A scalable carboxylation route to furan-2,5-dicarboxylic acid†

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Furan-2,5-dicarboxylic acid (FDCA) is a biomass-derived diacid that can be used to make polymers including polyethylene furandicarboxylate (PEF), a highly attractive substitute for petroleum-derived polyethylene terephthalate (PET). Current FDCA syntheses require edible fructose as the feedstock, entail a difficult oxidation step that generates undesirable aldehyde impurities, and have moderate yields. As an alternative, carbonate-promoted C–H carboxylation enables the synthesis of FDCA from 2-furoic acid and CO₂. This route is potentially advantageous because 2-furoic acid is made from furfural, a feedstock produced commercially from inedible lignocellulosic biomass, and it obviates late-stage oxidation. In the carboxylation reaction, salt mixtures composed of alkali furan-2-carboxylate (furoate) and alkali carbonate (M₂CO₃) are heated under CO₂ in the absence of solvent or catalysts to form furan-2,5-dicarboxylate (FDCA²⁻), which is subsequently protonated to produce FDCA. Previously, high yields were achieved on small-scale reactions using caesium furoate and Cs₂CO₃. In this work, we investigate the carboxylation reaction using alkali furoate/M₂CO₃ salts containing cation blends and describe reaction conditions that provide high yields on a preparative scale. We show that the carboxylation proceeds efficiently with K⁺/Cs⁺ blends that have a high K⁺ content (up to 4 : 1 K⁺ : Cs⁺). Removing H₂O, which is a by-product of the reaction, is important for suppressing decomposition pathways. The accumulation of the FDCA²⁻ product inhibits the reaction. Integrating these lessons, we demonstrate the carboxylation of furoate on a 1 mol scale using a fixed-bed flow reactor with 89% isolated yield of pure FDCA upon protonation.

Introduction

Polyethylene terephthalate (PET) and polyethylene furandicarboxylate (PEF) were both originally patented nearly 70 years ago.¹⁻² PET has since grown to become a >10⁷ ton per year polymer, with applications in rigid packaging, fibres, and films. This growth was made possible by the development of scalable syntheses of purified terephthalic acid (PTA), the diacid monomer, which is made by oxidation of petroleum-derived para-xylenes.³ PEF is an attractive replacement for PET because its diacid monomer, furan-2,5-dicarboxylic acid (FDCA), is derived from biomass,⁴ which provides an opportunity to produce a polymer with a much lower greenhouse gas (GHG) footprint.⁵ In addition, PEF has superior gas barrier and mechanical properties compared to PET for certain packaging applications such as bottled beverages.⁶⁻⁸

PEF and other FDCA-based polymers have attracted increased interest in the past several years.⁹⁻¹¹ A number of synthetic routes to FDCA and its derivative dimethylfurandicarboxylate (DMFD) have been advanced to pilot-scale production and plans have been announced for the first commercial scale plant.¹² All of these routes use a C₆ sugar (hexose) as the feedstock and follow a similar synthetic strategy. The hexose is first dehydrated to form hydroxymethyl furfural (HMF), which is then oxidized to FDCA (Scheme 1). DMFD is made either by esterifying FDCA or etherifying HMF to form methoxymethyl furfural (MMF) and then oxidizing it in methanol.¹³ This basic approach—hexose dehydration followed by oxidation—has several drawbacks. In their current form, these syntheses require edible fructose as the hexose feedstock. Edible fructose has a large GHG footprint³ and its use for commodity-scale plastic production would compete with food production. Using hexoses derived from lignocellulosic biomass would avoid these issues, but thus far it has proven very challenging to obtain FDCA economically from lignocellulose-derived hexoses.¹⁴ Another major drawback is the difficulty of oxidizing HMF to FDCA (or MMF to DMFD). This reaction is typically performed under highly corrosive conditions in acetic acid solvent,¹⁵⁻¹⁷ similar to the conditions used to oxidize para-xylenes to terephthalic acid.¹⁸ Moreover, even under optimized conditions, the reaction also forms alde-
hyde impurities that cause chain terminations during polyester synthesis and discolour the polymer. Removing these impurities requires a separate chemical step—either hydrogenation or a second oxidation.\textsuperscript{18,19} While much progress has been made in advancing FDCA and DMFD synthesis toward commercial production, alternative routes that avoid these drawbacks are highly desirable.

We recently described a C–H carboxylation reaction that makes it possible to synthesize FDCA from 2-furoic acid and CO\(_2\) in high yield without energy-intensive reagents or transition metal catalysts.\textsuperscript{20} This reaction is performed by heating a salt mixture composed of alkali furoate (the deprotonated form of 2-furoic acid) and alkali CO\(_3^{2-}\) under a CO\(_2\) atmosphere. With the appropriate salt composition (see below), CO\(_3^{2-}\) promotes the C–H carboxylation to form furan-2,5-dicarboxylate (FDCA\(^{2-}\)). Protonation with strong acid (e.g. HCl) in water yields precipitated FDCA product and an aqueous salt solution (e.g. MCl) (Scheme 1). The stoichiometric base and acid consumed in this synthesis can be regenerated by subjecting the salt solution to bipolar membrane electrodialysis.\textsuperscript{21,22}

This carboxylation route to FDCA has a number of potential advantages over conventional hexose-based routes. First, 2-furoic acid is made from furfural, a compound that has been produced from lignocellulosic biomass industrially for almost a century.\textsuperscript{23,24} Furfural is made by depolymerizing and dehydrating the pentose-rich hemicellulose component of lignocellulose, which is much easier to process than the hexose-rich cellulose component. Multiple biomass waste streams have been used for furfural production, including corncobs, bagasse, and the hemicellulose waste of wood pulp production.\textsuperscript{23} Second, oxidizing furfural to 2-furoic acid is easier than oxidizing HMF to FDCA. Although 2-furoic acid is not currently synthesized on a commodity scale, multiple reports describe high-yielding oxidations of furfural or furfuryl alcohol to 2-furoic acid using O\(_2\) under relatively mild conditions (e.g. 50 °C, 1 bar).\textsuperscript{25–28} Lastly, CO\(_3^{2-}\)-promoted C–H carboxylation requires no solvent or transition metal catalysts and installs the final carbon in the appropriate oxidation state.

Utilizing this chemistry to supply FDCA for polymer production requires finding carboxylation conditions that are amenable to very large-scale reactions with minimal by-products and facile purification. In our previous work, carboxylation reactions were performed by heating mixtures of caesium furoate and Cs\(_2\)CO\(_3\) under static CO\(_2\) pressure.\textsuperscript{20} High yields of up to 89% for FDCA\(^{2-}\) were obtained on a 1–10 mmol scale, but a diminished yield of 71% was obtained upon scaling to 100 mmol. Isotope exchange experiments suggested that the reaction proceeds by deprotonation of the C–H bond at the 5 position of 2-furoate by CO\(_3^{2-}\) to form a carbanion that undergoes a C–C bond-forming reaction with CO\(_2\). CO\(_3^{2-}\) is ordinarily incapable of deprotonating this C–H bond (pK\(_a\) 35),\textsuperscript{29} but in a solvent-free caesium furoate/Cs\(_2\)CO\(_3\) mixture there is a high concentration of Cs\(^+\) cations that can stabilize the anionic species. At the temperatures required for carboxylation, the mixture is semi-molten, providing sufficient ion mobility for the reaction to occur. We attributed the diminished yield upon scaling to 100 mmol to a reduced surface area-to-volume ratio, which impedes transport of CO\(_2\) into the salt and removal of H\(_2\)O. In the absence of other additives, alkali furoate/alkali CO\(_3^{2-}\) mixtures with a single cation other than Cs\(^+\) do not
undergo C–H carboxylation, suggesting that these salts remain in an unreactive crystalline form at elevated temperatures. However, we demonstrated that furoate carboxylation could be achieved in small-scale (1 mmol) reactions with all K+ salts by combining potassium furoate/K2CO3 with a potassium carboxylate co-salt (e.g. potassium isobutyrate) to increase ion mobility at elevated temperatures.20

In this work, we investigate furoate carboxylations with salts containing cation mixtures and develop conditions for mole-scale carboxylation in high yield using fixed-bed flow reactors. We show that carboxylation proceeds efficiently with alkali furoate/M2CO3 salts if K+/Cs+ cation mixtures are used, even with high K+ :Cs+ ratios. This advance enables carboxylation with a reduced Cs+ loading without requiring a co-salt. Although the cations would be recycled in a practical application, reducing the Cs+ loading is desirable because the amount of Cs+ salts mined annually is relatively low.30 More importantly, alkali furoate/M2CO3 salts with K+/Cs+ mixtures do not undergo a bulk phase transition to a molten phase, which facilitates scale-up. Using a fixed-bed reactor under flowing CO2, we demonstrate furoate carboxylation with K+/Cs+ salts on a 1 mol scale with 89% isolated yield for FDCA upon acidic work up.

Results
Small-scale reactions
The synthesis of FDCA2− via C–H carboxylation is performed by heating furoate and CO22− under CO2. The yield and reaction rate depend on the precise composition and morphology of the salt mixture, the temperature, and CO2 mass transport. To assess whether pure Cs+ salts could be substituted with cation blends, we initially surveyed the reaction on an analytical scale (0.5 mmol substrate) using different K+ :Cs+ ratios. To prepare the solid reactants, 2-furoic acid was added to an aqueous K2CO3/Cs2CO3 solution (1.25 total molar equivalents of CO32−) in a glass vial and dried to a solid, which is composed of 2-furoate and 0.75 equivalents of residual CO32−. This material was then heated in a vial block with a constant purge of CO2 through the headspace for 17 h. The product mixture was analysed directly by NMR using an internal standard. The yields are far from optimal in this vial block reactor (see below), but the setup permits rapid initial assessment of the effects of varying the salt composition.

Fig. 1 shows the FDCA2− yield as a function of temperature for several K+ :Cs+ ratios. As a reference point for these vial block reactions, the yield with only Cs+ (caesium furoate + Cs2CO3) reached a maximum of 71% at 260 °C. Reactions with only K+ in the absence of co-salts (potassium furoate + K2CO3) do not form any FDCA2− regardless of the temperature (data not shown). However, K+/Cs+ blends containing a high proportion of K+ (1:1 to 4:1 K+ :Cs+) gave 60–70% yield of FDCA2−. The optimal temperature for the K+/Cs+ reactions increased with the K+ content. The mass balance of the reactions was composed of unreacted furoate and decomposition products. The decomposition products consist mostly of insoluble char and smaller amounts of acetate and malonate.

The cation composition affects the morphology of the salt under the reaction conditions. In the all Cs+ reaction, the salt mixture is partially molten at the temperatures where good yields are observed. With a K+/Cs+ blend, however, the salts do not appear to undergo a bulk phase transition. The ability to synthesize FDCA2− without forming a bulk molten solution provides flexibility in reactor design and facilitates scale-up (see below).

To gain insight into the origin of the decomposition products, we first assessed the effect of the cation composition on the thermal stability of the substrate and product in the absence of CO2. Heating furoate and 0.75 equivalents of CO32− under N2 for 6 h at 265 °C to 295 °C caused decomposition to similar products seen in the carboxylation reaction (Fig. 2). The amount of decomposition increased with temperature and with the Cs+ content of the salt mixture. Thus, the higher the K+ loading, the greater the intrinsic thermal stability of furoate. Regardless of the cation composition, the amount of decomposition observed under N2 was comparable to or greater than the amount of FDCA2− produced under CO2 at the same temperature. For example, at 285 °C, the 2:1 K+ :Cs+ blend produced 63% FDCA2− under CO2 after 17 h, whereas >90% of the furoate decomposed after only 6 h under N2. This
result suggests that CO₂ greatly curtails the rate of furoate decomposition, in addition to making the carboxylation reaction possible. In contrast to furoate, FDCA₂⁻ showed good thermal stability under N₂ with all cation compositions up to 285 °C (Fig. 2). Some decomposition was observed at 295 °C, with a similar cation dependence as seen for the substrate. The decomposition products observed during carboxylation therefore arise from furoate decomposition rather than the FDCA₂⁻ product.

Water is a by-product of CO₃²⁻-promoted C–H carboxylation. We hypothesized that water could be deleterious to furoate carboxylation by providing a source of hydroxide ions that cause decomposition via nucleophilic attack on furoate. To test this hypothesis, the all Cs⁺ and the 2 : 1 K⁺ : Cs⁺ carboxylations were repeated at their optimal temperatures using a CO₂ stream passed through a water bubbler to hydrate the gas before flowing into the glass vials (Fig. 1, “+ water” conditions). Under these conditions, the FDCA₂⁻ yield was reduced from 71% to 41% in the all Cs⁺ reaction and from 70% to 31% in the 2 : 1 K⁺ : Cs⁺ reaction. Analysis of the mass balance for the all Cs⁺ reaction indicated that H₂O mostly slowed down FDCA₂⁻ synthesis without substantially accelerating decomposition (i.e. both yield and furoate conversion were reduced). In contrast, H₂O greatly increased the decomposition products for the 2 : 1 K⁺ : Cs⁺ reaction. This result suggests that removing the H₂O by-product is important for suppressing decomposition during carboxylation when cation blends are used, which is further supported by experiments in the fixed-bed reactor (see below).

We next probed the kinetics of carboxylation in the vial block reactor by performing a time course experiment. A set of identical reaction mixtures with 2 : 1 K⁺ : Cs⁺ was heated under CO₂ at 285 °C and individual reactions were stopped at different reaction times for analysis (Fig. 3). The FDCA₂⁻ yield rose steadily to 50% in the first 5 h, but thereafter the reaction slowed dramatically, requiring an additional 12 h to reach 63% yield. Quantification of the substrate consumption indicated that 14% decomposed in the first 5 h and an additional 10% decomposed over the next 12 h. The greatly attenuated substrate decomposition relative to experiments under N₂ (Fig. 2) confirms that CO₂ inhibits the decomposition pathways. Additional time course experiments were performed with different amounts of CO₃²⁻. Increasing the CO₃²⁻ loading beyond 0.75 equivalents increased the initial reaction rate, but did not eliminate the sharp drop in the reaction rate after...
~50% FDCA$^{2-}$ formation (Fig. S8†). To see if FDCA$^{2-}$ itself slows the furoate carboxylation, a time course was performed using a salt mixture spiked with 0.5 equivalents of FDCA$^{2-}$. Under these conditions, the synthesis rate and yield of FDCA$^{2-}$ were reduced, and furoate decomposition increased (Fig. 3). This experiment shows that the build-up of FDCA$^{2-}$ slows down the carboxylation of remaining furoate, either by impeding CO₂ transport or slowing the rate of deprotonation.

**Fixed-bed flow reactor**

The vial block reactor provides relatively poor gas transport because CO₂ can only be flowed through the headspace above the solid reactants. To determine whether increased contact between the salt mixture and CO₂ improves the yield, we assembled a fixed-bed flow reactor. In brief, the reactor consists of a temperature-controlled stainless steel tube (the reaction vessel) connected to a CO₂ pre-heating apparatus (see ESI† for details). The reactor accommodates 8 bar CO₂ at elevated temperature and flow rates up to several hundred ml min$^{-1}$. For fixed-bed flow experiments, we used industrial grade CO₂ (99.5%). We first evaluated the effects of static vs. flowing CO₂ on a 10 mmol scale for different cation compositions (Table 1). The solid reactants were prepared as described above and transferred to the reaction vessel as dry powders. The reactions were performed at 265 °C to 300 °C under 8 bar CO₂ for 14 h with either no flow or a flow rate of 140 ml min$^{-1}$. With all Cs$^+$, the FDCA$^{2-}$ yield was 91% in the absence of flow at 265 °C. This result is consistent with the high carboxylation yield observed on the 10 mmol scale with all Cs$^+$ in a Parr reactor.²⁰ For reactants with 1:1 K$^+$:Cs$^+$ ratio (Table 1), providing proof-of-concept for the ability to perform carboxylation with cation blends that have very low Cs$^+$ content.

**Preparative-scale reactions**

Fixed-bed flow conditions were used to evaluate the carboxylation on preparative scales. Experiments were performed with 2:1 K$^+$:Cs$^+$ blends using the reactor design described above with larger reaction vessels to accommodate the increased reactant volumes (see ESI†). At the conclusion of the reactions, the solid products were dissolved in H₂O, filtered to remove insoluble by-products, and acidified with HCl to precipitate FDCA. Isolated yields are reported for dry, purified FDCA (Table 2). The reaction was first attempted on a 100 mmol scale at 285 °C with 140 ml min$^{-1}$ CO₂ at 8 bar. After a 24 h

<table>
<thead>
<tr>
<th>Scale</th>
<th>T (°C)</th>
<th>Ramp rate</th>
<th>Soak time</th>
<th>FDCA(^{3-})</th>
<th>Starting material</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mmol</td>
<td>285</td>
<td>N/A</td>
<td>24 h</td>
<td>66%</td>
<td>0%</td>
</tr>
<tr>
<td>100 mmol</td>
<td>260–285</td>
<td>2 °C h$^{-1}$</td>
<td>24 h</td>
<td>86%</td>
<td>3%</td>
</tr>
<tr>
<td>1 mol</td>
<td>260–285</td>
<td>2 °C h$^{-1}$</td>
<td>24 h</td>
<td>89%</td>
<td>2%</td>
</tr>
</tbody>
</table>

The temperature was ramped from 260 °C to 285 °C at the specified ramp rate and then held (soaked) at 285 °C for 24 h. Isolated yield of the diacid.

**Table 1** Effect of flowing CO₂ on CO₃$^{2-}$-promoted C–H carboxylation of furoate

<table>
<thead>
<tr>
<th>K$^+$ : Cs$^+$</th>
<th>Scale</th>
<th>T (°C)</th>
<th>FDCA$^{2-}$</th>
<th>Starting material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cs$^+$ only</td>
<td>1 mmol</td>
<td>265</td>
<td>91%</td>
<td>4%</td>
</tr>
<tr>
<td>Cs$^+$ only</td>
<td>10 mmol</td>
<td>265</td>
<td>91%</td>
<td>0%</td>
</tr>
<tr>
<td>1 : 1</td>
<td>10 mmol</td>
<td>275</td>
<td>56%</td>
<td>12%</td>
</tr>
<tr>
<td>2 : 1</td>
<td>10 mmol</td>
<td>290</td>
<td>22%</td>
<td>0%</td>
</tr>
<tr>
<td>3 : 1</td>
<td>10 mmol</td>
<td>290</td>
<td>39%</td>
<td>0%</td>
</tr>
<tr>
<td>4 : 1</td>
<td>10 mmol</td>
<td>290</td>
<td>33%</td>
<td>0%</td>
</tr>
<tr>
<td>20 : 1</td>
<td>10 mmol</td>
<td>300</td>
<td>10%</td>
<td>69%</td>
</tr>
</tbody>
</table>

All yields were determined by comparison to an internal standard by NMR. The flow rate of CO₂ was 140 ml min$^{-1}$.

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reaction, FDCA was isolated in 66% yield, which is considerably lower than the 78% FDCA\(^2\) – yield observed in the 10 mmol scale reaction (Table 1). Large amounts of decomposition products were formed. These results reflect the challenge of maintaining good solid–gas contact as the scale is increased in the fixed-bed reactor. In particular, the solid reactants start as a fine powder, but compact into a large mass over the course of the reaction. This process reduces solid–gas contact, which may impede the removal of water and slow carboxylation, thereby increasing decomposition.

To reduce decomposition and improve the yield, we investigated the effects of using a temperature gradient. A 100 mmol scale reaction was performed with the same CO\(_2\) flow rate using a 2 °C h\(^{-1}\) ramp from 265 °C to 285 °C, followed by 24 h at 285 °C. This protocol resulted in nearly complete conversion of furoate and an 86% isolated yield of FDCA. Gratifyingly, when the same temperature ramp was used on a 1 mol scale, FDCA was isolated in 89% yield (139 g). The gradient may improve the reaction by slowing or subtly altering the compaction of the solids, thereby enabling better CO\(_2\) access to the reactants in the centre of the reactor and more effective water removal.

**Discussion**

Our results demonstrate that furoate carboxylation can be used to synthesize FDCA in high yield on a preparative scale (>100 g) and provide insights for further scale-up. The simplicity of the carboxylation reaction is potentially advantageous for process development. No solvent or catalyst is used, which obviates the burden of recovering and/or replenishing these components. Furthermore, the carboxylation performs well with relatively low-purity CO\(_2\) (99.5%), which avoids costly and energy-intensive purification steps required for high-purity gases. The CO\(_2\) could easily be re-circulated in a large-scale process to maximize CO\(_2\) conversion. One possible concern for scale-up is the use of caesium. In the absence of a co-salt, some Cs\(^+\) is required for efficient carboxylation, and the results here indicate that a K\(^+\):Cs\(^+\) ratio of 2 : 1 to 4 : 1 is desirable. Although caesium is more abundant than tin,\(^{31}\) caesium salts have historically been mined on a small scale because of their low demand.\(^{30}\) It is important to emphasize that the use of carboxylation for large-scale FDCA synthesis would not consume caesium salts because the cations would be recycled after protonation by using bipolar membrane electrodialysis (Fig. 1). Because of its very high water solubility, Cs\(^+\) can be quantitatively recovered upon FDCA precipitation.\(^{20}\) Assuming Cs\(^+\) has similar transport properties to Na\(^+\) and K\(^+\) in cation exchange membranes, bipolar membrane electrodialysis would require a modest energy demand of a few kWh per kg FDCA.

The reaction kinetics must be substantially improved in order for carboxylation to be used on much larger scales. Our results suggest that this challenge can be addressed by improving mass transport. For the 100 mmol and 1 mol scale reactions, the salt mixture slowly compacts as the reaction proceeds, which greatly slows the reaction and promotes decomposition. These problems are intrinsic to the use of a fixed bed reactor. Strategies that improve the mixing between CO\(_2\) and the solid reactants, such as fluidization or other modes of agitation,\(^{32}\) are expected to greatly improve the rates and diminish decomposition products upon further scale up. Such approaches have been used for the carboxylation of solid sodium phenolate in the industrial synthesis of aspirin.\(^{33}\)

The use of CO\(_2\) for the synthesis of high-volume chemicals and fuels has been a longstanding goal in chemistry.\(^{34,35}\) Carbonate-promoted C–H carboxylation is distinguished from other chemical approaches to CO\(_2\) utilization because it forms C–C bonds without resorting to expensive, energy intensive reagents. While FDCA has yet to be proven as a viable commodity, it has thus far shown great potential to replace terephthalic acid in high volume (>10\(^7\) ton per year) applications. The carboxylation route described here provides a unique opportunity to use CO\(_2\) and waste biomass for a high-volume chemical synthesis.

**Conclusions**

We have shown that CO\(_3^{2–}\)-promoted C–H carboxylation of furoate using K\(^+\)/Cs\(^+\) mixtures is an efficient method for synthesizing FDCA on a preparative scale. Salt mixtures with high K\(^+\):Cs\(^+\) ratios retain their bulk solid morphology under the reaction conditions, which facilitates reactions under flowing CO\(_2\). Carboxylation competes with furoate decomposition. Removal of the H\(_2\)O by-product suppresses decomposition and improves the yield of FDCA. Using a simple fixed bed reactor, we have demonstrated mole-scale furoate carboxylation using a 2 : 1 K\(^+\):Cs\(^+\) blend with 89% isolated yield of FDCA. Further improvement of mass transport is expected to enable similar performance on a larger scale.

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**Notes and references**
