

Article

Selective Reduction of Ketones and Aldehydes in Continuous-Flow Microreactor—Kinetic Studies

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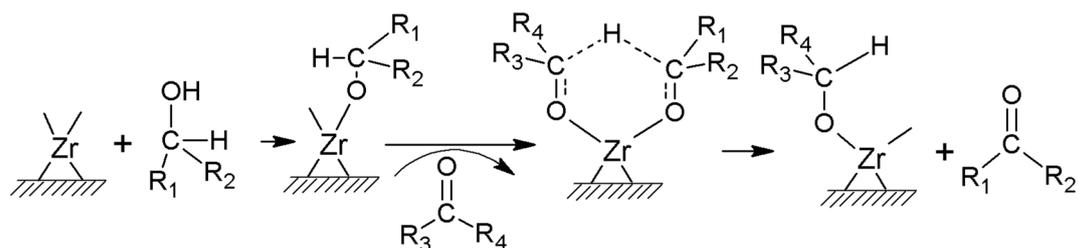


Abstract: In this work, the kinetics of Meerwein–Ponndorf–Verley chemoselective reduction of carbonyl compounds was studied in monolithic continuous-flow microreactors. To the best of our knowledge, this is the first report on the MPV reaction kinetics performed in a flow process. The microreactors are a very attractive alternative to the batch reactors conventionally used in this process. The proposed micro-flow system for synthesis of unsaturated secondary alcohols proved to be very efficient and easily controlled. The microreactors had reactive cores made of zirconium-functionalized silica monoliths of excellent catalytic properties and flow characteristics. The catalytic experiments were carried out with the use of 2-butanol as a hydrogen donor. Herein, we present the kinetic parameters of cyclohexanone reduction in a flow reactor and data on the reaction rate for several important ketones and aldehydes. The lack of diffusion constraints in the microreactors was demonstrated. Our results were compared with those from other authors and demonstrate the great potential of microreactor applications in fine chemical and complex intermediate manufacturing.

Keywords: Meerwein–Ponndorf–Verley reduction; kinetics; flow microreactor

1. Introduction

A reduction of carbonyl bond is a widespread route for the synthesis of alcohols. However, the reaction, classically catalyzed by noble metals and carried out in the presence of molecular hydrogen, reveals significant limitations, including low selectivity, high sensitivity to sulfur-containing substrates, and high-pressure requirements. The pharmaceutical industry is concerned with the purity of its products. The Meerwein–Ponndorf–Verley (MPV) reaction is an attractive method of synthesizing unsaturated alcohols from ketones or aldehydes using secondary alcohols instead of gaseous hydrogen. According to a generally accepted mechanism of the MPV reaction, the carbonyl group acts as a hydrogen acceptor and alcohol as a hydrogen source. The hydrogen transfer occurs when both substrates are simultaneously coordinated to the same Lewis acidic site (Scheme 1). The formation of a six-membered transition state ring is considered to be a determining step in the reaction rate.



Scheme 1. The mechanism of Meerwein–Ponndorf–Verley (MPV) reduction.

Inexpensive and non-toxic hydrogen donors and catalysts, mild reaction conditions, and exceptional chemoselectivity render this method of reduction favorable over alternatives. Among many active species, such as Zr [1,2], Al [3,4], Mg [3,5], and B [6,7], which are considered to be active catalysts for MPV reduction, zirconium has been shown to be one of the most promising. In the literature, batch processes are predominantly described with the use of numerous catalysts, e.g., homogeneous alkoxides [8,9], zeolites [10,11], mesoporous sieves [12–14], and hydrotalcite [15]. Nevertheless, the tedious separation of homogenous catalysts at the end of the process leads to its deactivation and non-reusability. Powdered catalysts ensure significant benefits over its homogeneous counterparts. However, filtration is an additional time- and cost-consuming step in the technological line. Flow microreactors allow one to overcome these drawbacks and have additional advantages, i.e., high surface-to-volume ratio, improved reaction parameter control, a small equipment size, and a flexibility of module arrangement.

Flow chemistry is perspective and still not explored field in the area of chemoselective MPV reduction. Battilocchio et al. reported the protocol for synthesizing various alcohols from aromatic and aliphatic carbonyl compounds using a packed-bed reactor filled with zirconium hydroxide catalyst [16]. In our previous works [17–19], we demonstrated excellent activity of zirconium-doped silica monolithic microreactors in cyclohexanone reductions and their improved performance compared with the batch process. It was shown that zirconium species terminated with propoxy ligands featured the highest activity in MPV reduction among various Lewis centers immobilized onto monoliths' surfaces used as reactive cores in microreactors. Extensive studies of structural, physicochemical, and catalytic properties revealed the high efficiency of the proposed microreactors.

In this work, we present the kinetic studies of MPV reduction with the use of various carbonyl compounds and 2-butanol as a hydrogen donor. The experiments were performed in continuous-flow zirconium-propoxide-functionalized microreactors of different lengths.

We determined the kinetic parameters, hardly presented for the MPV reduction process carried out in a flow regime. The results of the flow and batch reactors were compared with those of other authors. The kinetic data are crucial to determine the optimum process conditions through the selection of appropriate catalysts and reaction parameters. The knowledge of basic issues related to the course of reactions allows one to set new, more effective paths for conducting processes. Despite the possibility of theoretical computer simulation of the behavior of the reaction system, the experimental determination of the kinetic equation parameters is still necessary for the development of the reactor model.

2. Results

The characterization of siliceous monolithic microreactors functionalized with zirconium species and their catalytic properties were described in our previous papers [17,18]. Kinetic studies were performed in the microreactors featured by the exceptionally low back-pressure. It resulted from the unique structure of cylindrical-shape monoliths applied as reactive cores [20]. Briefly, monoliths were characterized by a continuous, macroporous flow-through structure (macropores in the range of 30–50 μm), extended with mesopores of bimodal size distributions (3/20 nm) and a high surface area (340 $\text{m}^2\cdot\text{g}^{-1}$) (Figure 1). The monoliths were functionalized with zirconium propoxide to obtained

Lewis acid sites on the silica surface. The zirconium cations were terminated by propoxy/hydroxy ligands, which appeared to be very active catalytic centers [18,19]. The concentration of zirconium, determined by ICP MS analysis, was 7.03 wt % (in relation to the mass of silica support) in all studied microreactors.

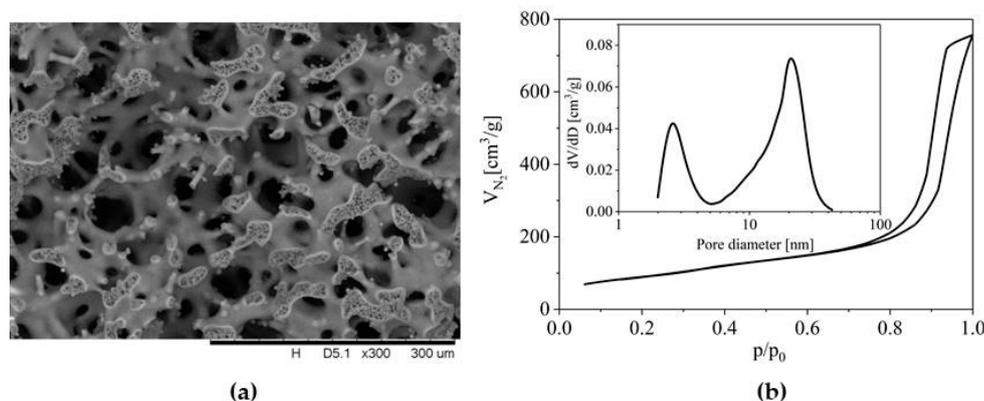


Figure 1. (a) SEM image of silica monolith structure; (b) nitrogen adsorption/desorption isotherm and pore size distribution (insert).

Material functionalization with zirconium precursor did not considerably influence the structural properties of the support. Only a small decline of the surface area and mesopore volume was observed. All features have been preserved after multiple reaction cycles.

Detailed studies of the kinetic experiment were performed for the MPV reduction of cyclohexanone with 2-butanol. First, we checked whether diffusion or activation controls the reaction rate. External mass transfer limitations are a common phenomenon in porous materials. To exclude the impact of diffusional effects on the reaction kinetics, the performance of microreactors with monolithic cores of different lengths were compared with respect to the same residence time, equal to 5 min. Similar conversions of cyclohexanone, about 40%, were achieved in all microreactors of a 1–8 cm length, which evidenced the lack of transport constraints (Figure 2).

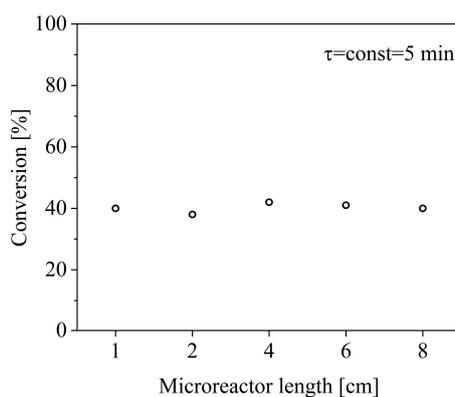


Figure 2. Conversion of cyclohexanone in microreactors of different lengths for a residence time of 5 min.

The results of kinetic experiments for cyclohexanone reduction are depicted in Figure 3. Figure 3a shows the single experimental run carried out for 6 h at 95 °C in a 6 cm long microreactor. The reaction rate constant (Figure 3c) was determined by assuming the first order kinetics and was calculated using Equation (1):

$$\ln(C_0/C) = k\tau \quad (1)$$

where C_0 [$\text{mmol}\cdot\text{cm}^{-3}$] is the initial concentration of ketone, C [$\text{mmol}\cdot\text{cm}^{-3}$] the substrate concentration after the reaction in the microreactor of a fixed length, k [min^{-1}] the rate constant, τ [min] the residence time.

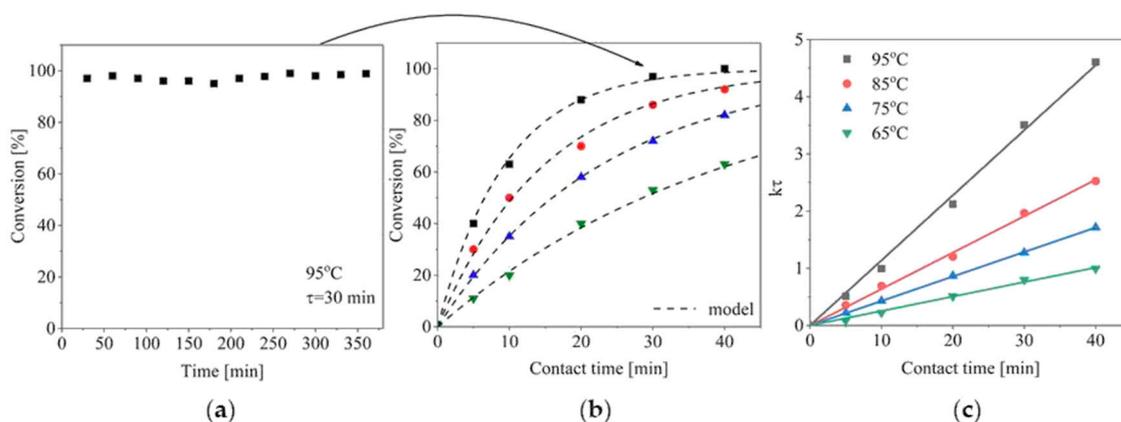


Figure 3. (a) Conversion of cyclohexanone in the 6-cm-long microreactor. (b) Catalytic results for MPV reduction at 65 °C (▼), 75 °C (▲), 85 °C (●), and 95 °C (■) in the microreactor (points—experiments, lines—model). (c) Plot of $\ln(C_0/C)$ versus contact time.

Figure 3b confirms good agreement between the experimental data and the model prediction of the first-order kinetics for the MPV process carried out at different temperatures and contact times in the range of 5–40 min. Each point corresponds to the average conversion obtained in microreactor during 6-h-long tests.

The linear relationship rate constant vs. the contact time was observed through the whole temperature range used in the experiments. The experimental data are in line with those calculated from first-order kinetics equation.

Temperature dependence of the rate constant was examined in the range of 65–95 °C and is shown in Figure 4. The activation energy was estimated from linear regression analysis, and it appeared to be $52 \text{ kJ}\cdot\text{mol}^{-1}$, and frequency factor $k_\infty = 2.69 \text{ min}^{-1}$.

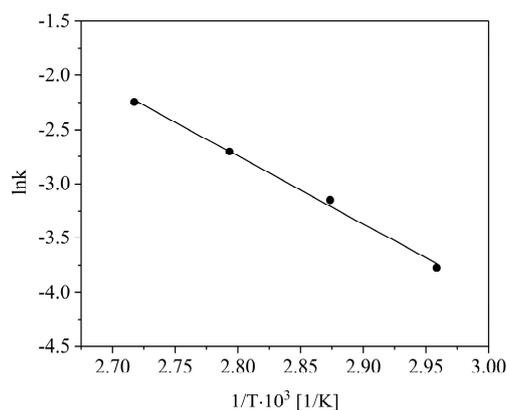
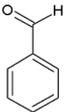
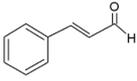
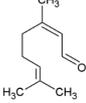
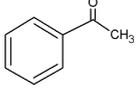
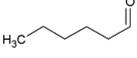


Figure 4. Arrhenius plot for the MPV reduction of cyclohexanone.

The studies of the MPV reduction in the flow process were extended to other ketones and aldehydes, and the results, i.e., the conversion, productivity, and reaction rate constant are summarized in Table 1. Analysis of these data shows that aldehydes are easier to be reduced than ketones. The reaction rate constant of benzaldehyde reduction was 0.212 min^{-1} , while that for cyclohexanone was twice lower. Battilocchio et al. also found that aldehydes, compared with aliphatic ketones,

required a shorter reaction time for complete conversion to alcohols [16]. Steric hindrance is a prevalent factor that affects the reactivity of the substrates. Citral is a mixture of cis- and trans-isomers signified as neral and geranial, respectively. The MPV reduction of citral reveals the preferential formation of its trans product. The yield of geraniol was 20% higher than nerol. The orientation of the carbonyl group to the molecular chain in geranial reduces steric limitations for binding between the Zr center and C=O.

Table 1. Data from catalytic experiments.

Substrate	K^1 [min^{-1}]	Conversion ^{1,*} [%]	Productivity ^{1,*} [$\text{mmol}\cdot\text{g}_{\text{cat}}^{-1}\cdot\text{h}^{-1}$]	Productivity ² [$\text{mmol}\cdot\text{g}_{\text{cat}}^{-1}\cdot\text{h}^{-1}$]	Productivity ³ [$\text{mmol}\cdot\text{g}_{\text{cat}}^{-1}\cdot\text{h}^{-1}$]
	0.106	88	2.22	-	2.28 [21]
	0.021	35	0.9	-	0.11 [15]
	0.212	99	2.64	1.14 [16]	0.36 [10]
	0.081	80	1.92	0.66 [16]	0.48 [5]
	0.031/0.047 ⁴	46/61	0.48/0.9	-	0.54 [5]
	0.026	40	0.96	0.48 [16]	0.12 [22]
	0.08	80	2.1	-	-
	0.041	56	1.32	-	0.72 [23]

¹ this work (reaction temp. 95 °C), ² in the flow process (data from literature), ³ in the batch process (data from literature); ⁴ nerol/geranial; * data for the 4-cm-long microreactor.

The impact of both the steric and electronic effect can be observed in the case of cinnamaldehyde reduction. The low activity can be attributed to the presence of a bulky chain in this substrate and double bond. The productivity in the reduction process of cinnamaldehyde was significantly lower than that for benzaldehyde. The reduction of unsaturated ketone, 2-cyclohexen-1-one, is difficult without affecting the conjugated C=C bond. A significant decrease in conversion was observed compared to the saturated cyclic carbonyl compound (cyclohexanone); nevertheless, the product was obtained with 100% selectivity. Aromatic ketones, compared with cyclic ketones, are more difficult to reduce due to the resonance and inductive effect of the benzene ring [22]. It explains the difference in conversions of cyclohexanone and acetophenone. No products arising from the Tischenko cross reaction or from the aldol condensation [24], were detected for any of the investigated substrates. This evidenced the excellent selectivity of the proposed catalyst.

It should furthermore be highlighted that alcohols produced by the selective hydrogenation of carbonyl-bearing substrates are fine chemicals of primary interest. They are used as flavor additives, and intermediates in drug production. Products of the esterification of cinnamyl alcohol, indole-3-acetic acid, or α -lipoic acid were studied for their antioxidant and anti-inflammatory activity [25], and geraniol was checked in colon cancer chemoprevention and treatment [26].

Our results were compared to the literature data for flow and batch processes. To the best of our knowledge, the MPV process using heterogeneous powdered catalyst at flow conditions has only been published in one paper [16]. The productivities of ZrO₂-based reactors toward benzyl alcohol, cinnamyl alcohol, and 1-phenylethanol are nearly 4 times lower than those achieved in the studied monolithic microreactors. Table 1 shows the productivities from batch reactors obtained by other research. They are significantly lower than those obtained in the proposed flow system (except one case). It was due to excellent mixing and mass transfer conditions, offered by innovative monolithic microreactor characterized by high surface-to-volume ratios. Application of the proposed continuous-flow microreactor for the MPV process offers not only enhanced productivity, but also facilitates process handling by excluding contact with reaction media. The latter is of importance when working with dangerous substances.

3. Materials and Methods

Microreactors were fabricated using silica monoliths as cores. The monoliths were obtained by combined sol-gel and phase separation methods described in details in [20]. Briefly, polyethylene glycol (PEG 35 000, Sigma-Aldrich, St. Louis, MO, USA) was dissolved in 1 M nitric acid (Avantor, 65%, Gliwice, Poland). The mixture was cooled in the ice bath and subsequently tetraethoxysilane (TEOS, ABCR, 99%, Karlsruhe, Germany) was added dropwise. After 30 min of stirring, cetyltrimethylammonium bromide (CTAB, Sigma-Aldrich) was added. After complete dissolution, the sol was transferred to the polypropylene molds and stored at 40 °C for 8 days for gelation and aging. Next, rod-shaped monoliths were washed with deionized water and treated with 1 M ammonia solution (Avantor, 25%) for 8 h at 90 °C. Afterward, the materials were washed, dried at 40 °C for 3 days, and finally calcined at 550 °C for 8 h to remove organic templates. The prepared monoliths of diameter 4.5 mm were put into heat-shrinkable tubes and equipped with connectors to obtain flow microreactors.

Zirconium propoxide moieties were grafted onto silica carriers, maintaining Zr/Si ratio fixed at 0.14 and using a solution of zirconium(IV) propoxide (Sigma Aldrich, 70% in 1-propanol) in anhydrous ethanol (Avantor, 99.8%). Reactive cores were impregnated with the solution and kept for 24 h at 70 °C. Finally, they were washed with ethanol and dried at 110 °C in nitrogen flow conditions.

Structural properties were analyzed by electron microscopy (TM 30000, Hitachi, Chiyoda, Tokyo, Japan) and adsorption-desorption measurements (ASAP 2020, Micromeritics, Norcross, GA, USA).

The continuous-flow microreactors were tested in the MPV reduction of various carbonyl compounds (cyclohexanone: Sigma Aldrich, 99%, benzaldehyde: Sigma-Aldrich, 99%, acetophenone: Acros, Geel, Belgium, 98%, cinnamaldehyde: Acros, 99%, citral: Roth, 95–98%, Karlsruhe, Germany, hexanal: Aldrich, Saint Louis, MO, USA, 98%, nonanal: Aldrich, 95%, 2-cyclohexen-1-one: Acros, 97%) with 2-butanol (Avantor 99%). The molar ratio of substrates was 1:52. The flow rate was changed in the range of 0.03–0.24 cm³·min⁻¹. The progress and selectivity of the reaction were monitored by gas chromatography (FID detector, HP-5 column, 7890A, Agilent, Santa Clara, CA, USA).

The kinetic experiments were carried out in setup shown in Figure 5 for a flow rate fixed at 0.03 cm³·min⁻¹, at the temperature range of 65–95 °C. The mass of the 1-cm-long microreactor was 0.0375 g. The length of reactive cores was changed from 1 to 8 cm (weight form 0.0375–0.3 g) and enabled the obtainment of data for different residence times, calculated using Equation (2):

$$\tau = \frac{m_k \cdot l \cdot V_T}{F} = \frac{0.0375 \cdot l \cdot V_T}{F} \quad (2)$$

where m_k is the mass of monolith per length unit [g·cm⁻¹], l is the microreactor length [cm], V_T is the total pore volume, equal to -4 [cm³·g⁻¹] (data from mercury porosimetry), and F is the flow rate [cm³·min⁻¹].

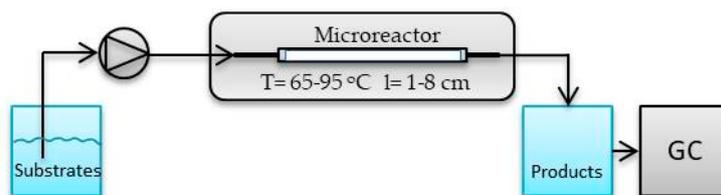


Figure 5. Scheme of the reaction setup.

4. Conclusions

The outstanding potential of continuous-flow microreactors in the area of selective reduction of carbonyl compounds was demonstrated. Broad-range and long-term experiments were conducted to determine the kinetics of the MPV reaction of cyclohexanone in the zirconium-functionalized flow microreactors. The lack of diffusion constraints in the microreactors was shown. The activation energy was calculated to be $52 \text{ kJ}\cdot\text{mol}^{-1}$. Moreover, reaction rate constants for several ketones and aldehydes were collected. The rate of the process is necessary to design the apparatus and reaction systems. Significant differences in process efficiency were recorded for various carbonyl compounds. They were assigned to steric effects caused by bulky chains, electronic effects of an additional double bond, and an inductive effect of the benzene ring. We believe that the proposed system can be effectively exploited for fine chemical and pharmaceutical production.

Author Contributions: A.C. and K.M. conceived, designed, and performed the experiments; A.C., K.M., and J.M.-B. analyzed the data and wrote the paper.

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Conflicts of Interest: The authors declare no conflict of interest.

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