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Process development in the fine chemical industry

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Abstract

Fine chemicals are an important group of products consisting of pharmaceuticals, agrochemicals, dyes, photographic chemicals and intermediates of all these groups as well as chemicals for the textile industry. They are typically high value-added products. The processes for manufacturing these products are mostly batch and semibatch processes. The development of kinetic models for complex chemical reactions occurring in the fine chemical processes and including these models into batch and semibatch reactor models for scale-up are presented in this paper. A methodological approach to the modelling of these complex systems and the estimation of model parameters is proposed. The methodologies were applied to two case studies: reductive *N*-alkylation of an aromatic amine with homogeneous reactions and a heterogeneously catalysed reactions and Claisen condensation as organic liquid–solid reaction.

Keywords: Process development; Dynamic models; Kinetics; Reductive alkylation; Claisen condensation

1. Introduction

Fine chemicals form a large portfolio of products consisting of pharmaceuticals and their intermediates, agrochemicals, agrochemical intermediates, dyestuffs and dyestuff intermediates, photographic chemicals and their intermediates as well as chemicals for the textile industry, etc. The processes for manufacturing these products are mostly batch or semibatch processes. In today's competitive environment, one of the key issues for fine chemical companies is to reach the market with new products as quickly as possible to guarantee a competitive edge over the other players in the field. This means that the whole chain from the idea via R&D activity to the commercialisation and marketing has to form a fluent workflow to meet the project targets according to the pre-determined timescale. The tasks in the process development are executed more or less in parallel in different parts of the development organisation and efficient information generation and exchange and technology transfer are of the greatest importance. A typical interrelated workflow and the tasks involved for the development of fine chemical manufacturing processes is schematically presented in Fig. 1.

1.1. Conceptual chemical phase

The main activities in the conceptual chemical phase are the identification of different chemical routes and the generation of alternative chemical synthesis pathways and process schemes. Relevant routes are evaluated experimentally and preliminary cost estimations are performed to select the best alternative for further development as to production capacity, product quality, safety and feasibility. *Statistical experimental design* combined with *empirical* or *simple mechanistic models* are used as tools to study the reactions in order to select proper reaction conditions (pressure, temperature, concentration), solvents, catalysts and to optimise selectivity and yields.

1.2. Conceptual process development phase

In this development phase, which is iteratively linked to the chemical development phase, the process concept for the selected chemical route is evaluated, *mass balances*, *preliminary energy balances* and *basic recipes* are generated for the process. *Block diagrams* and preliminary *flowsheets* are produced and the process is implemented to the existing production facility or a new production line is designed. In this procedure, *short-cut models for the reactions and separations* are used. The physical properties for pure compounds and mixtures are acquired from literature and data banks or they are estimated with appropriate physical property

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Nomenclature

a	shape factor or interfacial area-to-volume
A	mass transfer area or cross-section
c	concentration
D	diffusion or dispersion coefficient
k	rate constant
k_G	gas phase mass transfer coefficient
k_L	liquid phase mass transfer coefficient
K	equilibrium constant
K', K'', K'''	lumped parameters
l	length coordinate
L	length
m	mass
M	molar mass
n	molar amount of substance
n_p	number of particles
$\dot{n}$	molar flow
N	flux
P	parameter vector
Q	objective function
r_i	generation/consumption rate of compound (i)
r'	particle radius
R	initial radius of particle, reaction rate
s	shape factor
t	time
V	volume
$\dot{V}$	volumetric flow rate
w	weight fraction
w_G, w_L	gas and liquid superficial velocities
y	state(concentration variable), dimensionless particle radius

Greek letters

α	experimental coefficient, adjustable parameter
ε	hold-up, void fraction
η	catalyst effectiveness factor
θ	fractional coverage
ν	stoichiometric coefficient
ρ	density
ω	weight factor

Subscripts and superscripts

B	bulk
G	gas phase
i	component index
j	reaction index
L	liquid phase
p	particle
S	solid phase
0	inlet or initial condition
$*$	saturated state

estimation methods. This phase also involves an introductory *safety evaluation* of the process. A preliminary *scheduling* of the operation steps is performed and *Gantt charts* are generated to characterise interrelated time-dependent operations and to identify process's bottlenecks. The production capacity is calculated and basic cost estimation is performed to obtain the feasibility of the process. This is the major decision point in the continuation of the development of the process.

1.3. Chemical development phase, process development phase and process engineering phase

The chemical development, process development and process engineering phases proceed both consecutively and parallel. In the unit process and equipment levels, the reactions and separations of the process are studied more thoroughly in laboratory and bench-scale by chemists. Reaction enthalpies are estimated or measured with reaction calorimetry. The thermal stabilities of raw materials, products and other process streams, especially distillation residues are determined. *Dynamic mechanistic reactor models* and dynamic separation models (i.e. batch distillation models) are developed for scale-up in co-operation with chemists and chemical engineers. *Kinetic models* are derived or extracted from existing *model library*. *Mass- and heat balances* for the reactor configurations are generated and reaction kinetics is included in the models. *Mass and heat transfer correlations* are introduced into the reactor models as needed. Systematic *experimental planning* is utilised in experimentation to improve the identifiability of the *kinetic and transfer parameters*. *Consistent physical properties* for pure components and component mixtures are used throughout the chemistry and process development cycle. From the modelling point of view, pilot-plant experiments are carried out only when it is necessary to get more confidence for scale-up and to improve and *validate models*. A typical reason for piloting is to obtain representative product samples in order to promote marketing. Dynamic *mass and energy balances* of the whole process and single process units are scaled-up to designed plant capacity. Production *recipes* are updated and *scheduling* of the operation steps and equipment utilisation within operation steps are carried out. *Control* systems are implemented into dynamic reactor models. Controllability studies are performed and measures to avoid runaway situations are implemented. The whole safety health environment (SHE) area of the process is evaluated.

1.4. Commissioning and start-up phase

In the commissioning and start-up phase, dynamic models are used in the plant for the operator training and to assist the decision making in what/if situations (malfunctioning of feeding system causing improper reactant ratios, overdosing active reactant, reduced heat and/or mass transfer, collapsing of mixing or cooling system, etc.).

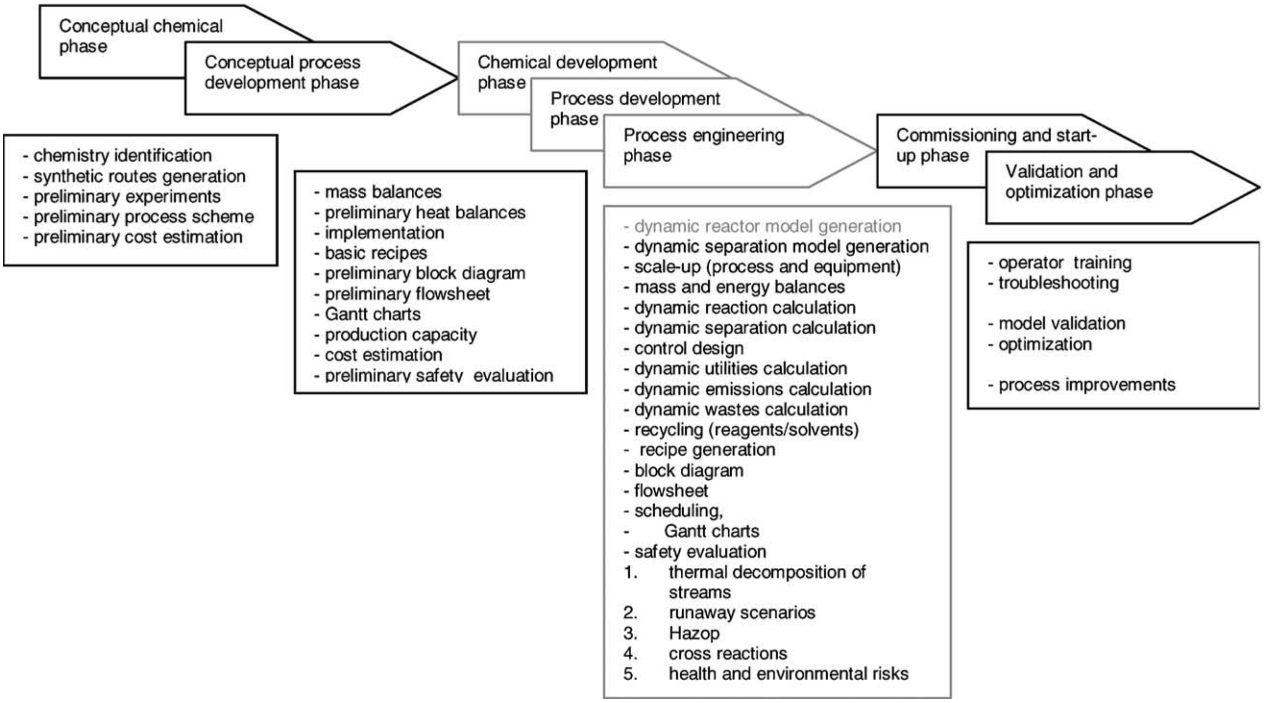


Fig. 1. Workflow and tasks for the development of a fine chemical manufacturing process.

1.5. Validation and optimisation phase

In the validation and optimisation phase, models are validated using relevant plant data. Information is fedback to the R&D function to refine the models and improve the process for future production campaigns. Single operation steps and process units are optimised after validation and the optimal conditions are linked to overall process and plant optimisation. Evolutionary process improvements should be carried out through the whole life cycle of the process.

In the presented process development work flow, this contribution is focused on the methodologies in the development of dynamic mechanistic kinetic and reactor models, on the methods for generating reliable and consistent data for modelling purposes and on the tasks required in the estimation of parameters for those models. The procedures and modular tools for dynamic modelling are presented in Fig. 2. The application of procedures is illustrated with two case studies: reductive *N*-alkylation of an aromatic amine and a Claisen condensation reaction.

2. Process models

2.1. Principles for the development of kinetic models

The reactions in the fine chemicals manufacturing are often very complex involving consecutive and parallel reaction steps, which take place simultaneously. This leads as such to complex and very detailed kinetic rate equations with numerous adjustable parameters, which are often correlated and difficult to identify accurately. In addition, many of the short-lived chemical intermediates are not detectable by chemical analysis and thus no information of their real concentrations in the reaction medium is available.

A practical method of simplifying the kinetic equations for reaction systems with slow and fast reactions is to apply the *quasi-steady-state* approximation, i.e. to assume the intermediates to be very reactive and thus their generation rates to be approximately zero: $r_i = \sum_{j=1}^{n} \nu_{ij} R_j = 0$ [1,2]. This approach enables the elimination of the concentrations of the intermediates from the generation rate equations of other components and the reduction of the number of adjustable parameters in the kinetic equations.

An alternative method for simplifying the kinetic equation is to apply the *quasi-equilibrium* approximation for fast reactions or adsorption and desorption processes of reactive species at the catalyst surface. This treatment implies that the ratio of the forward and backward reaction rates is almost equal to 1: $R_{j+}/R_{j-} = 1$ for the fast reactions. The equilibrium ratio is introduced into the rate equations of the slow reaction steps enabling the elimination of non-detectable components, model simplification and reduction of the number of parameters by lumping them into single entities. In fact, the quasi-equilibrium hypothesis is a special case of the quasi-steady-state hypothesis: the rate equations corresponding to the quasi-equilibrium case can be obtained from the quasi-steady-state equations by giving large values to the rate constants of the fast steps.

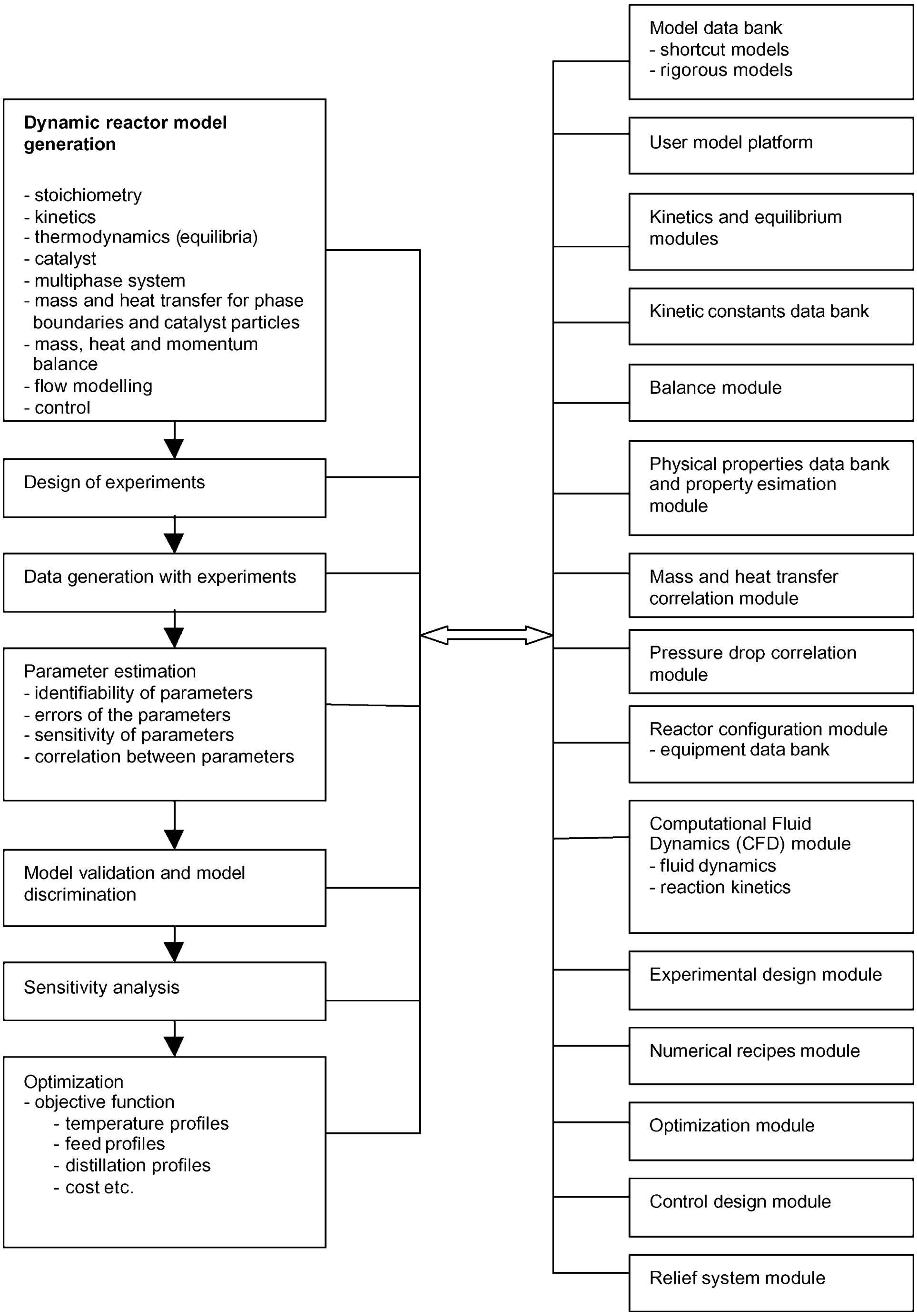


Fig. 2. Procedures and tools for dynamic modelling.

2.2. *Principles for the development of reactor models*

The reactors used in the manufacturing of organic fine chemicals are mostly multipurpose semibatch and batch reactors equipped with necessary auxiliary equipment for mixing, heating and cooling as well as for distillation or evaporation of solvents or light reaction products. The reactions typically take place in the liquid phase, and only very seldomly gas phase reactions occur in these kind of systems. In this section, we summarise the reactor models considering true mass balances only.

2.2.1. *Liquid phase*

The following fundamental assumptions are made in deriving the balance equations for the liquid phase:

- Plug flow and axial dispersion or complete backmixing prevail in gas and liquid phases.

- No reactions take place in the gas phase.
- The reactions proceed in the liquid phase and/or solid phase.

$$\frac{\mathrm{d}c_{\mathrm{Li}}}{\mathrm{d}t} = -\frac{\mathrm{d}(c_{\mathrm{Li}}w_{\mathrm{L}})}{\mathrm{d}l} + D_{\mathrm{L}}\frac{\mathrm{d}^2c_{\mathrm{Li}}}{\mathrm{d}l^2} + \frac{N_{\mathrm{SLi}}a_{\mathrm{SL}}}{\varepsilon_{\mathrm{L}}} + \frac{N_{\mathrm{GLi}}a_{\mathrm{GL}}}{\varepsilon_{\mathrm{L}}} + r_i \tag{1}$$

Typically w_{L} is approximately constant, i.e.

$$\frac{\mathrm{d}(c_{\mathrm{Li}}w_{\mathrm{L}})}{\mathrm{d}l} = w_{\mathrm{L}}\frac{\mathrm{d}c_{\mathrm{Li}}}{\mathrm{d}l} \tag{2}$$

Some special cases of interest are listed below:

(a) Non-volatile component: $N_{\mathrm{GLi}} = 0$.
(b) No homogeneous reactions in liquid phase: $r_i = 0$.
(c) No heterogeneous reaction: $N_{\mathrm{SLi}} = 0$.
(d) No axial dispersion: $D_{\mathrm{L}} = 0$.
(e) High degree of dispersion; complete backmixing: $\mathrm{d}^2c_{\mathrm{Li}}/\mathrm{d}l^2 = 0$, $\mathrm{d}(c_{\mathrm{Li}}w_{\mathrm{L}})/\mathrm{d}l$ is replaced by $(c_{0\mathrm{Li}}w_{0\mathrm{L}} - c_{\mathrm{Li}}w_{\mathrm{L}})/L$, which is equal to $(c_{0\mathrm{Li}}\dot{V}_{0\mathrm{L}} - c_{\mathrm{Li}}\dot{V}_{\mathrm{L}})/V$.
(f) No flow, infinite dispersion (or perfect mixing): $\mathrm{d}^2c_{\mathrm{Li}}/\mathrm{d}l^2 = 0$ and $w_{\mathrm{L}} = 0$.

2.2.2. *Gas phase*

Analogously, the balance equation for the gas phase takes the form

$$\frac{\mathrm{d}c_{\mathrm{Gi}}}{\mathrm{d}t} = \mp\frac{\mathrm{d}(c_{\mathrm{Gi}}w_{\mathrm{G}})}{\mathrm{d}l} + D_{\mathrm{G}}\frac{\mathrm{d}^2c_{\mathrm{Gi}}}{\mathrm{d}l^2} + \frac{N_{\mathrm{GLi}}a_{\mathrm{GL}}}{\varepsilon_{\mathrm{G}}} \tag{3}$$

where (−) denotes co-current and (+) is for counter-current flow.

Special cases of interest are:

(a) Non-volatile component, the balance is omitted ($c_{\mathrm{Gi}} = 0$), ($N_{\mathrm{GLi}} = 0$).
(b) No axial dispersion: $D_{\mathrm{G}} = 0$.
(c) High degree of dispersion; complete backmixing: $\mathrm{d}^2c_{\mathrm{Gi}}/\mathrm{d}l^2 = 0$, $\mathrm{d}(c_{\mathrm{Gi}}w_{\mathrm{G}})/\mathrm{d}l$ is replaced by $(c_{\mathrm{Gi}}w_{\mathrm{G}} - c_{0\mathrm{Gi}}w_{0\mathrm{G}})/L$, which is equal to $(c_{0\mathrm{Gi}}\dot{V}_{0\mathrm{G}} - c_{\mathrm{Gi}}\dot{V}_{\mathrm{G}})/V$.

2.2.3. *Interfacial fluxes*

2.2.3.1. Gas–liquid interface: N_{GLi}. In the case of non-reactive films, the mass transfer is determined by the diffusivities in the gas and liquid phases. Two principal approaches can be used: complete Maxwell–Stefan model and Fick's law with interfacial diffusion. Use of the simple two-film theory for gas and liquid phases with Fick's law gives for the gas–liquid interfacial flux:

$$N_{\mathrm{GLi}} = \frac{(c_{\mathrm{Gi}}/K'_i) - c_{\mathrm{Li}}}{(1/k_{\mathrm{Gi}}K'_i) + (1/k_{\mathrm{L}}a)} \tag{4}$$

2.2.3.2. Solid–liquid interface: N_{SLi}. The interfacial flux N_{SLi} is expressed with: the diffusion through the liquid film surrounding the solid particle and the diffusion in/and out from the solid particle (in case of catalytic reactions).

2.2.4. *Solid–liquid reaction*

For solid–liquid reactions, the interfacial flux is directly related to the reaction rate:

$$N_{\mathrm{SLi}}A_{\mathrm{p}} = k_{\mathrm{Li}}(c^{\mathrm{S}}_{\mathrm{Li}} - c_{\mathrm{Li}})A_{\mathrm{p}} \propto r_iA_{\mathrm{p}} \tag{5}$$

where $r_i = r_i(c^{\mathrm{S}}_{\mathrm{Li}})$ calculated with surface conditions and A_{p} is the outer surface of the particle. A complete wetting of the solid is presumed here. In case that k_{Li} is high, $c_{\mathrm{Li}} \approx c^{\mathrm{S}}_{\mathrm{Li}}$, a direct relation is obtained between the balances of solid and liquid components.

2.2.5. *Catalytic reactions*

For catalytic reactions, the flux at the outer surface of the catalyst is given by

$$N_{\mathrm{SLi}}A_{\mathrm{p}} = k_{\mathrm{Li}}(c^{\mathrm{S}}_{\mathrm{Li}} - c_{\mathrm{Li}})A_{\mathrm{p}} = -\left(D_{\mathrm{ei}}\frac{\mathrm{d}c_{\mathrm{Li}}}{\mathrm{d}r}\right)_{r=R}A_{\mathrm{p}} \tag{6}$$

where D_{e_i} is the effective diffusion coefficient of a species (i) in the catalyst particle and r the coordinate of the catalyst particle.

The gradient $(D_{\mathrm{e}_i}(\mathrm{d}c_{\mathrm{Li}}/\mathrm{d}r))_{r=R}$ is obtained from the solution of the mass balance in the catalyst particle:

$$\frac{\mathrm{d}c_{\mathrm{Li}}}{\mathrm{d}t} = \varepsilon_{\mathrm{p}}^{-1}\left(D_{\mathrm{e}_i}\frac{\mathrm{d}((\mathrm{d}c_{\mathrm{Li}}/\mathrm{d}r)r^s)}{r^s\,\mathrm{d}r} + r_i\rho_{\mathrm{p}}\right) = 0 \tag{7}$$

where s is a shape factor: $s = 2$ for spheres, $s = 1$ for long cylinders, $s = 0$ for slabs.

The effectiveness factor η_{e_i} is defined as

$$\eta_{\mathrm{e}_i}r_i(c^{\mathrm{S}}_{\mathrm{Li}})\Delta m_{\mathrm{cat}} = N_iA_{\mathrm{p}},\ \text{which gives}\ N_ia_{\mathrm{SL}} = \eta_{\mathrm{e}_i}r_i(c^{\mathrm{S}}_{\mathrm{Li}})\rho_{\mathrm{B}}, \quad \rho_{\mathrm{B}} = \frac{m_{\mathrm{cat}}}{V_{\mathrm{R}}} \tag{8}$$

If the diffusional resistance is negligible inside the particle, the effectiveness factor equals 1 and N_ia_{SL} is replaced by $r_i\rho_{\mathrm{B}}$ in the balance equations of the liquid phase components. A complete wetting of the catalyst surface was presumed in the previous discussion and no deactivation of the catalyst was taken into account.

3. Experimental methodology

3.1. *Experimental planning from a practical point of view*

The economical objective in the manufacture of fine chemicals is to maximise the volume yield per time unit of the desired product with a maximum selectivity and to minimise the use of raw materials and utilities. The proposed reactor model is the basis for the experimental design. The reactor model based on kinetics gives guidelines, which phenomena have to be studied experimentally to identify the necessary parameters in the equations in such a way that the fit of the model and the identifiability of the parameters is good enough for the utilisation purposes of the model during the lifecycle of the process.

The first task in the design of experiments for a reaction system is to define the feasible area of the experimental domain, that is typically constrained by temperature, pressure, concentrations, solubilities, slurry density, mixing effects, kinetic rates, mass transfer rates, reaction enthalpies, heat transfer rates and the thermal stability of the species in the reaction medium. The preferable procedure is to try to separate the reaction kinetics from transfer phenomena and to carry out kinetic experiments under mass transfer-free conditions to measure the real chemical kinetics and not the apparent mass transfer-limited pseudo-kinetics. This implies in practice that the experiments are carried out at lower temperatures and at lower catalyst loadings with small catalyst particle sizes under efficient mixing to ensure that the rate reflects intrinsic reaction kinetics being slower than the slowest mass transfer phenomenon (dissolution rate, gas–liquid- or liquid–solid-transfer rate or intraparticle transfer rates). The concentrations of the reactive components are varied within the range of the future industrial process. For semi-batch operation, the feed rate of the reactant should be faster than its consumption rate in the reaction to guarantee that the availability of the reactant feed does not become rate limiting. The feed rate should, however, be constrained to minimise the concentration and temperature gradients in the close proximity of the feed point under the prevailing mixing conditions not to have negative local effects on the reaction selectivity. The measurements of reaction rates are in practice carried out preferably as at least at three temperature levels in order to define the pre-exponential kinetic parameters and the activation energies reliably in the Arrhenius' type rate-temperature dependence equation.

The experimental conditions which define the mass transfer parameters in the rate equations are designed in such a way that the kinetic rate of the slowest significant chemical reaction is faster than the fastest mass transfer rate in the system. In case of coupled kinetic and mass transfer phenomena, it is necessary to assume, which one is the rate-limiting

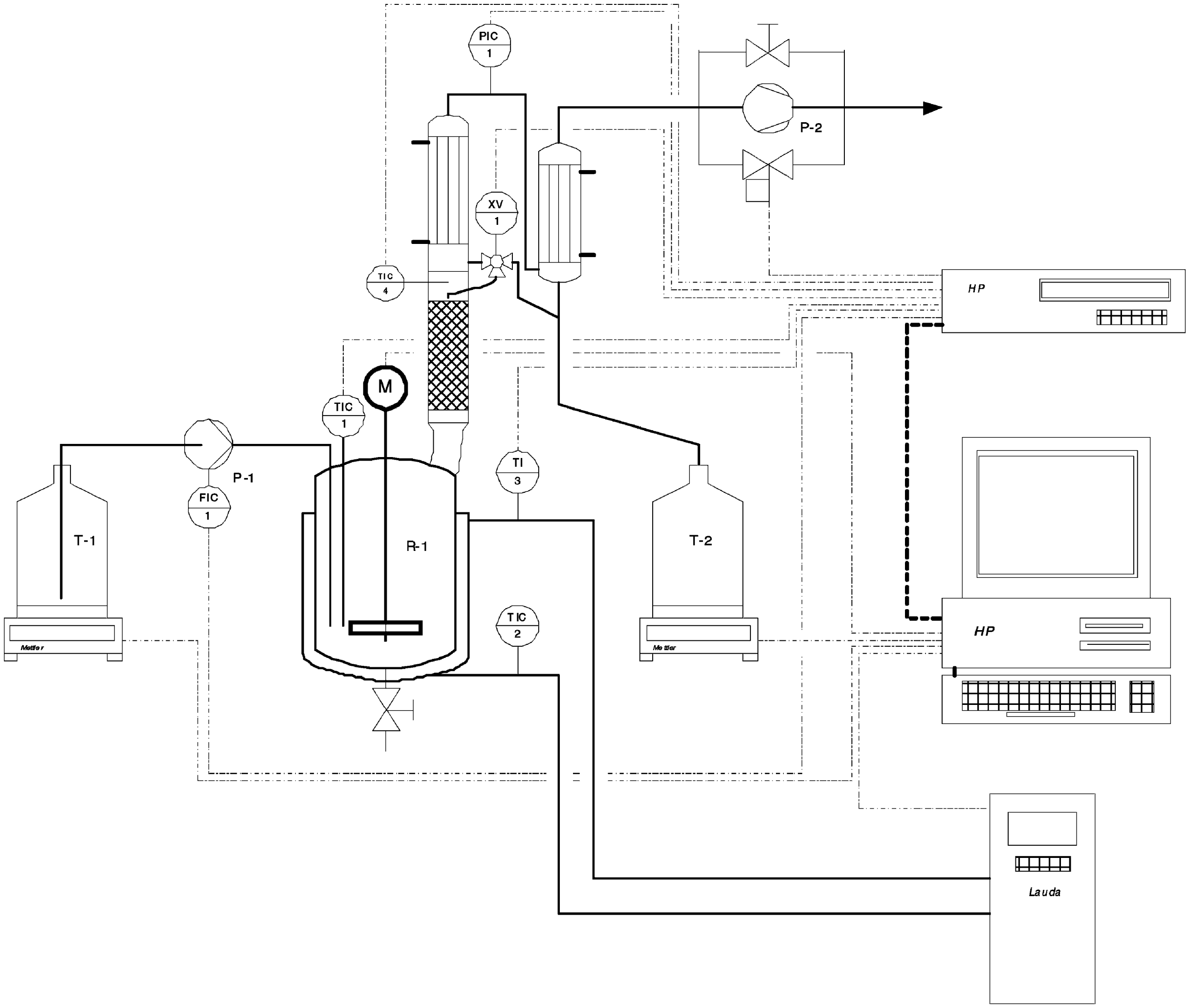


Fig. 3. Typical experimental reactor equipped with PC-based data acquisition and control systems.

step and design the experiments accordingly. When the kinetic parameters are available, they are implemented as fixed parameters in the overall model and only the mass transfer parameters are estimated in this case. Often the mass transfer rate is determined 'off-line' by the so-called mock-up experiments utilising, for example, the physical absorption method. The obtained parameters for the used mass transfer correlation are then introduced into the overall reactor model. The mass transfer rates may be so fast that the transfer rate equations can be substituted with equilibrium equations in the model, which simplifies the treatment of the kinetic data. The experimental work then reduces to separate measurements of solubility equilibria of the species in the reaction mixture at different temperature–pressure–concentration combinations.

In fitting the model to the experimental data, the obtained accuracy of fit and the identifiability of the parameters gives feedback, i.e. what complementary experiments have to be carried out and which experimental domains improve the fit and which assumptions used in the derivation of the model should be refined to better describe the behaviour of the system and also, which simplifications can be introduced without a loss of the fit or the parameter identifiability. The chemical analysis may also reveal, if the concentrations of some reaction components are so low that they can be discarded from the reaction matrix.

The model is validated by comparing the simulated results with the results of independent experiments preferably carried out under industrial conditions. The whole experimental design process is iterative.

3.2. *Experimental equipment in the development of fine chemical reactions*

Typical laboratory (0.05–1 l) and bench-scale (1–2 l) reactors, equipped with PC-based data acquisition and control systems, are used in the kinetic measurements of fine chemical reactions (Fig. 3). The reactors are usually operated batch or semibatchwise. The normal procedure to monitor the extent of the reaction is to take samples of the reaction mixture and to analyse them off-line using high pressure liquid chromatography (HPLC) and gas chromatography (GC). The problem is the instability of the samples (unless thermally or chemically passivated) and the time for analysis, which limits the number of data points for modelling purposes. Modern in situ UV, NIR, FTIR or Raman probes coupled to spectrometers and data acquisition systems enabling continuous monitoring of the spectral information from the reaction mixture, are the future trend in experimental reaction engineering.

4. Numerical methods and parameter estimation procedure

The previously presented (Chapter 2) mechanistic mathematical models for dynamic processes occurring in fine chemical manufacturing can be presented in the form of ordinary differential equations (ODE):

$$\frac{\mathrm{d}y}{\mathrm{d}t} = f(y, t) \tag{9}$$

with the initial conditions $y = y_0$ at $t = t_0$ where t is typically reaction time and y represents concentrations of chemical species. In case of flow and axial dispersion spatial coordinates appear. The system of parabolic partial, differential equations (PDEs) is converted to ODEs by discretising the spatial coordinates. This can be done by several methods, e.g. with finite differences or with approximation functions, such as orthogonal collocation. The ODE systems derived from chemical kinetics are in many cases stiff because the highly different rates of the reactions, some are slow and others are very rapid, approaching the equilibrium. Furthermore, discretisation of the spatial coordinate increases the stiffness of the system. Numerical problems may appear in solving these stiff ODEs. Software tools such as the MODEST software [3] can be used in solving the ODEs. This software applies backward difference method for stiff systems implemented in ODESSA, which is based on the LSODE software [4] The recently developed software of Buzzi-Ferraris and Manca [5] has shown to be very efficient for stiff systems, particularly in the simulation of concentration profiles inside catalyst particles [6].

The objective function to be minimised in the estimation of kinetic parameters can be written as

$$Q(p) = \sum_i (y_i - \hat{y}_i)^{\mathrm{T}} \omega_i (y_i - \hat{y}_i) \tag{10}$$

where p is the vector of adjustable parameters, y_i the vector of experimental values and $\hat{y}_i$ the vector of model predictions at ith sample point and ω_i the diagonal matrix of weights for the experimental values at the same sampling point. The objective function can be minimised with the Levenberg–Marquardt method [7], which is effective in finding a sharp optimum, but requires initial values close enough to the optimum. A more robust simplex algorithm can be used to find an approximate optimum quickly, when only poor initial values are available.

Complex kinetic and reactor models involve many adjustable parameters, some of which may be heavily correlated. These correlated parameters cannot be simultaneously estimated independently and this may lead to physico-chemically unrealistic parameter values for the model, even though the fit of the model to data is excellent. In these cases one has to re-parameterise the model or to merge mutually correlated parameters to a single apparent parameter that can be estimated independently or to fix the values of some of the parameters to physico-chemically reasonable values and estimate the remaining ones. A stagewise strategy is recommendable, i.e. to estimate the parameters first for individual data sets to obtain good initial values for parameters and only after that fit the model to all data sets simultaneously. Two criteria can be used to evaluate the quality of the model and discriminate between different model candidates: goodness of fit, i.e. the degree of explanation is defined by (R^2-value) and the identifiability of the parameters.

$$R^2 = 1 - \frac{\sum_i (\hat{y}_i - y_i)^2}{\sum_i (y_i - \bar{y}_i)^2} \qquad (11)$$

where $\bar{y}_i$ is the average value of the concentration or molar amount of component (i).

The standard deviations of the parameters and the correlation matrix of binary parameters are used a priori to give information of the identifiabilities of the parameters. The sensitivities of individual parameters can be studied by plotting the objective function (Q) as a function of the parameter value. The mutual correlation of parameters can be studied with the method of maximum likelihood. Two-dimensional contour plots can be used to demonstrate, whether two parameters were correlated or not [8]. The procedure for parameter estimation with interactive experimental design and experimental data generation is summarised in Fig. 4.

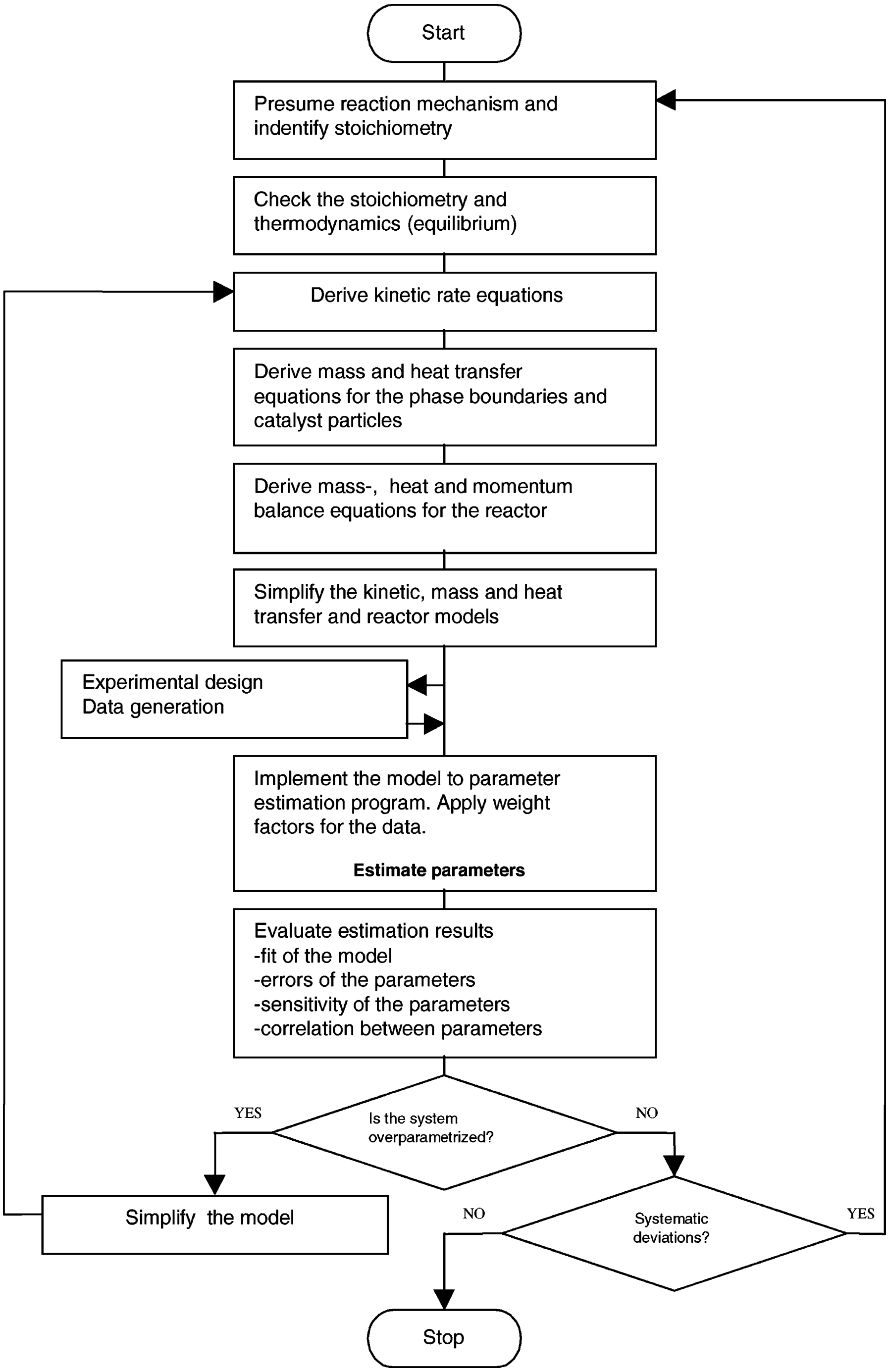


Fig. 4. Practical procedures for parameter estimation with interactive experimental design and experimental data generation developed.

5. Case studies

5.1. *Case 1: Reductive N-alkylation of an aromatic amine, a homogeneous–heterogeneously catalysed reaction*

Reductive *N*-alkylation of an aromatic amine is presented here as an example of a complex reaction system involving homogeneous reactions and a heterogeneously catalysed double bond reduction and/or hydrogenolysis [9,10].

5.1.1. *Derivation of kinetic equations*

The reaction proceeds in three steps. In the first step, the amino group reacts with an aldehyde in liquid phase producing an intermediate (M1). In the second step, the intermediate (M1) decomposes to imine, Shiff's base (M2) and water [11]. The third step is the heterogeneously catalysed hydrogenation of the double bond of the imine giving secondary amine (B) [12]. In principle, (B) can also be formed directly from carbinolamine (M1) by hydrogenolysis [13] (Scheme 1).

The initiating homogeneous steps can be written

$$\mathrm{A} + \mathrm{R'CHO} \Leftrightarrow \mathrm{I1} \tag{I}$$

$$\mathrm{I1} \Leftrightarrow \mathrm{I2} + \mathrm{H_2O} \tag{II}$$

Presuming that the reaction with the aldehyde is slow and as such rate determining compared to rapid water elimination, the following kinetic equation can be written for the homogeneous liquid phase reactions applying quasi-equilibrium to the rapid step:

$$r_1 = k_1 \left(\frac{c_{\mathrm{A}} c_{\mathrm{R'CHO}} - c_{\mathrm{I2}} c_{\mathrm{H_2O}}}{K_1 K_2} \right) \tag{12}$$

where $K_1 K_2 = c_{\mathrm{I2}} c_{\mathrm{H_2O}} / c_{\mathrm{A}} c_{\mathrm{R'CHO}}$.

For the surface reaction that takes place on the Pt catalyst, assuming dissociative hydrogen adsorption, consecutive hydrogen addition and product desorption, the following mechanism can be expressed to describe the reactions:

$$\begin{array}{ccccccccc}
\mathrm{I2}^* & + & \mathrm{H}^* & \rightarrow & \mathrm{I2\,H}^* & + & * \\
\mathrm{I2\,H}^* & + & \mathrm{H}^* & \rightarrow & \mathrm{B}^* & + & * \\
\hline
\mathrm{I2}^* & + & 2\mathrm{H}^* & \rightarrow & \mathrm{B}^* & + & 2^*,
\end{array}$$

where I2 can be M2, M4, N2, N4, O2, O4 or O6.

We obtain a rate equation for the surface reaction:

$$r_3 = \frac{k'_3 c_{\mathrm{I2}} C_{\mathrm{H_2}}}{\left(1 + K_{\mathrm{I2}} c_{\mathrm{I2}} + \sqrt{K_{\mathrm{H}} c_{\mathrm{H_2}}} + \sum K_j c_j\right)^3} \tag{13}$$

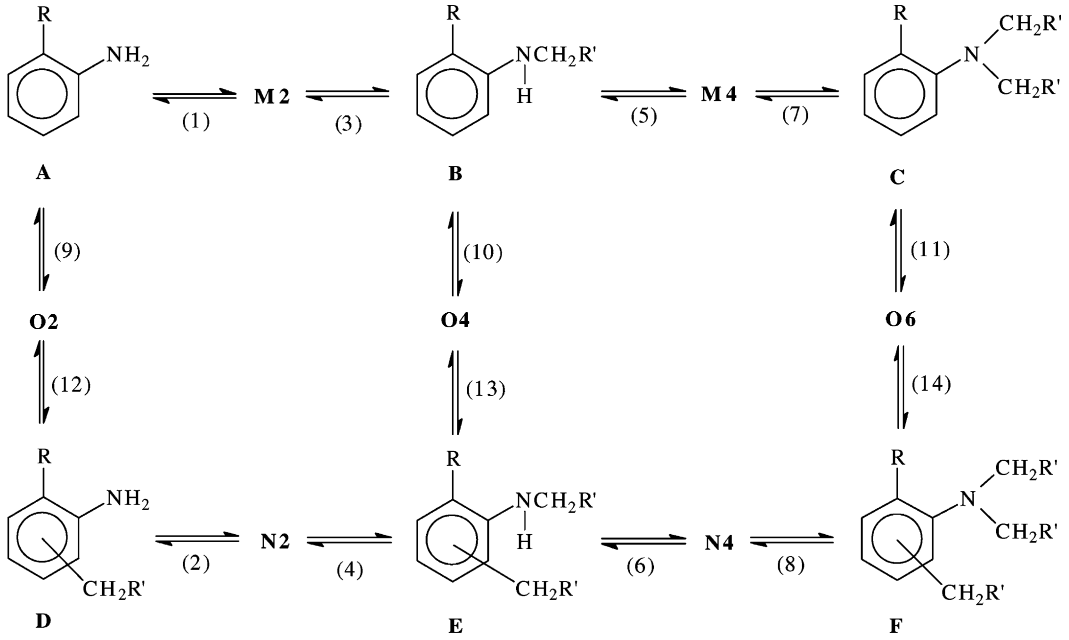
where $k'_3 = k_3 K_{\mathrm{I2}} K_{\mathrm{H}}$.

The rate of formation or consumption of a component i is the sum of the homogeneous non-catalytic reaction and heterogeneous catalytic reaction:

$$r_i = \sum r_{j,\text{non-cat}} + \left(\sum r_j\right) \eta_{\mathrm{e}} \rho_{\mathrm{B}} c_{\mathrm{M}} \tag{14}$$

where η_{e} is the effectiveness factor for the catalyst particle ($0 \le \eta_{\mathrm{e}} \le 1$), ρ_{B} the bulk density of the catalyst and c_{M} the concentration of the active metal in the catalyst.

In this particular complex case, the system is simplified by assuming that the catalyst particles are small enough and the metal crystallites are situated at the surface of the catalyst particles or at the mouth of the macropores of the particles being easily accessible, which implies that the diffusion resistances are negligible. The effectiveness factor η_{e} equals 1 and can be omitted from the component formation and consumption equations. The generation rates of chemical



Scheme 1. Reaction scheme for the reductive alkylation of aromatic amines.

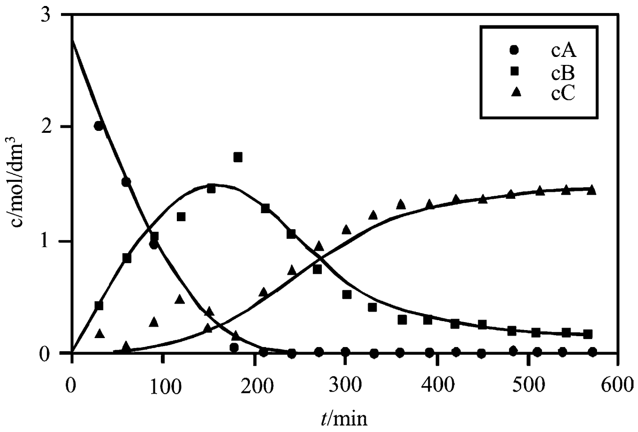


Fig. 5. Fit of the kinetic model for reductive *N*-alkylation of aromatic amine with aldehyde.

species are summarised below:

$$r_A = -R_1 - R_9 \quad (15)$$

$$r_B = -R_5 - R_{10} + R_3 \rho_B c_M \quad (16)$$

$$r_C = -R_{11} + R_7 \rho_B c_M \quad (17)$$

$$r_D = -R_2 + R_{12} \rho_B c_M \quad (18)$$

$$r_E = -R_6 + (R_4 + R_{13}) \rho_B c_M \quad (19)$$

$$r_F = (R_8 + R_{14}) \rho_B c_M \quad (20)$$

$$r_{M2} = R_1 - R_3 \rho_B c_M \quad (21)$$

$$r_{M4} = R_5 - R_7 \rho_B c_M \quad (22)$$

$$r_{N2} = R_2 - R_4 \rho_B c_M \quad (23)$$

$$r_{N4} = R_6 - R_8 \rho_B c_M \quad (24)$$

$$r_{O2} = R_9 - R_{12} \rho_B c_M \quad (25)$$

$$r_{O4} = R_{10} - R_{13} \rho_B c_M \quad (26)$$

$$r_{O6} = R_{11} - R_{14} \rho_B c_M \quad (27)$$

The reaction scheme was further simplified and the number of rate equations was reduced based on the experimental finding that the ring alkylation reactions are minor and so those reactions could be omitted in the final kinetic treatment. An example of the fit of the kinetic model for a batch reactor is presented in Fig. 5.

5.2. Case 2: Kinetics and mass transfer of organic liquid phase reactions in the presence of a sparingly soluble solid phase

Claisen condensation is presented here as an example of an organic liquid phase reaction, which takes place in the presence of a reactive, but sparingly soluble solid compound, in this case a methoxide [14].

5.2.1. Reaction mechanism and rate equations

Based on a simplified treatment of the reaction pathway, the elementary steps leading to the formation of the final product (D) and methanol (E) can be compressed to (Scheme 2)

$$\begin{array}{lcl} A + B & \Leftrightarrow & A1 + E \\ A1 + C & \Leftrightarrow & A2 \\ A2 & \Leftrightarrow & A3 + B \\ \underline{A3 + B} & \underline{\Leftrightarrow} & \underline{D + E} \\ A + B + C & \Leftrightarrow & D + 2E \end{array}$$

where A, B, C, D and E are analytically detectable compounds while A1 (carbanion), A2 and A3 are reaction intermediates. The quasi-steady-state hypothesis implies that the generation rates intermediates are approximated to zero [1,2]. Applying the quasi-steady-state hypothesis on the reactive intermediates (A1, A2 and A3) gives the generation rates for the compounds: $r_{A1} = r_1 - r_2 = 0$, $r_{A2} = r_2 - r_3 = 0$, $r_{A3} = r_3 - r_4 = 0$, where $r_1, \ldots, r_4$ denote the rates of steps (1)–(4). These conditions imply that the overall rate is equal to $r = r_1 = r_2 = r_3 = r_4$. By eliminating the concentrations of the intermediates, an analytical expression is obtained for the reaction rate:

$$r = k\left(c_A c_B c_C - \frac{c_E^2 c_D}{K}\right) \times \left(k_2 k_3 k_4 c_C + \left(\frac{k_2 k_3}{K_2 K_3} + \frac{k_2 k_4}{K_2} + k_3 k_4\right)\frac{k_1 c_E}{K_1}\right)^{-1} \quad (28)$$

where $k = \prod_{j=1}^{4} k_j$ and $K = \prod_{j=1}^{4} K_j$. The rate equation (28) can be written in a more general form by introducing merged parameters K' and K'':

$$r = k\left(c_A c_B c_C - \frac{c_E^2 c_D}{K}\right)(K' c_C + K'' c_E)^{-1} \quad (29)$$

Claisen condensation can in practice be regarded as an irreversible process, i.e. K is large.

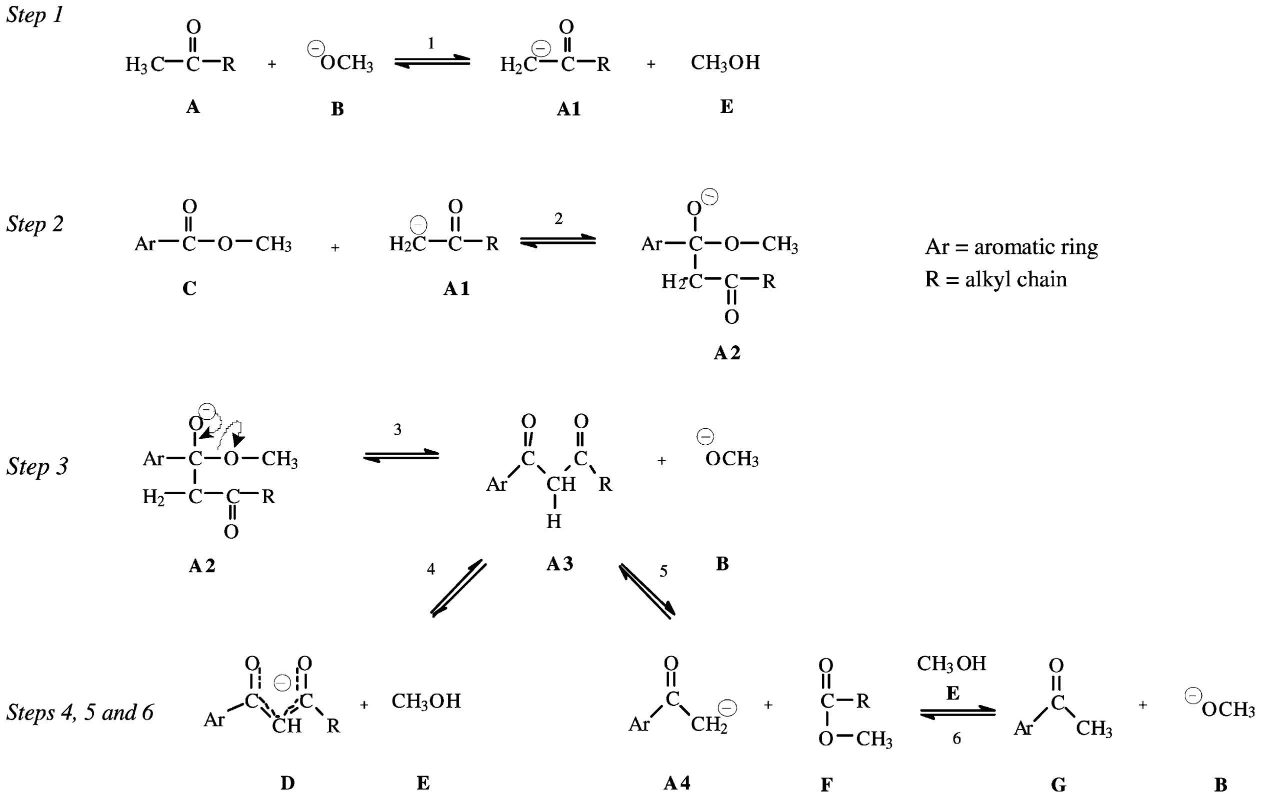
For the side reactions, a simplified kinetic treatment was applied. The consumption velocity of C and B in these reactions is expressed by [14]:

$$r_{S2S3} = k_{S2S3} c_C c_B \quad (30)$$

5.2.2. Reactor model

5.2.2.1. Mass balance equations for liquid phase components. The rate equations are coupled to the mass balances of the compounds in the reactor. The mass balance of an arbitrary compound (i) in a semibatch reactor model can be defined as (see Chapter 2)

$$\frac{dn_i}{dt} = \dot{n}_{0_i} + N_i A + r_i V \quad (31)$$



Scheme 2. The reaction scheme of Claisen condensation.

The generation rates of chemical species are summarised below:

$$r_A = -r \tag{32}$$

$$r_B = -r - r_{S2S3} \tag{33}$$

$$r_C = -r - r_{S2S3} \tag{34}$$

$$r_D = +r \tag{35}$$

$$r_E = +2r + \alpha r_{S2S3}, \quad \alpha = (0, \dots, 1) \tag{36}$$

As the density change due to reactions is negligible, the liquid phase volume is updated with the formula

$$V = V_0 + \int_0^t \dot{V}_0 \, dt, \quad t \le t_f \tag{37}$$

5.2.2.2. Modelling solid compound consumption. In this particular case, the compound (A) is fed into the reactor and one of the compounds (B, in this case sodium methoxide) exists predominantly in the solid phase due to its limited solubility. The mass transfer of B is rapid, i.e. the film diffusion resistance is negligible, c_B can be directly replaced with c_B^* in the rate expression [14].

For a particle with arbitrary geometry can be written:

$$a y^{a-1} \frac{dy}{dt} = \frac{M_B}{m_{0B}} r_B V, \quad y = \frac{r'}{R} \tag{38}$$

The shape factor a is defined as $a/R = A_{0p}/V_{0p}$. For the actual case, the shape factor was obtained from [14].

$$a = \frac{2(1 + 2R/L)}{1 + 4/3R/L} \tag{39}$$

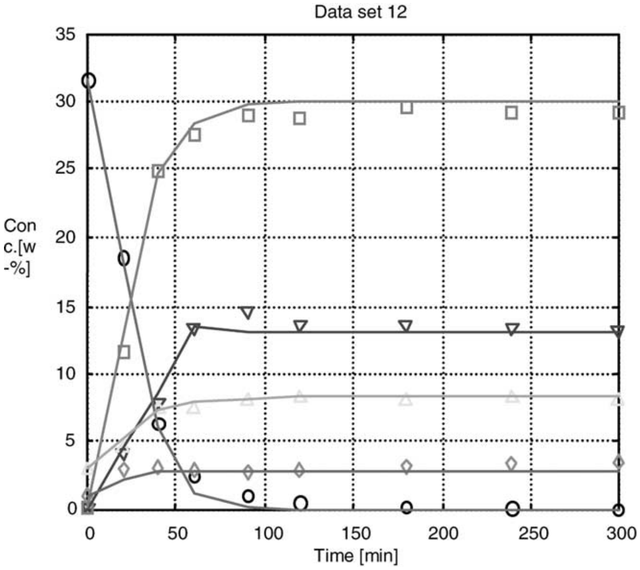


Fig. 6. Comparison of experimental data and model simulation of Claisen condensation for data set 12 (75 °C, A: 2.5, B: 1.4). Symbols: A (▽), C (○), D (□), E (△), S21 (◇).

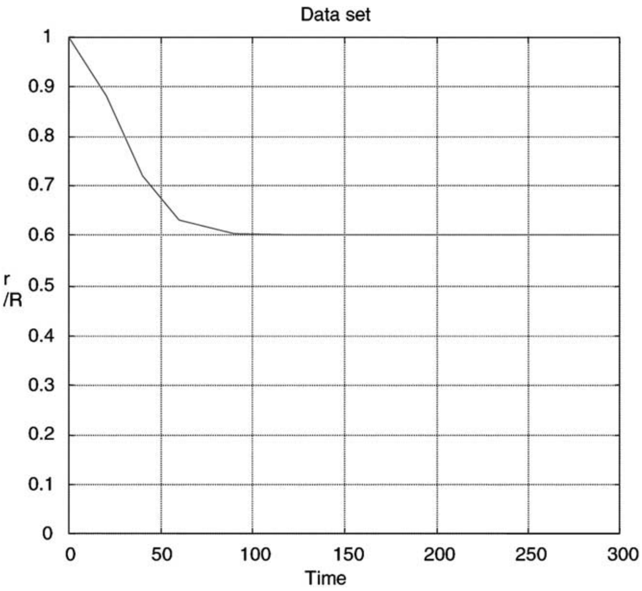


Fig. 7. The simulated dimensionless radius (r'/R) of the methoxide particles (shape factor $a = 2.5$).

5.2.2.3. Kinetic modelling results. For modelling purposes, Eq. (29) was further simplified to improve the identifiability of the parameters in the estimation. The kinetic equation (40) was applied in the model for the main reaction scheme,

$$r = \frac{k_1 c_A c_B c_C}{c_C + K''' c_E} \tag{40}$$

As an example of the model fit to the experimentally measured concentrations is presented in Fig. 6. An example of the simulated dimensionless radius (r'/R) of the methoxide particles with the average shape factor of 2.5 is presented in Fig. 7.

6. Conclusions

This paper deals with the methodologies in the development of dynamic mechanistic kinetic and multiphase reactor models for batch and semibacth reactors for processes which take place in the manufacturing of fine chemicals. In addition, the practical methods for generating experimental data for the modelling purposes and the tasks required in the estimation of parameters for the models were covered. These methodologies are an essential part of the process development workflow concept and improve the utilisation of models as tools during the process development cycle enabling a shorter development time and a higher performance of the new processes.

One of the objectives in process development in the field of fine chemicals is to provide an integrated dynamic modelling, simulation and optimisation platform that covers the whole process development workflow and allows different levels of complexity to be included in modular form into the overall process model as the work proceeds and more information is obtained. Internet and Intranet will be an attractive way to operate these tools and to communicate and transfer information during the lifecycle of the process [15].

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