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Tin-Containing Silicates: Identification of a Glycolytic Pathway via 3-Deoxyglucosone

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Inorganic glycolytic systems, capable of transforming glucose through a cascade of catalytic steps, can lead to efficient chemical processes utilising carbohydrates as feedstock. Tin-containing silicates, such as Sn-Beta, are showing potential for the production of lactates from sugars through a cascade of four to five sequential steps. Currently, there is a limited understanding of the competing glycolytic pathways within these systems. Here we identify dehydration of glucose to 3-deoxyglucosone as an important pathway that occurs in addition to retro-aldol reaction of hexoses when using tin-containing silicates. It is possible to influence the relative carbon flux through these pathways by controlling the amount of alkali metal salts present in the reaction mixture. In the absence of added potassium carbonate, at least 15–30% carbon flux via 3-deoxyglucosone is observed. Addition of just a few ppm of potassium carbonate makes retro-aldol pathways dominant and responsible for about 60–70% of the overall carbon flux. The 3-deoxyglucosone pathway results in new types of chemical products accessible directly from glucose. Furthermore, it is argued that 3-deoxyglucosone is a contributing source of some of the methyl lactate formed from hexoses using tin-containing silicates in the presence of alkali metal salts. Further catalyst design and system tuning will permit even better control between these two different glycolytic pathways and will enable highly selective catalytic transformations of glucose to a variety of chemical products using tin-containing silicates.

Introduction

Processes, in which glucose is directly converted to useful chemical products, have a high potential for industrial implementation.¹ Inorganic catalytic systems, although with limited examples of industrial implementation, have potential advantages over enzymatic and fermentative systems in terms of scalability, tolerance to a broad range of harsh reaction conditions and remain unaffected of cytotoxic intermediates.² So far, direct industrial conversion of glucose with inorganic catalytic systems has been limited to the production of sorbitol and gluconic acid, but several other chemicals have been reported as being accessible directly from glucose in high yields. These include fructose, ethylene glycol, propylene glycol, levulinic acid, 5-(hydroxymethyl)furfural (HMF) and lactic acid derivatives.^{3–9}

The use of tin-containing silicates for the conversion of sugars to lactates has received considerable attention. The first report from 2009 described the isomerisation of triose sugars to lactic

acid and methyl lactate (ML) in near quantitative yields using Sn-Beta at low temperatures.¹⁰ The scope was expanded the following year with a report that also hexoses can be converted to ML at higher temperatures (160 °C) in 68% yield, with formation of small amounts of methyl vinyl glycolate (MVG).⁴ At the same time, Sn-Beta was reported to be an active catalyst for the isomerisation of glucose to fructose and mannose in water at moderate temperatures (100 °C).³

This dependence on temperature enables some degree of versatility in the use of Sn-Beta as a catalyst. At moderate temperatures the Lewis acidic tin sites primarily catalyse a 1,2-hydride shift leading to isomerisation. At higher temperatures a C–C bond cleaving retro-aldol reaction is catalysed resulting in the fragmentation of monosaccharides to either the aforementioned triose sugars, which subsequently lead to ML (in methanol) or to C₂- and C₄-sugar fragments (glycolaldehyde and tetrose sugar) that form MVG (and glycolaldehyde dimethyl acetal, GA-DMA).^{11, 12} Additionally, Sn-based catalysts have also been used to catalyse the C–C bond formation to form similar products (e.g. MVG, α -hydroxy- γ -butyrolactone) starting from small sugar-like fragments, such as formaldehyde, glycolaldehyde and the triose sugars.^{11, 13–15}

In addition to the reaction temperature, the presence of co-solutes is known to affect tin-catalysed reactions dramatically. Especially the presence of alkali metal salts has been reported to influence the catalytic properties of stannosilicate materials in a variety of reactions involving monosaccharides.^{16–19}

It was reported in 2012 by Gunther *et al.* that addition of sodium tetraborate to aqueous glucose solutions, using Sn-Beta

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as catalyst at 80 °C, promotes an intramolecular 1,2-carbon shift over a 1,2-hydride shift. This leads to the epimerisation of glucose into mannose, rather than the isomerisation to fructose. In 2014 it was reported by Bermejo-Deval *et al.* that addition of sodium chloride and sodium exchanged Sn-Beta displays a similar catalytic performance as the one described by Gunther *et al.*, suggesting that the observed change in reaction pathway is attributable to the sodium ions and not to the tetraborate anion as first reported.^{16, 17} The epimerisation reaction has been hypothesised to occur as an intramolecular 1,2-carbon shift.^{17, 20} An alternative interpretation of the observed results could be that the 1,2-carbon shift occurs via a retro-aldol reaction of glucose to erythrose and glycolaldehyde, followed by an aldol reaction of the same species to form either glucose or mannose, effectively leading to the observed epimerisation.

An effect of alkali salts on the conversion of sugars into methyl lactate in reactions using stannosilicates was first reported in 2013.¹⁸ It was found that addition of alkali metal salts to the reaction medium increases the yield of methyl lactate obtained from sugars in methanol using Sn-Beta at 170 °C from 30 to 75%.¹⁹ The pronounced effect of alkali ions at trace amounts has led us to identify alkali metal contaminants, originating from the templating agent used in the synthesis of the Sn-Beta zeolite.

While Sn-Beta is not a commercial catalyst, recent developments have facilitated the production of the catalyst and thus increased its availability and attractiveness. Two approaches are currently employed to obtain active stannosilicate catalysts: (i) a direct synthesis route in which tin atoms are incorporated in the zeolite framework during hydrothermal synthesis, and (ii) a post-synthetic procedure, where vacancies are created within a crystalline Beta zeolite, in which tin is subsequently introduced. For Sn-Beta, approach (i) involves reacting a silicate- and a tin source at hydrothermal conditions (140 °C) in the presence of an organic structure directing agent, in an autoclave. This results in aluminium-free, highly hydrophobic and defect-free crystals.^{21, 22} Though currently only possible on laboratory scale, optimisations have been implemented to make the preparation more industrially feasible.²³⁻²⁵ Several stannosilicate materials are obtainable by direct synthesis including the zeotype Sn-MFI and the amorphous ordered mesoporous stannosilicates; Sn-SBA-15 and Sn-MCM-41.²⁶⁻²⁸

Using the post-synthetic technique (ii), active Sn-Beta catalyst can be obtained for instance through dealumination of a commercial Beta zeolite, followed by incorporation of tin within the vacancies formed in the lattice.^{29, 30} This approach, which can also include deboronation or desilication, has expanded the accessible framework types, in which tin can successfully and with relative ease be incorporated (Sn-MWW, Sn-USY, etc.).³¹⁻³⁴ Changes in pore dimensions of various silicates can result in a complete change in product selectivity as recently shown by De Clercq *et al.*³⁵

Despite of the great interest in catalytic glucose conversion to produce lactates, mechanistic details of the conversion and its modulation by co-solutes have remained sparse. The catalytic cascade involved in the conversion of sugars using Sn-Beta can be compared to its biological counterpart, the Embden-Meyerhof-Parnas glycolysis (EMP). Several main features are present in

both cases: the isomerisation of glucose to fructose, the retro-aldol reaction to form two trioses and the isomerisation of the two trioses to the thermodynamic sink, lactic acid.⁴ An additional glycolytic pathway, the Entner-Doudoroff glycolysis (ED), is also found in some bacteria and archaea. This biological pathway involves oxidation of phosphorylated glucose to gluconic acid followed by dehydration to produce 3-deoxyglucosonic acid. This intermediate then undergoes a retro-aldol reaction to produce a triose and glycerate, which are subsequently transformed to lactate.³⁶

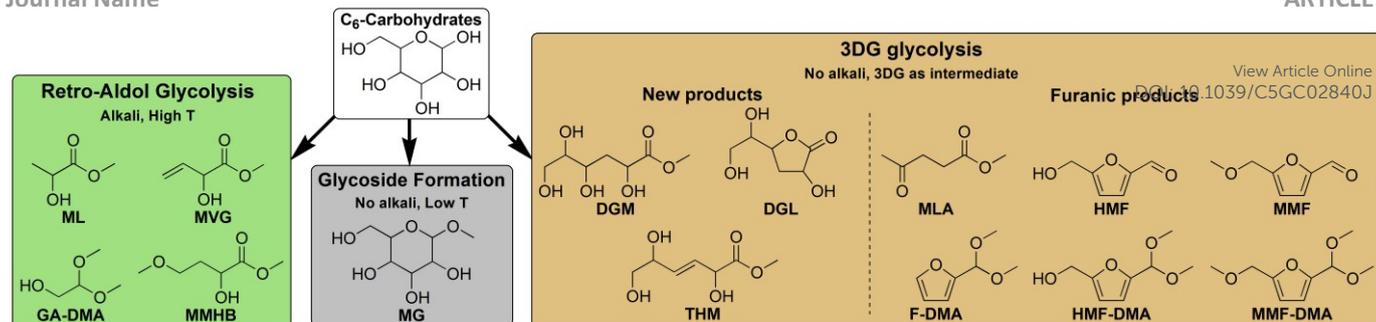
We report here, that stannosilicates in the absence of alkali metal salts catalyse a reaction which bears resemblance to the first part of the ED glycolysis. The central intermediate in the inorganic glycolysis is 3-deoxyglucosone (3-Deoxy-D-erythro-hexosulose, 3DG) instead of 3-deoxyglucosonic acid in the ED glycolysis. Further conversion of 3DG can lead to several products, most notably unbranched and deoxygenated C₆-esters and -lactones. They comprise multi-functionalised molecules, which could find applications within the specialty polymer segment. Finally, we argue that in the presence of alkali metal salts, some of the 3DG formed also undergoes a retro aldol reaction, forming pyruvaldehyde and glyceraldehyde which contributes to the overall yield of ML. This final pathway is an inorganic analogue to the ED pathway.

Results and discussion

Identification of the reaction products

The pronounced effect of alkali metal salts on the selectivity towards methyl lactate demands a further understanding of all the other products formed, especially in the absence of alkali metal salts. Therefore, the first step towards the unveiling of the reaction mechanism was the identification of all the by-products formed (Scheme 1). These were identified by means of NMR spectroscopy (assignment spectra recorded of the reaction mixtures) and GC-MS. Apart from the known retro-aldol reaction products methyl vinyl glycolate (MVG), glycolaldehyde dimethyl acetal (GA-DMA) and methyl 4-methoxy-2-hydroxybutyrate (MMHB) and unconverted sugars, the presence of several other major end-products were observed.

Among the most abundant species many were anticipated: Methyl glycosides ('MG'), i.e. acetals of hexoses consisting primarily of methyl glucopyranoside and methyl mannopyranoside were formed. Furanic end-products represented as 'FUR' including 5-(hydroxymethyl)furfural (HMF) and 5-(methoxymethyl)furfural (MMF), and the corresponding dimethyl acetals (HMF-DMA and MMF-DMA). Furfural dimethyl acetal (F-DMA) and methyl levulinate (MLA), although found in very small amounts, are also considered as furanic end-products. We speculate that F-DMA is formed by aldol reaction of C₂- and C₃-sugars to form small amounts of C₅-sugars, some of which are transformed to furfural by dehydration. We confirmed that F-DMA is not formed from HMF under the reaction conditions, ruling out this alternative explanation. Small amounts of formaldehyde dimethyl acetal were also observed.



Scheme 1. Identified products from the conversion of glucose with Sn-Beta in methanol.

In addition to the expected products, three interesting compounds were identified in the reaction mixture. They are partially dehydrated C₆-sugar acid derivatives, both in acyclic methyl ester form and cyclic lactone forms. These new compounds were identified by multidimensional NMR spectroscopy (Figure 1) as *trans*-2,5,6-trihydroxy-3-hexenoic acid methyl ester (THM), 3-deoxy- γ -lactones (DGL) consisting of 3-deoxy- γ -gluconolactone and 3-deoxy- γ -mannonolactone and 3-deoxy-gluconic acid methyl ester (DGM). Identification of the products is provided in SI (Figures S1 to S5). A pure sample of THM was isolated from a scaled-up experiment (18 g of glucose, see SI for more information), and NMR spectroscopy was used to confirm the structure on this pure sample.

These new findings enable the catalytic production of new molecules from sugars. THM in particular possesses a very interesting structure, where multiple functionalities are found. Promising applications, for instance, as a monomer or additive to synthesise materials with improved properties, can be foreseen. Earlier studies related to the degradation of sugars under alkaline conditions had reported the presence of *trans*-2,5,6-trihydroxy-3-hexenoic acid in very small amounts (<0.5%).^{37, 38} However, much higher THM yields are reported here (up to 18%).

Effect of the addition of alkali

In order to study the effect of alkali metal salts, 9 wt% solutions of glucose in methanol were reacted at 160 °C with Sn-Beta catalyst (alkali free) in the presence and in the absence of potassium carbonate in methanol (0–1.0 mM solutions) in high pressure glass reaction vessels. The yields of different components were calculated from GC, HPLC and multidimensional NMR spectroscopy and are shown in Figure 2 and are grouped into three main classes, as shown in Scheme 1, based on the type of glycolytic reaction pathway they are formed in: 1) methyl glycosides (MG); 2) retro-aldol reaction products comprising ML, MVG, MMHB and GA-DMA; 3) glycolytic reaction involving dehydration to 3DG and further reaction products comprising furanics ('FUR'), such as HMF, MMF and F-DMA; methyl levulinate (MLA); 3-deoxy- γ -lactones (DGL) as well as THM, which is the main product in this category. These three product categories are respectively termed 'Methyl Glycosides' (MG), 'RA products' and '3DG products' throughout this paper.

It can be observed that the addition of alkali changes the distribution of the products drastically. While the '3DG products' represent almost 35% of the yield in the absence of alkali, 'RA products' become dominant for K₂CO₃ concentrations above 0.1 mM. In the presence of alkali metal salts, the retro-aldol reaction pathway is responsible for about 70% of the overall glucose conversion.

Here, the main products are the C₂–C₄ products methyl lactate (ML, ~50%), methyl vinyl glycolate (MVG, ~18%), glycolaldehyde dimethyl acetal (GA-DMA) and methyl 4-methoxy-2-hydroxybutyrate (MMHB). THM is formed in yields of 6% in the presence of 0.31 mM K₂CO₃, illustrating that carbon flux via the 3DG pathway is still occurring even under these conditions.

Standard deviation was calculated for triplicates of selected alkali concentrations and the results are shown in Table S2. It can be observed that the deviation is below 3% in all the cases, indicating that the results obtained are reliable.

From the results depicted in Figure 2, it is clear that the 3DG reaction pathway is dominant in the absence of added alkali metal salts. In this case, THM is formed in a yield of 14%, together with 6% lactones (DGL) and 13% furanics. The effect of alkali metal salts results primarily from favouring the RA reaction pathway over the 3DG reaction pathway. This might suggest that the glycolytic pathways are affected by the acidic environment in the stannosilicate material. Hydroxyl groups in the near vicinity of the active site, as well as partially-hydrolysed tin-sites have been proposed to constitute the active site in Sn-Beta.^{20, 39, 40} The observed effect of alkali metals is thus likely related to an ion-exchange of these Brønsted acidic sites, as has been hypothesised for comparable materials (TS-1 and Ti-Beta) in various reports.^{41–43} Homogeneous systems involving tin are also affected by the presence of alkali salts, which could indicate a degree of simultaneous homogeneous catalytic activity of the alkali metal salts.^{44, 45}

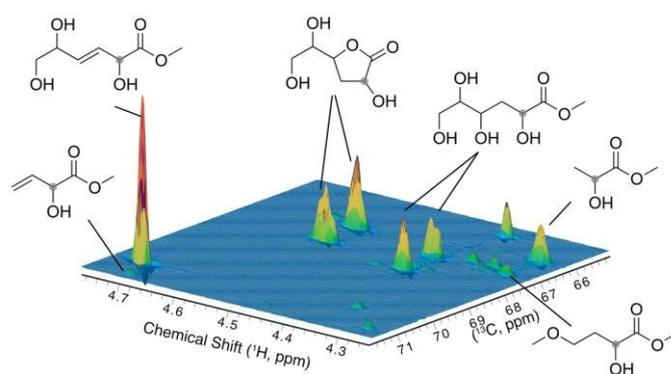


Figure 1. ¹H-¹³C spectral region of secondary alcohol CH-groups (indicated by small spheres) adjacent to carboxylic groups in the displayed compounds of a reaction mixture produced by the catalytic conversion of glucose in methanol at 140 °C. Compounds were identified by homo- and heteronuclear NMR assignment spectra recorded on the mixture.

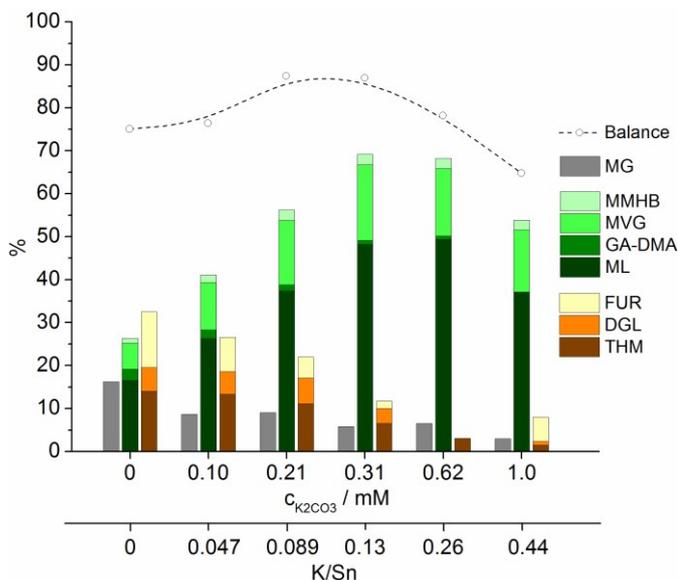


Figure 2. Effect of alkali concentration on glucose conversion by Sn-Beta. Nuances of green and brown are retro-aldol and 3DG products, respectively. Reaction conditions: 0.180 g Sn-Beta (PT, Si/Sn = 125), 0.360 g glucose, 4.0 g of a solution with 0–1.0 mM K_2CO_3 in methanol, 160 °C, 6 h. The data is reported in supplemental Table S1.

For Sn-Beta, the mass balance in the absence of added alkali metal salts is 75% and has an optimum at almost 90% for alkali concentrations between 0.21 and 0.31 mM (Figure 2). For higher amounts of alkali a decrease in the carbon balance to 65% occurs, which is accompanied by a darkening of the product mixture after reaction, as shown in Figure S6. Blank experiments without Sn-Beta both with and without addition of alkali metal salts lead to formation of methyl glycosides (see table S4, entries 4 and 5). Again, the addition of alkali decreased the mass balance considerably, showing that the stability of the sugar is low under alkaline conditions.

ICP analyses of the liquid after reaction in the absence of added alkali indicated the presence of very low amounts of sodium (Na^+ , 4 wt. ppm). This minor contamination was constant in all of the reactions, without any correlation to the addition of K_2CO_3 and is probably due to small amounts of sodium remaining in the catalyst or the borosilicate glassware used for the reactions.

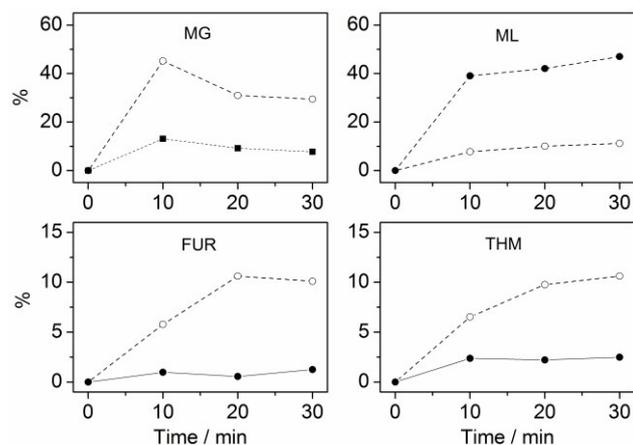


Figure 3. Kinetic experiments on product formation at low conversion with (open circle) and without (solid circle) addition of alkali metal salts. Reaction conditions: 0.180 g Sn-Beta (PT, Si/Sn = 125), 0.360 g glucose, 4.0 g of a solution with either 0 or 0.62 mM K_2CO_3 in methanol, 160 °C. The data is reported in supplemental Table S3.

This alkali should therefore be considered as 'background' alkali and it is likely that higher selectivity via the 3DG pathway than reported here could be reached.

A series of kinetic experiments were conducted in order to better evaluate the effect of the presence of alkali. It is clear from Figure 3 that the addition of alkali ions to the reaction medium modifies the progress of the reaction. The conversion of glucose to methyl glycosides is lowered in the presence of alkali. While almost 50% MG are produced after ten minutes in the absence of added alkali, this amount decreases to 15% when the experiment was performed in the presence of 0.6 mM K_2CO_3 . When attempting to convert the commercially available methyl glycosides (methyl α -D-glucopyranoside, methyl β -D-glucopyranoside and methyl α -D-mannopyranoside) almost no conversion was achieved after 6 h at 160 °C in the absence of added alkali (3–15%, see Table S4, entries 1–3). The formation of MG as pyranosides essentially limits the further reaction towards the desired products. No methyl furanosides were observed, which is in good agreement with previous studies showing that furanosides have an increased reactivity.⁴⁶ Moreover, the rate of formation of ML and the other 'RA products' is substantially increased upon addition of small amounts of alkali. The ML yield increased from 4 to 20% after ten minutes in the presence of 0.6 mM K_2CO_3 . Finally, the formation of furanics ('FUR') and THM was also minimised in the presence of added alkali. The addition of alkali diminishes both THM and furanics in a comparable manner, indicating that they are indeed formed along similar reaction pathways. These kinetic experiments further illustrate the pronounced effect of alkali metal salts and the delicate balance of Brønsted acidity in the Sn-Beta catalyst when using sugars. Selectivity to different products is clearly affected by small changes in acidity of the system.

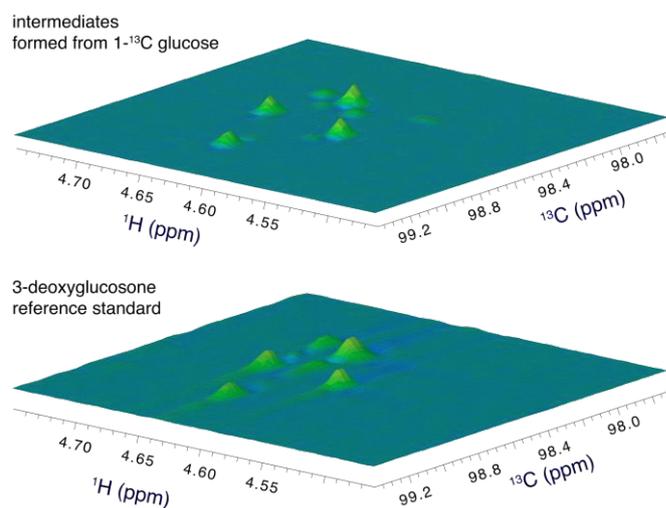
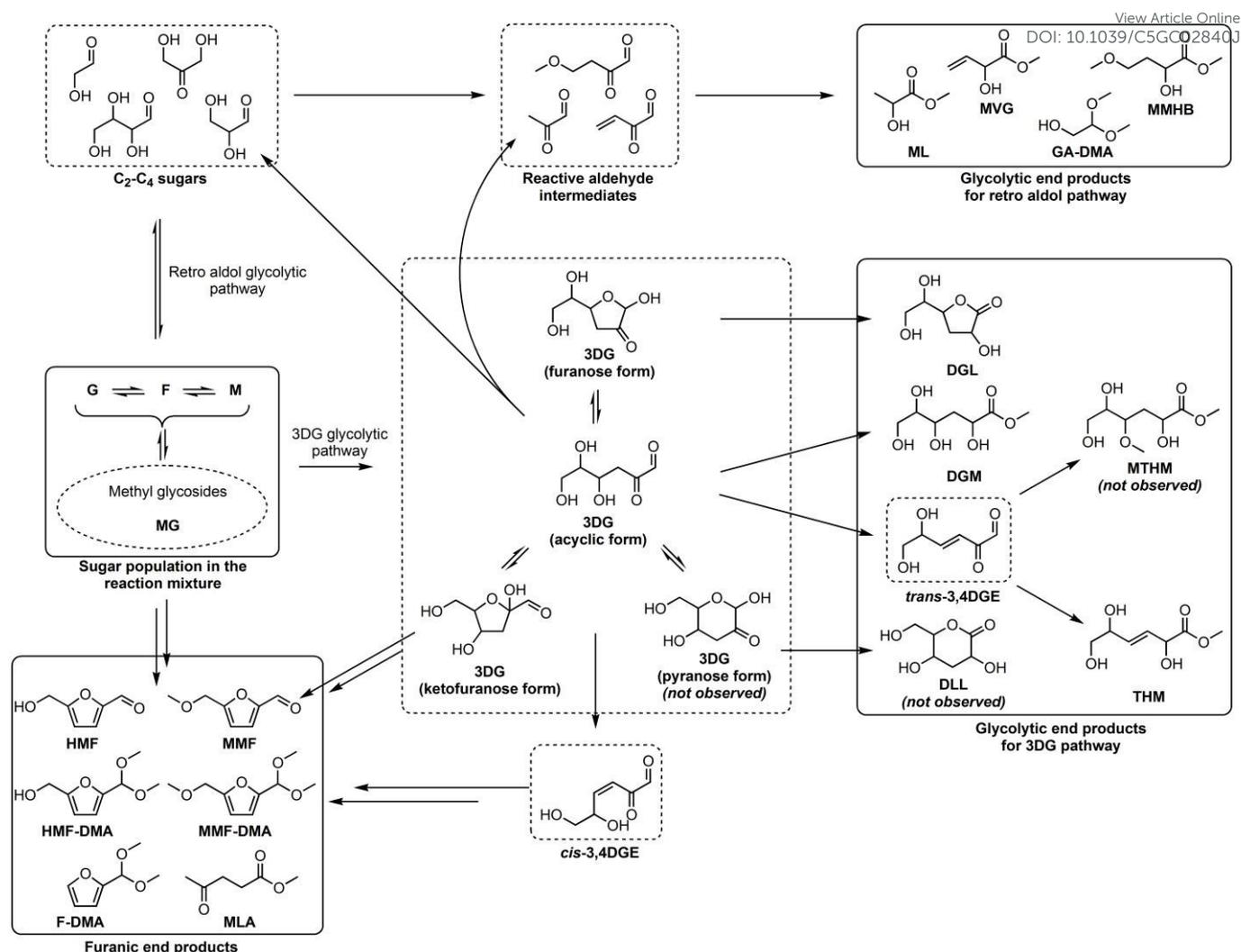


Figure 4. Identification of 3DG as a reaction intermediate by comparison of the acetal region between a reaction mixture and an authentic standard by 2D 1H - ^{13}C HSQC.



Scheme 2. Different glycolytic pathways in the conversion of glucose by Sn-Beta in methanol.

Elucidation of the reaction mechanism

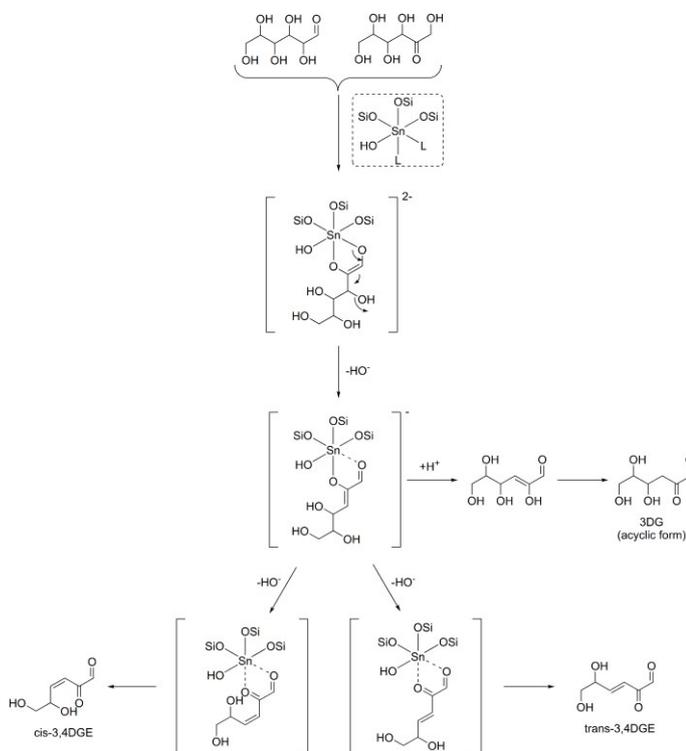
Based on these results, a comprehensive reaction scheme (Scheme 2) can be proposed, in which 3-deoxyglucosone (3DG) is the central intermediate. The presence of 3DG in the reaction solutions was confirmed by direct observation of the methyl acetal of 3DG at incomplete conversion (Figure 4). At full conversion, the presence of 3DG isomers is greatly diminished, confirming its role as a reaction intermediate.

The formation of 3DG from glucose is effectively a β -dehydration reaction that is likely to proceed via a retro-Michael addition of water from the 1,2-enol form of the sugar (Scheme 2). Hence, it is not a dehydration that is likely to be catalysed by conventional Brønsted acid catalysis. This reaction pathway has been suggested by Sels and co-workers for the analogous formation of C₄-compounds from tetroses.¹² The outcome is that glucose is transformed into the enol form of 3DG, which upon tautomerisation is fully converted into 3DG. This dehydration reaction is likely irreversible under the applied reaction conditions in analogy to pyruvaldehyde, which is known not to undergo rehydration to form trioses. In addition, fructose should follow the same reaction pathway once it has enolised on an active tin-site,

since the 1,2-enol form of fructose is identical to the enol form of glucose (and mannose). Hence, the same distribution of end-products for 3DG should be expected from glucose, fructose and mannose.

The further conversion of 3DG can occur via several routes. The most important ones involve further dehydration of 3DG via a subsequent β -elimination of water (Scheme 2) to form 3,4DGE. We have not observed 3,4DGE directly in our reaction mixture, and its presence is hypothesised from the formation of THM and HMF.⁴⁷ We speculate that *trans*-3,4DGE is converted into THM in an analogous fashion as vinyl glyoxal is transformed into MVG, i.e. by addition of methanol to the aldehyde moiety, followed by a 1,2-hydride shift resulting in the formation of the resulting α -hydroxy ester.¹² Interestingly, the THM identified in the reaction product is entirely the *trans*-isomer and no traces of the *cis*-isomer are seen in the reaction mixtures. We speculate that the *cis*-3,4DGE is also formed on the active sites of Sn-Beta, but that it is readily converted into HMF via an intramolecular cyclisation and dehydration reaction, and this is the major source of HMF and other derivatives formed from hexoses (in the absence of strong Brønsted acids).⁴⁷ It is likely that different *cis/trans* ratios are in part defined by the stereochemistry of the C₄ (or more precisely

on the relative stereochemistry of the C₄- and C₅-positions). However, when comparing glucose-fructose-mannose and galactose-tagatose (Table 1), we did not observe any major differences in the ratios of HMF and THM, suggesting that this effect is not significant, if present at all.



Scheme 3. Proposed mechanism for the dehydration of sugars to 3DG.

A minor part of the 3DG does not undergo β -elimination of water, and is instead converted to end-products via 1,2-hydride shift reactions. In methanol, at $T > 140$ °C, 3-deoxy γ -gluconolactone and γ -mannonolactones (DGL) are the main end-products from 3DG in combined yields of about 8%. These are either formed by direct lactonisation of the 3DG furanoside or from methyl 3-deoxygluconolactone, which undergoes lactonisation and elimination of methanol. Addition of methanol to 3,4DGE (Scheme 3) would lead to the formation of 4-methoxy-2,5,6-trihydroxyhexanoic acid methyl ester (MTHM), but this compound is below the detection limit in our reaction mixture.

When using commercial 3DG as substrate, the main products from the glycolytic 3DG pathway (DGL, THM and furanics) are observed as end-products (Figure S7). In contrast to experiments using monosaccharides as substrates, the major products formed from commercial 3DG are a complicated mixture with the two 3-deoxy- γ -lactones being predominant. Small amounts of THM and HMF derivatives are seen from 3DG, suggesting that a commercial sample of 3DG does not fully represent the reactive 3DG formed from monosaccharides in the pores of Sn-Beta. It has been reported previously that 3DG consists of a complex mixture of aldo-furanosides, ketofuranosides and pyranosides in methanol, with very little acyclic 3DG.⁴⁸ It is therefore likely that the product composition of commercial 3DG reflects preformed conformational distributions rather than the inherent reactivity of 3DG formed as a pathway intermediate. Interestingly, the ratio of THM to furanics obtained from 3DG seems to be lower than in the

case of glucose. This means that more furanics are produced from 3DG. This fact supports the hypothesis that most of the furanics produced in the reaction from sugars are indeed formed via 3DG as intermediate, and not directly from sugars. This has previously been confirmed for the formation of furanics via 3DG by Bols and coworkers.⁴⁹

It has been reported that 3DG can undergo a retro-aldol reaction and form glyceraldehyde and pyruvaldehyde (enol form) which are both readily transformed into methyl lactate.⁵⁰⁻⁵² If 3DG is indeed a major source for methyl lactate, then the reaction cascade would greatly resemble the ED glycolysis. From the commercial 3DG sample there was also observed trace amounts of methyl lactate in product mixture (1–2%). Again, the absence of acyclic 3DG in the commercial reference might explain the low amount of methyl lactate obtained. However, due to the complexity of the commercial 3DG used in this experiment, it is not possible to use this direct experiment to determine the extent of retro-aldol reaction products formed via 3DG versus direct reaction from sugars. An indirect indication of the contribution of the 3DG pathway to the production of methyl lactate can be obtained from the effect of alkali addition (Figure 2, data of Table S1). The ratio of methyl lactate to the total amount of 'RA products' has been calculated (ML/RA products). The retro-aldol reaction from 3DG will only lead to ML. The only route for the formation of C₂ and C₄ products is via a 'conventional' retro-aldol reaction of the aldohexoses. An increase in the percentage of methyl lactate will thus indicate the contribution of the 3DG route to ML formation. From the results in Table S1, it is clear that there is an increase in the proportion of methyl lactate (from 63% to 72% of the total 'RA products') when increasing the concentration of alkali (Table S1, entries 1–5). This observed deviation is corroborated by the kinetic experiments shown in Figure 3 (data shown in Table S3), where the percentage of methyl lactate follows the same trend with the addition of alkali (from 59% to 69%). The percentage seems to be independent of the conversion level and it is only related to the amount of alkali added to the reaction medium. Bearing this in mind, we propose that 3DG can be a source of methyl lactate, despite the very low amounts we observed in our experiment using authentic 3DG as a substrate. Further studies are needed to determine the extent of retro-aldol reaction of 3DG and evaluate whether ED glycolysis mechanism has a significant contribution to the formation of methyl lactate using stannosilicates.

Table 1. Conversion of monosaccharides in the absence of alkali using a selection of Beta-framework and/or tin containing catalysts.

Entry	Catalyst	Substrate	Temperature °C	MG %	Retro-aldol products ^a %	3DG products	
						FUR ^a %	THM %
1	Sn-Beta (PT)	Glucose	120	44	4	10	8
2	Sn-Beta (PT)	Glucose	140	21	10	16	12
3	Sn-Beta (PT)	Glucose	160	13	17	13	14
4	Sn-Beta (PT)	Glucose	180	5	26	10	8
5	Sn-Beta (PT)	Fructose	160	9	19	14	18
6	Sn-Beta (PT)	Mannose	160	12	20	12	15
7	Sn-Beta (PT)	Sorbose	160	13	15	14	17
8	Sn-Beta (PT)	Galactose	160	26	10	13	12
9	Sn-Beta (PT)	Tagatose	160	11	11	18	9
10	Sn-Beta (PT)	Sucrose	160	10	22	13	15
11	Sn-Beta (HF)	Glucose	160	8	24	9	16
12	Zr-Beta (HF)	Glucose	160	27	25	2	2
13	Ti-Beta (HF)	Glucose	160	14	28	3	3
14	Hf-Beta (HF)	Glucose	160	35	18	8	4
15	Al-Beta	Glucose	160	32	<1	14	<1
16	deAl-Beta	Glucose	160	86	<1	<1	<1
17	deAl-Beta	Fructose	160	51	2	14	<1
18	Sn-MCM-41	Glucose	160	16	26	13	18
19	Sn-MFI	Glucose	160	40	8	<1	<1
20	SnO ₂ -Beta (HF)	Glucose	160	37	1	2	<1
21	Si-Beta (HF)	Glucose	160	46	3	3	<1

Yields (carbon%) of methyl glycosides (MG), methyl lactate (ML), methyl vinylglycolate (MVG), glycolaldehyde dimethylacetal (GA-DMA), methyl 4-methoxy-2-hydroxybutanoate (MMHB), combined yield of 5-(hydroxymethyl)furfural (HMF), 5-(methoxymethyl)furfural (MMF) and furfural dimethylacetal (F-DMA) denoted FUR and *trans*-2,5,6-trihydroxy-3-hexenoic acid methyl ester (THM) from the conversion of various sugars using a variety of catalysts, different sugars and at different temperatures. Reaction conditions: 160 °C, 360 mg substrate, 4 g methanol, 180 mg catalyst, 6 h, 600 rpm stirring.

a) Combined yield of quantified retro-aldol products (ML, GA-DMA, MVG and MMHB) and furanics (HMF, MMF, MLA and F-DMA). For yields of the individual products see Table S5.

Other important parameters affecting the reaction

Different reaction parameters and catalysts were investigated in the absence of added alkali and the reaction mixtures were analysed thoroughly by HPLC and GC. As can be seen in Table 1

(entries 1–4), the temperature plays an important role. When the reactions were carried out at 120 °C, 40% of methyl glycosides (MG) were obtained as the main product formed at low temperatures. As the temperature increases, 'RA glycolysis' products become dominant. The production of THM reached a

maximum at 160 °C (14%, Table 1, entry 3), while the furanics (FUR) were formed in similar amounts over the temperature range tested.

The effect of the preparation method of the Sn-Beta and the metal incorporated in the framework of the zeolite Beta were also investigated. Characterisation of the catalysts can be found in supplemental Figures S8, S9 and Table S6. A slightly higher yield of 16% THM was observed when using a Sn-Beta catalyst crystallised in a fluoride medium (entry 10) compared to a catalyst prepared by post-treatment of a commercial Beta, which gave 14% THM (entry 3).

Other metals (Zr, Ti and Hf) showed a considerably lower yield of '3DG glycolysis' products (entries 12–14). Only small amounts of THM were observed, suggesting that these catalysts are not highly active catalysts for β -elimination of water. It is interesting to note that only minor changes in product distribution were observed with increase in alkali content with Zr-Beta (see Table S7), indicating that the alkali effect is directly related to the nature of the tin site.

Different Sn-based catalysts were also tested. It was found that Sn-MCM-41 (entry 18) displays a similar reaction profile as Sn-Beta and a substantial yield of THM (18%) was observed for this catalyst. Sn-MCM-41 has also been reported previously to be capable of forming high amounts (~60%) of methyl lactate from sucrose in the presence of alkali metal salts,¹⁹ suggesting that it has a similar catalytic behaviour as Sn-Beta both in the presence and in the absence of alkali. The other stannosilicate material, Sn-MFI, was not very active in the formation of products from hexoses, as has been reported previously and related to its smaller pores limiting its usefulness as a catalyst for the conversion of hexoses.³⁵ As expected, SnO₂ on Si-Beta and pure Si-Beta (entries 20 and 21) were inactive for the formation of both RA products and 3DG products. Using these catalysts, most of the glucose was transformed into methyl glycosides (MG). No THM was observed using Al-containing zeolites as catalysts. Commercial zeolite Beta (Si/Al = 12.5) yielded some FUR (14%) from glucose but the mass balance was low (<50%), illustrating that high concentration of Brønsted acidity catalyses degradation reactions under the applied reaction conditions. At lower temperature it is, however, possible to suppress such degradation reactions and obtain a high carbon balance along with a high yield of fructose.⁴⁶ Using the de-aluminated Beta zeolite, which has been used as the precursor in the preparation of the post-treated Sn-Beta zeotype, resulted in the formation of large amounts of MG and neither 3DG nor RA products were observed. From fructose, some furanics (FUR, 14%) and small amounts of RA products (~2%) were formed as expected, but no THM was observed. It can therefore not be ruled out that residual Brønsted acidity in the finished Sn-Beta zeolite could contribute to the formation of furanics during conversion of the aldohexoses. On the other hand, THM is formed by catalysis involving the Sn-site, clearly demonstrating the unique catalytic properties of tin-containing silicates.

Conclusions

We report a detailed investigation of the glycolytic reaction pathways that are catalysed by stannosilicates. A new glycolytic reaction pathway involving 3DG as the central intermediate was

discovered. This reaction pathway could lead to new ways of converting abundant and cheap glucose into new and interesting chemicals such as THM and 3-deoxy- γ -lactones. In the absence of alkali metal salts, stannosilicates catalyse the β -elimination of water converting glucose-fructose-mannose into 3DG. Under the reaction conditions studied here, most of the 3DG underwent a further β -elimination of water leading to 3,4DGE which was converted into THM (*trans*-3,4DGE) and HMF (*cis*-3,4DGE) and related derivatives. In the presence of alkali metal salts the rate of formation of retro aldol products is increased, making the retro aldol pathway dominant. Further, alkali metal salts reduce the rate of formation of methyl glycosides, thereby effectively leading to more free monosaccharides in solution than in the absence of alkali. It is remarkable that the presence or the absence of ppm levels of alkali metal salts can influence the catalytic properties of stannosilicates so dramatically. From the increase of methyl lactate with respect to the total 'RA products', indirect evidence for a ED type glycolysis pathway has been found. The presence of this alternative pathway may be responsible for the improvement of the yield of ML. We envisage that further control of the active sites of stannosilicate materials such as Sn-Beta will enable a much higher degree of control between these two glycolytic pathways, and thereby enable the low cost transformation of glucose into a variety of chemicals using inorganic catalytic systems.

Experimental

Catalytic tests. Catalytic conversion of sugars was performed in a 5 mL glass microwave reaction vial (Biotage). Typically, 120 mg (0.67 mmol) of glucose (Sigma-Aldrich, >99.0%), 60 mg of catalyst (prepared as described in the supporting information), and 4.0 g of methanol (Sigma-Aldrich, >99.8%) were added to the reaction vial. The reactor was sealed and heated to 160°C under stirring (600 rpm) in a microwave synthesiser (either a Biotage Initiator or a Biotage Initiator+). After 6 h, the reaction was cooled and aliquots were retrieved from the reactor vessel and filtered using a 0.22 μ m syringe filter. In reactions involving alkali-containing solutions, the alkali metal source (K₂CO₃, Sigma-Aldrich, \geq 99.0%) was dissolved directly in methanol before use in the desired concentration.

Analysis. Reaction solutions were analysed thoroughly using NMR spectroscopy and the reaction components were identified. Quantification was performed using NMR spectroscopy, GC-FID/MS and HPLC-RI/DAD. The reported yields of the individual components are carbon yields based on glucose (further information in SI).

The yields of methyl lactate (ML), methyl vinyl glycolate (MVG), glycolaldehyde dimethylacetal (GA-DMA) and methyl 4-methoxy-2-hydroxybutanoate (MMHB) were quantified using a 7890A Series GC system (Agilent Technologies) with a SolGel-WAX column (Phenomenex). No commercial source of MMHB was available and the response factor of MVG was used to approximate the amount of the compound.

Trans-2,5,6-trihydroxy-3-hexenoic acid methyl ester (THM) was identified and quantified by GC-MS on an Agilent 6890 with a Phenomenex Zebron ZB-5 column equipped with an Agilent 5973 mass selective detector. Since no commercial source was available for THM, this compound was purified and used for calibration, see supporting information for purification method.

Methyl levulinate (MLA) was likewise analysed and quantified from GC-MS spectra of the reaction liquids.

For the quantification of furanics an Agilent 1200 series HPLC equipped with an Aminex HPX-87H (BioRad) column (0.004 M H₂SO₄, 0.6 mL/min, 65 °C) using a refractive index and diode array detector was used. During the reaction, any furanics formed will undergo acetalisation with the methanol solvent. These acetals hydrolyse under the acidic conditions during the HPLC analysis and are therefore quantified as 5-(hydroxymethyl)furfural (Aldrich, ≥99%), 5-(methoxymethyl)furfural (Manchester Organics) and furfural (Sigma-Aldrich, 99%) using the appropriate standards.

Sugar conversion as well as an estimation of the remaining methyl sugars were quantified on an Agilent 1200 series HPLC equipped with a Carbohydrate (Zorbax) column (60 wt% acetonitrile/water, 0.5 mL/min, 30 °C). The response factor used for the combined methylated sugar yield was based on an average of the three commercially available methyl sugars; methyl α-D-glucopyranoside (Sigma, ≥99%), methyl β-D-glucopyranoside (Sigma, ≥99%) and methyl α-D-mannopyranoside (Sigma, ≥99%), see supporting information Figure S10. The estimate was additionally verified by NMR of the reaction liquids.

For the discovery of chemicals formed in the stannosilicate-catalysed conversion of glucose, high-field NMR spectroscopy was employed on a Bruker Avance II 800 MHz spectrometer equipped with a TCI Z-gradient CryoProbe and an 18.7 T magnet (Oxford Magnet Technology, Oxford, U.K.). To this end, 10% (w/v) natural abundance glucose in methanol was reacted at 140 °C in the absence of added alkali ions for 6 h in methanol. Subsequently 1 mL of the sample was condensed and re-dissolved in d₄-methanol (99.96 atom%, Sigma-Aldrich, St. Louis, MO). Standard homonuclear 1D, 2D COSY and 2D TOCSY were carried out on the non-enriched sample in addition to heteronuclear ¹H-¹³C HMBC and highly ¹³C resolved ¹H-¹³C HSQC and ¹H-¹³C HSQC-TOCSY spectra. All spectra were recorded at 30°C. Identification of compounds in the reaction mixture was aided by the use of pure reference standards (including 3DG, monosaccharides, methyl-glycosides, furanics and methyl lactate).

The NMR quantification of identified compounds in reaction mixtures was performed by addition of 10% d₄-methanol to 500 μl of reaction mixture and subsequent ¹³C 1D NMR spectroscopy sampling 16384 complex data points during an acquisition time of 1.6 seconds and using a recycle delay of 58.4 seconds between 400 scans. This method was used for verification of other analysis procedures and quantification of 3-deoxy-γ-lactones (DGL).

The metallosilicate materials used were synthesised according to previously published procedures.^{21, 22, 26, 27} More details on each individual synthesis and characterisation are included in the supporting information.

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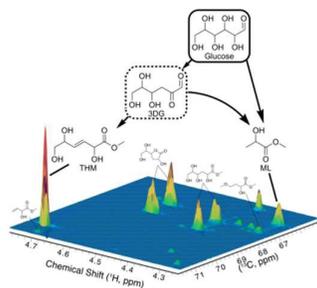
spectra were recorded on the spectrometer of the Danish National Instrument Center for NMR Spectroscopy of Biological Macromolecules at the Technical University of Denmark.

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We identify a glycolytic pathway through 3-deoxyglucosone using Lewis acid catalysts resulting in the formation of bio-based monomers.