Green Chemistry

Accepted Manuscript

Recovery and esterification of aqueous carboxylates by using CO_2-expanded alcohols with anion exchange

*Carlos I. Cabrera-Rodríguez[a], Laura Paltrinieri[b], Louis C.P.M. de Smet[b,c], Luuk A.M. van der Wielen[a], Adrie J.J. Straathof[a]**

[a]*Department of Biotechnology, Delft University of Technology, van der Maasweg 9, Delft, The Netherlands*

[b]*Department of Chemical Engineering, Delft University of Technology, van der Maasweg 9, Delft, The Netherlands*

[c]*Laboratory of Organic Chemistry, Wageningen University, Stippeneng 4, Wageningen, The Netherlands*

[*]Corresponding author.

Mailing address: Department of Biotechnology, Delft University of Technology, van der Maasweg 9, 2629 HZ, Delft, The Netherlands. Phone: +31 15 278 2330; Fax: +31 15 278 2355; E-mail: A.J.J.Straathof@tudelft.nl

Keywords: CO_2-expanded alcohols, carboxylate, esterification, methyl acetate, ethyl acetate, succinic acid, lactic acid, dimethyl succinate, methyl lactate, dimethyl carbonate

Abstract

The recovery of carboxylic acids from fermentation broth is one of the main bottlenecks for the industrial production of bio-based esters. This paper proposes an alternative for the recovery of carboxylates produced by fermentations at pH values above the pK_a of the carboxylic acid. In this approach, the aqueous carboxylate anion is recovered using anion exchange, followed by desorption and esterification with CO_2-expanded alcohols. Using CO_2-expanded methanol, we achieved a high desorption yield at 10 bar of CO_2 and 20 °C. An ester yield of 1.03±0.07 mol methyl acetate/ $acetate_{in}$ was obtained for the combined desorption-esterification at 5 bar of CO_2 and 60 °C. The proposed process has low chemicals consumption and low waste production. The proposed process works, with a lower yield, for other carboxylates (e.g. lactate and succinate) and alcohols (e.g. ethanol).

1. Introduction

Many carboxylic acids can be produced by bacterial fermentation. The most efficient bacterial fermentation methods for producing carboxylic acids require a titration with base to maintain a neutral pH, because the pK_a values of the acids are normally 3-5.[1, 2] The result is a carboxylate solution at a pH above the pK_a of the carboxylic acid. Some reported methods to recover carboxylates from these carboxylate solutions are shown in Table 1.

Table 1. Reported schemes for the recovery of carboxylates from fermentation broth at pH > pK_a

Primary Recovery	Concentration	Purification (Regeneration)	Salt co-produced	Ref.
Carboxylate precipitation	Water evaporation	Protonation with H_2SO_4	$CaSO_4$	3
		Ketonization	$CaCO_3$	4
Protonation with H_2SO_4 or CO_2	Extraction with tertiary amine	Thermal decomposition	$CaCO_3$	5, 6
		Esterification	$CaCO_3$	7-9
	Adsorption	Desorption e.g. with MeOH	$CaSO_4$ or $CaCO_3$	10-12
Monopolar electrodialysis	Bipolar electrodialysis	Water removal/ nanofiltration	NaOH	13
Membrane electrolysis	Extraction	Esterification	none	14, 15
Protonation with cation exchange resin	Desorption with HCl	Precipitation or water evaporation (Regeneration by thermal decomposition of $MgCl_2$)	$MgCl_2$	16, 17
Anion exchange resin	Desorption with NaCl or H_2SO_4	Water evaporation or crystallization	NaCl or Na_2SO_4	18, 19
	Desorption with MeOH (EtOH) + H_2SO_4	Esterification	Na_2SO_4 or $CaSO_4$	10, 20
	Alkylation	Distillation	$NaHCO_3$	21, 22

Traditional recovery of carboxylic acids from this carboxylate solution coproduces stoichiometric amounts of waste inorganic salt and/or is energy intensive. The reason is that at this pH the acid is dissociated, and the primary recovery uses mainly electrostatic interactions (e.g. precipitation, electrodialysis, anion/cation exchange), or protonation of the carboxylate anion. Precipitation and protonation of the acids traditionally involve the formation of stoichiometric amount of salts as waste, while electrodialysis requires high amounts of energy.

Anion exchange resins are used to recover carboxylates because of the high affinity of the resin's quaternary ammonium group for the dissociated form of the acid.[23, 24] In the traditional anion exchange process, the main drawback is related to desorption of the carboxylate from the anion exchange resin. This desorption process involves adding an extra chemical (e.g. NaCl, H_2SO_4) which produces a stoichiometric amount of salt waste.[19, 25] Another option is to use methanol and H_2SO_4 to protonate the carboxylate anion, and then the carboxylic acid is esterified using the remaining H_2SO_4 as catalyst.[10, 19, 20] Unfortunately, in this case there is also a stoichiometric amount of salt produced as waste.

To avoid the salt waste co-production, we have explored the direct downstream transformation of carboxylate salts,[21, 22] by coupling anion exchange to an alkylation using dimethyl carbonate (DMC), which produces a methyl ester and regenerates the resin into the bicarbonate form. The bicarbonate liberated upon ion exchange should be used during the fermentation for pH control, to be not counted as waste. Carbonate and bicarbonate anions have been used as neutralizing agents in fermentation with favorable results.[26] Additionally, some bacterial fermentations required carbonate species as carbon source besides carbohydrates to achieve high yields.[27] The alkylation reaction proceeds with high yield of methyl ester on carboxylates but with modest selectivity with respect to DMC.[28] The modest selectivity becomes a limiting factor for using this technology to produce non-expensive esters such as methyl acetate.

A new option for the direct downstream transformation is to use methanol and carbon dioxide. As DMC can be formed from methanol and carbon dioxide,[29-31] we wondered if it might be possible to use methanol and carbon dioxide for the desorption of the carboxylate from the anion exchange resin, and to subsequently produce a methyl ester. It has been reported that at 30 bar of CO_2 and 170

°C, alkali metal salts of carboxylates in methanol can be converted into esters with a molar yield of 0.81.[32]

These CO_2/alcohol systems at relatively low pressures (<P_c (CO_2)) are known as gas-expanded liquids, and have been studied in detail for esterification, alkylation and carboxylation reactions, amongst others.[33] The addition of CO_2 to the alcohol makes it possible to tune the polarity of the system, and as a consequence, control the solubility of solutes.[34]

The aim of this study is to explore the effect of protonating a carboxylate anion recovered by an anion exchange resin with a CO_2-expanded alcohol, and to further esterify the carboxylic acid. Our option clearly differs from methods in which CO_2 pressure is applied to aqueous carboxylate solutions in order to facilitate transfer of carboxylate to an extractant or adsorbent phase.[35, 36] In our approach, the starting point is loading an anion exchange resin (Q^+) with a carboxylate, such as acetate (Ac^-) (R.1).

$$NaAc_{(aq)} + Q^+ HCO_3^- \rightleftharpoons NaHCO_{3\ aq)} + Q^+Ac^- \qquad R.1$$

Then, we use a CO_2/alcohol system for the desorption of the carboxylates from the anion exchange resin with subsequent esterification (R.2).

$$Q^+Ac^- + MeOH + CO_2 \rightleftharpoons Q^+HCO_3^- + MeAc \qquad R.2$$

The overall stoichiometry is the combination of R.1 and R.2 (R.3).

$$NaAc_{(aq)} + MeOH + CO_2 \rightleftharpoons NaHCO_{3\,(aq)} + MeAc \qquad R.3$$

In this paper, we study the effect of the CO_2 pressure on the desorption of acetate in methanol and ethanol; the effect of water on the protonation and esterification steps; and the application of the technology for other carboxylates produced by fermentation, e.g. lactate and succinate.

2. Material and Methods

2.1. Materials

Potassium acetate (≥99.9%), Dowex Marathon MSA resin (type I; macroporous, chloride form), methyl acetate (≥99.9%), anhydrous methanol (≥99.8%), succinic acid (≥99%), dimethyl succinate (≥99%), monomethyl succinate (≥95%), lactic acid (≥90%), methyl lactate (≥97%), and anhydrous ethyl acetate (≥99.8%) were from Sigma-Aldrich, and acetic acid (≥99%) from J.T. Baker B.V. Ethanol extra dry/absolute (≥99.5%) was from Fischer Scientific. Carbon dioxide (≥99.8%) as compressed gas was from Linde. Amberlyst15 hydrogen form (4.7 meq/g by dry weight, Serva Heildelberg) was washed with methanol and dried at 60 °C in an oven before use. Aqueous solutions were prepared by diluting with deionized water from a Milli-Q water purification system (Millipore).

2.2. Resin Preparation and adsorption

The adsorption experiments were performed with potassium acetate, sodium succinate and sodium lactate solutions to mimic fermentation broth..[37] Column elution was used to convert the resin Dowex Marathon MSA from the chloride form to the acetate, succinate, lactate or bicarbonate form. The resin was washed at 2 mL/min with potassium acetate, sodium bicarbonate, sodium succinate or sodium lactate solution (20 g/L), until the concentration of chloride in the outlet was below 9 mg/L and the absorbance at 210 nm at the outlet of the column was constant. Outlet samples were colorimetrically analyzed for chloride concentration. The resin was washed 3 times in a batch with 50 mL deionized water, filtered at 20 mbar using Millipore Steriflip 60 µm nylon net filtration unit, washed 3 times with 30 mL methanol, filtered using the same system, and dried in an oven at 60 °C for 16 h. The elemental composition of the surface of the resin was measured in triplicate using X-ray photoelectron spectroscopy (XPS), and the presence of water in the resin in duplicate by thermogravimetric analysis (TGA).

2.3. Desorption with a carbon dioxide expanded alcohol

The desorption of acetate from the resin was performed in a 50 mL Büchi glass stirred autoclave reactor. The reactor was equipped with a magnetically driven four blade impeller controlled by an overhead motor, thermocouple for temperature control, pressure sensor, pressure relief valve, nitrogen and carbon dioxide inlet, reagent addition and sampling ports.

The experiments were performed adding 0.5-1 g of Dowex MSA-acetate (2.2 mmol acetate/ g dry resin) to 30 g of anhydrous methanol (or ethanol). Then, the reactor was flushed with N_2 to achieve inert atmosphere. Agitation was at 600 rpm, and a pressure of 5 bar of N_2 was maintained (control experiment). For the other experiments, it was flushed 5 more times with CO_2, and then the pressure was set to the desired value (2, 5 or 10 bar of CO_2). The reactor was repressurized with CO_2 until constant pressure. The experiments were performed for 4 h in duplicate. Liquid samples were obtained at the set pressure. Initial samples of the solvent, and final samples were analyzed for the specific methyl esters, carboxylic acid and water content on weight basis of alcohol.

2.4. Esterification reactions

Esterification reactions were carried out in closed glass tubes in a Greenhouse Plus Parallel Synthesizer (Radleys). The experiments were performed in duplicate. In a typical experiment, 4 g of a solution of 2% or 4% w/w of acetic acid in methanol was added to the reaction tubes. A catalyst was added to different reaction tubes (0.06 g of dried Amberlyst15 hydrogen form or 4 µL of 96 %w/w H_2SO_4) The tubes were flushed with N_2 to have an inert atmosphere. The conditions were kept at 60 °C and agitated with a magnetic stirrer at 600 rpm 4 h. Final samples were analyzed for methyl acetate, acetic acid and water content.

For the simultaneous desorption and esterification reactions, a similar procedure as explained in section 2.3 was followed. The difference was the addition of 0.5 g of pre-washed Amberlyst15 in a separate chamber in the reactor to catalyze the esterification reaction. The reaction was performed at 60 or 78 °C for 4 h. Final samples were analyzed for the methyl esters, carboxylic acids and water content.

2.5 Recycle of the resin

The resin Dowex Marathon MSA was washed with deionized water and converted from chloride bicarbonate form by the column elution technique described in section 2.2. Then the resin was washed 3 times with 30 mL of deionized water, and the excess water was removed with a vacuum filter (20 mbar). The adsorption experiments were performed in batch, in which 1.5 g of wet resin was added to 30 g of a 10 g/L solution of potassium acetate. The batch was kept for 16 h, in which initial and final liquid samples were taken, and analyzed by HPLC (section 2.6). The mixture was filtered and the resin was washed 3 times with 30 mL with deionized water, 3 times with methanol, and dried at 60 °C for 3 h. The desorption experiments were performed using the simultaneous desorption-esterification method described in section 2.4. Liquid samples were analyzed for methyl acetate as described in section 2.6. The Dowex Marathon MSA resin was recovered and washed 3 times with 30 mL deionized water, and the excess water was removed with a vacuum filter (20 mbar). The resin was then reused in the next adsorption batch. The procedure was repeated until 5 consecutive adsorption and desorption steps were performed.

2.6. Analytical Methods

Dimethyl carbonate, methyl acetate, ethyl acetate, dimethyl succinate, methyl lactate and acetic acid were analyzed by gas chromatography (GC) using a ZB-WAXplus column (20 m length × 0.18 mm internal diameter, 0.18 μm film) and a flame ionization detector (FID). Injection and detector conditions were maintained. Liquid samples were conditioned with formic acid and anisole as internal standard. The sample (0.5 μL) was injected at 200 °C with a split flow of 30 mL/min. The oven temperature was maintained at 60 °C for 10 min, then a 10 °C/min temperature ramp was used up to 200 °C. Succinic acid, methyl succinate and lactic acid concentrations were analyzed on a

Waters HPLC system using a Bio-Rad Aminex HPX-87H column (78 × 300 mm) at 60 °C. Phosphoric acid (1.5 mmol/L at 0.6 mL/min) was used as an eluent. Water content was measured by Karl Fischer titration (Metrohm 831 KF coulometer).

The elemental analysis of the anion exchange resin was carried out using an X-ray Photoelectron Spectrometer (Thermo Fisher Scientific K_{α} model). A monochromatic Al K_{α} X-ray source was used with a spot size of 400 μm at a pressure of 10^{-7} mbar. A constant pass energy of 200 eV for the survey and 50 eV for the high-resolution region was used. The flood gun was turned on during the measurement in order to compensate the potential charging of the surface. The peak position was adjusted based on the internal standard C 1s peak at 284.8 eV, with an accuracy of ± 0.05 eV. *Avantage* processing software was used to analyze all spectra, and the peak fitting was done on the basis of mixed Lorentian-Gaussian function.

Thermogravimetric analysis (TGA) measurements were performed with a TA Instruments thermo gravimetric analyzer from RT to 150 °C. The heating rate was 10 °C·min^{-1} and the purge gas was air.

Results and Discussion

3.1 Characterization of the anion exchange resin used for the recovery of acetate

In the proposed process, the acetate anion is recovered from the fermentation broth (at pH > pK_a) using an anion exchange resin. A quaternary ammonium anion exchange resin (Dowex Marathon MSA provided in Cl^- form) is used because at this pH (7.7) electrostatic interactions are needed to bind acetate. The loading of acetate to the resin was 0.043 g acetate/ g of wet resin. The surface composition of the resin loaded with acetate was measured with XPS and compared with the chloride and bicarbonate form of the resin (Table 2). The bicarbonate form of the resin is obtained upon regeneration of the resin using the proposed method (as mentioned in R.2). For this reason, the variation in the composition between chloride, acetate and bicarbonate on the resin was measured.

Table 2. X-ray photoelectron spectroscopy analysis of dried Dowex Marathon MSA resin*

Resin Counter-ion	Surface atomic composition (%)			
	C	O	N	Cl
Chloride	82.6 ± 0.3	5.4 ± 0.2	6.3 ± 0.3	5.6 ± 0.1
Acetate	77.3 ± 0.8	18.5 ± 1.4	2.7 ± 2.1	Not detectable
Bicarbonate	79.3 ± 0.8	12.9 ± 1.6	4.8 ± 0.5	Not detectable

* Relative constitution as C, O, N, Cl.

Table 2 presents the surface atomic composition of the dried resin in the chloride, acetate and bicarbonate form. Results clearly show that there is no chloride detectable after loading the resin with acetate or bicarbonate using the column elution technique, which is in good agreement with the chloride and UV measurements in the outlet of the column (Section A.1). The absence of chloride in the acetate and bicarbonate resins confirms the success of the reactions. Furthermore, oxygen is present (~5 to ~18%) in all samples. The detection of oxygen in the chloride form of the resin might be associated to surface contaminations as suggested by C-O and C=O contributions in the XPS C1s spectrum (Section A.2.2 and A.2.3). In addition, water can be strongly adsorbed to resin, even at a pressure of 10^{-7} mbar during the XPS analysis. After all, ion-exchange resins are highly hydrophilic as also shown by our TGA results, which were performed on the chloride, bicarbonate and acetate form. The thermogravimetric curves reveal a degradation step within 150 °C both in the wet and dry resin with values of 65-68% w/w and 5-8% w/w, respectively.

Nevertheless, the oxygen composition significantly increases upon the addition of acetate and bicarbonate, which is again supporting the anion exchange reactions.

We further note that the presence of adsorbed water is important for the further desorption and esterification steps. The variation in the nitrogen content is related to the non-homogeneous distribution of the quaternary ammonium group on the resin surface.[38] This is observed in the acetate sample in which the nitrogen atomic composition is 2.7±2.1%, for which the measurements varied in the range of 4.2% (similar as the bicarbonate form) to 1.2%. In another set of samples (Table A.2), the nitrogen compositions of the acetate and bicarbonate form of the resin were fluctuating from 3.2 to 5.7%.

Once the target carboxylate is bound to the resin, desorption of the carboxylate from the anion exchange resin has to overcome the strong binding energy of the electrostatic interactions between the carboxylate and the quaternary ammonium group of the resin. To solve this problem, a new approach for the desorption of the carboxylate using CO_2-expanded alcohols is explored.

3.2 Desorption of acetate with CO_2-expanded methanol

The innovative step in the process is the desorption of the acetate from the anion exchange resin. The acetate anion is desorbed from the resin using CO_2-expanded methanol. Table 3 shows the effect of CO_2 pressure on the desorption of acetate. At low CO_2 pressures (2-10 bar) a high recovery yield (mol acetic acid/mol $acetate_{in}$) ranging from 0.55-0.79 is observed. In contrast, a 0.38±0.05 mol acetic acid/$acetate_{in}$ desorption yield was found at a CO_2 pressure of 10 bar in water (Table A.5).

Table 3. Desorption of acetate from an anion exchange resin with CO_2-expanded methanol at 20-22 ^oC with a resin loading of 3.4 %w/w dry resin/ methanol

Equilibrium CO_2 pressure (bar)	Final water (mmol/g solvent)	Desorption (mol acetic acid/mol acetate$_{in}$)
0	0.30±0.04	0
2.12	0.35±0.04	0.55 ±0.09
5	0.37±0.07	0.72 ±0.02
10	0.38±0.05	0.79 ±0.04

With this desorption, the anion exchange resin might be converted into the methylcarbonate or bicarbonate form (R.4 and R.5), and the acetate is protonated.

$$Q^+Ac^- + MeOH + CO_2 \rightleftharpoons Q^+MeCO_3^- + HAc \quad R.4$$

$$Q^+Ac^- + H_2O + CO_2 \rightleftharpoons Q^+HCO_3^- + HAc \quad R.5$$

The high solubility of carbon dioxide in methanol (Table 4) enhances the desorption of acetate from the anion exchange resin. This allows the utilization of a much lower CO_2 pressure than in water to protonate the carboxylate anion. Other low CO_2 pressure research has been conducted in water in which CO_2 and amines are used for the recovery of acetic acid.[8] In that approach, aqueous calcium acetate is protonated using CO_2, and the formed acetic acid is bound to tributylamine. The amine complex is extracted using a water insoluble alcohol. Downsides of that approach are the losses of extractant and CO_2 dissolving in the aqueous phase, and the requirement of hydrophobic alcohols (butanols to octanols) to extract acid. In contrast, using the proposed method we can get the acetic acid dissolved in hydrophilic alcohols such as methanol, which enables more interesting esterification reactions.

Table 4. Solubility of carbon dioxide (10 bar) in different solvents at 25 °C [39, 40]

Solvent	Mole fraction	Mass Fraction
Water	0.00592	0.0144
Methanol	0.0772	0.1030
Ethanol	0.1110	0.1065

In the case of methanol and acetate, the reactions considered are: the protonation of the acetate bound to the resin via the formation of the methylcarbonate anion[41] (from MeOH and CO_2, R.4); the protonation by the formation of bicarbonate anion (R.5); the hydrolysis of the methylcarbonate anion (R.6); the formation of dimethyl carbonate (DMC) from the methylcarbonate anion and methanol (R.7); and the conversion of the hydroxide to the bicarbonate form of the resin (R.8). During the experiments, DMC was detected in low concentrations. Because of the low concentrations detected, DMC might play no role as an alkylating agent in a reaction with acetate.

$$Q^+MeCO_3^- + H_2O \rightleftharpoons Q^+HCO_3^- + MeOH \qquad R.6$$

$$Q^+MeCO_3^- + MeOH \rightleftharpoons Q^+OH^- + Me_2CO_3 \qquad R.7$$

$$Q^+OH^- + CO_2 \rightleftharpoons Q^+HCO_3^- \qquad R.8$$

As a result, the formed acetic acid (protonated acid) is in solution with methanol and CO_2. The next downstream process step might be a recovery (e.g. distillation) of the protonated acid, an esterification of the acid or another reaction step. In this paper, we explore the integration of the desorption in CO_2-expanded methanol with an esterification reaction (R.9). Once the system is at equilibrium, an excess of methanol and CO_2 might direct the equilibrium to the products (ester and water) formation.

$$HAc + MeOH \rightleftharpoons MeAc + H_2O \qquad R.9$$

In the next section, we compare different reactor configurations for the integration of the desorption and esterification steps. Furthermore, the requirements of catalyst and the effect of the CO_2 and methanol excess in the shift of the desorption and esterification equilibrium are studied.

3.2 Integration of esterification with CO_2-expanded methanol desorption

The esterification of acetic acid with methanol is a well-studied topic.[42-45] It has been reported that CO_2 can improve the molar yield of esterification reactions from 0.64 to 0.72-0.80 (without catalyst).[43] However, the reaction kinetics are not improved, and the time to reach equilibrium is long (>20 h). For our system, preliminary experiments demonstrated that the reaction is too slow and that a catalytic agent is required. Catalytic agents that are commonly used are H_2SO_4, strong cation exchange resins (with sulfonic acid groups) and zeolites.[42, 45, 46] Some other carboxylic acids are sufficiently strong acids to catalyze their own esterification reaction. The type of catalyst, the reaction temperature, the CO_2 pressure used and the stability of the catalyst and anion exchange resin are factors that determine optimal reactor(s) configuration. The different reactor(s) configuration that are considered: consecutive 2-compartments; simultaneous 1-compartment; and simultaneous 2-compartments (Figure 1). These reactor(s) configurations are studied to determine the effect of integrating the desorption and esterification steps.

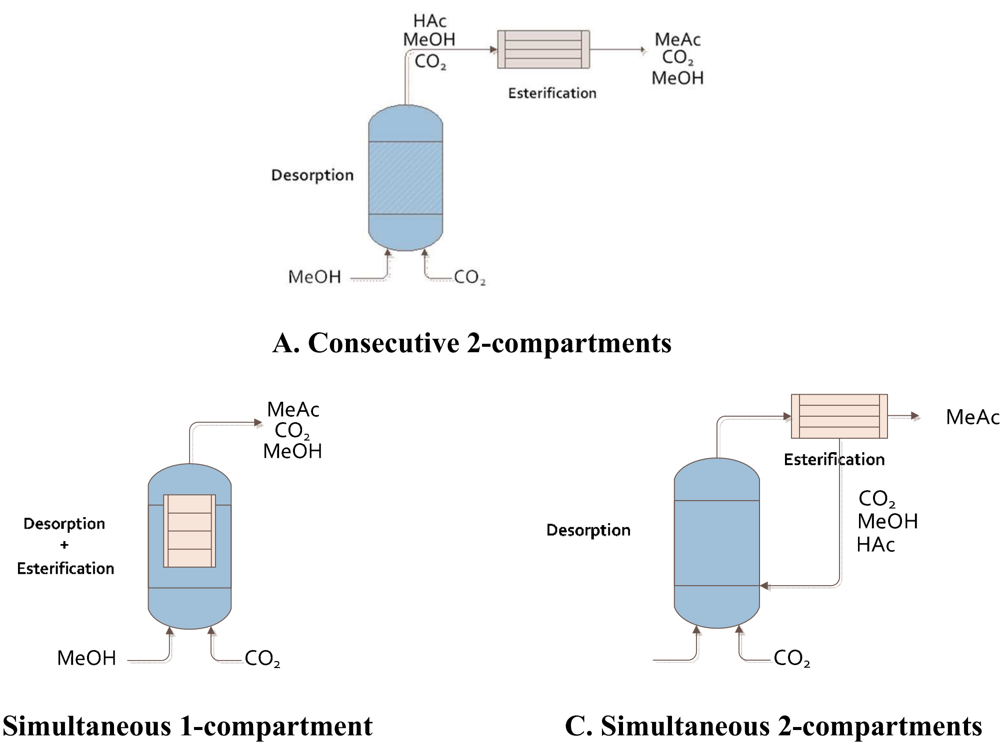


Figure 1. Options for process integration for the desorption and esterification steps

Our experiments were performed using the simultaneous 1-compartment system and the consecutive 2-compartment systems. Experiments with a simultaneous 2-compartment system are more difficult to implement on lab scale, but we expect the degree of conversion to be similar as for the 1-compartment system at the same operating temperature for both compartments and high recycle rates. The main results are shown in Table 5.

Table 5. Effect of the catalyst on the esterification of acetic acid with methanol at 60 °C for 4 h at different process configurations.

Experiment	Process configuration	Solution	Esterification Equilibrium CO_2 pressure (bar)	Catalyst[a,b]	Final water (mmol/g solvent)	Yield (mol methyl acetate/mol $acetate_{in}$)
1	Only esterification	0.4 %w/w HAc in MeOH	0	none	Not available	0
2	Only esterification	0.4 %w/w HAc in MeOH	0	H_2SO_4	Not available	0.86±0.02
3	Only esterification	0.2 %w/w HAc in MeOH	0	H_2SO_4	0.06±0.02	0.76±0.02
4	Only esterification	0.4 %w/w HAc in MeOH	0	Amberlyst	0.27±0.02	0.81±0.02
5	Only esterification	0.2 %w/w HAc in MeOH	0	Amberlyst	0.12±0.01	0.85±0.02
6	Consecutive	Desorbed effluent CO_2-expanded protonation (10 bar)	0	H_2SO_4	0.60±0.03	0.87±0.02
7	Simultaneous	3.3 %w/w Dowex MSA acetate form in MeOH	5	none	0.40±0.06	0
8	Simultaneous	3.3 %w/w Dowex MSA acetate form in MeOH	5	Amberlyst	0.39±0.07	0.58±0.07

a. 0.08 % w/w H_2SO_4
b. 1.4 %w/w dry Amberlyst 15

It can be observed that the maximum methyl acetate yield achieved is 0.87, which is the same as reported in literature with different catalyst systems.[42, 45, 47] The simultaneous desorption and esterification process configuration presented a yield of 0.58±0.07 mol methyl acetate per mole of $acetate_{in}$. This value is comparable to the overall yield of the consecutive configuration which the desorption step yield is 0.79±0.03 mol of acetic acid per mole of $acetate_{in}$, and the further esterification reaction is 0.87±0.02 mol methyl acetate per mole of acetic $acid_{in}$, which gives an overall yield of 0.68 mol of methyl acetate per mole of $acetate_{in}$.

Envisaged advantages and disadvantages vary for the process integration options shown in Figure 1. For example, the 2-compartments options can potentially operate at individual optimum conditions for desorption and esterification. A major advantage of the simultaneous options (1- and 2-compartments) is an equilibrium shift of the desorption step to the product side by the consumption of acetic acid during esterification. This should allow the utilization of lower CO_2 pressures. On the other hand, a heterogeneous acid catalyst will be desired, because otherwise the acid catalysts' anion (e.g. sulfate) can exchange in the anion exchange resin in the desorption compartment. The main disadvantage of the simultaneous 1-compartment option is that this heterogeneous acid catalyst will have to be separated from the anion exchange after this resin has been fully desorbed.

3.3. Effect of water on the simultaneous desorption and esterification of acetate with CO_2-expanded methanol

Generally, water counteracts esterification. In our system, water is introduced to the reaction with the utilization of resins (anion and cation exchange) in each of the systems. Water has been largely removed from both resins by washing them with methanol and drying it in an oven at 60 °C. At industrial scale this would be done in a different way but it might still be an expensive step because of energy and equipment requirements. For this reason, the effect of a higher initial water concentration on the desorption and esterification of acetate with CO_2-expanded methanol has been studied.

It can be advantageous for an industrial process if merely filtering the resin would remove water to a sufficient extent. A comparison between the yields obtained with a dry (methanol dried) and wet resin (filtered) are presented in Table 6. The wet resin was obtained after washing the resin a couple of times with deionized water and the water was filtered off while using a vacuum pump (10 mbar). The esterification reactions were performed without CO_2 since we expected a small effect of CO_2 on the esterification at this low concentration (0.02 mmol acetic acid/g). As mentioned earlier, the amounts of adsorbed water were found to be 68-71% for wet resin and 7-8% for dry resin.

Table 6. Effect of water on the desorption and esterification using 0.02-0.04 mmol/g acetic acid with methanol for 4 h

Exp.	Process config.	Resin (Dowex MSA) pretreatment	Desorption equilibrium CO_2 pressure (bar)	Temp. (°C)	Catalyst [a,b]	Final water (mmol/g solvent)	Total desorption yield ((mol MeAc+mol HAc)/mol acetate$_{in}$)	Yield (mol methyl acetate/mol acetate$_{in}$)
9	Desorption	Dry resin	10	20	none	0.42±0.03	0.79 ±0.04	-
10	Desorption	Wet resin	10	20	none	1.90±0.40	0.50±0.01	-
11	Esterification	Dry resin [d]	-	60	H_2SO_4	0.60±0.03	-	0.87±0.02
12	Esterification	Wet resin [e]	-	60	H_2SO_4	1.95±0.14	-	0.97±0.01
9+11	Consecutive	Dry resin	exp. 9 & 11	exp. 9 & 11	exp. 9 & 11	0.60±0.03	0.79 ±0.04	0.68±0.03
10+12	Consecutive	Wet resin	exp. 10 & 12	exp. 10 & 12	exp. 9 & 11	1.95±0.14	0.50±0.01	0.48±0.01
13	Simultaneous	Dry resin	5	60	Amberlyst	0.39±0.07	0.66±0.07	0.58±0.07
14	Simultaneous	Wet resin	5	60	Amberlyst	3.42±0.5	0.57±0.01	0.37±0.02

a. 0.1 % w/w H_2SO_4
b. 1.4 %w/w dry Amberlyst 15
c. Dry resin (8 %w/w water) and wet resin (68 %w/w water)
d. Effluent exp. 9
e. Effluent exp. 10

The desorption of acetate from the anion exchange resin decreases from 0.79 to 0.50 mol of acetic acid/ mol of acetate$_{in}$ when changing from a dry to a wet resin. It seems that the desorption equilibrium with methanol is more favorable (R.4), and it is easily affected by the presence of water (R.5-R.6). Esterification of acetic acid with methanol is not affected by a water content of 1.95±0.14 mmol/g at a lower initial acetic acid concentration (~1.5 mg acetic acid/ g solution). The reason is that the concentration of acetic acid in this treatment is lower than in the others, and the excess methanol improves the yield until almost full conversion of methyl acetate. However, in the consecutive desorption and esterification the total methyl acetate yield is reduced from 0.68 to 0.48 in the presence of the wet resin. Interestingly, for the simultaneous desorption and esterification the total desorption is only slightly affected by the increase in water content (yield decreases from 0.66-0.57), but the overall ester yield is reduced from 0.58±0.07 to 0.37±0.02 mol of methyl acetate/ mol of acetate$_{in}$. For both systems, the extra water present in the reaction medium (coming from the different ion exchange resins) affects the esterification equilibrium and reduces the methyl acetate formation. The concentration of water introduced to the system by the anion exchange resin is 20 higher in the case of the wet resin (3.3 mmol water/ g solvent), in comparison to the dry resin (0.16 mmol water/ g solvent). In general terms, the overall yield might be improved by the removal of water from the system, but also by using a higher excess of methanol to push the equilibrium to the products. To increase the esterification yield, esterification may be performed as reactive distillation or reactive SMB chromatography.[48, 49]

3.4 Desorption and esterification with other carboxylates: lactate and succinate

The yield of the desorption and esterification of acetate can be improved using a higher excess of methanol to push the equilibrium further. In this section, we decreased the amount of resin from 3.4 to 1.7 %w/w dry resin Dowex MSA/ methanol to increase the methyl carboxylate yields. Table 7 shows that at this condition the yield of methyl acetate formation increased to completion (1.03±0.07). The higher excess of methanol improves the reaction. However, it decreases the overall productivity of the process and increases costs of ester recovery by methods such as distillation. This might compromise the process feasibility, especially for low-priced products such as methyl acetate. The same ratio of resin and methanol was used for the desorption and esterification of succinate and lactate. These two carboxylates are attractive platform chemicals because of their chemical functionality and valuable derivatives.

Table 7. Simultaneous desorption and esterification of acetate, succinate and lactate with CO_2-expanded methanol at 60 °C and 5 bar CO_2 [a,b]

Carboxylate	Time (h)	mmol carboxylate/ g dry resin	Final water (mmol/g solvent)	Final acid (mmol/ g solvent)	Yield monoester (mol methyl carboxylate/mol carboxylate$_{in}$)	Yield diester (mol dimethyl carboxylate/mol carboxylate$_{in}$)
Acetate	4	2.2	0.31±0.12	0.0034±0.0005	1.03 ±0.07	-
Succinate	4	1.8	0.20	0.0013	0.02	<0.04
Succinate	20	1.8	0.32±0.04	0.0005 ±0.0001	0.017±0.003	0.18±0.03
Lactate	4	2.0	0.16±0.05	0.004±0.001	0.70 ±0.02	-

a. 1.7 %w/w dry resin Dowex Marathon MSA / methanol
b. 1.4 %w/w dry Amberlyst 15

Table 7 shows that the desorption and esterification of succinate with CO_2-expanded methanol is possible with a modest yield of 0.18 mol dimethyl succinate/mol succinate$_{in}$ at 60 °C and 5 bar of CO_2. From the residual amount of succinic acid (0.0006 mmol/g) and methyl succinate (yield of 0.01 mol monoester/mol carboxylate$_{in}$) in the methanol solution, it seems that most of the dicarboxylate anion is still bound to the resin. Apparently, 5 bar CO_2 pressure is not enough to protonate the two carboxylate groups of succinate and push it out of the resin. Moreover, an increase in the yield for the esterification for 20 h suggests that there is room for optimization of catalyst, temperature, and reaction time. It has been reported that for the esterification of succinic acid with ethanol a major difference on the rate in diethyl succinate formation is achieved with different cation exchange resins as catalyst.[50]

A yield of 0.70 mol methyl lactate/mol lactate$_{in}$ is observed for the desorption and esterification of lactate at 60 °C and 5 bar of CO_2. The yield of methyl lactate is higher than reported [51] for the esterification of lactic acid (0.4 mol of methyl lactate/mol lactic acid) at a lower excess of methanol (5 mol methanol/mol lactic acid) in comparison with our excess (~460 mol methanol/mol lactic acid).

It would be interesting to explore the utilization of this method for other industrial relevant carboxylates such as propionic acid, 3-hydroxypropionic acid, levulinic acid, itaconic acid and 2,5-furandicarboxylic acid (FDCA).

3.5 Stability and regeneration of the anion exchange resin

Dowex Marathon MSA resin maintained its performance after five reuse cycles in a regeneration step with ethyl chloride at 100 °C.[21] The conditions used in our new method with CO_2-expanded alcohols are at lower temperature (60 °C) than in previously reported studies[21, 22], which might improve the stability and regenerability of the resin, because quaternary ammonium groups suffer deamination under long term exposure to high temperatures. Decoupling desorption and esterification steps in a consecutive system such as described in Figure 1 also provides the option to perform the anion exchange at ambient temperatures.

Table 8. Performance of Dowex Marathon MSA in cycles of 16 h of adsorption of potassium acetate (RT) and 4 h of desorption + esterification (60 °C) in CO_2-expanded methanol.

Process step	Cycle				
	1	2	3	4	5
Adsorption (g acetate/g wet resin)	0.059	0.055	0.056	0.061	0.068
Desorption + esterification (mol methyl acetate/ mol acetate in)	1.01	1.12	1.00	0.92	1.00

Table 8 shows that the resin performs similarly in 5 successive adsorption- desorption + esterification cycles. The adsorption capacity remains 0.060 ± 0.005g acetate/ g wet resin and the desorption + esterification yield remains 1.01 ± 0.07 mol methyl acetate/mol $acetate_{in}$, also in line with previous experiments (Table 7). The resin was exposed to total experimental time of 100 h, however a longer period is necessary to evaluate its long term stability.

3.6 Perspectives for other CO_2-expanded alcohols: ethanol as example

In previous sections, we demonstrated that CO_2-expanded methanol can be used for the desorption and esterification of carboxylates from a strong anion exchange resin. The main advantage of this method is the high solubility of CO_2 in methanol. CO_2 has also a high solubility in other alcohols such as ethanol (Table 3). Ethanol is a suitable chemical because it is a non-expensive, bio-based and produced worldwide. Moreover, the produced ethyl carboxylates compounds are industrially interesting products. Ethyl acetate and ethyl lactate have several industrial applications.[52]

Table 9. Simultaneous desorption and esterification of acetate with CO_2-expanded ethanol at 5 bar CO_2 for 4 h

Process Step	Temperature (°C)	Catalyst[a]	Dry Dowex MSA-acetate in ethanol (% w/w)	Final water (mmol/g solvent)	Total desorption yield ((mol EtAc + HAc)/ mol $acetate_{in}$)	Yield (mol ethyl acetate/mol $acetate_{in}$)
Desorption	20	None	3.5	0.16±0.01	0.50±0.03	-
Desorption and esterification	78	Amberlyst	3.5	0.27±0.04	0.71±0.02	0.55±0.02
Desorption and esterification	78	Amberlyst	1.7	0.30±0.15	0.87±0.05	0.67±0.04

a. 1.4 %w/w dry Amberlyst 15

Table 9 shows the results for desorption and esterification of acetate with CO_2-expanded ethanol at 5 bar. The desorption yield at 20 °C is 0.50±0.03, which is lower than the amount achieved with methanol (0.72±0.02). A lower rate with a higher alcohol is expected because of steric effects and slower diffusion. Besides, at similar mass concentrations the molar excess of alcohol decreases. Similar results were reported for the transesterification of ethylene carbonate with different alcohols, in which the yield decreases with an increase of the carbon atoms of the alcohol.[53] This indicates that a higher pressure is required for CO_2-expanded ethanol to achieve higher desorption yields. As in the methanol case, the desorption yield increases when a simultaneous esterification occurs. The desorption increases to 0.71±0.02 mol (HAc + MeAc)/ mol $acetate_{in}$ with an esterification yield of 0.55±0.02 with an excess of ethanol of 3.5%w/w $acetate_{in}$/ethanol. A further excess of ethanol (1.7%w/w $acetate_{in}$/ethanol) increases the esterification yield to 0.67±0.01, which is in accordance with reported esterification data.[54]

The method might be applicable for a range of other alcohols such as butanol, benzyl alcohol, isoamyl alcohol, and geraniol. These alcohols can be used to produce esters such as butyl butyrate, benzyl acetate, isoamyl acetate and geranyl acetate, which are important in the solvent, fragrance and flavor industry.[55] The specific process conditions to achieve high conversion depend on each scenario and industry.

Recovery and esterification of carboxylates from fermentation broth still has to be tested. Sorption studies using carboxylates from actual fermentation on the current resin[37] indicate that contaminating anions, which are fermentation-specific, will have to be dealt with. Furthermore, other impurities (*e.g.* solid impurities and inorganic anions) might affect the long term stability and regeneration of the resin. The effect of these impurities in the feasibility of the process and the regeneration of the resin has to be study in detail for each application. In some cases, an extra conditioning step of the resin (to remove the impurities) might be needed in between each of the cycles .

Additionally, the high dilution of the produced esters (0.1-0.3 wt%) complicates their purification. In the case of methyl acetate, the ester can be concentrated at least to its azeotrope with methanol (81.3 wt%) by distillation. For dimethyl succinate and methyl lactate, having boiling points higher than methanol, no such azeotrope exists and recovery becomes a bottleneck. A higher concentration of the esters in CO_2-expanded alcohols would facilitate ester recovery. Currently, we are exploring the limits of achieving a higher concentration of esters (using changes in alcohol excess and CO_2 pressure), and studying their recovery including excess solvent recycle.

4 Conclusions

This paper has presented a new method for the recovery and esterification of carboxylates using CO_2-expanded alcohols. Using this method, the carboxylates are recovered using an anion exchange resin, and CO_2-expanded alcohol is used for the desorption and subsequent esterification of the carboxylates. The main advantages are: no stoichiometric waste production, low pressures of CO_2 needed and integration of the unit operations. Using CO_2 -expanded methanol, we achieved a desorption yield of 0.79 mol acetic acid/ $acetate_{in}$ at 10 bar of CO_2, and an ester yield of 1.03 mol methyl acetate/ $acetate_{in}$ in the combined desorption-esterification at 5 bar of CO_2 and 60 °C. The method might be applied for the recovery of different carboxylates produced by fermentation at pH > pK_a, such as lactate (0.70 methyl lactate/$lactate_{in}$) and succinate (0.18 dimethyl succinate/$succinate_{in}$), however has to be improved further, especially for dicarboxylates such as succinate. Moreover, a lower yield of 0.67 mol of ethyl acetate/ mol $acetate_{in}$ was obtained with CO_2-expanded ethanol. The method is versatile and can be optimized with respect to reactor configuration, catalyst, CO_2 pressure, alcohol excess, temperature and reaction time, depending on the specific application.

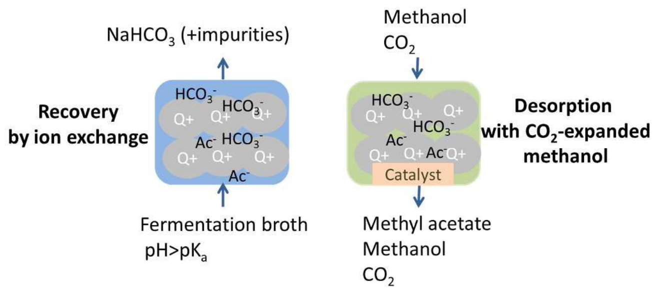
5 Acknowledgements

This research was financed by the Dutch Technology Foundation STW and Paques B.V. partnership: The Volatile Fatty Acid Platform. The authors thank Patricia van Dam and Max Zomerdijk for analytical support.

6 References

1. A. J. J. Straathof, *Chem. Rev.*, 2014, **114**, 1871-1908.
2. C. S. López-Garzón and A. J. J. Straathof, *Biotechnol. Adv.*, 2014, **32**, 873-904.
3. G. C. Inskeep, G. G. Taylor and W. C. Breitzke, *Ind. Eng. Chem.*, 1952, **44**, 1955-1966.
4. P. Viet, M. Holtzapple and M. M. El-Halwagi, in *Integrated Biorefineries*, CRC Press, 2012, DOI: 10.1201/b13048-8, ch. 6, pp. 157-192.
5. B. Urbas, CPC International Inc., Recovery of acetic acid from a fermentation broth, U. S. Patent, US4405717 A, 1983
6. V. Pham, M. Holtzapple and M. El-Halwagi, *J. Ind. Microbiol. Biotechnol.*, 2010, **37**, 1157-1168.
7. P. C. Walkup, C. A. Rohrmann, R. T. Hallen and D. E. Eakin, Battelle Memorial Institute, Production of esters of lactic acid, esters of acrylic acid, lactic acid, and acrylic acid, U. S. Patent, US5252473, 1993
8. T. Eggeman and D. Verser, in *Twenty-Sixth Symposium on Biotechnology for Fuels and Chemicals*, ed. B. H. Davison, B.R. Evans, M. Finkelstein, J.D. McMillan, Springer, New York City: Humana Press, 2005, ch. 52, pp. 605-618.
9. R. W. Miller, M. C. M. Cockrem, J. J. de Pablo and E. N. Lightfoot, *Ind. Eng. Chem. Res.*, 1996, **35**, 1156-1162.
10. H. G. Joglekar, I. Rahman, S. Babu, B. D. Kulkarni and A. Joshi, *Sep. Purif. Technol.*, 2006, **52**, 1-17.
11. S. M. Husson and C. J. King, *Ind. Eng. Chem. Res.*, 1999, **38**, 1625-1632.
12. S. M. Husson and C. J. King, *Ind. Eng. Chem. Res.*, 1998, **37**, 2996-3005.
13. C. Huang, T. Xu, Y. Zhang, Y. Xue and G. Chen, *J. Membr. Sci.*, 2007, **288**, 1-12.
14. J. Xu, J. J. Guzman, S. J. Andersen, K. Rabaey and L. T. Angenent, *Chem. Commun.*, 2015, **51**, 6847-6850.
15. S. J. Andersen, T. Hennebel, S. Gildemyn, M. Coma, J. Desloover, J. Berton, J. Tsukamoto, C. Stevens and K. Rabaey, *Environ. Sci. Technol.*, 2014, **48**, 7135-7142.
16. A. M. Eyal and P. Elankovan, Process for the recovery of lactic acid from aqueous lactate salt solutions, involving the use of ion exchangers, U. S. Patent, US7238837, 2007
17. A. D. Kon, A. B. De Haan, P. L. J. Van Der Weide, T. D. Zivkovic and L. H. L. J. De Koninck, Carboxylic acid recovery from magnesium carboxylate mixture, W. O. Patent, WO2013174911 A1, 2013
18. M. Okabe, D. Lies, S. Kanamasa and E. Park, *Appl. Microbiol. Biotechnol.*, 2009, **84**, 597-606.
19. X. Cao, H. S. Yun and Y.-M. Koo, *Biochem. Eng. J.*, 2002, **11**, 189-196.
20. A. Orjuela, A. J. Yanez, L. Peereboom, C. T. Lira and D. J. Miller, *Sep. Purif. Technol.,*, 2011, **83**, 31-37.
21. C. S. López-Garzón, M. Ottens, L. A. M. van der Wielen and A. J. J. Straathof, *Chem. Eng. J.*, 2012, **200**, 637-644.
22. C. S. López-Garzón, L. A. M. van der Wielen and A. J. J. Straathof, *Chem. Eng. J.*, 2014, **235**, 52-60.
23. L. A. Tung and C. J. King, *Ind. Eng. Chem. Res.*, 1994, **33**, 3217-3223.
24. S. T. Yang, S. A. White and S. T. Hsu, *Ind. Eng. Chem. Res.*, 1991, **30**, 1335-1342.
25. K. Zhang and S. T. Yang, *Biochem. Eng. J.*, 2015, **96**, 38-45.
26. C. Andersson, J. Helmerius, D. Hodge, K. A. Berglund and U. Rova, *Biotechnol. Prog.*, 2009, **25**, 116-123.
27. K.-K. Cheng, X.-B. Zhao, J. Zeng and J.-A. Zhang, *Biofuels Bioprod. Bioref.*, 2012, **6**, 302-318.

28. C. I. Cabrera-Rodríguez, L. A. M. van der Wielen and A. J. J. Straathof, *Ind. Eng. Chem. Res.*, 2015, **54**, 10964-10973.
29. J. Sun, B. Lu, X. Wang, X. Li, J. Zhao and Q. Cai, *Fuel Process. Technol.*, 2013, **115**, 233-237.
30. V. Eta, P. Mäki-Arvela, E. Salminen, T. Salmi, D. Y. Murzin and J.-P. Mikkola, *Catal. Lett.*, 2011, **141**, 1254-1261.
31. M. Cao, Y. Meng and Y. Lu, *React. Kinet. Catal. L.* , 2006, **88**, 251-259.
32. P. P. Barve, S. P. Kamble, J. B. Joshi, M. Y. Gupte and B. D. Kulkarni, *Ind. Eng. Chem. Res.*, 2011, **51**, 1498-1505.
33. G. R. Akien and M. Poliakoff, *Green Chem.*, 2009, **11**, 1083-1100.
34. P. Pollet, E. A. Davey, E. E. Ureña-Benavides, C. A. Eckert and C. L. Liotta, *Green Chem.*, 2014, **16**, 1034-1055.
35. A. M. Eyal, P. R. Gruber, P. Mcwilliams and D. R. Witzke, Cargill, Inc., A process for the recovery of lactic acid esters and amides from aqueous solutions of lactic acid and/or salts thereof, W. O. Patent, WO1998015519A2, 1998
36. A. M. Eyal, Cargill, Inc., A process for the production of a condensation product of a carboxylic acid, WO1997030964 A1, 1997
37. C. S. López-Garzón, L. A. van der Wielen and A. J. Straathof, *RSC Adv.*, 2016, **6**, 3823-3829.
38. G. C. Allen, N. R. Holmes, B. J. Lee and R. R. Harries, *J. Chem. Soc. Faraday Trans.1*, 1988, **84**, 3891-3904.
39. J. J. Carroll, J. D. Slupsky and A. E. Mather, *J. Phys. Chem. Ref. Data*, 1991, **20**, 1201-1209.
40. C. J. Chang, C.-Y. Day, C.-M. Ko and K.-L. Chiu, *Fluid Phase Equilib.*, 1997, **131**, 243-258.
41. J. L. Gohres, A. T. Marin, J. Lu, C. L. Liotta and C. A. Eckert, *Ind. Eng. Chem. Res.*, 2009, **48**, 1302-1306.
42. Y. Liu, E. Lotero and J. G. Goodwin, *J. Catal.*, 2006, **242**, 278-286.
43. L. A. Blanchard and J. F. Brennecke, *Green Chem.*, 2001, **3**, 17-19.
44. Y. Liu, E. Lotero and J. G. Goodwin, *J. Mol. Catal. A: Chem.*, 2006, **245**, 132-140.
45. Y. Liu, E. Lotero and J. G. Goodwin, *J. Catal.*, 2006, **243**, 221-228.
46. S. R. Kirumakki, N. Nagaraju and K. V. R. Chary, *Appl. Catal., A*, 2006, **299**, 185-192.
47. M. Mallaiah and G. Reddy, *Kinet. Catal.*, 2015, **56**, 419-427.
48. M. Mazzotti, A. Kruglov, B. Neri, D. Gelosa and M. Morbidelli, *Chem. Eng Sci.*, 1996, **51**, 1827-1836.
49. K. Sandesh, P. JagadeeshBabu, S. Math and M. Saidutta, *Ind. Eng. Chem. Res.*, 2013, **52**, 6984-6990.
50. J. H. Clark, V. Budarin, T. Dugmore, R. Luque, D. J. Macquarrie and V. Strelko, *Catal. Commun.*, 2008, **9**, 1709-1714.
51. M. T. Sanz, R. Murga, S. Beltrán, J. L. Cabezas and J. Coca, *Ind. Eng. Chem. Res.*, 2002, **41**, 512-517.
52. C. S. M. Pereira, V. M. T. M. Silva and A. E. Rodrigues, *Green Chem.*, 2011, **13**, 2658-2671.
53. Z.-Z. Yang, X.-Y. Dou, F. Wu and L.-N. He, *Can. J. Chem.*, 2011, **89**, 544-548.
54. N. Calvar, B. Gonzalez and A. Dominguez, *Chem. Eng. Process.*, 2007, **46**, 1317-1323.
55. J. Otera and J. Nishikido, *Esterification: methods, reactions, and applications*, John Wiley & Sons, 2009.



For graphical abstract only