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Design of Reaction Systems for Specialty Organic Chemicals

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Design of reaction systems for specialty organic chemicals requires utilization of chemical reaction engineering principles for a wide variety of kinetic problems. Kinetic analysis must include breakdown of the overall reaction into definable components in order to identify parallel and/or consecutive reactions that result in by-product formation. Once identified, methods of minimizing by-product formation can be developed.

Examples are described of complex reaction systems which have required development of specialized procedures to minimize by-product formation. Each example represents a different kinetic problem and method of solution. Emphasis is placed on the close interaction between chemists and chemical engineers during laboratory development and plant reaction system design to achieve successful commercial operation.

I. Introduction

Development and scale-up of reaction systems for specialty organics requires application of the chemical reaction engineering discipline to solve a wide range of problems. While defying systematic categorization because of their variety, these reaction systems may be broadly characterized according to their kinetic complexity as will be developed in the discussions below.

Plant design in this segment of the industry can be regarded as complex in terms of the chemistry of the larger molecules and the number of steps to complete the synthesis of a specialty chemical. Another obvious generalization is that the volume of production is modest in comparison to the heavy chemical industry, thereby allowing effective utilization of batch and semi-continuous reactor systems instead of continuous operations. Indeed, the use of continuous systems may be dictated not on throughput or other economic grounds but rather on kinetic restrictions which preclude batch or semi-batch operations because of scale-up considerations. Thus, while batch operations may be economically viable because of limited production requirements and even desirable for plant versatility in multi-product utilization, the use of continuous or semi-continuous systems may be required to achieve satisfactory kinetic scale-up and in some cases to minimize in-process inventory of potentially hazardous reagents.

The purpose of this paper is to investigate the kinetic characteristics of specialty organic chemical reaction systems to accomplish successful scale-up from laboratory through pilot plant to plant operations. Specific complex reaction systems that have required special design considerations to achieve successful scale-up will be described. The analysis of each system will include an outline of the kinetic models involved, the reasons that special designs are necessary, and the specific operational and equipment design considerations that were applied to achieve successful scale-up.

II. General Scale-up Considerations

Before getting into the specifics of the individual reaction systems that have been chosen as models, a few observations on the scale-up of batch reactions in general may be in order.

Many reactions require no special design or operational considerations once the reacting system has been established and its requirements determined. For these reactions a laboratory scale sensitivity analysis and pilot plant evaluation may be sufficient to demonstrate the feasibility of successful direct scale-up to production operation. Successful scale-up can be defined as plant operation that achieves the same conversion, selectivity, and product distribution as defined in the laboratory. Reactor design is then accomplished through direct volume scale-up permitting utilization of standard batch reactor configurations. These simple cases require that those parameters which are inherently different on direct volume scale-up are not significant in terms of changing the course of the reaction within the scale-up factor required. These variables include the following:

- Reduction in surface area/volume ratio does not limit heat transfer or vapor-liquid characteristics so that heat-up, cool-down, or temperature maintenance limits are achievable with standard equipment and gas or vapor dissolution and/or evolution are not limiting.

- Sensitivity to mixing (i.e. circulation time, shear, mass transfer between phases, etc.) does not affect reactor performance.

- Time of addition of a reactant and/or removal of a product in semi-batch mode is not a significant variable.

While these considerations are well known, it is sometimes difficult in laboratory evaluation to arrive at definitive conclusions for individual reactions regarding their response to these parameters because the responses may be masked or not separable from the overall results. It may be informative during the laboratory development phase to attempt to categorize the various possible factors that may disguise the true kinetics. Attempts at characterization of reactions leads directly into the main body of this paper in which more complex kinetic systems are considered as those which are affected by any or all of these scale-up considerations.

III. Complex Kinetics

The opportunity for chemical engineers to influence the outcome of the design of reaction systems is emphasized by Levenspiel (Ref. 1) in his chapter on "Design for Multiple Reactions". He points out that most systems can be reduced to an analysis of combinations of parallel and series reactions. More complex reactions obviously provide more formidable technical challenges to both chemists and chemical engineers and the interdependence of chemistry and reactor design requires close integration of the development skills of both disciplines. Indeed, the possibility always exists that a reaction system that can be operated on a laboratory scale is judged to be unfeasible for successful operation on a plant scale because of insufficient understanding of the system. Such an extreme result could invalidate an otherwise elegant synthesis necessitating development of a less favorable alternative and inducing some loss of confidence in our chemical colleagues for our design abilities.

It is also possible that these colleagues could dismiss as obviously unscalable an otherwise attractive reaction system because of incomplete understanding of the potential contributions of chemical engineers by the creative application of chemical reaction engineering principles and methods.

Developmental strategy must be focused on defining the kinetic relationships of the reaction system so that the strictly chemical issues can be addressed and separated from the scale-up issues. This type of analysis can lead to a further broad characterization of complex reaction systems for purposes of this discussion as follows:

- reactions that require resolution of kinetic problems in order to be run successfully in the laboratory;

- reactions which can be run successfully in the laboratory but which require special plant design considerations and equipment;

- reactions which pose both special laboratory and scale-up problems.

During early laboratory development studies of any individual reaction system, the role of kinetics may not be obvious since a kinetically feasible maximum selectivity may as yet be unknown. Kinetic complications are, of course, implicated when actual selectivities fall short of values that can be reasonably expected. Therefore, assignment of a reaction system to one of the categories described above may be difficult without some early scale-up experience to determine response to changes in scale of conversion, selectivity, and product distribution.

The first category - that of unfeasibly low selectivity even in the laboratory - is even more difficult to identify since discrimination between inherently low selectivity and failure to control a parallel or consecutive reaction may not be possible in these early stages when a kinetic model has not been established.

The first example to be discussed is drawn from this category of complex reactions where identification of the impact of a consecutive reaction leads to development of a solution to achieve its minimization. This kinetic solution is essential for achievement of reasonable selectivity on a laboratory scale and is, therefore, primarily a chemical problem. Successful implementation of the method for kinetic control in production then depends on successful scale-up of the revised laboratory system.

IV. Examples of Complex Kinetic Systems

Example 1

The first example is of a reaction system in which a by-product (HCl) that is generated by the primary reaction would decompose both the desired product and the starting material to give essentially no yield unless its concentration were controlled. In addition, the actual selectivity as well as the conversion rate is a function of the method and extent of this control. The chemistry is shown in Figs. 1 and 2 and the kinetic system summarized in Fig. 3. This chemistry is discussed extensively by Weinstock (Ref. 2).

FIGURE 1

OVERALL CHEMISTRY

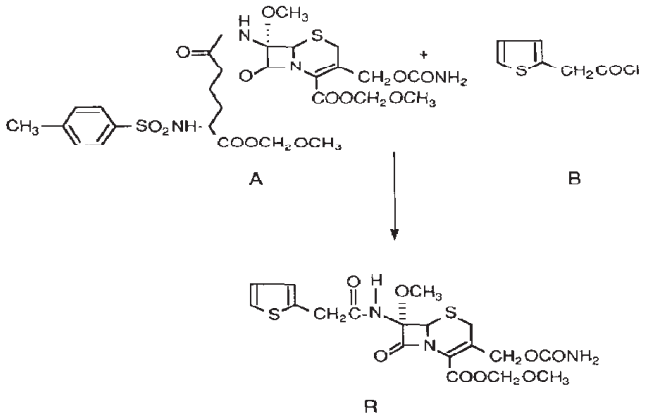


FIGURE 2

INTERMEDIATES

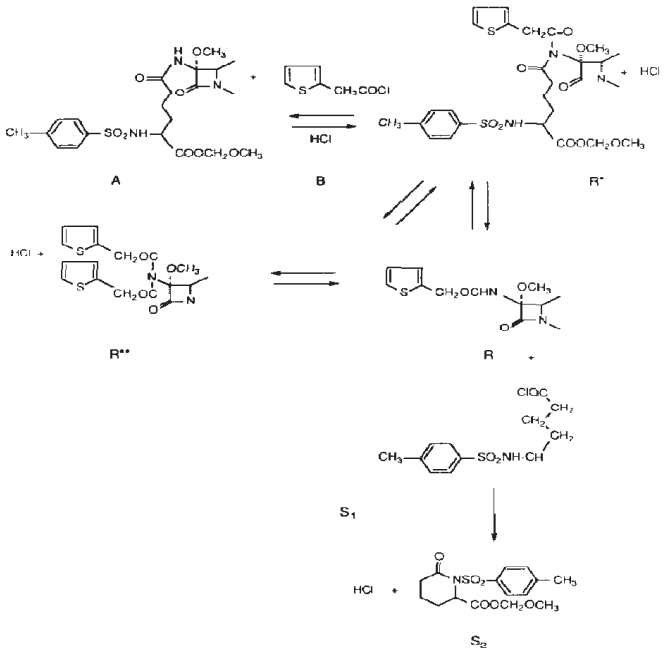
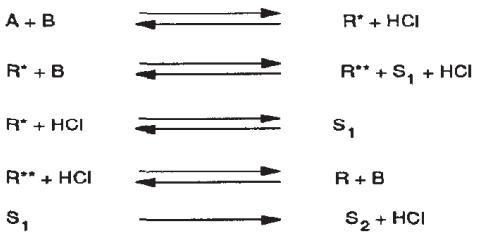


FIGURE 3

TRANSACYLATION KINETICS



The method of mediating the concentrations of HCl below that causing excessive decomposition while maintaining its concentration high enough for its participation in the required reactions is, therefore, critical to the success of the overall scheme. The product, R, after hydrolysis is now one of the world's leading parenteral antibiotics and is made in relatively large volume. A feasible, commercially-viable synthesis of this compound was essential for operation in a manufacturing environment.

There are two distinct reaction types taking place: (1) acylations to form imides and (2) HCl-promoted imide cleavages producing amides and an acid chloride. Consecutive decomposition by reaction with HCl is always proceeding depending on the concentration of HCl. If no method of mediating the HCl concentration was applied, the concentration of HCl would increase to 0.1M and result in complete decomposition of R. It was determined *that an optimum concentration of ∿0.004M is required for imide cleavage.*

Molecular sieves (3A or 4A) were found to be very effective for this mediation under very well-defined conditions. The HCl concentration in solution is determined by both the amount of sieves used as well as their external surface area. Thus, sieve pellets (∿400μ) are not satisfactory because of rate-controlling diffusion in the pores whereas powdered sieves (1-4μ) are satisfactory. It is also apparent that the rate of HCl removal is critical as well as its actual concentration. This criticality is also underscored by the improvement in selectivity that was subsequently achieved through development of a homogeneous HCl mediator, trimethyl silyl methyl carbamate. Elimination of the mass transfer resistance at the sieve surface by the presence in solution of a reagent to react directly with HCl resulted in a significant yield increase. Comparison of selectivity of R by four different methods of HCl mediation is shown in Table IV-1.

TABLE IV-1

Method	Relative Selectivity
None	- Essentially Zero
Distillation	- " "
Molecular Sieves	+
Homogeneous Scavenger	++

All of the above reaction studies were carried out in the laboratory. Scale-up of both sieve and homogeneous scavenger mediated reactions was relatively straight-forward once the concentrations and reaction were defined in the laboratory. Successful plant-scale operation did require rapid heat-up and cool-down, however, to minimize time at other than optimum temprature. Typical production scale reaction kinetic profiles, as determined by HPLC, are shown in Figs. 4 and 5 illustrating consistency of overall performance despite a significant difference in time to termination of reaction. Thus, if the run shown in Fig. 4 had been allowed to continue as long as that shown in Fig. 5, a significant yield loss would have been experienced as projected in Fig. 4.

FIGURE 4
KINETIC PROFILE PRODUCTION PLANT-HPLC

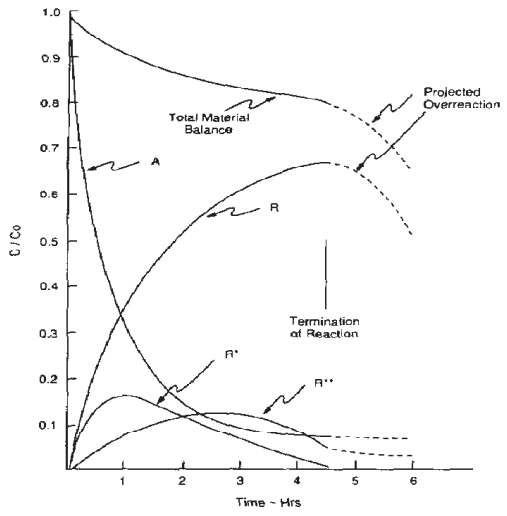
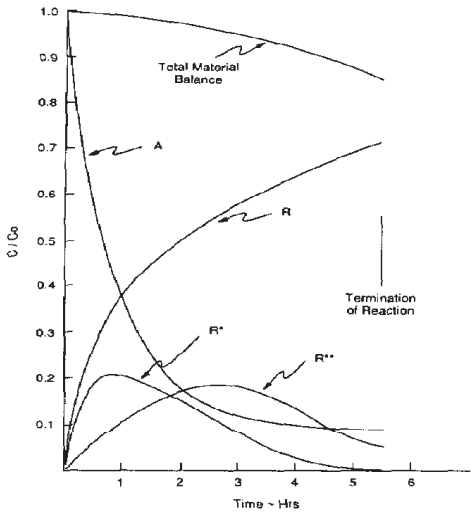


FIGURE 5
KINETIC PROFILE PRODUCTION PLANT-HPLC



Example 2

The second example reaction system is quite different from the first in that successful laboratory operation was quickly established but scale-up to the pilot plant resulted in reduced selectivity. The laboratory synthesis is discussed by Blacklock, et. al (Ref. 3). The cause of scale-up complications is over-reaction of primary product by rapid, consecutive reaction with one of the starting materials. The reaction involves formation of the dipeptide L-alanyl-L-proline from L-alanine-N-carboxyanhydride and L-proline. The chemistry is shown in Fig. 6 and the kinetics in Fig. 7.

FIGURE 6
COUPLING REACTION L-ALANYL-L-PROLINE

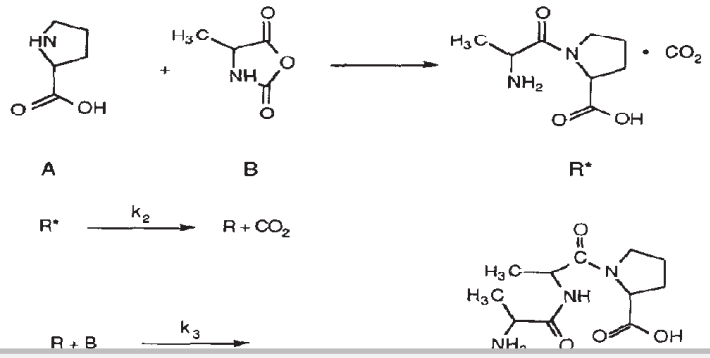
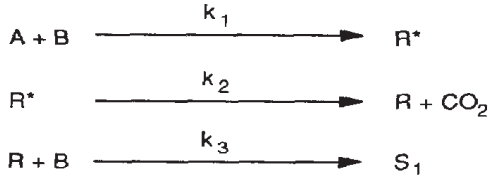


FIGURE 7
KINETICS OF THE COUPLING REACTION



$k_1 \cong 100$ l / mol. sec.

$k_3 / k_1 \sim 0.1$

L-alanyl-L-proline will further react with additional L-alanine N-carboxyanhydride as shown. The primary rate constant, k_1, is large enough to result in completion of the primary reaction in the order of one second. The rate of loss of CO_2 to form R is significant enough to affect the overall kinetics. If it were very rapid compared to k_1, the system would demonstrate simple consecutive-competitive kinetics and the selectivity would depend only on k_3/k_1 and be independent of addition time of B. However, a dependency on this addition time has been shown in the laboratory. Long addition time (1000 sec.) results in a reduction in selectivity of ∿10%. Rapid addition, therefore, results in reduced opportunity for R to react with B, thereby diminishing the importance of k_3 on selectivity. R^* is less reactive with B than R.

Scale-up (50-fold) to pilot plant equipment resulted in significant yield reduction and increased by-product formation compared to laboratory results as would be expected from the fast kinetics and significant consecutive reaction. Furthermore, additional scale-up (∿20-fold) was required for production-scale operation and an additional loss in yield was anticipated. The reduced selectivity of the initial scale-up and the on-going definition of the rapid kinetics of the system combined with the requirement for minimization of by-product formation necessitated evaluation of an alternative reactor configuration. An in-line mixer was chosen and was successfully developed for production scale operation. The in-line mixer chosen was the Koch static mixer with an L/D ratio of 4. The nominal residence time of the combined 2-liquid phase stream was 1 sec. Reynolds number in the mixer was 2000 based on empty tube diameter. The reactant mol ratio was 0.95-1.0 mol alanine NCA/proline.

Results of the in-line mixer in both laboratory scale (0.8 cm) and plant scale (2.54 cm) operation were excellent. No change in selectivity or product distribution occurred over this scale-up so that the expected selectivity was achieved.

This reaction system and its requirements for successful scale-up raise the issue of identification of reaction systems with potential for mixing-related scale up problems and selection of mixing devices for proper contacting. The kinetics of this system, while not identical, are similar to the consecutive-competitive reactions that have been used to study the effect of mixing on the selectivity of reaction systems. These studies include the work of Bourne and co-workers (Refs. 4, 5, 6, 7) in development of the diazotization reaction sequence that has been used so effectively both in the experimental definition of the micro-mixing problem as well as in modeling for prediction of mixing effects. It has been long recognized that any reacting system in which the primary rate is on the same time scale as the time required for molecular mixing of the reagents is in the regime of mixed diffusion/kinetic control.

Whether or not the product distribution for a specific system is significantly affected by mixing depends in turn on the relative magnitudes of the rates of other possible reactions. Finally, the significance of these by-product reactions in scale-up of an industrial process depends on their impact on the final reaction mixture. Three effects could be anticipated on scale-up of a mixing sensitive reaction, all of which are potentially detrimental. The effects are:

- reduced conversion
- reduced selectivity
- increased impurity levels in reaction products

The actual economic impact is obviously specific for each reaction system. The negative effects on downstream processing in terms of separation of increased levels of impurities and their possible effect on subsequent reactions cannot be underestimated. Even in the case of acid or base additions to change pH in the presence of organic substrates, parallel decomposition reactions of the substrates with the acid or base can occur in the entering reagent stream leading to unanticipated loss of substrate.

The negative impact of mixing sensitive reactions on scale-up can be minimized by design of reagent mixing systems as discussed by many authors (Refs. 8, 9, 10, 11). Bourne and Dell'Ava (Ref. 12) have published data on the diazotization reaction on scale-up to ∿70 l. A dependence on addition rate was observed which is attributed to decreased circulation which causes a decrease in molar ratio at the point of addition.

At Merck Sharp & Dohme, in a joint project with a student of Bourne's, scale-up studies have been extended to 4000 liters. The critical nature of circulation was again observed. Power requirements on scale-up are also significantly increased as shown in Figs. 8, 9, and 10, in which scale-up in three different mixing configurations is summarized. For similarly positioned addition points in each mixing configuration, the power required to achieve equivalent selectivity and product distribution was greater than would be predicted by equal P/V. More data is required to establish a quantitative relationship, however.

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