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Microreactors

Functionalized Inorganic Monolithic Microreactors for High Productivity in Fine Chemicals Catalytic Synthesis**

*Abdelkrim El Kadib, Ricardo Chimenton, Alexander Sachse, François Fajula, Anne Galarneau, and Bernard Coq**

Continuous-flow catalytic microreactors offer safe, eco-friendly, and intensified processes for the long-term production of fine chemicals.[1] In many cases, flexible production with higher yields in much shorter time can be achieved than in batch reactions. One can identify three kinds of flow microreactors, namely parallel open microchannels, packed beds, and monoliths. The use of monolithic structured catalysts overcomes some physico-chemical drawbacks, such as fluid dynamics, pressure drop, heat and mass transfer, low contacting efficiency, and mechanical attrition, associated with conventional packed-bed reactors.[2] However, the monolithic structured catalysts will not solve any issue related to chemical deactivation of the catalyst. Monolith reactors are composed of 1–5 mm parallel channels or foams with interconnected 0.1–1.0 mm flow-through pores, and are mainly used in gas phase reactions or catalytic combustion.[3]

For the synthesis of fine chemicals, there is a need for smaller convection pores and skeleton thickness (struts) ranging from 5 to 50 μm to process bulky molecules efficiently with fast diffusion to and from the active sites within the mesopores. The required specifications for these materials would be: 1) monolith diameter of about 0.5–10 mm to perform nano- and microsynthesis; 2) narrow size distribution of flow-through and diffusion pores, which should guarantee a flat flow profile and a uniform residence time for reactants through the monolith and is an improvement over randomly packed-bed microreactors in which uncontrolled fluid dynamics may generate stagnation and broader residence time distribution; 3) high thermal (200–300 °C) and mechanical stability; and 4) easy generation of a variety of catalytic active sites at the surface.

Polymer-based monolithic supports first received great attention with regards to catalytic applications in fine-chemicals synthesis.[1h,4] However, the possible swelling of these polymeric materials may cause pressure drops along the microchannel resulting in variations in the residence time for pressure-driven microreactors.[1c,5] Associated drawbacks are the typically limited mechanical resistance, lower thermal stability, chemical inertness, and non-uniformity of radial permeability. Furthermore, a complex synthesis of the functionalized active polymers is required, limiting the ease of tenability. To circumvent, at least in part, some of these disadvantages, composite materials consisting of inorganic carrier materials with incorporated polymers were designed.[1h] A highly promising alternative to these materials are the inorganic carriers. Such materials have recently received a great deal of interest, with flow-through pores at the micrometer scale and a second network of homogeneously distributed mesopores within the struts.[6] These materials were essentially designed for HPLC applications with columns featuring flow-through pores smaller than 2 μm. Although heterogeneous catalysis extensively uses silica-based materials, to the best of our knowledge, these materials have not yet been evaluated in catalytic reactions in flow conditions. The versatility of inorganic silica supports is the availability of surface silanols that are prone to react allowing the grafting of a wide variety of active organic functional groups (e.g. acidic, basic, and chelating ligands). Functionalized ordered mesoporous silica have received considerable interest for broad applications including catalysis.[7] The knowledge gained in this field appears very promising for extrapolation of the design concept of functionalized silica to their monolithic version for catalysis, which has to date not been reported.

Herein two main innovations are proposed. 1) The on-line grafting of catalytic functions on monolith silica matrices by a continuous cyclic process; 2) the first examples of catalytic reactions carried on shaped and functionalized inorganic monolith microreactors featuring flow-through pores of 9 μm and diffusion pores of 13 nm. These materials demonstrate unique hydrodynamic behavior in liquid-phase reaction processes.

Monolith samples, hereafter called MonoSil (6.3 mm diameter, ca. 0.08 g silica per centimeter length; Figure 1 a), featuring reproducible textural properties were synthesized according to a previous report.[6e] They exhibited the following characteristics:[8] average cavities of 9 μm connected through 4.3 μm windows (mercury porosimetry); skeleton thicknesses of 3 μm (SEM, Figure 1 d,e); diffusive mesopores of about 13 nm (nitrogen sorption); volume of flow-through and diffusion pores of circa 1.95 $\mathrm{mL\,g^{-1}}$ (mercury porosimetry), and 1.25 $\mathrm{mL\,g^{-1}}$ (nitrogen sorption), respectively. The total porosity and the surface area of the monoliths are 0.86

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[*] Dr. A. El Kadib, Dr. R. Chimenton, A. Sachse, Dr. F. Fajula, Dr. A. Galarneau, Dr. B. Coq
Institut Charles Gerhardt Montpellier—UMR 5253 CNRS/ENSCM/UM2/UM1, 8, rue de l'Ecole Normale
34296 Montpellier cedex 5 (France)
E-mail: bernard.coq@enscm.fr

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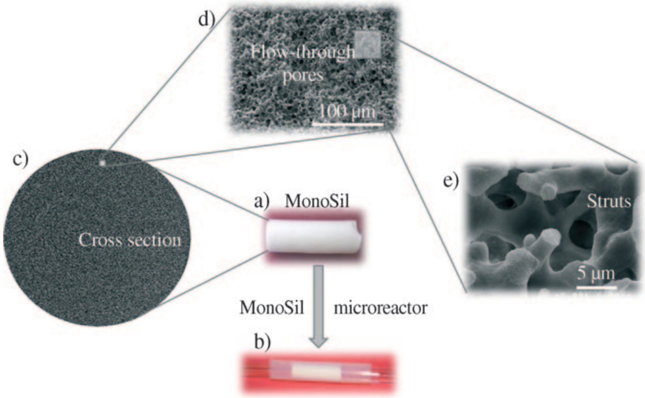
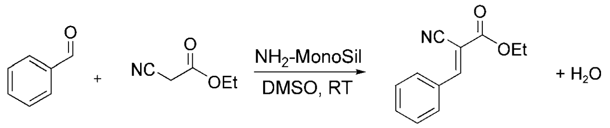
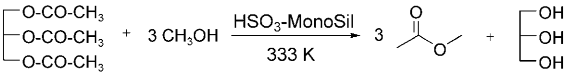


Figure 1. a) MonoSil as prepared; b) MonoSil microreactor; c) X-rays tomography of a cross section; SEM images of d) flow-though pores and e) struts.



Scheme 1. The Knovenagel reaction between benzaldehyde and ethyl cyanoacetate.



Scheme 2. Transesterification of triacetine by methanol.

and 650 m^2 g^{-1}, respectively. The open-cell structure of MonoSil ressembles that of ceramic foams,[3b] but 100 times smaller. The MonoSil exhibits a high mechanical strength as shown by mercury porosimetry.[8] Two striking features of MonoSil are:

1) A uniform radial distribution of voids and struts, as shown by X-ray tomography (Figure 1 c), and a very narrow size distribution of windows and diffusion pores.[8] These characteristics guarantee an extremely flat flow profile and the same residence time for all reactant molecules. The flow resistance through the MonoSil can be compared to that of a microreactor packed with irregularly shaped particles of about 50 µm.[8]
2) A very short diffusion path of 3 µm in the struts. Compared to a microreactor packed with 50 µm particles (same flow resistance), the typical diffusion time scale τ is then 200 times smaller in MonoSil ($\tau = l^2/2D$, l is the diffusion length and D is the diffusion coefficient). This smaller time scale is an outstanding characteristic of the microreactor that processes bulky molecules in fine chemical synthesis.

The targeted catalysts, basic NH$_2$-MonoSil and acidic HSO$_3$-MonoSil, were prepared by grafting aminopropyltriethoxysilane or 2-(4-chlorosulfonylphenyl)ethyltrimethoxysilane through a one-step cyclic flow process, without the addition of a catalyst to avoid self-polymerization of the species to be grafted (see the Experimental Section). Nitrogen sorption isotherms of hybrid monoliths exhibit the same profile as those of parent MonoSil, with a decrease in surface area, total pore volume, and pore diameter as expected for grafted silica.[8] ^{29}Si CP MAS displays T-type resonances, demonstrating that the organosilanes are covalently bonded to the MonoSil matrix.[8] To the best of our knowledge, this is the first example of catalytic activity in post-grafted silica performed under flow conditions. The amount of grafted species was found to be 1.41 mmol g^{-1} for NH$_2$-MonoSil and 0.95 mmol g^{-1} for HSO$_3$-MonoSil. The behavior of the catalysts was evaluated in two reactions: 1) The base-catalyzed Knovenagel reaction between benzaldehyde and cyanoethyl acetate (Scheme 1); 2) the acid transesterification of triacetine with methanol (Scheme 2). These model reactions may be poisoned by their co-products, water (Scheme 1) and glycerol (Scheme 2). The former constitutes an efficient strategy for the creation of C–C bond.[9] The latter is considered as a model for the transesterification of triacylglycerol. MonoSils proved very active and selective (> 99 %) in these two kinds of reactions. In a continuous process, the long-term stability of the catalyst activity is a key point. For the two reactions, MonoSils did not show any deactivation over several hours, as examplified for the Knovenagel reaction using NH$_2$-MonoSil, which maintained 84 % cyanoethyl acetate conversion for at least 28 h on stream (Figure 2), exhibiting a TON (turnover number is the number of reactant moles converted per mole of catalyst) of 2280. This is an outstanding performance, as silica may suffer some textural and/or structural alterations from interaction with water.[10] The stability of the catalytic properties of NH$_2$-MonoSil is most likely due to the continuous exclusion of the formed water from the monolith. Fine chemicals syntheses using heterogeneous catalysts are commonly carried out in batch reactors and more recently in packed-bed microreactors.[9c] Therefore, the performances of the MonoSil catalysts (1.9 cm length, 0.160 g) were compared with a closed stirred-tank reactor (batch) and a packed-bed microreactor (4.2 mm

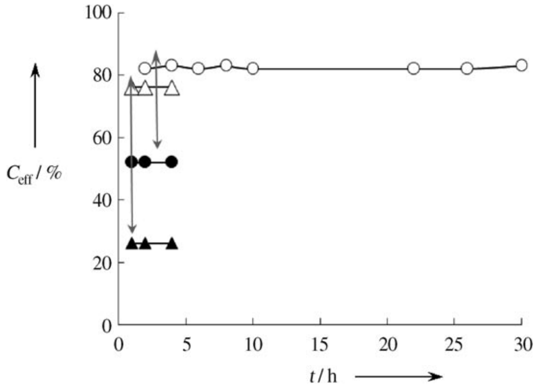
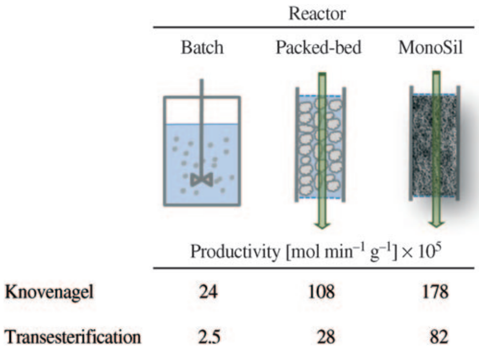


Figure 2. Conversion efficiency (C_{eff}) as a function of time and flow conditions in monolith (○, △) and packed-bed (●, ▲), for the Knovenagel (○, ●) and transesterification (△, ▲) reaction.

inner diameter), both containing 0.160 g of a sieved fraction (50–100 μm) of crushed MonoSil. Batch and flow experiments have been compared in terms of conversion and efficiency (Figure 2 and Figure 3).



	Batch	Packed-bed	MonoSil
	Productivity [mol min^{-1} g^{-1}] × 10^5		
Knovenagel	24	108	178
Transesterification	2.5	28	82

Figure 3. Productivity of NH_2- and HSO_3-MonoSil in batch (powder), packed-bed (powder), and monolith reactors. The productivity in the batch reactor was compared at a similar extent of conversion as in the monolith (i.e. 84% for the reaction in Scheme 1 and 79% for the reaction in Scheme 2).[8]

It is clear in the flow mode that the MonoSil catalysts are significantly more efficient than in batch mode for the two reactions (Figure 3). HSO_3-MonoSil was 18 times more efficient in the monolith than in the batch reactor. NH_2-MonoSil was 13 times more effective in monolith than in the batch mode. Several physical and chemical factors, alone or in combination, allowed for a faster molecular flow to and from the active sites and can explain the higher efficiency of the MonoSil microreactors. These factors are:

1) A larger contact area between the reaction medium and the catalyst, owing to the large surface area of the solid in contact with the flow (convective mass transfer).
2) A much shorter diffusion path for the molecules through the struts (3 μm) compared to that through grains, which are ten times larger in size.[8] This is helpful for the reactant molecules and for the product, which will be scavenged out of the pore network faster.
3) The non-accumulation of co-products, which strongly adsorb on active sites, in the reservoir containing the reactants prevents the inhibition effect by water and glycerol in case of the model reactions. In contrast, the inhibition becomes more and more sensitive as the conversion proceeds in the batch reactor. This point is certainly of great importance.[8]

It is also noticeable that the MonoSil is more effective than the packed-bed reactor. Non-accumulation of co-products is also observed in case of packed-bed reactor, and thus the reasons for lower efficiency might be due to the first two explanations.

Herein the potential of an inorganic monolith microreactor with micrometer flow-through pores is demonstrated. With the knowledge gained in the preparation of silica monoliths,[6e] breakthroughs in catalysis can be contemplated by using monoliths designed with an independent control of the distribution of flow-through pores in the 5–50 μm range and diffusion pores (ordered or disordered) within 3 to 10 nm in size and strut thicknesses of 1–10 μm. These materials can be made catalytically active using the grafting or anchoring of acid, base, and redox functionalities. A new area will open up in the field of heterogeneous catalysis for the synthesis of fine chemicals (and microsynthesis), where mass transfer of bulky molecules is of utmost importance. In spite of their promising potentials, the loss of the catalyst's effectiveness and selectivity owing to pore clogging arising from mass transfer and site inhibition is the main limitation for the development of porous solid catalysts (including zeolites and structured mesoporous materials) for the synthesis of fine chemicals.[11] The implementation of the MonoSil reactor may circumvent these phenomena. Another potential advantage of the MonoSil type reactor compared to a batch reactor is the higher solid/liquid ratio in the reaction volume, which minimizes the risk of homogeneous side reactions. Therefore, a great future lies ahead for the use of nanostructured inorganic monolith microreactors (silica, titania, zirconia, and others) in the field of catalysis.

Experimental Section

To generate a monolith microreactor, the MonoSil rod (6.3 mm diameter, 1.9 cm length) was inserted in a heat-shrinkable PTFE tube together with two glass tubes (4 mm inner diameter) at each end, which was then placed within a heat shrinkable PTFE tube (Figure 1b). NH_2-MonoSil and HSO_3-MonoSil were prepared on the monolith that had been activated overnight at 423 K using a solution containing the precursor functionalities: aminopropyl triethoxysilane to yield NH_2-MonoSil, and 2-(4-chlorosulfonylphenyl)-ethyltrimethoxysilane to yield HSO_3-MonoSil, both in 60 mL of ethanol. Precursors were allowed to flow at a rate of 2.5 mL min^{-1} (343 K for 10 h). The amount of catalytically active precursors was about 5 molecules per nm^2 silica. NH_2- and HSO_3-MonoSil were then washed several times with ethanol, methanol/water (50:50), and acetone to recover the catalyst. The monoliths were successively dried for 2 h at RT, 2 h at 323 K, and 8 h at 273 K. The materials were characterized by chemical analyses, 3D X-ray tomography, SEM, TGA, solid-state NMR, mercury porosimetry, and nitrogen sorption. The test reactions were carried out in liquid phase and flow conditions, feeding the MonoSil and packed-bed reactors with a HPLC micropump (0.5 mL min^{-1}, 0.43 mm s^{-1}, pressure drop ca. 300 kPa). Reaction conditions for a) Knovenagel reaction: cyanoethyl acetate (0.68 mol L^{-1}), benzaldehyde (0.80 mol L^{-1}), solvent DMSO, RT; b) transesterification reaction: triacetine (0.70 mol L^{-1}), triacetine/methanol = 1:6, temperature 333 K. The concentrations of the reactants and products were determined by sampling periodically on line by using GC. For the reaction in batch, a closed stirred-tank reactor (100 mL, Autoclave Engineer, 1000 rpm) was used, fed with the reactant solution (60 mL) at the same concentration as in the flow experiments. The reaction in Scheme 1 was processed with 150 mg catalyst, reaction in Scheme 2 with 780 mg catalyst. Under these conditions, the conversion was not greatly affected by external and internal mass transfer. Solution aliquots were periodically withdrawn for GC analysis.

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