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Synthesis of Isosorbide: Overview of challenging reactions

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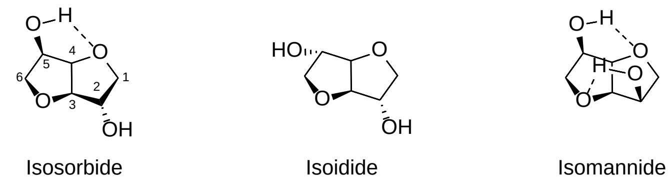
Isosorbide is a diol derived from sorbitol and obtained through dehydration reactions that has raised much interest in the literature over the past decades. Thus, this platform chemical is a biobased alternative to a number of petrosourced molecules that can find applications in a large number of technical specialty fields, such as plasticizer, monomer, solvent or pharmaceutical. The synthesis of isosorbide is still a technical challenge, as several competitive reactions must be simultaneously handled to promote a high molar yield and avoid side reactions, like degradation and polymerization. In this purpose, many studies have proposed innovative and varied methods with promising results. This review gives an overview of the synthetical strategies and catalysts developed to access this very attractive molecule, pointing out both the results obtained and the remaining issues connected to isosorbide synthesis.

1. Introduction

Isosorbide is a 1,4:3,6-dianhydrohexitol industrially produced from the double dehydration of D-sorbitol. It is noteworthy that D-sorbitol is obtained from the hydrogenation of glucose, a readily accessible starting material obtained from the hydrolysis of starch, and in a lesser extent, sucrose or cellulose. This molecule has thus a high production potential in comparison to isomannide and isoidide, two 1,4:3,6-dianhydrohexitol isomers that are obtained from D-mannitol and L-iditol (Scheme 1). Isosorbide is a chiral renewable diol with a V-shaped backbone composed by two fused furan units. The chirality arises from the asymmetric carbons of the D-sorbitol molecule whose chirality is retained during the dehydration steps. The two hydroxyl groups are not equivalent and bear somewhat different reactivities. The hydroxyl group in the endo position is sterically shielded and more acidic than the second less sterically hindered hydroxyl groups on the exo-position.[1] The difference of acidity is explained by the intramolecular hydrogen-bonding between the endo-hydroxyl group and the closely located furanic oxygen.[2-6] This difference between the two hydroxyl groups of isosorbide allows the selective monofunctionalization of the diol. Isosorbide can be selectively monotosylated[6], alkylated[7, 8] or acetylated[9-11]. Because of the fused skeleton structure composed of the two furan units, the overall structure is rigid and this particular feature is at the source of its originality in comparison to more flexible diols such as glycols, 1,3-propanediol or 1,4-butanediol that are actually essentially obtained from non-renewable resources. Of strong significance in a context of green chemistry, isosorbide is a biobased platform molecule highlighted as an alternative to a number of petrosourced compounds. Up to now, isosorbide has been used to access a large panel of molecules with relevant applicative properties and industrial reality (Scheme 2).[12] Isosorbide dinitrate is used since several decades as vasodilator.[13, 14] The dimethyl isosorbide is for example used as solvent in cosmetics[15-17] and isosorbide diesters[18-22] are actually industrially produced and commercialized as surfactants[23-27] and PVC plasticizer[28, 29]. The rigid scaffold associated to the bifunctionality of the molecule has attracted a strong interest in the field of polymers chemistry. Isosorbide and derivatives have thus been shown as suitable monomers for the industrial production of polycarbonates[30, 31], polyesters[32-41] or polyamides[42-44], with attractive applicative properties. For example, isosorbide allows the increase of Tg, improves the scratch resistance and gives excellent optical properties to polymers. Polyesters and polycarbonates containing isosorbide have now commercial developments in food packaging, spray container, automotive, material for electronic devices … .



Scheme 1 Structures of dianhydrohexitols.

As isosorbide production should largely increase in the future due to its actual and potent industrial applications, efficient synthesis is a real challenge. Taking into account the large

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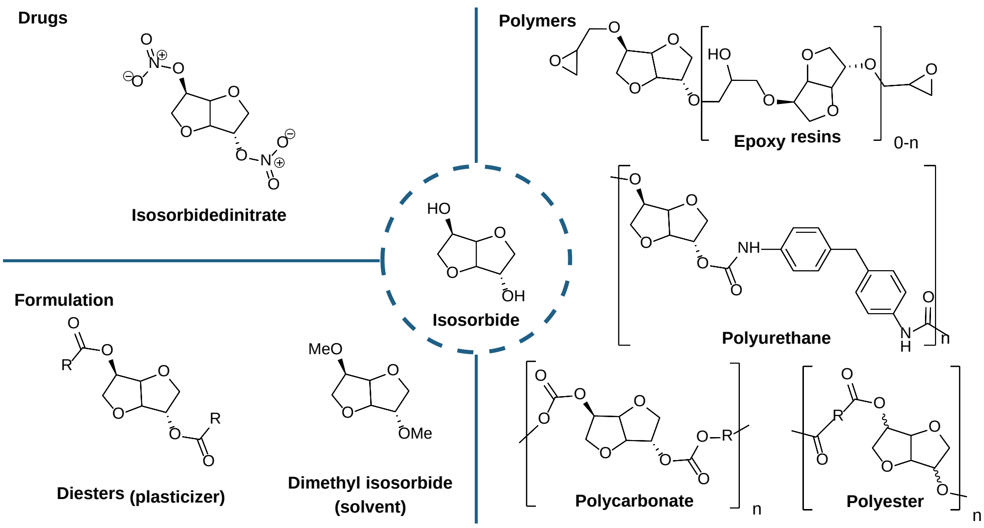


Scheme 2 Applications of isosorbide derivatives

industrial production of this molecule, further yields improvements would be clearly economically relevant. This review describes all the achievements in isosorbide synthesis. The first section will first focus on the mechanism of dehydration from sorbitol to isosorbide. This part emphasizes the selectivity issues associated to the double dehydration of sorbitol. The following sections describe the homogeneous catalysts and heterogeneous catalysts that have been developed and evaluated in sorbitol dehydration. A last section gives the most recent results concerning the direct access to isosorbide from glucose and cellulose.

2. Mechanism of the dehydration reaction of sorbitol

The synthesis of isosorbide is a two-steps reaction process from glucose. Glucose is first hydrogenated into sorbitol according to very large scale processes that are well established and cost-effective.[45-47] The key step to isosorbide is then the double dehydration of sorbitol that requires complete conversion and selectivity. This dehydration process is promoted by acids that are discussed in the following sections. However the reaction is well known to lead to the formation of several side-products that are due to chemo- and regioselectivities issues. The resulting side reactions largely contribute to non-quantitative overall yields in diol. Considering the structure of sorbitol, several dehydration products can be indeed obtained from the first dehydration step (Scheme 3). The productive pathway in the synthesis of isosorbide implies the first formation of 1,4-monoanhydrosorbitol (1,4-sorbitan) or 3,6-monoanhydrosorbitol (3,6-sorbitan). The former is generally produced as the main reaction intermediate and its formation is the first step of the synthetic pathway that leads to isosorbide formation after the internal second dehydration step. The latter is generally observed in very low amount. In comparison to the first step, the second step of 1,4-monoanhydrosorbitol dehydration requires higher reaction temperatures and reaction times at such point that under soft reaction conditions, the monoanhydrosorbitol isomers (also called sorbitans) can be isolated as main reaction products.[48] Kinetics have been measured for the dehydration of sorbitol by three different groups and the reaction rates have been measured for the dehydration of sorbitol with sulfuric acid (Table 1 and Scheme 3).[49-51]

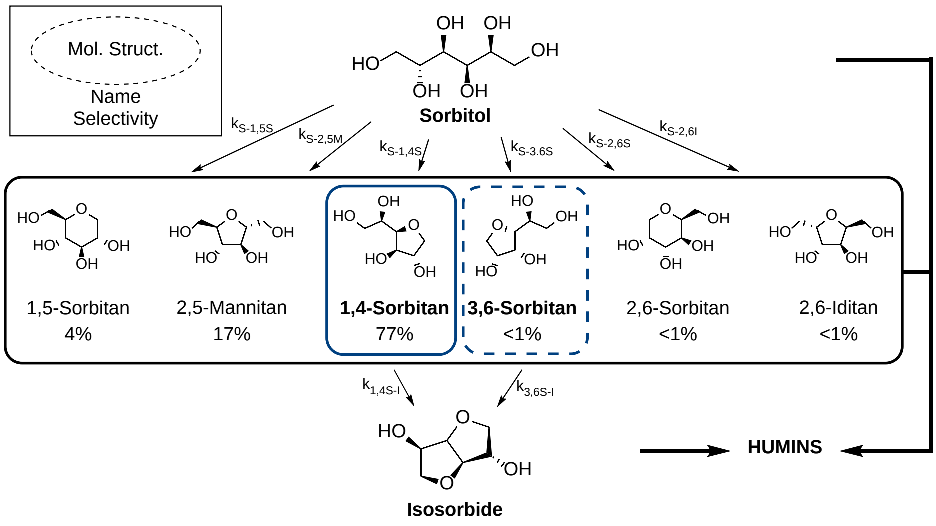
Table 1 : Measured rate constants (h^{-1}) during dehydration of D-sorbitol.

k_0	$k_{S-1,4S}$	$k_{S-3,6S}$	$k_{S-2,6I}$	$k_{S-2,5M}$	$k_{1,4S-I}$	$k_{3,6S-I}$
0.109	0.092	0.008	0.007	0.002	0.0059	0.136

Conditions: Sorbitol (2.9 g) in 3 M sulfuric acid (6.6 mL) at 104°C

k_0 = rate constant for the disappearance of D-Sorbitol (h^{-1})

From these values, it appears that 1,4-sorbitan is formed more rapidly and dehydrated slowly whereas 3,6-sorbitan is formed



Scheme 3 Isosorbide production from sorbitol, synthesis and limitations. Note that intermolecular dehydrations can occur at any step to form “humins” compounds.

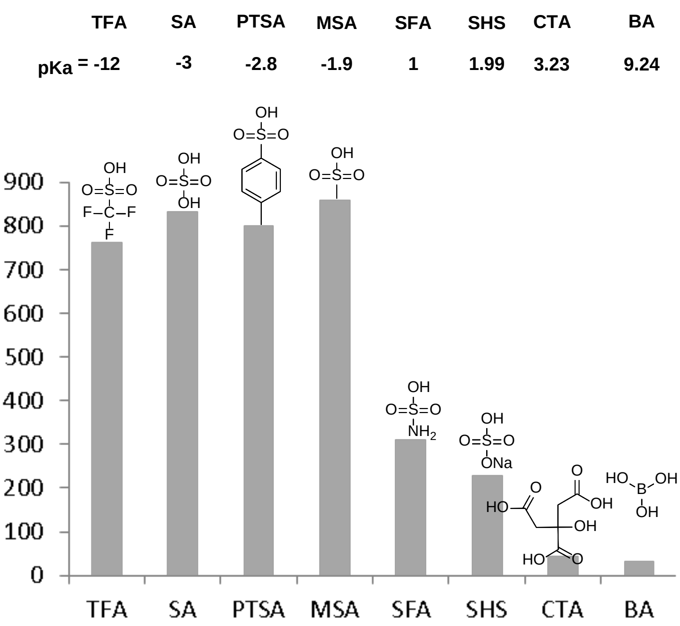
rather slowly but rapidly dehydrates to isosorbide. The more recent work from Yabushita *et al.* explains an overall reaction rate faster for the first dehydration in comparison to the second from a higher association constant between sulfuric acid and sorbitol compared to the association constant between sulfuric acid and 1,4-sorbitan.[51] This difference of association constants would be thus at the origin of the sequential synthesis of 1,4-monoanhydrosorbitol and isosorbide.

The commonly accepted mechanism involves SN_2 substitution reactions with a protonated hydroxyl group as leaving group. This mechanism is often observed in the general case of tetrahydrofuran formation from the dehydration of 1,4-butanediols and explains the high stereoselectivity of the cyclisation reactions. All the other possible isomers formed during the first dehydration reaction irremediably lead to the formation of side products that largely account to decreased overall yields in isosorbide. Most of them are converted into polymeric structures so-called "humins" with undefined structures and a dark brownish colour that limits further industrial uses. It is noteworthy that 1,4-monoanhydrosorbitol or 3,6-monoanhydrosorbitol and isosorbide itself can also be involved in oligomerization processes in order to form oligomeric / polymeric by-products. Both selectivities on the first and second dehydration steps thus contribute to limited yields (commonly lower than 75 %).

3. Sorbitol dehydration via homogeneous catalysis

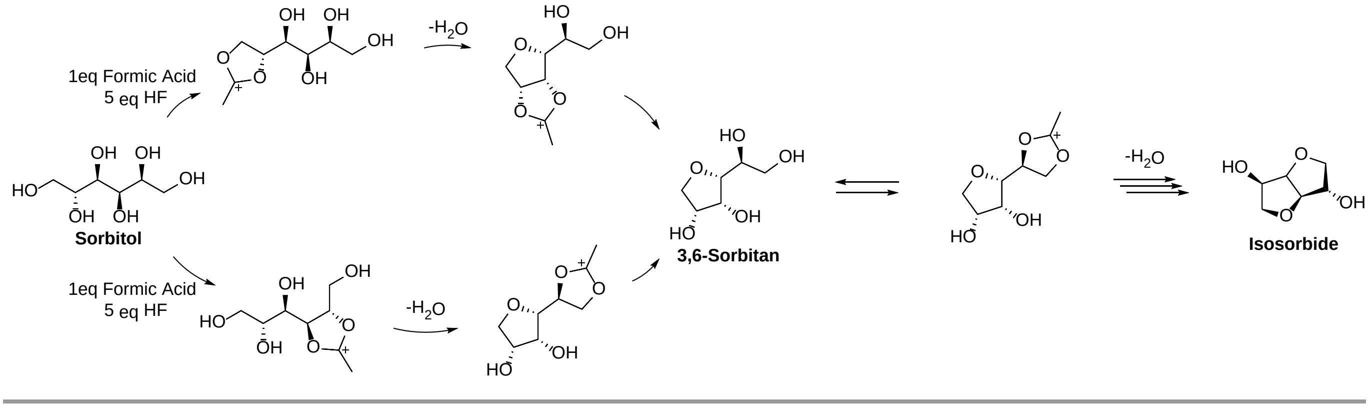
3.1 Brønsted acids

Strong acids are needed to efficiently protonate hydroxyl groups of sorbitol and thus generate water as leaving group in the nucleophilic substitution. Mineral acids have been very early used in the synthesis of isosorbide. The parent substrate, isomannide obtained from mannitol has for example been synthesized in 1884 by Fauconnier from the use of sulfuric acid.[52] The synthesis of isosorbide with sulfuric acid has been early patented in 1930.[53] Other mineral acids were compared with sulfuric acid in 1986.[54] Hydrochloric acid, whose use has been elsewhere patented[55], showed a comparable isosorbide yield to sulfuric acid after 20 h of reaction at 135 °C but it should be noticed that this acid is in general less suitable as it readily distils with water under low pressure reactions. Phosphoric acid did not lead to a complete conversion of sorbitol under the same reaction conditions. Dabbawala has confirmed this first work by comparing the turn over frequencies of acids that bear various acid strengths (Scheme 4).[56] Mineral and organic acids were both used in this study. PTSA and trifluoromethane sulfonic acid gave turnover frequencies that compared well with those obtained with sulfuric acid. Strong acids with pKa below -1.7 showed similar reactivities whereas weaker acids with higher pKa values showed lower. Most of the evaluated acids did not show any catalytic activity with pKa values below 3. It is however noteworthy that in the presence of a stoichiometric amount of chloropyridinium salt (pKa = 5.2), the reaction proceeds and leads to a mixture of sorbitans and isosorbide after 20 h at 160 °C.[57] Weaker acids can also be used providing that higher reaction temperatures and microwaves are used to promote the reaction. It has been for example shown that at 210 °C under microwave irradiation in a water/ dioxane solution with $NaHSO_4$ (HSO_4^- / SO_4^{2-}, pKa = 1.9) as acid, sorbitol is readily converted into isosorbide after 90 min.[58]



Scheme 4 TOF calculated during dehydration of sorbitol into isosorbide with various Brønsted acids.

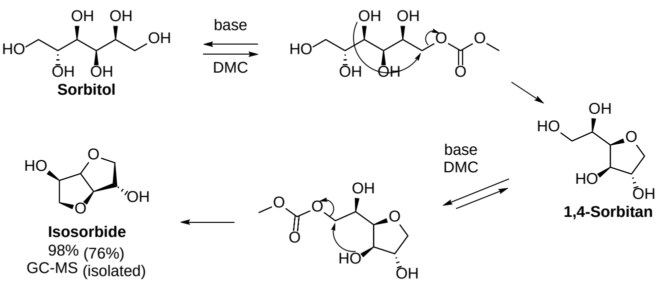
Mixtures of acids have also been used to promote the



Scheme 5 Acetoxonium synthetic pathway described by Defaye et al. [59,60].

synthesis of isosorbide from sorbitol: Organic acids such as formic acid or acetic acid have been used in combination with fluorohydric acid HF at room temperature.[59, 60] The yield determined by ^{13}C analysis of the crude evidenced the full conversion of sorbitol in isosorbide (95 %) and the product was finally isolated with 57 % yield. Very interestingly, this example shows a very different selectivity in sorbitans after the first dehydration step. With this cocktail of acids, 3,6-sorbitan is intermediately formed as main sorbitan whereas with more conventional acids, this isomer is generally not observed. This observation is explained by the intermediate formation, with acetic acid in anhydrous HF, of acetoxonium ions observed by ^{13}C NMR (Scheme 5). Nevertheless, as several acetoxonium ions are formed in the case of sorbitol, this unusual selectivity could not be clearly explained. The use of leaving groups has been tackled by different research groups. The dehydration of sorbitol diesters, obtained from the reaction between sorbitol and an acetylating reagent such as acetic acid, acetyl chloride or acetic anhydride, has been patented.[61] The procedures directly led to the isolation of anhydrohexitol diesters that can be further hydrolysed. The mixture is finally composed of mainly isosorbide (ca 80 %) along with 7-12 % of dianhydromannitol and 6-9 % dianhydroiditol.

Numerous patents applications using Bronsted acids for isosorbide production are regularly submitted. Most recent describe more complex catalytic systems using mixture of acids.[62] Methods and processes are also very challenging in that field in order to reduce production costs. Recent advances describe dehydration continuous process using hot steam[63] or a two-step decomposed reaction.[64]



Scheme 6 DMC pathway.

Interestingly, the combination of sorbitol with dimethylcarbonate DMC (transcarbonatation) followed by an intramolecular nucleophilic substitution under basic conditions at reflux in methanol led to the formation of isosorbide with high yields (Scheme 6).[65, 66]

High conversions with low amounts of polymers have been patented with organic acids under hydrogenation conditions (P H_2 and metallic hydrogenation catalysts) at 270°C. Although complete conversion of sorbitol led to yields in isosorbide lower than 50 %, it is noteworthy that low contents of oligomeric / polymeric by-products have been obtained.[67] The reductive conditions with H_2 are often shown as suitable to reduce the colour of the reaction crude.

Table 2 Dehydration of sorbitol in presence of metal triflate salts.

Acid	Sorbitol Conversion (%)	Yield (mol%)		
		Isosorbide	1,4-Sorbitan	2,5-Sorbitan
$Bi(OTf)_3$	99	25	60	9
$In(OTf)_3$	100	31	56	10
$Sc(OTf)_3$	97	15	68	8
$Ga(OTf)_3$	100	71	8	6
$Sn(OTf)_3$	86	11	69	7
$Al(OTf)_3$	100	26	59	9
H_2SO_4	69	4	54	6

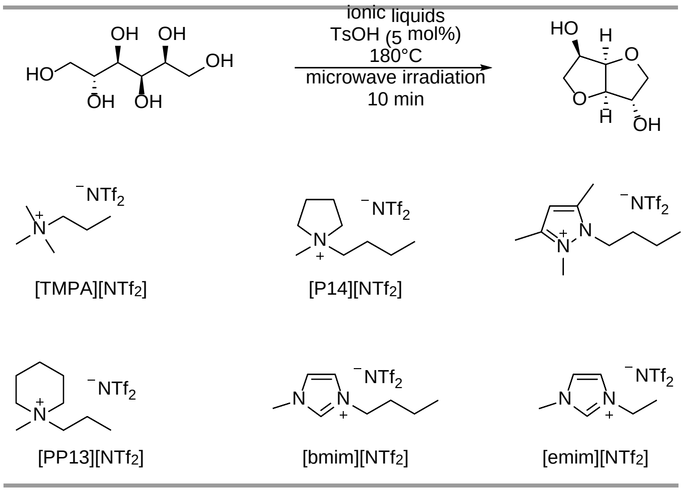
Reaction conditions : 100 g sorbitol, 0.05 mol% triflate salt, 160°C, 5 mbar, 1h

3.2 Lewis acids

Lewis acids are widely used as catalysts in organic synthesis. Fleche et al. early used Lewis acids such as $AlCl_3$ and $SnCl_4$ to convert sorbitol into isosorbide.[54] The Lewis acids with chlorides as counter anions however showed lower reactivities compared to sulfuric acid. Among the Lewis acids used in organic synthesis, metal triflates, in particularly those with rare earth metals, are interesting candidates even in the presence of water (Table 2).[68, 69] Bismuth (III) triflate (3.6 mol %) has been efficiently used to promote the synthesis of isosorbide from sorbitol at 150 °C for 16 h with 85 % yield.[70] This work has been shortly followed by a patent that gives a comparison between the catalytic activities obtained with various Lewis acids in comparison to sulfuric acid.[71] The reactions were performed at 140 °C for 2 h with 0.1 mol % and 1 h at 150°C with 0.01 mol % of catalyst. With these conditions, the conversions of sorbitol were higher with $Ga(OTf)_3$, $Sc(OTf)_3$, $Al(OTf)_3$, $In(OTf)_3$, $Bi(OTf)_3$, $Al(OTf)_3$, $Sn(OTf)_3$, than with sulfuric acid.

3.3 Synthesis of isosorbide in water or ionic liquids

The dehydration reactions are classically performed under solvent free conditions as sorbitol melts at 95 °C and water is continuously removed through a distillation at low temperature. An alternative approach involves the use of water as reaction solvent. As water is also the product of reaction, the use of aqueous media to perform the reaction often leads to limited reaction rates. However, it has been shown that under high temperature conditions, the self-ionization of water is sufficient to promote the dehydration process. In that case, no additional acid is needed thus avoiding, during a workup, the use of bases to neutralize the reaction medium prior to isosorbide isolation.[72, 73] The yield of isosorbide reaches 57 % yield at 315°C after 2 hours of reaction ([sorbitol] = 1 $mol.L^{-1}$) and the addition of CO_2 of at least 300 MPa could accelerate the reaction rate.[74] In that latter case, carbonic acid probably acts as a weak acid.



Scheme 7 Ionic liquids used in dehydration of sorbitol.

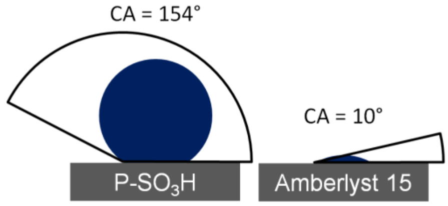
As an alternative to melted sorbitol or water, ionic liquids (Scheme 7) have also been used as solvents of reaction. Ionic solvents, due to their high polarity, are suitable to solubilize hydrophilic polyols such as sorbitol. $ZnCl_2$ molten salt hydrate medium allows an efficient solubilisation and conversion of sorbitol into isosorbide without any additional co-catalyst.[75, 76] The yield determined by HPLC after 270 min at 200 °C (1:12 weight of sorbitol in 70% weight of $ZnCl_2$ in water) reaches 85%. The reaction was in that case strongly favoured, according to molecular modelling,[77] by the zinc centre that a) enhances the leaving group ability of the primary OH-group through coordination of sorbitol and b) coordinates the released molecule of water. Hydrophobic ionic liquids have also been used as reaction media.[78] The reactions were promoted by 5% of PTSA at 180°C under microwave irradiation and afforded 50-60 % yields depending on the ionic liquid used. Interestingly, the hydrophobic ionic liquids could be reused thanks to an extraction with dichloromethane (100 mL for 2.5 g of ionic liquid) while isosorbide was readily solubilized in water. More recently, new catalytic systems using Bronsted acidic ionic liquids have been developed for isosorbide synthesis from sorbitol.[79] These compounds have shown very interesting results with a 75% isosorbide yield during 5 consecutive runs. These results show interesting perspectives in order to develop a continuous process for isosorbide production.

4. Sorbitol dehydration via heterogeneous catalysis

The recycling of the catalyst is a key issue in dehydration reactions. Acidic homogeneous catalysts tend to be corrosive for the reactors and have to be ultimately separated from isosorbide. Taking into account these drawbacks, several heterogeneous alternatives have been employed to promote the dehydration reaction. Heterogeneous catalysts advantageously allow the separation of catalysts from the products through a simple filtration. Moreover, the filtrated catalyst can be reused in a further dehydration reaction or continuously used.

4.1 In the presence of acid resins

Early article from Goodwin reports attempts of dehydration of sorbitol with Amberlite IR-120 (33 % weight / sorbitol).[80] An organic co-solvent was used and isosorbide was obtained, at reflux of dioxane/ethyl acetate (1/1: v/v) for 24 h, with 39 % yield after distillation. 57 % of isolated yield was later obtained with similar catalyst loading by using solvent free conditions and harsher reaction conditions (170°C for 2 h under 10 mmHg).[50] These results have rapidly attracted a strong interest concerning applicative synthetic approaches as shown by the patents literature. Batch reactors [81] and fixed bed reactors[82, 83] have been in this context used. 74 % yield of isosorbide has been reported with Amberlyst 35 after 2 h at 135 °C under 10 mm Hg. Clearly, it turns out from the reported results that higher acid loadings are needed if sulfonic resins are used. More activating conditions based on the use of microwave irradiation have thus been investigated. In sorbitol medium with 2% of Amberlyst 15 system, the microwave power is efficiently converted into heat, thus allowing energy saving in comparison to thermal heating.[84] Moreover, it has been observed that performing the reaction under microwaves allows enhancement of the reaction rates of a factor 20 to 34 in comparison to simple thermal activation.[85] The selectivity of the reaction toward isosorbide remains however limited to similar values whatever the heating system used. Catalysts recycling or continuous processes are limited by catalysts poisoning. One expects the oligomeric / polymeric by-products formed in the course of the reaction obstruct the pores of the solid material. Accordingly, washing cycles with organic solvents is used for the regeneration of the catalyst.[82]



Scheme 8 Water droplet contact angle on hydrophobic P-SO_3H and Amberlyst 15.

New hydrophilic sulfonic acid-functionalized micro-bead silica catalysts named SA-SiO_2 gave complete sorbitol conversions and high isosorbide selectivities (up to 84%, determined by HPLC).[86] The catalyst was reused 10 times without noticeable loss of activity and selectivity. The excellent performance of this catalyst was attributed to its suitable large pore diameter and high surface hydrophilicity.

The commercially available sulfonic resins are hydrophilic. It has elsewhere been postulated that more hydrophobic resins, with lowered charges of sulfonic groups, would favour the dehydration step (Scheme 8).[87] Such materials have been synthesized according to a solvo-thermal co-polymerization of styrene and divinylbenzene followed by ion-exchange with an aqueous solution of H_2SO_4. The catalytic activities were higher with this material in comparison to the results obtained with Amberlyst 15 or sulfuric acid. Moreover, the hydrophobic resin turned out to be more recyclable.

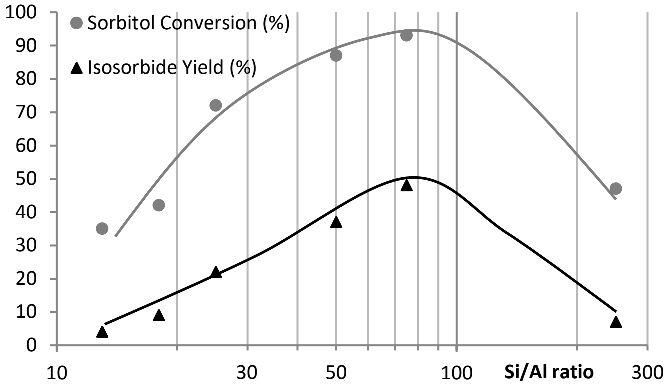
More recently, other commercial Purolite and Amberlyst type resins were evaluated for isosorbide production from sorbitol.[88] Authors have shown isosorbide yields of up to 75% with almost no loss of activity after 4 catalytic runs. Isosorbide esters synthesis starting from sorbitol and using sulfonic resins have been recently reported with interesting yields.[89] Authors noticed a 83% isosorbide yield with Nafion-Type resins under mild conditions (1%mol catalyst, 130°C for 24h under 0.3 mbar vacuum). This system is reported to promote both dehydration and esterification reactions.

Very recently, propyl sulfonic acid functionalized mesostructured SBA-15 silica have been used to promote the dehydration of sorbitol to isosorbide, in melted phase, under atmospheric pressure.[90] These materials were prepared with different acid capacities and modified with different types of methylsilane functionalities, leading to isosorbide productions, over 70% in the optimum case. Nevertheless, catalyst recycling led to a loss of catalytic activity even after regeneration of the catalyst by washing procedures.

Magnetic sulfonic acids are accessible from the reaction between glucose, $FeCl_3$ and PTSA followed by calcination at 140°C. The acidic material baptized Glu-Fe_3O_4-SO_3H has been used in several acid catalysed reactions including the dehydration of sorbitol. [91] According to the authors, the isolated yield of isosorbide reached 94 % after 1 hour at 140 °C with 20 wt% of catalyst. The purity of the product was attested by ^{13}C NMR. This analytical technic doesn't however take into account the formation of oligomeric / polymeric by-products that can be elsewhere obtained. Interestingly, the catalyst could be separated using external magnetic force and reused up to five times without any significant loss in yields of the products after every recycling step.

4.2 Zeolites as catalysts

Zeolites are aluminosilicates that have found applications as acid catalysts in petrochemical processes. Zeolites are for example used as dehydration catalysts for the synthesis of olefins[92-97] or ethers[96, 97] from alcohols. Recently, 3 Å molecular sieves have been used to promote dehydration reactions of tetritols[98] and hexitols[99]. Reaction temperature as high as 290 °C under argon was necessary to obtain isosorbide with 45 % yield after 1 hour with 40 % weight of molecular sieves. A larger scope of zeolite type catalysts has been later evaluated at 280 °C under hydrogen thus yielding isosorbide with yields lower than 60 %.[100] It is noteworthy that 38 % yield of isosorbide was obtained with H-beta (Si/Al ratio of 12.5) after 12 h at rather lower reaction temperature (150 °C). This latter study has been recently pushed further by varying the Si/Al ratio in a larger extent (Scheme 9).[101] Interestingly, it has been shown that an optimum Si/Al ratio of 75 allows the highest reaction rates (76 % yield of isosorbide at 127°C for 1 hour with 27 % weight of zeolite HB75). Similar results have been obtained from the group of Yokoi that obtained 80 % by using beta zeolite with a Si/Al ratio of 75.[102] The catalyst was recycled up to four times providing calcination at 550 °C was performed between each step. The study evidences the importance of framework structure (large pores into zeolites are more efficient), composition (i.e. Al content) and hydrothermal stability.



Scheme 9 Influence of the Si/Al ratio in dehydration of sorbitol to isosorbide in the presence of beta zeolite.

As observed with sulfonic resins, the catalyst is rapidly deactivated. In the case of zeolites, the deactivation was attributed to cocking and this is very likely related to oligomeric / polymeric by-products deposition in the solid catalyst. Analysis of the zeolites after the first catalytic run evidenced lower surface area and micropore volumes. A calcination of the zeolite at 823 K for 8 hours allowed recovering the initial values as well as high yields in isosorbide. According to this protocol, the zeolite could be recycled up to five times. Very recently, a detailed kinetic study on the behaviour of several zeolites for isosorbide synthesis was published by Morales et al.[103] Authors have confronted results obtained from commercially available zeolites and acidic resins such as Amberlyst 70 to conclude on the increased selectivity to isosorbide using H-Beta type zeolites despite a lower reaction rate. It is described that this unusual behaviour is due to catalyst textural properties.

4.3 Supported metal oxides

Nickel oxides, elsewhere used as weak acid catalysts in dehydration reactions, [104] have been evaluated in the context of sorbitol dehydration. Nickel oxide deposited on activated carbon (1 weight %) allowed the synthesis of sorbitans and isosorbide at 250 °C under H_2 pressure. The highest yield of isosorbide is 28 % after 6 hours of reaction whereas no isosorbide is formed with activated carbon alone.[105]

Bifunctional catalytic systems using noble metals (Pt, Pd and Ir) on zirconia in mechanical mixture with tungstated titania have also been developed to promote hydrocarbons production from sorbitol.[106, 107] As intermediate, isosorbide was obtained with interesting yields up to almost 80% (determined by GC analysis) at 240°C in the presence of Pd based catalysts.

4.4 Metal phosphates

Metal phosphates are since a long time recognized as useful acid heterogeneous catalysts in alcohols dehydrations[108] or syntheses of cyclic ethers from diols.[109, 110] Gu et al. have synthesized and characterized tin (IV), zirconium (IV) and titanium (IV) phosphates.[111] The heterogeneous catalysts showed interesting activities toward sorbitol dehydration at a reaction temperature of 300 °C. The reactions were performed in a fixed bed reactor with a continuous feeding of vaporized 10% aqueous solution of sorbitol carried out by nitrogen. Tin phosphate showed the highest selectivity toward isosorbide whereas titanium phosphate proved to be the most active. As observed with other heterogeneous catalysts, the system showed a decay of activity with time of reaction. However, catalysts could be regenerated by calcination at 773 K thus allowing initiating another run. More recently, B-, Al-, Fe- Ce- and La- trivalent cations containing phosphates as well as tetravalent Zr-phosphates (noted MP) have been prepared and evaluated as heterogeneous catalysts for the dehydration of sorbitol to isosorbide under batch conditions in the presence of water (70 wt.% sorbitol was used). The conversion of sorbitol measured after 2h at 200 °C varies as follows : AlP < ZrP < FeP < LaP < CeP < BP. With the most active catalyst, boron(III) phosphate (BP), the yield in isosorbide starting from aqueous 70 wt.% of sorbitol reaches 79.9 mol% (determined by quantitative GC with ethylene glycol as internal standard).[112]

4.5 Sulfated and phosphate metal oxides

Metal sulfates are heterogeneous catalysts that bear large amounts of moderate strength acidic sites. Hence, they have found numerous uses as promoters of acid catalysed transformation such as dehydration of ethanol to ethylene or cyclododecanol to cyclododecene.[113-115] Sulfated metal oxides have been only recently used as catalysts for the dehydration of sorbitol.[116] The catalysts were prepared by calcination of $NiSO_4·6H_2O$, $CuSO_4·5H_2O$ and $Al_2(SO_4)_3·18H_2O$ at temperatures ranging from 300 °C to 650 °C under flowed air. The best selectivities in isosorbide were obtained at 200 °C with the copper based catalyst obtained from the calcination at 650 °C (99.7 % conversion of sorbitol and 67.5 % selectivity). This study evidences the importance of the calcination temperature that leads to crucial changes in surface properties and the crystalline structure of the catalysts. Sulfated zirconia obtained from zirconium (IV) hydroxide and sulfuric acid followed by calcination at 600 °C have been evaluated in batch conditions (three necked balloon at 0.3 bar) at 210 °C.[117] Selectivities in isosorbide of up to 61 % have been obtained and the catalyst could be recycled 4 times without loss of selectivity. Later on, sulfated titanium[118] and sulfated tin oxides[119] have been shown as efficient and recyclable catalysts providing that a regeneration step is processed on the used catalyst (washings with water and ethanol followed by calcination). According to a similar synthetical approach, phosphoric acid modified niobium oxide (Nb_2O_5) [120] and tantalum oxides [121] ($Ta_2O_5·nH_2O$) have been prepared by reaction with aqueous phosphoric acids followed by calcination. Both families of catalysts have been evaluated under continuous conditions. The niobium based catalysts obtained after calcination at 400 °C showed the highest efficiency and isosorbide was obtained with 62.5 % selectivity at 225 °C. The tantalum oxide based catalysts showed a similar behaviour. At the same optimum reaction temperature, 48.3 % of selectivity in isosorbide (determined by HPLC) was obtained. In both cases, the phosphorylation affords more active catalysts compared to the free metal oxide.

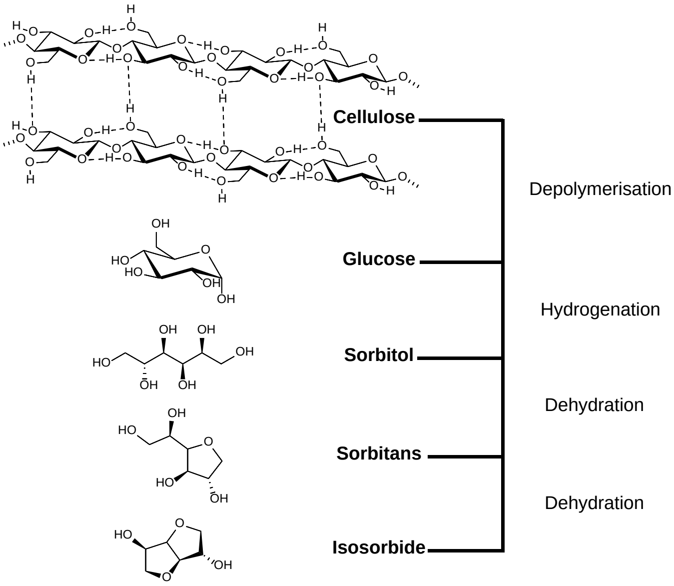
4.6 Supported HPA[122]

Tungstophosphoric acids (PW) have been supported on metal oxides (SiO_2, γ-Al_2O_3, TiO_2, ZrO_2 and CeO_2) and used as catalysts for sorbitol dehydration to isosorbide. The catalysts were prepared from the impregnation of HPA solutions on the supports followed by calcination at 300 °C. All the catalysts prepared from this impregnation procedure showed higher catalytic activities than the free support. The activity obtained for the supported catalysts varies with the nature of the support. The activities (based on sorbitol conversion) obtained with different PW supported catalyst varies according to the nature of the support and decreases as follows: $SiO_2>\gamma\text{-}Al_2O_3>TiO_2\approx ZrO_2>CeO_2$ which is in agreement with the order of acidity of the catalysts measured by NH_3 temperature-programmed desorption. The PW supported on silica showed the highest catalytic activity and selectivity in isosorbide determined by HPLC. The selectivity reached 60 % at 250 °C and the catalytic efficiency could be retained after regeneration of the catalyst through washings with dichloromethane. A very recent work has also explored the use of a cellulose derived solid catalyst for isosorbide production.[123] Catalysts were synthesized by hydrothermal carbonization and sulfonation of microcrystalline cellulose. Isosorbide was obtained with a moderate yield of 67% but the catalytic system did not show any activity loss after 4 runs and was easily recoverable.

5. One step synthesis from Glucose and cellulose

The synthesis of isosorbide can be directly performed from glucose by combining a hydrogenation catalyst with an acid. Heterogeneous bifunctional catalysts comprising 0.2% (w/w) ruthenium onto a Brønsted acid solid support (Ru@Dowex-H) have been prepared and evaluated in one-stage conversion of glucose into isosorbide with no need for organic solvent, high metal loadings, strong soluble acid additives or purification steps.[124] Quantitative analysis carried out via HPLC based on calibration curves of the pure products indicates 84.9% isosorbide yield from glucose at 190°C, under 30 atm H_2 and 0.2 % Ru after 48 h.

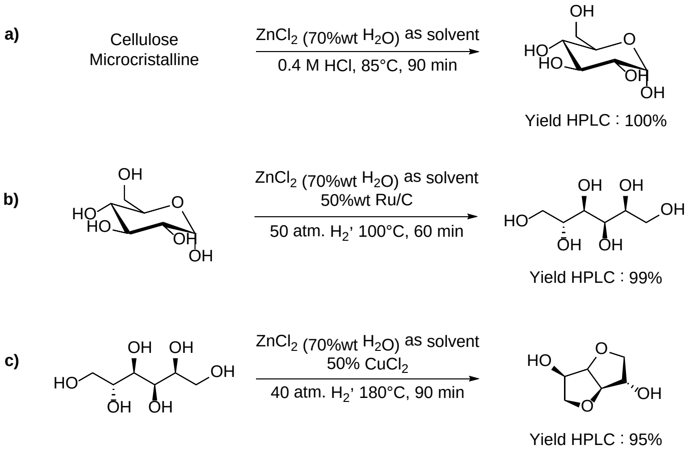
Direct utilization of lignocellulosic biomass as feedstocks for the production of platform molecules is nowadays a great challenge. Among the different molecules present in biomass, cellulose is the most abundant component and conversion of cellulose to chemicals is of a great interest for industrial applications.[125] Depolymerization of cellulose to glucose can be performed either via thermochemical processes at high temperature or in the presence of enzymes or via chemical approaches using homogeneous or heterogeneous catalysts. Glucose can then be hydrogenated to sorbitol which led after the two steps of dehydration to isosorbide (Scheme 10). Thus, the synthesis of isosorbide from cellulose through a direct conversion process could then be an interesting orientation for future, based on several major challenges to be worked out. Design of a relevant polyfunctional catalyst is probably the cornerstone of such a development; the targeted catalyst needing to perform cellulose destructuration to glucose, chemical reduction to sorbitol and dehydration to obtain isosorbide with high yield and selectivity. For a few years, many researchers focused theirs efforts towards this process and a few publications have appeared in the literature.



Scheme 10 From cellulose to Isosorbide.

Makkee first proposed an integrated process involving the dissolution of cellulose and their chemical conversion into isosorbide in $ZnCl_2$ hydrate as molten salt.[126] Isosorbide can be separated from the reaction mixture by extraction followed by crystallization. The three steps are described in Scheme 11. As each different step appeared to be highly selective into the desired product, including the first sorbitol dehydration step to 1,4-sorbitan, the authors report that it is feasible to convert 85 % of the carbon present in cellulose to isosorbide. The selectivity arises from the sorbitol conformation in the medium due to the hydroxyl groups interacting with the $ZnCl_2$ salt hydrate ionic species.

Zhao reported the selective conversion of concentrated microcrystalline cellulose to isosorbide over Ru/C catalysts in acidic medium with yields of 35-50%.[127] The reaction conditions are important factors to control the reaction rate and products distribution. The maximum yield of isosorbide was obtained after 6h of reaction at 215°C, under 6 MPa H_2 and with 0.1 M HCl as catalyst. By using Ru/C in the presence of heteropoly acids as $H_4SiW_{12}O_{40}$, Sels et al. converted microcrystalline Avicel PH-101 cellulose to isosorbide under H_2 pressure and high temperature.[128] High cellulose and SiW concentrations promote fast and selective formation of isosorbide with up to 50% yield. The optimal reaction conditions were used to process crude or pre-treated lignocellulosic biomass feedstocks highlighting the importance of fractionation and purification to increase reactivity and convertibility of the cellulose feedstocks.



Scheme 11 Dehydration of sorbitol to isosorbide in molten salt media

Li et al. have developed bifunctional and recyclable solid ruthenium catalysts for an efficient transformation of cellulose to isosorbide without the addition of any soluble acid.[129] Catalysts were prepared from Ru NPs supported on mesoporous niobium phosphate to afford Ru@mNbPO with strong acidity, large surface area and adequate pores size that promotes direct production of isosorbide (50% yield) from cellulose (100% conversion) under 6 MPa H_2 and at 220°C. Moreover, the catalyst could be reused up to six times without loss of activity. In a same way, Wang reported a two-steps sequential process where cellulose is firstly depolymerized with 5% Ru/$NbOPO_4$-pH_2 catalyst via hydrolysis and hydrogenation and then the resultant sorbitol and sorbitans are dehydrated to isosorbide in presence of $NbOPO_4$-pH_2. 56.7% isosorbide yield can be obtained under the optimum conditions with excellent cycling stability. Authors demonstrated that the total acidity (Brønsted and Lewis) of the catalyst is the key factor for the dehydration reaction.[130]

Supported metal catalysts coupled with resins have recently been reported. Yamaguchi proposed sorbitol dehydration on supported Pt/C or Ru/C and Amberlyst 70 in water at 463K under 5 MPa H_2.[131] Ruthenium based catalysts proved to be the most efficient and isosorbide yield increased with the loading of ruthenium on carbon support to reach a maximal value of 56% with 4% of Ru loaded on carbon. The same authors have extended their work to the one-pot conversion of lignocellulosic biomass to isosorbide in the same catalytic conditions.[132] For example, isosorbide yields from eucalyptus and bagasse were 8.3% and 12.8% respectively. Catalytic valorization of cellulose is a topic of intense research and efficient one-pot conversion of cellulose to isosorbide is challenging. It is then necessary to develop new very specific and robust catalysts with dual activity of hydrogenation and dehydration. Efforts should be focused on this purpose.

6. Conclusions

Isosorbide is a versatile platform molecule that shows key features to make it a credible alternative to petro-based products. The molecule is already available on large industrial scale (tens of thousands tons per years), which allows its development in commercial products such as active pharma ingredient, additive for cosmetic, speciality chemicals and polymers (ex: polycarbonates – polyesters). The development of more selective and higher yields syntheses of isosorbide are greatly needed to consolidate isosorbide production in view of a large expansion of its uses. Sorbitol conversion to isosorbide, relying on a starch route, is already a tough challenge. In a farther future, development of a credible path to isosorbide relying on cellulose source could even be thought of, provided that very versatile innovative catalysts will be developed in the next years. In all cases, a key issue is to develop catalysts that will avoid the massive production of “oligomeric/polymeric” by-products in order to access more sustainable processes by limiting the amounts of wastes produced during the synthesis. For this purpose, more selective homogeneous catalysts than the conventional Brønsted acids or alternative reaction conditions would be of strong interest. Selective and recyclable heterogeneous catalysts would be even more profitable as they would allow the continuous production of catalyst free isosorbide. This latter approach faces strong limitations due to the need of high reaction temperatures that often result in high amounts of side-products and the need of frequent and often tedious catalyst regeneration. Innovation concerning isosorbide synthesis is still an open field on which the design of efficient and robust catalysts, either homogeneous or heterogeneous, is a key issue. Such developments would pave the way to high scale effective processes considering altogether synthesis and purification of isosorbide.

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The review gives an overview of the catalysts and technologies developed for the synthesis of Isosorbide, a platform molecule derived from biomass (sorbitol, cellulose).