Electrochemical \([^{11}\text{C}]\text{CO}_2\) to \([^{11}\text{C}]\text{CO}\) conversion for PET imaging†

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The development of a novel electrochemical methodology to generate carbon-11 carbon monoxide (\([^{11}\text{C}]\text{CO}\)) from cyclotron-produced carbon-11 carbon dioxide (\([^{11}\text{C}]\text{CO}_2\)) using \(\text{Ni}(\text{cyclam})\) and \(\text{Zn}(\text{cyclen})\) complexes is described. This methodology allows up to 10% yields of \([^{11}\text{C}]\text{CO}\) from \([^{11}\text{C}]\text{CO}_2\). Produced \([^{11}\text{C}]\text{CO}\) was subsequently converted to \([^{11}\text{C}]\text{N}-\text{benzylbenzamide}\) under mild conditions with a radiochemical purity (RCP) of >98%.

Electrochemical reduction of \(\text{CO}_2\) to \(\text{CO}\) has long been considered an important issue for tackling environmental sustainability. The challenge lies in converting the thermodynamically stable \(\text{CO}_2\) molecule into more energetic compounds. The largest thermodynamic barrier is the first electron addition to convert the linear \(\text{CO}_2\) molecule to a bent anion radical (\(\text{COO}^-\)) at \(E = -1.90\) V.\textsuperscript{1} So far, 2nd and 3rd row transition metal elements have dominated this area although only \(\text{Au}\) and \(\text{Ag}\) generate \(\text{CO}\) with Faradaic efficiencies (FE) above 80% and maintain high current densities.\textsuperscript{2,3} Their activities have been boosted by nanostructuring techniques controlling the surface morphology.\textsuperscript{4} Other cheaper metals such as \(\text{Sn}, \text{Sb}, \text{Pb}\) and \(\text{Bi}\) have been used to convert \(\text{CO}_2\) to \(\text{CO}\) with high current efficiencies using ionic liquids to stabilise the \(\text{COO}^-\) intermediate.\textsuperscript{5} Ionic liquids have been increasingly studied for their role in lowering thermodynamic barriers in \(\text{CO}_2\) reduction and so too have group 1 cations such as \(\text{K}^+\) and \(\text{Cs}^+\).\textsuperscript{6}

Homogenous electrocatalysts for \(\text{CO}_2\) reduction, such as cathode materials, have previously been dominated by metals such as \(\text{Pd}, \text{Ru}, \text{Rh}\) and \(\text{Re}\).\textsuperscript{7} Over the last few decades, many complexes of the first row transition metal elements such as \(\text{Fe}, \text{Co}, \text{Cr}, \text{Cu}, \text{Mn}\) and \(\text{Ni}\) have been used as electrocatalysts. Most notably metal cyclams (metal = \(\text{Ni}\) and \(\text{Co}\)),\textsuperscript{8} metalloporphyrins (\(\text{Fe}, \text{Co}\) and \(\text{Ni}\)),\textsuperscript{9} metal polypyridines (\(\text{Cr}, \text{Fe}, \text{Co}\) and \(\text{Ni}\)), and metal phthalocyanines (\(\text{Ni}, \text{Co}, \text{Mn}, \text{Fe}\) and \(\text{Cu}\)).\textsuperscript{10} Most of these catalysts act as electron shuttles between the electrode and the \(\text{CO}_2\) molecule and so generally the metal is in a low oxidation state and the ligand stabilises the intermediates by some inner-sphere effect. Recently, several groups have also highlighted that the activity of these catalysts can be boosted by adding protons on addition of mild acids (\(\text{CF}_3\text{CH}_2\text{OH}\))\textsuperscript{11} and further increases in activity were realised when these acidic groups were added to the surrounding ligand.\textsuperscript{9}

One of the most well-studied transition metal catalysts is \(\text{Ni}(\text{cyclam})\)\textsuperscript{12} which demonstrates very good \(\text{CO}\) selectivity at relatively low overpotentials in aqueous conditions. Most studies have been conducted at a \(\text{Hg}\) electrode due to the large negative potential window. Furthermore, \(\text{Ni}(\text{cyclam})\)\textsuperscript{12} has been shown to adsorb to the \(\text{Hg}\) electrode and increase its reactivity to \(\text{CO}_2\) as a result.\textsuperscript{12} Recent studies by Kubiak and co-workers have demonstrated effective \(\text{CO}_2\) reduction at a glassy carbon electrode\textsuperscript{13} with the catalyst efficiency boosted by a \(\text{CO}\) scavenger \([\text{Ni}(\text{tetramethylcyclam})]^{2+}\)\textsuperscript{14}.

Our interest was to apply the electrochemical reduction to carbon-11 \(\text{CO}_2\) (\([^{11}\text{C}]\text{CO}_2\)) generating \([^{11}\text{C}]\text{CO}\). The range of functionalities that can be synthesised from \([^{11}\text{C}]\text{CO}\) make it an attractive precursor for positron emission tomography (PET) radiotracer development.\textsuperscript{15,16} However, the poor solubility of \([^{11}\text{C}]\text{CO}\) in organic solvents and low partial pressure, adds to the challenge of a short half-life (\(t_{1/2} = 20.4\) min). A number of methodologies have been developed to convert cyclotron-produced \([^{11}\text{C}]\text{CO}_2\) to \([^{11}\text{C}]\text{CO}\): (1) gas phase reduction method, which involves passing \([^{11}\text{C}]\text{CO}_2\) through a heated column of zinc or molybdenum at 400 °C or 850 °C respectively.\textsuperscript{17} Whilst molybdenum is preferred, both methods suffer reliability and repeatability issues making clinical production difficult from a regulatory stand-point; (2) chemical reduction methods that have been trialled use reactive silane lithium reagents that must be prepared beforehand.\textsuperscript{18}

The aim of this work was to conduct a proof-of-principle study into the viability of electrochemical \([^{11}\text{C}]\text{CO}_2\) reduction to \([^{11}\text{C}]\text{CO}\) within a radiochemical setting. Trapping efficiencies...
represent decay-corrected trapped radioactivity as a percentage of dispensed radioactivity. RCY's are decay corrected and are estimated from dispensed $^{11}$C\textsubscript{2}O converted to $^{11}$C\textsubscript{12}N-benzylbenzamide (5).

A DropSens\textsuperscript{6} screen printed electrode with a carbon working electrode (WE), a counter electrode (CE) and a silver reference electrode (RE) was used for the electrochemical conversion (Fig. 1A). Fig. 1B and C show how the electrodes and electrode connector fit inside Vial A.

Initial experiments were conducted using a two vial set-up (set-up I – Vials A and B, Fig. 2). Vial A (used to convert $^{11}$C\textsubscript{2}O to $^{11}$C\textsubscript{12}C) contains the electrodes and the electrocatalysts Ni(cyclam)$^{2+}$ or Zn(cyclen)$^{2+}$ (1–2, Scheme 1) complexes in 0.1 M KCl (aq.) solution at 20 °C.\textsuperscript{19} Vial B (used to trap and fix $^{11}$C\textsubscript{12}C) containing the carboxylation reagents to produce $^{11}$C\textsubscript{12}C-N-benzylbenzamide ($^{11}$C\textsubscript{12}C, Scheme 1).\textsuperscript{20} An ascarite trap was placed between the two vials to capture any untrapped $^{11}$C\textsubscript{2}O (Fig. 2).

### Set-up I

![Diagram of the set-up](Fig. 2) Schematic of the two-vial, one-valve setup. (1) $^{11}$C\textsubscript{2}O delivered to Vial A with potentiostat switched on for 5 min (prior to and during delivery). (2) Helium sweep gas applied for 30 s through Vial B. (3) Carboxylation reaction in Vial B conducted for 10 min at 40 °C.

Radioactivity distribution for reduction of $^{11}$C\textsubscript{2}O to $^{11}$C\textsubscript{12}C and subsequent $^{11}$C\textsubscript{12}C capture conducted with 1 (50 mg, 227 mmol) or 2 (65 mg, 227 mmol) in 0.1 M KCl (aq.) (1 mL). Radiochemical purity (RCP) of $^{11}$C\textsubscript{12}C determined by analytical radio HPLC. \textsuperscript{b} Decay corrected radiochemical yields (RCY) are based on the radioactivity of Vial B multiplied by the radiochemical purity of $^{11}$C\textsubscript{12}C compared to the total radioactivity measured at end of cyclotron target bombardment (EOB).

| Entry | Complex | $E_{app}$ (V) | Radioactivity Vial A remaining at EOS (%) | Radioactivity Vial B at EOS (%) | $^{11}$C\textsubscript{3}C\textsubscript{4}RCP (%) | $^{11}$C\textsubscript{3}C\textsubscript{4}RCY (%) |
|-------|---------|-------------|------------------------------------------|-----------------|----------------------|----------------------|
| 1     | 1       | 0           | 5.5                                      | 0.5             | 75                   | <1                   |
| 2     | 1       | −1.8        | 3.5                                      | 7.2             | 97                   | 7                    |
| 3     | 2       | −1.8        | 1.2                                      | 9.8             | 98                   | 10                   |

The setup tested is shown in Fig. 2. As the first experiment, $^{11}$C\textsubscript{2}O was bubbled through the system with no potential applied to the electrodes. A low percentage (~1%) of $^{11}$C\textsubscript{12}C was detected and this was believed to be from cyclotron generated $^{11}$C\textsubscript{12}C. When a potential of −1.8 V vs. Ag/AgCl was applied (in non-radioactive experiments (see ESI†)) potentials of −1.4 and −1.6 V were used to allow full quantification of CO production, at −1.8 V, the detector was quickly saturated by CO. At more negative potentials H2 production was thought to become more favourable). $^{11}$C\textsubscript{12}C was produced with high RCP’s (>98%) but low RCY’s (Table 1, entries 2 and 3). The low RCY was thought to be due to the low trapping efficiency of $^{11}$C\textsubscript{2}O within Vial A. From these preliminary results it appeared that complex 2 performed marginally better than complex 1. The predicted trapping of $^{11}$C\textsubscript{2}O as an adduct of 114 [ESI, S2] was not observed in any usable quantity so experiments were conducted with 2.

In order to evaluate and improve the trapping of $^{11}$C\textsubscript{2}O in Vial A we designed a two-vial, one-valve set-up (set-up II) shown in Fig. 3. During $^{11}$C\textsubscript{2}O delivery, Vial A was connected to ascarite 1 (Eckert & Ziegler Modular-Lab). By placing ascarite 1 after Vial A, the amount of $^{11}$C\textsubscript{2}O trapped in Vial A before starting the electrolysis step could be assessed. At end of
delivery (EOD) electrolysis would begin at −1.8 V and on completion of electrolysis, the valve was moved to divert gases ([11C]CO2 and [11C]CO) to Vial B by Helium purge. Ascariate 2 was placed after Vial B so that relative amounts of [11C]CO2 and [11C]CO (the latter assumed to be converted to [11C]5) in Vial B could be established by radio HPLC (see ESI†).

The performance of set-up II was evaluated using complex 2 at 150 and 15 mM (Table 2, entries 1 and 2). Increasing the concentration of 2 from 15 to 150 mM resulted in higher trapping (56% and 66% respectively) and conversion (<1% and 4% RCY, respectively). The improvements in trapping [11C]CO2 have been previously achieved using bases such as diazabicyclo[5.4.0]undecene (DBU), 2-tert-butyllimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP), tetramethylethlyenediamine (TMEDA)21 and triethanolamine (TEA).22 For our study we chose the strong base DBU and a weaker base TEA.

The next experiments were performed using 150 mM of 2. To improve [14C]CO2 trapping, DBU was added. A high concentration of base was used initially to improve the trapping of [14C]CO2 and subsequently promote the formation of [14C]5. Although 75 mM of bases increased the trapping of [14C]CO2 (Table 2, entry 1 versus entry 3) the high concentration appeared to prevent the formation of [14C]CO. No conversion was observed until HCl was added (0.2 mL of 0.1 N HCl, Table 2, entry 4). This was thought to be due to a change of pH from 6.5 to 12–13 from using DBU in water solution. The resultant acidification of Vial A (on addition of HCl) released the trapped [14C]CO2 so it was free to be converted to [14C]CO.

On addition of HCl, entry 4 showed a RCY of 3%. A lower concentration of base (7.5 mM) was used to investigate if the concentration of 2 and the concentration of base had an optimum combination, perhaps acting through the base binding with 2. Substitution of DBU for TEA was added as a more moderate base (pH 9–10) and the trapping efficiency varying from 23–65% in Vial A (Table 2, entries 6–10). Table 2, entries 7 and 8, showed trapping efficiencies of ~60%. On reducing the concentration of 2 to 15 mM, the trapping efficiency is halved (~30%) irrespective of the concentration of TEA suggesting that the concentration of 2 plays a larger role than TEA in trapping [14C]CO2. This variety of trapping efficiencies shown in Table 2 was thought to be a consequence of the high flow rate (50 ml min⁻¹) of [14C]CO2 into an aqueous solution.23

The optimum RCY achieved (Set-up II, Fig. 3) was 5% (Table 2, entry 8) which was obtained when 7.5 mM of TEA was used. These results appeared to show that a compromise of a milder base would still facilitate reasonable trapping whilst not hindering [14C]CO2 reduction. In order to simplify the reaction set-up and increase electrode surface area, a 2-electrode set-up was used in Vial A. This involved using just the working electrode (WE) and the counter electrode (CE) (Table 2, entries 11–13). The optimum conversion achieved by the 2-electrode cell was 6% (Table 2, entry 13) with 52% of [14C]CO2 initially trapped in Vial A.

In conclusion, the first electrochemical [14C]CO2 to [14C]CO reduction has been achieved with a 2-vial set-up to incorporate the [14C]CO product into [14C]N-benzylbenzamide in a proof-of-principle study. 2 showed good [14C]CO2 trapping and conversion to [14C]CO. The effectiveness of 2 compared to 1 for [14C]CO2 reduction was surprising and further studies are needed to investigate this fully although we believe that ZnO nanoparticles are being generated at the electrode. Improvements in the performance of 1 could come from binding the catalyst to the electrode.8,25 Furthermore, the application of a two-electrode design of Vial A was shown to be viable. We believe that a pre-concentration step of [14C]CO2 prior to vial A would lead to better performance both in trapping of [14C]CO2 and conversion.

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Table 2 Conditions and results using Set-up II for the reduction of [14C]CO2 to [14C]CO by 2 and subsequent [14C]CO capture as [14C]5

| Entry | Base (mM) | HCl added (0.1 N, 0.2 mL) | Est. [14C]CO2 trapping in Vial A at EODa (%) | RCPb [%] | RCY [%] |  
|-------|-----------|--------------------------|-------------------------------------------|----------|--------| 
| 1     | 150       | —                        | 66                                        | 7        | 4      | 
| 2     | 15        | —                        | 56                                        | 3        | 1      | 
| 3     | 150       | DBU (75)                 | 80                                        | —        | —      | 
| 4     | 150       | DBU (75)                 | 48                                        | 3        | 3      | 
| 5     | 150       | DBU (7.5)                | 18                                        | —        | —      | 
| 6     | 150       | TEA (7.5)                | 23                                        | —        | —      | 
| 7     | 150       | TEA (7.5)                | 65                                        | 29       | 1      | 
| 8     | 150       | TEA (7.5)                | 60                                        | 7        | 5      | 
| 9     | 150       | TEA (7.5)                | 32                                        | 10       | <1     | 
| 10    | 15        | TEA (7.5)                | 35                                        | 8        | 2      | 
| 11a   | 150       | —                        | 12                                        | 8        | 3      | 
| 12d   | 150       | TEA (7.5)                | 64                                        | 5        | <1     | 
| 13d   | 15        | TEA (7.5)                | 52                                        | 20       | 6      | 

Reaction conditions: 2 (15–150 mmol), base (7.5–75 mM) in 0.1 M KCl(aq) (1 mL). The acid was added after peak [11C]CO2 trapping in Vial A was achieved. a Trapping in A = % radioactivity in Vial A versus total radioactivity released by the cyclotron. b RCP determined by analytical radio-HPLC. c Radiochemical yield (RCY) = [(Radioactivity in Vial B × RCP [14C]5)/Radioactivity in Vial A at EOD] × 100. d Only WE and CE used.
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