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Surface effects in the esterification of 9-pyrenebutyric acid within a glass micro reactor

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Received (in Cambridge, UK) 9th May 2003, Accepted 16th June 2003
First published as an Advance Article on the web 27th June 2003

Surface phenomena are an important contribution to the "chip effect", leading to higher yields and shorter reaction times, as demonstrated for the acid-catalysed esterification of 9-pyrenebutyric acid within a glass fabricated micro reactor.

In the past two decades the rapid development of microfabrication technologies and the corresponding design strategies have given an enormous impetus to progress in the field of microfluidics. Not only for analytical applications,[1–4] but, recently, micromachining technologies have also been applied to synthetic organic chemistry leading to the development of micro reactors. In general, miniaturization is a valuable tool to decrease time and costs of performed processes. Furthermore, significant enhancements in efficiency of mixing and separation[5,6] and increased selectivity and safety[7] can be achieved, when performing chemical reactions in microfluidic devices. A number of liquid and gas phase reactions have been demonstrated to show improved reactivity in terms of product yield and selectivity when performed on the microscale, as compared to conventional lab-scale equipment.[8] Most microscale syntheses such as Wittig reaction,[9,10] enamine formation,[11] aldol reaction,[12] preparation of enolates from diketones[13,14] and peptide synthesis,[15,16] have been carried out under electrokinetic fluidic (EOF) control. The improved reactivity found for these reactions has mainly been attributed to the high degree of spatial and temporal reaction control achievable in the electrokinetically driven micro reaction system.[8,17] Other features that enhance the reactions in micro reactors involve the fast diffusive mixing under laminar flow conditions and the high efficiency of heat transfer.[18] †

Only a few examples of organic reactions performed in a pressure-driven glass micro reactor have been reported in the literature.[19–21] In this communication we present the considerable increase in reaction efficiency observed in a systematic study of the acid-catalysed esterification of 9-pyrenebutyric acid **1** with ethanol (Scheme 1),[22] performed in a microchannel with a high surface to volume ratio.

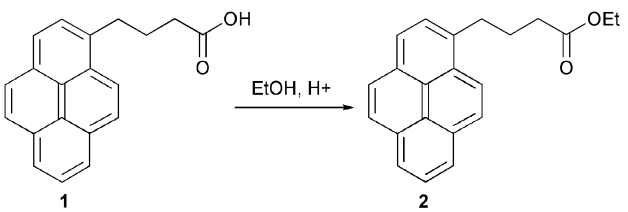
The borosilicate micro reactor (Fig. 1a) used in this study was prepared in the cleanroom laboratories of the MESA+ Research Institute. High precision powderblast micromachining was used for the fabrication of inlet and outlet connections, while the reaction microchannel was made with HF chemical etching.

The on-chip reactions were carried out in a 197 mm long, 200 μm wide and 100 μm deep microchannel under pressure-driven flow conditions. During the experiments the chip was placed in a holder (Fig. 1b) designed for fitting fused silica fibers into the inlet/outlet chip reservoirs by means of commercially available Upchurch Nanoport™ assemblies. Using these fittings allows reagent injection in a continuous flow fashion, eliminating the risk of adhesive contamination and offering the great advantage of adding only insignificantly low dead volume to the flow path. The reagent flows were controlled by two 100 μl syringes, mounted on a microdialysis pump. The reaction products were directly transferred from the outlet silica fiber to a Matrix-Assisted Laser Desorption ionization Time of Flight (MALDI-TOF) mass spectrometer sample plate in a continuous flow fashion by collecting individual droplets, after which the samples on the plate were analyzed batch-wise. After the individual droplets were placed on the plate, the solvent quickly evaporates so that no further reaction could take place. In this way the reaction-to-analysis delay time is eliminated, which is inherent to off-line chip analysis. High Pressure Liquid Chromatography (HPLC) was used for the quantitative determination of the conversions.

The target reaction was performed both in glass microchips and in conventional lab-scale glassware. All experiments were carried out under the same conditions using solutions of 10^{-4} M 9-pyrenebutyric acid **1** in ethanol and of 10^{-4} M sulfuric acid in ethanol both at room temperature and at 50 °C.

No ester formation could be detected in aliquots taken from a lab scale experiment at 4, 10, 20, 30, and 40 min at both room temperature and 50 °C. However, in the on-chip experiments carried out at room temperature, about 15–20% of ester **2** was already formed after 40 min. When the on-chip experiments were performed at 50 °C higher yields of ester **2** were obtained. The dependence of the conversion on the residence time is clearly demonstrated in the MALDI-TOF mass spectra (Fig. 2), while the yields are summarized in Table 1. These results clearly show the large positive effect of a glass microchip on the target reaction.

To study the possible influence of the silanol groups at the inner channel surface, the on-chip experiments summarized in Table 1 were repeated at room temperature and at 50 °C, without injecting the sulfuric acid. No ester **2** could be detected in any of the collected samples. However, when activating the glass surface hydroxy goups by pretreating the channel with a solution of sulfuric acid and hydrogen peroxide (3 : 1), 9% of



Scheme 1

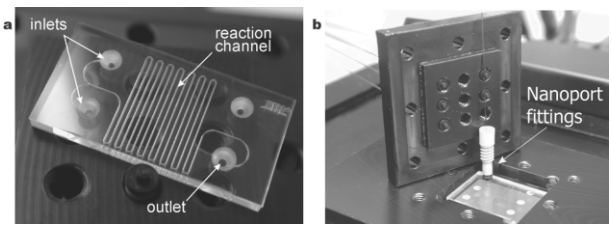


Fig. 1 Pictures of (a) the glass micro reactor and (b) the self-developed chip holder.

DOI: 10.1039/b305226p

ester **2** was formed in the glass microchannel after 40 min at 50 °C. These results demonstrate the active role of the microchannel glass surface on the formation of ester **2**.

To exclude that the rate enhancement is partially due to the dynamics of mixing at the microscale, the esterification was repeated in a fused silica fiber with an inner diameter (100 μm) comparable with that of the micro reactor channel. The silica fiber was filled with a premixed 1 : 1 solution of carboxylic acid **1** and sulfuric acid in ethanol, and heated at 50 °C for 2, 4, 8, 10, and 20 min, respectively. The MALDI-TOF mass spectra of the samples showed that the conversions at comparable residence times were similar to those obtained in the corresponding on-chip experiments. Subsequently, the experiments were repeated in a glass fiber, the inner surface of which was coated by reaction of the SiOH groups with the lipophilic octadecyltrichlorosilane. However, no product formation could be detected, again substantiating the effect of the microchannel surface on the esterification reaction. Probably, the large number of acidic hydroxy groups within the glass micro reactor and the uncoated silica fiber activate the ethanol, present in large excess, facilitating the esterification.

Finally, the same reaction was done at lab-scale in the presence of silica gel, imitating the same glass-surface to chemicals-volume ratio (~1 : 34). At reaction times of 4, 10, 20, and 40 min conversions of 8%, 9%, 10%, and 15%, respectively, were obtained at 50 °C. The conversions are substantially lower than those obtained at the same residence times in the on-chip experiments (Table 1). This clearly indicates a higher efficiency of the micro- over the macroscale reaction.

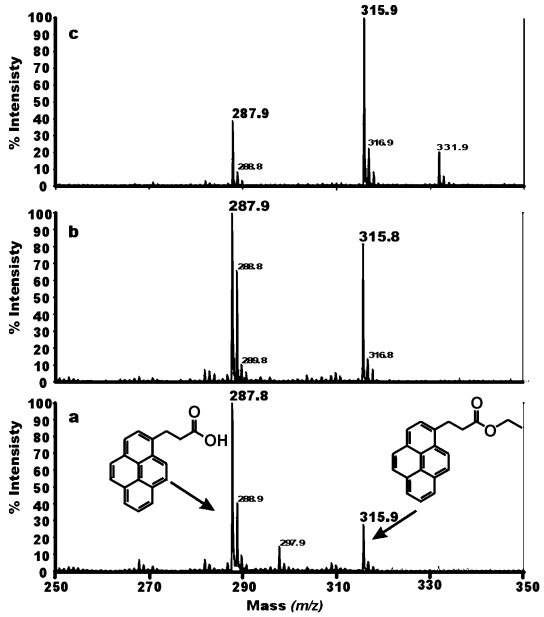


Fig. 2 MALDI-TOF mass spectra of samples collected from on-chip reactions carried out at 50 °C at residence times of 4 (a), 10 (b), and 20 (c) min, respectively.

Table 1 Yields[a] of ester 2 obtained in the on-chip and lab scale (in the presence of silica gel) experiments carried out at 50 °C

Residence time/ min	On-chip flow rate/ μl min^{-1}	Yield (%)	
		On-chip	Lab SiO_2 gel
4	1	17	8
10	0.4	33	9
20	0.2	51	10
33	0.12	71	n.d.
40	0.1	83	15

[a] Yields were determined by HPLC, using a LUNA 3 μm C18 (2) column (dimensions: 100 × 4.60 mm). A 60 : 40 mixture of acetonitrile and an aqueous solution of 20 mM NaH_2PO_4 at pH = 4.3 was used as eluent. From t = 0 up to t = 25 min the mixture composition was changed in a gradient resulting in 100% acetonitrile at t = 25 min. The initial composition was finally regenerated to the initial value (60:40) at t = 30 min.

Upon miniaturization there is an increasing surface to volume ratio. The importance of chip-surface phenomena has already been described for electroosmotic flow-based microreactors,[17] the first example of which was the Suzuki coupling performed by Greenway *et al.*,[23] and particularly in nanochannels.[24] To the best of our knowledge, we have presented for the first time a systematic study of the influence of the channel surface in pressure-driven glass microchips illustrated for the acid-catalysed esterification of 9-pyrenebutyric acid **1**. Our results clearly demonstrate the important contribution of surface phenomena to the "chip effect", giving rise to much shorter reaction times and higher yields than on conventional lab scale.

The authors like to thank Jeroen Bode for the synthesis of ester **2** and Avantium B.V. for financial support.

Notes and references

† This esterification reaction was selected since it has a relatively short reaction time and in addition, the progress can be easily monitored with MALDI-TOF ms on account of the presence of the pyrene group.

1 D. R. Reyes, D. Iossifidis, P.-A. Auroux and A. Manz, *Anal. Chem.*, 2002, **74**, 2623.
2 P.-A. Auroux, D. Iossifidis, D. R. Rreyes and A. Manz, *Anal. Chem.*, 2002, **74**, 2637.
3 A. van den Berg and T. S. J. Lammerink, *Top. Curr. Chem.*, 1997, **194**, 21.
4 M. Brivio, R. H. Fokkens, W. Verboom, D. N. Reinhoudt, N. R. Tas, M. Goedbloed and A. van den Berg, *Anal. Chem.*, 2002, **74**, 3972.
5 J. Branebjerg, P. Gravesen, J. P. Krog and C. R. Nielsen, *Fast Mixing by Lamination, Proceedings of the "IEEE-MEMS '96"*, San Diego, CA, 1996, pp. 441–450.
6 J. B. Knight, A. Vishwanath, J. P. Brody and R. H. Austin, *Phys. Rev. Lett.*, 1998, **80**, 3863.
7 D. C. Hendershot, *Chem. Eng. Progr.*, 2000, **96**, 35.
8 P. D. I. Fletcher, S. J. Haswell, E. Pombo-Villar, B. H. Warrington, P. Watts, S. Y. F. Wong and X. Zhang, *Tetrahedron*, 2002, **58**, 4735.
9 V. Skelton, G. M. Greenway, S. J. Haswell, P. Styring, D. O. Morgan, B. Warrington and S. Y. F. Wong, *Analyst*, 2001, **126**, 7.
10 V. Skelton, G. M. Greenway, S. J. Haswell, P. Styring, D. O. Morgan, B. Warrington and S. Y. F. Wong, *Analyst*, 2001, **126**, 11.
11 M. Sands, S. J. Haswell, S. M. Kelly, V. Skelton, D. O. Morgan, P. Styring and B. H. Warrington, *Lab Chip*, 2001, **1**, 64.
12 C. Wiles, P. Watts, S. J. Haswell and E. Pombo-Villar, *Lab Chip*, 2001, **1**, 100.
13 C. Wiles, P. Watts, S. J. Haswell and E. Pombo-Villar, *Lab Chip*, 2002, **2**, 62.
14 C. Wiles, P. Watts, S. J. Haswell and E. Pombo-Villar, *Chem. Commun.*, 2002, 1034.
15 P. Watts, C. Wiles, S. J. Haswell, E. Pombo-Villar and P. Styring, *Chem. Commun.*, 2001, 990.
16 P. Watts, C. Wiles, S. J. Haswell and E. Pombo-Villar, *Tetrahedron*, 2002, **58**, 5427.
17 P. D. I. Fetcher, S. J. Haswell and V. N. Paunov, *Analyst*, 1999, **124**, 1273.
18 S. J. Haswell, *Miniaturization-What's in it for chemistry, Proceedings of the Micro Total Analysis Systems, μ-TAS '01*, Kluwer Academic Publishers, Dordrecht, The Netherlands, 2001, p. 637.
19 M. Fernandez-Suarez, S. Y. F. Wong and B. H. Warrington, *Lab Chip*, 2002, **2**, 170.
20 S. J. Haswell, B. O'Sullivan and P. Styring, *Lab Chip*, 2001, **1**, 164.
21 H. Hisamoto, T. Saito, M. Tokeshi, A. Hibara and T. Kitamori, *Chem. Commun.*, 2001, 2662.
22 R. E. Lehr, C. W. Taylor, S. Kumar, H. Duck Mah and D. M. Jerina, *J. Org. Chem.*, 1978, **43**, 3462.
23 G. M. Greenway, S. J. Haswell, D. O. Morgan, V. Skelton and P. Styring, *Sens. Actuators B*, 2000, **63**, 153.
24 S. C. Jacobson, J. P. Alarie and J. M. Ramsey, *Electrokinetic transport through nanometer deep channels, Proceedings of the Micro Total Analysis Systems, μTAS '01*, Kluwer Academic Publishers, Dordrecht, The Netherlands, 2001, p. 57.