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# Catalytic access to anhydrohexitols and their isomerization

Mathieu Sauthier,<sup>\*a</sup> Isabelle Suisse<sup>a</sup> and Florence Popowycz<sup>b</sup>, Sylvie Moebs-Sanchez<sup>b</sup> and Maïwenn Jacolot<sup>b</sup>

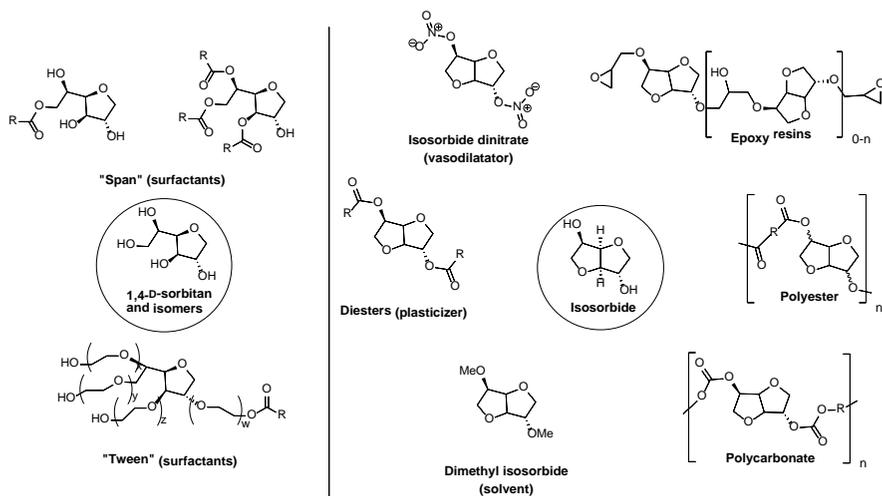
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Abstract: Anhydrohexitols are industrially relevant and agro-based polyhydroxylated derivatives. Isosorbide and sorbitans are obtained from sorbitol and are used for the production of surfactants, plasticizers and solvents. Isomannide and isoidide are stereoisomers of isosorbide with a high industrial potential which  
10 is hampered essentially by their poor accessibility. The efficient chemical access to these key molecules is an issue for further industrial developments and this has prompted academics and industrials to search for efficient processes. This chapter gives an overview of the industrial interest of anhydrohexitols and more particularly focuses on their synthesis by catalytic means from biobased molecules.  
15 Dehydration and isomerization reactions that involve polyols or biopolymers are presented and discussed from the point of view of selectivity issues.

## 1 Introduction: The industrial leading Anhydrohexitols

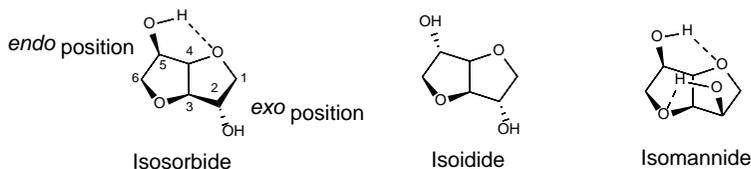
The family of anhydrohexitols is obtained from the intramolecular mono- or di-dehydration of hexoses. The most largely available hexose is sorbitol,<sup>1</sup> obtained  
20 from the hydrogenation of glucose. This large availability is due to the fact that glucose is clearly the most abundant natural molecule available on Earth, widely found in the composition of cellulose, starch and sucrose. Sorbitol dehydration has been, since decades, a major industrial process used for the production of sorbitans and isosorbide (Scheme 1). Sorbitans are mainly composed of mono-  
25 tetrahydrofuranic compounds typically used for the production of neutral and agro-based surfactants after an esterification step with fatty acids (“Span”). The hydrophilic lipophilic balance can be tuned by varying the substitution degree and length of the aliphatic chains. Ethoxylation of the free hydroxy groups of the sorbitans followed by an esterification step allows an access to a particular class of  
30 surfactants called “Tween”.<sup>2</sup> Both families of surfactants are generally regarded as safe<sup>3</sup> and are commonly used in pharmaceuticals, cosmetics, paints or as emulsifiers in food. Isosorbide is a diol with a fused bis(tetrahydrofuran) moiety. This rigid scaffold is clearly an important characteristic of the molecule in comparison to other industrially available and more flexible aliphatic diols such as ethylene glycol,  
35 propylene glycol, propane-1,3-diol or butane-1,4-diol. Isosorbide has found applications as monomer<sup>4</sup> for the production of polycarbonates and polyesters.<sup>5,6</sup> Further derivatizations have been used for the production of solvents (dimethyl isosorbide - DMI),<sup>7</sup> plasticizers (isosorbide diesters),<sup>8</sup> or vasodilator (mono and dinitrates).<sup>9</sup> This feature combined with the use of agro-resources (glucose and  
40 sorbitol) for the production of isosorbide are strongly attractive elements for the development of the production of the molecule in the coming years. However, if the hydrolysis and hydrogenation steps for the production of sorbitol<sup>10</sup> have proven a very high efficiency with nearly quantitative yields, the anhydrisation steps that lead

to sorbitans and isosorbide from sorbitol are clearly trickier. In particular for the synthesis of isosorbide, the reaction conditions are generally harsh, necessitate acidic conditions and lead to complex mixtures of products. This step is crucial for the whole process as the non-quantitative yields correspond to the production of large amounts of wastes and side products that are only poorly valorised. There is clearly in this field a great need for highly efficient industrial chemical processes for sorbitol anhydri-  
 5 sation. This means improved selectivities toward the targeted anhydrohexitols, soft reactions conditions, short reaction times, low cost starting reagents/catalysts, high reactant concentrations as well as simple purification  
 10 procedures (catalyst removal/recycling, product purification).



**Scheme 1** The industrial uses of sorbitans and isosorbide<sup>2-9</sup>

Beyond the transformation of sorbitol into the corresponding sorbitans and isosorbide, other less straightforwardly accessible stereoisomers are also of great significance. In particular, in the family of the dianhydrohexitols, isomannide and isoidide drive a particular interest. In comparison to isosorbide that bears an *exo* and an *endo* position, isomannide and isoidide are respectively bis-*endo* and bis-*exo*  
 15 derivatives (Scheme 2). The *endo* position favours the formation of an intramolecular hydrogen bond that explains its higher acidity in comparison to the hydroxy group on the *exo* position. The *exo* position is elsewhere less sterically hindered than the *endo* position. By choosing appropriate reaction conditions, both positions can be selectively alkylated or esterified.<sup>11</sup> Isomannide and isoidide have  
 20 different physico-chemical properties and chemical reactivities in comparison to isosorbide and, hence, can be more attractive for targeted applications. As example, polyesters prepared from dianhydrohexitols and aliphatic dicarboxylic acids show different properties.<sup>12</sup> The  $M_n$  and  $T_g$  of the polyesters are generally higher with isoidide than with isosorbide. For isoidide, the development of a selective and high  
 25 yield catalytic access is a key to envisage their industrial use.



5 **Scheme 2** The three isomers of the 1,4:3,6-dianhydrohexitols<sup>11,12</sup>

## 2 The synthesis of isosorbide from sorbitol

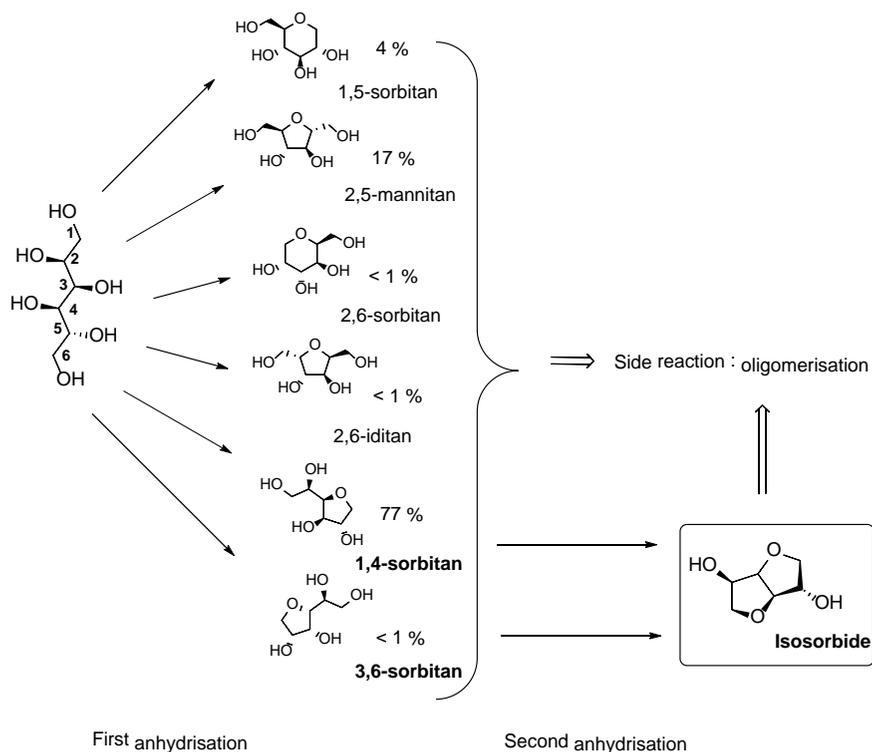
### 2.1 Selectivity issues in the sorbitol anhydriation steps

The anhydriation of sorbitol is an intramolecular reaction that leads to the  
 10 formation of molecules with one tetrahydrofuranic scaffold (monoanhydriation /  
 sorbitans) and two tetrahydrofuranic scaffolds (dianhydriation / isosorbide). Acids  
 are often used as catalysts (vide infra for catalysts used). It is noteworthy that  
 solvent free conditions can be advantageously applied as sorbitol and isosorbide are  
 melted at the reaction temperatures generally used (above 100 °C). By using  
 15 appropriate reaction conditions, the process can be efficiently limited to the products  
 of monoanhydriation. Typically, for preferential sorbitans synthesis, the first  
 anhydriation step promoted by acids such as PTSA or H<sub>2</sub>SO<sub>4</sub> is run at 100 °C to  
 120 °C.<sup>13</sup> Higher temperatures are needed to push the process up to the formation of  
 isosorbide. The more difficult second cyclisation can be attributed to cycle strains,  
 20 the formation of adducts with sulfuric acid has been also proposed to explain this  
 phenomenon.<sup>14</sup> Sorbitans are indeed obtained as a mixture of isomers. The formation  
 of the different products is due to the existence of several possible cyclisation  
 pathways (Scheme 3). 1,4-D-Sorbitan is commonly obtained as the major product of  
 reaction along with lower amounts of 2,5-mannitan and 1,5-mannitan. Other  
 25 monoanhydrohexitols are obtained in very low amounts. The reaction mechanism for  
 1,4-sorbitan formation is clearly a S<sub>N</sub>2 type mechanism (attack of the hydroxy group  
 of C4 on C1) as the carbon configurations are retained and a similar mechanism is  
 very likely to explain the formation of all the sorbitan isomers (See Scheme 4 for the  
 example of 1,4-sorbitan). Very low amounts of racemization evidence a negligible  
 30 contribution of S<sub>N</sub>1 mechanism.<sup>14</sup> The formation of 1,2-epoxide as intermediate has  
 also been postulated to account for the formation of 2,5-anhydro-D-mannitol (2,5-  
 mannitan in Scheme 3).<sup>15</sup>

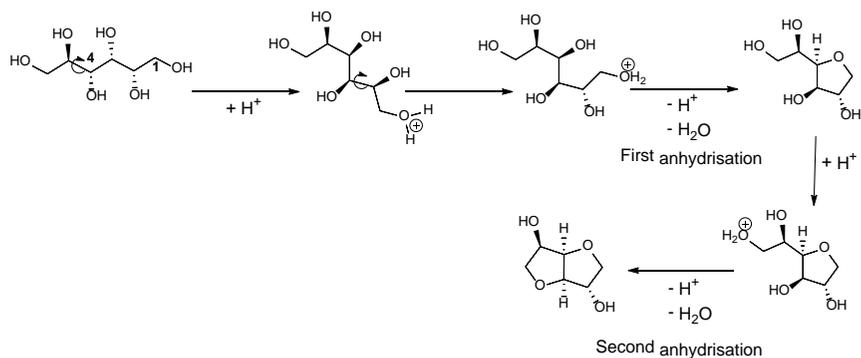
1,4-Sorbitan and 3,6-sorbitan are the two intermediate products issuing from the  
 first dehydration step that will lead to the formation of isosorbide after the second  
 35 dehydration step (See Scheme 4 for the example of the transformation of 1,4-  
 sorbitan in isosorbide). The formation of other isomers after the first dehydration  
 step is thus not productive for isosorbide synthesis and largely contributes to the loss  
 in isosorbide yield. The polymerisation of monoanhydrohexitols under acidic  
 conditions is also a source of production of waste. Sorbitol and isosorbide are

susceptible to be involved in such processes and drops of yields with long reaction times are commonly observed. The corresponding products often referred as “humins” are waxy and strongly coloured. In comparison to sorbitans and humins, isosorbide is solid at room temperature with a lower boiling point. Isosorbide is thus generally separated from the crude through distillation and can be further purified by crystallisation. Depending on the level of purity, polymer grade (> 99.5 % purity) and technical grade (> 98 % purity) are accessible.

Improved regioselectivities on cyclisation steps (formation of 1,4-sorbitan and 3,6-sorbitan) as well as the limitation of the polymerisation processes are targeted to get high reaction yields in isosorbide. Choice of homogeneous and heterogeneous catalysts and optimization of reaction conditions are keys to address these issues.



15 **Scheme 3** First and second sorbitol anhydridation reactions / selectivity issues<sup>5</sup>

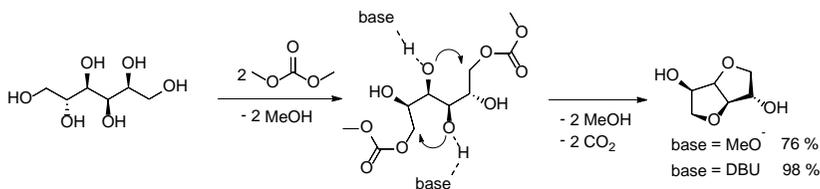


**Scheme 4** Mechanism of the acid catalyzed sorbitol anhydriation. Example of the main anhydriation pathway: Sorbitol to 1,4-sorbitan to isosorbide.<sup>14</sup>

## 2.2 Homogeneous catalysts for sorbitol dehydration

The dehydration steps are clearly favoured by strongly acidic catalysts that activate the hydroxy groups through a protonation step. It is thus not surprising that mineral strong acids<sup>16</sup> and in particular sulfuric acid (1 mol %; 135 °C under vacuum; 77 % isolated yield after 20 h)<sup>17</sup> or hydrochloric acid<sup>18</sup> have been early used. Very short reaction times are accessible by using microwave activation and this approach has for example been performed for the synthesis of [U-<sup>14</sup>C] labelled isosorbide (3 min of reaction under 1300 W for 34 mg of sorbitol with 5 µL of H<sub>2</sub>SO<sub>4</sub> and 500 µL of undecane).<sup>19</sup> Strong organic acids such as sulfonic acids (methanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid) have also shown their efficiency and typically give identical yields (between 65 % and 70 %) to the experiments with sulfuric acid under similar reaction conditions (1 mol % acid, 160 °C, 0.5 h).<sup>20</sup> The strength of the acid is a key parameter for the efficient anhydriation of sorbitol and negative pK<sub>a</sub> values are needed to access the higher reaction rates. The comparison of the reaction rates obtained with various acids shows that no improvement is obtained by using stronger acids than methanesulfonic acid (pK<sub>a</sub> = - 1.9).<sup>20</sup> Weaker acids have however been used in stoichiometric amounts (chloropyridinium salt, pK<sub>a</sub> = 5.2)<sup>21</sup> at 160 °C or catalytic amount of NaHSO<sub>4</sub> (HSO<sub>4</sub><sup>-</sup> / SO<sub>4</sub><sup>2-</sup>, pK<sub>a</sub> = 1.9) with harsh reaction conditions (MW, 210 °C)<sup>22</sup> without noteworthy selectivity improvement in comparison to stronger acids. The nature of the used acid has a clear impact on the reaction rate but, surprisingly, doesn't affect the selectivity of the reaction. Whatever the nature of the acid, the isosorbide selectivity remains rather similar with most acids used in catalytic amounts. Cheap and non-volatile inorganic acids such as H<sub>2</sub>SO<sub>4</sub> are thus industrially preferred to more costly strong organic acids. The use of a mixture of formic acid or acetic acid with fluorhydric acid is a rare example of dramatical change in selectivity issues.<sup>23</sup> After 20 h of reaction at 20 °C, by using 1 equivalent of formic acid and five parts of HF, isosorbide was obtained with 70 % yield. It is however particularly noteworthy that 3,6-sorbitan was obtained as intermediate product of reaction. The dramatic change of selectivity in the first dehydration step was

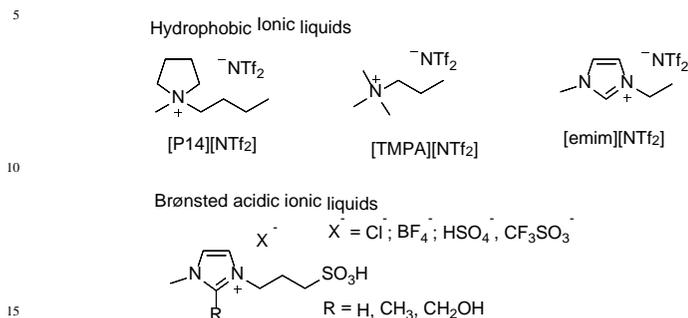
explained by the intermediate formation of cyclic acetoxonium (with acetic acid) intermediate that favours the formation of 3,6-sorbitan in respect to other isomers. This can be understood by considering *in situ* protection/deprotection steps that favour changes in the reaction selectivity. Acetoxonium ions were in that case first formed from sorbitol and one equivalent of carboxylic acid as evidenced by  $^{13}\text{C}$  NMR analysis. The thus formed intermediate was further involved in an intramolecular anhydridisation step that led to the preferential formation of 3,6-sorbitan instead of 1,4-sorbitan. In line with this approach, isosorbide esters have been involved in dehydration reactions.<sup>24</sup> Isosorbide esters were thus obtained and free isosorbide could be recovered after ester hydrolysis. The high temperature used for the reaction led to the formation of isosorbide with 80 % of selectivity. The use of dimethyl carbonate as solvent with sorbitol and 5 mol % of DBU yielded isosorbide with an almost quantitative isolated yield after 24 h of reaction (reflux temperature).<sup>25</sup> In comparison to acid catalyzed processes, the mechanistic pathway is very different (Scheme 5). Sorbitol is first involved in a trans-carbonation reaction that leads to the carboxymethylation of the two primary hydroxy groups. The methoxycarbonyl groups then acts as leaving group in intramolecular nucleophilic substitutions leading to the construction of the furanic rings, highlighting the pivotal role of the base in both steps. The use of dimethyl carbonate is particularly attractive for the high selectivity and yield in isosorbide. Example of such high isolated yields in isosorbide are rare. Still, the protocol suffers from the use of dimethylcarbonate as stoichiometric reactant and solvent that needs to be removed from the product.



25 **Scheme 5** Isosorbide synthesis with dimethyl carbonate<sup>25</sup>

Solvents have been elsewhere used as reaction medium for sorbitol anhydridisation. If solvent-free conditions that avoid tedious recycling steps are generally preferred, other solvents than dimethyl carbonate have however been tested. Water and catalyst free conditions have been applied as under high temperature (higher than 300 °C) the water self-ionization is sufficient to promote the reaction (57 % yield of isosorbide after 2 h of reaction, [sorbitol] = 1 mol.L<sup>-1</sup>).<sup>26</sup> Addition of CO<sub>2</sub> (300 MPa) further accelerates the reaction rate by acidifying the medium.<sup>27</sup> As sorbitol is a very polar starting materials, it is not surprising that ionic liquids have also been evaluated as reaction media. ZnCl<sub>2</sub> molten salts have been used and 85 % of HPLC yield in isosorbide has been obtained after 270 min of reaction at 200 °C (1:12 weight of sorbitol:70% ZnCl<sub>2</sub> in water).<sup>28</sup> Hydrophobic organic ionic liquids (Scheme 6) were also used with PTSA as catalyst (5 mol %) and afforded 60 % yield of isosorbide after 10 min under microwave irradiation. The product of reaction was extracted from ionic liquid by using a water/dichloromethane biphasic system and thus allowed the solvent recycling up to five times.<sup>29</sup> Brønsted acidic ionic liquids (Scheme 6) have been also used and despite of their recyclability, they don't

drastically improve the yields obtained with other catalytic systems (85 % HPLC yield with 0.6 mol % catalyst: R=CH<sub>3</sub>, X<sup>-</sup>=CF<sub>3</sub>SO<sub>3</sub><sup>-</sup>, 130 °C, 4 h).<sup>30</sup>



**Scheme 6** Ionic liquids used as solvents<sup>29,30</sup>

Lewis acids are alternative catalysts that can be used to promote anhydri-  
 20 reactions. From the use of a metal, one can expect coordination with sorbitol that  
 would contribute to favour different reaction intermediates and thus, reaction  
 selectivities. AlCl<sub>3</sub> and SnCl<sub>4</sub> have been very early used as catalysts.<sup>16</sup> Metal  
 tosylates M(OTs)<sub>n</sub> have shown comparable catalytic activity with sulfuric acid under  
 similar reaction conditions.<sup>31</sup> Comparative experiments that imply a broad range of  
 25 metal tosylates showed that trivalent metals such as Cr(OTs)<sub>3</sub>, Fe(OTs)<sub>3</sub> and  
 Bi(OTs)<sub>3</sub> afforded more active catalysts than divalent species.<sup>32</sup> As the best activity  
 compared well with those obtained with sulfuric acid without noticeable selectivity  
 improvement, the use of more costly metal salts doesn't appear as a viable  
 alternative to simple inorganic acids.

30

### 2.3 Heterogeneous catalysts for sorbitol dehydration

While homogeneous catalysts present the advantages of high specific activities  
 and potential for selectivity tuning *via* ligands variation, heterogeneous catalysts  
 offer the advantages of simple separation and recovery. The possibility to synthesize  
 35 new catalytic materials with specific active sites on catalysts surface allowed the  
 development of heterogeneous catalysis in fine-chemicals production for which  
 selective reactions are highly required.<sup>33</sup> In that context, isosorbide anhydri-  
 sation has been largely studied in heterogeneous conditions in the presence of acidic solids  
 such as resins, zeolites and metallic catalysts. Moreover, these catalysts can  
 40 advantageously replace concentrated and corrosive acids.

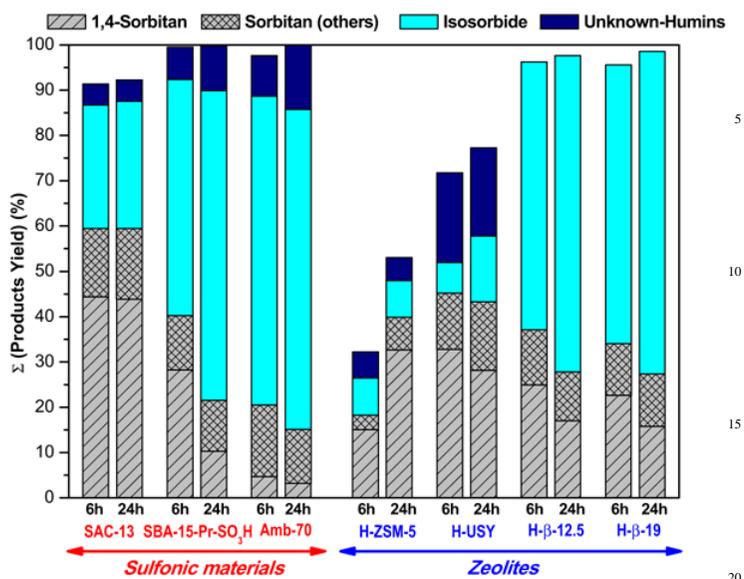
The first heterogeneous catalysis was developed by Goodwin in 1980 by using  
 acidic cation-exchange resin Amberlite IR-120 (Rohm and Haas).<sup>34</sup> Sorbitol, when  
 boiling under reflux in 1,4-dioxane and ethyl acetate in the presence of Amberlite IR  
 120 gave isosorbide together with the unreacted starting material. Isosorbide could  
 45 be distilled from the mixture in 39% yield. After this pioneering work, continuous  
 endeavours have been devoted in this field with numerous solid acidic catalysts as  
 zeolites, sulfonic acid resins and sulfonic acid-modified mesoporous silicas,  
 sulfonated activated carbon, phosphate or sulfated metal oxides, supported

phosphotungstic acid and many others. Several recent reviews are available on sorbitol dehydration to isosorbide covering this large scope of solid catalysts.<sup>1</sup> Here, a description of the most employed in literature, namely the zeolites and the sulfonated catalysts, will be reported together with very recently described particularly active catalysts.

Zeolites are microporous aluminosilicates minerals commonly used as commercial adsorbents and catalysts. Their well-defined pore structure and adjustable acidity make them highly active for many reactions. Therefore, sorbitol dehydration has successfully been performed in the presence of H- $\beta$  zeolites with specific Si/Al ratios.<sup>35</sup> A 76 % isosorbide yield was obtained with the high-silica H $\beta$ (75) zeolite (Si/Al ratio equal to 75) after a reaction time of 2 h at 127 °C. The authors proposed that acidic sites on internal surface of H $\beta$  with hydrophobic natures are active for this reaction. At the same time, similar results have been described by Yokoi using a temperature of 200 °C.<sup>36</sup> The influence of reaction parameters such as temperature and the catalyst amounts were investigated leading to a maximal yield of isosorbide of 80 %. The reason for this high catalytic activity is ascribed to hydrophobicity of the catalyst surface. Hydrothermal stability is another critical factor in determining the catalytic performance. The zeolite proved also to be reusable four times without loss of activity after calcination at 550 °C allowing the regeneration of the catalyst which was deactivated by the deposition of carbonaceous matters during the dehydration process. Very recently, continuous-flow sorbitol dehydration has been proposed by two groups using mild conditions. First, continuous dehydration of sorbitol was successfully achieved in the presence of H- $\beta$  (38) zeolite at 200 °C, achieving 82% sorbitol conversion and an average of 28% isosorbide yield.<sup>37</sup> In the same manner, continuous-flow sorbitol dehydration in liquid water was performed on various  $\beta$  zeolites (Si/Al molar ratio used in the study = 12.5; 75 and 150) with conversions up to 94 % and 83 % isosorbide yield. Direct isosorbide production from aqueous glucose solution *via* hydrogenation on Ni catalyst supported on nitrogen-doped carbon, followed by dehydration of the formed sorbitol to isosorbide was also successfully performed leading to a promising process for further isosorbide industrial production.<sup>38</sup>

A novel strategy has been proposed by Xu to control the etherification site of the polyol by ketalization of the terminal-diol group of sorbitol with ketones : highly selective isosorbide formation from sorbitol has been demonstrated in 93 % yield by using methyl isobutyl ketone over the H-beta(20) zeolite catalyst at 170 °C for 2 hours.<sup>39</sup> Recently, the catalytic performances of sulfonic acid-functionalized materials and aluminum containing zeolites in the dehydration of sorbitol to isosorbide in solventless conditions have been described.<sup>40</sup> The authors studied the effects of textural properties of these heterogeneous catalysts on the kinetics and the selectivity of the reaction. Reactions are performed at relatively moderate temperature (170 °C) with a sorbitol/catalyst mass ratio equal to 20 (Figure 1).

45



**Figure 1** Product yields contained in the dehydration of sorbitol over solid acid catalysts. T = 170 °C, sorbitol/catalyst (wt/wt)= 20/1.<sup>40</sup>

Sulfonic acid-based catalysts bearing strong Brønsted acid sites (Amberlyst-70, SBA-15-Pr-SO<sub>3</sub>H and Nafion SAC-13) provided high activities and production of isosorbide even at moderate temperatures. However, the production of side products as humins was also observed. In the case of zeolites, the authors indicated that the catalytic performance is clearly determined by their framework structures: the β zeolite are the most selective catalyst for the production of isosorbide, though following a slower kinetics than the sulfonic materials. The comparison with an equivalent hierarchical β zeolite (H-β-19) resulted in a slight improvement of the catalytic performance ascribed, according to the authors, to their superior textural properties. Lastly, the use of microporous zeolites with various physical properties presented Table 1 during sorbitol dehydration was recently proposed under high temperature and high pressure.<sup>41</sup>

**Table 1** Physical properties of the zeolite catalysts and results obtained with these materials during dehydration of sorbitol to isosorbide after 5 h of process at 200 °C in an autoclave.<sup>41</sup>

Zeolite	Si/Al Molar ratio	Pore diameter (Å)	BET Surface area (m <sup>2</sup> /g)	Micropore volume (cm <sup>3</sup> /g)	Acidity Strength (NH <sub>3</sub> -TPD)	Conv. (%)	IS yield (%)
MWW	13	5.6 x 5.6	420	0.15	++	15.7	11.2
BEA	13	7.6 x 6.4 5.5 x 5.5	690	0.19	+	81.1	41.2
FAU	5	7.4 x 7.4	700	0.24	+	53.0	26.1
MOR	10	6.5 x 7.0	410	0.13	+++	n.d.	< 10

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		2.6 x 5.7					
MFI	50	5.3 x 5.6	260	0.12	++	39.1	18.5
		5.1 x 5.5					

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While the isosorbide (IS) yield doesn't exceed 41.2%, the BEA zeolite proved to be the most interesting catalyst due to its relatively high pores size and its medium acid strength. If the acid strength is too strong as in the case of MFI or MOR, the conversion and yield decreased largely.

Concerning the sulfonic materials, after the initial works of Goodwin<sup>34</sup> with Amberlite IR 120, this family of solid acids have been largely used as catalysts in the dehydration reaction of sorbitol. As example, the resin catalyst Amberlyst-15 was evaluated in this process under conventional electric heating or by using microwave irradiation.<sup>42</sup> By using MW heating, the dehydration can be accelerated 20-34 times compared with traditional thermic heating leading to 100 % sorbitol conversion and 60 % isosorbide yield within 2 h (determined by HPLC analyses). There is however little change in the selectivity for isosorbide and sorbitans whatever the heating used. Amberlyst 15 was also used by Lemaire *et al.*<sup>43</sup> during the preparation of amphiphilic sorbitan monoethers. Thus, sorbitol was heated at 140 °C under 50 bars of hydrogen in the presence of ion-exchange resin such as Amberlyst 15 (0.1 wt%) leading to 83 % conversion of sorbitol. 1,4-Sorbitan and isosorbide were obtained in a ratio of 72:28. Increasing the Amberlyst 15 loading to 10 wt% slightly improved the conversion up to 86 % but isosorbide was then obtained as the major product (81 %). On the same manner, Polaert and coworkers studied the dehydration of sorbitol to isosorbide in the presence of Amberlyst 35 in a solvent-free system and under MW heating.<sup>44</sup> The obtained HPLC yield is up to 70 % and the authors showed that the kinetics of the reaction is only correctly described by a Langmuir-Hinselwood type model, including the adsorption-desorption equilibrium of sorbitol. More recently, other commercial sulfonic acid resins (Purolite and Amberlyst type) have also been evaluated as acid catalysts for the dehydration of sorbitol to isosorbide by the group of Maireless-Tores.<sup>45</sup> These resins differ in their acid properties, as well as in their thermal and mechanical stabilities. Dehydration of sorbitol has been carried out in that case under solvent-free conditions, by melting sorbitol. A maximum yield of 75 % was reached after 12 h at 140 °C under atmospheric pressure by using a 5 wt% of Purolite CT269. A recent study with the ion exchange resin Amberlyst 36 under mild conditions proposed by Chin showed the higher efficiency of that solid catalyst with sorbitol conversion and isosorbide yield >99% after a 4 h reaction at 423 K with catalyst loading of 5 wt%.<sup>46</sup>

Numerous other sulfonic acid resins have also been described.<sup>47,48,49,50</sup> As expected, the activities of the catalysts are reliable also to the acidity of the surface. It should be noted the important activity of a superhydrophobic mesoporous polymer-based acid catalyst (P-SO<sub>3</sub>H) which was synthesized from solvothermal copolymerization.<sup>51</sup> This acid solid catalyst is particularly attracting as it promoted significantly the dehydration reaction giving sorbitol conversion higher than 99 % and isosorbide yield at 87.9 % at 140 °C and after 10 h. The unique catalytic properties are reasonably related to the superhydrophobicity and porosity of P-SO<sub>3</sub>H. To our knowledge, it is the best result at that moderate temperature with regards to yield.

Active sulfonic catalysts included a sulfonated activated carbon (AC-SO<sub>3</sub>H) whose catalytic performance was compared with those of the commercial solid

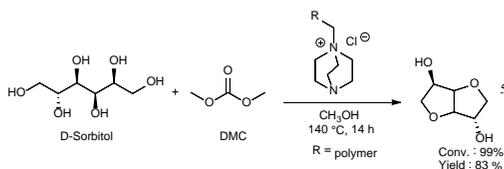
Amberlyst-36 and sulfated copper oxide.<sup>52</sup> The best result with 100 % sorbitol conversion and 52 % isosorbide selectivity was obtained over AC-SO<sub>3</sub>H at 250 °C. Although AC-SO<sub>3</sub>H possessed only 0.5 mmol/g of sulfur content, it showed a similar dehydration activity as Amberlyst-36 (5.4 mmol/g).

5 Solid sulfonic acids as sulfonic-acid-functionalized micro-bead silica catalysts named SA-SiO<sub>2</sub>-X (X = (3-mercaptopropyl)trimethoxysilane = MTPS) has been easily synthesized from micro-bead silica and MTPS and showed excellent catalytic performances.<sup>49</sup> With 60.5 wt.% MPTS loading, 100 % sorbitol conversion and 84 % yield of isosorbide are achieved at 120 °C for 10 h under vacuum. With these  
10 conditions, water formed in the reaction is instantly removed from the reactor. The authors attributed this high selectivity to the suitable large pores diameter and high hydrophilicity of the surface which is beneficial to feed (sorbitol) adsorption and product (isosorbide) desorption and inhibits the deposition of coke. Then the catalyst was reused 10 times without noticeable loss of activity and selectivity.

15 Lastly, there have been a few new interesting mesoporous catalysts described in literature. For example, noticeable active catalysts have been proposed by Dabbawala *et al.*<sup>53</sup> using sulphated titania MST, a solid acid catalyst prepared in one step by organic template free straightforward hydrolysis of titanium oxysulfate and subsequent calcination at different temperatures. The best catalyst of this type MST-  
20 450, corresponding to a calcination at 450 °C, led to a complete conversion of sorbitol with 70 % isosorbide selectivity in 2 h at 180 °C. The authors attributed the activity to the high specific areas and large pore sizes of the materials. Diffusion of reactants into the pores to the active sites are then facilitated. Mesoporous aluminum-promoted sulfated zirconia was easily prepared and firstly used to  
25 catalyzed solvent-free dehydration of sorbitol to isosorbide.<sup>54</sup> These catalysts possessed high surface areas and pores volumes which eliminated the diffusion restriction and abundant acidic sites, especially Brønsted acidic sites. Furthermore, aluminum promoters could contribute to the considerable increase of the strong acidic sites and ratio of Brønsted to Lewis acidic sites. A full sorbitol conversion  
30 with 73 % isosorbide selectivity could be achieved under milder conditions (175 °C, 2 h) with this type of materials.

Heterogeneous cyclodehydration of sorbitol to isosorbide under basic conditions was realized for the first time with a novel porous polymer-supported ionic liquid (PVDD = poly(4-vinylbenzyl chloride-divinylbenzene)-DABCO) as catalyst.<sup>55</sup>  
35 These polymer-supported ILs were synthesized through the suspension polymerization of 4-vinylbenzyl chloride and divinylbenzene, followed by quaternization reaction. These catalysts exhibited excellent catalytic activity in the cyclization of sorbitol with dimethyl carbonate (DMC) to isosorbide leading to a high conversion of sorbitol (99 %) with 83 % yield of isosorbide under optimized  
40 conditions (Scheme 7). Importantly, the catalysts could be easily separated by decantation and reused five times without obvious loss of catalytic activity.

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### Scheme 7 Cyclization of sorbitol with DMC catalyzed by PVDD<sup>55</sup>

Catalytic performances of solid catalysts for the double dehydration of sorbitol could be improved by using catalysts with specificities as:

- 15 - high total acidity of the solid catalysts
- large surface areas for a better activity
- hydrophilic surfaces displaying stronger affinity for sorbitol compared to isosorbide. The synthesized diol leaves the active site rapidly, avoiding possible undesirable side reactions, which cause large humins production.
- 20 - large pore sizes and pore volumes which allowed the better diffusion of the reactants into the pores and facilitated interactions with active sites.

Lastly, the reutilization of the solid catalyst is a key issue in the development of heterogeneous processes. As few catalysts seemed to be effective after several runs, 25 some authors pointed out a decrease of activity of the catalysts which could be due to the formation of organic deposits onto the catalyst surface which hindered access of the reactant molecules to the catalytic acid sites. In that case, regeneration treatment either by washing with various acids (HCl, H<sub>2</sub>SO<sub>4</sub>) and/or organic solvents or water could be possible. In the case of zeolites, calcination of the materials 30 proved to be a valuable solution.

## 3 The direct synthesis of isosorbide from cellulose

As cellulose is the most abundant component present in biomass with 35-50 % weight, valorisation of cellulose to produce valuable chemicals is currently the 35 subject of intense research.<sup>56</sup> In this context, direct transformation of cellulose to isosorbide is very interesting but remains a real challenge due to the three steps (depolymerisation of cellulose to glucose by hydrolysis of glycosidic bonds, hydrogenation of glucose to sorbitol and double dehydration of sorbitol to isosorbide) that should be performed in one-pot.<sup>57</sup> Selective depolymerisation of 40 cellulose to glucose could be performed either by enzymatic routes<sup>58</sup> or under chemical approaches in the presence of solid or liquid acids as catalysts. Recently, Jérôme *et al.* has proposed the efficient selective radical depolymerisation of cellulose to glucose induced by high frequency ultrasound.<sup>59</sup> Use of acidic catalysts is particularly attracting in the hydrolysis of cellulose to isosorbide because acids 45 are also needed in the final dehydration step. On the other hand, the transformation of glucose to sorbitol necessitates to use hydrogenation ruthenium or nickel based-catalysts.

The first example of isosorbide production from cellulose was proposed by Makkee who performed this transformation in a  $\text{ZnCl}_2$  molten salt hydrate media allowing dissolution of cellulose and chemical conversion to isosorbide.<sup>60</sup> In that case, authors actually reported a three-step process without intermediates separation: cellulose hydrolysis was first realized in the presence of  $\text{HCl}$ , then hydrogenation of glucose to sorbitol was performed in the presence of ruthenium on activated carbon under 50 bar  $\text{H}_2$  at 85 °C and lastly dehydration of sorbitol could be achieved in the same medium. The authors reported that the hydrolysis and hydrogenation steps occurred with complete conversion while the conversion rate for dehydration was higher than 95 %. Consequently 95 % of cellulose could be converted to isosorbide leading to an efficient continuous process.

Apart from this case, conversion of cellulose to isosorbide has been performed by some research groups in aqueous solution using a one or two steps process: Table 2 reports all the catalysts described in literature with their optimal conditions and the isosorbide yield. In most cases, the catalysts could maintain their activity for at least 4 consecutive runs.

**Table 2** Catalysts and optimal conditions used for the production of isosorbide (IS) from cellulose.

Entry	Catalyst	T (°C)	P( $\text{H}_2$ ) bar	Conv. (%)	IS yield (%)	Ref.
1	Ru/C and $\text{H}_2\text{SO}_4$	160	50	74	5.7	61
2	Ru/C and $\text{HCl}$	215	60	100	49.5	62
3	Ru/C and $\text{H}_3\text{PO}_4$	230	60	99.9	28.6	63
4	Pt/C and Amberlyst 70	180	50	n.d.	9.3	64,65
5 <sup>a</sup>	Ru/C and Amberlyst 70	190	50	n.d.	55.8	42,43
6 <sup>a</sup>	Ru/C and $\text{H}_4[\text{Si}(\text{W}_3\text{O}_{10})_4]$	160	50	98.8	18.7	66
7 <sup>a</sup>	Ru/C and $\text{H}_4\text{SiW}_{12}\text{O}_{40}$	210	50	n.d.	52.0	67
8	5 wt% Ru/C + 0.5 M $\text{H}_2\text{SO}_4$	220	40	n.d.	51.0	68
9 <sup>b</sup>	1) $\text{RuO}_x/\text{C}_{10\text{M},3\text{h}}$ 2) no catalyst	170 200	20 40	n.d.	57.0	47
10	Ru/C + $\text{NbOPO}_4$	230	40	n.d.	19.9	69
11 <sup>b</sup>	1) Ru/ $\text{NbOPO}_4$ 2) $\text{NbOPO}_4$	170 230	40 -	n.d.	56.7	48
12	Ru@mNbPO	220	60	100	50.0	70
13	Ni/ $\text{NbOPO}_4$	200	30	100	47.0	71
14	$\text{Ru}^{2-2}/\text{Fe}_3\text{O}_4@void @\text{PMO-SO}_3\text{H}^{0.43}$	220	60	95	58.1	72

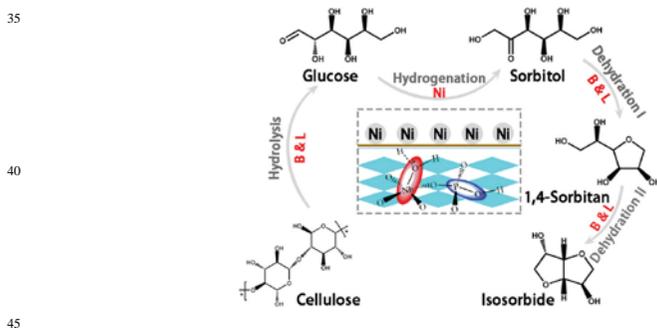
<sup>20</sup> <sup>a</sup> Recycling failed or not described

<sup>b</sup> two-steps reaction

Among the different catalysts, a combination of homogeneous acids (Entries 1-3) or solid acids (Entries 4-8) together with supported metal catalysts as Ru, Pt or Pd led to a yield in isosorbide up to 55.8 %. Keskiväli *et al.* compared commercial Ru/C catalysts in solution in 0.5 M H<sub>2</sub>SO<sub>4</sub> with new Ru catalysts synthesised after oxidative and sulfonation treatments generating strong acid sites on the surface of the catalyst support (Entry 8) with an isolated yield in isosorbide measured at 51 %. Using the optimized reaction conditions (an efficient two-step synthesis setup and the best catalyst RuO<sub>x</sub>/C<sub>10M</sub>, 3h), isosorbide was generated in 57 % yield from different cellulosic substrates (Entry 9). Performing the reaction in two steps allowed to use a higher temperature for sorbitans dehydration to isosorbide after simple filtration of the Ru catalyst.

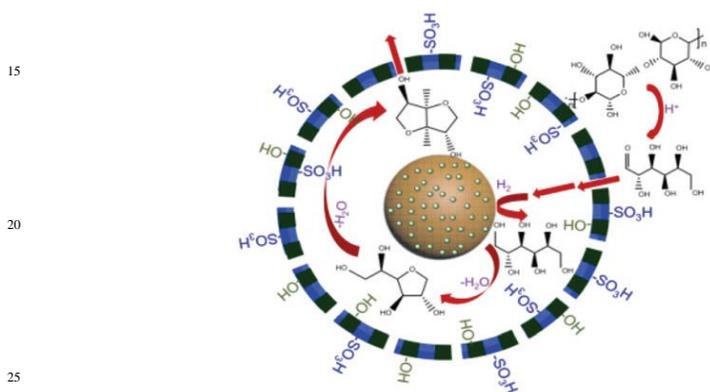
The combination of Ru/C and mesoporous strong acid NbOPO<sub>4</sub> catalyst was evaluated in a one-step reaction (Entry 10) generating less than 20 % isosorbide yield. The authors then proposed a two steps reaction: cellulose was firstly hydrolyzed to glucose and then hydrogenated to sorbitol over a bifunctional 5 wt.% Ru/NbOPO<sub>4</sub> catalyst under mild conditions. Then the catalyst was filtered off and NbOPO<sub>4</sub> catalyst was added to the reaction mixture (mainly including sorbitol and sorbitans) directly for further dehydration to isosorbide (Entry 11).

Ru NPs supported on niobium phosphate proved to be also a good alternative for a one-step reaction without addition of any soluble acids (Entry 12). This bifunctional catalyst possessed strong acidity, good hydrothermal stability and mesoporous character together with appropriate size of the NPS leading to a reusable active catalyst. Very recently, bifunctional supported Ni/NbOPO<sub>4</sub> catalysts with both acid sites and hydrogenation sites were synthesized by a simple method and developed for the one-pot conversion of cellulose into isosorbide (Entry 13). A mechanism was further inferred based on the catalyst characterization results (Scheme 8) : hydrogenation is performed on the surface of the reduced Ni catalyst while hydrolysis and dehydration originated from the Brønsted acidity of the surface P–OH or Nb–OH groups and the Lewis acidity of the partially hydrolyzed framework Nb species or coordinatively unsaturated Nb(V) sites.



**Scheme 8** Proposed reaction mechanism for the one-pot conversion of cellulose to isosorbide in the presence of Ni/NbOPO<sub>4</sub> catalyst. (B=Brønsted and L = Lewis acid sites) (Reproduced from Ref. 71)

A new type of metal–acid nanocatalyst for the efficient one-pot conversion of cellulose to isosorbide has been developed by dispersing Ru NPs on magnetic yolk–shell nanoarchitectures comprising a  $\text{Fe}_3\text{O}_4$  core and an  $\text{SO}_3\text{H}$ -containing periodic mesoporous organosilica (PMO) shell (Table 2, Entry 14). The optimized nanocatalyst could deliver a high yield of isosorbide of 58.1% with almost complete conversion of cellulose. The reaction route used to explain the high efficiency of the Ru– $\text{SO}_3\text{H}$  nanoreactor is depicted in Scheme 9. Cellulose is hydrolyzed to glucose which diffuses through the porous shell and is converted to sorbitol in the presence of Ru NPs supported on the  $\text{Fe}_3\text{O}_4$  core. The intermediate sorbitol is finally transformed into isosorbide through the  $\text{SO}_3\text{H}$  moieties on the shell.



**Scheme 9** Schematic illustration of the cascade reactions in a Ru- $\text{SO}_3\text{H}$  nanoreactor (Reproduced from Ref. 72)

The efficient transformation of cellulose to isosorbide remains a synthetic challenge. Therefore, direct transformation of cellulose to isosorbide could be performed in one or two steps using catalysts either with a combination of homogeneous acids or solid acids together with supported metal catalysts or with a bifunctional catalyst with both acid sites and hydrogenation sites.

#### 4 The synthesis of isomannide

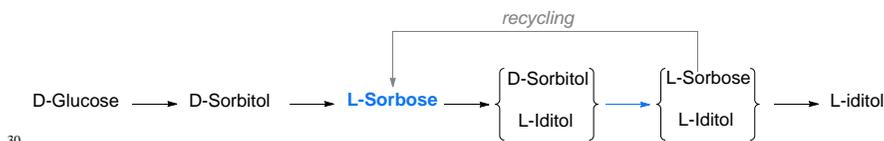
Isomannide corresponds to the 1,4:3,6-dianhydrohexitol sugar diol with the two hydroxy groups at the *endo* position. This compound has been widely used in many areas such as building blocks for polymers synthesis and pharmaceutically important compounds.<sup>73</sup> Isomannide results from the double dehydration of naturally occurring D-mannitol. Nevertheless, isomannide is largely less studied because of the lower availability of mannitol. Regarding the synthesis of isomannide through anhydriation processes, the examples reported in literature are always extensions of isosorbide syntheses. In the case of homogeneous acid catalyzed dehydration, isomannide yield (35 %) from mannitol was found to be lower than isosorbide yield (64 %) in the presence of sulfuric acid at 104 °C for 172 h.<sup>74</sup> Yamaguchi proposed dehydration of mannitol in high temperature (250–300 °C) liquid water without adding any acid catalyst leading to isomannide in only 20 % yield.<sup>75</sup> For

heterogeneous catalysts, H $\beta$  zeolites with specific Si/Al ratios proved to be efficient catalysts leading to isomannide in 63 % yield.<sup>76</sup> The use of H-beta(20) zeolite at 170 °C in presence of MIBK to control the etherification sites in the polyol allowed the synthesis of isomannide from mannitol with 75.2 % yield.<sup>39</sup> Additional recent studies have been reported in the literature without significant improvement.<sup>77</sup> On the other hand, isomannide could also be obtained by isomerization reactions as described in the following section.

## 5 The synthesis of isoidide

While double dehydration of D-mannitol and D-glucitol have afforded isomannide and isosorbide in a wide range of conditions, isoidide is the sole diastereomer that is not produced on industrial scale because L-iditol is barely present in nature. The limited industrial access to isoidide has narrowed its application mainly to academic projects. Research to get an industrial economically viable process for isoidide has though been being active for 60 years.<sup>78</sup>

Quantitative access to L-iditol was first investigated and isomerisation of D-mannitol and D-sorbitol in the presence of Ni (at 170 °C under P<sub>H<sub>2</sub></sub> = 130 bar) led to an equilibrium composed of 50 % sorbitol, 25 % mannitol and only 25 % of iditol.<sup>79</sup> In 2006, Roquette patented a process based on the reduction of L-sorbose (produced in thousand tons per year) into a mixture of D-sorbitol and L-iditol. A selective bacterial oxidation gave a mixture of L-sorbose and L-iditol, easily separated by cationic exchange chromatography,<sup>80</sup> and the recycling of the enriched fraction in L-sorbose led to an almost quantitative yield in L-iditol but with a difficult and poorly efficient industrial implementation (Scheme 10).<sup>81</sup> The strategy was developed, starting from D-glucose with a combination of hydrogenations and fermentations, judiciously adapted in orderly fashion. The purity of final enriched fraction of L-iditol was assumed to be at least 80%.



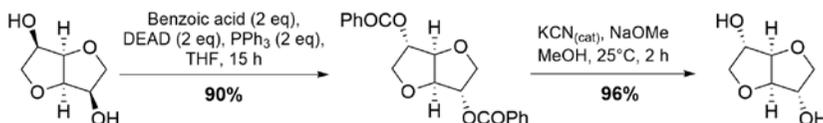
**Scheme 10** Industrial sequence for the production of L-iditol from D-glucose<sup>81</sup>

In the following sub-section are presented the known preparations of isoidide, limited to classical sequences or isomerisation reactions from isosorbide and isomannide. As it appeared to us important to evaluate the state of the art of the global process, a last part independently discuss related studies of potential ketone intermediates involved in the first step of isomerization. Few studies then suggested original applications involving these isohexides ketones through *in situ* or not processes somehow different from the second reductive step.

## 5.1 Laboratory scale synthesis of isoidide

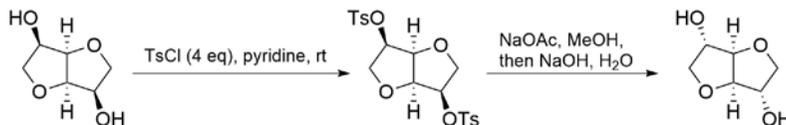
To our knowledge, two examples of two-step sequences from up to 10 g of isomannide are classically used in literature.

Van der Eycken reported in 2002 the preparation of isoidide in a two-step procedure in 86 % global yield. A Mitsunobu reaction under classical conditions allowed the access to the diester with complete inversion of configuration in excellent yield (Scheme 11). The final hydrolysis provided the isoidide almost quantitatively.<sup>82</sup>



**Scheme 11** Synthesis of isoidide through Mitsunobu reaction<sup>82</sup>

In 2010, the group of Gilmer inverted the sequence, proceeding to the inversion of configuration in the second step. In this strategy, isoidide was thus prepared in three steps from isomannide by double tosylation, followed by nucleophilic substitution with sodium acetate (Scheme 12). The release of isoidide was performed by aqueous hydrolysis of the acetates (no detailed experimental part, no yield given).<sup>83</sup>



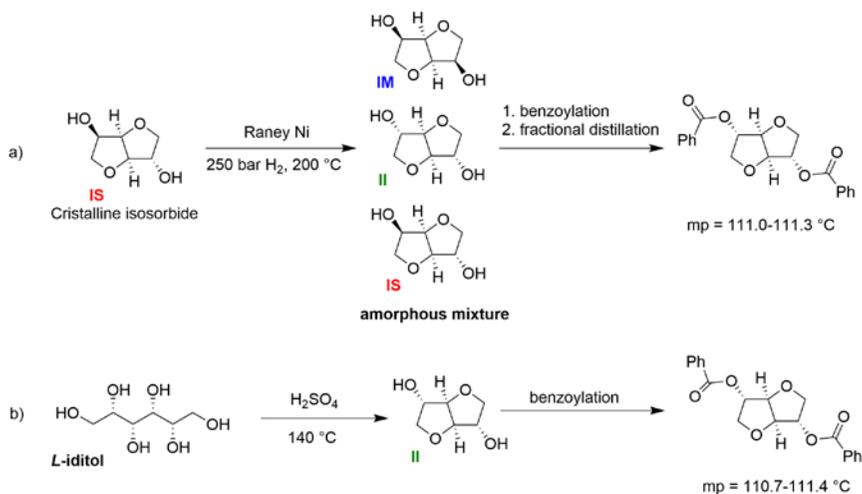
**Scheme 12** Synthesis of isoidide through activation/SN<sub>2</sub> reaction<sup>83</sup>

## 5.2 Direct isomerization from isosorbide or isomannide

### 5.2.1 Heterogeneous organometallic catalysis

The first isomerization of isohexides under heterogeneous catalysis was observed by Goepp and Fletcher in 1945, when attempting the reduction of isomannide (**IM**) and isosorbide (**IS**).<sup>84</sup> Crystalline isosorbide was treated with Raney nickel at 200 °C, under 250 bar of hydrogen providing an amorphous mixture. After a complete benzylation and a fractional crystallization, a new dianhydrohexitol dibenzoate was formed. The authors assumed that this new compound was the epimerized dibenzoate isosorbide with the two hydroxy groups in *exo* position (Scheme 13, a). In a control experiment, following the procedure described to convert sorbitol to isosorbide, a sample of L-iditol was dehydrated under acidic conditions to afford the corresponding dianhydrohexitol with the two hydroxy groups in *exo* position (Scheme 13, b). After benzylation, a comparison of their melting points confirmed

that the two obtained products were the dibenzoate of a single new compound, named isoidide (**II**).<sup>85</sup>



**Scheme 13** First synthesis of isoidide *via* isosorbide isomerization<sup>84,85</sup>

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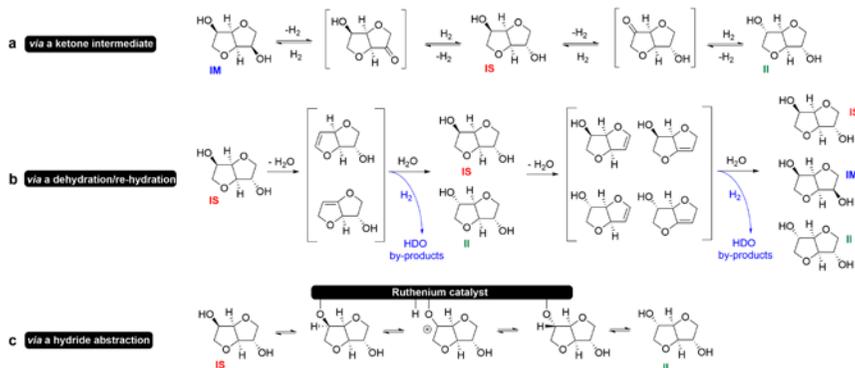
Following their study of the isomerization equilibrium between **D**-glucitol, **D**-mannitol and **L**-iditol,<sup>86</sup> Wright and Brandner also discussed the isomerization of isosorbide when treated with nickel-kieselguhr under 100 bar of hydrogen.<sup>87</sup> The isomers distributions of the crude mixture were determined using gas-liquid chromatography. While no significant influence of the reaction time (1 hour *vs* 2 hours) and catalyst loading (1.0 *vs* 2.0 wt %) was observed, the isosorbide epimerization into isoidide was shown to be strongly dependent on the temperature (200-210 °C *vs* 230 °C) and on the initial pH (8 *vs* 10) of the solution. Equilibrium could be reached after heating isosorbide in aqueous solution (pH 10) at 230 °C under hydrogen pressure (100 bar) using 2.0 wt % of nickel-kieselguhr catalyst for 2 hours. In the optimized conditions, the reaction medium was composed of 39 % isosorbide **IS**, 56 % isoidide **II** and 5 % isomannide **IM**.

The first ruthenium catalyzed isomerization of isosorbide was reported in 1991 by Montassier *et al.* treating **IS** with Ru/SiO<sub>2</sub> solid catalyst under hydrogen pressure. After 5 hours at 220 °C, a mixture of isosorbide **IS**, isoidide **II** and isomannide **IM** was obtained in a ratio  $\Sigma$  **55:40:5**.<sup>88</sup> Interestingly, when copper was deposited on the surface of the ruthenium catalyst, no isomerization was observed.

In 2013, van Es *et al.* reported the synthesis of isoidide *via* the epimerization of isosorbide using Ru/C under hydrogen pressure.<sup>89</sup> Using Ru/C instead of nickel catalyst,<sup>87</sup> they could improve the reaction by using lower catalyst loading (0.04 mol% *vs* 2.0 mol%) and lower hydrogen pressure (40 bar *vs* 100 bar). Also, Ru/C catalyst showed a better recyclability compared to Ni/SiO<sub>2</sub> which is an important point for its commercial viability. Contrary to what had been reported by Wright and Brandner with nickel-kieselguhr catalyst,<sup>87</sup> the initial pH has no influence on the product distribution when using Ru/C catalyst (ratio **IS:II:IM**  $\Sigma$  **38:56:6**). However, pH has a significant effect on the mass loss. Indeed, at pH = 7, a mass loss of 25% was observed, which could be the result of the acid-catalyzed hydrodeoxygenation

(HDO) side reactions (Scheme 13, b). As previously reported,<sup>87</sup> an optimum initial pH round 8-10 minimized alkaline degradation and the mass-loss could be reduced to 6 %.

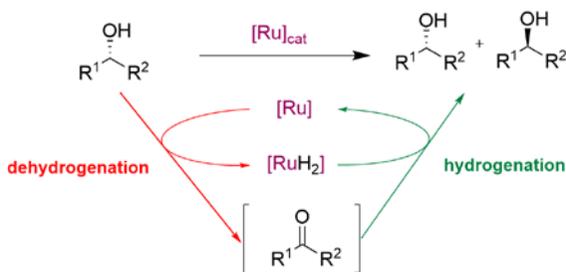
The mechanism was then deeply investigated by Rose *et al.*<sup>90</sup> While the most discussed mechanism for the isomerization of isohexides proceeded *via* a ketone (or keto-enol) intermediate (Scheme 14, a),<sup>85</sup> two other plausible mechanisms had also been envisioned: dehydration/re-hydration (Scheme 14, b)<sup>89</sup> and hydride abstraction (Scheme 14, c).<sup>85</sup> First, the pathway **b** was dismissed because no HDO side-products had been observed under the optimized conditions. A deuterium labelling allowed to confirm that isomerization could happen *via* a ketone or keto-enol intermediate but at temperature higher than 160 °C, hydride abstraction could also occur. A cooperation of the two mechanisms **a** and **c** was thus proposed.



**Scheme 14** Possible mechanisms for the solid metal catalyzed isomerization of isohexides<sup>85,89,90</sup>

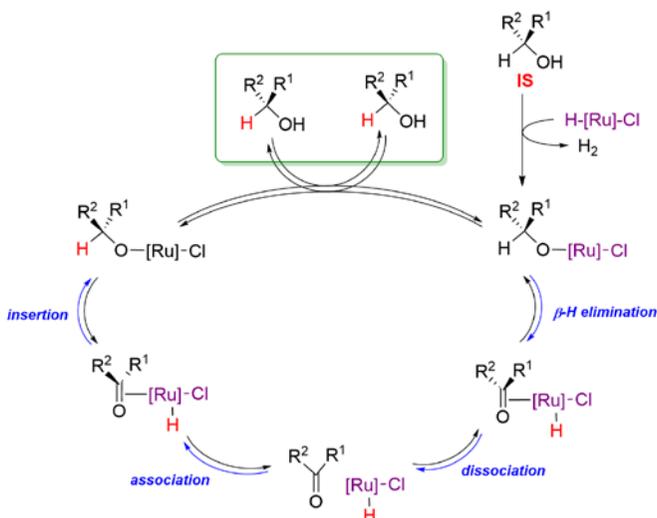
### 5.2.2 Homogeneous organometallic catalysis

Unlike heterogeneous catalysis, when molecular Ru catalyst is used, no hydrogen is required for isohexide isomerization. The reaction thus occurs *via* a hydrogen borrowing process. After a first step of catalytic dehydrogenation, the molecular hydrogen is stored by the catalyst and used for the hydrogenation of the ketone intermediate leading to a mixture of stereoisomers (Scheme 15). In the course of direct amination of isohexides *via* hydrogen borrowing methodology, isomerization has first been observed as a side reaction. Indeed, when reporting the direct amination of isosorbide using ammonia in combination with molecular ruthenium catalyst and a phosphorus ligand, Beller *et al.* highlighted the challenging nature of this reaction due to the unwanted isomerization of isosorbide.<sup>91</sup> Vogt *et al.* then reported the isomerization of isomannide using  $\text{Ru}_3(\text{CO})_{12}$  in the presence of an **acridine-based diphosphane** at 170 °C for 21 h affording a mixture of **IS**, **II** and **IM** in a ratio  $\Sigma$  **44:33:23**.<sup>92</sup>



**Scheme 15** Isomerization of secondary alcohol *via* borrowing hydrogen process<sup>91</sup>

5 Homogeneous ruthenium catalyzed epimerization of isosorbide was very recently further studied in detail by Monflier *et al.* as a possible route towards the industrial production of isoidide.<sup>93</sup> Reaction could either be performed using  $\text{RuClH}(\text{CO})(\text{PPh}_3)_3$  in the presence of Xantphos in 'amyl alcohol or using  $\text{RuCl}_2(\text{PPh}_3)_3$  with Xantphos but requiring 20 mol% of an additional base. A  
10 thermodynamic equilibrium was reached within 60 min at 170 °C or within 8 hours at 100 °C. The three isomers **IS**, **II** and **IM** were obtained in a ratio  $\Sigma$  **37:57:6**. A catalytic cycle involving the oxidation of isosorbide could be proposed (Scheme 16).



**Scheme 16** Mechanism of isosorbide epimerisation under ruthenium catalysis<sup>93</sup>

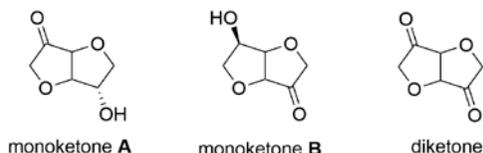
15 To overcome the difficult recyclability of homogeneous catalysts, the reaction could be carried out in a biphasic system (isosorbide/toluene) catalyzed by  $\text{RuClH}(\text{CO})(\text{PPh}_3)_3$  in the presence of Xantphos, at 110 °C for 8 hours. Despite the efficiency of the catalytic layer up to nine cycles, the purification of isoidide  
20 remained still challenging. Indeed, while Monflier obtained isoidide as a mixture of isomers, van Es succeeded in its isolation, after *vacuum* distillation, but leading to a poor yield of only 15%.<sup>89</sup>

### 5.2.3 Related intermediates to the oxidation step and further applications

The most presumed mechanism so far involves an oxidation step despite no ketone intermediate was necessarily detected. Nevertheless, a few independent research projects had focused specifically onto this step. For better clarity, the following section reviews them briefly.

#### 5.2.3.1 Specific studies on the first step of oxidation

As suggested in Scheme 15, a possible mechanism could involve *in situ* oxidation of isosorbide into monoketones **A** or **B** (Scheme 17), the reduction of which can afford isomeric isomannide and isoidide. Elements of syntheses of isohexide ketones have been, though hardly disclosed in the literature. Chemical synthesis of monoketone **A**<sup>94</sup> had been reported in the 1980s *via* an anodic oxidation of isosorbide using NaBr in water. It was rather selective as **A** was favoured over **B** issued from the oxidation of the hydroxy in *exo* position. Only traces of diketone were detected. Analytical tools were developed to analyse mixtures and isolate the product from residual isosorbide and salts *via* electrodialysis then HPLC. <sup>13</sup>C NMR analysis allowed to unambiguously identify isosorbide, isomannide and the three ketones. Meanwhile, Thiem *et al.* described aerobic Pt<sup>0</sup> catalyzed oxidation of isomannide into **B** with 70 % yield, under ultrasound activation. The diketone could also be obtained by oxidation of isomannide with pyridinium dichromate with 59 % yield.<sup>95</sup> Eventually, the oxidation of isomannide into the diketone could be obtained without metal catalyst using a combination of TEMPO, Br<sub>2</sub>, NaNO<sub>2</sub> and air as oxidant.<sup>96a</sup> The halogenated oxidant could be avoided and optimized reactional conditions were patented by Evonik.<sup>96b</sup>



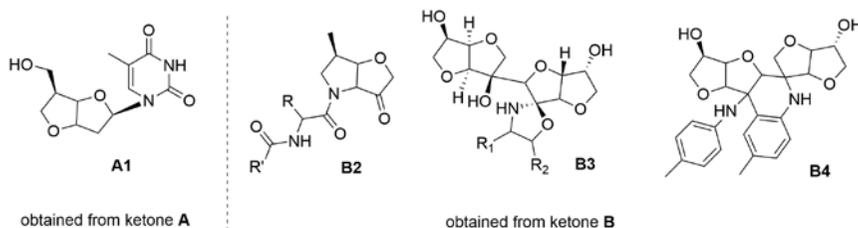
**Scheme 17** Monoketones (**A** and **B**) and diketone derived from isosorbide oxidation<sup>94-97</sup>

Very few reports have been made about the enzymatic oxidations of isohexides. The oxidation of isosorbide or isomannide into the diketone was achieved using a soluble mediator, TEMPO, together with a laccase/O<sub>2</sub> regeneration system, without selectivity but with a quasi-quantitative conversion at the milligram scale.<sup>97</sup> Whatever the chemical or enzymatic reaction-type, an *endo*-selectivity was so far observed, probably due to a higher thermodynamic barrier for the oxidation of the *exo* position (8.9 kcal.mol<sup>-1</sup> vs 6.7 kcal.mol<sup>-1</sup>).<sup>9</sup>

#### 5.2.3.2 Applications

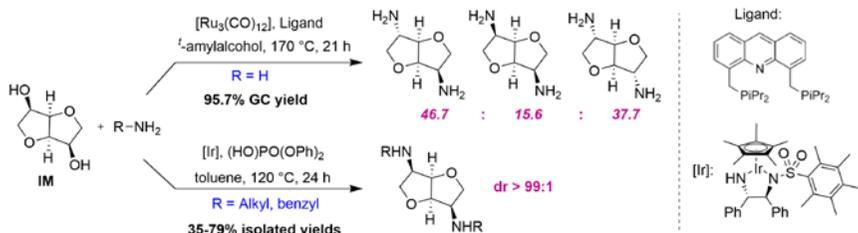
The following examples aim to unveil the field of possibilities opened by the

elementary processes mentioned above. Multi-step synthesis with classical protection protocols led to protected ketones used as intermediates for the preparation of antiviral agents (compound **B2**)<sup>98</sup> potential inhibitors of cysteine proteases (compound **A1**)<sup>99</sup> (Scheme 18). The monoketone **B** was obtained as a by-product during the chromatography of 4-chloro-4-deoxy- $\alpha$ -D-galactose without any other experimental details.<sup>100</sup> It was self-condensed in an aldolisation reaction, in the presence of triethylamine, in refluxing ethanol with 80 % yield.<sup>101</sup> To our knowledge, it remains the sole example exploiting this reactivity of the oxidized unprotected isohexide skeleton. The resulting dimeric ketone was then condensed with a range of 1,2-aminoalcohols providing the corresponding oxazolidine **B3**. The same ketone could react with *p*-toluidine to afford novel spirotetrahydroquinoline **B4** (Scheme 18).



**Scheme 18** Examples of molecules prepared from mono-ketones<sup>98-101</sup>

The mono- and diketones could also be used as precursors for the synthesis of aminated isohexides *via* a reductive amination as reported by Thiem *et al.*<sup>95</sup> To avoid the synthesis of an intermediate ketone, borrowing hydrogen methodology appeared as an interesting tool for the direct amination of isohexides. Beller *et al.* first reported the direct amination of isosorbide with ammonia using  $\text{RuClH}(\text{CO})(\text{PPh}_3)_3$  in the presence of Xantphos in *t*-amyl alcohol at 170 °C affording the diamino-isohexide as a mixture of the 3 stereoisomers, in 95.7% GC yield.<sup>91</sup> Similar results were obtained by Vogt *et al.* with isomannide under Ru-catalysis (Scheme 19).<sup>92</sup>



**Scheme 19** Direct amination of isohexides *via* the borrowing hydrogen strategy<sup>91,92,95,102</sup>

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Noticeably, switching from ruthenium to iridium complex, an excellent diastereoselectivity was observed. Indeed, Jacolot and Popowycz recently reported the direct amination of isomannide using a cooperative catalysis between an iridium

catalyst (chiral or achiral) and a Brønsted acid yielding to chiral diamino-isohexides within excellent diastereoselectivities (Scheme 19).<sup>102</sup>

The switch from organometallic catalysis to biocatalysis is an attractive challenge, especially in the pharmaceutical industry, due to very low metal content requirements in the active pharmaceutical ingredient. Monoketone **A** was involved in the transformation of isosorbide *via* a two biocatalytic reactions sequence, associating an alcohol dehydrogenase (a NAD-dependent enzyme) and a transaminase together with a third enzyme necessary for cofactor recycling: a monoamine could be obtained albeit with a yield of only 7 %.<sup>103</sup> The equilibrium constant measured for the NAD-dependent oxidation of isosorbide was as low as  $K_{\text{eq}} = 8.6 \cdot 10^{-7}$ . Low yield could also be due to instability of keto intermediates, hypothesis which has never been evaluated. This proof of concept could have been a breakthrough as an alternative to classical techniques in use.

## 6 Conclusion

The synthesis of anhydrohexitols is an intense area of research that has been activated by recent industrial successes. The dehydration of sorbitol for the synthesis of sorbitans is often considered as already well optimized. This is related to the fact that the selectivity between the different possible isomers is not a key issue for the production of surfactants. This is not true if one considers the synthesis of isosorbide. In this case, the selectivity of the first anhydrisation of sorbitol is clearly a key to access high yields in isosorbide as only two sorbitan isomers lead to the title product after the second anhydrisation. Selective catalysts are from this point of view intensively searched. Beyond the selectivity, catalyst recyclability is also an important issue. Heterogeneous catalysts that can be implemented in continuous processes would clearly be very attractive. However, polyols tend to oligomerize/polymerize during the reaction and thus rapidly deactivate the catalytic surface. Catalyst regenerations are possible but need to be frequent and this is a strong limitation to further industrial setup. If improvements have been reached, the development of both highly selective and recyclable catalysts is a big challenge that has, up to now, never been fully addressed and simple inorganic acids tend to remain the used catalysts for isosorbide production. Sorbitol is often used as starting material for the synthesis of isosorbide. However, it is noteworthy that the “one pot” accesses to anhydrohexitols from starch or cellulose would be very attractive. This however necessitates the design of catalysts able to depolymerize the biopolymer, reduce glucose in sorbitol through a hydrogenation reaction and perform the anhydrisation steps. Several progresses have been obtained in this field that faces the need for complementary multi-catalytic system with redox and acidic sites.

The synthesis of isoidide and isomannide is less straightforward than the synthesis of isosorbide as the starting hexols are not as accessible as sorbitol. Their synthesis often requires additional steps that allow the inversion of configuration of the carbons that bear the hydroxy groups. An elegant approach is the catalytic isomerisation of isosorbide into isomannide and/or into isoidide from deshydrogenation/hydrogenation processes. The full conversion of isosorbide into either isomannide or isoidide is however clearly an important issue that still needs to be fully addressed.

<sup>a</sup> Univ. Lille, CNRS, Centrale Lille, ENSCL, Univ. Artois, UMR 8181 – UCCS Unité de Catalyse et Chimie du Solide, F-59000 Lille, France. E-mail: mathieu.sauthier@univ-lille.fr

<sup>b</sup> Univ Lyon, INSA Lyon, Université Lyon 1, CNRS, CPE Lyon, UMR 5246, ICBMS, 1 rue Victor Grignard, 69621 Villeurbanne Cedex, France. E-mail: Florence.popowycz@insa-lyon.fr

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