

## Supplementary data

# Substantial rate enhancements of the esterification reaction of phthalic anhydride with methanol at high pressure and using supercritical CO<sub>2</sub> as a co-solvent in a glass microreactor

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### Batch reaction at a pressure of 1 bar

Table 1 shows the methanol concentration at different temperatures according to its density values at 1 bar.

**Table 1** Methanol concentration at different temperatures<sup>1</sup> for different densities. V<sub>methanol</sub>: 25 mL

<i>T</i> / °C	<i>ρ</i> / gmL <sup>-1</sup>	<i>C</i> <sub>methanol</sub>
0	0.81	25.3
25	0.79	24.6
50	0.77	23.9
60	0.76	23.6

### Esterification reaction in a microreactor at pressures up to 10 bar

A vessel containing methanol (25 mL) was placed in a Dewar flask filled with dry CO<sub>2</sub> (-79 °C) and after three minutes (time enough to cold the methanol down) 37 mg of phthalic anhydride (**1**) were added. The solution was sonicated for 30 s to be sure that everything is dissolved. A UV/Vis spectrum was recorded to ensure that the initial concentration of **1** is 0.01 M. The reaction was quenched by the temperature of the dry CO<sub>2</sub>.

During these pressure experiments, the flow was kept constant with a syringe pump at 0.075 and 0.125 μL/min. The pressure was induced via the fluidic resistor of the microreactor. The temperature was regulated by heaters and Peltier elements, which are controlled by

temperature sensors. In Table 2, the calculated experimental error and the values of

$\ln\left(\frac{C_{A\ total}^{0\ ^\circ C}}{C_{A\ microreactor}^T}\right)$  are shown for both flows.

**Table 2** Logarithm of the difference in concentrations between the experiment at batch (0 °C) and the same experiment using the microreactor, for the esterification reaction of phthalic anhydride (**1**) in methanol at pressures up to 10 bar

$T / ^\circ C$	$\ln\left(\frac{C_{A\ total}^{0\ ^\circ C}}{C_{A\ microreactor}^T}\right)$ Flow: 0.075 $\mu L\ min^{-1}$				
	1	2	3	Average	Error /%
25	0.120	0.119	---	0.120	4.5
50	0.417	0.411	0.417	0.412	1.6
60	0.616	0.618	0.610	0.618	0.3
70	1.028	0.988	---	1.092	5.1
$T / ^\circ C$	$\ln\left(\frac{C_{A\ total}^{0\ ^\circ C}}{C_{A\ microreactor}^T}\right)$ Flow: 0.125 $\mu L\ min^{-1}$				
	1	2	3	Average	Error /%
25	0.079	0.073	---	0.076	5.1
50	0.252	0.251	0.252	0.252	0.3
60	0.382	0.392	---	0.387	1.7
70	0.649	0.642	0.653	0.648	0.9

**Esterification reaction in the microreactor at pressures of 90 and 110 bar.**

A 0.01 M phthalic anhydride solution in methanol was introduced in the loop (7) (Fig. 3 in manuscript) kept at 0 °C. The solution was injected into the microreactor at the desired pressure when open valve (8). The microreactor was heated at the desired temperature of the experiment using the Peltier elements. The product was collected in a small vessel maintained at 0 °C at the microreactor outlet. In Table 3, the calculated experimental error and the values of

$$\ln\left(\frac{C_{A\ total}^{0\ ^\circ C}}{C_{A\ microreactor}^T}\right)$$

are shown for both pressures.

**Table 3** Logarithm of the difference in concentrations between the experiment at batch (0 °C) and the same experiment but using the microreactor, for the esterification reaction phthalic anhydride (**1**) in methanol at pressures of 90 and 110 bar

$T / ^\circ\text{C}$	$\text{Ln}\left(\frac{C_{A \text{ total}}^{0 \text{ } ^\circ\text{C}}}{C_{A \text{ microreactor}}^T}\right)$ Pressure: 90 bar			
	1	2	Average	Error /%
20	0.183	0.181	0.182	0.6
40	0.265	0.261	0.263	1.1
60	0.378	0.378	0.378	0.1
80	0.546	0.543	0.545	0.4
100	0.795	0.784	0.789	1.0

$T / ^\circ\text{C}$	$\text{Ln}\left(\frac{C_{A \text{ total}}^{0 \text{ } ^\circ\text{C}}}{C_{A \text{ microreactor}}^T}\right)$ Pressure: 110 bar			
	1	2	Average	Error /%
20	0.276	0.278	0.277	0.7
40	0.402	0.380	0.391	4.0
60	0.572	--		
80	0.800	--		
100	1.126	--		

#### Esterification reaction in the microreactor using *sc*CO<sub>2</sub> as a co-solvent

The experimental procedure was the same than above but maintaining the valve 9 opened (Fig. 3 in the manuscript). This valve ensured that CO<sub>2</sub> was introduced in the microreactor via inlet (2) at the desired pressure. In Table 4, the calculated experimental error and the values of  $\text{Ln}\left(\frac{C_{A \text{ total}}^{0 \text{ } ^\circ\text{C}}}{C_{A \text{ microreactor}}^T}\right)$

are shown for both pressures.

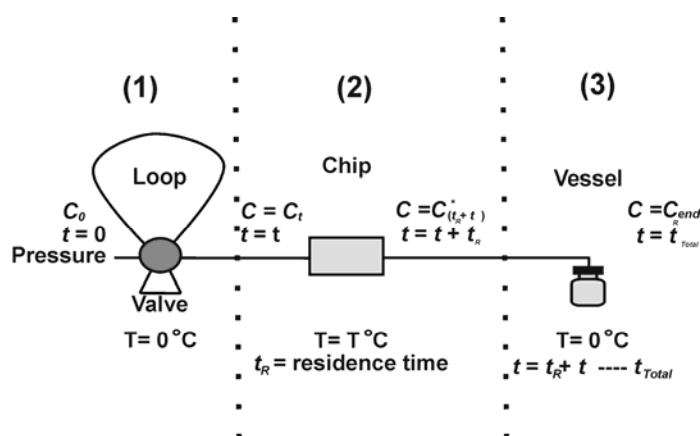
**Table 4** Logarithm of the difference in concentrations between the experiment at batch (0 °C) and the same experiment but using the microreactor, for the esterification reaction of phthalic anhydride (1) in methanol at pressures of 90 and 110 bar and using *sc*CO<sub>2</sub> as a co-solvent

$T / ^\circ\text{C}$	$\text{Ln}\left(\frac{C_{A\text{ total}}^{0\text{ }^\circ\text{C}}}{C_{A\text{ microreactor}}^T}\right)$ Pressure: 90 bar			
	1	2	Average	Error /%
40	0.567	0.572	0.569	0.6
60	0.819	0.800	0.809	1.7
80	1.173	1.220	1.197	2.8
100	1.542	1.629	1.585	3.9

$T / ^\circ\text{C}$	$\text{Ln}\left(\frac{C_{A\text{ total}}^{0\text{ }^\circ\text{C}}}{C_{A\text{ microreactor}}^T}\right)$ Pressure: 110 bar			
	1	2	Average	Error /%
40	0.856	0.834	0.845	1.9
60	1.227	1.300	1.263	4.1
80	1.803	1.800	1.802	0.1
100	2.623	2.620	2.622	0.1

**Calculation of equations 3 and 4 in the manuscript**



**Fig. 1** Scheme of the set-up used for the equation calculation.

The system is divided in three parts (Figure 1):

- Loop (1), where the reagents are stored before introducing them in the microreactor; the temperature is 0 °C.
- Microreactor (2), where the reaction mostly takes place. This part of the set-up is where the temperature is varied for each experiment (20-100 °C).
- Vessel (3), the collector vessel at 0 °C.

At the beginning of the experiment:

At  $t = 0$ :

Loop:	$t = 0:$	$C = C_0$	$\text{Ln}\left(\frac{C_{(t+t_{Total})}^*}{C_t}\right) = -k^T(t_R)$	
Microreactor:	inlet: $t = 0:$	$C = C_0$		
	outlet: $t = t_R:$	$C = C^*(t_R)$		
Vessel:				(1)
			$\text{Ln}\left(\frac{C_{end}(t_{Total})}{C_{(t_R)}^*}\right) = -k^0(t_{Total} - t_R)$	

At  $t = t$ :

Loop:		$\text{Ln}\left(\frac{C_t}{C_0}\right) = -k^0 \cdot t$ where $C_t = C_0 \cdot \text{Exp}(-k^0 \cdot t)$	
Microreactor:	inlet: $t = t:$	$C = C_t$	
	outlet: $t = t + t_R:$	$C = C^*(t + t_R)$	
Vessel:			$\text{Ln}\left(\frac{C_{end}(t_{Total})}{C^*(t + t_R)}\right) = -k^0(t_{Total} - t - t_R)$

The system is working in continuous flow mode. Therefore the total converted amount is:

$$\begin{aligned} V(C_0 - C_{end}) \\ FR \cdot t_{Total} = V \end{aligned}$$

$$\text{Amount converted at } 0^\circ\text{C: } \int_0^V (C_0 - C_t) dV = \int_0^{t_{Total} - t_R} C_0 \cdot (1 - \text{Exp}(-k^0 \cdot t)) \cdot FR dt \quad (2)$$

A volume element  $dV$  exists in the loop at  $t = t$ .

$$C(t) = C_0 \exp(-k^0 \cdot t) \quad (3)$$

$$C^*(t + t_R) = C(t) \cdot \text{Exp}(-k^T \cdot t_R) \quad (4)$$

From equation (1) it is possible to calculate the  $C_{end}(t_{Total})$ :

$$C_{end}(t_{Total}) = C^*(t + t_R) \cdot \text{Exp}(-k^0 \cdot (t_{Total} - t - t_R)) \quad (5)$$

using eqns. (3) and (4)

$$C_{end}(t_{Total}) = C_0 \exp(-k^0 \cdot t) \cdot \text{Exp}(-k^T \cdot t_R) \cdot \text{Exp}(-k^0 \cdot (t_{Total} - t - t_R)) =$$

$$C_0 \exp(-k^\circ \cdot (t_{Total} - t_R) - k^T \cdot t_R) \quad (6)$$

Vessel: it is empty at the beginning, but it is filled with the applied flow (see figure attached).

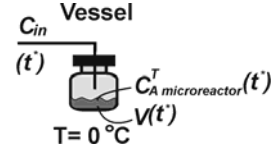
At  $t^* = 0$ :

$$C_{in}^o = C_0 \cdot \text{Exp}(-k^T \cdot t_R)$$

$$V^o = 0$$

At  $t^* = t^*$

$$C_{in}(t^*) = C_0 \cdot \text{Exp}(-k^\circ \cdot t^*) \cdot \text{Exp}(-k^T \cdot t_R) \quad (7)$$



$$\left. \begin{aligned} V(t^*) &= FR \cdot t^* \\ C_{A \text{ microreactor}}^T(t^*) & \end{aligned} \right\} \quad (8)$$

$$n(\text{mol}) : \quad n(t^*) = V(t^*) \cdot C_{A \text{ microreactor}}^T(t^*)$$

At  $t^* = t^* + dt^*$

$$C_{in}(t^* + dt^*) = C_0 \cdot \text{Exp}(-k^\circ \cdot (t^* + dt^*)) \cdot \text{Exp}(-k^T \cdot t_R) \approx C_0 \cdot \text{Exp}(-k^\circ \cdot t^*) \cdot \text{Exp}(-k^T \cdot t_R)$$

$$dV = FR \cdot dt^*$$

$$n(t^* + dt^*) = n(t^*) + dn$$

The value of  $dn$  depends on the flow, but also the batch-reaction that is taking place in the vessel:

$$dn = dn_1(\text{flow}) + dn_2(\text{reaction}) \quad (9)$$

$$dn_1 = C_{in}(t^*)dV = C_{in}(t^*) \cdot FR \cdot dt^*$$

$$\begin{aligned} dn_2 &= V(t^*)dC_{A \text{ microreactor}}^T(t^*) = V(t^*) \cdot C_{A \text{ microreactor}}^T(t^*) \cdot d\text{Exp}(-k^\circ \cdot t^*) = \\ &= -V(t^*) \cdot C_{A \text{ microreactor}}^T(t^*) \cdot k^\circ \cdot dt^* = -k^\circ \cdot n(t^*) \cdot dt^* \end{aligned}$$

Where  $C_{A \text{ microreactor}}^T(t^*)$  is the concentration of **A** in the microreactor.

$$dn = dn_1 + dn_2 = C_{in}(t^*) \cdot FR dt^* - k^\circ \cdot n(t^*) dt^*$$

$$\frac{dn}{dt^*} = C_{in}(t^*)FR - k^\circ \cdot n(t^*) \quad (10)$$

From equation (7), equation (10) becomes:

$$\frac{dn}{dt^*} = C_0 \text{Exp}(-k^\circ \cdot t^*) \cdot \text{Exp}(-k^T \cdot t_R) = A \cdot \text{Exp}(-a \cdot t^*) - B \cdot n(t^*)$$

where  $a = B = k^\circ$  and  $A = C_0 \cdot \text{Exp}(-k^T \cdot t_R) \cdot FR$

So equation (8) is now:

$$n(t^*) = A \cdot t^* \cdot \text{Exp}(-k^{\circ} \cdot t^*)$$

$$V(t^*) = FR \cdot t^*$$

$$C_{A \text{ microreactor}}^T(t^*) = \frac{A \cdot t^* \cdot \text{Exp}(-k^{\circ} \cdot t^*)}{FR \cdot t^*} = C_0 \text{Exp}(-k^{\circ} \cdot t^*) \cdot \text{Exp}(-k^T \cdot t_R)$$

In conclusion at  $t = t_{Total}$ , and  $t^* = t_{Total} - t_R$

$$C_{A \text{ microreactor}}^T = C_0 \text{Exp}(-k^{\circ} \cdot (t_{Total} - t_R)) \cdot \text{Exp}(-k^T \cdot t_R) =$$

$$C_0 \text{Exp}(-k^{\circ} \cdot (t_S)) \cdot \text{Exp}(-k^T \cdot t_R)$$

for  $t_S = t_{Total} - t_R$  The comparison with the experiment done at 0 °C which runs til  $t_S$  is

$$C_{A \text{ Total}}^{0 \text{ } ^{\circ}\text{C}} = C_0 \cdot \text{Exp}(-k^{\circ} \cdot t_S) \quad \text{Exp}(-k^T \cdot t_R) = \frac{C_{A \text{ microreactor}}^T}{C_{A \text{ Total}}^{0 \text{ } ^{\circ}\text{C}}}$$

$$k_{obs}^T \cdot t_{\text{microreactor}} = \ln \left( \frac{C_{A \text{ Total}}^{0 \text{ } ^{\circ}\text{C}}}{C_{A \text{ microreactor}}^T} \right) \quad (11)$$

where  $t_{\text{microreactor}}$  is the residence time of the reagents in the microreactor. This relationship is correct when  $t_{\text{microreactor}} \ll t_0 \tau_c$ . Subsequently, the second-order rate constants ( $k$ ) were calculated by dividing the observed rate constants ( $k_{obs}$ ) by the methanol concentration (eqn (12)).

$$k^T = \frac{k_{obs}^T}{C_{Methanol}^T} \quad (12)$$

## References

1. Lide, D.R., Handbook of Chemistry and Physics, 86th ed. (2005-2005), CRC Press, Michigan MI, USA, 2005.