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Quantitative determination of Pt- catalyzed D-glucose oxidation products using 2D NMR

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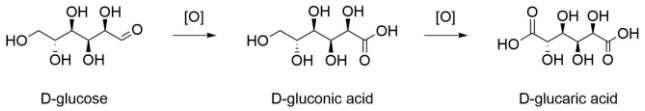
ABSTRACT: Quantitative correlative ^{1}H – ^{13}C NMR has long been discussed as a potential method for quantifying the components of complex reaction mixtures. Here we show that quantitative HMBC NMR can be applied to understand the complexity of the catalytic oxidation of glucose to glucaric acid, which is a promising bio- derived precursor to adipic acid, under aqueous aerobic conditions. It is shown through 2D NMR analysis that the product streams of this increasingly studied reaction contain lactone and dilactone derivatives of acid products, including glucaric acid, which are not observable/ quantifiable using traditional chromatographic techniques. At 98 % glucose conversion, total C_6 lactone yield reaches 44 %. Furthermore, a study of catalyst stability shows all Pt catalysts to undergo product-mediated chemical leaching. Through catalyst development studies, it is shown that sequestration of leached Pt can be achieved through use of carbon supports.

KEYWORDS Partial Oxidation, Quantitative 2D NMR, Glucose, Glucaric Acid, Gluconic Acid, Carbohydrates.

1. Introduction

Combined environmental, economic and political pressures are incentivising the drop-in integration of bio-derived, sustainable feedstocks within the chemical industry. As a highly abundant C_6 monosaccharide, the selective oxidation of glucose has received significant attention in recent years. In particular, research has focussed upon the selective oxidation of glucose to gluconic acid, which is used in the food, pharmaceutical and paper industries. A number of heterogeneous, precious metal catalysts have been reported to catalyze this reaction using molecular oxygen as oxidant. These often comprise Pt, Pd and Au,[1-6] and might also contain promoters such as Bi.[2, 7-9] Less extensively studied is the selective oxidation of glucose to glucaric acid, an aldaric acid which was recently recognised by the US Department of Energy as a key bio- derived platform molecule.[10]

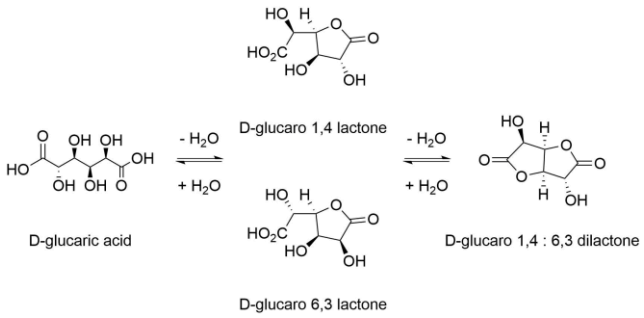
Glucaric acid is produced industrially through oxidation of glucose with nitric acid, a process which dates back to 1888 and affords *ca.* 40% yield of the mono-potassium salt.[11-13] By-products for this reaction include oxalic, tartaric and 5-ketogluconic acid.[12] With potential applications in food, pharmaceutical and polymer industries, global demand for glucaric acid is predicted to increase through the 21st century.[14-21] Processes for the enzymatic, electrocatalytic and heterogeneously catalysed synthesis of glucaric acid from glucose have also been reported.[19, 20, 22-33] The TEMPO- promoted oxidation of glucose to glucaric acid (> 90% yield), with NaBr, bleach and strict pH control has also been reported,[34] however, these reactions generate toxic by-products. Of the many approaches taken, the heterogeneously catalyzed systems utilizing molecular oxygen present the most atom efficient, inherently green approach to glucaric acid production. Studies into heterogeneously catalyzed oxidation processes typically fall into two categories; (i) pH controlled [6, 27, 32, 35] and (ii) non pH controlled.[21, 29-31, 33] Dirkx et al.,[27] reported that strict control of pH at 9-10 enhances the activity of Pt catalysts, which was attributed to more rapid desorption of free- acid products from the active site. Meanwhile Rennovia Inc. recently claimed glucaric acid yields of 66 % in the absence of pH control, over a range of monometallic Pt and bimetallic AuPt catalysts.[20, 29, 30] To date however, studies have failed to address either spectroscopic analysis of product streams or the long term stability of catalysts operating under autogeneous pH. The latter is particularly pertinent as products of glucose oxidation; gluconic, glucaric and tartaric acids, are known metal- sequestering agents.[27, 36] Indeed, Karski et al., reported leaching of M (M= Bi, Tl, Sn and Co) and low levels of Pd when bimetallic Pd-M/ carbon and silica catalysts were used to catalyze the oxidation of glucose to gluconic acid.[37] This was attributed to the strong chelating properties of gluconic acid.[37]



Scheme 1. Oxidative conversion of glucose to glucaric acid

Chromatographic techniques are favoured for separation and quantification of the products of glucose oxidation and C_6 products are accepted to form according to the pathways shown in Scheme 1.[19-21, 27, 29-33, 35, 38, 39] Glucaric acid is generally accepted to be the terminal C_6 oxidation product, with lower molecular weight carboxylic acids formed through undesirable C-C scission pathways. However, juxtaposed with high reported mass balances in catalysis studies, are equilibria known to establish between D-glucaric acid and its mono and di- lactone derivatives; D-glucaro 1,4 lactone, D-glucaro 6,3 lactone

and D-glucaro 1,4: 6,3 dilactone under acidic conditions (Scheme 2).[40] Whilst never reported as quantified products of glucose oxidation, Boussie et al., implied that these derivatives might form *in situ* under their reaction conditions.[20] Meanwhile, reported short chain acid by-products of Pt- catalysed aerobic glucose oxidation include tartronic acid, tartaric acid, oxalic acid, formic acid, glycolic acid and glyceric acid.



Scheme 2. Equilibration of D-glucaric acid with its mono and dilactone derivatives

Of the analytical techniques available, nuclear magnetic resonance (NMR) is amongst the most versatile, with the potential for simultaneous quantification of multiple small organic molecule components within a complex mixture.[41, 42] Two dimensional NMR, in particular heteronuclear multiple- bond correlation (HMBC) spectroscopy, exemplifies this due to its ability to separate overlapping ^{1}H resonances. However, a key drawback with 2D techniques is that the intensity of a 2D NMR correlation is molecule and environment dependant, leading to difficulty in determining absolute concentrations. Whilst it has been shown that this can be mitigated to some degree through addition of a standard,[42] the correlations representative of the standard molecule also suffer environmental effects, leading to non-linear calibrations.[42]

In the current study, aerobic oxidation of glucose over supported Pt catalysts is studied under autogenous pH. Both C_6 products and glucose conversion are quantified using quantitative ^{13}C-^{1}H HMBC NMR. It is shown that the mono and dilactone derivatives of D-glucaric acid featured in Scheme 2 form *in situ* and at appreciable selectivities, as do D-glucuronic and L-guluronic acids, the derived 5- membered lactones thereof and also carbon dioxide. Elemental analyses of product streams show that heterogeneous Pt- catalysts undergo product- mediated chemical leaching. This non- transient leaching increases with glucose conversion, with leaching levels of up to 24 % of total supported Pt observed. It is shown that by supporting Pt on a carbon support, or addition of carbon, leached Pt can be effectively sequestered to yield a product stream which is effectively platinum- free. At 98 % D-glucose conversion, a catalyst comprising 5 wt.% Pt/C prepared by wet impregnation afforded 59 % yield of D-glucaric acid and its lactone derivatives, mass balance of 93 % and low Pt-concentration of 1.4 ppm.

2. Results and discussion

2.1 Product identification by NMR. To date, all studies relating to catalytic D-glucose oxidation have utilized chromatographic (HPLC/ IC) techniques for quantification of reaction products, substrate conversion and for identifying products based on retention times. Indeed, these techniques are favored for such processes, owing to the availability of a wide range of stationary phases for the separation of low molecular weight organic acids. Our previous studies into the preparation of crystalline D-glucaric acid showed its rapid lactonization to occur at mild temperatures (< 50 °C), despite being in an aqueous environment.[43] Indeed, the pathways shown in Scheme 2 have previously been studied using ^{1}H NMR.[40] However, whilst alluded to within the patent literature,[30, 38, 44] no study has as yet reported formation of lactone or dilactone derivatives of D-glucaric acid under catalytic conditions, let alone sought to quantify these potential reaction products. Similarly, often overlooked are D-glucuronic and L-guluronic acids, both glucose- derived uronic acids which have been reported to undergo oxidation to yield glucaric acid.[27, 45] In line with previous studies these molecules and other potential C_6 products of D-glucose oxidation were analyzed via HPLC using an acid- specific stationary phase (Agilent, Metacarb 67H)(ESI Fig. 1). Despite method optimization, significant overlapping of peaks was observed in both RID and DAD (210 nm) signals. Indeed, it was apparent that separation of D-glucurono, L-gulurono, D-glucono and D-glucaro- products was not feasible, as shown in Fig. S1.

To determine which C_6 products form under glucose oxidation conditions, 5 wt. % Pt on TiO_2 (P25) was prepared by wet impregnation (5 wt. % $Pt/TiO_2^{IMP\ Red\ 400}$). This catalyst was assessed in D_2O under the following reaction conditions; 40 mg catalyst, 1000 rpm, $P(O_2)$ = 20 bar, 80 °C, 24 h, [D-glucose] = 0.554 M, 5.54 mmol (D-glucose/ Pt = 540 : 1 mol : mol). The ^{1}H NMR spectrum of aqueous products (ESI Fig. 2) showed multiple overlapping resonances within the δ = 3.0 ppm to δ = 5.6 ppm region, with a strong solvent resonance centered at δ = 4.79 ppm attributable to H_2O. Objective assignment of ^{1}H resonances in ESI Fig. 2 was not possible, therefore 2D HMBC NMR was employed, with an aim to separate ^{1}H environments along the ^{13}C axis. The ^{13}C-^{1}H HMBC spectra are shown in Fig. S3, with correlations assigned through analysis of commercial standards where possible (alternately, synthesized standards) and chemical structures are shown in Table S1, with ^{13}C-^{1}H assignments shown in Table S2. An expanded region of this spectrum is shown in Fig. 1, with spectral features assigned through false coloring based on analysis of standards. It is clear from Fig. 1 that Pt- catalyzed aerobic oxidation of glucose under autogeneous pH affords a far more complex mixture of C_6 oxidation products than shown in Scheme 1. Indeed, ^{13}C- ^{1}H correlations consistent with three uronic acids; D-glucuronic acid, D-gluconic acid and L-guluronic acid are observed. Lactone derivatives of these; D-glucurono 6,3- lactone, D-glucono 1,4- lactone and L- gulurono 6,3- lactone were also observed, with integrated peak areas suggesting that these form in significant concentrations. D-glucaro 1,4 lactone and D-glucaro 6,3 lactone are also confirmed, for the first time, to be products of D-glucose oxidation under aqueous conditions. Potential pathways to formation of these C_6 products are shown in Scheme 3. 5-Keto D-gluconic acid and the hemiacetal forms of D-fructose; α-D fructofuranose / α-D fructopyranose however, were not observed as reaction products. No dialdehyde products were observed. Meanwhile, studies on commercial standards of D-glucono-1,5 lactone **(10)** showed it to undergo spontaneous conversion (STP) to D-gluconic acid **(8)**. This was characterised by a shift in δ ^{13}C from 173.8 ppm to 175.9 ppm

and decreased intensity of correlations at δ ^{13}C = 81.6 ppm. Thermodynamic instability of 6- membered D-glucono 1,5-lactone **(10)** relative to 5- membered D-glucono 1,4- lactone **(9)** is consistent with previous studies.[46]

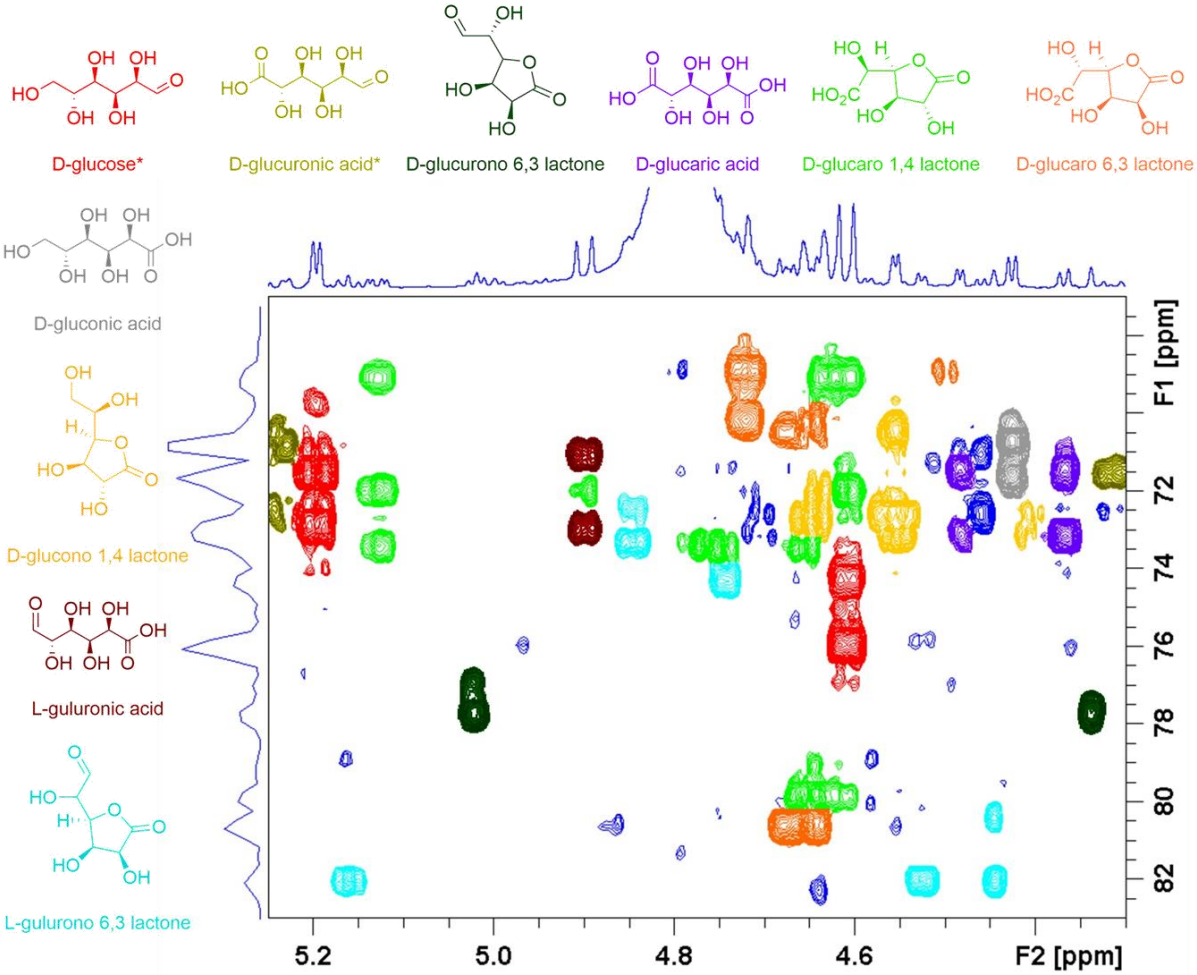


Figure 1. Expanded region of a false- colored ^{13}C-^{1}H HMBC-NMR spectrum of the product stream from D-glucose oxidation catalyzed by 5 wt. % Pt/TiO_2 $^{IMP\ Red\ 400}$ with O_2. The structures of C_6 gluconic, glucuronic, guluronic and glucaric acids and their derivative products are shown. F1 axis is the ^{13}C spectrum, F2 is the ^{1}H spectrum. (■ Unassigned). *D-glucose and D-glucuronic acid present in solution as α/β cyclic anomers. Conditions; 5 % $Pt/TiO_2$$^{IMP\ Red\ 400}$ (40 mg), [D-glucose] = 0.554 M (5.54 mmol in D_2O), 80 ^{o}C, 1000 rpm, $P(O_2)$ = 20 bar, 24 h.

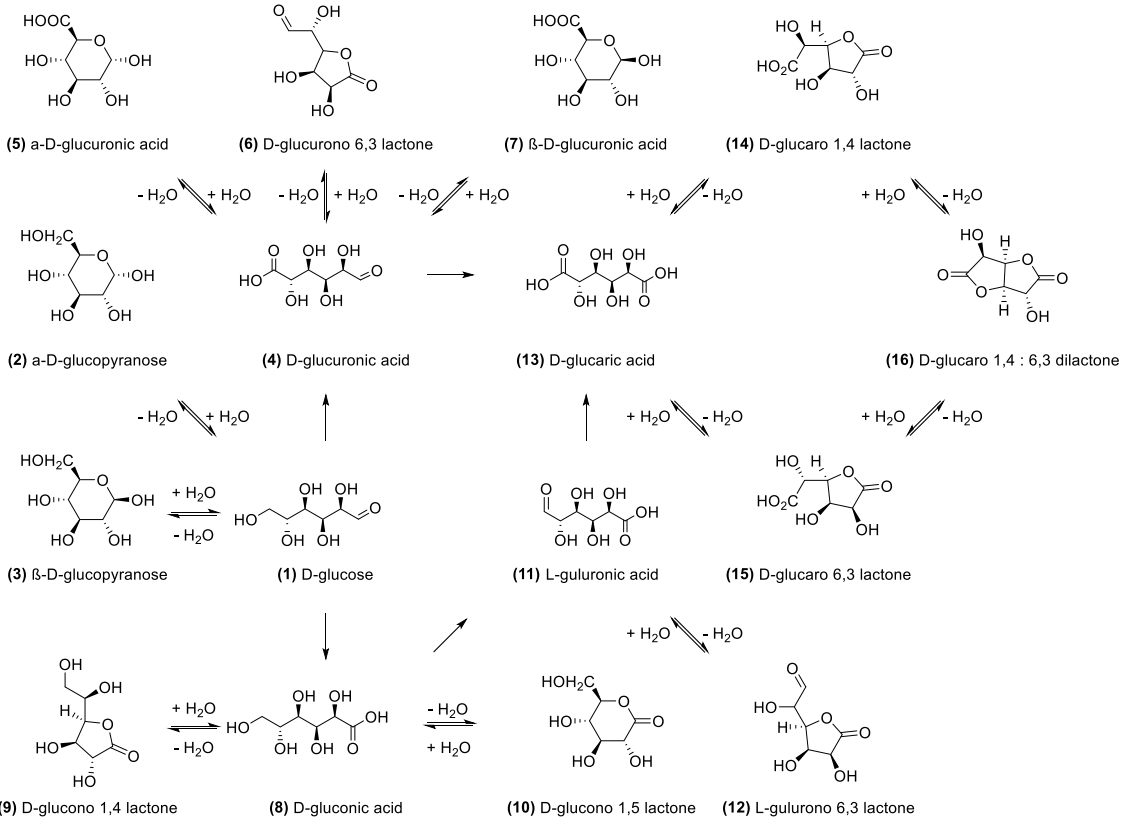
To confirm the C_6 pathways proposed in Scheme 3, the three uronic acid products identified in Fig.1; D-glucuronic acid **(4)**, D-gluconic acid **(8)** and L-guluronic acid **(11)** were treated under oxidation conditions in the presence of 5% Pt/TiO_2 $^{IMP\ Red\ 400}$. Conversion of the target aldaric acid; D-glucaric acid **(13)** was also assessed under the same conditions and HMBC NMR spectra of product streams are shown in Table S3, Entries 1-4. These studies confirmed that the three uronic acids undergo oxidation to yield D-glucaric acid **(13)**. An equilibrium with D-glucaro 1,4 lactone **(14)** and D-glucaro 6,3 lactone **(15)** is then established. Dehydrogenation of D-gluconic acid **(8)** was observed, yielding L-guluronic acid **(11)** and L-gulurono 6,3- lactone **(12)**(Table S3, Entry 1), with D-glucono- 1,4 lactone **(9)** also observed. This was found to be consistent with previous work by Dirkx et al., who reported that for Eq. (i), $K_1 << K_2$.[27]

$$\mathbf{D-gluconic\ acid} \xrightarrow{k_1} \mathbf{L-guluronic\ acid} \xrightarrow{k_2} \mathbf{\mathit{D}-glucaric\ acid} \qquad \text{(i)}$$

$$\mathbf{D-glucose} \xrightarrow{k_4} \mathbf{D-gluconic\ acid} \xrightarrow{k_5} \mathbf{\mathit{D}-glucaric\ acid} \qquad \text{(ii)}$$

Recently, Lee et al., identified dehydrogenation of D-gluconic acid as a potential rate limiting step in formation of D-glucaric acid from glucose, though reported no formation of L-guluronic acid or any derivatives.[33] Indeed, Scheme 1 and Eq. 2 are representative of C_6 pathways reported in the vast majority of D-glucose oxidation studies, with K_4 >> K_5 widely reported.[27, 35, 39] In addition to limitation arising from K_1, the observed formation of thermodynamically stable γ-lactones; D-glucono 1,4- lactone and L-gulurono 6,3 lactone, would also slow the rate of D-glucaric acid formation. Experimentally determined initial rates of D-gluconic acid **(8)** and D-glucono 1,4 lactone **(9)** conversion over 5% $Pt/TiO_2$$^{IMP\ Red\ 400}$ are shown in Table S4. The equilibrium between acid and γ- lactone dominates under reaction conditions, with comparable conversion rates observed for both substrates under aerobic conditions. Conversion of D-gluconic acid **(8)** under anaerobic conditions (Table S4, Entry 3) afforded D-glucono 1,4 lactone **(9)** and L-guluronic acid **(11)** only, suggesting that the transformation of D-gluconic acid **(8)** to L-guluronic acid **(11)** shown in Equation 1 proceeds via non- oxidative catalytic dehydrogenation with respect to PO_2. Given the literature precedent for adding Cu

as a promotor in Pt catalysts for non- oxidative dehydrogenation,[47, 48] this correlates well with the findings of Jin *et al.*, who reported enhanced D-glucaric acid productivities from glucose for Pt-Cu/TiO_2 catalysts, relative to Pt/TiO_2 analogues.[35] Based on NMR and product conversion studies, the C_6 product pathways in operation under aerobic D-glucose oxidation conditions is now reported for the first time in Scheme 3.



Scheme 3. Proposed reaction network for formation of C_6 derivatives in catalytic aerobic D-glucose oxidation

2.2 Quantification of reaction products using HMBC NMR. Application of NMR techniques as quantitative tools in catalytic processes is not a novel concept. Indeed, quantitative ^{1}H NMR has previously been employed in a number of studies.[49-54] 2D NMR techniques, however, have not been broadly adopted due to the limitations previously described. To remove one of these limitations, specifically, interaction of reaction products with the NMR standard itself, a melt- sealed glass ampule containing 1 wt.% TMS/$CDCl_3$ was used as internal standard in calibrations and product analyses. Two different methods were then used in calibrating for glucose oxidation reaction products using HMBC NMR. These were; (i) linear calibrations using commercially available standards and (ii) calibration through equilibrium studies. Approach (ii) was adopted in calibration of molecules which could be neither purchased nor isolated in pure, quantifiable crystalline form, but rather exist as equilibrium mixtures. These include; (a) α-D- glucopyranose (**2**) ⇌ β-D- glucopyranose (**3**) the aqueous forms of D-glucose (**1**), (b) α-D- glucuronic acid (**5**) ⇌ β -D-glucuronic acid (**7**) and (c) D-glucaro 6,3 lactone (**15**), which was cross- calibrated via the equilibria shown in Scheme 2 using rFs derived for D-glucaric acid (**13**), D-glucaro 1,4 lactone (**14**) and D-glucaro 1,4: 6,3 dilactone (**16**). For a range of concentrations (in D_2O), each characteristic ^{1}H-^{13}C correlation was normalised to the TMS standard at δ ^{1}H = 0 ppm, δ ^{13}C = 0 ppm to afford a response factor (rF). Sensitivity Analyses were then carried out for the rFs of each ^{1}H-^{13}C correlation within a specific HMBC spectrum of a product using model reaction solutions. In this way those correlations were identified which were least susceptible to drift from their linear calibrations when present in complex product streams. In addition to sensitivity analyses, only distinct, non- overlapping peaks were considered for quantitative analyses. An example of route (i) depicting calibration of D-glucaric acid (**13**) is shown in Fig. S4 and Tables S5 – S6, whilst calibration of D-glucaro 6,3 lactone (**15**) via route (ii) is shown in Figs. S5-S6 and Tables S7- S9. A truly quantitative, standardised first order NMR method for determining the concentration D-glucose (as α- and β- D-glucopyranose) in solution was employed (Fig. S7), with validation of rFs shown in Fig. S8. A representative sensitivity analysis is shown in Table S6. Such an analysis was carried out for all derivatives shown in Table S1, with the exception of D-glucaro 6,3 lactone and α/ β -D- glucuronic acid – for which pure standards were unavailable. For these, non-overlapping correlations (where $R^2 > 0.99$) were used in quantification. The ^{1}H-^{13}C correlations used in quantifying unreacted glucose and oxidation products are shown in Table S10. ^{13}C-^{1}H HSQC NMR was also considered for use in product stream analysis due to its being a more sensitive technique and less susceptible to variation in ^{13}C-^{1}H couplings. However, observed ^{13}C-^{1}H correlations were too intense for objective TMS- normalised quantitative analysis of product streams without product stream dilution (Fig. S9), which could shift the position of the dynamic equilibria shown in Scheme 3.

Table 1 The aqueous aerobic oxidation of glucose over various supported 5 wt. % Pt catalysts; catalytic activity and stability

Entry	Cat	χ / % [a]	Product Selectivities / % [b]												C_{bal} / %	[M] ppm [e]
			GLU	$GLU_{1,4}$	5K-GLU	GLA	$GL_{1,4}$	$GL_{6,3}$	$GL_{1,4:6,3}$	GLUU [c]	$GLUU_{6,3}$	GUL	$GUL_{6,3}$	Other [d]	CO_2		
1	None	0	-	-	-	-	-	-	-	-	-	-	-	-	-	101	-
2	TiO_2	0	-	-	-	-	-	-	-	-	-	-	-	-	-	99	-
3	SiO_2	0	-	-	-	-	-	-	-	-	-	-	-	-	-	101	-
4	C (XC72R)	0	-	-	-	-	-	-	-	-	-	-	-	-	-	101	-
5	Pt/TiO_2^{IWI}	42.2	14.8	11.4	0.0	8.5	1.7	9.1	0.6	11.1	10.6	15.6	11.0	5.2	0.4	100	6.8
6	Pt/TiO_2^{CVI}	55.5	22.7	18.6	0.0	5.7	2.0	7.5	0.5	4.0	5.1	13.8	12.5	6.0	1.6	95	7.0
7	Pt/TiO_2^{IMP}	49.0	17.9	16.6	0.0	6.7	1.7	6.0	0.4	6.1	7.6	14.2	13.2	5.7	3.9	97	7.9
8	Pt/SiO_2^{IWI}	26.0	19.3	16.4	0.0	4.5	1.6	5.2	0.8	10.4	11.6	14.4	13.5	1.7	0.6	102	2.0
9	Pt/SiO_2^{CVI}	76.9	2.9	1.5	0.0	11.5	3.0	8.0	1.0	11.6	17.0	15.8	10.3	13.5	3.9	74	12.6
10	Pt/SiO_2^{IMP}	16.2	34.3	26.1	0.0	0.0	2.9	1.0	0.0	6.7	5.2	9.2	9.7	3.6	1.2	96	1.1
11	Pt/C^{IMP}	44.3	32.2	27.2	0.0	4.6	1.2	5.4	0.2	3.1	4.1	11.0	8.3	2.3	0.4	102	1.0
12	Pt/C^{IWI}	57.8	24.8	22.8	0.0	6.5	2.1	5.8	0.7	4.4	5.2	12.1	10.8	3.9	0.8	102	1.0
13	Pt/C^{CVI}	56.9	25.5	22.0	0.0	5.9	1.8	6.6	0.4	4.0	4.2	13.6	10.2	4.6	1.2	95	1.0

GLU (D-gluconic acid), $GLU_{1,4}$ (D-glucono 1,4- lactone), 5K-GLU (5-keto D-gluconic acid), GLA (D-glucaric acid), $GL_{1,4}$ (D-glucaro 1,4 lactone), $GL_{6,3}$ (D-glucaro 6,3 lactone), $GL_{1,4:6,3}$ (D-glucaro 1,4:6,3 dilactone), GLUU (D-glucuronic acid), $GLUU_{6,3}$(D-glucurono 6,3- lactone), GUL (L-guluronic acid), $GUL_{6,3}$ (L-gulurono 6,3-lactone)

Conditions; 40 mg catalyst, [D-glucose] = 0.554 M (5.54 mmol in D_2O), 80 °C, 1000 rpm, P(20 % O_2/ N_2) = 25 bar, 24 h, Glucose : Pt (mol: mol) = nominal 540 : 1 where applicable.

[a] Glucose conversion quantified from disappearance of glucose (α & β glucopyranose) using HMBC NMR. [b] Based on observed reaction products. [c] Quantified as α- and β- D-glucuronic acid. [d] Other (tartaric acid, tartronic acid, glycolic acid, glyceric acid, oxalic acid, acetic acid) [e] Determined by MPAES (note: where applicable, 100 % Pt leaching would afford a [Pt] of 200 ppm).

To further validate the applicability of quantitative ^{13}C-^1H HMBC NMR in these systems, 5% $Au/TiO_2^{IMP\ Red\ 400}$ was prepared and assessed for non pH- controlled D-Glucose oxidation, a reaction which is broadly reported to yield D-gluconic acid **(8)** as the terminal C_6 product. Two C_6 products were observed in HMBC NMR spectra of reaction solutions across 20 h on line; D-gluconic acid **(8)** and D-glucono 1,4 lactone **(9)**. As was shown in Fig. S1, these products are separable via HPLC. Comparative quantitative analyses of product streams at 2- 20 h on line via HMBC NMR and HPLC are shown in Fig. S10. Ring- opening of the lactone was observed during calibration and is attributed to the polar mobile and strongly cationic stationary phase within the HPLC column. This was characterised by a consistently lower lactone: acid ratio observed in HPLC relative to HMBC NMR data (Figs. S10a and 10b respectively). Nonetheless, the Σ yield of D-gluconic acid derivatives (D-gluconic acid + D-glucono 1,4 lactone) was consistent between analytical techniques (Fig. S10c).

To discount any potential effects from the use of D_2O as solvent, 5% Pt/TiO_2 $^{IMP\ Red\ 400}$ was also assessed in deionised H_2O. A comparison of HMBC NMR spectra for reactions carried out in either D_2O or H_2O can be found in Fig. S11. Whilst the same distribution of products formed as in Fig. 1, spectral resolution is significantly obscured by the presence of a strong solvent resonance centred at *ca*. δ ^1H = 4.9 ppm (± 0.25 ppm), with certain characteristic ^1H - ^{13}C interactions effectively obscured. These are indicated in Fig. S11a. Analysis of the product streams from Fig. S11 using ^2H NMR indicated that no deuterium exchange occurred during catalytic assessments (Fig. S12). All reactions and calibrations were therefore carried out in D_2O to allow for accurate quantification of products. In addition and for the first time, CO_2 is quantified as a product of Pt-catalyzed D-glucose oxidation, as determined through GC-FID analysis of gaseous product streams.

2.3 Assessment of supported Pt catalysts in the aerobic oxidation of D-glucose. Blank reactions were carried out in the absence of a catalyst (Table 1, Entry 1) and also in the presence of unmodified support materials P25 TiO_2, SiO_2 and carbon (Table 1, Entries 2, 3 and 4 respectively). No glucose conversion was observed in the presence of these unmodified support materials. For these experiments, the carbon mass balance at t = 24 h was 100 % ± 1 %, with glucose quantified post-reaction (as α & β glucopyranose) using HMBC NMR. Direct quantification of glucose conversion in this way is a key distinction between the reported quantitative NMR technique and chromatographic methodologies, which suffer from co-elution of products and substrate. Consistent with previous reports on the oxidation of D-glucose to D-glucaric acid, a range of catalysts containing a nominal 5 wt.% loading of Pt supported on SiO_2 (Divasil 635), TiO_2 (Degussa, P25) and carbon (Vulcan, XC72R) were prepared via IMP, IWI and CVI. This being a representative sample of preparation methodologies, support materials and Pt- precursors. To allow for comparison of catalysts, assessments were carried out at < 100 % conversion; [D-glucose] = 0.554 M, 24 h, 80 °C, P(20 % O_2 / N_2) = 25 bar. Through quantitative HMBC analysis of product streams shown in Table 1, 6 additional C_6 products of Pt- catalyzed D-glucose oxidation are now reported for the first time (Table 1, Entries 5-13). These are; D-glucono 1,4 lactone ($GLU_{1,4}$)**(9)**, D-glucaro 1,4 lactone ($GL_{1,4}$)**(14)**, D-glucaro 6,3 lactone ($GL_{6,3}$)**(15)**, D-glucaro 1,4:6,3 dilactone ($GL_{1,4:6,3}$)**(16)**, D-glucurono 6,3 lactone ($GLUU_{6,3}$)**(6)** and L-gulurono 6,3 lactone ($GUL_{6,3}$)**(12)**. Total oxidation to CO_2 was also assessed, with yields of up to 2.0 % determined (Table 1, Entry 7). In the presence of Pt- catalysts, low glucose conversion correlated with high selectivity towards D-gluconic acid and its derivatives (Table 1, Entry 10). With increasing conversion, selectivity towards derivatives of D-glucaric **(13,14,15,16)** and L-guluronic acid **(11,12)** increases. At near isoconversion, comparable product selectivities were observed for Pt/TiO_2^{CVI}, 5% Pt/C^{CVI}

and 5% Pt/C^{IWI} (Table 1, Entries 6, 12 and 13). Despite the significant disparity in BET surface areas of the TiO_2 and carbon supports (48 and 226 m^2g^{-1} respectively). Indeed, the physicochemical property which best correlated with observed D-glucose conversion rates was Pt- surface area, as determined by CO pulse titration (Fig. S13a). ICP-MS analysis of the product streams also showed leaching of Pt into solution. This was determined to be product- mediated, with leaching observed only when the reactor was charged with both the O_2 and D-glucose (Table S11). At isoconversion, lower [Pt] concentrations were observed for Entries 12 and 13 than Entry 7 and this can be attributed to the ability of carbon to effectively sequester leached Pt from aqueous solution as confirmed by studies shown in Fig. S14. To determine whether the observed product- mediated leaching of Pt was a transient phenomenon, 5% Pt/TiO_2 $^{IMP\ Red\ 400}$ was assessed under continuous flow conditions in a trickle flow regime (Fig. S15a). Pt- leaching was observed to continue at steady state over 40 h on stream, in line with steady state glucose conversion. Consistent with batch reaction studies in Table 1, it is shown in Fig. S15b that through addition of carbon extrudates (Norit ROW Supra, Sigma Aldrich) after the Pt-catalyst bed, leached Pt can be effectively sequestered from the product stream onto the carbon. It is perhaps serendipitous therefore, that Rennovia Inc. recently patented the synthetic procedure for a series of shaped porous carbons.[55-57] Further still, that the examples in said patents featured use of the synthesized carbons as supports for Pt- based glucose oxidation catalysts.[55-57] To further study the complex reaction pathways in operation in Pt- catalyzed glucose oxidation, a time on line study of the catalytic performance of 5% Pt/$TiO_2$$^{IMP\ Red\ 400}$ was carried out and data is shown in Fig. 2.

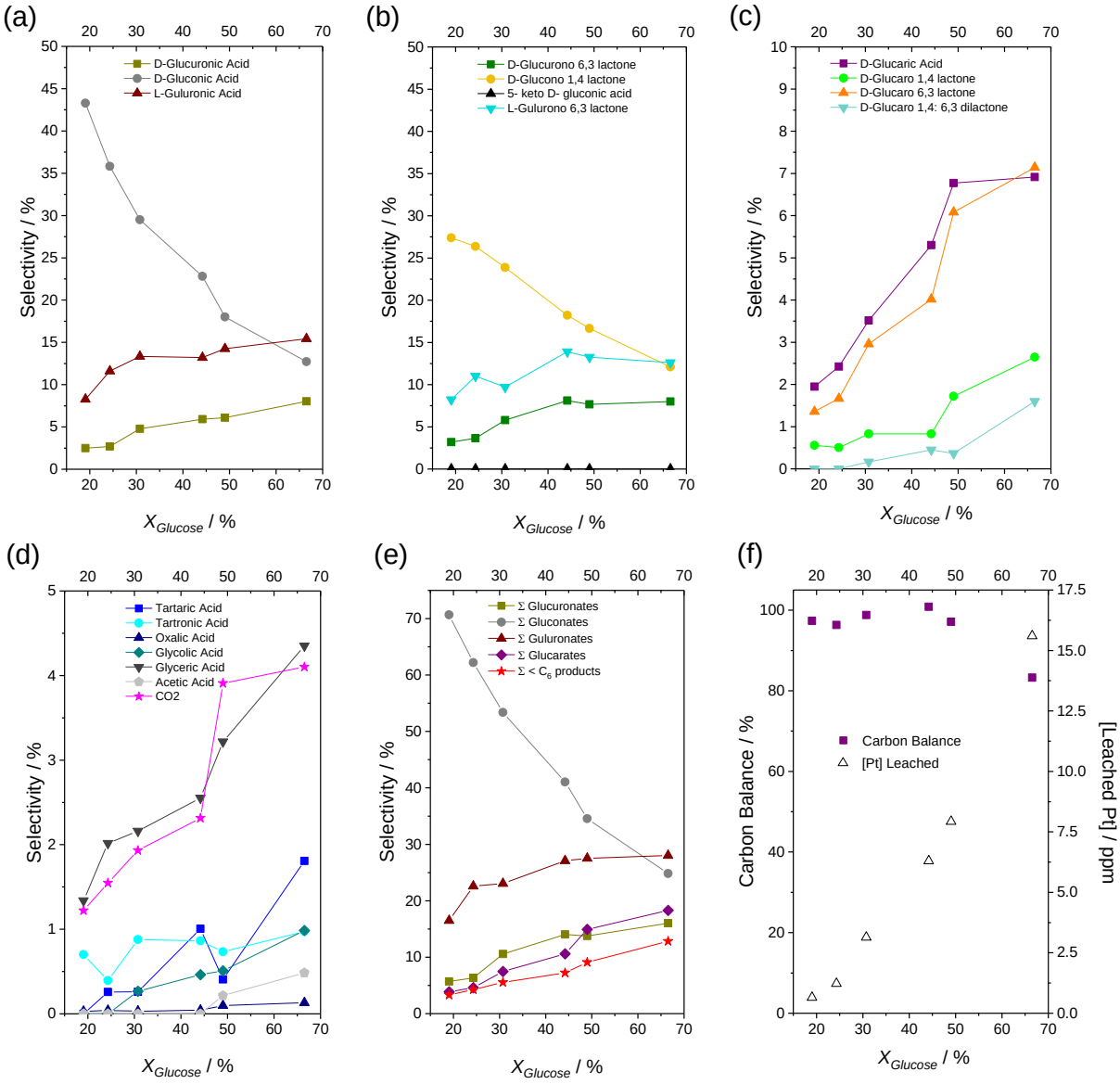


Figure 2. The temporal evolution of products in aerobic D-glucose oxidation catalyzed by 5% Pt/$TiO_2$$^{IMP\ Red\ 400}$ showing glucose conversion ($X_{Glucose}$), selectivities towards (a) uronic acid products, (b) lactone- derivatives of uronic acid products, (c) glucarate products and (d) < C_6 products. Also showing (e) Σ selectivities towards product groups and (f) carbon mass balances + Pt leaching. Conditions; 5 % Pt/$TiO_2$$^{IMP\ Red\ 400}$ (40 mg), [D-glucose] = 0.554 M (5.54 mmol in D_2O), 80 °C, 1000 rpm, P(20% O_2/ N_2) = 25 bar.

Table 2 A parametric study of 5% $Pt/TiO_2^{IMP\ Red\ 400}$ and 5% $Pt/C^{IMP\ Red\ 400}$ catalyzed D-glucose oxidation

Entry	Conditions; % O_2/ Temp °C/ mg cat	χ / % [a]	Observed Product Yields / C-mol % [b]												C_{bal} / %	[Pt] ppm [e]
			GLU	$GLU_{1,4}$	GLA	$GL_{1,4}$	$GL_{6,3}$	$GL_{1,4:6,3}$	GLUU [c]	$GLUU_{6,3}$	GUL	$GUL_{6,3}$	Other [d]	CO_2		
1	20% O_2/ 60 °C/ 40 mg	34.6	13.2	7.0	1.3	0.2	1.0	0.0	1.5	1.2	3.7	2.0	0.4	0.1	97	1.8
2	20% O_2/ 80 °C/ 40 mg	49.0	8.3	7.7	3.1	0.8	2.8	0.2	2.8	3.5	6.6	6.1	2.6	1.8	97	7.9
3	20% O_2/ 100 °C/ 40 mg	90.0	1.2	3.1	1.2	0.3	0.9	0.8	1.3	4.6	5.5	7.5	4.2	2.2	43	34.8
4	100% O_2/ 60 °C/ 40 mg	43.1	15.7	9.7	2.0	0.4	1.9	0.	2.4	1.4	5.0	2.5	3.4	0.3	102	3.5
5	100% O_2/ 80 °C/ 40 mg	59.5	12.4	10.2	3.8	1.6	4.1	0.5	3.3	5.0	7.1	8.2	3.1	0.3	100	11.3
6	100% O_2/ 100 °C/ 40 mg	89.8	3.0	2.9	5.1	2.0	5.3	0.6	2.3	5.3	4.5	4.2	7.1	2.6	55	48.8
7	100% O_2/ 80 °C/ 80 mg	90.6	5.2	4.4	3.4	0.8	2.3	0.2	1.0	2.1	9.9	3.3	2.9	0.8	43	27.4
8	20% O_2/ 60 °C/ 40 mg	41.6	18.4	11.3	1.4	0.3	1.2	0.1	1.0	0.9	4.7	1.3	0.7	0.1	100	0.4
9	20% O_2/ 80 °C/ 40 mg	44.3	14.9	12.6	2.2	0.6	2.5	0.1	1.4	1.9	5.1	3.8	1.1	0.2	102	1.0
10	20% O_2/ 100 °C/ 40 mg	69.8	9.9	10.5	5.2	1.3	5.0	0.9	2.1	3.9	5.6	6.4	2.9	1.1	85	11.6
11	100% O_2/ 60 °C/ 40 mg	44.4	20.1	14.3	1.0	0.1	0.5	0.1	0.6	0.7	3.4	1.6	0.4	0.1	98	0.1
12	100% O_2/ 80 °C/ 40 mg	57.9	18.5	16.6	2.3	0.6	2.5	0.4	1.6	1.7	6.0	4.6	1.7	0.3	99	1.1
13	100% O_2/ 100 °C/ 40 mg	90.7	6.8	7.2	3.3	1.0	2.4	0.8	0.7	1.5	2.1	4.3	4.8	1.1	45	10.0
14	100% O_2/ 80 °C/ 80 mg	82.7	17.8	15.8	9.2	3.2	8.2	0.9	2.7	2.3	10.0	7.1	3.0	0.5	98	2.3
15	100% O_2 / 100 °C/ 80 mg	99.5	3.2	3.6	4.2	1.2	3.4	1.9	0.1	0.7	2.0	2.4	5.4	2.8	31	12.4
16	100% O_2/ 100 °C/ 80 mg + 80 mg XC72R[f]	98.2	4.1	4.1	16.7	6.2	14.9	2.6	0.5	1.0	4.0	3.6	8.4	2.9	71	5.2
17	100% O_2/ 100 °C/ 80 mg+ 160 mg XC72R[f]	98.4	4.1	4.1	23.8	7.5	23.0	6.0	0.6	0.7	3.7	3.3	11.5	2.8	93	1.4

GLU (D-gluconic acid), $GLU_{1,4}$ (D-glucono 1,4- lactone), GLA (D-glucaric acid), $GL_{1,4}$ (D-glucaro 1,4 lactone), $GL_{6,3}$ (D-glucaro 6,3 lactone), $GL_{1,4:6,3}$ (D-glucaro 1,4:6,3 dilactone), GLUU (D-glucuronic acid), $GLUU_{6,3}$(D-glucurono 6,3- lactone), GUL (L-guluronic acid), $GUL_{6,3}$ (L-gulurono 6,3-lactone)

General conditions; [D-glucose] = 0.554 M (5.54 mmol in D_2O), 1000 rpm, P_{total} (X % O_2/ N_2) = 25 bar, 24 h. Entries 1-7; 5% $Pt/TiO_2^{IMP\ Red\ 400}$, Entries 8-17; 5% $Pt/C^{IMP\ Red\ 400}$.

[a] Glucose conversion quantified from disappearance of glucose (α & β glucopyranose) using HMBC NMR. [b] As CMB deviated from 100 % under certain conditions, data presented as yield in C-mol%, [c] Quantified as α- and β- D-glucuronic acid. [d] Other (tartaric acid, tartronic acid, glycolic acid, glyceric acid, oxalic acid, acetic acid), [e] Determined by MPAES (note: where 40 and 80 mg catalyst were used, 100 % Pt leaching would afford a [Pt] of 200 and 400 ppm respectively). [f] Reactor charged with Carbon XC72R at t=0.

D-Gluconic acid **(8)** and D-glucono 1,4 lactone **(9)** are apparent primary products (Fig. 2a), with their total selectivity decreasing from 70.7 % at 2 h on line (χ = 19 %) to 24.8 % at 40 h (χ = 65 %). Selectivity to L-guluronic acid **(11)** and the derived lactone L-gulurono 6,3 **(12)** increases, consistent with their forming through dehydrogenation of D-gluconic acid **(8)**. Selectivity towards D-glucuronic acids **(4)** and D-glucurono 6,3 lactone **(6)** also increase with increasing time on line, which suggests that this competing reaction pathway (Scheme 3) becomes more favorable at low pH. This is a minor pathway however, with formation of D-gluconic acid favored. This is consistent with more facile oxidation of D-glucose **(1)** at the terminal RCHO functional group than at the RCH_2OH. Selectivity towards D-glucaric acid and its derivatives also increases with increasing glucose conversion, with comparable selectivity towards D-glucaric acid **(13)** and D-glucaro 6,3 lactone **(15)** observed across 40 h on line (Fig. 2c). Given the co-elution of products shown in Fig. S1, it should be noted that had product streams from Fig. 2 been analyzed by HPLC, it would not have been possible to distinguish between key major products, for example D-gluconic acid **(8)** and D-glucaro 6,3 lactone **(15)**. Indeed, whilst lactone products have never been reported in catalytic D-glucose oxidation literature, C_6 lactones accounted for 45 ± 2.0 % of all products represented across the 40 h time period in Fig.2. Consistent with Scheme 3, D-glucaric acid and its derivatives are the terminal C_6 oxidation products, and C-C scission yields increasing selectivity towards < C_6 products (Fig. 2d and Fig. 2c). Indeed, total selectivity towards < C_6 products (tartaric, tartronic, oxalic, glycolic, glyceric and acetic acids in addition to CO_2) reached 12.8 % at 40 h on line (Fig. 2e). Selectivity towards the total oxidation product; CO_2 reached 4.1 % at χ = 65 % (1.96 % yield) based on observed products. A decrease in specific activity was observed with increasing time on line (Fig. S13b) suggesting either competitive adsorption of reaction products or the onset of mass transport limitation at high degrees of either D-glucose or O_2 conversion. Indeed, using the CO chemisorption- determined Pt-surface site density (4.43 $m^2_{Pt}\ g_{cat}^{-1}$), the TOF of 5% Pt/TiO_2 $^{IMP\ Red\ 400}$ at 2 h on-line was calculated as 144 $mol_{Glucose\ converted}\ mol_{Surface\ Pt\ sites}h^{-1}$. This decreased to 25 $mol_{Glucose\ converted}\ mol_{Surface\ Pt\ sites}h^{-1}$, averaged at t= 39 h. Up to 24 h on-line (χ = 49.0 %), the average observed carbon mass balance (CMB) was 98 % ± 2, but this fell to 83 % at 40 h on-line (χ = 65 %)(Fig. 2f). This decrease in CMB might be attributed to formation of insoluble humins, a process which is favorable under acidic conditions and elevated temperatures.[58] To confirm this, 5% $Pt/TiO_2^{IMP\ Red\ 400}$ was assessed across a temperature range of 60 – 100 °C (Table 2, Entries 1-3).

Glucose conversion, measured at 24 h online, increased from 34.6 % at a reaction temperature of 60 °C to 49.0 % at 80 °C. Consistent with conversion selectivity relationships shown in Fig. 2(a-d), this increase in conversion was coupled with decreased selectivity towards primary products; D-gluconic acid/ D-glucono 1,4 lactone, with increased selectivity towards D-glucuronic acid, L-guluronic acid, D-glucaric acid, lactone

derivatives thereof and < C_6 products. At a reaction temperature of 100 °C, (25 bar of 20 % O_2/ N_2) the system became anaerobic (χ glucose = 90.0 %, 4.98 mmol glucose converted) with a 1: 1 stoichiometry of converted glucose: O_2 in the charge gas (5.05 mmol O_2) of 1: 1. The apparent CMB fell to 43 % under these conditions (Table 2, Entry 3). In the absence of O_2, formation of L-gulurono products (GUL/ $GUL_{6,3}$) continued. Indeed, L-guluronic acid and its lactone derivative accounted for 40 % of observed products (Table 2, Entry 3). This is consistent with previous observations shown in Table S4, which further indicates that conversion of D-gluconic acid to D-glucaric acid proceeds via L-guluronic acid and, furthermore, that this proceeds via dehydrogenation of D-gluconic acid with zero order dependence with respect to PO_2. In the absence of O_2, oxidation of L-guluronic acid to yield D-glucaric **(13)** was prevented, with the total yield of D-glucaric acid and lactone derivatives thereof, falling to 3.2 % (c.f 6.9 % at 80 °C Table 2, Entries 2 and 3). This represents a potential chemocatalytic route towards the selective synthesis of L-guluronic acid, the monomer which affords rigidity in alginate biopolymers which have proven biomedical applications.[59-61] L-Guluronic acid is currently produced commercially by hydrolysis of alginic acid, yielding the monomers; L-guluronic acid **(11)** and D-mannuronic acid.

Analysis of the liquid and gaseous products streams of reactions represented in Table 2, Entries 1-7 with low apparent CMBs showed no unidentified by-products. To determine the fate of the missing carbon, the solid residue for reactions in Table 2 Entries 1-3, representing a CMB range of 97 – 43 %, were recovered by filtration, washed (100 ml H_2O) and dried (16 h, 110 °C) prior to thermogravimetric analysis (TGA)(5 °C min^{-1}, 20 ml min^{-1} air, 800 °C). Despite showing markedly different CMBs, no significant difference in mass loss was observed, suggesting that insoluble humin products or other carbonaceous species did not form under reaction conditions (Fig. S16). Spectroscopic, chromatographic and thermogravimetric analyses therefore offered no explanation as to the fate of the -57 % CMB deficit in Table 2, Entry 3. In a parametric study of 5% $Pt/TiO_2^{IMP\ Red\ 400}$ catalyzed D-glucose oxidation (Table 2, Entries 1-7) isoconversion of 90.1 % ± 0.4 was observed under three different reaction conditions (Table 2, Entries 3, 6 and 7). Under these conditions, the observed CMB was < 50 % and significant Pt- leaching was observed, exceeding 24 % of total supported Pt (Table 2, Entry 6).

It is well known that the intensity of ^1H NMR resonance peaks is directly proportional to the population of ^1H. Indeed, that is the basis of quantitative ^1H NMR techniques. The intensity of HMBC NMR correlation peaks however, are determined by through-bond coupling of two different spin active nuclei; ^{13}C – ^1H. At 100 °C, $P(O_2)$ = 5 bar, a significant concentration of Pt was leached into solution (34.8 ppm, Table 2, Entry 3) This equated to leaching of *ca*. 17 % of supported Pt. Low CMB reactions in Table 2 also correlated well with formation of orange product solutions which is consistent with observations by Dirkx et al., Sugar acids are effective chelating agents, indeed this an established commercial application for D-glucaric acid [27, 36, 62] and a general transfer of electron density occurs when an organic acid chelates a cationic metal center. This might be expected to effect changes in absolute areas of ^1H-^{13}C through- bond couplings. The role of leached Pt in effecting low CMBs was confirmed through analysis of combined data from Tables 1 & 2 and Figure 2.

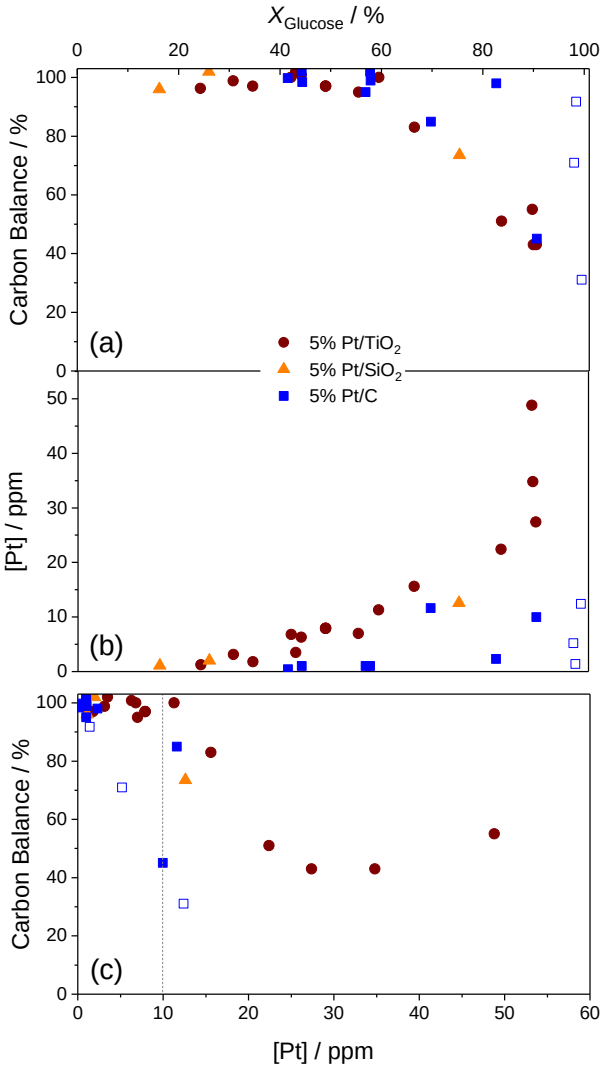


Figure 3. The interdependency between $\chi_{Glucose}$, observed CMB and [Pt] showing data from Tables 1 & 2 and Figure 2 - representing ■ 5% Pt/C, ▲ 5% Pt/SiO2 and ● 5% Pt/TiO2 catalysts prepared by CVI, IMP and IWI. (□ 5% $Pt/C^{IMP\ Red\ 400}$ from Table 2, Entries 15-17)

For all Pt- catalysts, increasing D-glucose conversion correlated well with decreasing CMB (Fig. 3a) and increasing Pt-leaching (Fig. 3b). When the [Pt] remaining in solution post-reaction exceeded 10 ppm, a rapid decrease in CMB was observed (Fig. 3c). In general, 5% Pt/C catalysts showed lower [Pt] at isoconversion than did SiO_2 - and TiO_2 – supported analogues (Fig.3b), which is consistent with the ability of carbon to sequester leached Pt from solution, as shown in Fig. S14. To confirm the role of leached metal species in effecting decreased CMBs, 5% $Pt/C^{IMP\ Red\ 400}$ was assessed under high conversion conditions with an increasing mass of XC72R (0 – 160 mg) added at t=0 to promote sequestration of metals from solution (Table 2, Entries 15-17). Isoconversion of glucose was observed across these conditions (98.7 ± 0.7 %). Addition of 160 mg carbon led to decreased [Pt] (12.4 – 1.4 ppm) and increased observed CMB (31 – 93 %) (Table 2, Entries 15 and 17).

The total yield of C_6 lactones in Table 2, Entry 17 was 43.6 %. HMBC NMR quantification of D-glucaric acid and D-tartaric acid, both well-known chelating agents, suffered significantly in the presence of leached cations. Indeed, the observed D-glucaro (GLA, $GL_{1,4}$, $GL_{6,3}$ and $GL_{1,4:6,3}$)/ D-tartaric acid yields increased from 8.8 % / 2.3 % to 60.3 % / 8.4 % when 160 mg carbon XC72 R was added to the reactor. The average mass-normalized D-glucaro (GLA, $GL_{1,4}$, $GL_{6,3}$, $GL_{1,4:6,3}$) productivity across 24 h on-line for data in Table 2 Entry 17 was 1.71 mol $_{D\text{-}glucarates}$ kg_{cat}^{-1} h^{-1}. This compares favorably with the optimal D-glucaric acid synthesis rate previously reported by Boussie et al. for a 4 % Pt/SiO_2 catalyst (1.42 mol $_{D\text{-}glucaric\ acid}$ kg_{cat}^{-1} h^{-1})(8 h, 90 ^{o}C, PO_2 = 5 bar, Pt: Glucose = 1: 84 mol: mol). Dirkx et al., previously reported increased rates of D-glucaric acid formation over Pt-catalysts when the reaction pH was maintained at pH 9-10 through autotitration of $NaOH_{aq}$.[27, 39] This was attributed to more efficient desorption of acid products from the catalyst surface under basic conditions. [27, 39] Such decreased contact times could decrease product- mediated chemical leaching and therefore [Pt]. Unfortunately, addition of NaOH (1 eq.) at t=0 caused a significant decrease in the resolution of HMBC NMR spectra (Fig. S17). As a result, it was not possible to quantify either D-glucose conversion or formation of products under such pH- controlled conditions.

It is clear from Figs. 3a and 3b that addition of increasing masses of carbon (XC72R) significantly decreased observed [Pt] and consequently led to increased CMB. To avoid introduction of mass transport limitation effects, the carbon additive charge was limited to ≤ 160 mg in the 10 ml reaction. Extrapolation of data in Table 2, Entries 15-17 suggests that further addition of carbon would yield a metal-free product stream and closed CMB. Based on trends in closed batch (Fig.3b) and trickle flow regimes (Fig. S15) it is therefore clear that operation in continuous flow would be favorable on scale-up. Use of a Pt/C catalyst with downstream high purity carbon beds, might be expected to afford product streams rich in D-glucaric acid/ its lactone derivatives, with leached metal sequestered and thereby recoverable. Development of such a process will be addressed in a future study.

3. Conclusions

For the first time, quantitative 2D HMBC NMR has been applied in both determining and quantifying the products of chemocatalytic reactions. Linear, 1st order calibrations, use of a self-contained TMS standard and sensitivity analyses remove degrees of uncertainty encountered in previous attempts to employ 2D NMR as a quantitative tool for analysis of complex mixtures. The developed analytical technique was then employed in identifying and quantifying the myriad C_6 products; both carboxylic acids and lactones, which form spontaneously during non-pH controlled aerobic oxidation of D-glucose over heterogeneous Pt catalysts. For the first time, CO_2 has been quantified as a product of this oft studied reaction, with not- insignificant yields of up to 2.9 % observed. The reaction pathway is more complex than has previously been reported, with C_6 5-membered lactone products accounting for *ca*. 45 % of all products observed over 40 h on line. All lactonizations proceed with retention of stereochemistry at the secondary alcohol center, that is, by activation of the carboxylic acid, followed by nucleophilic attack by said alcohol (hydroxyl) and loss of a hydroxyl from the acid. Two primary uronic acid products form; D-glucuronic acid (**4**) and D-gluconic acid (**8**). These both establish equilibria with their 6,3 (**6**) and 1,4 (**9**) lactones respectively. Whilst D-glucuronic acid and its lactone undergo direct oxidation to yield D-glucaric acid (**13**), D-gluconic acid and its derivative lactone are shown to undergo dehydrogenation to yield L-guluronic acid (**11**), which rapidly dehydrates to form L-gulurono 6,3 lactone (**12**). Oxidation of L-guluronic acid and its lactone leads to the desired product of Pt-catalyzed D-glucose oxidation; D-glucaric acid (**13**). Equilibration of D-glucaric acid to D-glucaro 1,4 lactone (**14**), D-glucaro 6,3 lactone (**15**) and D-glucaro 1,4: 6,3 dilactone (**16**) is then observable and quantifiable via HMBC NMR, with D-glucaro 6,3 lactone yields often equaling those of D-glucaric acid itself. Crucially, observation of D-glucaro lactones is not possible using chromatographic techniques used in all previous studies of this reaction, indeed we attribute the low D-glucaric acid yields reported in many previous studies, to co-elution of D-glucaro lactones with D-gluconic acid, which is normally reported to be both primary and major reaction product. Extensive product- mediated leaching of the active phase – Pt, is reported and attributed to chelation of oxidized Pt-species by carboxylic acid products. A strong chelating effect was confirmed, with the ^{13}C-^{1}H correlation peaks of D-glucaric acid shown to be significantly quenched by [Pt] of as low as 10 ppm. This was shown to impact significantly upon product quantification, with carbon mass balances of < 50 % observed. Catalyst design studies showed D-glucose conversion to increase proportional to Pt- surface area. Through supporting of Pt onto carbon black (XC72R) via a range of preparation techniques, catalysts can be synthesized which afford appreciable specific activities and product streams containing a low [Pt]. Rather than being due to enhanced stability towards leaching, the latter is attributed to carbon's affinity for adsorbing leached Pt *in situ*. Preliminary parametric optimization of reaction conditions employed in assessing 5% Pt/C prepared by IMP led to high D-glucose conversion (98.4 %), relatively low [Pt] in solution (1.4 ppm) and consequently high CMB (93 %). Under said condition, the total yield of previously unreported C_6 lactones was 43.6 %, with 35.5 % yield being D-glucaro lactone and dilactone products. This work therefore lays the foundation for future studies into catalytic biomass- valorization; detailing a new approach to analysis of complex reaction mixtures and application thereof to provide vital insight as to the true pathways in operation during the Pt-catalyzed oxidation of D-glucose to D-glucaric acid. This should inform future kinetic studies of the competing pathways in operation during catalytic D-glucose oxidation as well as catalyst design/ screening studies.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information. Detailed NMR spectral assignments, details pertaining to development of the quantitative HMBC protocol and data for product conversion reactions. Also includes plots showing specific catalyst activity, Pt-leaching/ sequestration studies and thermogravimetric analyses of catalysts prior to and following catalytic testing. This material is available free of charge via the Internet at http://pubs.acs.org.

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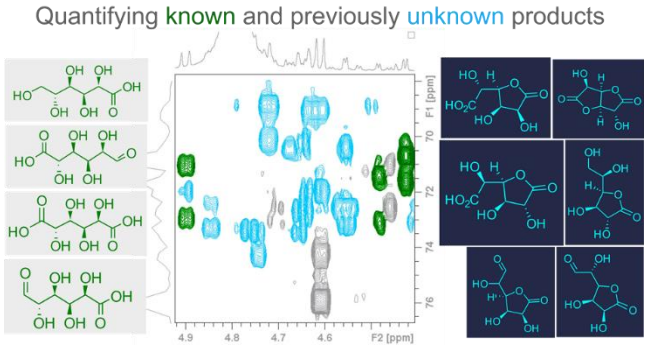
ABBREVIATIONS

HMBC, heteronuclear multiple bond correlation spectroscopy. NMR, nuclear magnetic resonance.

TOC GRAPHIC



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