

“GREEN” OXIDATION REACTIONS USING A PORPHYRIN-IMMOBILISED MICROFLUIDIC DEVICE

Emily K. Lumley¹, Charlotte E. Dyer², Nicole Pamme¹, Ross W. Boyle¹

¹The University of Hull, Department of Chemistry, UK

²Postgraduate Medical School, University of Hull, UK

ABSTRACT

A microfluidic device has been fabricated in glass and functionalized with photoactive molecules for use in singlet oxygen (¹O₂) mediated oxidations. Porphyrins are a group of photosensitizers that efficiently produce reactive oxygen species (ROS) in the presence of molecular oxygen and light of a specific wavelength. These properties were found to remain upon immobilization whilst ensuring contamination does not occur. The porphyrin-immobilized device was used for the photochemical oxidations of cholesterol, α -terpinene and citronellol on-chip. On comparison with batch reactions it was found that these reactions were possible on-chip and produced moderate yields with improved efficiency.

KEYWORDS

Photooxidation / Photosensitizer / Porphyrin / Immobilization

INTRODUCTION

Conducting chemical reactions within microreactors is becoming increasingly popular, it enables greater control over mixing and thermal transfer.[1] In addition photochemical reactions on-chip provide shorter path lengths for light penetration and small volumes (nL) aiding in the efficiency of the method. Safety is also improved for handling of hazardous reactants and specifically by reducing the quantity of oxygenated solvents at any one time.[2] The number and scope of photochemical reactions conducted on-chip is growing as these improvements in light penetration are being exploited.[3] The immobilization of photosensitizers is not a new concept[4] and has been investigated for many decades to improve separation of reaction catalyst from reaction mixture.[5] The use of immobilized photosensitizers on-chip has been conducted through the use of packed chip designs[6] and with TiO₂ coatings.[7] However, to our knowledge we are the first group to investigate immobilizing the photosensitizer directly to the channels of the microfluidic device. This ensures no contamination of the reaction mixture with the photosensitizer and also allows for efficient fluid flow through the channels.

EXPERIMENT

The design (figure 1a) was fabricated to a depth of 30 μm in glass using photolithography and wet etching procedures, and featured 16 channels of 260 μm width branching from three convergent inlets and meeting at one outlet. Silanization was performed by allowing a 5 % solution of (3-aminopropyl)triethoxysilane (APTES) in dry toluene to react in the channels for 1 hour before sonicating in toluene. A 1 mM solution of the molecule to be immobilized (Rhodamine B isothiocyanate (RBITC) or 5-(4-isothiocyanatophenyl)-10,15,20-tris (4-*N*-methylpyridiniumyl) porphyrin triiodide (porphyrin)) was prepared in methanol with the addition of triethylamine to make the solution basic. This was pumped through the chip at 3 $\mu\text{L min}^{-1}$ for 3 hours, before sonicating the chip in methanol and drying with a flow of nitrogen to yield channels featuring the immobilized compound on the surface. RBITC was used to investigate the success of the immobilization process itself, while the porphyrin was the photosensitizer used for the oxidation experiments (figure 1b).

Three methods of cholesterol oxidation by singlet oxygen were investigated. An off-chip batch reaction was conducted in which 5 mL of a 20 μM solution of porphyrin, capped with propylamine to protect the reactive isothiocyanate group, was mixed with 5 mL of a 10 mM solution of cholesterol in 1:9 methanol:dichloromethane. The reaction mixture was irradiated with a Xe light source, using white light over the full visible spectrum, and supplied with oxygen for 1 hour. On-chip flow experiments were conducted using the same reaction composition, which was pumped through the chip at two different flow rates, i.e. 5 $\mu\text{L min}^{-1}$ and 2.5 $\mu\text{L min}^{-1}$, with a constant flow

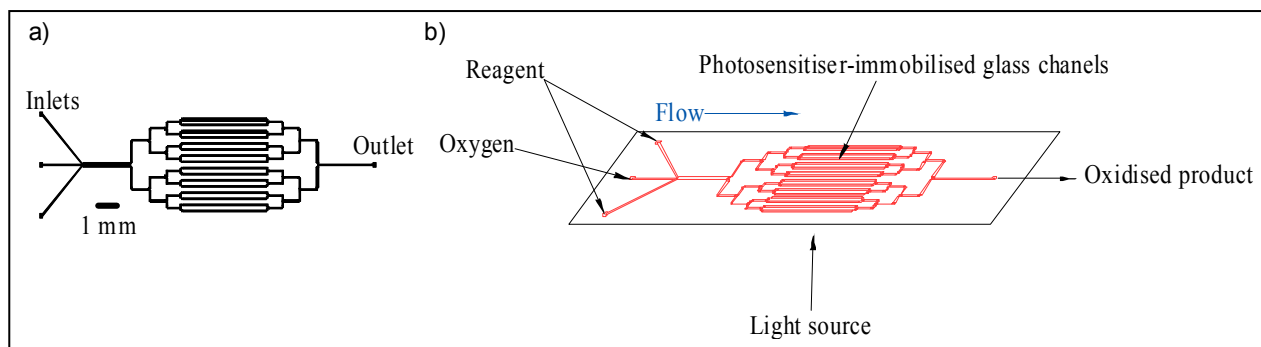


Figure 1: Experimental set-up; (a) chip design and (b) schematic of the oxidation procedure.

of oxygen and irradiation with the same light source. Finally an experiment using the porphyrin-immobilised chip was conducted in which a 5 mM solution of cholesterol was pumped through the chip with a supply of oxygen at the flow rates described from the flow reaction above. The resulting cholesterol mixture in each case was tested using HPLC with a C18 column, 40:60 CH₃CN:MeOH mobile phase using a UV detector at 205 nm. In order to determine the % conversion of cholesterol to oxidized products, area-under-the-peak analysis was performed.

For the photooxidation reactions of α -terpinene and citronellol the batch reactions and the porphyrin-immobilized chip reactions were conducted. For the batch reactions 5 mL of a 20 μ M solution of porphyrin was mixed with 5 mL of a 0.15 mM solution of the reagent in methanol. The reaction mixture was irradiated with the Xe light source and supplied with oxygen. For the porphyrin-immobilized chip reactions a 0.15 mM solution of the reagent in either methanol or hexane was pumped through the chip whilst irradiated with the same light source. The resulting α -terpinene mixture was analysed on GC-MS with an HP-1 column (0.2 mm x 12 m x 0.33 μ m) using He carrier gas at 1 mL min⁻¹; injector and detector temperature set at 250 °C and 280 °C, respectively. The sample size was 1 μ L with a split ratio of 52:1:1 and area-under-the-peak analysis performed on the resulting spectra. The resulting citronellol reaction was analysed on HPLC again with a C18 column, but with 70:30 CH₃CN:0.1 M formic acid as mobile phase at 1 mL min⁻¹ using a UV detector at 215 nm performing area-under-the-peak analysis.

RESULTS AND DISCUSSION

The immobilization of molecules bearing the isothiocyanato group on the aminated surface of the glass channels on-chip was demonstrated with RBITC. The resultant color change of the channels to a bright pink which remained after sonication of the chip in methanol confirmed the validity of the immobilization technique. The porphyrin was immobilized using the same technique and compared to batch and solution phase oxidation methods for cholesterol. For the photooxidation reactions of α -terpinene and citronellol the batch reaction was compared to the reaction using the immobilized porphyrin using both methanol and hexane on-chip to determine any solvent effects. The results are shown in figures 2 and 3.

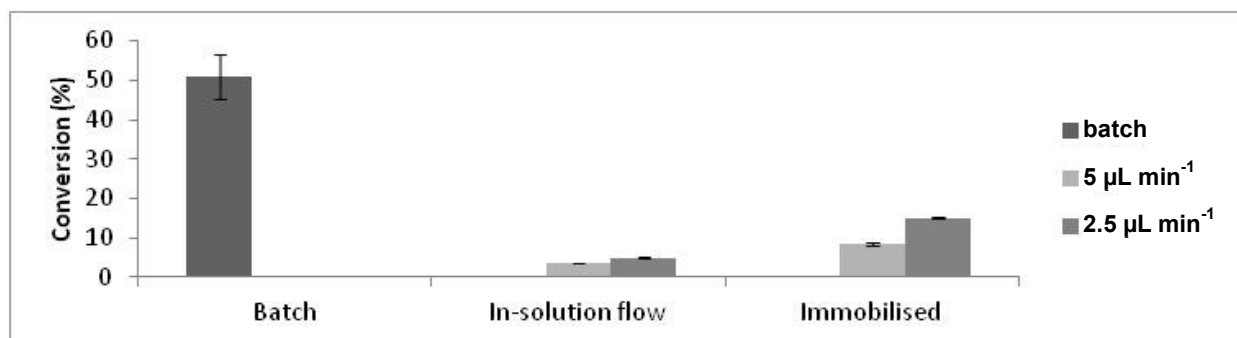


Figure 2: Graph showing the conversion of cholesterol to oxidized products by singlet oxygen produced from porphyrin in (i) a batch procedure, (ii) free solution in continuous flow, and (iii) when immobilized on the channels of a microfluidic chip.

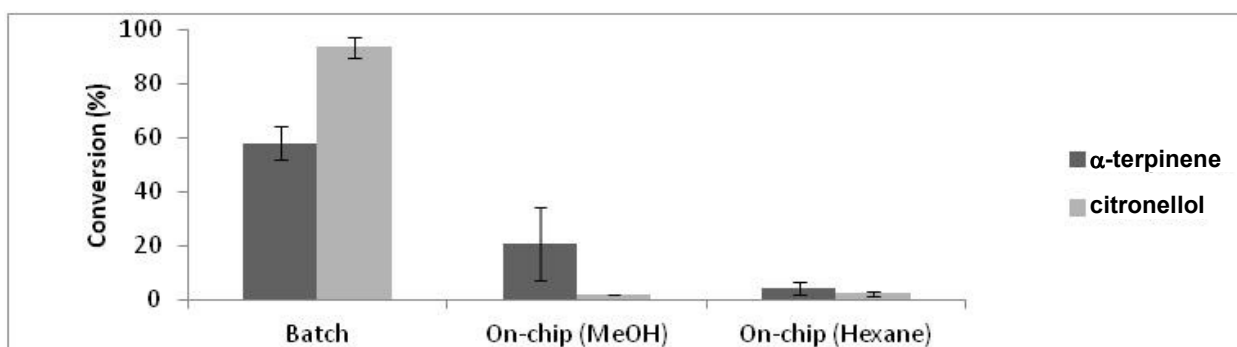


Figure 3: Graph showing the conversion of α -terpinene and citronellol, in methanol or hexane, to oxidized products by singlet oxygen produced from porphyrin in batch procedures (methanol only) and when immobilized on the channels of a microfluidic chip.

This shows that for the oxidation of cholesterol the immobilized porphyrin outperforms the porphyrin in solution on-chip. This is most likely due to the residence time of the porphyrin in solution as opposed to the immobilized porphyrin which undergoes constant irradiation. The batch reaction results in a much higher yield, however, it takes place over a much longer time span (1 hour vs 15 or 30 seconds on-chip). The oxidation of α -terpinene on-chip is much higher than for citronellol, but with much greater variance over numerous reactions. The use of hexane for the oxidation of α -terpinene appears to be detrimental, but had little effect on the oxidation of citronellol. Overall the yields are higher in all these reactions in batch than on-chip. However, this does not take into consideration the

reaction time. A method of comparing the efficiency of reactions in various reaction vessels is the space-time yield (STY). [8] The results for the STY analysis of these reactions is shown in figures 4 and 5.

From these results it is clear that all the on-chip experiments were much more efficient than the batch reactions. The STY for cholesterol and α -terpinene show a marked improvement in STY on-chip as compared to batch, however, as expected, the citronellol STY is only slightly better than batch.

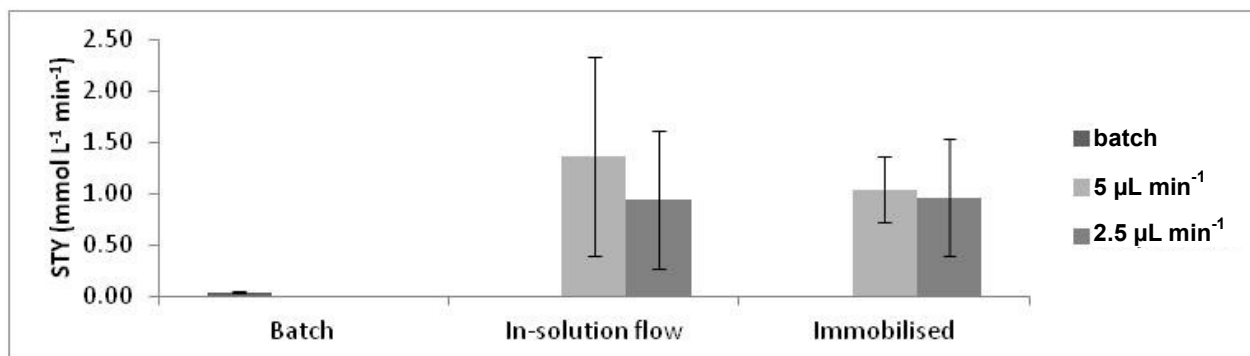


Figure 4: Graph showing the effective space-time yields (STYs) for the oxidation of cholesterol by singlet oxygen produced from porphyrin in (i) a batch procedure, (ii) free solution in continuous flow, and (iii) when immobilized on the channels of a microfluidic device

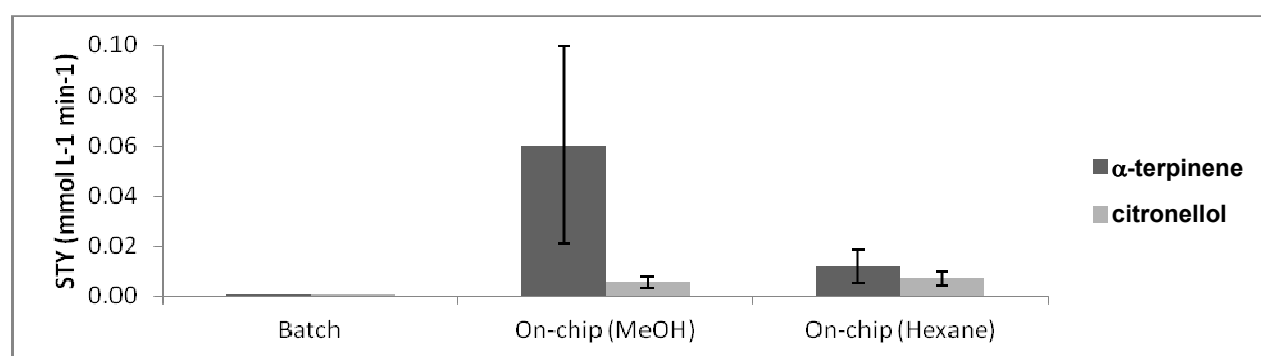


Figure 5: Graph showing the effective space-time yields (STYs) for the oxidation of α -terpinene and citronellol by singlet oxygen produced from porphyrin in a batch procedure (methanol only) when immobilized on the channels of a microfluidic device with methanol or hexane as the solvent.

CONCLUSION

We have shown that porphyrin immobilized on the glass channels of a microfluidic chip was capable of producing singlet oxygen and other ROS with high efficiency. Although the yields are lower than the batch reaction the ability to conduct photooxidation reactions on small samples, with improved efficiency and purity could be useful in the synthesis of natural products where sample sizes are often limited and finite.

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CONTACT

Prof. Ross W. Boyle, +44 1482 466353 or r.w.boyle@hull.ac.uk