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Development of a Continuous Homogeneous Metal Complex Catalyzed, Asymmetric Hydrogenation under High Pressure (270 bar)

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Abstract:

A kinetic model and simulation as well as a continuous stirred tank reactor (CSTR) system for the synthesis of (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid, an important optically active intermediate in the synthesis of mibefradil (POSICOR, a new type of calcium antagonist), by asymmetric hydrogenation of 2-(4-fluorophenyl)-3-methylbut-2-enoic acid under high pressure (270 bar) are described. It was demonstrated that a continuous, homogeneous metal complex catalyzed, enantioselective hydrogenation under high pressure is not only feasible but also a very attractive possibility. Using such a CSTR system one may achieve a space-time yield of 5.0 kg/L/day. Compared to a batch mode under high pressure, the CSTR reactor system has a more favourable space-time yield, is safer, would need less investment, and allows easier temperature control.

1. Introduction

The (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid (**2**) is an important optically active intermediate in the synthesis of mibefradil (POSICOR), a new type of calcium antagonist which is being marketed in several countries.[1] In the choice between a synthesis of **2** by asymmetric hydrogenation or resolution, the design of an appropriate high-pressure equipment plays a crucial rule.

Mathematical modeling for investigating and developing a technical process in the basic chemical and petrochemical industry has been widely applied.[2] However, for the production of pharmaceuticals, where much smaller volumes are required and generally most processes are run batchwise, this is rarely the case. In the past, the costs of producing pharmaceutical products have been considered unimportant; as a consequence, the cost of goods has been usually rather high. With the increasing public pressure to lower the ever-rising costs for medical care, decreasing the prices for pharmaceuticals and, hence the costs for their production becomes an important goal. The availability of reliable mathematical models could therefore be of great help to develop economic processes.

In this investigation the mathematical models and simulation as well as the design of a suitable reactor system for the synthesis of (*S*)-acid **2** by continuous asymmetric hydrogenation of 2-(4-fluorophenyl)-3-methylbut-2-enoic acid (**1**) under high pressure with the [Ru((*R*)-MeOBIPHEP)-(OAc)$_2$]-catalyst[1] in a continuous stirred tank reactor (CSTR) system are described. The following procedure has thereby been employed: designing first a mathematical kinetic model estimated from experimental data obtained in batch experiments and using then this model to simulate a continuous process (applying a continuous stirred tank reactor model). On the basis of the simulation, continuous experiments were then carried out. Using this method, not only starting material and solvents could be saved but also the development time could be shortened, too, because the flow rate for the continuous operation can be calculated in advance and does not have to be determined by experimentation.

Table 1. **Influence of pressure**[a]

pressure [bar]	180	230	270	270 (20 °C)
conversion [%]	93.7	99.1	99.7	90.9
ee [%]	89.8	91.3	92.1	94.2

[a] 30 min, at 30 °C.

Table 2. **Influence of temperature**[a]

temperature [°C]	20	26.5	30
conversion [%]	96.54	100	100
ee [%]	93	91.5	90.5

[a] 60 min, at 180 bar.

Table 3. **Influence of rpm**[a]

rpm [1/min]	800	1200
conversion [%]	100	100
ee [%]	89.9	90.5

[a] 60 min, at 30 °C, $P = 180$ bar.

2. Investigation of the Basic Reaction Conditions

To optimize the process, the influence of pressure, temperature, rpm, and solvents on the reaction rate and enantiomeric excess (ee) was investigated. The experiments were carried out mainly in 30 mL autoclaves with magnetic stirring ($S/C = 1000$, 30% in MeOH, 0.6 mol Et$_3$N). The results are given in Tables 1−3, where the conversion and ee were analyzed by GC (Perkin-Elmer model AutoSystem; column SE 54 for conversion and column OV-61/P-DiMe-B-CD for ee).

As the temperature is increased, the reaction rate increases; however, the ee decreases. If one increases the

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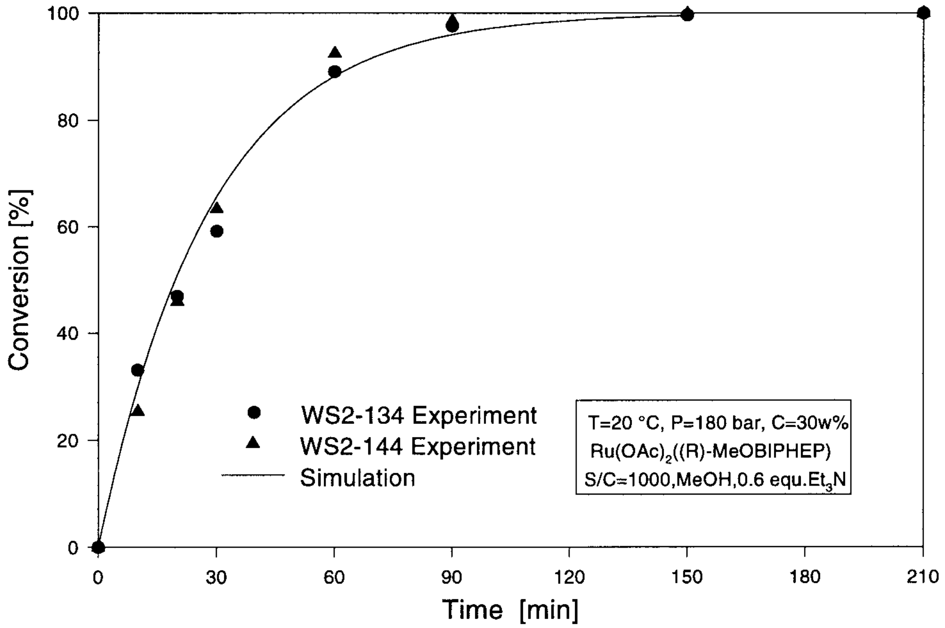


Figure 1. **Batch operation.**

Table 4. **Investigation of catalyst deactivation**[a]

time [h]	0	24	48	72
conversion [%]	99.9	100	100	99.9
ee [%]	92.0	92.2	92.3	92.2

[a] 30 min, at 30 °C, $P = 270$ bar.

pressure, both reaction rate and ee are affected positively; at low pressure, for example 30 bar, the reaction runs very slowly and the ee (<80%) is not acceptable. The higher the rpm, the higher is the ee. The quality of the methanol (industrial or highly purified) has no influence on conversion and ee.

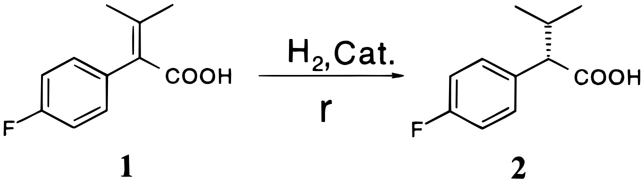
In addition, the catalyst is fortunately not sensitive against oxygen; no matter how the reactant and catalyst solution was prepared either in a glovebox under Ar atmosphere or in free air, the reaction rate and ee remained the same. The catalyst is also not deactivated when left standing with the substrate in solution. Ten milliliter samples of a pre-prepared solution each hydrogenated at 0, 24, 48, and 72 h gave nearly the same conversion and ee as shown in Table 4. For a continuous operation, these findings are important because a substrate/catalyst solution can be easily prepared and left in a feed tank for days without the danger of deactivation.

3. Kinetic Investigation

To gather kinetic data, experiments were carried out in a 380 mL autoclave with mechanical stirring. The experimental conditions were so selected that one investigated the kinetic data near to the optimal condition based on the basic study before (e.g. 20 °C, 180 bar; 30 °C, 270 bar, so ee or reaction rate is as high as possible). With this strategy one can not only get a more reliable formal kinetics for simulating the continuous process but also many experiments could be avoided. The samples were taken at different times, a curve of conversion vs time was obtained, and the kinetic data analysis was then performed on the basis of the kinetic curves.

Due to the high conversion and yield, any byproduct formation in this reaction system may be ignored; thus, the reaction pathway and kinetics, which can be used to describe the observed phenomena in the range of 20−30 °C and 180−270 bar, may be given as follows:

Reaction pathway:



kinetics

$$r = k_0 e^{-E_a/RT} P_{H_2} C_{cat}^{1.5} [C_{acid}^0 (1 - X)]$$

$$k_o = 21\,800\ [\mathrm{L/min/bar/(ppm)^{1.5}}]; \qquad E_a = 69\,000\ [\mathrm{J/mol}]$$

The parameters in the kinetics were estimated from experimental data by employing the Marquardt−Levensberg optimisation method,[3] where the following reactor models were applied, i.e., an isothermal ideally mixed reactor model for the batch reactor and an isothermal continuous stirred tank reactor (CSTR) model for the continuous reactor system:

Batch reactor model

$$\frac{dX}{dt} = k_0 e^{-E_a/RT} P_{H_2} C_{cat}^{1.5} (1 - X)$$

$$t = 0; \qquad X = 0; \qquad X = \frac{c_{acid}^0 - c_{acid}}{c_{acid}^0}$$

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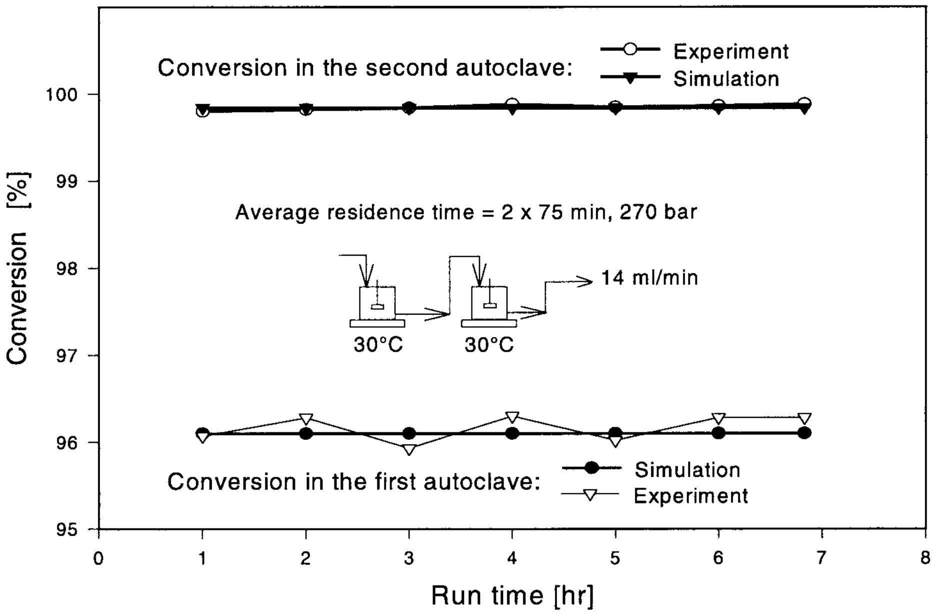

Figure 2. **Continuous operation.**

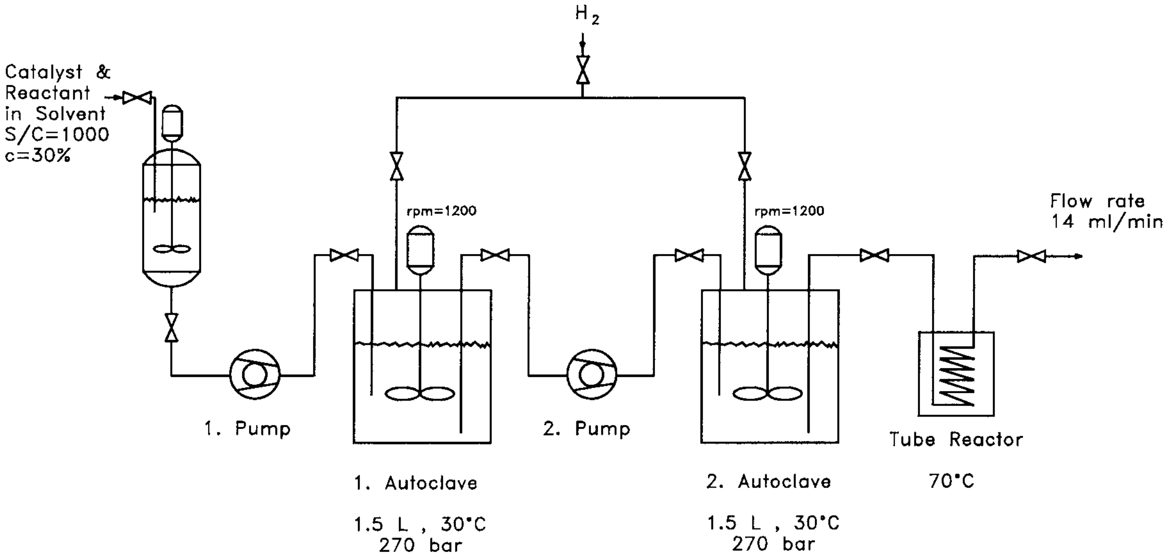

Figure 3. **Continuous stirred tank reactor (CSTR) system.**

CSTR model

$$\frac{c_i^k - c_i^{k-1}}{\tau^k} = \sum_{j=1}^{M} \nu_{ij} r_j$$

$$\tau^k = \frac{V_R^k}{V_0}, \qquad i = 1 \ldots N; \qquad k = 1 \ldots K$$

Figures 1 and 2 show results simulated with these models and the data gathered from both batch and continuous experiments. One can see that the models describe this reaction system very well.

4. Experimental Apparatus for Continuous Hydrogenation

Figure 3 shows a sketch flowchart of the apparatus used for continuous hydrogenation. This CSTR system consists of two autoclaves in series, two electric heating/cooling systems for the two autoclaves, a reactant/catalyst solution liquid feed glass tank, two hydrogen feed systems, two pumps, and an effluent flow controller. After the second autoclave, the reactant was led through a tube reactor heated to 70 °C to allow, if necessary, completion of the reaction. A personal computer (PC) was used for data gathering and system control.

When the effluent flow controller (after the second autoclave) was set to the expected flow rate, the levels in the two autoclaves did continuously change. At the same time, the two pumps controlled by the PC fed the catalyst/reactant solution from the feed glass tank into the first autoclave and the effluent from the first autoclave into the second autoclave, respectively, where they reacted with the hydrogen from the hydrogen feed system. The temperature and pressure in the two autoclaves was easily set independently. During operation, the temperature, pressure, rpm, liquid level, H_2 and effluent flow rate, and their total integral values were recorded on line and controlled through a PC data gathering and control system.

On the basis of the simulation, a series of continuous experiments were carried out in a CSTR system consisting of two 380 mL autoclaves. The results (analogue to Figure 2) showed that the simulated and experimental data agreed well with each other. This suggests that the model would not need any further modification and could thus be used directly for scale-up. Therefore, two 1.5 L autoclaves were installed instead of the 380 mL autoclaves in the CSTR reactor system and used to produce (*S*)-acid **2**.

The optimized production conditions for (*S*)-acid **2** were selected as follows: temperature = 30 °C, pressure = 270 bar, concentration of unsaturated acid in MeOH and NEt_3 = 30 wt% (NEt_3/unsaturated acid = 0.6 mol equiv), catalyst $Ru(OAc)_2$((*R*)-MeOBIPHEP) $S/C = 1000$, hydrogen 60, flow rate Vo = 14 mL/min, liquid level L1 = L2 = 1.05 L, rpm = 1200 L/min, temperature of spiral after (2) autoclave $T_{\text{spiral}} = 70$ °C (spiral length = 2 m, $\phi = {}^1/_8$ in.).

Under these conditions, 38.8 kg of unsaturated acid **1** were hydrogenated in 168 h of continuous operation. A constant conversion of 99.8% with 93.4% ee was observed.

5. Conclusion

It has been demonstrated that a continuous metal complex catalyzed homogeneous enantioselective hydrogenation under high pressure is in this particular case not only feasible but also a very attractive possibility. Compared to a batch mode, the major advantage of the CSTR reactor system lies in the large reduction in total reactor volume and as a consequence in considerably higher safety, lower investment cost, and easily controllable temperature. In a batch process, especially at the beginning of the reaction, when the reaction heat is greater, the temperature control may be difficult. In this example, higher temperatures would have a negative influence on the ee of the product; an exact control of the temperature is therefore important. Under the best reaction conditions using such a CSTR system, one may achieve a space-time yield of 5.0 kg/L/day for the continuous hydrogenation of 2-(4-fluorophenyl)-3-methylbut-2-enoic acid (**1**) to produce (*S*)-acid **2**.

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