

Control of Hazardous Processes in Flow: Synthesis of 2-Nitroethanol

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After a short section of safety aspects related to 2-nitroethanol, the paper describes a powerful methodology for developing flow processes based on a proof of concept (1), an optimization and modeling analysis (2), and a long run study in a mini-plant (3). The proof of concept is the initial stage where the solubilities and concentrations are fixed, taking into account the rough kinetics with a mass transfer understanding. It is followed by a complete kinetic analysis including activation energy to model the reaction under various conditions to optimize different targets (yield not being the only driver!). The last section shows the operation of a mini-plant including a microreactor and work-up unit operations. The approach is extremely powerful as it enables the study at laboratory scale of all the features that are usually associated with a pilot plant namely: stability over time on stream, solvent recirculation, model prediction, and robustness.

Keywords: continuous flow, microreactor technology, nitromethane, 2-nitroethanol, formaldehyde, paraformaldehyde, Henry reaction, energetic compound, hazardous chemistry

1. Introduction

In the context of an alternative process toward Aliskiren [1], kg-amounts of 2(R)-isopropyl-4-nitro-propan-1-ol were required. In an organo-catalytic reaction, nitroethene and isovaleic aldehyde react smoothly and with high stereoselectivity to form 2(R)-isopropyl-4-nitro-1-aldehyde, which is subsequently reduced by sodium borohydride to furnish the desired 2(R)-isopropyl-4-nitro-propan-1-ol. Nitroethene is a highly energetic compound which has been described in the literature for a long time. The preparation and use of nitroethene in the laboratory require adequate safety precautions and already the synthesis of gram-amounts is challenging. Typically, nitroethene is prepared and used in a diluted solution. For the generation of larger amounts of this compound, the application of continuous technologies is imperative. So far, all published laboratory protocols for the preparation of nitroethene have described it in batch mode. Therefore, we have evaluated several synthesis routes for its suitability in a continuous mode and finally selected a sequence starting from formaldehyde and nitromethane. The resulting 2-nitroethanol is dehydrated with the aid of dehydration agents to directly form nitroethene. This paper describes the preparation of 2-nitroethanol in a continuous mode as a foundation for further engineering and scale-up into a pilot plant. The generation and use of nitroethene and its transformation into 2(R)-isopropyl-4-nitro-propan-1-ol will be described in subsequent papers.

Most aldehydes react conventionally with nitroalkanes in the presence of a base to the next higher homologs (Scheme 1). The condensation of formaldehyde (**1**) with nitromethane (**2**), for example, affords nitroalcohols (**3**, **4**, and **5**). Due to the explosive properties of lower nitroalkanes, a synthesis of nitro derivatives by a continuous process is favorable not only to study the reaction parameters but also to produce safely larger amounts of nitro compounds. Microreactors have been successfully used for the synthesis of explosive substances, such as nitroglycerine [2]. The reaction of nitromethane with formaldehyde is not hazardous, but the removal of excess nitromethane as well as the isolation of a low molecular weight nitro derivative requires special precautions. The consequences of a runaway have to be avoided by all means in all the unit operations of the process.

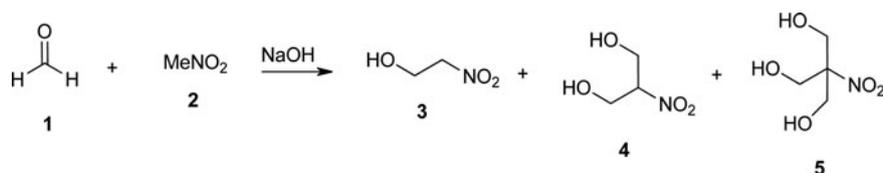
Continuous flow (CF) and microreactor technology (MRT) have demonstrated a clear advantage for rapid and exothermic reactions, where a tight control of the process parameters is required, the so-called Type A and Type B reactions [3–5]. CF is also of advantage for slower reactions (Type C) when particular hazards are associated with the process or when the reaction requires extreme conditions such as high temperature and/or high pressure [6,7]. Contrary to a batch process, the optimization of such reactions in CF is attractive as conditions can be selected in a wider domain. The outcome of a CF optimization study is often a highly intensified process at increased reaction rate; the Type C reaction becomes Type B. Thus, CF/MRT enables the rapid development of such processes under intense mixing, excellent heat transfer, and optimal residence time in a modular and high throughput fashion [8,9]. This work will show the overall optimization strategy including a proof of concept in flow, a modeling analysis, and a long run study in a mini-plant to ascertain process robustness and stability. To begin with, the first section will address some important safety aspects.

2. Results and Discussion

Among the numerous published methods [10–14] for the preparation of 2-nitroethanol, the method from Noland [15] has been chosen since this protocol can easily be carried out in a continuous manner (Scheme 1): following this procedure, formaldehyde (**1**) is converted in a typical Henry Reaction with nitromethane (**2**) and catalytical amount of base (e.g., NaOH) to 2-nitroethanol (**3**). A drawback of this reaction is the fact that the formed product (**3**) can further react with formaldehyde forming by-products **4** or **5**. Gorski [19] has shown that the molar ratio of nitromethane (**2**) to formaldehyde (**1**) (*N/F* ratio) has a significant impact on the selectivity of the reaction. The more nitromethane is used, the less by-products are formed. With 50 equivalents of nitromethane, 2-nitroethanol was formed in 88% selectivity; with 100 equivalents of nitromethane, a selectivity of 93% could be achieved.

2.1. Safety Aspects. Since nitromethane (**2**) has an explosion heat of 4974 kJ/kg and a detonation velocity as high as 6210 m/s it has to be handled as an explosive material (for comparison: nitroglycerine has an explosion heat of 6770 kJ/kg and a

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Scheme 1. Henry Reaction of formaldehyde (**1**) with nitromethane (**2**) to yield 2-nitroethanol (**3**), **4**, and **5**.

detonation velocity of 7600 m/s) [16]. However, compared to other explosive materials, **2** is very stable under normal conditions, and shipment is allowed in thin-walled drums of a maximum of 200 L that would rupture readily in case of accident to avoid pressure buildup. Surprisingly, in such circumstances, **2** will not detonate and will instead burn like a flammable liquid.

Detailed safety analysis in cooperation with the Swiss Institute of Safety & Security has shown that 2-nitroethanol (**3**) behaves similarly to **2**. A typical DSC for **3** is depicted in Figure 1. Two exotherms with onset temperatures at 164 °C and 219 °C, respectively, have been observed. The 2nd exotherm is associated with a huge rise in pressure (>200 bar/min). The overall decomposition energy was estimated to be 3400 kJ/kg and, fortunately, **3** has not demonstrated shock-sensitive properties. However, compared to **2**, the lower onset temperature was measured showing that **3** is less stable at higher temperatures than **2**.

The aforementioned properties are based on the measurements of pure substances. Performing the reaction in basic conditions or removing nitromethane from a basic reaction mixture might have severe influence on the stability of the residue (crude nitroethanol). Within the risk assessment, a large number of measurements were implemented even at laboratory scale and the following five are of utmost importance: (1) ensure that no pressure buildup can occur at any location of the process setup; (2) use of a microreactor during process development to minimize volume and flow rate and ensure excellent cooling at any location (in case of unexpected runaway); (3) the imperative use of a film distillation column for **2** to have a minimal holdup of reaction mixture at higher temperatures; (4) the control of acidic conditions before distillation (avoid distillation under basic conditions by all means!); and (5) no rectification of **3** allowed at any stage.

It is important to mention that the objective of this work is not to describe the risk assessment in detail; it has been performed by a specialized team including external consultants. Thus, this work shall not be taken as a base of a risk assessment for those who are willing to work with nitromethane/2-nitroethanol or other substances with (potential) explosive properties.

2.2. Proof of Concept. The key activities at the proof of concept stage can be summarized as follows:

- Determination of feed/product solubility in various solvents at different temperatures (lower temperature range is often critical);
- Determination of reaction class: Types A, B, and C, namely, the qualitative kinetics [17];
- Basic understanding of key parameters: temperature, N/F ratio, and type and amount of base;
- Flow rate variations at constant residence time to study mixing influence (if required) [18].

The first objective is to transfer the batch process into flow. Performing reactions in flow means that all reagents, intermediates, and products should be soluble in the reaction media in order to avoid plugging of the microreactor. Since paraformaldehyde is a solid, it has to be depolymerized prior to

introduction into the flow system. Thus, Feed-1 with a typical composition of paraformaldehyde (40.0 wt%), KOH (3.0 wt%), and methanol (57.0 wt%) leads to a clear homogenous solution. The use of methanol was not impeding the reaction; however, it influenced salt solubility and required attention during recycling of nitromethane (vide infra). Feed-2 is a pure nitromethane used as a reagent and solvent.

The basic reaction kinetics are depicted in Figure 2 at different catalyst concentrations. The reaction is rather fast with ca. 50 % conversion after 25 s; a typical Type B reaction [3]. Higher catalyst concentrations increase the reaction rate and the selectivity decreases at longer residence since more by-products are formed with time (Scheme 1).

In order to analyze whether a factor has an influence on the reaction selectivity, it is plotted as a function of conversion as shown in Figure 3. From these experiments, it can be concluded that the temperature has no influence on the selectivity. Higher amounts of **2** afforded **3** in much higher selectivity. This observation is in agreement with previously published data [19]. In addition, it could be shown that the catalyst concentration and the type of base do not have an influence on the selectivity (results not shown here). In conclusion, the N/F ratio was the only factor strongly influencing the selectivity. A higher N/F ratio increased selectivity toward **3**, particularly at high conversion. In Figure 3, by extrapolation, the curve to 0% conversion, one can observe a selectivity close to 100% which is a good indication that the reaction is truly controlled by the kinetics and not by the mass transfer regime (mixing process).

Although mixing limitations are not expected in a microreactor (Type B reaction), a mixing study was undertaken since the initial reaction rate was rather high (see K_1 vide infra) by varying the flow rate and keeping all other parameters constant (Figure 4). The residence time was kept constant by increasing the reaction volume with additional reactor plates. For the experiments, the KOH/1 molar ratio was kept high to favor more severe reaction conditions. Indeed, the yield was quite constant, and no correlation between the yield and the flow rate was observed (R^2 close to zero). In case of mixing constrains, an increase of yield at higher flow rate would have been expected [18]. Under such circumstances, Figure 4 also nicely depicts the reproducibility of the reaction at a defined experimental condition.

2.3. Optimization and Modeling. Depending on the type of reaction (A or B), the reaction optimization is performed differently. For a Type A reaction, a design of experiments to obtain a response surface modeling based on 3–4 key factors would have been the strategy of choice. For a Type B reaction, a complete kinetic study of the reaction including activation energy to enable reactor and process modeling is beneficial. In order to study the reaction of formaldehyde with nitromethane, three factors have to be considered: residence time, temperature, and of course the N/F ratio. Catalyst concentration was kept low to avoid the handling of hazardous waste at a later stage (K_2SO_4 salts wetted with nitromethane, vide infra).

Figures 5 and 6 visualize the quality of the model obtained for conversion and selectivity, respectively. The model is rather simple and is based on four key parameters: k_1 , k_2 , k_3 , and E_a . The model was fitted by a combination of Excel and Matlab

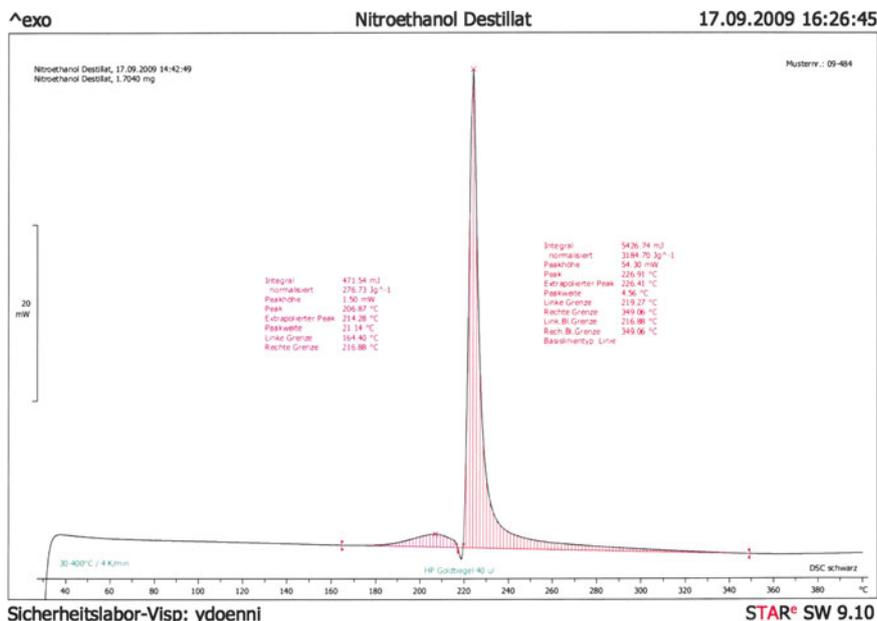


Figure 1. Differential scanning calorimetry (DSC) of pure 2-nitroethanol (3)

using the Excel solver to semi-automatically fit the parameters and Matlab for handling the differential equations. With four parameters only, it was possible to obtain an excellent model ($R^2=0.994$) which lead consequently to an excellent predictability. The model is summarized as follows in the following rate Eq. (1):

$$r_3 = [K_1 C_1 C_2 - K_2 C_1 C_3] \times a; r_{4,5} = [K_2 C_1 C_3] \times a; \frac{da}{dt} = k_3 a \quad (1)$$

where K_1 and K_2 are linked via the same activation energy (E_a) as depicted in Eq. (2):

$$K_1 = k_1 e^{-\frac{E_a}{RT}}; K_2 = k_2 e^{-\frac{E_a}{RT}} \quad (2)$$

where r is the reaction rate in mol/L/s, C is the concentration in mol/L, and the subscript number indicating the compound that is formed (in bold). The value of K_1 at a temperature (T) of 293 K (20 °C) is high (0.026 L/mol/s), and it is interesting to observe a k_2/k_1 ratio of 8.0, meaning that the side products formation (4 and 5 taken as a lump sum) are favored over 3. As a consequence, a very high N/F ratio is required to lead to good yields. The parameter k_3 (38 s⁻¹) is an additional term that was added to the model to take into account a form of catalyst

deactivation (KOH deactivation). Indeed, the reaction is very rapid at the beginning, and a strong curvature is observed during its progression (Figure 5). The deactivation equation was a pragmatic approach to model this effect and more effective than considering higher reaction orders. The initial catalytic activity was considered as unity ($a=1$, no units). Finally, the activation energy was moderate with a value of 55 kJ/mol.

The optimization cannot be based on solely getting the highest yield which would lead to an infinite N/F ratio. The model predicts yields over 80 % for N/F ratios higher than 40. The reaction optimization was based on model and process simulations, including energy consideration (evaporation and recycling of 2), safety constrains, waste minimization, and reactor costs. Thus, for the operation of the mini-plant at kg-scale, it was decided to work under the following conditions:

- A residence time to enable conversion higher than 90% as 1 cannot be recycled easily.
- To operate at the highest temperature allowed by the safety department. At this stage, it was 40 °C, and it is worth to mention that such a limit can be eventually

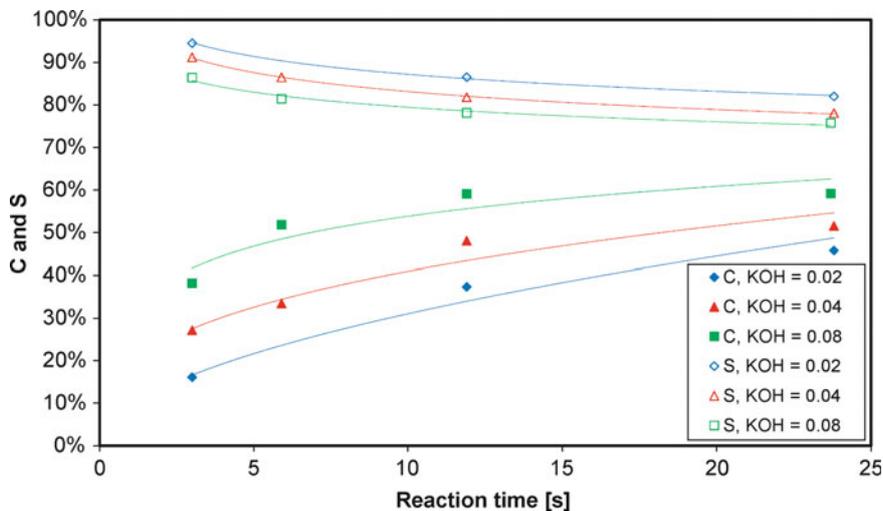


Figure 2. Basic reaction kinetics at different catalyst concentrations (in mol of KOH per mol of 1), a temperature of 20 °C, and a N/F ratio of 9. Conversion (C) and selectivity (S)

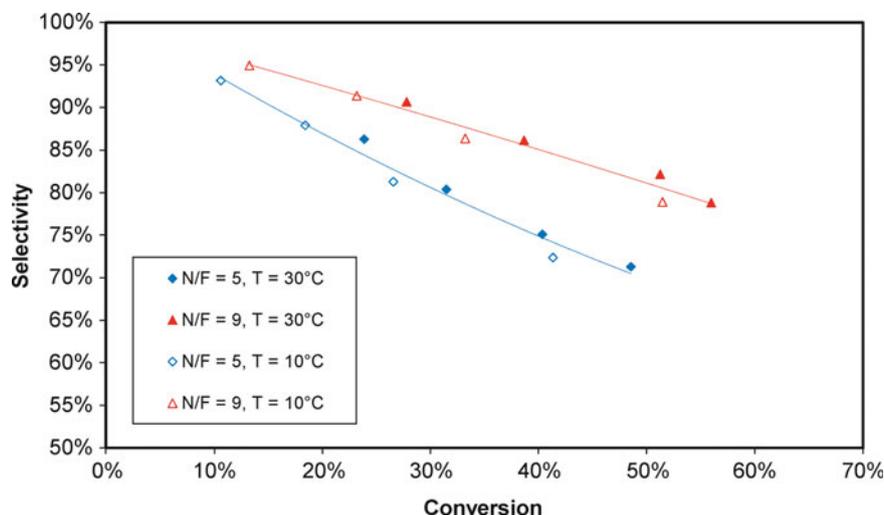


Figure 3. Selectivity as a function of conversion to analyze the effect of the N/F ratio, the temperature, and the residence times at a KOH/1 molar ratio of 0.04

extended when hazard understandings are improved. A higher temperature means also a smaller reaction volume decreasing the investment costs for the microreactor (gain of volume is expensive!).

To operate with a high N/F ratio between 20 and 80, preferably between 60 and 80 and drastically increase reaction selectivity/yield. A high purity of **3** is a must for the synthesis of nitroethene, and due to safety considerations, a rectification of **3** was not considered to be feasible. Key issue was to demonstrate an effective recirculation of **2** to make the process economically attractive. Energy costs remained moderate even at such high N/F ratio.

2.4. Long Run Study in a Mini-Plant. The overall process that was investigated in this work is presented in Figure 7. The figure shows a mini-plant setup build in a laboratory environment which includes reaction and workup unit operations. The plant can be operated to mimic a full CF process on large scale embracing solvent recycling via distillation. It shows the power of combining a microreactor (MR) with a mini-plant setup such as a continuous-stirred tank reactor (CSTR), a small filter (FIL), and a wiped film distillation column (DISTILLATION).

The reaction was performed in MR with a residence of few minutes as depicted in the next figures. Once the reaction was

completed the reaction mixture was acidified with concentrated H_2SO_4 in CSTR. In terms of safety, this acidification is really crucial since a removal of nitromethane from a basic reaction mixture could result in an explosion. In order to be on a safe side, an additional pH sensor was added. CSTR had to cope with the precipitation of a salt (K_2SO_4), which could be removed in-line, by FIL. This acid-base reaction is a classical Type A reaction, and CSTR was the most appropriate reactor to deal with the solid formed. The final step of the process was achieved via DISTILLATION to remove **2** via a short residence time (small hold-up) at higher temperature ($70\text{ }^\circ\text{C}$) and vacuum. **2** could be condensed and recycled back in the process reducing drastically its hold-up in the laboratory. Crude **3** could be produced in fractions at the bottom of the distillation column. Figure 8 is a picture visualization of the overall CF process.

One of the main goals of a mini-plant operation is to study the long-term stability of a process. The stability is shown in Figure 9 where factors, such as pressure, temperature, and flow rate, are plotted over the time on stream. The sharp line disruptions were caused by short interruption periods where vacuum was broken to allow removal of the product and recycling of **2**. During the long run, a constant pressure increase was observed with a pressure of ca. 4 bar after 8 h of operations. This clearly shows that the given process is not stable over time and will lead to plugging. Fortunately, performing the reaction

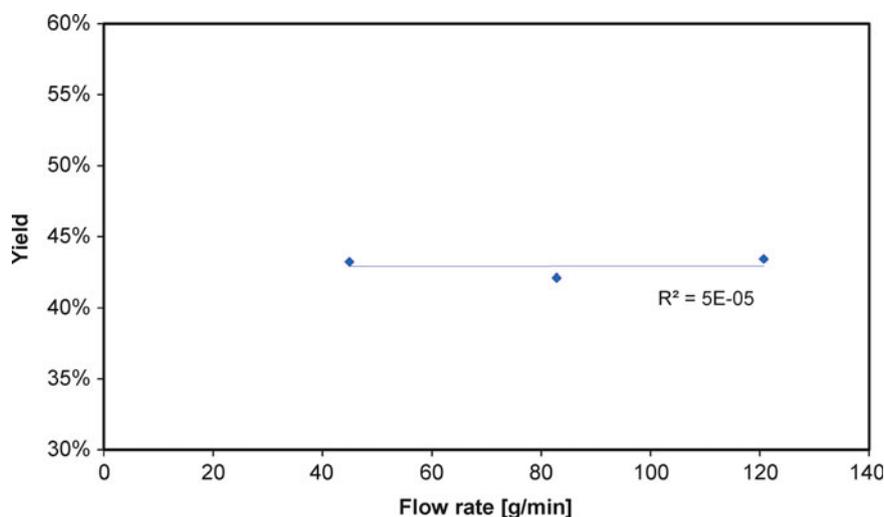


Figure 4. Yield as a function of the flow rate under a constant residence time of 7 seconds at a N/F ratio of 9 and a KOH/1 molar ratio of 0.08

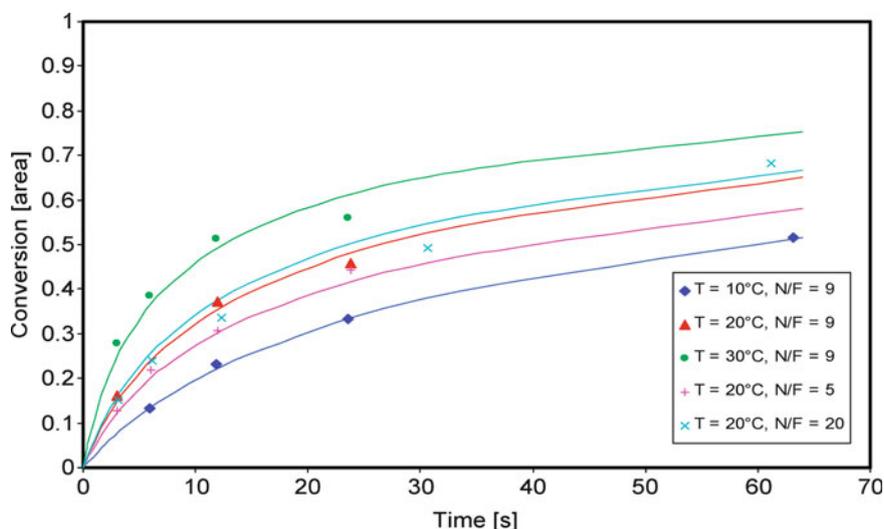


Figure 5. Conversion as a function of residence time at 3 different temperatures and different N/F ratios (KOH/1 ratio of 0.02). The points are the experimental data and the lines the modeling results

with freshly recycled **2** did not show this tendency to form a precipitation. Based on this finding, commercially available **2** was always distilled prior to use. At this stage, it is worth to mention that the microreactor is a unique tool to mimic what would potentially occur in a large-scale unit and shed light on any potential problems.

The yield of the long run studies are summarized in Figure 10 (N/F ratio of 40). As expected, the temperature and the residence time did not have a big influence on the yield at high conversions (vide supra). The overall yield for 2-nitroethanol was around 82% which is lower than expected (vide infra). When freshly distilled nitromethane is used, the yield is even lower since the distillation of **2** also favors some stripping of **3**, which is counted as loss unless **2** is recirculated. The analytical results show that 7% of **3** is effectively lost in **2** at an N/F ratio of 40. In general, the higher the N/F ratio, the higher are the losses. The mini-plant operation allows a real simulation of the recirculation effect which is very often only possible at pilot scale with large amount of material. Another fundamental aspect of the recirculation assessment is the accumulation of potential volatile compounds. Indeed this is a real problem with methanol that is introduced in Feed-1 to solubilize **1**. However, this problem was overcome in this study by a dual condensation strategy at two temperature

levels using two different product traps; with the colder trap to catch methanol. Under such conditions, the accumulation of volatile side products was not observed in **2** and a “classical” purge of the recycled stream was not required.

The reaction selectivity is depicted in Figure 11 where it is plotted as a function of the time on stream at three different N/F ratios. The selectivity increased with the N/F ratio being ca. 82% at 20, 88% at 40, and 93% at 80. However, a lower selectivity was obtained with a longer residence time, which is expected since the formed product can undergo further reaction with **1** forming the two side products **4** and **5**.

The situation is, however, a little bit different when considering the yield (Figure 12). With an N/F ratio of 20, the experimental yield was around 72%, while a yield of ca. 78% was expected. Even by increasing the residence time to 5.4 min, the yield only increased slightly; with a residence time of 2.8 min the conversion was already high. Surprisingly, significantly lower yield was observed for an N/F ratio of 80 at a residence time of 5.7 min. Higher yields could be achieved by doubling the residence time (>11 min). However, the obtained yield was again lower than expected (average 88% instead of a possible 94% based on selectivity at high conversion). This difference can be explained by a rather obvious reason: since

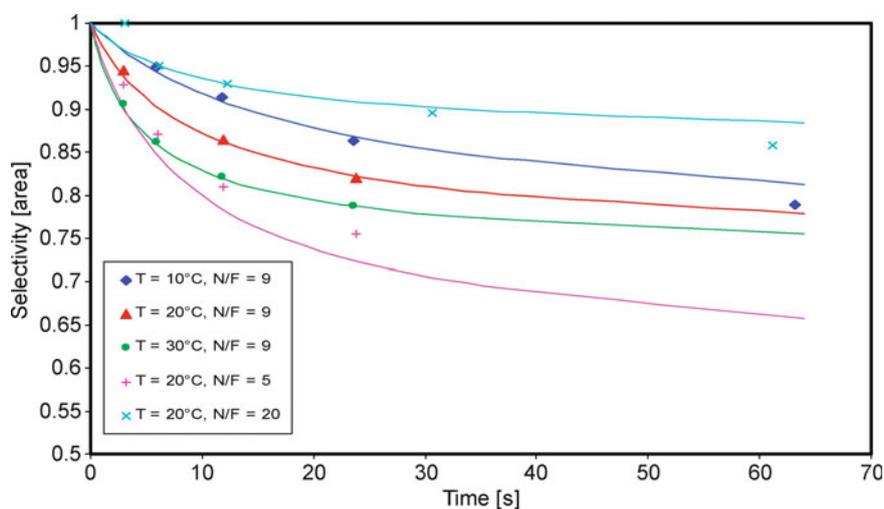


Figure 6. Selectivity as a function of residence time at 3 different temperatures and different N/F ratios (KOH/1 ratio of 0.02). The points are the experimental data and the lines the modeling results

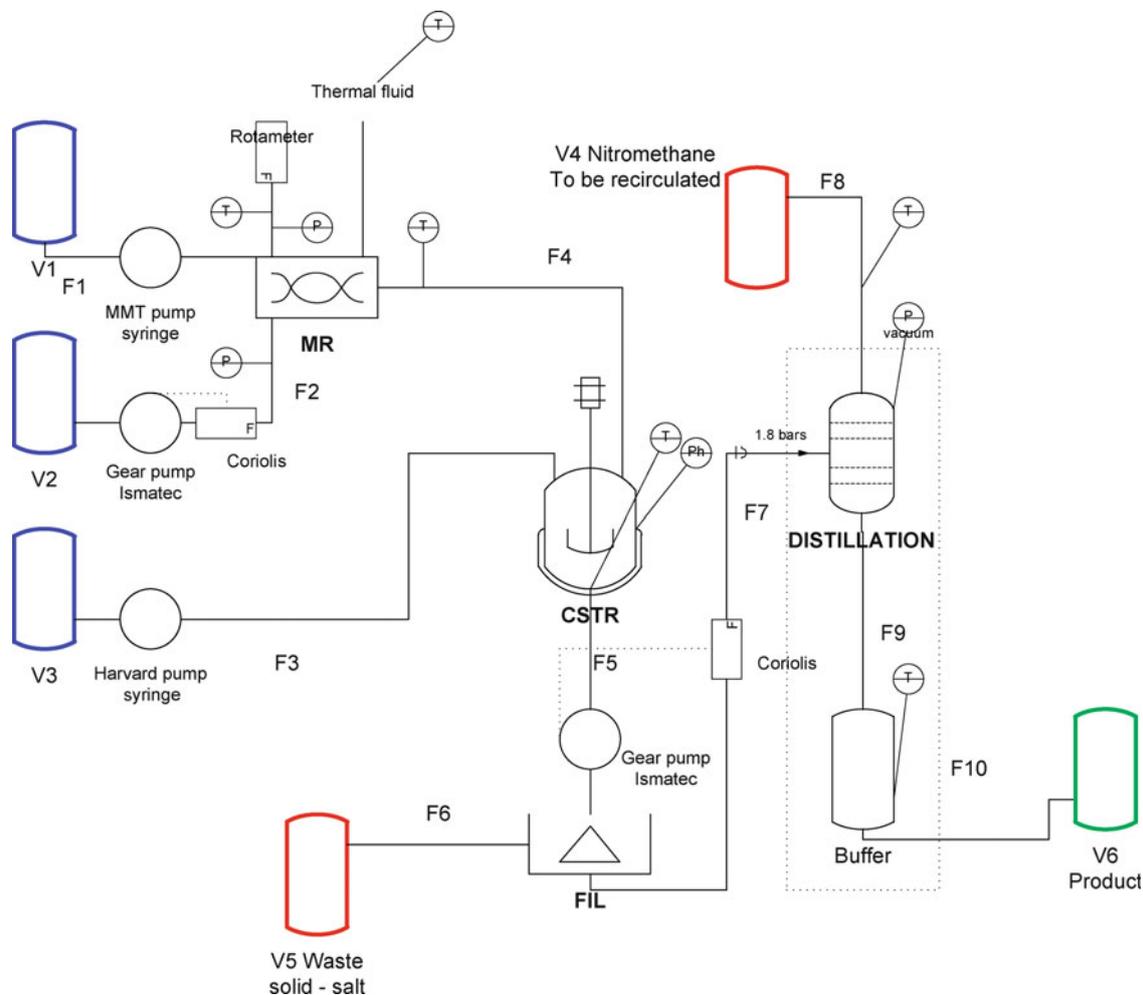


Figure 7. Process flow diagram of the mini-plant including reaction and work-up unit operations

1 is rather volatile, it escaped from Feed-1. Therefore, a cooling of Feed-1 was necessary to minimize losses. Thus, under such conditions ($N/F=80$), crude 2-nitroethanol was obtained with an average yield of 93% and an HPLC purity of 94 area%. This crude material was used without further purification for the synthesis of nitroethene. In total, more than 5 kg of 2-nitroethanol were produced by the mini-plant.

Concerning the significant longer residence times to reach high conversion for an N/F ratio of 80, the reaction kinetics were surprisingly variable at such a high N/F ratio. A repeated

run (Figure 12) with a residence time of 5.6 min gave a different trend than the initial experiment. This result can be caused by the following two problems: (1) some impurities present in **2** (particularly in non-distilled) and (2) a deactivation pathway where a chemical reaction between KOH and **2** was taking place. Indeed, this deactivation pathway was taken into account empirically in the reaction model. A high N/F ratio also means a lower concentration of KOH in **2**, leaving KOH more exposed to such phenomenon. Finally, the selectivity and yield were quite consistent when high conversions were achieved.

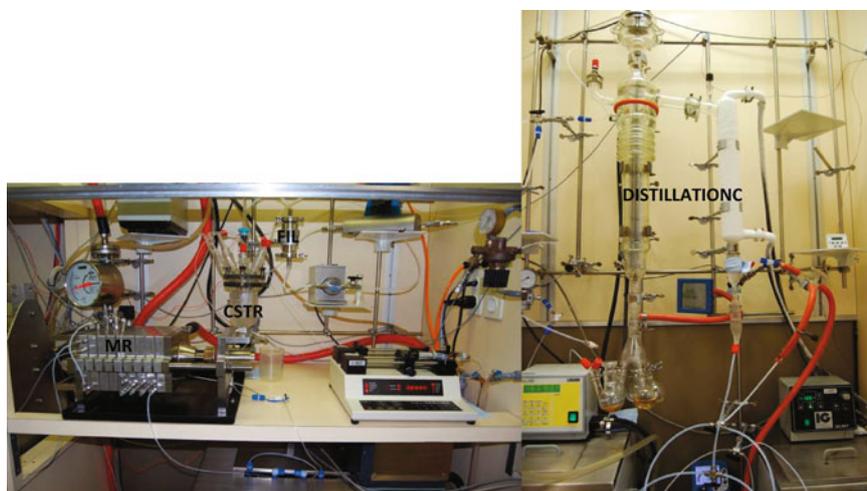


Figure 8. Picture of the mini-plant process as schematically depicted in Figure 7 with its key unit operations in bold

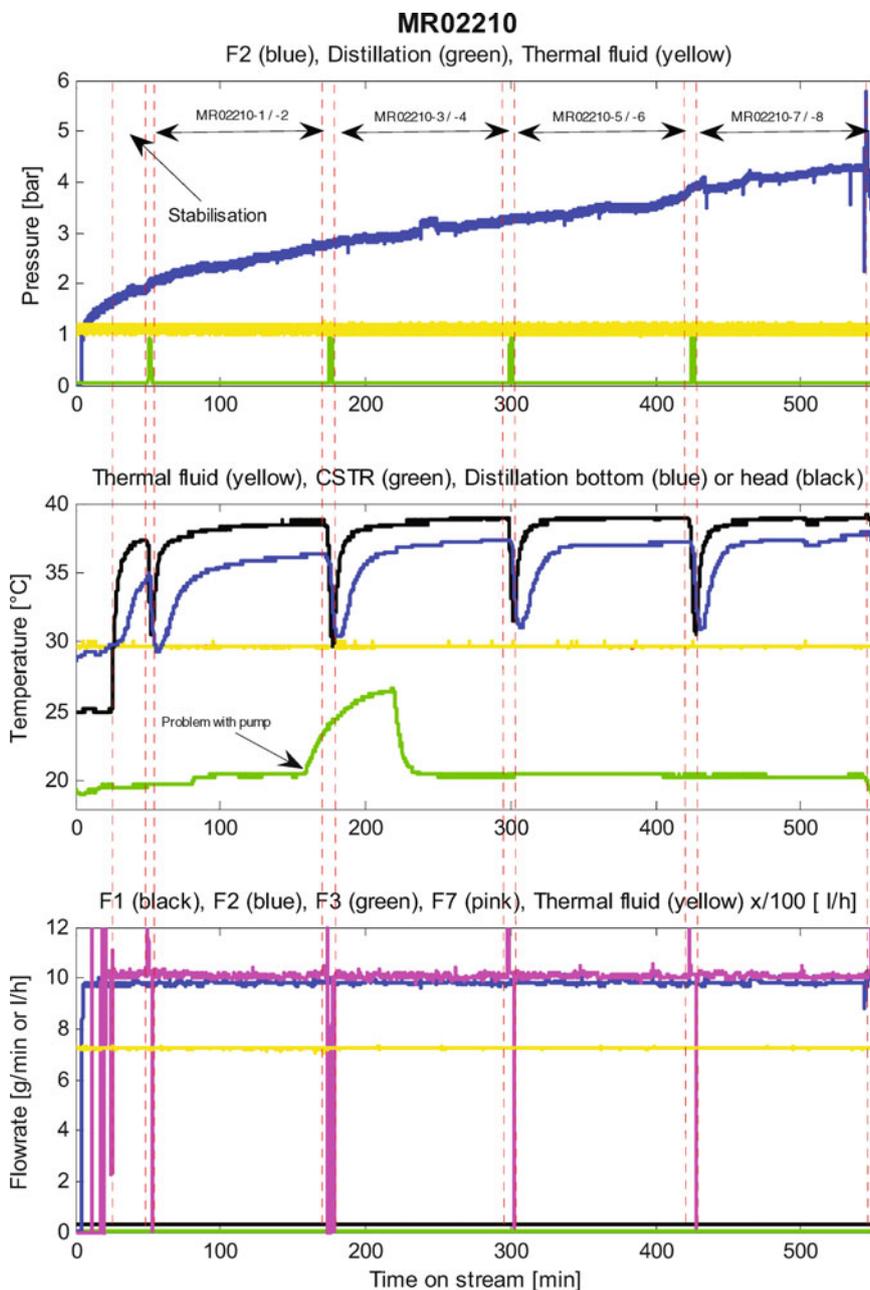


Figure 9. Long-term stability of the mini-plant operation observed via factors such as pressure, temperature, and flow rate

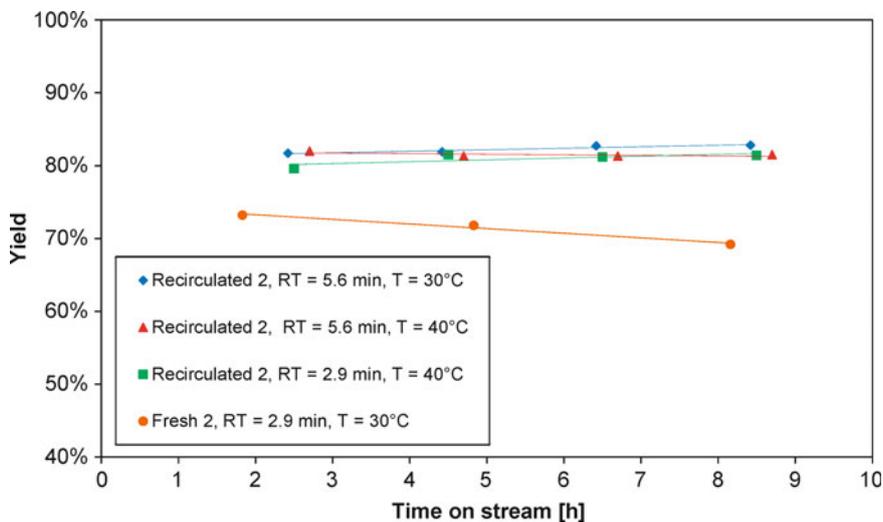


Figure 10. Stability of the yield during the operation of the mini-plant at an N/F ratio of 40 at different residence times (RT) and temperatures (T) with a $KOH/1$ ratio of 0.02

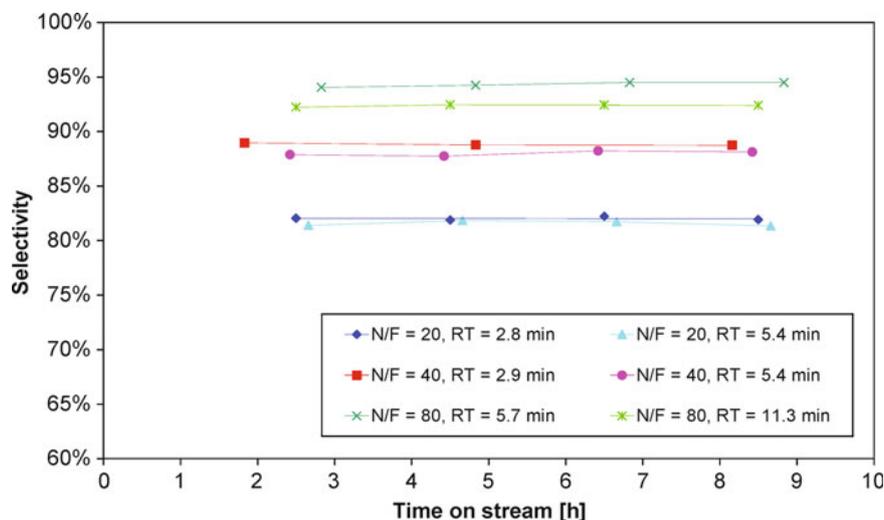


Figure 11. Selectivity during the time on stream for three different N/F ratios and different residence times (RT) at 30 °C with KOH/1 ratio of 0.02

3. Conclusion

The proof of concept and optimization studies for the synthesis of 2-nitroethanol have shown that the N/F ratio is the crucial parameter to control product selectivity and to obtain the product in high purity. The temperature and catalyst amount did not have a significant impact on the selectivity. The Henry Reaction is a Type B reaction with reaction times for high conversion in the range of 2 min. A complete kinetic model was obtained that was used to predict conditions for the operation of the mini-plant. 2-nitroethanol was obtained in 93% yield and with a HPLC purity of 94%.

The long-run study included the operation of a complete process with reaction and workup unit operations. The operation of this mini-plant based on MRT is a powerful tool to study, in a laboratory environment, all the features that are usually associated with pilot plant studies, namely, reactor scalability, stability over time on stream, solvent recirculation, model prediction, and robustness of reaction kinetics. The last item, namely, the variable reaction kinetics at a high N/F ratio over 40, is a fundamental problem when operating a continuous process. Contrary to a batch process, a continuous process has a sharp end point with a determined residence time that cannot be easily adapted. Thus, the understanding of this problem would have required most of the attention in case the project would have been pursued on a larger scale.

Finally, it is worth mentioning that the scale-up of this Henry Reaction is possible in conventional technology using static mixers and classical coils for gaining residence time. The reaction is operated under diluted conditions (high N/F ratio), and the exothermic is negligible. However, the use of a micro-structure reactor remains an important safety advantage when dealing with highly energetic materials. In fact, explosion propagation would be significantly impeded in structures smaller than millimeters. The goal would have been to operate with a reactor that is inherently safe. However, much more safety analysis and data would have been required to assess precisely when a micro-structured reactor becomes an intrinsically safe reactor. A recent study has shown that even a microreactor cannot be considered automatically such a safe reactor [20].

4. Experimental

The Henry Reaction has been conducted in the FlowPlate™ A5 microreactor (MR) available via Ehrfeld Mikrotechnik BTS. To increase residence time, additional plates of varying channel depth have been connected together by an approach described by Kockmann and Roberge [21]. The overall process is well depicted in Figure 7. The reaction in MR is performed using two feeds: Feed-1 (V1, F1) is the depolymerized formaldehyde (1) from paraformaldehyde (Sigma-Aldrich) at a constant

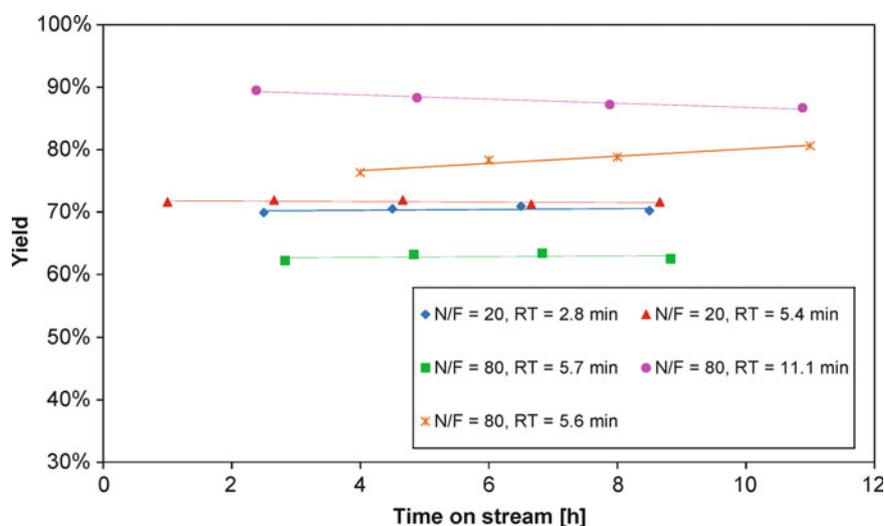


Figure 12. Stability of the yield at two different N/F ratio and residence times at 30 °C with recirculated 2 and a KOH/1 ratio of 0.02.

40.0 wt% concentration, KOH (Merck) or another base like NaOH (1.5 wt.% concentration for a KOH/1 molar ratio of 0.02), and the remaining is methanol (Lonza). Under such conditions, it was possible to obtain a homogeneous solution of F1. Feed-2 (V2, F2) was pure nitromethane (**2**, Sigma-Aldrich) used fresh or recirculated in the process. A key parameter for this reaction was the so-called *N/F* ratio, representing the molar ratio of nitromethane (**2**) to formaldehyde (**1**). The detailed experimental conditions, including the base type and concentration, the *N/F* ratio, the temperature (*T*), the residence time (i.e., reaction time, *RT*), and the time on stream, are described in the title and legend of each figure.

A typical long-run experiment (Experiment number MR02210) is presented in Figure 9. In this experiment, the feeds were having the following flow rates: F1=0.29 g/min, F2=9.85 g/min, and F3 =0.0047 g/min; the third feed being H₂SO₄ (96 wt.%, Lonza) to neutralize KOH. Such feed flow rates lead to a *N/F* ratio of 40 mol/mol and a H₂SO₄/KOH ratio of 0.60 mol/mol (KOH/1=0.02). Additional information on the equipment and instrumentations is presented in Figure 7. For example, the large flow rates were achieved by a gear pump controlled via a coriolis flow meter, while the small flow rates were performed via high-precision syringe pumps. MR was operated with a large excess of thermal fluid up to 600 L/h controlled by a rotameter to ensure isothermal conditions. The acid neutralization took place in a continuous-stirred tank reactor of 200 ml made out of glass (CSTR), while the precipitated salt (K₂SO₄) was filtered by an in-line filter from Pall for laboratory applications (FIL). The distillation took place in a laboratory wiped film evaporator (0.02 m²) from Glass Keller (DISTILLATION).

With the exception of **1**, the compounds **2**, **3**, **4**, and **5** (Scheme 1) were evaluated via HPLC using a Zorbax RX-C8 (5 μm; 4.5 × 250 mm) and acetonitrile as the mobile phase. The reaction yield has been quantified using an external standard, and in some cases, it was cross-checked via a wt.% NMR

method. The reaction selectivity (*S*) is calculated in area% based on the following equation: $S = \text{area\% of } \mathbf{3} / (\text{Sum of area\% of } \mathbf{3}, \mathbf{4}, \text{ and } \mathbf{5})$. Pure **3** has been obtained via rectification of a tiny amount of crude **3** and the molecular weights of **4** and **5** have been determined via LC-MS. In some experiments, a GC method was used to ensure that no other by-products were formed; the GC method was important to follow-up the buildup of Methanol in **2**. Pragmatically, the conversion was calculated by the yield divided by the selectivity as the consumption of **1** was difficult to monitor.

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