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Recovery and esterification of aqueous carboxylates by using CO₂-expanded alcohols with anion exchange

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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 pKₐ of the carboxylic acid. In this approach, the aqueous carboxylate anion is recovered using anion exchange, followed by desorption and esterification with CO₂-expanded alcohols. Using CO₂-expanded methanol, we achieved a high desorption yield at 10 bar of CO₂ and 20 °C. An ester yield of 1.03±0.07 mol methyl acetate/acetate was obtained for the combined desorption-esterification at 5 bar of CO₂ 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 pKₐ values of the acids are normally 3-5.¹,² The result is a carboxylate solution at a pH above the pKₐ 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 > pKₐ

<table>
<thead>
<tr>
<th>Primary Recovery</th>
<th>Concentration</th>
<th>Purification (Regeneration)</th>
<th>Salt co-produced</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxylate precipitation</td>
<td>Water evaporation</td>
<td>Protonation with H₃SO₄</td>
<td>CaSO₄</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ketonization</td>
<td>CaCO₃</td>
<td></td>
</tr>
<tr>
<td>Protonation with H₂SO₄ or CO₂</td>
<td>Extraction with tertiary amine</td>
<td>Thermal decomposition</td>
<td>CaCO₃</td>
<td>5, 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Esterification</td>
<td>CaCO₃</td>
<td>7, 9</td>
</tr>
<tr>
<td></td>
<td>Adsorption</td>
<td>Desorption e.g. with MeOH</td>
<td>CaSO₄ or CaCO₃</td>
<td>10-12</td>
</tr>
<tr>
<td>Monopolar electrodialysis</td>
<td>Bipolar electrodialysis</td>
<td>Water removal/ nanofiltration</td>
<td>NaOH</td>
<td>13</td>
</tr>
<tr>
<td>Membrane electrolysis</td>
<td>Extraction</td>
<td>Esterification</td>
<td>none</td>
<td>14, 15</td>
</tr>
<tr>
<td></td>
<td>Desorption with HCl</td>
<td>Precipitation or water evaporation (Regeneration by thermal decomposition of MgCl₂)</td>
<td>MgCl₂</td>
<td>16, 17</td>
</tr>
<tr>
<td>Protonation with cation exchange resin</td>
<td>Desorption with NaCl or H₂SO₄</td>
<td>Water evaporation or crystallization</td>
<td>NaCl or Na₂SO₄</td>
<td>18, 19</td>
</tr>
<tr>
<td>Anion exchange resin</td>
<td>Desorption with MeOH (EtOH) + H₂SO₄</td>
<td>Esterification</td>
<td>Na₂SO₄ or CaSO₄</td>
<td>10, 20</td>
</tr>
<tr>
<td></td>
<td>Alkylation</td>
<td>Distillation</td>
<td>NaHCO₃</td>
<td>21, 22</td>
</tr>
</tbody>
</table>

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 electro dialysis 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.\textsuperscript{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\textsubscript{2}SO\textsubscript{4}) which produces a stoichiometric amount of salt waste.\textsuperscript{19, 25} Another option is to use methanol and H\textsubscript{2}SO\textsubscript{4} to protonate the carboxylate anion, and then the carboxylic acid is esterified using the remaining H\textsubscript{2}SO\textsubscript{4} as catalyst.\textsuperscript{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,\textsuperscript{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.\textsuperscript{26} Additionally, some bacterial fermentations required carbonate species as carbon source besides carbohydrates to achieve high yields.\textsuperscript{27} The alkylation reaction proceeds with high yield of methyl ester on carboxylates but with modest selectivity with respect to DMC.\textsuperscript{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,\textsuperscript{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\textsubscript{2} and 170
C, alkali metal salts of carboxylates in methanol can be converted into esters with a molar yield of 0.81.\textsuperscript{32}

These CO\textsubscript{2}/alcohol systems at relatively low pressures (<\(P_c\) (CO\textsubscript{2})) are known as gas-expanded liquids, and have been studied in detail for esterification, alkylation and carboxylation reactions, amongst others.\textsuperscript{33} The addition of CO\textsubscript{2} to the alcohol makes it possible to tune the polarity of the system, and as a consequence, control the solubility of solutes.\textsuperscript{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\textsubscript{2}-expanded alcohol, and to further esterify the carboxylic acid. Our option clearly differs from methods in which CO\textsubscript{2} pressure is applied to aqueous carboxylate solutions in order to facilitate transfer of carboxylate to an extractant or adsorbent phase.\textsuperscript{35, 36} In our approach, the starting point is loading an anion exchange resin (Q\textsuperscript{−}) with a carboxylate, such as acetate (Ac\textsuperscript{−}) (R.1).

\[
\text{NaAc}_{(aq)} + \text{Q}^+\text{HCO}_3^- \rightleftharpoons \text{NaHCO}_3_{(aq)} + \text{Q}^+\text{Ac}^- \quad \text{R.1}
\]

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

\[
\text{Q}^+\text{Ac}^- + \text{MeOH} + \text{CO}_2 \rightleftharpoons \text{Q}^+\text{HCO}_3^- + \text{MeAc} \quad \text{R.2}
\]

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

\[
\text{NaAc}_{(aq)} + \text{MeOH} + \text{CO}_2 \rightleftharpoons \text{NaHCO}_3_{(aq)} + \text{MeAc} \quad \text{R.3}
\]

In this paper, we study the effect of the CO\textsubscript{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 Heidelberg) 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. 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 0.501 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\textsubscript{2} to achieve inert atmosphere. Agitation was at 600 rpm, and a pressure of 5 bar of N\textsubscript{2} was maintained (control experiment). For the other experiments, it was flushed 5 more times with CO\textsubscript{2}, and then the pressure was set to the desired value (2, 5 or 10 bar of CO\textsubscript{2}). The reactor was repressurized with CO\textsubscript{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\textsubscript{2}SO\textsubscript{4}) The tubes were flushed with N\textsubscript{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 Kα model). A monochromatic Al Kα 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\textsubscript{a}) using an anion exchange resin. A quaternary ammonium anion exchange resin (Dowex Marathon MSA provided in Cl\textsuperscript{-} 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*

<table>
<thead>
<tr>
<th>Resin Counter-ion</th>
<th>Surface atomic composition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Chloride</td>
<td>82.6 ± 0.3</td>
</tr>
<tr>
<td>Acetate</td>
<td>77.3 ± 0.8</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>79.3 ± 0.8</td>
</tr>
</tbody>
</table>

* 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\textsuperscript{-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.\textsuperscript{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\textsubscript{2}-expanded alcohols is explored.

### 3.2 Desorption of acetate with CO\textsubscript{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\textsubscript{2}-expanded methanol. Table 3 shows the effect of CO\textsubscript{2} pressure on the desorption of acetate. At low CO\textsubscript{2} pressures (2-10 bar) a high recovery yield (mol acetic acid/mol acetate\textsubscript{in}) ranging from 0.55-0.79 is observed. In contrast, a 0.38±0.05 mol acetic acid/acetate\textsubscript{in} desorption yield was found at a CO\textsubscript{2} pressure of 10 bar in water (Table A.5).
Table 3. Desorption of acetate from an anion exchange resin with CO\textsubscript{2}-expanded methanol at 20-22 °C with a resin loading of 3.4 %w/w dry resin/methanol

<table>
<thead>
<tr>
<th>Equilibrium CO\textsubscript{2} pressure (bar)</th>
<th>Final water (mmol/g solvent)</th>
<th>Desorption (mol acetic acid/mol acetate\textsubscript{in})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.30±0.04</td>
<td>0</td>
</tr>
<tr>
<td>2.12</td>
<td>0.35±0.04</td>
<td>0.55±0.09</td>
</tr>
<tr>
<td>5</td>
<td>0.37±0.07</td>
<td>0.72±0.02</td>
</tr>
<tr>
<td>10</td>
<td>0.38±0.05</td>
<td>0.79±0.04</td>
</tr>
</tbody>
</table>

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.

\[
\text{Q}^+\text{Ac}^- + \text{MeOH} + \text{CO}_2 \xrightleftharpoons{R.4} \text{Q}^+\text{MeCO}_3^- + \text{HAc} \\
\text{Q}^+\text{Ac}^- + \text{H}_2\text{O} + \text{CO}_2 \xrightleftharpoons{R.5} \text{Q}^+\text{HCO}_3^- + \text{HAc}
\]

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\textsubscript{2} pressure than in water to protonate the carboxylate anion. Other low CO\textsubscript{2} pressure research has been conducted in water in which CO\textsubscript{2} and amines are used for the recovery of acetic acid\textsuperscript{8}. In that approach, aqueous calcium acetate is protonated using CO\textsubscript{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\textsubscript{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\textsuperscript{39, 40}

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Mole fraction</th>
<th>Mass Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>0.00592</td>
<td>0.0144</td>
</tr>
<tr>
<td>Methanol</td>
<td>0.0772</td>
<td>0.1030</td>
</tr>
<tr>
<td>Ethanol</td>
<td>0.1110</td>
<td>0.1065</td>
</tr>
</tbody>
</table>

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\textsuperscript{41} (from MeOH and CO\textsubscript{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.

\[
\text{Q}^+\text{MeCO}_3^- + \text{H}_2\text{O} \rightleftharpoons \text{Q}^+\text{HCO}_3^- + \text{MeOH} \quad \text{R.6}
\]

\[
\text{Q}^+\text{MeCO}_3^- + \text{MeOH} \rightleftharpoons \text{Q}^+\text{OH}^- + \text{Me}_2\text{CO}_3 \quad \text{R.7}
\]

\[
\text{Q}^+\text{OH}^- + \text{CO}_2 \rightleftharpoons \text{Q}^+\text{HCO}_3^- \quad \text{R.8}
\]

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.

\[
\text{HAc} + \text{MeOH} \rightleftharpoons \text{MeAc} + \text{H}_2\text{O} \quad \text{R.9}
\]

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\(_2\)SO\(_4\), strong
cation exchange resins (with sulfonic acid groups) and zeolites.\textsuperscript{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\textsubscript{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.

\begin{itemize}
  \item[A. Consecutive 2-compartments]
  \item[B. Simultaneous 1-compartment]
  \item[C. Simultaneous 2-compartments]
\end{itemize}

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.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Process configuration</th>
<th>Solution</th>
<th>Esterification Equilibrium CO$_2$ pressure (bar)</th>
<th>Catalyst$^{ab}$</th>
<th>Final water (mmol/g solvent)</th>
<th>Yield (mol methyl acetate/mol acetate$_{in}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Only esterification</td>
<td>0.4 %w/w HAc in MeOH 0</td>
<td>none</td>
<td>Not available</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Only esterification</td>
<td>0.4 %w/w HAc in MeOH 0</td>
<td>H$_2$SO$_4$</td>
<td>Not available</td>
<td>0.86±0.02</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Only esterification</td>
<td>0.2 %w/w HAc in MeOH 0</td>
<td>H$_2$SO$_4$</td>
<td>0.06±0.02</td>
<td>0.76±0.02</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Only esterification</td>
<td>0.4 %w/w HAc in MeOH 0</td>
<td>Amberlyst</td>
<td>0.27±0.02</td>
<td>0.81±0.02</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Only esterification</td>
<td>0.2 %w/w HAc in MeOH 0</td>
<td>Amberlyst</td>
<td>0.12±0.01</td>
<td>0.85±0.02</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Consecutive</td>
<td>Desorbed effluent CO$_2$-expanded protonation (10 bar)</td>
<td>0</td>
<td>H$_2$SO$_4$</td>
<td>0.60±0.03</td>
<td>0.87±0.02</td>
</tr>
<tr>
<td>7</td>
<td>Simultaneous</td>
<td>3.3 %w/w Dowex MSA acetate form in MeOH 5</td>
<td>none</td>
<td>0.40±0.06</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Simultaneous</td>
<td>3.3 %w/w Dowex MSA acetate form in MeOH 5</td>
<td>Amberlyst</td>
<td>0.39±0.07</td>
<td>0.58±0.07</td>
<td></td>
</tr>
</tbody>
</table>

a. 0.08 % w/w H$_2$SO$_4$
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. 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.
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

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Process config.</th>
<th>Resin (Dowex MSA) pretreatment</th>
<th>Desorption equilibrium CO₂ pressure (bar)</th>
<th>Temp. (°C)</th>
<th>Catalyst a,b</th>
<th>Final water (mmol/g solvent)</th>
<th>Total desorption yield (mol MeAc+mol HAc/mol acetate in)</th>
<th>Yield (mol methyl acetate/mol acetate in)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Desorption</td>
<td>Dry resin</td>
<td>10</td>
<td>20</td>
<td>none</td>
<td>0.42±0.03</td>
<td>0.79±0.04</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Desorption</td>
<td>Wet resin</td>
<td>10</td>
<td>20</td>
<td>none</td>
<td>1.90±0.40</td>
<td>0.50±0.01</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>Esterification</td>
<td>Dry resin d</td>
<td>-</td>
<td>60</td>
<td>H₂SO₄</td>
<td>0.60±0.03</td>
<td>-</td>
<td>0.87±0.02</td>
</tr>
<tr>
<td>12</td>
<td>Esterification</td>
<td>Wet resin e</td>
<td>-</td>
<td>60</td>
<td>H₂SO₄</td>
<td>1.95±0.14</td>
<td>-</td>
<td>0.97±0.01</td>
</tr>
<tr>
<td>9+11</td>
<td>Consecutive</td>
<td>Dry resin</td>
<td>exp. 9 &amp; 11</td>
<td>exp. 9 &amp; 11</td>
<td>exp. 9 &amp; 11</td>
<td>0.60±0.03</td>
<td>0.79±0.04</td>
<td>0.68±0.03</td>
</tr>
<tr>
<td>10+12</td>
<td>Consecutive</td>
<td>Wet resin</td>
<td>exp. 10 &amp; 12</td>
<td>exp. 10 &amp; 12</td>
<td>exp. 9 &amp; 11</td>
<td>1.95±0.14</td>
<td>0.50±0.01</td>
<td>0.48±0.01</td>
</tr>
<tr>
<td>13</td>
<td>Simultaneous</td>
<td>Dry resin</td>
<td>5</td>
<td>60</td>
<td>Amberlyst</td>
<td>0.39±0.07</td>
<td>0.66±0.07</td>
<td>0.58±0.07</td>
</tr>
<tr>
<td>14</td>
<td>Simultaneous</td>
<td>Wet resin</td>
<td>5</td>
<td>60</td>
<td>Amberlyst</td>
<td>3.42±0.5</td>
<td>0.57±0.01</td>
<td>0.37±0.02</td>
</tr>
</tbody>
</table>

a. 0.1 % w/w H₂SO₄
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.\textsuperscript{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$_2$\textsuperscript{a,b}

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

\textsuperscript{a.} 1.7 %w/w dry resin Dowex Marathon MSA / methanol  
\textsuperscript{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.\textsuperscript{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 \textsuperscript{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. The conditions used in our new method with CO$_2$-expanded alcohols are at lower temperature (60 °C) than in previously reported studies, 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.

<table>
<thead>
<tr>
<th>Process step</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adsorption (g acetate/g wet resin)</td>
<td>0.059</td>
<td>0.055</td>
<td>0.056</td>
<td>0.061</td>
<td>0.068</td>
</tr>
<tr>
<td>Desorption + esterification (mol methyl acetate/ mol acetate in)</td>
<td>1.01</td>
<td>1.12</td>
<td>1.00</td>
<td>0.92</td>
<td>1.00</td>
</tr>
</tbody>
</table>

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

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

$^a 1.4 \%$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/ethanol) increases the esterification yield to 0.67±0.01, which is in accordance with reported esterification data.\textsuperscript{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.\textsuperscript{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\textsuperscript{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\textsubscript{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\textsubscript{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 CO₂-expanded alcohols. Using this method, the carboxylates are recovered using an anion exchange resin, and CO₂-expanded alcohol is used for the desorption and subsequent esterification of the carboxylates. The main advantages are: no stoichiometric waste production, low pressures of CO₂ needed and integration of the unit operations. Using CO₂-expanded methanol, we achieved a desorption yield of 0.79 mol acetic acid/mole acetate in at 10 bar of CO₂, and an ester yield of 1.03 mol methyl acetate/mole acetate in the combined desorption-esterification at 5 bar of CO₂ and 60 °C. The method might be applied for the recovery of different carboxylates produced by fermentation at pH > pKₐ, 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/mole acetate in was obtained with CO₂-expanded ethanol. The method is versatile and can be optimized with respect to reactor configuration, catalyst, CO₂ pressure, alcohol excess, temperature and reaction time, depending on the specific application.

5 Acknowledgements

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6 References


For graphical abstract only