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Knoevenagel condensation reaction in a membrane microreactor

Sau Man Lai,[a] Rosa Martin-Aranda[b] and King Lun Yeung*[a]

[a] *Department of Chemical Engineering, the Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, SAR-PR China. E-mail: kekyeung@ust.hk; Fax: 852 2358 0054; Tel: 852 2358 7123*

[b] *Departamento de Química Inorgánica y Química Técnica (UNED), Senda del Rey, 9, 28040 Madrid, Spain*

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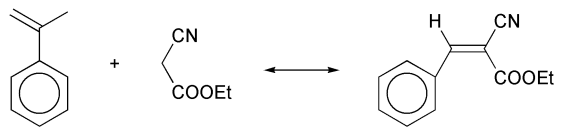
A multi-channel membrane microreactor was fabricated and tested for Knoevenagel condensation of benzaldehyde and ethyl cyanoacetate using Cs-exchanged faujasite NaX as the catalyst; the membrane microreactor achieves supra-eqiulibrium conversion at higher product purity.

Fine chemicals and pharmaceuticals are high value products that are produced in modest quantities. They are usually seasonal products that are customer specific and have a short shelf life. These characteristics usually place significant constraints in their production, such that it is not uncommon to see labour intensive batch processes being used instead of the more efficient continuous process. This usually leads to a significant waste generation during the scale-up from the laboratory to production scale. In addition, the use of hazardous and often toxic homogeneous catalysts makes product purification and waste disposal important issues in today's stringent environmental regulations. Microchemical systems offer a new paradigm for meeting these challenges.[1] Recent advances in the design and fabrication of micromixers, microseparators and microreactors bring closer the realization of desktop miniature factories and micro-pharmacies.[1,2] They represent a cheap alternative for the production of speciality chemicals and pharmaceuticals by a *continuous* process,[3,4] allowing simpler process optimization, rapid design implementation, better safety and easier scale-up through replication.[5] This enables rapid product deployment to the marketplace and thus ensures a significant competitive edge.

Knoevenagel condensations of carbonylic compounds and malonic esters yield several important key products such as the nitriles used in the anionic polymerization and the α,β-unsaturated ester intermediates employed in the synthesis of several therapeutic drugs that include niphendipine and nitrendipine. Unlike most condensation reactions, Knoevenagel condensation is base-catalyzed. Strong bases such as sodium and potassium hydroxides, and piperidine are traditionally used for these reactions. However, basic zeolites such as Cs-exchanged faujasite NaX and faujasite GeX, as well as the amino-modified mesoporous silica are also able to catalyze these reactions.[6–8] The use of heterogeneous catalyst significantly simplifies product separation and purification. It also eliminates the need for solvents. However, the water formed by the reaction is a poison for the zeolite catalyst, and its removal is a must if we are to expect optimum catalyst performance. The removal of water has the added benefit of increasing the conversion for this equilibrium limited reaction.[9] This study investigates the performance of a membrane microreactor for the Knoevenagel condensation of benzaldehyde and ethyl cyanoacetate (Scheme 1) to produce α-cyanocinnamic acid ethyl ester, a known intermediate for the production of an antihypertensive drug. The presence of the miniature membrane enables continuous and selective removal of water during the reaction.



Scheme 1 Knoevenagel condensation of benzaldehyde and ethyl cyanoacetate

A multi-channel membrane microreactor was fabricated using a porous stainless steel plate (0.2 μm pore SS-316L, Mott Metallurgical Corp.) as a substrate. Thirty-four microchannels were cut into one face of the 25 mm × 25 mm plate using electrical discharge micromachining (AGIE Wirecut 120). Each microchannel is 300 μm wide, 600 μm deep and 25 mm long as shown in Fig. 1a and 1b. A 30 μm thick ZSM-5 zeolite membrane (Fig. 1c) was grown on the back of the micromachined plate from a synthesis solution containing a molar ratio of 80 tetraethylorthosilicate : 10 NaOH : 1 tetrapropylammonium hydroxide : 8 aluminum : 20 000 water. The zeolite has a Si : Al ratio of 30 and an effective membrane area of 4 cm^2. The catalyst was prepared by ion exchange of faujasite NaX powder (Molecular Sieve 13X, Aldrich) with 0.5 M CsCl solution at 353 K for 6 h. This procedure was repeated three times to obtain a Cs-exchanged NaX catalyst with Cs : Si loading of 0.32. 0.02 g of the catalyst powder was uniformly coated onto the microchannels and was activated by pretreatment in air at 623 K for 4 h. The multi-channel membrane plate was then placed in a stainless steel housing for the reaction study. A mixture containing a stoichiometric amount of benzaldehyde (RDH, 99%) and ethyl cyanoacetate (Aldrich, 98+%) was fed to the microreactor at flowrates of 0.2 to 12 ml h^{-1} and was allowed to react over the catalyst at 373 K. The products were analysed by gas chromatography (HP 5890) equipped with a HP-5 column and FID detector. The pervaporation of water across the zeolite membrane was achieved at a permeate pressure of 735 torr.

Fig. 2 plots the product yield as a function of the residence time for the fixed bed reactor (FBR), microreactor and membrane microreactor. The catalyst loading per reactor volume (W_{cat}/V = 0.4 g cm^{-3}) was kept constant and the residence time was calculated from the ratio of the reactor volume to the fed flowrate ($\tau = V/F$). The fixed bed reactor experiment was conducted in a tubular reactor (7 mm ID, 7.5 cm

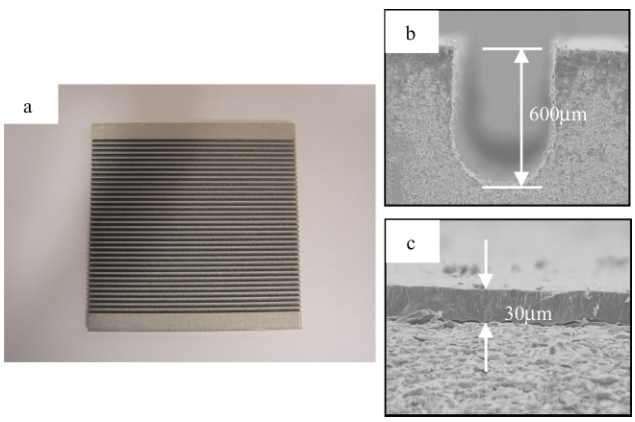


Fig. 1 (a) A picture of the multi-channel membrane plate with (b) 300 μm wide microchannels etched onto the porous stainless steel substrate and (c) a 30 μm thick ZSM-5 membrane grown onto its backside.

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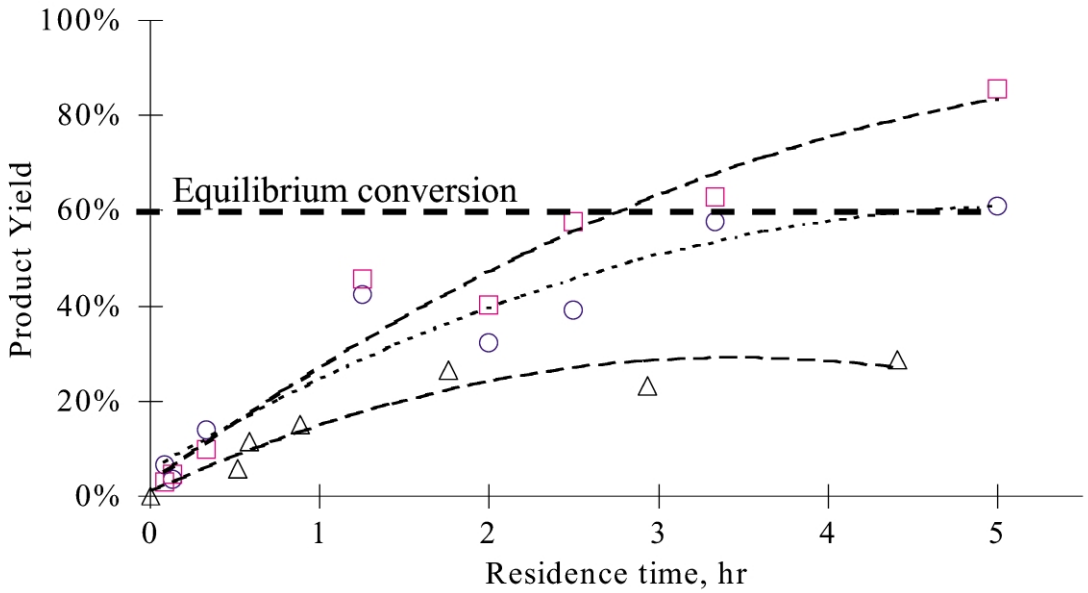

Fig. 2 Product yield as a function of residence time for fixed bed reactor (△), multi-channel microreactor (○) and multi-channel membrane microreactor (□).

long) packed with 3.6 g of catalyst. It is clear from the results that the performance of the fixed bed reactor is poor when compared to the microreactor. The highest yield obtained from the fixed bed reactor is about 40%, whereas the microreactor reaches the maximum yield expected at equilibrium of 60%. This is due to the large external mass transfer resistance along the catalyst bed in the FBR that is absent in the microreactor. Better mass transfer rate is one of the known characteristic of a microreactor, which also includes high heat transfer rate, narrow residence time distribution and laminar fluid flow.

Most separation processes can benefit directly from the large surface area-to-volume ratio that can be obtained in a micro-separator. In fact, a few separation processes, such as extraction and membrane separation have been successfully miniaturized.[10] Pervaporation experiments were conducted on a multi-channel membrane microreactor using a benzaldehyde–water mixture containing 1–5 wt. % water. A separation factor of 10 000 was obtained for water at a permeance flux of about 0.1 kg m^{-2} h^{-1} indicating that the ZSM-5 is an excellent membrane for the selective removal of water. Supra-equilibrium conversion was obtained from the membrane microreactor with 85% product yield (Fig. 2c). Calculations indicated that all the water produced by the condensation reaction was completely removed by the membrane. The membrane is operating below its known capacity, which suggests that the performance of the membrane microreactor is limited mainly by the kinetics. A better catalyst is needed to obtain a higher product yield.

This work clearly demonstrates the potential use of the microreactor for the production of fine chemicals and pharmaceuticals. It also shows the benefits that one could obtain in using a membrane microreactor for reactions that are constrained by unfavorable thermodynamics. Supra-equilibrium conversion was achieved at higher product purity through selective removal of water by-product from the condensation reaction. It is conceivable that pure product could be obtained from the membrane microreactor with better catalyst formulation.

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