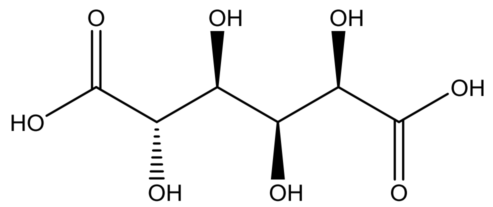
UK BioChem 10 – 8 Glucaric acid

Name	D-Glucaric acid
Synonyms	Saccharic acid
CAS Number	87-73-0
Molecular formula	$C_6H_{10}O_8$
MW	210.14 g mol^{-1}
Patents related to synthesis	20



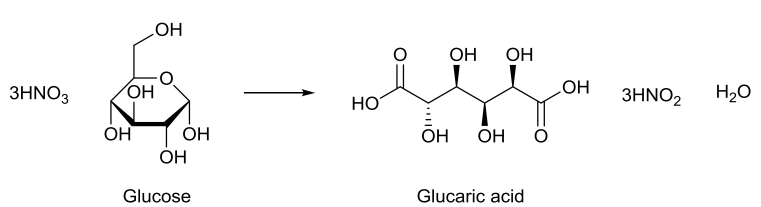
Why is it of interest?

Glucaric acid is a polyhydroxy dicarboxylic acid which is accessed from the oxidation of glucose. Glucaric acid has been known of for a long time and there are a number of applications for it directly, in addition to its use in a number of routes to bio-derived drop in replacements, such as to adipic acid for nylon 6-6 production. However, despite being identified as a significant platform molecule by the US Department of Energy,[1] it has yet to reach its potential due to the moderate selectivity and yield of the current industrial route.[2] If more efficient pathways can be brought to industrialisation, glucaric acid markets in food, pharmaceuticals and as a building block are expected to grow significantly.

Feedstocks for glucaric acid

The molecular formula for glucaric acid is very similar to that of glucose, having two more oxygens and two less hydrogens, as well as preserving the chirality of the sugar. As such, any feedstock must be converted to glucose before being utilised to form glucaric acid. All chemocatalytic pathways thus far reported start from a pure glucose stream although there is no reason why more complex starches or cellulose itself could not be employed. Fermentation pathways directly to glucaric acid thus far reported have also only used glucose as the carbon source. Again there is no reason to assume other methodologies to produce free sugars would not function. Routes to gluconic acid however have been shown in good yield from a variety of feedstocks including waste paper.[3] Gluconic acid conversion to glucaric acid can proceed in moderate yield.

Highlighted routes of production



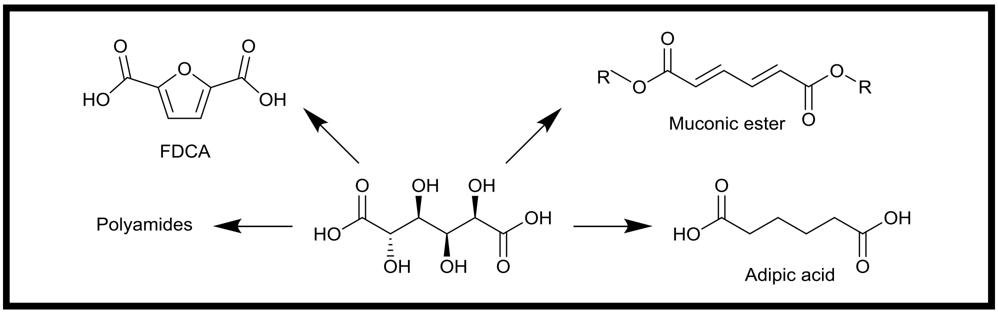
Glucaric Acid was first identified in 1888 through acid treatment of sugar.[3] This methodology has been refined and patented, utilising nitric acid as both the oxidant and solvent, with the addition of catalytic sodium nitrate to ease thermal control. Total conversion of the sugar is observed, with the excess nitric acid recovered and recycled, while the crude product is neutralised with sodium or potassium hydroxide and glucaric acid isolated in its mono-salt form. Yields here are 46.9% (AE 56.9%, RME 24.1%) and this is the method of synthesis for commercial glucaric acid production. Further investigation into this methodology has been undertaken, including real time reaction monitoring, use of oxygen to reform nitric acid and improved work up, although yields were similar to those previously reported.[4] More recently a range of other precious metal catalyst and conditions have also been investigated, with the highest yield of 74% being reported using platinum on carbon with oxygen as the oxidant, although still with total conversion of glucose and range of side products.[5] Away from chemocatalytic routes, synthetic biology has allowed for the production of a pathway to glucaric acid to be constructed in *E coli*. Here the oxidants are water and oxygen, with glucose converted to myo-inositol and then glucuronic acid as intermediates. Best yields reported thus far are 56.7% (AE 84.7%, RME 47.9%).[6]

Current applications of glucaric acid

The current largest market for glucaric acid is in water softening, where the chelating ability of glucaric acid has also seen it be applied in water treatment and detergent formulations.[7] Similarly another metal scavenging application is the inclusion of glucaric acid and its salts in de-icing technologies where its presence hinders corrosion of iron/steel materials.[8] Other uses are as a food supplement where it has been shown to have many beneficial properties. Mammalian studies showed a diet high in glucaric acid significantly reduced cholesterol levels in rats, specifically that of LDL and serum cholesterol.[9] More significantly, it has been shown to be active in anti-cancer applications, specifically reducing levels of carcinogenesis.[10]

Future markets and applications

As with a number of platform molecules, one of the highest volume markets for potential applications is conversion to adipic acid for use in the production of bio-derived nylon 6-6. This requires dehydration to remove the 4 secondary alcohols (as water) followed by hydrogenation of the alkene functionality formed which is not very atom ecconomical.[11] Dehydration with the loss of 3 equivalents of water gives FDCA (BioChem 10 – 2) in reasonable yields (68%).[12] Similarly reaction of glucaric acid over a rhenium catalyst with an alcohol as solvent and reactant gives the respective ester of muconic acid (BioChem 10 – 5) in up to 71% yield.[13] Both of these compounds can be used to give a variety of other products, most notably polyester plastics such as PEF and PET. Glucaric acid can also be applied directly in the production of polymers; the reaction with diamines gives rise to a range of polyamides, both aromatic and aliphatic.[14] Protection of the secondary alcohols prior to polymerisation gives rigid 5 membered rings along the polymer backbone. This results in the production of polyamides with significantly greater glass transition points for high temperature applications.



References: **1.** www.nrel.gov/docs/fy04osti/35523.pdf, **2.** WO2008021054A2, **3.** DOI.org/10.1002/jlac.18882450102, **4.** DOI.org/10.1016/j.carres.2011.12.024, **5.** DOI.org/10.1039/C6GC00460A, **6.** DOI.org/10.1016/j.enzmictec.2016.05.009 **7.** EP0892040A2, **8.** US20120119152A1, **9.** DOI.org/10.1016/0271-5317(96)00045-0, **10.** DOI.org/10.1177/1534735403002002005, **11.** US20100317823A1, **12.** WO2019014393 (A1), **13.** DOI.org/10.1002/anie.201307564, **14.** DOI.org/10.1002/app.47255, US2009131259 (A1), **15.** DOI.org/10.1016/j.polymer.2017.07.069

Additional feedstocks

As only glucose has been applied in the production of glucaric acid, the feedstocks will be limited to primary biomass. Here this class of feedstock has been investigated to determine how much would be required to supply a 20 kton glucaric acid plant.

The chemo-catalytic pathway to glucaric acid should function with any free sugar, including depolymerised cellulose. If sufficiently robust, the bio-catalytic *E.Coli* fermentation could also use similar feedstocks as carbon source. However until this has been demonstrated, the lack of data in this area means that this method should be treated as unfeasible.

First generation biomass

The crops presented are those that are most intensively farmed in the UK, principally as food crops, although a small percentage of wheat, maize and sugar beet are also utilised in industrial applications. Sugar cane figures are from Brazil.*

crop	ktons needed to supply a 20 kton glucaric acid plant	ktons produced per annum (UK)	% required
wheat	47.6	14837	0.32
barley	47.6	7169	0.66
maize	46.9	3054	1.54
sugar beet	204.3	8325	2.45
potatoes	198.4	5075	3.91
field beans	192.9	965	19.99
oats	52.6	875	6.01
sugar cane*	347.2	666925	0.05