suppressed by possibly keeping the catalyst concentration low, without compromising the catalyst requirement for the main synthetic scheme.
- The main synthetic scheme (Reaction 2) would be favoured by a high concentration of amine in the organic phase. This would suggest using a high concentration of KOH to favour a higher partitioning of the organic substrate into organic phase. Of course, this would not be an attractive strategy as it favours the competitive hydrolysis scheme.

Contacting Patterns. A commonly used means of manipulating reaction outcome is the selection of an appropriate contacting strategy. The combination of the DFA and the phase strategy provides the process engineer with the information relevant to the selection of appropriate contacting patterns. For single-phase systems this is often very straightforward. In the reaction system under study and using a single-phase reaction, it would be appropriate to add alkali semibatch-wise to the premixed reactants to minimise concentration excesses of the catalyst and thereby reduce the extent of Reactions 3 and 4 (see Figure 8). It would be an inappropriate strategy to add the premixed reactants slowly to the catalyst, as the Boc_2O/K^+ transition complex would

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(15) Bruice, P. Y. *Organic Chemistry*, 2nd ed.; Prentice Hall: New Jersey, 1998.

Table 4. **Experimental observations explained by the qualitative approach**

parameter/ descriptor	experimental observation	qualitative evidence/explanation
solute partitioning	(a) Increasing *K* (org/aq) values with electrolyte ionic strength at fixed temperature (see Figure 3).	Higher proportion of original substrate species present in organic phase due to the salting-out effect.
	(b) Very little influence of temperature on *K* (org/aq) values at fixed electrolyte ionic strength (see Figure 4).	Model shows no effect of temperature on reaction equilibrium, although significant effect of temperature on reaction rate is predicted.
agitation intensity	Linear rise in initial reaction rate with agitator speed, outside the chemical regime (see Figure 7a).	Model shows strong influence of agitation intensity on reaction rates in all liquid phases.
temperature	(a) Increasing reaction rates with temperature (see Figure 6a) for temperatures <50 °C).	Hydrolysis reaction rate is influenced by temperature, resulting in byproduct formation with low selectivity to the desired product.
	(b) Unfavorable reaction outcomes (i.e., low substrate conversions, low desired product yields/selectivities and high byproduct formation) at high temperatures.	
KOH concentration	Although reaction rates generally increase with KOH concentration, complete substrate conversions are not attainable at low KOH concentrations (see Figure 6b).	KOH becomes limiting as it is mopped up by CO_2 to produce the series of ionic equilibria in the aqueous phase, which results in low pH. Quantitative evidence of hydroxide consumption is shown by the elemental balance in Appendix B.
Boc_2O concentration	Almost linear increase in initial reaction rate with Boc_2O concentration, which subsequently plateaus off (Figure 7c).	Strong evidence of side reaction, which can be proven by the parallel competitive hydrolysis scheme using Boc_2O as substrate.
	Unfavorable reaction outcomes (i.e., low substrate conversions, low desired product yields/ selectivities) at near stichiometric quantities of the main reactants, with high conversions of Boc_2O.	Quantitative yields of the desired product are best achieved with high (>1) Boc_2O/amine feed molar ratios.
amount of gaseous CO_2 evolved	CO_2 mass balance shows a 95% reduction in molar amount produced, relative to the expected value released from the main synthetic reaction.	Much of the evolved CO_2 dissolves in the aqueous phase and is used up by KOH to initiate the series of aqueous phase ionic equilibria (see Figure 8).

Table 5. **Experimental observations not explained by the qualitative approach**

parameter/ descriptor	experimental observation	qualitative prediction	comments
site of main synthetic reaction	(a) The organic phase reaction kinetics follows approximate first-order decay, whereas aqueous phase amine conversions are apparently time invariant (see Figure 6b). (b) No influence of the initial aqueous phase volume on the reaction rate and conversion.	DFA remains unclear as to the relative component phase concentrations and assumes their presence in both liquid phases.	Experimental evidence reveals that the main synthetic reaction is *likely* to be favored in the bulk organic phase.

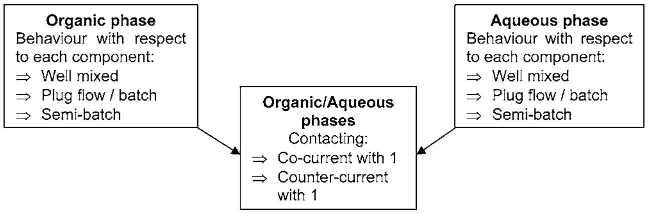

Figure 9. **Possible two-phase contacting patterns.**

always be in the presence of excess hydroxide ions to favour the observed hydrolytic instability of the reactive species. The biphase liquid system could be operated in a number of different ways. The wide range of possible strategies available is illustrated in Figure 9. Batch processing limits the range of available contacting patterns. An appropriate strategy would be the use of concurrent flow of the two phases. Counter-current flow may be inappropriate as Boc_2O entering the reactor is likely to be immediately hydrolysed by high hydroxide concentration in the inlet stream.

Discussion

Translating chemistry “in a flask” to manufacturing-scale chemistry requires not only know-how, creativity, and skill but also time to develop and test ideas. As speed to market has become more and more critical, the time for process development has correspondingly shrunk. It is only by understanding the science of the various transformations occurring in a chosen synthetic route that various processing options can be identified and assessed. For manufacture of fine chemical intermediates the two key disciplines necessary to map the various transformations are the synthetic organic chemist and chemical engineer. Neither discipline alone has the complete skills set (of kinetics, thermodynamics, heat/ mass transfer, fluid mechanics [micro/meso/macro mixing],

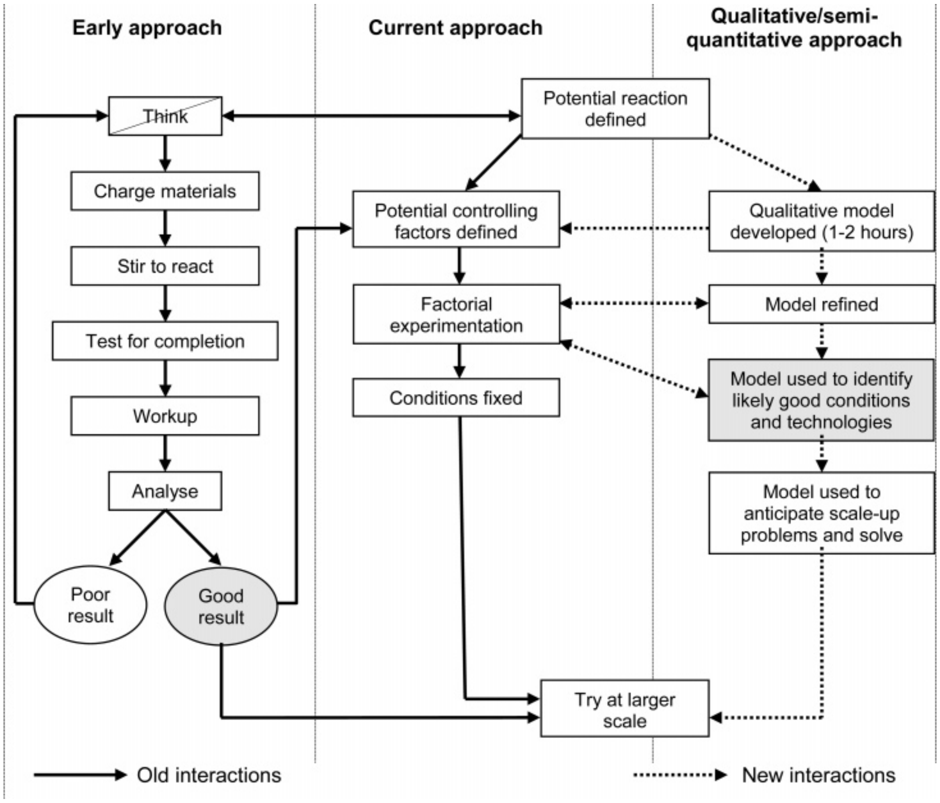

Figure 10. **Qualitative/semiquantitative versus conventional approaches to process development.**

mechanistic chemistry, physical organic chemistry, etc.) to complete this task. Integration of the disciplines enables some of these aspects to be considered, and a map outlining the transformations possible in a given process to be developed. This integration needs to occur in a structured rather than an ad hoc manner in order to deliver maximum benefit.

A methodical approach (based on the BRITEST methodology) has been devised to interface laboratory experimentation with novel qualitative modelling tools. Contrary to conventional process development practices (see Figure 10), the approach demonstrates that process development should not only be focused at developing a process but should also exploit available process knowledge so as to provide a comprehensive understanding of the process chemistry, especially at the critical early stages, where chemistry is being developed against a background of limited (and inaccurate) data. The simple interactions of process model, experimentation, and process development that arise from the use of the DFA is seen as key to rapid process development. The model also provides a tool for early identification of viable processing options to allow for the timely development of experimental programmes to evaluate the options.

Although the qualitative model and its predictions remain sound in relation to the observed experimental data, the use of rigorous process analysis tools (e.g., quantitative modelling techniques) is recommended only if there is need to extrapolate to behaviours that are difficult to observe experimentally and to explain the observed anomalous behaviours that may not lie within the scope of the model predictions. In addition to incorporating limited experimental data into a comprehensive representation of the process chemistry, a more robust process design is likely to be obtained from the approach discussed in this paper, since the chances of process failure on scale-up are reduced.

Appendices

A. Isothermal Reaction Calorimetry.

1. Overall energy balance: $\dot{Q}_{\mathrm{acc}} = \dot{Q}_{\mathrm{rxn}} + \dot{Q}_{\mathrm{dose}} + \dot{Q}_{\mathrm{add}} + \dot{Q}_{\mathrm{jac}} + \dot{Q}_{\mathrm{loss,overall}}$ (A-1)

where,

$$\dot{Q}_{\mathrm{accum}} = (m_{\mathrm{rxt}}c_{\mathrm{p,rxt}} + m_{\mathrm{sam}}c_{\mathrm{p,sam}})\frac{\mathrm{d}T_{\mathrm{rxt}}}{\mathrm{d}t}$$

$$\dot{Q}_{\mathrm{rxn}} = \text{objective value as residuum}$$

$$Q_{\mathrm{dose}} = \sum_i \dot{m}_{\mathrm{dose},i}c_{\mathrm{p},i}(T_{\mathrm{dose},i} - T_{\mathrm{rxt}})$$

$$\dot{Q}_{\mathrm{add}} = \text{directly measured}$$

$$\dot{Q}_{\mathrm{jac}} = m_{\mathrm{cool}}c_{\mathrm{p,cool}}(T_{\mathrm{jac,out}} - T_{\mathrm{jac,in}})$$

$$\dot{Q}_{\mathrm{loss,overall}} = \text{not known}$$

2. Heat tone: $Q_{\mathrm{rxn}} = \int_{t_{\mathrm{o}}}^{t_{\mathrm{f}}} \dot{Q}_{\mathrm{rxn}}\mathrm{d}t$ (A-2)

3. Reaction enthalpy change: $\Delta H_{\mathrm{rxn}} = \frac{Q_{\mathrm{rxn}}}{n_i}$ (A-3)

4. Thermal conversion: $\mathrm{X}(t)_{\mathrm{th}} = \int_{t_{\mathrm{o}}}^{t} \frac{\dot{Q}_{\mathrm{rxn}}\mathrm{d}t}{Q_{\mathrm{rxn}}}$ (A-4)

B. Elemental Balance Calculations. The total mass of each element (C, H, O, N, K) participating in the reaction was gravimetrically calculated (eq B-1) and a comparison between the gravimetric mass initially charged and the

Table B.1. **Detailed elemental balance for a typical experimental run**

Gravimetric

component	C	H	O	N	K
amine	3.60774	0.35075	0	0.70151	0
Boc_2O	9.00550	1.35083	6.00367	0	0
KOH	0	0.40071	6.41143	0	15.62786
total (g)	12.61325	2.10229	12.41509	0.70151	15.62786

Experimental

component	C	H	O	N	K
Main Synthetic Scheme (i.e., Figure 1) only					
amine	0.54000	0.05250	0	0.10500	0
Boc_2O	1.35000	0.20250	0.90000	0	0
KOH	0	0.19800	3.16800	0	7.72200
N-Boc carbamate	5.54400	0.63000	1.34400	0.58800	0
t-butanol	0.04800	0.01000	0.01600	0	0
CO_2	0.01200	0	0.03200	0	0
total (g)	7.49400	1.09300	5.46000	0.69300	7.72200
mass %	**59.41**	**51.99**	**43.98**	**98.79**	**49.41**
Overall Reaction Network (i.e., Figure 9)					
amine	0.54	0.0525	0	0.105	0
Boc_2O	1.35	0.2025	0.9	0	0
KOH	0	0.387	6.192	0	15.093
HCO_3^-	0.156	0.013	0.624	0	0.507
N-Boc carbamate	5.61	0.6375	1.36	0.595	0
t-BuOH	1.584	0.33	0.48	0	0
$BocO^-$	2.7	0.45	2.16	0	0
CO_2	0.24418	0	0.65114	0	0
total (g)	12.18418	2.0725	12.36714	0.7	15.6
mass %	**96.60**	**98.58**	**99.61**	**99.79**	**99.82**

experimental values (eqs B-2, B-3) was performed. The results are given in Table B.1.

B.1. Atom Balance from Gravimetric Measurement.

$$\sum\left[(\text{No. } X - \text{atoms in component})\left(\frac{\text{atomic weight of } X}{\text{molecular weight of component}}\right)(\text{mass of component})\right] \tag{B-1}$$

B.2. Atom Balance from Experimental Concentrations.

$$\sum[(\text{No. } X - \text{atoms in reactant})(\text{atomic weight of } X)(\text{moles of reactant})] \tag{B-2}$$

$$\sum[(\text{No. } X - \text{atoms in product})(\text{atomic weight of } X)(\text{moles of product})] \tag{B-3}$$

Notation

A, B,...	reaction components (−)
C_i	concentration of species i (mol dm^{-3})
c_p	specific heat capacity at constant pressure (kJ kg^{-1} K^{-1})
F	Boc_2O/amine feed molar ratio (−)
ΔH	enthalpy change (kJ mol^{-1})
I	electrolyte ionic strength (mol dm^{-3})
K	liquid−liquid (org/aq) partition coefficient (−)
K	equilibrium constant (−)
N	agitator speed (rpm)
n	amount of substance (mol)
P	calorimeter heater power (W)
Q	total heat liberated (kJ)
$\dot{Q}$	instantaneous heat flow rate (W)
T	temperature (K)
Tr	transfer process (−)
t	time (s)
V	volume (L)
wt %	weight percent (%)

Greek Letters

α	organic to aqueous phase volumetric ratio (−)
Χ	fractional conversion (−)

Subscripts and Superscripts

acc	accumulation
add	additional heater
aq	aqueous
f	final condition
jac	jacket
o	initial condition
org	organic
rxn	reaction
rxt	reactor
th	thermal

B.3. Calculation of the Total Amount of Each Element Present.

$$X_{\text{total}} = (\text{eq C-2}) + (\text{eq C-3}) \tag{B-4}$$

B.4. Calculation of the Percentage of Each Element Present.

$$\%\, X = \frac{X_{\text{total}}}{X_{\text{gravimetric}}} \times 100\% \tag{B-5}$$

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