

Continuous-Flow Nitration of *o*-Xylene: Effect of Nitrating Agent and Feasibility of Tubular Reactors for Scale-Up

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 Supporting Information

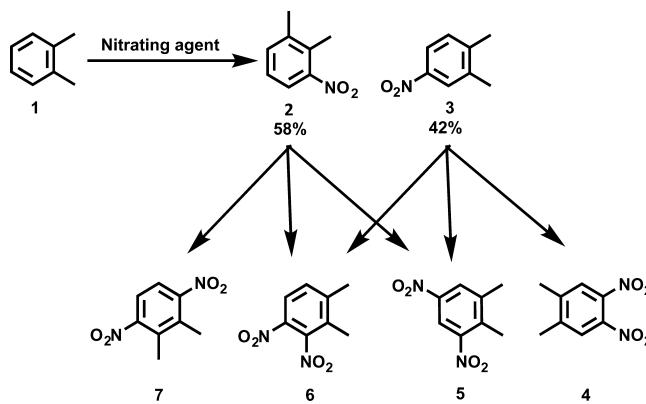
ABSTRACT: Continuous-flow nitration of *o*-xylene has been studied with different nitrating agents over a wide range of conditions for different parameters such as temperature, residence time, and concentrations. A nitrating mixture comprising sulfuric acid and fuming nitric acid was seen to yield higher selectivity for the isomer 1,2-dimethyl-3-nitrobenzene over the isomer 1,2-dimethyl-4-nitrobenzene and also a non-negligible quantity of dinitro derivatives of *o*-xylene. With only fuming nitric acid as the nitrating agent, the reaction was selective for 1,2-dimethyl-4-nitrobenzene over 1,2-dimethyl-3-nitrobenzene. Impurities mainly come from nitration of mononitro derivatives, and this occurs more from nitration of the 3-nitro isomer because of its higher reactivity with nitric acid. An economic analysis of the continuous-flow reactor for the production of 1,2-dimethyl-4-nitrobenzene at 100 and 500 kg/h in a jacketed tubular reactor showed that numbering-up is a more economical approach for higher production capacity. A combination of large- and small-sized tubes depending upon the relative rates of heat generation during a reaction will achieve more profit and a shorter payback period than having the entire reactor made of a single tube size.

1. INTRODUCTION

Continuous-flow synthesis using microreactors is now a well-known reaction engineering tool that facilitates rapid mixing as a result of the small dimensions, large heat transfer area, and narrow residence time distribution. Accurate control of the residence time of the reactants and the possibility of adding one of the substrates along the length of the reactor help to minimize sequential reactions. Several reactions have been reported in the literature to give better yields and selectivities when carried out in microreactors compared with conventional batch-mode operations. A comprehensive account of several such single-step and multistep reactions can be found in the literature.^{1–5} Reactions that are selectivity-sensitive (including polymerization reactions), radical reactions, reactions involving unstable intermediates, reactions involving toxic reagents, exothermic reactions, etc., are among the most suitable reactions that can be conducted in microreactors or flow reactors. Among many exothermic and selectivity-sensitive reactions that have been demonstrated in microreactors, aromatic nitrations form an important class of reactions. In general, aromatic nitration reactions are highly exothermic, and the heat of reaction per electrophilic substitution by a nitronium ion is typically -100 kJ/mol . The functional groups on the aromatic ring and their positioning decide the activity of the molecule and also the heat of reaction. In the presence of excess nitric acid, secondary and tertiary nitrations cannot be avoided if the reaction is not controlled properly.

Here we present the continuous-flow nitration of *o*-xylene (**1**) using a tubular reactor. Typical products from this nitration include mononitroxylenes, viz., 1,2-dimethyl-3-nitrobenzene (**2**) and 1,2-dimethyl-4-nitrobenzene (**3**), and also dinitro derivatives (**4–7**) depending upon the experimental conditions (Scheme 1). Reduction of **3** yields 1,2-dimethyl-4-aminobenzene (xylidine), which finds application in the synthesis of various important

Scheme 1. Nitration of *o*-xylene (**1**), giving 1,2-dimethyl-3-nitrobenzene (**2**), 1,2-dimethyl-4-nitrobenzene (**3**), 1,2-dimethyl-4,5-dinitrobenzene (**4**), 1,2-dimethyl-3,5-dinitrobenzene (**5**), 1,2-dimethyl-3,4-dinitrobenzene (**6**), and 1,2-dimethyl-3,6-dinitrobenzene (**7**)



products, including riboflavin (vitamin B₁₂),⁶ high-performance polyurethane resin, and herbicides.⁷ Isomer **2** is used for the synthesis of mefenamic acid.

In conventional batch-mode nitration of *o*-xylene, mixed acids are frequently used as the nitrating agent. The literature shows the possibility of getting an 80% yield of **2** when a nitrating mixture⁸ is used for nitration and only **3** when only fuming nitric acid (FNA) is used (10 equiv with respect to **1**).⁹ An analysis of yields of the isomers for different nitrating agents under different

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Table 1. Analysis of literature on *o*-xylene nitration (the last three entries are heterogeneous catalytic reactions)

authors	T (°C)	H ₂ SO ₄ :1 (w/w)	nitrating agent	yield (%)	isomer selectivity (%)	
					2	3
Nolting and Forel ⁸	0	1.96	HNO ₃	80	^a	—
Crossley ¹⁰	0	1.94	HNO ₃	61.8	88	11
Emerson and Smith ¹¹	−10 to 0	1.94	HNO ₃	85.6	^a	—
Farmer and Sutton ¹²	−10 to 0	1.94	HNO ₃	41.4	^a	—
Batchelder et al. ¹³	43.3	2.17	HNO ₃	87.9	—	—
Griesheim plant ¹⁴	0 to 15	1.19	HNO ₃	72.3 ^b 62.3 ^c	55	45
Kobe and Pritchett ¹⁵	25	2.15	HNO ₃	90	58	42
Olah et al. ¹⁶	25	—	FNA ^d + CH ₃ NO ₂	—	47	53
Lavy and Rauch ¹⁷	60	0.5	0.5 mol HNO ₃	—	55	45
	25–80 ^e	—	N ₂ O ₄ + O ₂ gas	75	18–27	82–73
Liu et al. ¹⁸	35 ^f	—	liq. NO ₂	81	11	89
Sengupta et al. ¹⁹	50 ^g	—	FNA	85	—	71

^aOnly this isomer was reported. ^bCrude. ^cPurified. ^dFNA = fuming nitric acid. ^eCatalyst: mercuric acetate in glacial acid. ^fH- β zeolite catalyst with Si/Al2 and molecular oxygen. The percent yield is for both isomers, and the percent selectivity is the fraction on GC. ^gH-Y zeolite catalyst, 115% H₃PO₄, FNA.

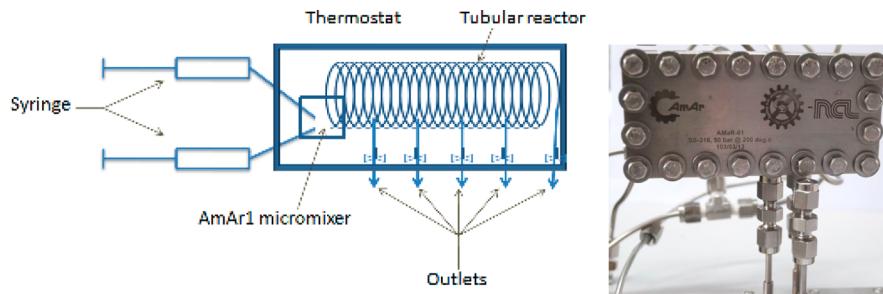


Figure 1. Schematic reaction setup.

conditions from the literature is given in Table 1. In general, with mixed acids the 2:3 mole ratio varies between 1.22 and 2.22 depending upon the experimental conditions. Among the two isomers, 3 is the more desired isomer because of a large number of intermediates where it is used, but in the conventional process, the yield of 2 is higher than that of 3.

In an attempt to replace the spent sulfuric acid, Sengupta et al.¹⁹ reported nitration of **1** using FNA with 115% polyphosphoric acid, nitrobenzene, and H-Y zeolite catalyst, which yields 85% conversion and 71% selectivity for 3. However, the use of polyphosphoric acid makes this approach uneconomical. Recently Liu et al.¹⁸ reported 89% selectivity for 3 at 35 °C in the presence of nitrogen dioxide, molecular oxygen, and zeolite H- β with Si/Al ~ 500. These reactions over zeolite, although green, are time-consuming (12 to 24 h) and may not be economically viable for large-scale production. In view of this, it is necessary to re-examine the nitration of **1** and find an approach that with the advent of a flow reactor can make it economically as well as environmentally friendly.

Nitration of **1** yields mononitro derivatives (**2**, **3**) as well as dinitro derivatives (**4–7**), as shown in Scheme 1. In general, unlike the mononitration of **1**, which needs low reaction temperatures to control the reaction, the nitration of mononitro derivatives has higher activation energy and needs higher temperatures to initialize the reaction. This paper is organized as follows: In the next section, we give the details of the experimental setup, procedure, and analysis. In section 3 the observations are discussed in detail and the instances that yield large quantities of impurities are also brought out. Also, the effect

of nitrating agents on the yields of different isomers and the synthesis of mononitro and dinitro derivatives are discussed in detail. The range of conditions that yield better selectivity for 3 has been identified, and an economic analysis of the different reactor configurations for such optimal conditions is presented before the work is summarized.

2. EXPERIMENTAL SECTION

For the continuous-flow experiments, the experimental setup (Figure 1) consisted of two syringe pumps (Holmarc Optomechatronics, India) loaded with stainless steel syringes (SS316 syringe, 50 mL volume), one containing nitric acid and the other containing *o*-xylene, connected to SS316 tubes (1/8 in. o.d.). The outlets of the pumps were connected to an AmAr1 micromixer (Figure 1) followed by a residence time tube (3.12 mm o.d. and 2.1 mm i.d.). The entire assembly had five outlets (one immediately after the micromixer and the remaining ones located along the length of the reactor at equal intervals) with needle valves for sampling. The entire assembly was immersed in a heating/chilling thermostat (Julabo ME12) to maintain the system under isothermal conditions.

The flow rates of the two reactants (**1** and nitrating agent) were varied to achieve the desired mole ratio and residence time. Samples were collected at the different outlets (corresponding to different residence times) in a fixed quantity of ice-cold water. A known quantity of toluene (Merck) was used to extract the organic phase from these samples. The extracted organic phase was washed two times with water and separated by gravity. It was further washed with brine to remove residual

water. Trace quantities of water were removed by passing the organic phase through a bed of anhydrous sodium sulfate. The samples were analyzed using gas chromatography with an HPS capillary column and a flame ionization detector (FID). Dinitro impurities were identified using GC–MS.

The influence of different parameters, including temperature, residence time, nitrating agent (viz., FNA or nitrating mixture [$\text{HNO}_3:\text{H}_2\text{SO}_4 \sim 40:60$ v/v and also 1:1 mole ratio]), and nitric acid equivalents, on the conversion of **1** and yield of **3** was investigated. It needs to be noted that nitration of **1** with the nitrating mixture is a two-phase reaction, and hence, mass transfer limitation needs to be overcome. Experiments were carried out to measure the liquid–liquid mass transfer coefficient over a range of flow rates.

In a separate set of experiments, the nitration of mononitro derivatives **2** and **3** was studied at concentrations that mimic the conditions at the outlet of various experiments performed in the nitration of *o*-xylene. The setup consisted of three syringe pumps loaded with stainless steel syringes containing nitric acid and *o*-xylene and a polypropylene syringe (20 mL volume) containing water. The rest of the setup was kept the same as discussed previously. Samples were collected from various ports in a finite quantity of ice-cold water and later extracted in toluene. The samples were analyzed using gas chromatography with an HPS capillary column. Products were identified using GC–MS and NMR analysis. The relevant spectra are given in the Supporting Information.

3. RESULTS AND DISCUSSION

3.1. Mononitration of *o*-Xylene. Initially a number of experiments were carried out using the nitrating mixture (NM) consisting of ~40:60 (v/v) $\text{HNO}_3:\text{H}_2\text{SO}_4$ at 40 °C. The results are summarized in Table 2. Sulfuric acid acts as a catalyst, and

Table 2. Nitration of *o*-xylene using nitrating mixture (40:60 v/v concentrated HNO_3 and concentrated H_2SO_4) at 40 °C with different amounts of nitrating agent; impurities include the dinitro derivatives

mole ratio (1:NA)	residence time (min)	impurity (%)	conversion (%)
2:1	1.5–5.28	3–7	56–57
1.5:1		5–7	66–70
1:1		7–12	76–90
1:2	4.6–20	18–27	96–100
1:3		18–61	98–100
1:4		39–97	96–100

being a strong acid, it protonates nitric acid and generates nitronium ion while also acting as a dehydrating agent.²⁰ With excess nitric acid, sequential nitration of mononitro derivatives can be expected, which reduces the selectivity for the desired products and needs more separation stages. With the NM containing 4 molar equiv of nitric acid, only dinitro derivatives of **1** were observed. In order to reduce the rate of generation of nitronium ions, thereby avoiding the formation of dinitro derivatives, experiments were carried out in which the quantity of sulfuric acid was decreased. A nitrating mixture comprising FNA and H_2SO_4 (1:1 mole ratio) was used. The flow rates of *o*-xylene and NM were maintained to achieve identical molar flow rates of *o*-xylene and FNA. The experiments were carried out with a residence time of 20 min over a temperature range of 0 to 70 °C. Although it was expected that the reaction would reach

completion early with an increase in the temperature, it was observed that no complete conversion of **1** was achieved. Moreover, the impurities formed were significant (Figure 2).

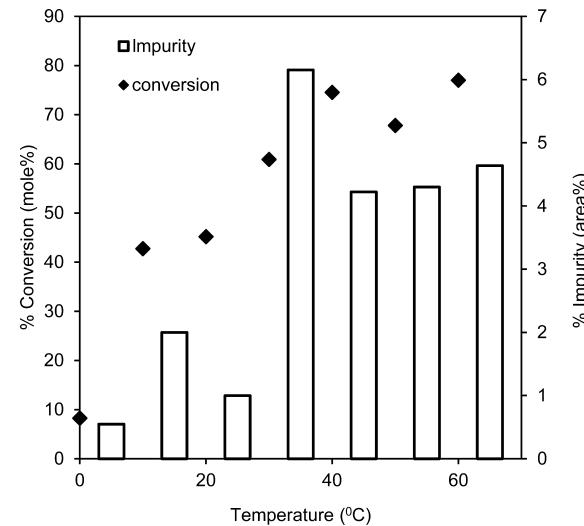


Figure 2. Effect of temperature on the conversion and formation of impurities in nitration of *o*-xylene with a 1:1:1 *o*-xylene: $\text{HNO}_3:\text{H}_2\text{SO}_4$ mole ratio and a residence time of 20 min.

This implied that an equimolar concentration of nitric acid needs significantly higher amounts of sulfuric acid to continuously generate nitronium ions and also absorb water. In the subsequent experiments, 2 or 3 molar equiv of nitrating agent (FNA + H_2SO_4) was used. Experiments were carried out at higher temperature (50 and 60 °C for 2 molar equiv of FNA and at 40 and 50 °C for 3 molar equivalents of FNA) with a residence time of 20 min at the final outlet. Over 91% conversion was achieved. More observations are given in the Supporting Information. These observations indicate that it is not possible to achieve complete conversion of **1** with less than 5% impurities (dinitroxylenes and other oxidized products) using equimolar or excess sulfuric acid. Hence, all further experiments were carried out using only FNA as the nitrating agent.

Initial experiments performed at 40 °C using equimolar FNA resulted in only 38% conversion of **1** in 4.46 min, which increased to 90% with 3 molar equiv of FNA. However, the yield of dinitro derivatives was also found to be higher with increasing concentration of FNA. The observations are shown in Figure 3. Thus, while the use of a larger quantity of FNA helps to achieve complete conversion of **1**, it severely affects the selectivity for mononitro derivatives. In order to get the maximum conversion and minimum amounts of dimethyldinitrobenzene and other impurities, a rapid screening was performed over a wide range of conditions at a 1:FNA mole ratio of ~1:6. The residence time was varied between 20 and 600 s, and the temperature was varied from 0 to 30 °C. It was observed that at 20 °C with a residence time of less than 40 s, 99% conversion of **1** and only 7.2% dinitro impurities were observed. Also, when only FNA was used as the nitrating agent, the selectivity for **3** was found to be higher than that for **2**. The observations on the effect of nitrating agent on the conversion and yield of the undesired products are shown in Figure 4. With the same amount of nitric acid in both nitrating agents, the nitrating mixture leads to higher conversion as well as much more significant quantities of the impurities. The nitronium ion concentrations estimated for only FNA and for the nitrating mixture (~40:60 v/v 69% HNO_3 :concentrated

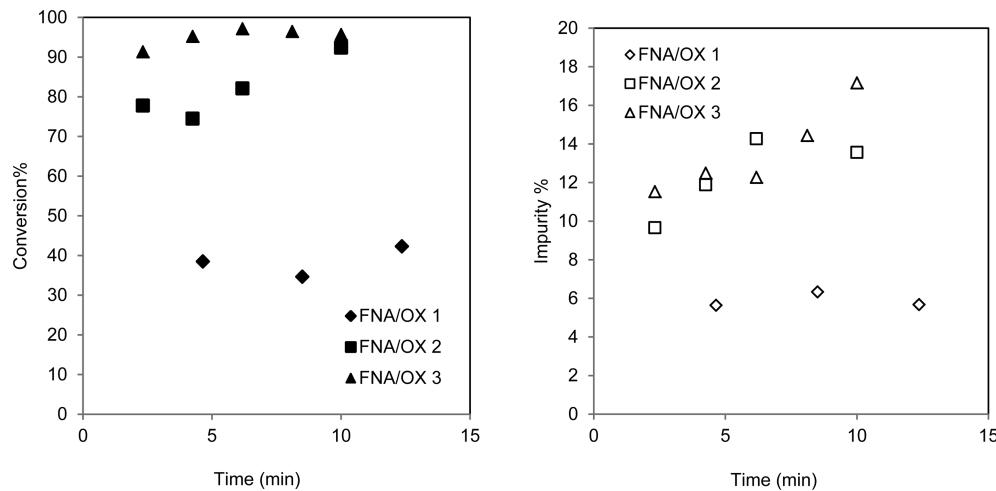


Figure 3. Effect of fuming nitric acid (FNA) concentration and residence time on the conversion and formation of impurities (mainly dinitro derivatives) at 40 °C.

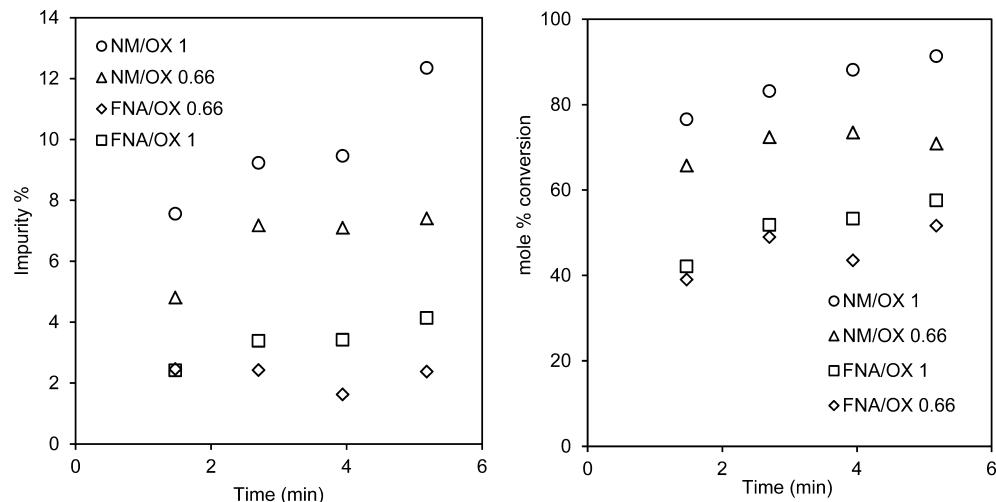


Figure 4. Effect of the presence of sulfuric acid on the conversion of **1** and dinitro formation using 1:1 (mol/mol) nitrating mixture (NM) at 40 °C. Legends show the mole ratio of nitric acid in the NM or fuming nitric acid (FNA) to *o*-xylene (OX).

H_2SO_4) are 4.7 and 20 mol % respectively, which support the above observations.²¹

In all of the experiments it was observed that with FNA as the nitrating agent, the selectivity for **3** was higher than that for **2**, which is almost opposite to the observations based on experiments using sulfuric acid. In some cases the selectivity for **3** was higher even with nitrating mixture, but that was mainly because of rapid sequential reactions of **2**, which reduced its selectivity. Increasing acidity substantially increases the proportion of reaction at C_4 and to a smaller degree that at C_3 , both at the expense of ipso nitration. The estimated possible percentage of initial attack at C_{ipso} , C_3 and C_4 are 64, 11, and 25% with 50% H_2SO_4 , 55, 15, and 30% with 60% H_2SO_4 , and 45, 18, and 37% with 70% H_2SO_4 . On the basis of the mechanism explained in the Supporting Information, in the presence of sulfuric acid this would always result in a higher yield of **2** than of **3**. Hence the ratio of **2** to **3** can be controlled by manipulating the instantaneous total acidity in the vicinity of **1**, and relevant observations can be seen in Figure 5.

Plots of the selectivities for the mononitro derivatives and the impurities versus the conversion of **1** for different experiments are shown in Figure 6. These results can be used to outline

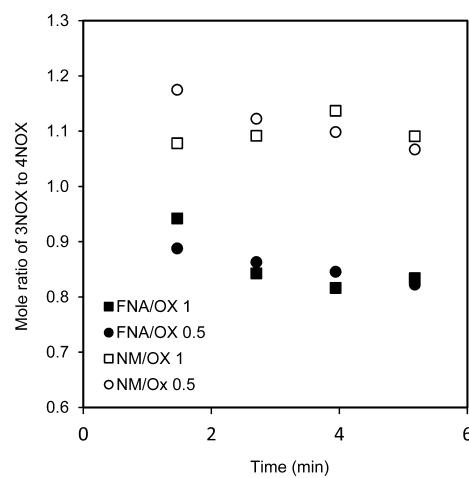


Figure 5. Effect of sulfuric acid on the selectivity at 40 °C.

general observations for comparing the effects of nitrating mixture and fuming nitric acid. It is quite clear that the selectivity for **3** is higher with fuming nitric acid than with the nitrating mixture. Also the amounts of impurities were smaller with

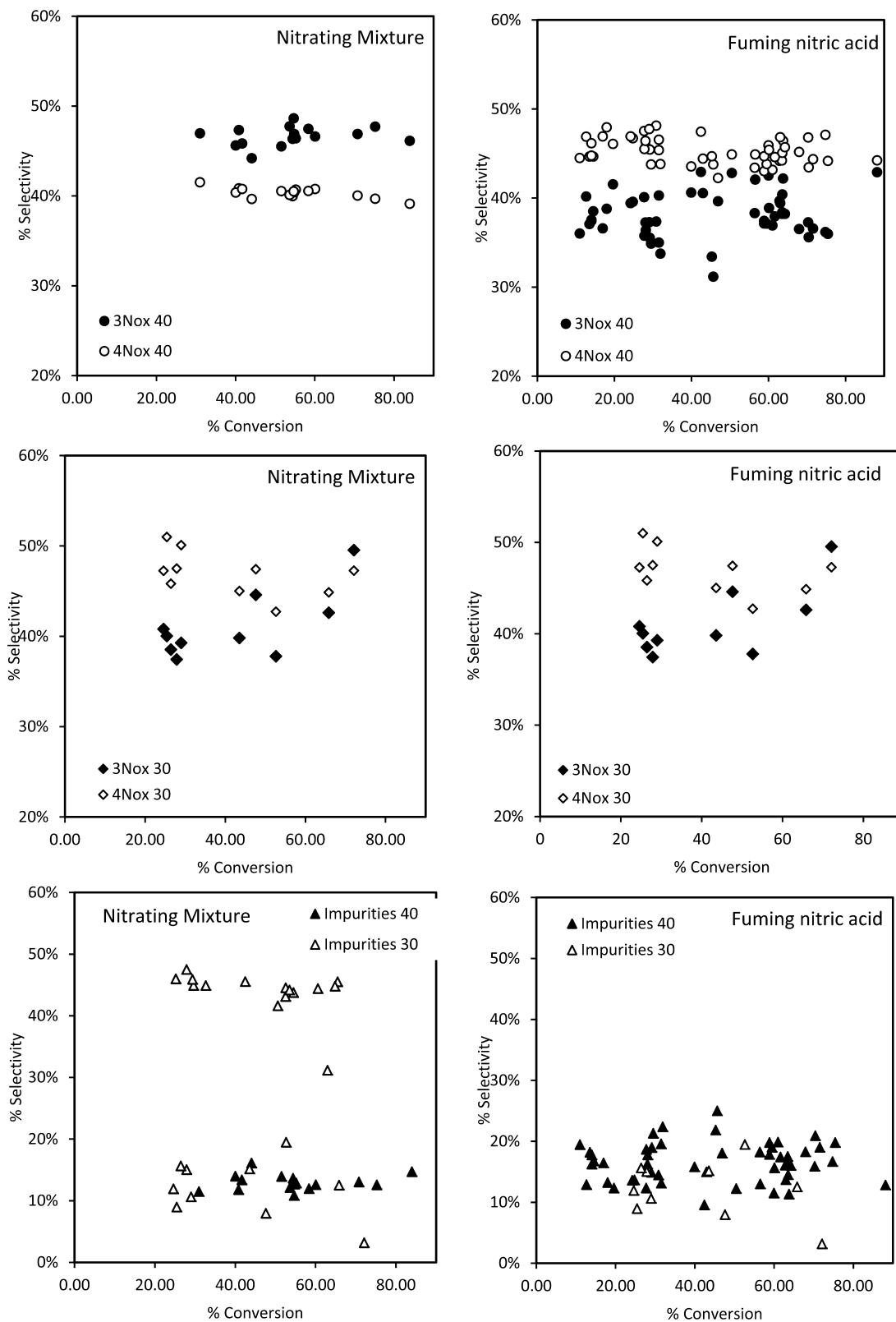


Figure 6. Variation in the % selectivities for the products and impurities at 30 and 40 °C as functions of the conversion of **1**. Only the points up to 90% conversion are included.

fuming nitric acid than with the nitrating mixture. While in general the amounts of impurities increased with increasing temperature, the larger amounts of impurities observed with nitrating mixture were mainly because isomer **2** underwent rapid reactions in the presence of excess nitrating agent. Thus, the

relative rates of generation of nitronium ions make a difference in the selectivity of nitronium attack on the aromatic ring. More work on a systematic evaluation of isomer selectivity based on relative rates of different steps in the mechanism of the nitration reaction is in progress and will be reported separately.

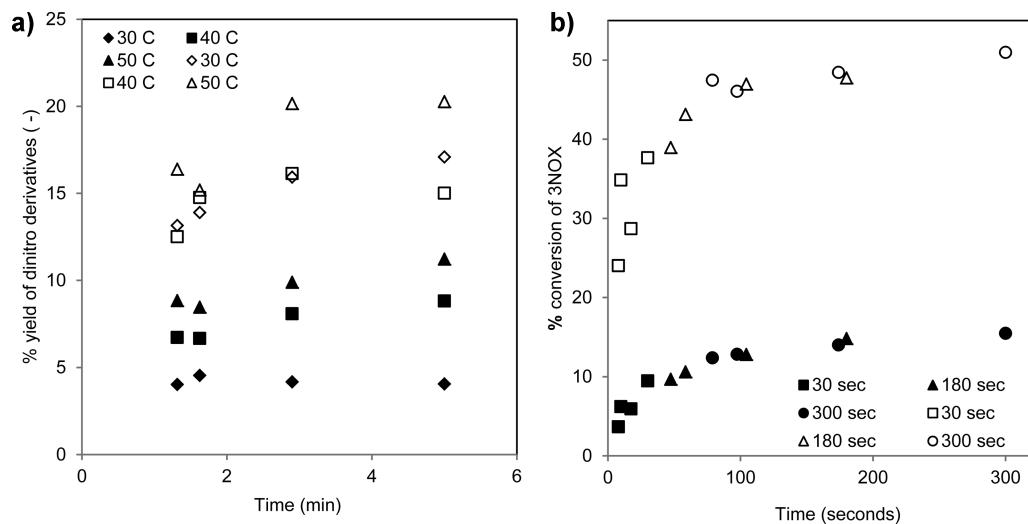


Figure 7. (A) Comparison of overall yields of dinitro derivatives of *o*-xylene from nitration of **2** and **3**. Solid and open symbols correspond to the dinitro derivatives obtained from **3** and **2**, respectively. (B) Effect of residence time on the conversion of **2** using 3 mol of fuming nitric acid and 1 mol of water. Open symbols correspond to conversion while solid symbols indicate impurities.

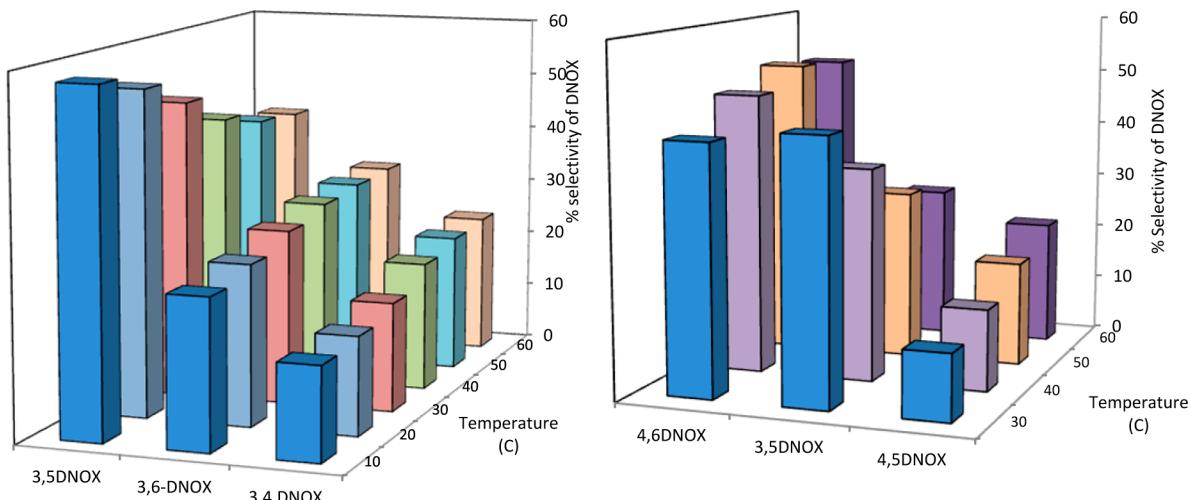


Figure 8. Variation in the selectivities for different dinitro derivatives obtained after nitration of **2** and **3** at different temperatures.

When the set of parameters at which isomer **2** gets further nitrated and results into less than 20% yield of the impurities, it was observed that the amount of impurities increased linearly at lower conversions and then increased exponentially at higher conversions, which implies that at relatively lower temperatures and with possibly no mass transfer limitations the presence of excess nitrating agent actually encourages sequential nitration or oxidation reactions of specific products. Thus, while nitration of all of the mononitro derivatives may not be possible and even the desired isomer may not undergo further rapid reactions (and its yield may remain unaffected), conditions that encourage the undesired isomers to undergo further reactions will have serious implications for the process. More observations are given in the Supporting Information.

3.2. Nitration of Mononitrated *o*-Xylenes. The impurities observed in the mononitration of **1** were the dinitro derivatives (mainly coming from sequential nitration of **2** and **3**) and trace quantities of phenolic impurities. It was observed that under specific reaction conditions the concentration of impurities was high, and hence, it was necessary to explore the conditions

leading to the formation of dinitro derivatives from mononitrated *o*-xylenes and to avoid them in order to achieve better yields of the desired products. In the observations discussed earlier, *o*-xylene nitration was carried out using 4 mol of FNA, where in the mononitration step 1 mol of nitric acid is consumed and 1 mol of water is generated, which basically dilutes the nitric acid when **2** and **3** undergo further nitration. In view of this, in order to maintain consistency in the approach, the synthesis of dinitro derivatives using **2** and **3** was carried out using 3 mol of FNA and 1 mol of water as the nitrating agent. For the nitration of **2**, the temperature was varied over the range from 10 to 60 °C, while for the nitration of **3** experiments were done at 30 to 50 °C. In both cases, the residence time was changed from 16 to 300 s. Increasing the temperature as well as the residence time resulted in higher conversions of **2**. However, the selectivity for dinitro derivatives was lesser than the extent of conversion of mononitro derivatives. In the presence of FNA, the mononitro derivatives of *o*-xylene can undergo partial oxidation leading to phenols and nitrophthalic acid. In general, the solubility of nitrophthalic acid in water is very high. In order to confirm the formation of

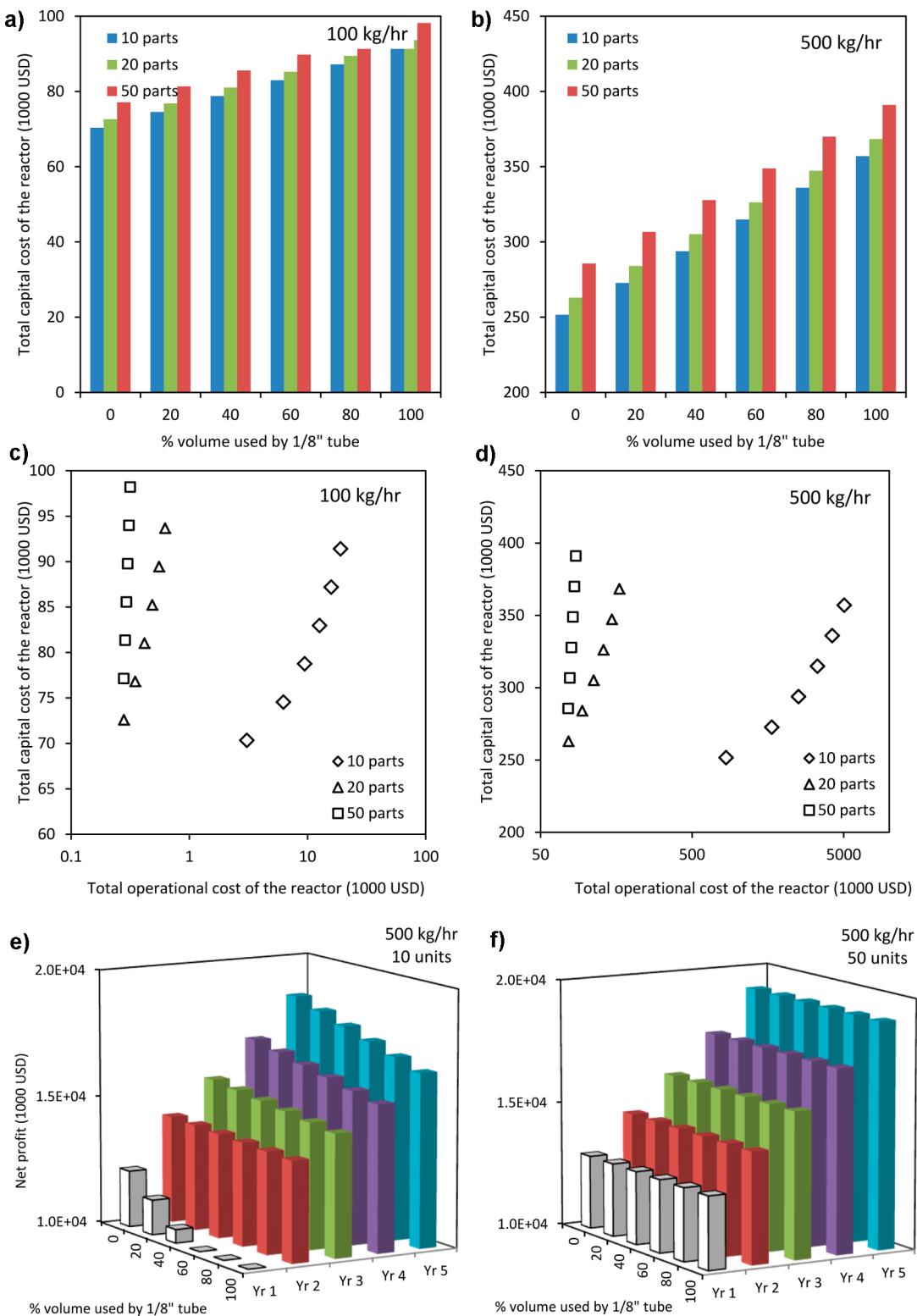


Figure 9. Economic analysis of the continuous-flow nitration of *o*-xylene using SS316 tubular reactors. (A, B) Variation in the CAPEX with the volume fraction of 1/8 in. o.d. tube used to construct a flow reactor (the remaining volume is occupied by 1/4 in. o.d. tube) for production of **3** at (A) 100 kg/h and (B) 500 kg/h. (B) Effect of numbering-up on the variation of CAPEX vs OPEX for production of **3** at (C) 100 kg/h and (D) 500 kg/h. (E, F) Net profits from the flow reactor under the assumption of complete recovery of products and complete conversion of *o*-xylene for numbering-up with (E) 10 and (F) 50 parallel units for the production of **3** at 500 kg/h.

nitrophthalic acid in the aqueous layer, it was extracted separately using ethyl acetate. The solid product was found to char immediately upon concentration, which supports the observations given in the literature.

Analysis of the product at different temperatures and residence times showed that the yields of dinitro derivatives resulting from nitration of **2** were always higher than those of **3** (Figure 7A). Analysis of the product composition showed that the reactivity of

2 for nitration is relatively higher than that of **3**. Furthermore, isomer **3** was found to have a greater tendency to yield oxidative products, although the rates of these oxidation reactions were relatively lower than those of nitration. In order to see the effect of dispersion and the nature of the flow (with 3 mol of FNA and 1 mol each of water and **2**, it becomes a two-phase flow), experiments in which the extent of mixing was varied by changing the flow rates and using longer residence time tubes were performed. It was observed that the extent of conversion was independent of the nature of mixing and that at identical residence times the conversion was almost identical ($\pm 2.4\%$ variation) (Figure 7B). This implies that the micromixer followed by a tubular reactor offers a system without any mass transfer limitations and is suitable for studying the reaction kinetics.

Upon analysis of the data obtained at different temperatures in continuous-flow mode at different residence times, it was observed that the selectivities for different dinitro derivatives from both **2** and **3** showed different rate behaviors (Figure 8). In nitration of **2**, increasing the temperature results in a reduction in the selectivity for **5** while the selectivities for **7** and **6** increased. These observations indicate that while the pre-exponential factor for the reaction giving **5** is higher than those for the other two isomers, the activation energies for the latter two are lower, which allows their selectivities to increase with increasing temperature. Similar trends were observed for the case of nitration of **3**. These observations are important if one wants to exclusively synthesize any of these dinitro derivatives of **1**. On the other hand, they also indicate that at a given reaction temperature for the mononitration of *o*-xylene, the residence time should be restricted to ensure that a complex mixture of dinitro derivatives is not formed. The literature shows that the melting points of the dinitro derivatives **7** (89 °C), **6** (82 °C), **5** (75 °C), and **4** (115 °C) vary closely and also over a wide range. This will require specific and controlled crystallization protocols to recover the pure mononitro derivatives, which will add more equipment as well as higher operational costs.

In view of the above observations on nitration of **1** and independent nitrations of **2** and **3**, it was thought desirable to use the optimal conditions to check the economic feasibility of the flow reactor.

3.3. Economics of a Continuous-Flow Reactor for Nitration of *o*-Xylene. Considering that the continuous-flow nitration of **1** is to be carried out for the production of **3** at 100 and 500 kg/h (i.e., about 72 TPM and 360 TPM, respectively), here we present a simple analysis of the economic feasibility of this nitration reaction in a jacketed tubular reactor. The conditions (residence time, temperature, and mole ratio of **1** to FNA) that yield the maximum selectivity for **3** were used as basis for the reactor design. As a simple system, it was considered that the reactor is to be fabricated using a combination of different sections made from SS316 tubes of 2.5 mm i.d. (i.e., 3.175 mm or 1/8 in. o.d.) and 4 mm i.d. (i.e., 6.3 mm or 1/4 in. o.d.). In order to produce a fixed quantity of **3** in a given time, knowledge of the specific residence time fixes the total reactor volume. The smaller-diameter tube (3.175 mm) is usually cheaper than the larger-diameter (6.3 mm) tube, and it provides 1.89 times higher heat transfer area. However it needs a 2.54 times longer tube length to occupy the same volume and hence would offer a higher pressure drop at identical flow rates to produce a fixed quantity of **3**. The tube with smaller diameter also yields relatively better mixing and higher mass transfer rates. Thus, depending upon the heat generation rate in a specific region along the length of the reactor, it is necessary to ensure that an

adequate heat transfer coefficient is achieved by providing the necessary heat transfer area as well as the Nusselt number on the tube as well as the shell side. Thus, it is always possible to design a flow reactor that can take care of location-specific heat duties as the reaction proceeds along the length of reactor. In the present exercise, it was assumed that for a fixed capacity and for a given set of conditions the selectivity is independent of the reactor design, and hence, the downstream processing costs will remain the same. Similarly, for a given throughput the pumps have a wide pressure range, and hence, the same pumps are used independent of the reactor design.

Considering the above criteria, here we give a quick approach that allows one to evaluate the possible design of a flow reactor. On the basis of the volume fraction of the reactor that yields a specific heat duty (or heat generation rate), its length can be estimated from its diameter, which eventually yields the cost of the specific section of the reactor. Thus, depending upon the fractions of the reactor used for different heat loads, the total capital cost of a reactor (including the cost of a jacket depending upon the geometrical configuration of reactor, viz., coil, double coil, triple coil, etc.) can be obtained. The cost of the fittings and connectors can be added to the capital cost (tubular reactor + jacket). The operating costs are primarily the cost of pumping due to the pressure drops at a given flow rate in different sections of the reactor and the cost of utility and its pumping through the jacket. Usually, single long tubular reactors are uneconomical because of the very high pressure drop, and hence, the numbering up approach is used, which reduces the flow rate through each reactor and therefore also the resulting pressure drop. Thus, while the capital cost of the reactor can be retained more or less the same (distributor cost gets added depending upon the numbering-up strategy), the operating costs can be reduced. Also, the capital costs and peripherals, including the control system, are a one-time investment, which usually depreciates and needs maintenance, adding to the recurring costs of a plant.

We have followed the approach discussed in detail by Joshi and Doraiswamy²² for the design of a flow reactor for production of **3** at 100 and 500 kg/h. Back of the envelope calculations showed that a tubular reactor when split into *N* parallel units (i.e., numbering-up) would yield a much lower pressure drop because of the lower velocities in individual tubes. The details of the reactor design procedure, optimization approach, integration of mixing, heat transfer, and reaction will be reported separately. In Figure 9, we have shown the observations from the calculations for reactors having 10, 20, and 50 units running in parallel to achieve the desired production rates at varying volume fractions of 3.175 mm diameter tube (the rest being the 6.3 mm diameter tube). It can be seen that the capital cost (CAPEX) of the reactor continued to increase significantly as the volume fraction of the reaction mixture through the smaller-diameter tube increased (Figure 9A,B). With 50 parallel reactors, this increase was not significant. A plot of the total CAPEX of the reactor (including reactor cost, peripherals, control system, etc.) versus the total operating cost (OPEX) showed a positive correlation, with the steepness increasing with the number of parallel units used to fabricate the reactor (Figure 9C,D). Also, the steepness in the trend decreases at higher OPEX, which indicates that the OPEX plays a significant part in the overall cost right from the first year of reactor operation. Thus, having more continuous reactor units running in parallel is always economical as it decreases the OPEX compared with having a single flow reactor. A few such assemblies of tubular reactors can be seen in the literature.^{23–27}

In the present case, the typical cost analysis was based on the present cost of the reactants, products, and reactor materials from various resources. It was observed that the net annual profit per year for the production rate of 100 kg/h did not vary significantly with change in the number of parallel tubular reactors. In order to explore the capacity where such an effect is noticeable, calculations were done for the production rate of 500 kg/h. The estimated net profits for a period of 5 years only from the reactor for the case of 500 kg/h production rate (reactor volume = 0.00328 m³) for 10 and 50 parallel reactors are shown in Figure 9E,F. The standard depreciation rates, escalation in prices of raw materials and products, variable price of electricity, maintenance and repair costs, and the down-time costs of the reactor (for 300 days of operation in a year) were taken into account.

With 10 parallel reactors, the estimated net profit per year was seen to decrease significantly when the fractional volume of the reactor made of 1/8 in. o.d. tube was higher. This effect on the net profit was noticeable for all five years. On the other hand, with 50 parallel reactors the net profit did not vary much irrespective of the fraction of the reactor made of 1/8 in. o.d. tube. Also the overall profit was much higher (by almost 40%) with the larger number of units running in parallel. It can be seen that if the reactor is made only of 6.3 mm diameter tubes, the net profit will continue to increase with time. However, if the reactor is made only of 3.175 mm diameter tubes, the overall net profit will always be lower, which will lead to a very long payback period. Also, numbering-up can be seen to increase the profit and hence reduce the payback period significantly. However, these possibilities exist only if the flow is distributed uniformly in the reactor, without which it will be difficult to attain identical residence times in all of the parallel units. This particular issue is important for two-phase flows, and the development of such designs needs immediate attention. More work on this aspect where the effects of nonuniform distribution of individual phases on the overall process economics will be presented separately.

4. CONCLUSIONS

Continuous-flow nitration of *o*-xylene (**1**) has been studied with different nitrating agents over a wide range of conditions of different parameters such as temperature, residence time, and concentrations. The effects of these parameters on the conversion of **1** and yield of **3** has been investigated in detail.

When 4 molar equiv or more of mixed acid (~40:60 v/v HNO₃:H₂SO₄) was used at 40 °C with a residence time of 10 min, only dinitro derivatives of *o*-xylene were observed. With a nitrating agent consisting of an equimolar nitrating mixture (i.e., 1:FNA:H₂SO₄ = 1:1:1), even at higher temperatures (50–70 °C) and a longer residence time (~20 min), no complete conversion of **1** was observed because of the lack of sufficient nitronium ion concentration. In the presence of sulfuric acid, the yield of **3** was always lower than in experiments performed using only FNA. The optimal conditions to achieve the maximum yield of **3** with minimum formation of dinitro derivatives in the nitration of **1** using only fuming nitric acid were found to be 20 °C and a residence time of less than 40 s. With a large excess of acids, higher temperature and/or longer residence time always resulted in large quantities of undesired products.

An economic feasibility analysis of the continuous-flow jacketed tubular reactor for the production of **3** at 100 and 500 kg/h has been presented. The analysis showed that having more continuous reactor units running in parallel is always economical if the production capacity is high. For smaller

production capacity, numbering-up does not have significant effect on the overall net profit. Also, reactors made of relatively larger tube diameter are expected to give better profit, provided that the design ensures that the local temperature in the reactor is controlled properly. Thus, the choice of suitable tube size needs to be made on the basis of the overall heat transfer coefficient (usually limited by the tube size heat transfer coefficient) and the ability to remove the heat efficiently throughout the reactor. The analysis showed that it is desirable to have a reactor made out of tubes of different sizes to achieve better heat transfer depending upon the local heat generation rates. This approach can be extended to different types of reactions, but the observations can change depending upon the type of reaction, rate of reaction, heat of reaction, number of phases involved, and the production capacity.

■ ASSOCIATED CONTENT

S Supporting Information

NMR spectra of mononitro and dinitro derivatives of *o*-xylene, mechanism of nitration with the nitrating mixture and fuming nitric acid, and additional experimental observations. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00064.

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Notes

The authors declare the following competing financial interest(s): The authors have filed a patent in which *o*-xylene is one of the examples of flow nitration using fuming nitric acid (WIPO Patent Application WO/2015/011729). The work was done under the Indus Magic Program of CSIR-NCL.

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