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Continuous Reactor Technology for Ketal Formation: An Improved Synthesis of Solketal

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Abstract:
The development of a fully continuous process for the synthesis of solketal (4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane) is described. The use of a heterogeneous catalyst, recycle of unreacted starting material, elimination of the need for an entraining solvent, and purification of the product in situ all afford improvements over existing processes. Data generated in model reactions is used to prove the applicability of the process to a counter-current distillation reactor design, and to compute the operating parameters of the reactor.

Introduction

Solketal (**3**, Scheme 1) is a versatile solvent and plasticiser, also used as a solubilising and suspending agent in pharmaceutical preparations.[1] Solketal is formed from glycerol (**2**) and acetone (**1**) in an equilibrium reaction (Scheme 1), which typifies the formation of acetals and ketals from alcohols and carbonyl compounds.[2] In a traditional batch process, the reaction is catalysed by a homogeneous acid catalyst (sulfuric or *p*-toluenesulfonic acid).[3] The equilibrium constant for ketalization is unfavourable, and the equilibrium has to be driven to the right by the use of a large excess of one of the reagents (acetone) or by the removal of water of reaction. This process suffers from the inefficiencies inherent in all batch processing (poor mass transfer, high down-time, significant by-product formation, intensive labour requirements); plus the cost of separating the product from the homogeneous catalyst and excess reagent. These problems have been addressed in the development of an improved, continuous process for the production of solketal.

Continuous process flowsheets have been previously proposed for the formation of solketal. Typically in these, the equilibrium reaction is driven by the continuous removal of water from the reaction mixture, usually by the use of an entrainer.[4] The low boiling point of the acetone reagent demands the use of an entrainer having a still lower boiling point; chloroform and petroleum ether[4a,b,5] have been employed. The use of an entrainer is undesirable from the aspect of product purity and (particularly in the case of chloroform) for environmental reasons; thus, the use of excess acetone as a stripping agent for water removal has been previously proposed.[6]

The use of a heterogeneous acidic catalyst would facilitate separation from the final reaction mixture. Such catalysts have been used in batch processes,[4a,b] and in continuous fixed-bed processes.[4d] Although offering improvements over the historical batch process, none of the continuous processes to be found in the literature offers an ideal process for the synthesis of solketal. It was proposed that the counter-current reaction column developed and patented by Kvaerner Process Technology[7,8] for esterification processes could be utilised in an extremely efficient synthesis of acetals; the parameters for this process have been established.

Reactor Design

The reaction column was originally developed for the commercial-scale production of methyl esters of fatty acids and has subsequently been applied to a range of other esterification reactions, including the esterification of monomethyl maleate to dimethyl maleate as part of the process for the synthesis of 1,4-butanediol.[8] The reactor is essentially a multitray reactive distillation column with deep reaction stages containing catalyst in suspension (Figure 1). The key factors of any esterification reaction that influenced the design of the reaction column are:

1. An equilibrium reaction, which can be driven to completion by the removal of one of the products.
2. A solid catalyst (ion-exchange resin) system facilitates separation and minimises waste.
3. A nonvolatile reagent, which flows down the column.
4. A volatile reagent, which passes up the column in the vapour phase, agitating the resin.
5. A nonvolatile product, which flows down the column.
6. A volatile by-product, which is stripped out of the reaction mixture by the upwards passage of the volatile reagent.

Each reaction stage in the reaction column holds a given amount of resin catalyst and provides residence time for the reaction to occur; thus, the liquid depth is greater than on a

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(2) Schmitz, E.; Eichhorn, I. In *The Chemistry of the Ether Linkage*; Patai, S., Ed.; Interscience: New York, 1967; pp 309−351.

(3) *Organic Syntheses*; Wiley & Sons: New York, 1955; Collect. Vol. III, p 504.

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(5) Japanese Patent JP10195067A2, 1998.

(6) U.S. Patent 5,917,059, 1999.

(7) Walker, A. J. *Spec. Chem.* **1999**, *19*(8), 364.

(8) (a) U.S. Patent 5,536,856, 1996. (b) U.S. Patent 5,157,168, 1992.

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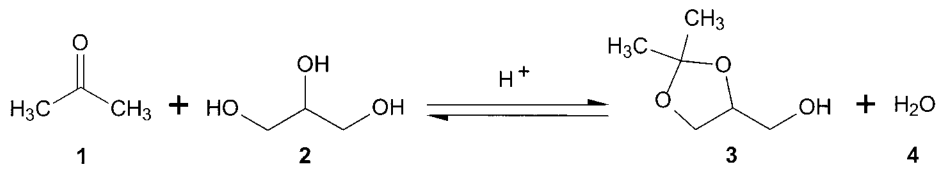
Scheme 1



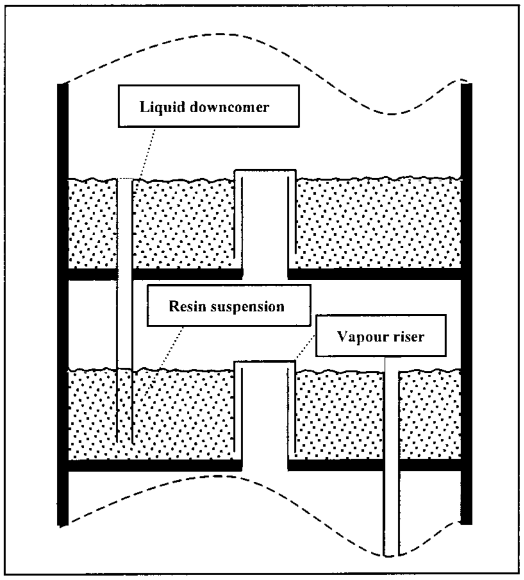


Figure 1. **Cross-section of a CCR tray.**

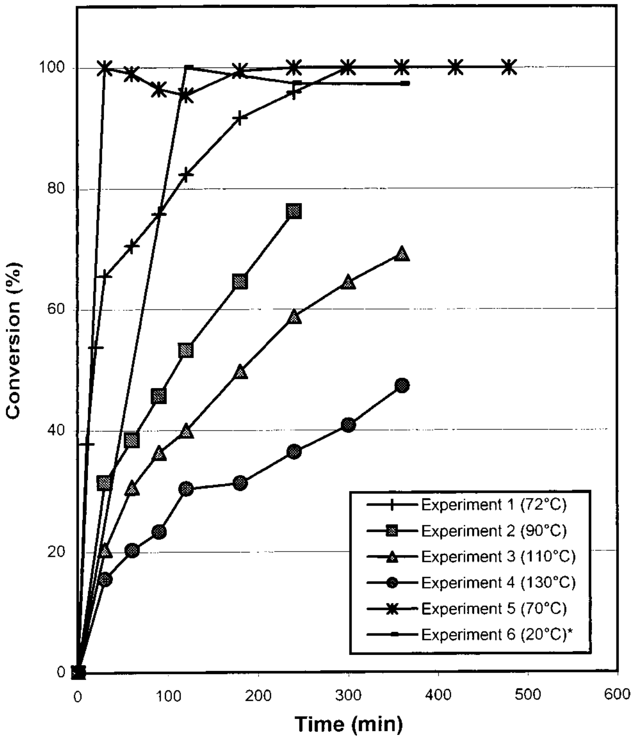


Figure 2. **Effect of reaction temperature on the conversion of glycerol over time. *Experiment 6: batch experiment, acetone: glycerol molar ratio 2:1.**

conventional distillation tray. Consequently, a proprietary tray design[8] was developed to accommodate the required liquid hold-up while retaining the fluidised catalyst within the stage. For a given reaction, reactor performance (kinetics, selectivity) and design (number of stages, internal dimensions) can be calculated from the results of small-scale tests carried out in sealed tubes and standard stirred-tank reactors.

Results and Discussion

The flowsheet concept proposed that acetone should serve three functions in the process; reactant, agent for three-phase mixing to enhance mass transfer, and stripping agent to remove water of reaction and to drive the reaction forward. In the reaction column, liquid glycerol would be fed into the top of the reactor. The simple test reactor comprised a stirred flask containing catalyst plus glycerol into which liquid acetone was fed via a dip tube. The reaction mixture was maintained at a temperature above the boiling point of acetone, and excess acetone and water of reaction were continuously distilled out. This is effectively a semi-continuous reactor (batch with respect to glycerol and solketal, continuous for acetone and water by-product).

Choice of Catalyst

Potential by-products of the process include the self-condensation products from both reagents. Ether formation by condensation of 2 mol of glycerol and aldol condensation between 2 mol of acetone both had to be minimised. A proprietary catalyst has been developed for esterification processes (fatty acid esters and dimethyl maleate) which specifically minimises ether-forming reactions, and this catalyst (a sulfonic acid-functionalised ion-exchange resin, Amberlyst DPT-1) was found to be the most efficient catalyst for the ketalisation of glycerol.

Reaction Kinetics

Initial experiments were carried out at over a range of temperatures to determine the kinetics of the reaction (Figure 2). To facilitate throughput of acetone vapour through the reaction system while avoiding the expense of constructing a reactor to handle reduced pressures, the baseline experiment (experiment 1, Figure 2) was performed at 72 °C, 15 °C above the boiling point of acetone. Quantitative conversion was achieved after 300 min. Surprisingly, increasing the reaction temperature resulted in considerably reduced conversion at 300 min (experiments 2−4). It was postulated that this was due to the decrease in the concentration of acetone present in the liquid reaction mixture (Figure 3). Consideration of the vapour pressure curve for acetone (Figure 4)[9] suggested that even a slight reduction in the reaction temperature would give a significant increase in acetone concentration of the reaction mixture, and this proved to be the case. Experiment 5, carried out at 70 °C, gave quantitative

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[9] *CRC Handbook of Chemistry and Physics*, 76th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, 1995; pp 6−82.

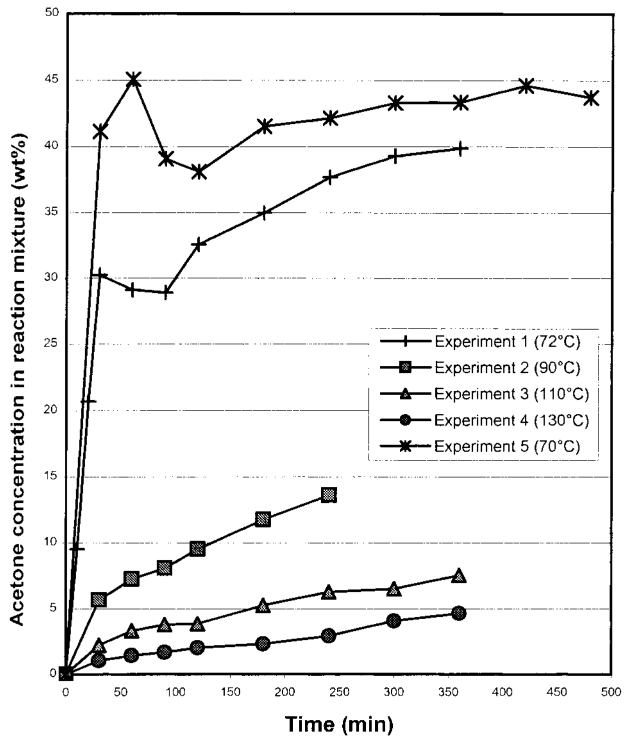


Figure 3. **Effect of reaction temperature on the acetone concentration in the reaction mixture over time.**

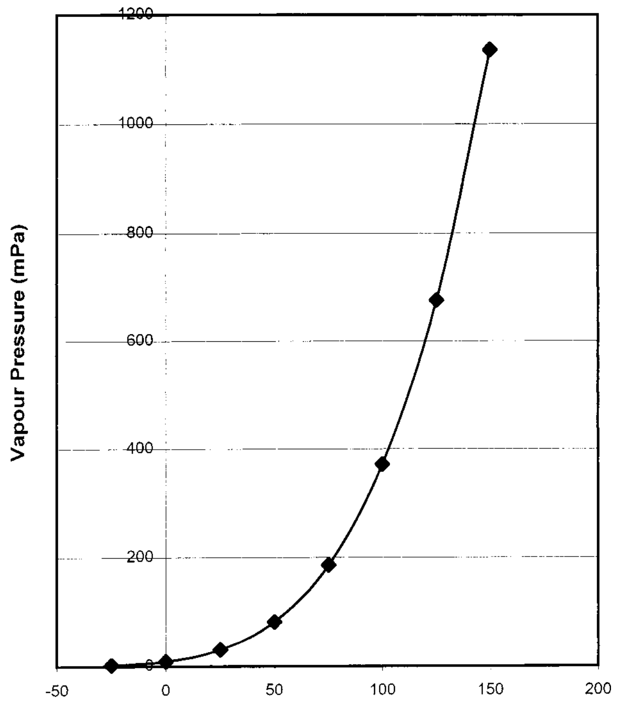


Figure 4. **Vapour pressure curve of acetone.**[9]

conversion in only 240 min. The net result is an increase in throughput, as the reduction in reaction time more than compensates for the increased dilution of the reaction mixture. Operating at a lower reaction temperature also minimises the formation of ethers (by-products from alcohol dehydration); final concentration is typically <0.1 wt %.

The high conversion in the early stages of the reaction carried out at 70 °C led us to speculate that the increased molar concentration of acetone was having a disproportionate effect on the rate of reaction towards equilibrium. A series of sealed-tube experiments were carried out to determine the equilibrium position of the reaction at 70 °C and at various acetone concentrations. The results are shown in Table 1. Using a 1:1 molar ratio of acetone to glycerol, the reaction mixture at equilibrium was found to contain 47% solketal (experiment 11), confirming results published in the literature.[4d] The resin from each of these tests was reused (without treatment) in a similar experiment (Table 1, experiments 14–16; resin from experiment 11 was used in experiment 14, etc); only a slight loss of catalytic activity was observed. A stirred-flask experiment was carried out at ambient temperature, in which a 100% mole excess of acetone was added to glycerol in the presence of Amberlyst DPT-1 resin (5 wt %), and the mixture was stirred as normal. The equilibrium concentration of solketal in the reaction mixture was confirmed to be in excess of 97% (experiment 6, Figure 2). It was difficult to determine the time taken to come to equilibrium at room temperature; glycerol and acetone are immiscible, and in the early stages of the reaction the mixture forms two phases.

Table 1. **Equilibrium composition of the reaction mixture at 70 °C**

expt	acetone:glycerol initial molar ratio	composition (wt %)			
		acetone	glycerol	solketal	water
		Fresh Ion-Exchange Resin			
11	1:1	23.8	22.2	46.5	5.4
12	2:1	45.5	0.4	46.1	6.4
13	3:1	53.2	0.2	38.8	6.5
		Recycled Ion-Exchange Resin			
14	1:1	29.1	18.4	43.7	5.4
15	2:1	52.5	1.5	39.1	5.4
16	3:1	61.7	<0.1	32.4	4.5

From these experiments at ambient pressure, an optimum acetone:glycerol molar ratio of 2:1 was determined, this being the ratio above which minimal improvement in glycerol conversion was obtained. The optimum reaction temperature corresponding to the optimum acetone:glycerol ratio at ambient pressure was thus determined to be 70 °C (representing a liquid acetone concentration of 43–45 wt %).

A series of experiments were carried out to determine the optimum catalyst loading; the results are depicted in Figure 5. The optimum level of 5 wt % with respect to glycerol was used as the standard when establishing the other parameters.

Use of Wet Starting Material

A considerable saving in the cost of the raw materials for this process can be made if wet glycerol is used (glycerol is hygroscopic).[5] To this effect, work was carried out to determine the most effective reaction parameters if solketal were to be synthesised in a reaction column from glycerol containing 20 wt % water (Figure 6). Carrying out the reaction at 70 °C (experiment 9) resulted in considerably decreased conversion at 300 min (72%, cf. 100% when using dry glycerol). However, utilising a ramped reaction temper-

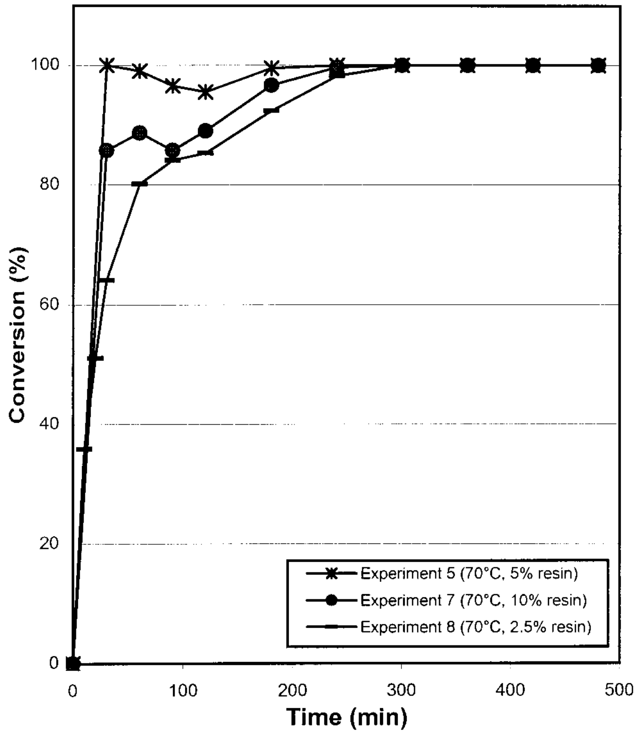


Figure 5. **Effect of catalyst loading on the conversion of glycerol over time.**

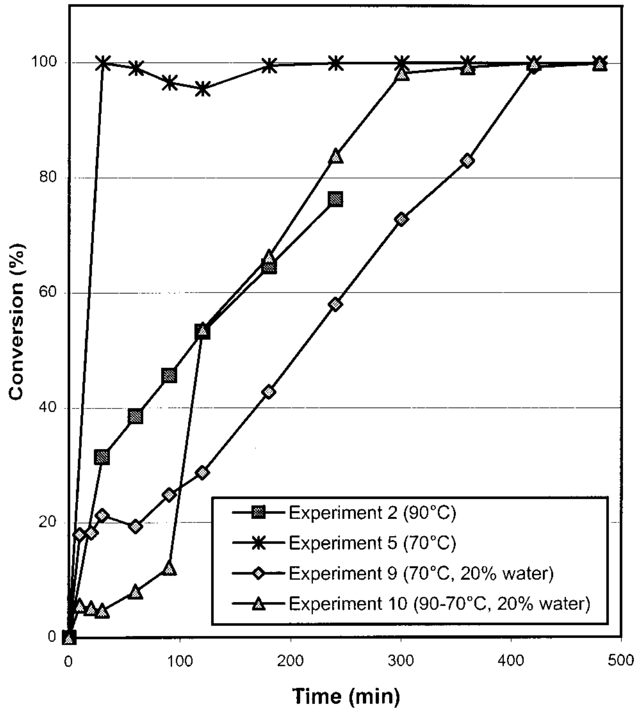


Figure 6. **Comparison of glycerol conversion rates starting with wet and dry feedstocks, using different temperature profiles.**

ature profile (experiment 10), which can be readily provided in a commercial reaction column, enabled the conversion at 300 min from wet glycerol to be increased to a level (>98%) approaching that achieved using dry glycerol (experiment 5). The ramped temperature profile involved carrying out the reaction at a higher temperature (90 °C) for the first 90 min to facilitate removal of water from the reaction mixture, then decreasing the temperature to 70 °C for the remainder of the reaction to build up the liquid acetone concentration and drive the equilibrium. In a fully continuous reactor, the same effect would be achieved by varying the temperature profile through the reactor, rather than by varying it with time.

In all experiments, the reaction was found to be particularly clean. The formation of the aldol condensation product of acetone (2-hydroxy-2-methylpentan-4-one) was the only side reaction, and this by-product was present only in low concentration (<1.0 wt %).

Flowsheet Design and Reactor Profile

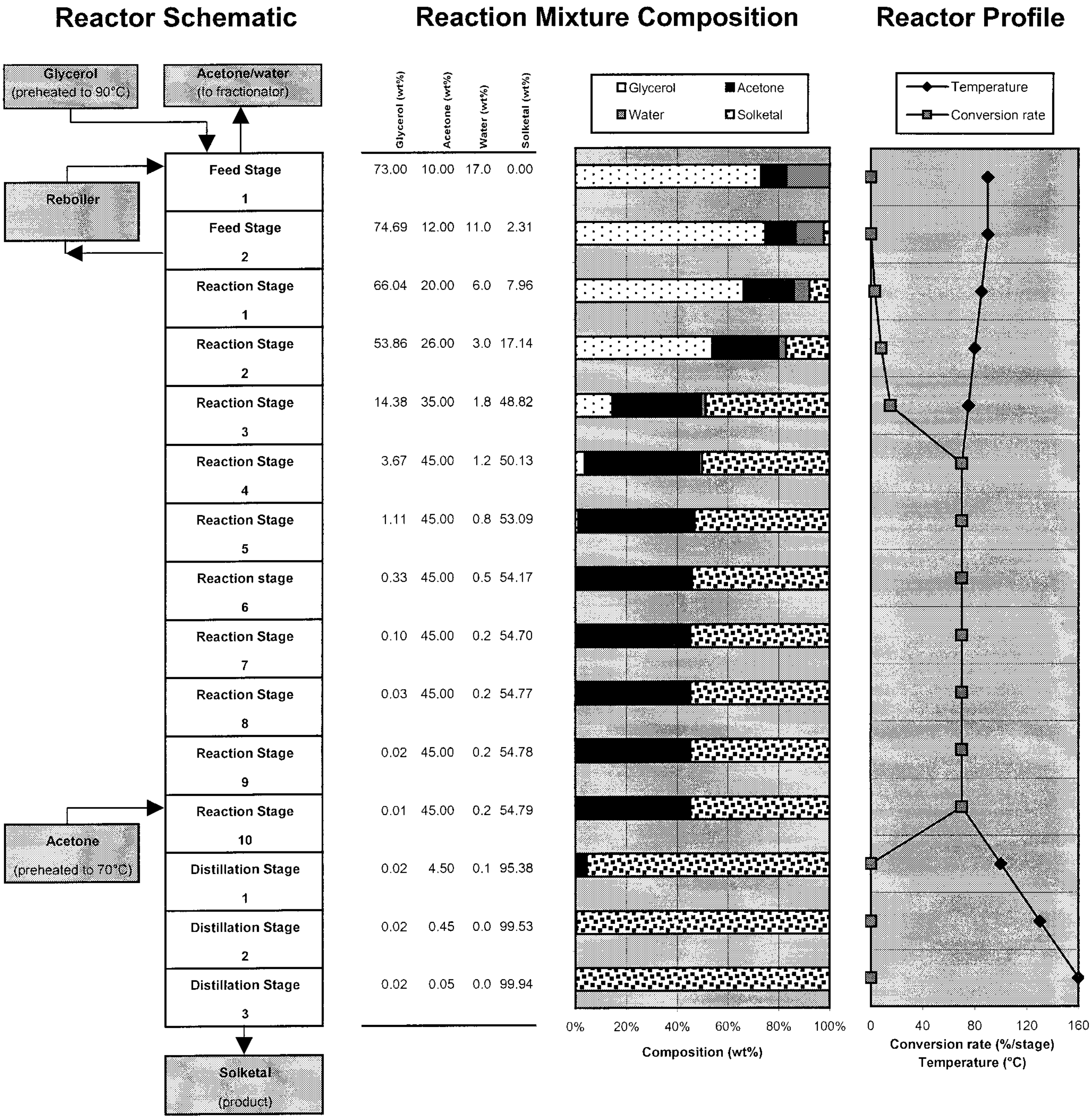
The results of the semi-continuous and sealed tube experiments were used to compute a reactor profile for the formation of solketal from a glycerol feedstock having a water concentration of 20 wt %. The reactor design (Figure 7) incorporated two high-temperature feed stages at the top of the reactor; these would operate empty of catalyst to remove water from the glycerol. The glycerol feed would be preheated and fed into feed stage 1, and a reboiler would be used to maintain feed stages 1 and 2 at 90 °C. A residence time of 30 min per stage should see water concentration reduced to 6 wt % in the first reaction stage.

The data from the laboratory experiments were used to calculate, that in a reaction column, a residence time of 30 min per stage would afford a minimum glycerol conversion of 70% per stage at 70 °C. The initial (higher) reaction stages would be constrained to operate at temperatures higher than the optimum (being directly below the feed trays) and would thus afford proportionately lower conversions. The temperature profile is set by the latent heat differences between the reactant (acetone) vapour and the product (water) vapour; heat-exchange coils on the reaction trays should not be required. It was calculated that, to give a final product purity >99.0 wt %, 10 reaction stages would be required, each affording a residence time of 30 min (at the specified 5 wt % catalyst concentration) and operating according to the temperature profile and rates of conversion depicted (Figure 7). The predicted composition of the reaction mixture on each stage is also shown in Figure 7 (formation of organic by-products has been ignored in these calculations, but by-product concentration in the final reaction tray would be expected to be <0.5 wt %). As there is a considerable difference in volatility between solketal and acetone, final product purification can be accomplished by having three distillation stages below the final reaction stage, each operating at a successively higher temperature. Residence time for the reactor as a whole is 7.5 h.

It should be emphasised that this section describes a model for a continuous commercial-scale reactor, the dimensions of which will be dependent on the product demand. For example, a reactor with an internal diameter of 6 in would afford approximately 15 kg solketal per h (120 tonnes per year).

Conclusions

The formation of solketal from glycerol and acetone is ideally suited to the reaction column reactor design, par-



	Glycerol (wt%)	Acetone (wt%)	Water (wt%)	Solketal (wt%)
Feed Stage 1	73.00	10.00	17.0	0.00
Feed Stage 2	74.69	12.00	11.0	2.31
Reaction Stage 1	66.04	20.00	6.0	7.96
Reaction Stage 2	53.86	26.00	3.0	17.14
Reaction Stage 3	14.38	35.00	1.8	48.82
Reaction Stage 4	3.67	45.00	1.2	50.13
Reaction Stage 5	1.11	45.00	0.8	53.09
Reaction stage 6	0.33	45.00	0.5	54.17
Reaction Stage 7	0.10	45.00	0.2	54.70
Reaction Stage 8	0.03	45.00	0.2	54.77
Reaction Stage 9	0.02	45.00	0.2	54.78
Reaction Stage 10	0.01	45.00	0.2	54.79
Distillation Stage 1	0.02	4.50	0.1	95.38
Distillation Stage 2	0.02	0.45	0.0	99.53
Distillation Stage 3	0.02	0.05	0.0	99.94

Figure 7. **Reactor design, operating parameters and calculated reaction mixture composition for continuous solketal production.**

ticularly when there is an extra need to drive the equilibrium (i.e., if water is present in the glycerol starting material). Features of the reaction column offering improvement over existing processes include:

1. Heterogeneous catalyst facilitates separation from product.

2. Stripping of water from the reaction mixture by entrainment drives the equilibrium.

3. Use of acetone as both reagent and entrainer simplifies product purification and improves throughput. The by-product wet acetone can be easily dried by distillation and recycled without the need for an expensive azeotrope splitter.

4. Different stages in the reaction column can be run at different temperatures. For example, if wet glycerol is used, the upper stages of the reaction column can be run at a higher temperature to drive water out of the reaction mixture. Middle and lower stages can be run at a lower temperature, driving the equilibrium further by building up the acetone concentration. Alternatively, the reactor can operate under a positive pressure, allowing acetone concentration to be increased without increasing the reaction temperature, or allowing reaction temperature and hence reaction kinetics to be increased.

5. Feeding acetone part-way up the column allows the bottom stages of the reaction column to act solely in a distillation capacity, eliminating the need for further product purification (solvent stripping).

Work is continuing on applying the reaction column reactor concept to other ketal-forming reactions (particularly acyclic ketals where the entropy of the reaction disfavours the equilibrium conversion) and to other types of reactions which meet the criteria for this type of reactor.

Experimental Section

Conversions and selectivities were determined by GC methods. GC were measured with a Perkin-Elmer Autosystem XL equipped with FID detection on a CP wax (30 m) column; data collection and evaluation were performed using Perkin-Elmer/Nelson Turbochrome 4. Products were identified by comparison with authentic standards.

Water concentrations were determined by a conventional Karl Fischer titrametric method.

All chemicals were purchased from standard sources.

Semi-continuous Reactor Experiments. Glycerol (204 g, 2.21 mol) and ion-exchange resin Amberlyst DPT-1 (10.2 g, 5 wt %) were charged to a 500 mL, four-necked flask equipped with a mechanical impeller stirrer, digital thermometer, dip-tube inlet, and total offtake distillation head. The reaction mixture was stirred (400 rpm) and warmed to the required reaction temperature. Acetone was fed continuously into the reactor via a metering pump (300 g/h) and dip-tube while the temperature of the mixture was maintained at a constant value. Any vapour was distilled off and collected by condensation. The reactor contents and distillate were sampled (0.1 mL) at 10 min intervals for 30 min, then 30 min intervals for 90 min, and 60 min intervals for a further 360 min, giving a total reaction time of 480 min.

Sealed-Tube Experiments. Glycerol (10.2 g, 110.7 mmol), acetone (6.4−19.3 g, 110.7−332.1 mmol), and ion-exchange resin Amberlyst DPT-1 (0.51 g, 5 wt %) were charged to a pressure-resistant tube. The tube was sealed and heated at 70 °C with shaking for 16 h. At the end of the reaction the mixture was decanted from the resin and analysed. The resin was recharged to the tube, and fresh glycerol and acetone were added in the same amount as previously. The experiment was repeated as before.

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