

REVIEW ON HIERARCHICALLY MICROSTRUCTURED MONOLITHIC REACTORS FOR HIGH YIELD CONTINUOUS PRODUCTION OF FINE CHEMICALS

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Dedicated to Professor Andrzej Burghardt on the occasion of his 90th birthday

Preparation and properties of hierarchically structured porous silica monoliths have been discussed from the viewpoint of their application as continuous microreactors for liquid-phase synthesis of fine chemical in multi kilogram scales. The results of recent topical papers published by two research teams of Institute of Chemical Engineering Polish Academy of Sciences (ICE) and Department of Chemical Engineering and Process Design, Chemical Faculty, Silesian University of Technology (SUT) have been analyzed to specify the governing traits of microreactors. It was concluded that even enhancement factor of 100 in activity, seen in enzyme catalyzed reactions, can be explained by a proportional reduction of its physical constraints, i.e. huge enhancement of external mass transfer and micromixing. It is induced by very chaotic flows of liquid in tens of thousands of waving connected channels of ca. 25–50 μm in diameter, present in the skeleton. The scale of enhancement in the case of less active catalysts was smaller, but still large enough to consider the most practical applications.

Keywords: microreactors, in-flow synthesis, process intensification, nanostructured materials

1. INTRODUCTION

Development of microreactors for the cost-effective continuous synthesis of fine chemicals or complex intermediates demanded by pharma, food and related industries, attracted considerable attention over the past two decades (Sachse et al., 2012; Tanimu et al., 2017; Wohlgemuth et al., 2015). The extensive research already proved viability of the concept and demonstrated important advantages of microreactor-based technologies: vastly improved efficacy and process safety at lower costs. Moreover, a considerable improvement in reaction control enabled to obtain much higher selectivity, and thus purity of the targeted chemicals. Overall, continuous microreactors usually performed much better than columns filled with fine particulate catalysts and/or batch slurry systems.

Initially, the major focus was on microscale devices, e.g. lab-on-a-chip, with fine/submillimeter channels made by micromachining and featured by microliter outputs. They were designed, primarily, for analytical

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and high throughput applications, and not the synthesis of fine chemicals in multi kilogram amounts. For that application test reactors were made either of metal or glass capillaries, typically 200–500 μm in diameter, either filled in or wall coated with a catalyst. The surface-to-volume ratios from the range of $10^5 - 5 \times 10^5 \text{ m}^2/\text{m}^3$, featured by such heterogeneous microreactors, compare most favourably with about $10^3 \text{ m}^2/\text{m}^3$ in present date industrial reactors, and it has a strong effect on kinetics, space-time yield and overall economy. But not less importantly, in the case of continuous microreactors typically expensive and time consuming scale ups are replaced by numbering up, i.e. parallel arrangement. Therefore, once elaborated in a lab-scale, the technology is ready for commercialisation. That is the advantage always worth keeping in mind when different reactor-technology options are considered.

In the capillary microreactors each channel needs a separate treatment to impart catalytic properties. If they are filled with fine (powder) catalysts, low velocities need to be applied, but even then the pressure drop (overpressure) is prohibitively high, 50 bar or more. Under these conditions, the overall kinetics is strongly affected by the external mass transfer to the catalysts surface. Alternatively, internal walls of capillaries can be coated with catalytic entities, but always at the expense and loss in the surface-to-volume ratio, and hence an overall activity, efficacy and space-time yield (productivity).

A major breakthrough was achieved more recently by application of silica monoliths with a multi-modal hierarchical pore structure as continuous flow microreactors (El Kadib et al., 2009; Sachse et al., 2011; Sachse et al., 2012; Szymańska et al., 2013). Those monoliths, synthesized using Nakanishi method (Nakanishi, 1997), feature a very open bi-continuous structure of silica skeleton and voids, the latter accounting for about 70% of total volume (Fig. 1). However, while the Montpellier-based group, which first adopted that approach, directly applied the Nakanishi's synthetic protocol the two Gliwice-based groups (one at ICE the other one at SUT), predominantly applied their own variant of a double templating approach proposed by Småt et al. (Smatt et al., 2003; Pudło et al., 2006). The monoliths/microreactors obtained on that way (GMRs) possess flow-through channels in the range of 25–50 μm in diameter, (Fig. 1A), and in that they strongly contrast with 3–6 μm diameter channels featured by the Montpellier group promoted monoliths/microreactors (MMRs, Fig. 1B). From the engineering standpoint, the former allow for much larger fluid velocities, and hence flow rates to be applied, even at overpressures reduced

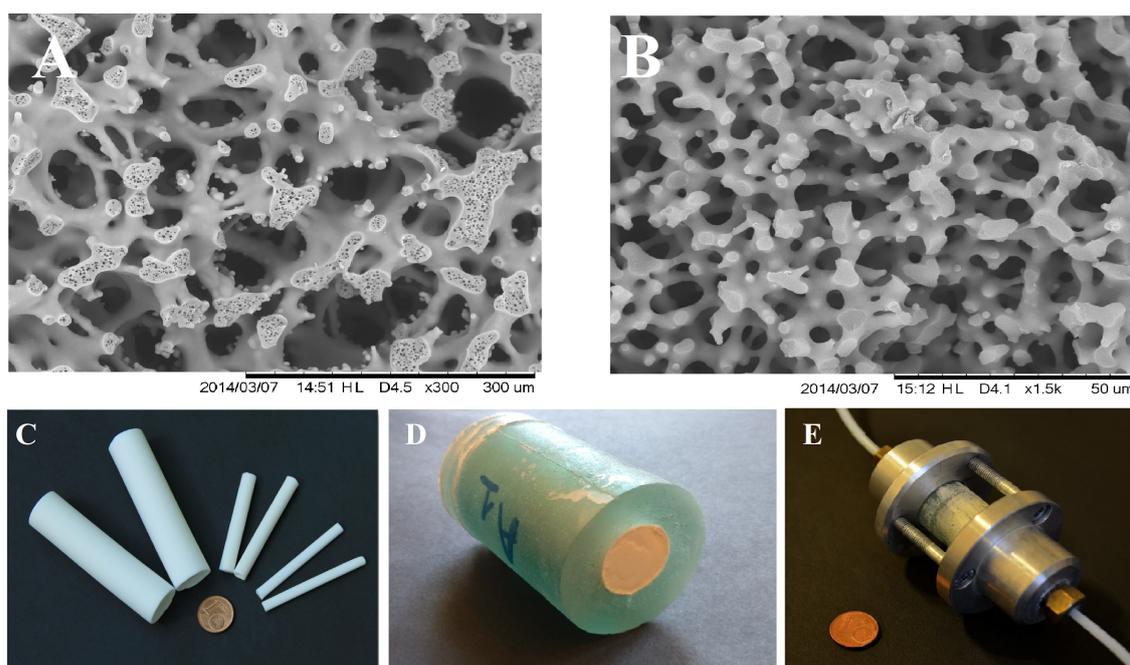


Fig. 1. SEM image of monolith structure applied as GMR- (A) and MMR- (B) type of microreactor, images of monoliths used in GMRs (C), a single monolith embedded into polymeric shell (D), image of a typical GMR (E)

to few bars (Szymańska et al., 2013). Larger liquid velocities directly enhance external mass transfer, and therefore boost an overall (apparent) reaction rate and hence space-time yield, whereas lower pressures additionally improve safety and reduce costs. But more importantly, the chaotic structure of tens of thousands of waving interconnected flow-through channels present in the monolith cross section (Fig. 1A), enforce and induce a chaotic movement of liquid blobs/elements which split and recombine, twist, stretch and permanently collide and impinge on walls of silica skeleton struts. In that the flows in microreactors under study portray the flows of liquid in intensive static micromixers (Stroock et al., 2002), and vastly contrast with ordered laminar flows in standard capillaries. Clearly, such a chaotic movement strongly impacts intensity of micromixing and external mass transfer to the expanded surface of the silica skeleton. Thus, the reaction rates and the space-time yields observed in such hierarchically microstructured monolithic reactors (HIMOR) may be expected to be vastly increased compared to capillary microreactors and related devices, to enable multi kilogram production scales to be very effectively realized in a short time.

The objective of this paper is to present and discuss some of the most important observations made by ICE PAS- and SUT-based teams while working on different projects and hence making use of different catalysts but embedded in the monoliths of a similar pore structure. The studies conducted at ICE focused on the development of HIMORs functionalized with more established catalytic moieties (e.g. Brønsted and Lewis acid centres), whereas SUT group aimed at the development of HIMORs with immobilized enzymes. We believe that an extensive and holistic analysis of the systems already developed, so similar in terms of the monoliths topology and so different in the applied catalyst (and hence intrinsic reaction kinetics), should lead to more conclusive findings and pave the way for better understanding and further progress in microstructured reactor-based technologies.

2. HIMORS FABRICATION AND PROPERTIES

The highly porous silica monoliths (rods) – cores of HIMORs, are prepared in a somewhat complex sol-gel chemistry process which combines thermally induced phase separation tuned in time to silica gel formation and mesopore templating. Precise descriptions of the preparation protocol applied by both Gliwice-based teams have been given elsewhere (Chrobok et al., 2009; Pudło et al., 2006; Szymańska et al., 2013). Of importance is that the same topology of pore network, but differing in pore sizes, can be obtained by changing composition and conditions of their synthesis (cf. Fig. 1A and 1B). But since pore structure is perhaps the most important single property of monolithic microreactors, critical for performance, it has to be well conceived and designed taking both the reactor- and the catalyst-related constraints into account. Subjects to be considered are: surface area to be activated, accessibility and surface concentration of the active sites and mass transfer to the external surface and then inside pores, and also the macroscopic flow through the monolith. Note that micromixing as well as both external and internal mass transfer very often appear to control an overall/apparent reaction rate, and it happens to be overlooked in many catalytic and/or technology oriented studies. Therefore, to make most of embedded/attached (heterogeneous) catalyst potential the internal pore structure of the monoliths needs to be easily accessible, therefore very open, to ensure high values of external mass transfer and low values of Thiele modulus. For that very reason in GMRs total porosity was about 87–89% (pore volume ca. 4 cm³/g of silica), over two thirds of which (ca. 2.8–3.0 cm³/g) fell to the flow-through (macro)pores and the rest (ca. 1–1.2 cm³/g) mainly to large (20 nm) mesopores present in the silica skeleton (Fig. 2A). Those large mesopores can conveniently host even larger catalytic entities (e.g. metal nanoparticles or enzyme molecules) still leaving room for an unhindered diffusion of reactants, and contribute to the specific surface area of about 300 m²/g that remains to be catalytically activated. But again, to facilitate access to active sites of catalysts, besides large mesopore diameter, also thickness of the silica skeleton (diffusion path) was set to be < 10 μm (Fig. 1A). It compares most favor-

ably with the size of fine catalysts (ca. 30–50 μm dia.) applied in most batch slurry technologies (over 60 μm in packed beds). For comparison (cf. Fig. 2A), the pore structure of MMRs features: macro-pore diameter in the range 3–6 μm , pore vol. $\sim 1.5 \text{ cm}^3/\text{g}$, mesopore diameter $\sim 10 \text{ nm}$, mesopore vol. $\sim 1.2 \text{ cm}^2/\text{g}$, surface area ca. $700 \text{ m}^2/\text{g}$, skeleton thickness $\sim 3 \mu\text{m}$, and overall porosity 76–78% (Galarneau et al., 2016a).

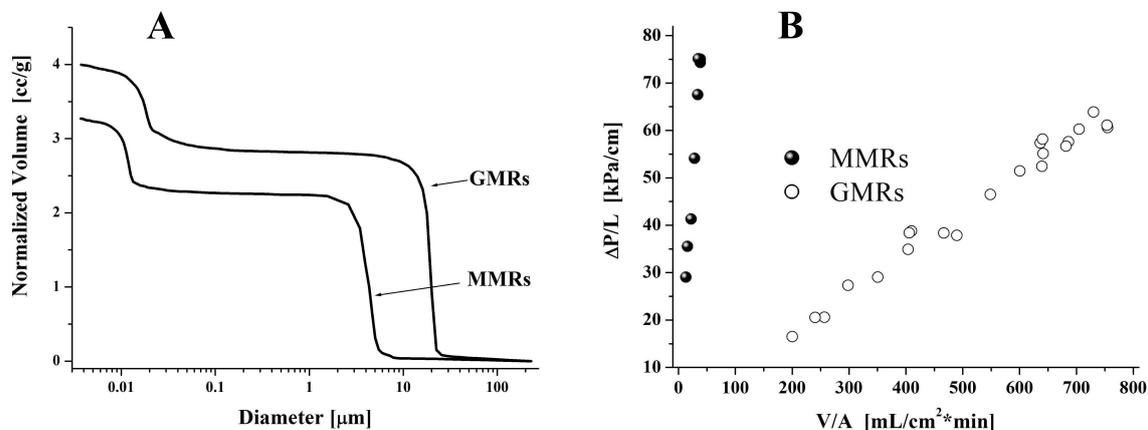


Fig. 2. Cumulative pore size distributions in pristine silica monoliths obtained by mercury porosimetry (A), and pressure drop gradient vs. flow rate determined for GMR- and MMR-type of structures (B)

Flows through the monoliths were shown to obey the Darcy law of permeability, as can be found from the linearity of pressure drop vs. liquid velocity plot shown in Fig. 2B. For GMRs the Darcy permeability coefficient (K) was found to be equal to $19 \mu\text{m}^2$, i.e. much beyond the threshold value of materials featuring excellent permeability ($1 \mu\text{m}^2$), and over twenty-fold larger than that for the MMRs ($K \sim 0.85 \mu\text{m}^2$) (Szymańska et al., 2013; Galarneau et al., 2016b). This proves that liquid velocities (and so flow rates) may even be twenty-fold larger in the GMRs than in the MMRs for the same value of overpressure. And not less importantly, the flows of hundreds mL/min of liquid across one cm^2 of the monolith's cross section can be readily realized (Fig. 2B). In effect, in the monoliths/microreactors 2 cm in diameter (ca. 3 cm^2 cross section) synthesized using the procedure recently claimed in (Szymańska et al., 2017), even the flow rates of one L/min can be realized at low pressure drops. Furthermore, these microreactors feature a surface-to-volume ratio in excess of $10^7 \text{ m}^2/\text{m}^3$, i.e. two orders of magnitude larger than conventional microreactors (vide supra), and that value is formidable. Irrespective of pore structure the monoliths can be converted into MIMORs using two methods, either by cladding with a polymeric resin at room temperature to form a rigid shell (Fig. 1C, D, E) (Szymańska et al., 2013), or by putting into a heat shrinkable PTFE (polytetrafluoroethylene) tube, as proposed in (El Kadib et al., 2009; Sachse et al., 2011), with ports/connections attached thereto. The latter process is very convenient, but as it involves heating to ca. $350 \text{ }^\circ\text{C}$, it is applicable to pristine, unmodified monoliths. Thus, surface functionalization and catalyst attachment need to be done in-flow; there is no such restriction when using the former method.

3. GMRS PERFORMANCE IN THE HETEROGENEOUS REACTION

The research conducted by SUT team focused on the application of MIMORs in enzyme catalyzed reactions with the enzymes immobilized on the monolith surface. Each study always began with elaboration of optimal procedure/conditions for enzyme immobilization. It was followed by extensive investigations of microreactor performance, from various perspectives, including a comparison with reference system(s) considered as benchmark. All the studies always made use of the same enzyme preparation.

The GMRs studies started with a model reaction of invertase-catalyzed continuous hydrolysis of sucrose into glucose and fructose (Szymańska et al., 2013). The initial results already exceeded all expectations. For a rod of 4×50 mm (diameter \times length) the reaction rate coefficient (V_m in Michaelis-Menten equation) was found to be over 1000 times larger than using a native enzyme and also when it was attached to particles of crushed monoliths or mesoporous silica of MCF family (both tested in a batch slurry system). In the continuous GMR operation the overpressure was below 2.5 bar and the reactor worked over two weeks with no loss in activity and pressure drop change. In more practical terms – substrate conversion of about 90% could be achieved in just 3.5 seconds of mean (hydraulic) residence time. Note that MCFs used as the benchmark enzyme support were earlier shown to give the most active biocatalysts among various mesoporous materials (Szymańska et al., 2007). A more meticulous study showed that concentration of the hosted enzyme was about ten-fold larger in GMR than in two batch systems under study (Szymańska et al., 2013). Clearly, that directly resulted in and explained a factor of ten increase in the value of V_m . Therefore, the remaining two orders of magnitude of the larger value of V_m , determined for GMRs were ascribed to a hundred-fold increase in the value of frequency constant (k_{cat}) compared to the both batch slurry systems.

A more recent study dealt with the GMR-immobilized trypsin and aimed at a high-yield and fast proteolysis (hydrolysis of proteins) for protein diagnostics, and also at paving the way to a continuous-mode synthesis of specific/active peptides demanded by food industry (Szymańska et al., 2016a). The proteolysis of cytochrome c (Cyt-c) and myoglobin (Myo), considered as model proteins, appeared to be exceedingly fast, even without any earlier pretreatment. But not less importantly, MALDI-TOF/TOF mass spectrometry analysis of sequence coverage was very high: 70% (Cyt-c) and 90% (Myo) after 24 min process, and 39% (Cyt-c) and 53% (Myo) when time was reduced tenfold, to just 2.4 min. Typically, this process is carried out overnight using a native form of the enzyme, and the values of sequence coverage are similar to those obtained in GMR within 24 min. This clearly demonstrates the scale of process speed up, with no compromise on the quality of mapping and safety.

In another recent study we showed that full transesterification of neopentylglycol (NPG) with ethyl acetate can take in GMRs less than one minute when carried out in a biphasic 50/50% system using acyltransferase from *Mycobacterium smegmatis* (MsAcT), whereas the corresponding batch process with the native enzyme took 3.5 h to reach a conversion of 84% (Szymańska et al., 2016b). MsAcT was attached either covalently via amino groups or by a specific His-tag mediated adsorption on Ni or Co sites, and both methods gave similar results for enzyme loading and specific activity.

Most recent studies of kinetic resolution of both non-equimolar and racemic mixtures of enantiomers (diastereoisomeric alcohol or aminoalkylphosphonic- and aminoalkylphosphinic acids and their esters) (Zielińska et al., 2017) also demonstrated a unique enhancement of enzyme catalyzed reactions in GMRs compared to batch systems with the same enzymes.

The research conducted by ICE PAS team focused on the application of HIMORs in acid catalyzed reactions with Brönsted and Lewis sites, which were studied in esterification reaction and Meerwein-Ponndorf-Verley (MPV) selective reduction of carbonyl compounds, respectively. Both types of acid sites were attached to the monolith surface by the same (impregnation) method. It appeared that the concentration of arenesulphonic acid sites (strong acidic Brönsted centers) depended on the structure parameters of pristine silica monoliths. More specifically, the larger surface area and thus the number of hydroxyls available for attachment, resulted in a higher (50%) concentration of the attached functional groups (Ciemiega et al., 2017a). However, this did not translate into the productivity (for the same conversion) related to mass of the monolith, which was practically the same in all tested monoliths, irrespective of the size of macropores present in monoliths: 25–50 μm /GMR, 3–6 μm /MMR, 1–3 μm (as in HPLC monolithic columns). However, the rate of butyl acetate formation related to the amount of active centres ($105.2 \text{ mol/molH}^+ \cdot \text{h}^{-1}$) achieved in the GMR was ca. 25–30% higher than in MMR microreactors. This clearly confirms that more

intensive homogenization (micromixing) and mass transfer to the skeleton surface seen in GMRs appear to boost an overall/apparent reaction rate, and that these effect prevail over the concentration of active sites. Moreover, performance of the best microreactor (GMR) was significantly better than that found for the reactor packed with Amberlyst 15 and the microreactors could operate up to 300 °C. The long term process of lactic acid esterification with butanol at 140 °C proved quite good stability of structural and catalytic properties of the proposed reactors (Koreniuk et al., 2015a).

The properties of microreactors functionalized with different Lewis acid centres were reported in the series of papers published recently in (Ciemięga et al., 2017b; Ciemięga et al., 2018a; Ciemięga et al., 2018b; Koreniuk et al., 2015b; Maresz et al., 2018). These microreactors were tested in MPV selective reduction of carbonyl compounds, which is of practical importance since it makes use of secondary alcohols instead of gaseous hydrogen. Detailed studies of Lewis acid sites derived from Zr, Al and Ti ions surrounded by various ligands, and obtained using different precursors, showed that the best catalytic performance revealed the monoliths modified with zirconium propoxide (Ciemięga et al., 2018b). The highest productivity in reduction of cyclohexanone and benzaldehyde with 2-butanol was reached in GMRs with Zr/Si mass ratio equal 0.14 (Ciemięga et al., 2017b), which provided the largest surface concentration of Lewis sites of a medium strength. UV-Vis studies confirmed the presence of zirconium in tetrahedral coordination, which is regarded to be most advantageous for the MPV reaction mechanism. Lewis sites in the form of metals terminated by alkoxy/hydroxo groups preserved their low coordination number in contrast to the oxide forms, enabling faster coordination of substrates to acid sites and thus higher reaction rate. Moreover, comparative studies of batch slurry reactors (powdered monolith) clearly confirmed much higher activity of the functionalized GMRs; in batch system 60% conversion was achieved after 300 min., whereas in GMR after only 10 min. This again was ascribed to much more intensive mass transport in the monolith. The most recent study of the MPV reaction kinetics in a Zr-modified microreactors reported in (Maresz et al., 2018) clearly corroborated huge potential of the GMR family of microreactors in fine chemical and complex intermediate manufacturing.

All the monoliths discussed above were made in a two-step process, i.e. immobilizing active species by impregnation of pristine silica monoliths. Owing to a sol-gel basis of the monolith synthesis a direct fabrication of catalytically active monoliths is possible and the case of mixed titania-silica monoliths was studied and reported in a paper published in (Koreniuk et al., 2016). Their performance was compared with those obtained using a two-step method in a continuous-flow oxidation of 2,3,6-trimethylphenol to 2,3,5-trimethyl-1,4-benzoquinone with hydrogen peroxide as oxidant. A direct incorporation of titanium (even in small concentration, ca. 1 wt.% and 2 wt.%) appeared to have a dramatic effect on pore structure of the monoliths thus obtained; they featured a continuous macropore network with diameters of 8–10 μm and 2–4 μm , and pore volumes of 0.9 cm^3/g and 0.5 cm^3/g , respectively (Fig. 3). In silica skeleton only

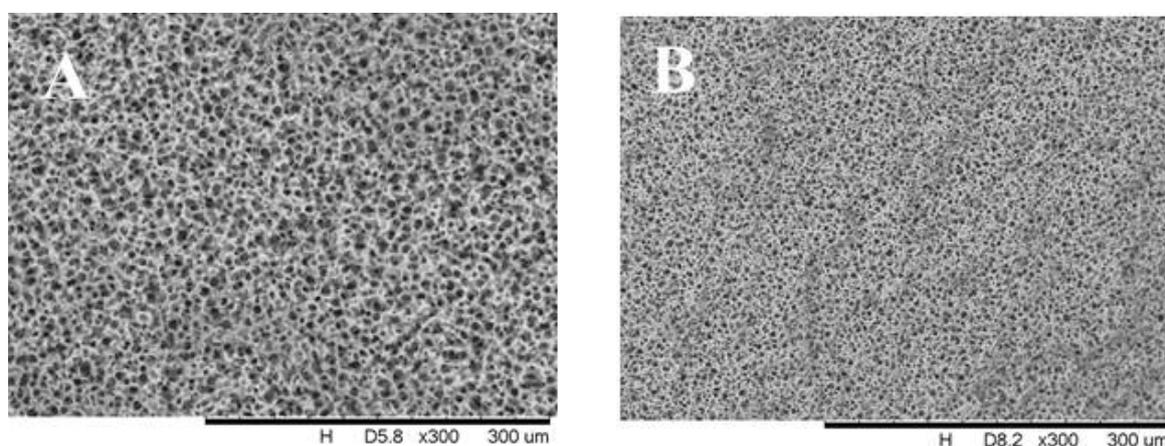


Fig. 3. SEM images of titania-silica monoliths with 1 wt.% (A) and 2 wt.% (B) of Ti

micropores ca. 1.5 nm in size were detected, and they were expected to pose a serious hindrance to diffusive transport. Because of lower porosity and much smaller flow-through pores the pressure drops were almost two orders of magnitude larger than those recorded in the corresponding GMRs functionalized by post-synthesis.

Despite the fact that the direct method favored a finer dispersion of Ti ions in silica skeleton, and therefore larger TOF, better performance, i.e. significantly higher conversion and about factor four increase in productivity (space-time-yield) were obtained for the reactors fabricated in the two-step process. Again, this could be explained by a very intensive mass transport in macro- and mesopore size scales.

4. CONCLUSIONS

Monolithic microreactors with a very open hierarchical pore structure (HIMORs) enable exceedingly fast and cost-effective synthesis (also kinetic resolution) of fine chemicals using various catalysts attached/embedded in the porous skeleton. The reaction rate enhancement, compared to batch slurry systems with the same catalyst, was found to depend on intrinsic activity of the catalysts. In the case of enzyme catalysts, which by nature feature very high activity (quantified by very high frequency constants), the external mass transfer and homogenization rate appeared to control an overall/apparent rate of the reaction. Consequently, a dramatic enhancement of the apparent reaction rate, even by two orders of magnitude, observed in enzyme functionalized HIMORs, can be ascribed to a symmetrical reduction of these physical constraints, induced by very chaotic flows of liquids through a waving, tortuous structure of HIMORs.

In the case of more standard (and typically much less active) catalysts, i.e. featured by frequency constants much lower than those in enzyme kinetics, the reaction rate enhancement in HIMORs was still pronounced but lower, rarely ten-fold. This trend was observed when the corresponding reaction rate time constants were expected to be of the same order (tens of milliseconds) as those of physical constraints of the reaction rate posed by kinetics of external mass transport and micromixing. We believe that this reasoning, proposed for the first time in HIMOR-related literature, paves the way to further progress in their development and well-conceived practical applications.

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