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Research Article

Multiphase Hydrogenation of D-Glucosamine Hydrochloride, N-Acetyl-D-Glucosamine, D-Glucose, and D-Maltose over Ru/C with Integrated Catalyst Recovery

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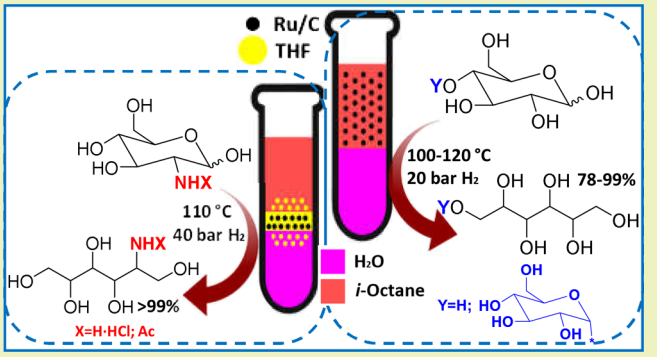
ABSTRACT: A multiphase (MP) system composed of two immiscible liquids, water and isooctane, and commercial 5% Ru/C as a catalyst, both with and without an additional organic liquid (OL: tetrahydrofuran (THF), 2-methyl-THF, *methyl* isobutyl carbinol, and cyclopentyl methyl ether) was designed and investigated for the chemoselective catalytic hydrogenation of four model examples of biobased sugars and amino/amido-sugars. At 110 °C and 40 bar of H_2, D-glucosamine hydrochloride and *N*-acetyl-D-glucosamine were converted selectively into their corresponding hydrogenated derivatives, 2-amino-D-sorbitol and 2-acetamide-D-sorbitol, respectively, isolated in >99% yields. Both the reagents and the products were converted and formed in the aqueous phase, respectively, while, by tuning the relative proportions of water, isooctane, and the third added liquid (particularly THF), the catalyst (Ru/C) was perfectly segregated in the organic layer, where it could be recycled and reused up to nine times without any loss of activity and selectivity, in a semicontinuous mode. Under such conditions, the reaction was implemented on a gram scale with a productivity up to 0.89 mmol 2-amino-D-sorbitol/(g_{cat} h). The same hydrogenation efficiency and reagent/product/catalyst separation were achieved during the MP reactions of D-glucose and D-maltose. In this case, however, results were independent of the MP composition: at 120 °C and 20−40 bar of H_2, using either H_2O/isooctane or H_2O/isooctane/OL systems, a quantitative conversion of D-glucose and D-maltose was reached with a selectivity up to 78 and >99% toward sorbitol and maltitol, respectively. Ru/C was perfectly separated out of the aqueous phase in both MP mixtures, with a negligible metal leaching, below 0.01 wt %. The multiphase approach for all the tested substrates proved not only to be an original and robust protocol to improve the product isolation and catalyst recycling, but also effective in preventing metal contamination in the synthesis of final derivatives.



KEYWORDS: *multiphase catalysis, biobased, sugars, sugar alcohols, aminosugars, amido-sugars, green chemistry*

INTRODUCTION

Multiphase (MP) systems obtained by the combination of two or more immiscible components, such as aqueous solutions, ionic liquids (ILs), nonpolar organic solvents, or thermoregulated phases consisting of mixtures of organic and perfluorinated compounds, have found a variety of applications to direct the selectivity and conversion of organic reactions toward specific target products, but also to promote the separation of products and catalysts.[1−3] Remarkable cases have been reported for the confinement/recycling of both heterogeneous and homogeneous metal-based catalysts in the implementation of hydrodehalogenation,[4] hydrogenation, and hydroformylation protocols (including enantioselective ones), oxidations of benzyl alcohols, formation of C−C and C−X bonds, tandem reactions, and others.[5−8] The use of MPs has also emerged in upgrading and purification of biomass derivatives.[9] Particularly, a recent review described MP catalytic transformations of representative biobased platform molecules aimed at the synthesis of furans and at the oxidation and hydrogenation/hydrogenolysis of furanics, glycerol, sugars, lactates, and lignin.[10]

One of the most investigated MP processes has been the acid-catalyzed conversion of mono- and polysaccharides into 5-hydroxymethylfurfural (HMF). A pioneering study reported that the dehydration of fructose produced HMF in yields higher than 90% in a biphasic system composed of ethyl acetate and an IL synthesized from choline chloride and citric acid.[11] Another seminal study explored both batch and

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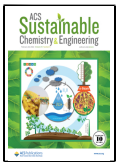

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continuous biphasic reactors where starting sugars were set to react at 180 °C in an acid aqueous-dimethyl sulfoxide (DMSO) solution while the HMF product was extracted in an organic layer of methyl isobutyl ketone (MiBK) and 2-BuOH.[12] Under these conditions, the continuous removal of HMF into the organic phase avoided its accumulation in water, thereby limiting the extent of side-reactions and allowing the reusability of the aqueous phase containing the catalyst. HMF was obtained in 76% yield and 85% selectivity. In the same MP system, other mono-, di-, and polysaccharides including glucose, sucrose, starch, cellobiose, and inulin provided HMF with variable yields of 23−75 wt %. A further development of these studies described a continuous dehydration of fructose to HMF using a water/dimethyl carbonate (1:3 v/v) biphase with added HCl catalyst: in a tube reactor at 1 min residence time, a 96.5% conversion and 87.2% HMF yield were reached at 200 °C.[13] Authors proposed that a H-bonding interaction between DMC and HMF strongly limited the onset of side-reactions and improved selectivity.

Other inventive MP protocols have been developed by combining the use of ILs as reaction media and compressed CO_2 as an extraction solvent, under the principle of univocal solubility; that is, ILs do not dissolve in dense CO_2, but dense CO_2 is soluble in ILs: these systems were used for both the synthesis of HMF and the purification/recovery of cellulose.[14−17]

In the recent past, the potential of MPs was also explored by our group for the conversion of levulinic acid − one of the most attractive derivatives of HMF − into products such as γ-valerolactone (GVL) and N-(cyclohexylmethyl)pyrrolidone obtained by hydrogenation/dehydration and reductive amination processes, respectively.[18,19] These reactions took place in an aqueous solution where products were obtained with a high selectivity (88−99%) at complete conversion, while the catalyst (5% Ru/C) was perfectly confined in an IL or a hydrocarbon phase (*i*-octane) where it could be efficiently recycled with no leaching in water (Figure 1).

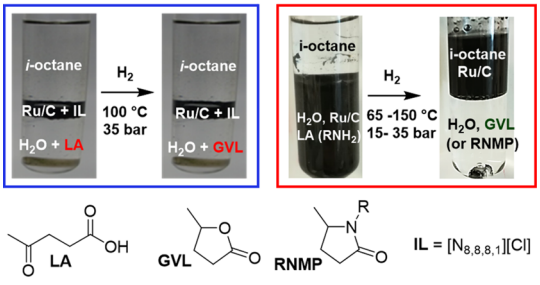

Figure 1. MP systems for the Ru/C-catalyzed hydrogenation/dehydration and/or reductive amination of LA. Left and right: in the presence (blue box) and in the absence (red box) of an IL, respectively. Photos are adapted with permission from ref 19. Copyright 2019, Wiley-VCH.

In the presence of ILs, *i*-octane played no apparent role as a solvent, but it was necessary to achieve phase separation and catalyst segregation (Figure 1, left). In a continuation of this research program, we were prompted to investigate and extend the application of the protocol for MP reductions to other relevant biobased platform molecules such as sugars and sugar-like substrates. The structural units of cellulose and chitin, D-glucose (**1**), D-glucosamine hydrochloride (**2**) and *N*-acetyl-D-glucosamine (**3**), and a model disaccharide as D-maltose (**4**) were chosen to the scope (Scheme 1).

It should be noted that although the catalytic hydrogenation of sugars (such as glucose and maltose) is an established process for the synthesis of the corresponding sugar alcohols (sorbitol and maltitol),[21] the implementation of the reaction is not without issues. Commercial processes are typically based on either Raney-Ni or carbon-supported Ru catalysts (such as Ru/γ-Al_2O_3 and Ru/C[8]), but the former undergoes strong leaching and fast deactivation, while the latter suffer from poisoning and, because of their low density, their sedimentation in the reaction mixture is often a processing bottleneck making filtration and reuse costly and time-consuming.[22,23] Another key aspect that often lowers the selectivity is the onset of hydrogenolysis/C−C bond cleavage reactions whereby the reduced products form side-derivatives such as for example, glycerol, ethylene glycol, and 1,2-propanediol (from sorbitol).[24,25] Very recently, an excellent performance has been reported for two novel classes of catalysts based on hydrotalcite (HT)-supported nickel phosphide nanoparticles (nano-Ni_2P/HT) and Ru nanoparticles dispersed on mesoporous carbon that allowed conversion of glucose to sorbitol with yields ≥99%.[26,27] The synthesis of such systems, however, is complex, and their recycling (described only for nano-Ni_2P/HT) implies discontinuous operations of centrifugation/isolation/reuse.

Current applications of chitin derivatives are mostly limited to functional materials,[28,29] while a scarce, if any, literature study is available on the reactivity of chitin-derived monosaccharides. To the best of our knowledge, there are only two papers on the catalytic hydrogenation of compounds **2** and **3**.[30,31] In the case of *N*-acetylglucosamine (**3**), a systematic catalyst screening demonstrated that in the presence of Ru/C, a single hydrogenated product, 2-acetoamido-2-deoxy-D-sorbitol (**3a**), was achieved in a nearly quantitative yield at 80 °C and 40 bar of H_2, whereas, at elevated temperatures, the complexity increased and besides the direct hydrogenation, multiple concurrent reactions of retro-aldol condensation, deacetylation, and dehydration took place yielding mixtures of C_2−C_4 polyols and (N-containing) C_6-polyols. Instead, the article on glucosamine referred to a Raney-Ni catalyzed reaction described in a very old procedure (dating back to 1937) with incomplete product characterization and a moderate yield (63%).

The overall scenario indicates that the design of new catalysts, reactors, and reaction conditions is a highly desirable target to run reactions of Scheme 1 in a greener and more sustainable way, particularly for the largely unexplored transformations of N-containing monosaccharides.

The present paper is aimed at integrating the catalytic hydrogenation of compounds **1**−**4** with an efficient protocol for product separation and catalyst recycling. A new MP process is described whereby the reduction reactions are carried out in two mutually immiscible aqueous/hydrocarbon phases, in the presence of commercial C-supported Ru, and with or without a third organic liquid (OL) chosen among THF, Me-THF, methyl isobutyl carbinol, and cyclopentyl methyl ether (CPME). By tuning the proportions of the liquid components, the full segregation of Ru/C in the organic phase was induced while the desired hydrogenation products were obtained in high yields and selectivity in the aqueous solution. At 110 °C and 40 bar H_2, in a H_2O/THF/isooctane system, both D-glucosamine hydrochloride and *N*-acetyl-D-glucosamine

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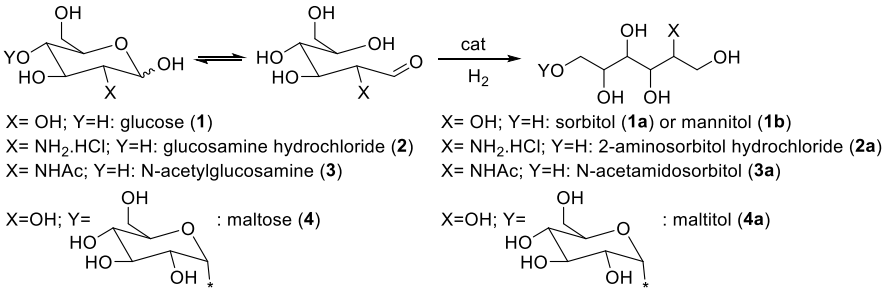
Scheme 1. Sugars and Sugar-Like Substrates Used in This Work (Left) and Their Hydrogenated Derivatives (Right)



were quantitatively converted into products **2a**−**3a** which were isolated in >99% yields. Under similar conditions (120 °C and 40−20 bar of H_2) in a H_2O/isooctane biphase, the hydrogenation of D-glucose and a D-maltose/D-glucose mixture (in a 3:1 ratio, wt/wt) afforded D-sorbitol (**1a**: 87%) and a mixture of D-maltitol (**4a**: 77%), D-sorbitol (19%), and D-mannitol (**1b**: 4%), respectively.

Ru/C remained in the organic phase and could be reused in a semicontinuous mode without being removed from the reactor and without leaching in the aqueous phase. In addition to the practical advantages and the robustness of the procedure, the study highlighted the role played by the added OL for both the outcome of the reaction and the segregation of the catalyst into the hydrocarbon/OL binary mixture.

EXPERIMENTAL SECTION

Materials and Equipment. D-(+)-glucosamine hydrochloride (>99%), *N*-acetyl-D-glucosamine (>99%), D-(+)-glucose (>99%), isooctane, tetrahydrofuran (THF), MiBK, methyl tetrahydrofuran, CPME, 5% Ru/C, and $RuCl_3$ were commercially available compounds sourced from Sigma-Aldrich. D-(+)-maltose was used as a mixture available in our laboratory composed of D-(+)-maltose/D-(+)-glucose in a 3:1 weight ratio, where the proportions of the di- and the monosaccharide were similar to those of a high-maltose syrup. If not otherwise specified, reagents and solvents were employed without further purification. ILs such as methyltrioctyl ammonium chloride ($[N_{8881}][Cl]$) and methyltrioctyl phosphonium bistriflimide ($[P_{8881}][Ntf_2]$) were prepared according to a method described by our research group.[32] Water was Milli-Q grade. H_2 gas was purchased from SIAD, Italy. Gas chromatography (GC) (flame ionization detector; FID) analyses were performed with an Elite-624 capillary column (L = 30 m, Ø = 0.32 mm, and film = 1.8 mm). The quantitative analyses were performed by high-pressure anion exchange chromatography with an ion chromatograph (Thermo Scientific Dionex ICS-5000) coupled to a single quadrupole mass spectrometer (Thermo Scientific MSQ Plus) (HPAEC-MS). ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz; chemical shifts are reported downfield from tetramethylsilane, and D_2O was used as the solvent. All reactions were performed in duplicate to verify reproducibility. Inductively coupled plasma (ICP) analyses were performed using a PerkinElmer Optima 5300DV.

Reaction Procedures. Protocols are detailed for the reactions of the most investigated substrate, glucosamine hydrochloride (**2**).

MP Hydrogenation of Glucosamine Hydrochloride. Two procedures A and B were used. *A.* Experiments were performed in a 25-mL tubular reactor of borosilicate glass (Pyrex), which was charged with D-glucosamine hydrochloride (**2**) (70 mg, 0.32 mmol), 5% Ru/C (150 mg, 24 mol % with respect to **2**), water (5 mL), and isooctane (5 mL).

B. Conditions were the same as those of procedure A, except for the addition of an OL (2.5 mL) which was selected among the following organic compounds: THF, methyl isobutyl carbinol, methyl tetrahydrofuran, or CPME.

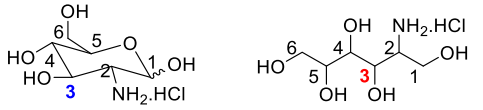
In both cases (A and B), the vessel was placed in a jacketed stainless-steel autoclave equipped with a manometer and two needle valves and pressurized with hydrogen pressure at 40 bar (room temperature). The autoclave was then heated by oil circulation at T = 90−130 °C, and the mixture was kept under magnetic stirring at a rate of 1500 rpm. After the desired reaction time (12−17 h), the autoclave was cooled to room temperature and gently purged. The catalyst (Ru/C) appeared perfectly confined out of the water phase, while the unconverted reagent and the product(s) were in the (perfectly clear) water solution. The latter (aq. solution) was withdrawn by a syringe and rotary-evaporated (60 °C, p = 15 mbar). A dried white sample was obtained and analyzed by nuclear magnetic resonance (NMR) in D_2O solvent. The NMR analyses confirmed the formation of 2-amino sorbitol hydrochloride (**2a**) as the sole product at complete conversion (details are in the Supporting Information, Figures S6−S10).

The method for the determination of the conversion of glucosamine hydrochloride (**2**) and the selectivity toward the hydrogenation product (**2a**) was based on ^{1}H NMR analyses. All NMR signals of the structures of the reactant and the product were first assigned by comparing the ^{1}H, ^{13}C, 135-DEPT, COSY, and HSQC spectra (Supporting Information). Thereafter, the conversion was calculated according to the following equation:

$$\text{Conversion} = \frac{A_{HA'}}{A_{HA} + A_{HA'}} \times 100$$

where $A_{HA'}$ and A_{HA} are the integrated areas under the resonance of the protons (HA and HA') at the C3 position of structures of both compounds **2** and **2a**, respectively (Scheme 2).

Scheme 2. C3 Position of the Reagent (Left) and the Product (Right): The Resonance of The Corresponding Protons Was Used To Calculate the Reaction Conversion



Further details with visual comparison of ^{1}H NMR spectra of **2** and **2a** are in the Supporting Information (Figure S16). This clearly highlighted that no other products were achieved, but 2-amino sorbitol hydrochloride with full selectivity.

Procedure B was also carried out by replacing the OL with an IL (500 mg) chosen between $[N_{8881}][Cl]$ and $[P_{8881}][Ntf_2]$.

For comparison, the hydrogenation of glucosamine hydrochloride was also carried out using water as the sole reaction solvent by adjusting conditions of procedure A (details are in the Supporting Information).

Hydrogenation of N-Acetyl-D-Glucosamine. The same MP hydrogenation protocols (A and B) described for D-glucosamine hydrochloride were used for the reduction of *N*-acetyl-D-glucosamine (**3**). At the end of the reactions, the aqueous solutions were withdrawn by a syringe and rotary-evaporated (60 °C, p = 15 mbar).

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Dried white samples were obtained and analyzed by NMR in D_2O solvent. The NMR analyses confirmed the formation of N-acetamidosorbitol (**3a**) as the sole product at complete conversion (details are in Supporting Information, Figures S11 and S12).

The conversion of *N*-acetyl-D-glucosamine (**3**) and the selectivity toward the hydrogenation product (**3a**) were determined by ^{1}H NMR according to the above-described method for glucosamine hydrochloride. The integrated areas under the resonance of the protons at the C3 position of the structure of both **3** and **3a** (analogous to those shown in Scheme 2 for glucosamine hydrochloride (**2**) and its hydrogenated derivative **2a**) were used. Also in this case, the comparison of ^{1}H NMR spectra clearly highlighted that no other products were achieved, but 2-acetamidosorbitol (**3a**) with full selectivity.

Hydrogenation of D-Glucose and D-Maltose. The same MP hydrogenation protocols (A and B) described for D-glucosamine hydrochloride were used for the hydrogenation of D-glucose (**1**) and D-maltose (**4**). To the scope, a mixture of D-glucose (75 mg, 0.42 mmol), 5% Ru/C (45 mg: 5 mol % with respect to **1**), H_2O (5 mL), and isooctane (5 mL) was used (procedure A). Procedure B was performed in the presence of additional THF (2.5 mL). The temperature and the pressure were set in the range of 100−150 °C and at 20−60 bar, respectively. Once the experiment was complete, the autoclave was cooled to room temperature and gently purged. The catalyst (Ru/C) appeared perfectly confined out of the water phase. The clear aq. solution was withdrawn by a syringe and rotary-evaporated (60 °C, p = 15 mbar). The residual white sample was dried and analyzed by high-performance anion exchange chromatography-mass spectrometry (HPAEC-MS).

The following procedure was used. Each sample of the aqueous solution collected at the end of MP experiments was 1:100 diluted with ultrapure water (Elga Purelab Ultra System, High-Wycombe, UK), and a labeled ^{13}C6-levoglucosan was used as an internal standard, spiked with a final concentration of 1 mg L^{-1}. Determination and quantification of all compounds were performed using an ion chromatograph (Thermo Scientific Dionex ICS-5000) coupled to a single quadrupole mass spectrometer (Thermo Scientific MSQ Plus). The chromatographic method was carried out using two separated methods: (a) seven saccharides (arabinose, fructose, galactose, glucose, mannose, ribose, xylose, and sucrose) and two alcohol-sugars (erythritol and maltitol) were separated using a CarboPac PA10 column (Thermo Scientific, 2 mm × 250 mm) equipped with a CarboPac PA10 guard column (2 × 50 mm). The sodium hydroxide gradient, generated by an eluent generator (Thermo Scientific, Dionex ICS 5000EG), was as follows: 0−3 min, 1 mM; 3−20 min gradient from 10 to 20 mM; 20−45 min isocratic elution with 20 mM; 45−55 min, column cleaning with 100 mM; 55−60 min, equilibration at 1 mM. (b) The separation of the alcohol-sugars (mannitol, ribitol, sorbitol, xylitol, and galactitol) was performed using a CarboPac MA1 analytical column (Thermo Scientific, 2 mm × 250 mm) equipped with an AminoTrap column (2 × 50 mm). The sodium hydroxide gradient was as follows: 20 mM (0−23 min), 100 mM (23−43 min), and 20 mM (43−53 min).

The injection volume for both methods was 50 μL, and the flow rate was 0.25 mL min^{-1}. Sodium hydroxide was removed using a suppressor (Thermo Scientific ASRS 500, 2 mm) before entering the mass spectrometer. To improve the ionization of the sugars in the aqueous eluent, a solution of methanol/ammonia (7‰) was added postcolumn with a flow of 0.025 mL min^{-1}. The MS was operated with an electrospray ionization (ESI) interface in negative mode with a temperature of 400 °C and a needle voltage of −2500 V. Selected ion monitoring was used for detection.

For comparison, the reaction of glucose was also carried out using water as the sole reaction solvent under the conditions of procedure A (details are in the Supporting Information).

D-maltose (**4**) was used in a mixture with D-glucose (**1**) which was available in our lab: the wt ratio of the di- and the monosaccharide was 3:1. The above-described procedures A and B were carried out using the **4**−**1** mixture (100 mg), 5% Ru/C (45 mg), H_2O (5 mL), and isooctane (5 mL) and for procedure B only, THF (2.5 mL). The conversion and product distribution were determined by HPAEC-MS.

Catalyst (Ru/C) Recycling. Protocols are detailed for the reactions of the most investigated substrate, glucosamine hydrochloride (**2**). The recycling/reuse of the catalyst was investigated after the hydrogenation of compound **2** was carried out in the triphasic water/isooctane/THF system (above-quoted procedure) B: (**2**: 70 mg; 5% Ru/C: 150 mg; H_2O: 5 mL; THF: 2.5 mL; 40 bar H_2; 110 °C; 12 h). After the experiment was complete, the aqueous phase (containing the reaction products) was withdrawn using a syringe and replaced with an equal volume (5 mL) of a fresh aqueous solution of glucosamine hydrochloride (70 mg). Thereafter, a second hydrogenation was run. The overall sequence was repeated for nine subsequent experiments. THF was topped up from one reaction to another because it partitioned in water (compare Figure 5).

Recycling tests were performed also using water as the sole reaction solvent. In the case, after each experiment, the resulting suspension was filtered, and the recovered Ru/C was washed several times with Milli-Q water (20 mL) and oven-dried (70 °C overnight, under vacuum) before reuse. The overall sequence was repeated for five subsequent runs (details are in the Supporting Information).

Leaching Tests. ICP analyses were carried out to determine the Ru content in the aqueous solution after the hydrogenation tests. To the scope, a set of five subsequent hydrogenation tests of D-glucosamine hydrochloride were run under the conditions of the above-described procedure B (**2**: 70 mg; 5% Ru/C: 150 mg; H_2O: 5 mL; THF: 2.5 mL; 40 bar H_2; 110 °C; 12 h). After each run, an aliquot (400 μL) of the aqueous solution was recovered at the end of the experiment and analyzed by inductively coupled plasma-mass spectrometry (ICP-MS) using a PerkinElmer NexION 350 spectrometer in standard mode. Details of the analytical protocol for ICP measurements are reported in the Supporting Information.

RESULTS AND DISCUSSION

General. C-supported Ru is among the most versatile and active heterogeneous catalysts for processing water-soluble biosourced organic reactants,[33,34] and, as already mentioned in the introduction, it is also one of the preferred systems for the hydrogenation of sugars. For these reasons and with the aim of designing protocols as easily accessible as possible, exclusively commercial 5% Ru/C was used throughout this study. The catalyst was characterized for its structural, morphological, and acid properties in recent papers by our group.[19,35] All the reported reactions were run in duplicate to ensure reproducibility and, unless otherwise specified, conversions and isolated yields differed by less than 5% from one test to another.

MP Hydrogenation of D-Glucosamine Hydrochloride (2). Exploratory hydrogenation tests of D-glucose (**1**) and D-glucosamine hydrochloride (**2**) proved that the reaction mixtures of the reaction of compound (**2**) could be far more conveniently characterized by ^{1}H-NMR than those deriving from glucose that instead, required HPAEC-MS analyses with several reference standards (see the Supporting Information). D-glucosamine hydrochloride was therefore chosen as a model substrate to begin a systematic investigation. Initial experiments were carried out by integrating the experimental conditions reported in the only paper available on the aq. phase hydrogenation of *N*-acetylglucosamine,[26] with the MP setup previously described by us for the conversion of levulinic acid to GVL (Figure 1). Accordingly, a biphasic water/isooctane mixture was employed in which the heterogenous catalyst was suspended, both with and without the presence of an IL. In the latter case, with an added IL, a liquid triphase system was obtained (Figure 1, left). A solution of **2** (70 mg, 0.32 mmol) in water (5 mL), isooctane (5 mL), and when

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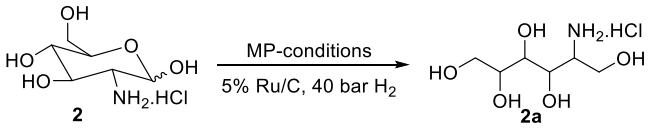
used, $[N_{8881}][Cl]$ or $[P_{8881}][Ntf_2]$ (500 mg), was set to react in an autoclave at T in the range of 90−110 °C and in the presence of variable amounts of 5 wt % Ru/C (50−150 mg: 8−24 mol % of Ru with respect to **2**). A constant H_2 pressure of 40 bar was applied. The results are reported in Table 1.

Table 1. MP Hydrogenation of D-Glucosamine Hydrochloride in H_2O/i-Oct with and w/o ILs



entry	T (°C)	MP system[a]	t (h)	cat. amount (% mol)[b]	conv. (%)[c]	sel. (2a, %)[d]
1	90	H_2O/*i*-Oct	17	24	<0.1	<0.1
2	110		17	8	3	nd
3	110		12	24	13	>99
4	110		17	24	28	>99
5[e]	110	H_2O/$[P_{8881}][Ntf_2]$/*i*-Oct	17	24		
6[e]	110	H_2O/$[N_{8881}][Cl]$/*i*-Oct	17	24		

[a] *i*-Oct: isooctane. [b] % mol of Ru with respect to **2**. [c] Selectivity toward 2-aminosorbitol hydrochloride (**2a**). Other conditions: **2** (70 mg, 0.32 mmol) in water (5 mL), isooctane (5 mL), and 5 wt % Ru/C (50−150 mg: 8−24 mol % of Ru with respect to **2**). [d] Conversion and selectivity to **2a** were determined by ^{1}H-NMR, nd, not determined. [e] Entries 6 and 7: reactions in the presence of $[N_{8881}][Cl]$ or $[P_{8881}][Ntf_2]$ (500 mg each), respectively.

We were pleased to notice that Ru/C appeared perfectly segregated in isooctane in the biphase- or in the IL-phase in the triphase system. Thus, the resulting final aqueous solution was easily recovered and analyzed by ^{1}H-NMR. Screening tests demonstrated for the first time that the MP hydrogenation of D-glucosamine hydrochloride was feasible: in the water/isooctane biphase, albeit with limited conversion (≤28%), the expected hydrogenation product, 2-aminosorbitol hydrochloride (**2a**), was achieved with excellent selectivity (>99%) at 110 °C (entries 2−4). The structure of the product was confirmed by ^{1}H, ^{13}C, COSY, DEPT-135, and HSQC NMR (details are in the Supporting Information, Figures S6−S10). Unsatisfactory results were instead obtained in the presence of the ILs that completely inhibited the reaction (entries 5 and 6). Attempts to improve the conversion by further increasing the temperature proved unsuccessful because the reaction selectivity was compromised: at 130 °C, compound **2a** was formed along with a mixture of unidentified byproducts detected by GC analysis of the water phase. In analogy to the result described during the high-temperature hydrogenation of *N*-acetyl glucosamine,[26] the observed compounds (side-products) were plausibly light polyols deriving from the hydrogenolysis of the reagent **2** or the product **2a**. It should be noted here that the deamination of glucosamine hydrochloride was described only at 200 °C, in acidic aqueous solutions.[36]

Additional tests carried out using a single water phase proved that the reaction was comparably faster than in the MP system; though, painstaking centrifugation and filtration steps were necessary for product isolation and catalyst recovery (details are in the Supporting Information, Table S1). This led to conclude that MP conditions of Table 1 were perfectly suited to separate Ru/C out of the aqueous phase, but that catalyst confinement was even too effective and unfavorable to the reaction kinetics (and conversion). A different approach was therefore envisaged to reduce the energy barrier at the water/isooctane liquid−liquid interphase.

MP Reactions in Water/Isooctane with OLs. Interactions and partitioning at the water−organic solvent(s) interphase strongly depend on specific characteristics of solvent(s) including polarity and surface tension (ST).[37] In this work, new MP systems were prepared by adding a third OL to the water/isooctane biphase. A literature survey and the visual inspection of a variety of ternary mixtures led us to choose THF, 2-methyl-THF (Me-THF), *methyl* isobutyl carbinol (MIBC), and CPME as most promising OLs not only for their suitability to generate stable MPs, but also for their commercial availability, moderate/low cost, and applications in the processing of biomass.[38−43] Interestingly, MiBK was another effective OL, but it could not be used under the conditions of Table 1 because it was fully converted into its hydrogenated derivative MIBC (details are in Supporting Information, Scheme S2).

Figure 2 shows the behavior of a model system used by us and composed of water, isooctane, and THF with and w/o the presence of Ru/C.

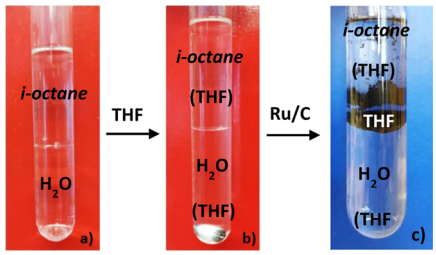


Figure 2. MP systems: (a) H_2O/isooctane; (b) H_2O/THF/isooctane; (c) H_2O/THF/isooctane/Ru-C.

At rt, when THF (2.5 mL) was added to an equivolume water/isooctane mixture (5 mL each; left), a clean biphase was obtained where THF was partitioned in the aqueous solution and the hydrocarbon (center). However, upon the further addition of powdered Ru/C (150 mg), mixing, and final settling (right), the catalyst was fully confined out of water and interestingly, a third liquid layer of THF appeared in between isooctane (top) and water (bottom) (right). This was very likely due to a strong interaction/adsorption of Ru/C and the OL: the same hypothesis was assumed in a study on the Ru/C-catalyzed hydrogenation of ketones where unusual kinetic effects were determined by aprotic polar solvents (γ-butyrolactone, acetonitrile, and THF).[44] The phase/catalyst separation of Figure 2 was effective even when D-glucosamine hydrochloride (up to 100 mg) was dissolved in the system, but it failed in the absence of isooctane. In the latter case, Ru/C was uniformly dispersed in a single THF/water liquid phase. The hydrocarbon, though just a spectator solvent, was crucial for phase segregation.

A similar result was achieved also with other OLs though the third liquid phase of Figure 2c was not observed. Moreover, in all cases, the catalyst segregation was observed even with smaller OL volumes in the range of 0.5−2.0 mL.

As for interphase phenomena in most mixtures of immiscible or partially miscible liquids and solids,[45] microscopic effects responsible for the behavior of Figures 1 and 2 are very hard to explain, but the resulting MP systems have remarkable

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applicative potential. Particularly, OLs with intermediate polarity between *i*-octane and ILs (less and more polar, respectively) may exhibit properties such as ST and solvency, suited to improve the contact between the catalyst and the reagents at the water/organic interphase and the transfer of gaseous hydrogen.

The water/isooctane/OL systems were therefore used to investigate the hydrogenation of compound **2**. Experiments were carried out under the conditions of Table 1, entry 4 (**2**: 70 mg, 0.32 mmol; 5% Ru/C: 150 mg, 24 mol % with respect to **2**; H_2O: 5 mL; isooctane: 5 mL; 110 °C; 40 bar of H_2; 12 h), in the presence of an OL.

Results are reported in Figure 3, which compares the effect of four OLs (THF, Me-THF, MIBC, and CPME) on the

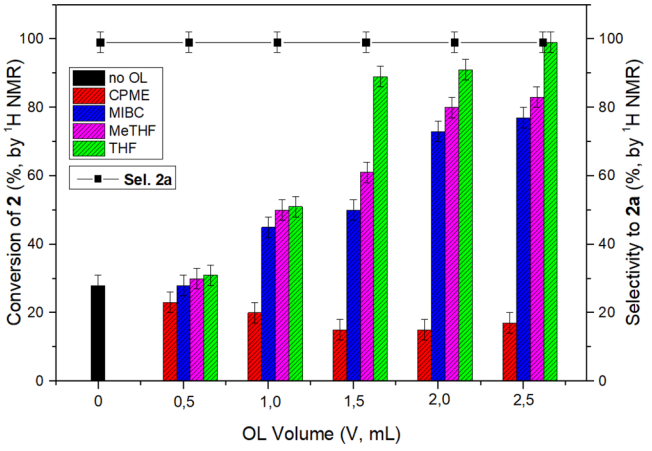
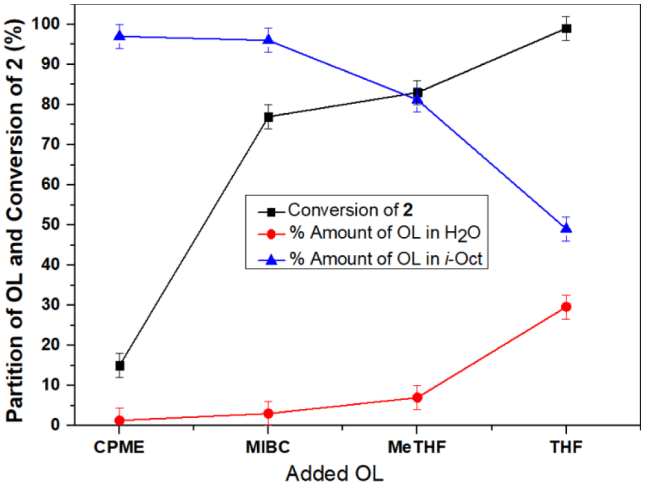


Figure 3. MP conversion of D-glucosamine hydrochloride (**2**) into 2-aminosorbitol hydrochloride. Conditions: **2** (70 mg, 0.32 mmol), 5% Ru/C (150 mg: 24 mol % with respect to **2**), H_2O (5 mL), isooctane (5 mL), OL (0.5−2.5 mL), 110 °C, 40 bar of H_2, 12 h. OLs were THF (green), MeTHF (pink), MIBC (blue), and CPME (red). (Average) Selectivity (%) to product **2a**: (black).

reaction conversion considering volumes of such additives in the range of 0.5 to 2.5 mL. For convenience, Figure 3 also shows the result of the reaction performed in H_2O/isooctane (entry 4, Table 1).

Not only the nature, but also the amount of the OL additives affected the reaction outcome. Except for CPME whose presence was detrimental compared to the use of the H_2O/*i*-Oct system alone (red and black bars, respectively), the increase of the volume (V) of any of the chosen OLs brought about a progressive increase of the conversion of glucosamine hydrochloride. The effect was evident starting from V = 1 mL at which a conversion of 45−50% was reached, and it became progressively more pronounced with further OL additions at the level that for V = 2.5 mL, a quantitative reaction was achieved with THF (green bar) and a conversion of 83 and 77% was obtained in the presence of MeTHF and MIBC, respectively (fuchsia and blue bars). Minimal, if any, improvements were noticed by further increasing the volume of both MeTHF and MIBC at 3 mL (not shown in the figure). In all cases, the selectivity toward product **2a** was >99% (black profile on top). At the end of the reaction carried out with added THF, the aq. solution was withdrawn using a syringe and rotary-evaporated (60 °C, p = 15 mbar). NMR analyses of the residual dried white sample confirmed the formation of 2-aminosorbitol hydrochloride (**2a**) in a >99% isolated yield (70.12 mg). No other resonance signals were detected, except for the expected ones, thereby proving a product purity >99%. For characterization details, see Figures S6−S10 in the Supporting Information.

Overall, the presence and nature of the added OLs dramatically impacted catalyst performance: results proved that the MP hydrogenation of **2** was achieved with full conversion and selectivity far higher than those achieved in a H_2O/*i*-Oct biphase. The reagent and products were confined in water, while the catalyst acted at the liquid/water interphase, in an *i*-Oct/OL suspension. To shed light on the mechanism at the basis of this finding and the different behavior of OLs, the partitioning of the four investigated liquid additives in water and in the hydrocarbon layer was studied. Experiments were performed as shown in Figure 3 at V = 2.5 mL: at the end of each MP reaction, the amount of the OL present in water and isooctane was measured by GC analyses upon calibration with solutions at known concentrations (further details are in the Supporting Information, Table S2 and Figures S1−S4). Results are reported in Figure 4. For convenience of discussion, a synoptic table at the bottom of this figure shows some selected



Entry	OL	Selected OL properties			
		WS (g/100 g)	ε	ST (mN/m)	η (cP)
1	THF	∞	7.60	26.40	0.55
2	MeTHF	14	6.97	3.29	0.60
3	MIBC	2.2	10.40	23.10	0.65
4	CPME	1.1	4.76	25.17	0.55

Figure 4. Partition of OLs in in water and in isooctane and conversion of **2** in MP experiments. All reactions were carried out under the conditions of Figure 2, using a H_2O/OL/*i*-Oct in 1:0.5:1 volumetric ratio, respectively (H_2O: 5 mL; isooctane: 5 mL; OL: 2.5 mL). Bottom: Selected properties of OLs from refs 40, 42: WS, water solubility; ε, dielectric constant; ST, surface tension; η, viscosity.

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properties (water solubility: WS; dielectric constant: ε; surface tension: ST; viscosity: η) of the used OLs.[46−48]

The partitioning of the OL was expressed as the percentage amount (amount of OL, %) of the additive found in water and in isooctane at the end of each reaction (red and blue profiles, respectively), with respect to the total volume (2.5 mL) of the OL added in the MP system. It should be noted that the sum of the % (H_2O + *i*-Oct) corresponded to the expected total (100%) in the case of MIBC and CPME, while it reached 87% (H_2O: 7%; *i*-Oct: 80%) and only 79% (H_2O: 30%; *i*-Oct: 49%) for Me-THF and THF, respectively. In the latter two cases, the complement to 100% was consistent with the formation of the third liquid layer of the OL described in Figure 2. From the visual inspection, the volume of this layer for THF was estimated at ca. 0.5 mL (ca. 20% of the total), while it was so small for Me-THF (ca. 0.2 mL) that it could not be even appreciated.

No immediate correlations were evident between the reaction outcome and the properties of the pure OLs and/or their partitioning in water and isooctane. The large drop of conversion observed by changing the OL from THF (99%) to Me-THF (84%), MBIC (79%), and CPME (15%) apparently followed the progressive decrease of WS from ∞ to 1.1 g/100 g, respectively (Table: entries 1−4). However, the minor differences between MIBC and CPME (in both the WS values and the H_2O/*i*-Oct partition) did not justify why the conversion was ca. 5-fold lower with CPME than with MIBC; also, except for WS, other properties of CPME (ε, ST, and η) were very similar to those of THF. This complexity suggested that the overall effect of the OL in the MP system had to be caused by multiple reasons including, among others, the catalyst−OL interactions and the behavior of the water-OL solution in which the reaction took place.

These aspects were examined through a literature analysis. The selective partitioning of 5% Ru/C, the same catalyst used in this study, in a hydrocarbon phase of a H_2O/*i*-Oct system was previously observed by us during MP reactions of levulinic acid (Figure 1).[19] This phenomenon was interpreted through in depth characterization of a variety of carbon samples which led us to propose the occurrence of catalyst−isooctane interactions mediated by both the low surface acidity of the C-support[49] and the presence of non-negligible quantities (0.1−0.2%) of Na-based impurities on commercial Ru/C. Particularly, the C-surface acidity (due to carboxylic, phenolic, lactonic, and ether groups) affected the catalyst hydrophobicity, which also meant that if different carbon supports were used, the catalyst partitioning changed in the MP system. Another study on the hydrogenation of carbonyl compounds reported that apolar hydrocarbon solvents were far loosely adsorbed by the catalyst (Ni/SiO_2) compared to aprotic polar media: for example, the adsorption enthalpy of cyclohexane and THF was 3 and 19 kcal/mol, respectively.[50] A similar strong adsorption of acetonitrile and THF over Ru/C was invoked to discuss the solvent effect on the reduction of 2-butanone.[36] Moreover, a specific interaction between the oxygen atom of polar solvents (acetone and THF) and surface Ru atoms of a Ru/Al_2O_3 catalyst was described to account for a drastic inhibition of the hydrogenation rate of aromatic substrates.[51] The unique properties of the THF−water pair should also be mentioned here: interestingly, at *T* between 60 and 145 °C and at 0.3−2.8 (THF/H_2O) mass ratios, the two solvents spontaneously phase-separate, while below and above this range, they are fully miscible with each other.[52,53] This temperature-mediated miscibility gap has proven attractive in the design of processing strategies involving both biphasic and monophasic solvent regimes, especially for lignin valorization.[54]

These findings allowed us to further comment the results of Figure 3 based on the OL adsorption on Ru/C. In particular: (i) the oxygenated polar aprotic OLs used in this work favored catalyst segregation in the OL/*i*-Oct phase plausibly because of H-bonding between the OL and the functional groups on the carbon surface and direct O-Ru interactions; (ii) OL−catalyst interactions could be so strong as to inhibit the metal active sites. The structure of CPME − for reasons that remain to be clarified − seemed the most suited to adsorb on Ru/C and deactivate it. Moreover, because of its hydrophobicity, CPME was fully available in the same phase (OL/*i*-Oct) with the catalyst during MP hydrogenations; (iii) Figure 3 indicated that the significant partitioning of THF in water was one of the crucial differences with the other OLs. However, under the conditions for MP experiments (110 °C, THF/H_2O = 0.45 mass ratio), the phase-separation effect induced by the above-discussed miscibility gap could generate a liquid triphase similar to that of Figure 2, where the intermediate layer, enriched in THF, could display a (reduced) energy barrier at the water/OL interphase favorable to the reaction.

Whatever the reasons, THF was by far the best OL among those tested in this study. It should be noted that THF is considerably less toxic than other widely used polar aprotic solvents [dimethylformamide, dichloromethane, and DMSO],[55] and there is a body of examples that largely recommends its use for the processing of biomass, one for all the cosolvent enhanced lignocellulosic fractionation processes for lignin deconstruction.[46,47] THF, however, is not listed among green solvents/compounds as MBIC, CPME, and Me-THF. To address this aspect, the investigation of the H_2O/THF/*i*-Oct MP system was continued to explore both the catalyst recycling and the recovery of the OL.

Catalyst Recycling and Leaching Tests. The cost of the catalyst in a liquid-phase reaction may represent up to one third of the total cost of the process, implying that its loss by leaching or other reasons is critical, and its recovery and reuse are crucial.[56] Accordingly, recycling experiments were designed under the MP conditions of Figure 3 (**2**: 70 mg, 0.32 mmol; 5% Ru/C: 150 mg, 24 mol % with respect to **2**; H_2O: 5 mL; isooctane: 5 mL; THF = 2.5 mL; 110 °C; 40 bar of H_2; 12 h): once the first reaction was complete, the lower aqueous phase was removed from the vessel and replaced with a fresh mixture of **2** (70 mg) in water (5 mL) to restore the initial solution. This sequence was repeated four times, and each reaction was run twice to ensure reproducibility. Thereafter, the recycling tests were continued further by replacing the aqueous phase with a fresh mixture of **2** (70 mg) in water (5 mL) both in the presence and in the absence of extra THF (0.75 mL). In all cases, the % amount of OL with respect to its initial volume was evaluated by GC in H_2O and isooctane. The results are illustrated in Figure 5. To not overburden the plot, the selectivity to product **2a** (always >99%) is not shown.

The MP system was suitable to recycle the catalyst without removing it from the reactor because Ru/C was perfectly confined out of water. However, the reaction conversion remarkably dropped from 99 to 58% from the first to the second run, to remain steady at ca. 55% in the two subsequent reactions (runs 3 and 4). The replacement of the aqueous solution of the product after the first reaction obviously

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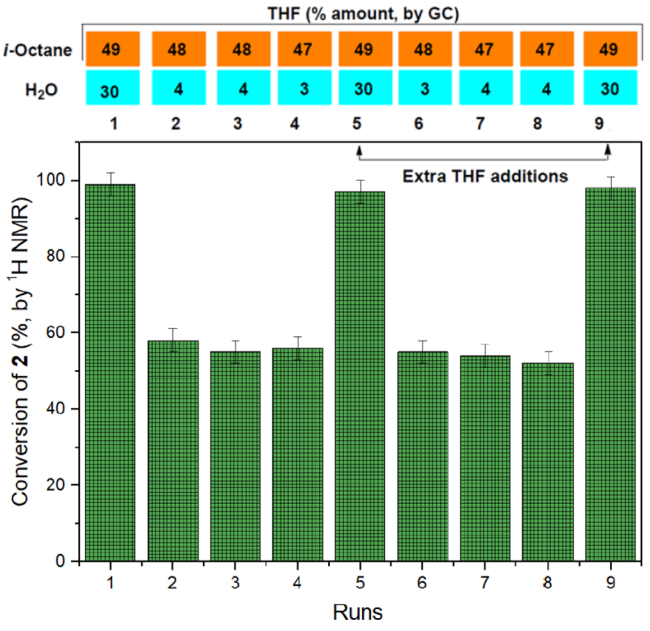

Figure 5. Recycling of Ru/C in nine subsequent runs in the conversion of D-glucosamine hydrochloride to 2-aminosorbitol hydrochloride. Conditions: **2**: 70 mg, 0.32 mmol; 5% Ru/C: 150 mg; H_2O: 5 mL; isooctane: 5 mL; THF = 2.5 mL; 110 °C; 40 bar of H_2; 12 h. In runs 5 and 9, extra THF (0.75 mL) was added to the fresh aqueous solution of the reagent. Top boxes: % amount of THF with respect to its initial volume, in isooctane (orange) and water (light blue).

implied the removal of THF partitioned in water which, according to Figure 2, amounted to approximately 30% (0.75 mL) of the starting volume. Intriguingly, when the fresh aq. phase was added in the second, third, and fourth runs, respectively, GC analyses proved that the residual THF continued to reside mainly in isooctane (1.1−1.2 mL which corresponded to 47−49% of the initial volume: orange boxes 2−4), with only a minimal amount distributed/partitioned in water (3−4% of the initial volume: light blue boxes 2−4). This observation led us to verify the effect of an extra addition of THF: after the fourth run, the fresh aq. solution of the reagent was added with THF (0.75 mL) to restore the conditions of run 1 (orange and light blue boxes, 5) and another reaction was started. Results showed that the conversion raised up to 97% which substantially matched the value reached in the first experiment. Further recycles corroborated the same trend: the conversion first decreased to ca. 52−55% without added THF (runs 6−8), but it readily improved again to 98% once the volume of THF was topped up to 2.5 mL (run 9). No clear reasons explained this behavior, especially the presence of a constant amount of the OL in isooctane regardless of composition of the water phase; the study, however, confirmed the role of THF which not only helped the catalyst/product separation but was fundamental to preserve the performance of Ru/C in the MP system.

Other recycling tests were performed under the conditions of Figure 5 (run 1) except that THF was topped up to keep its volume constant at the starting quantity (2.5 mL) after each reaction (details are in the Supporting Information, Figure S5A,B). Results demonstrated that both the conversion of **2** and the selectivity to **2a** were substantially steady and

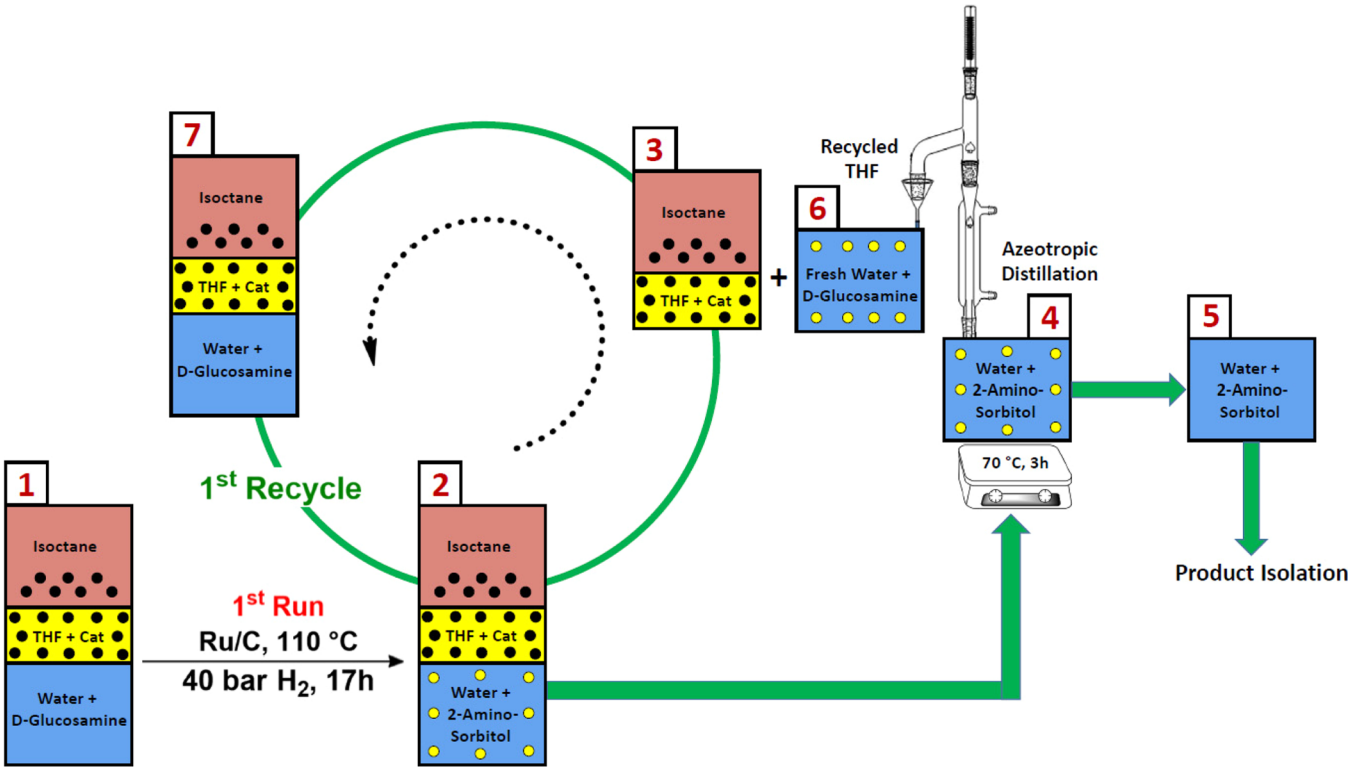

Figure 6. Semicontinuous catalytic hydrogenation of D-glucosamine under MP conditions, with integrated recycling of the catalyst and recovery/reuse of and THF. black circle = Ru/C; yellow circle = THF. The presence of THF was indicated only in boxes 2 and 4 to highlight the recovery of the OL and its reuse.

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quantitative through five subsequent runs. The visual inspection of these experiments highlighted the complete segregation of Ru/C in the OL/isooctane phase. However, to investigate any metal leaching/loss, aliquots (400 μL) of the aqueous/THF solutions recovered at the end of each recycling run were analyzed by ICP-MS to evaluate the Ru content. The dissolved Ru was <0.01 wt % with respect to the metal loading in the catalyst used for the reactivity tests, thereby proving that Ru/C was stable and reusable without loss of performance under MP conditions (details of ICP-MS measurements are in the Supporting Information, Table S3).

THF Recovery for Semicontinuous Hydrogenation of 2 and the Reaction Scale-Up/Productivity. With the aim of further improving the sustainability of the protocol, the study was focused on the design of a procedure for the recovery and recycling of THF without any topping up. The (extractive) distillation of THF from water, however, is complicated by the formation of a minimum-boiling azeotrope (63.5 °C, 1 bar; THF in an 83.69% mole fraction) which requires entrainers such as 1,2-propanediol, 1,4-butanediol, and DMSO able to disrupt H-bonding between the azeotrope components.[57,58] We were pleased to notice that the polyol structure of 2-aminosorbitol hydrochloride, the hydrogenation product of **2**, was perfectly suited to the scope. Indeed, the atmospheric distillation of the aqueous phase collected after the MP reactions carried out under the conditions of Figure 5 (runs 1, 5, and 9) allowed isolating THF in nearly quantitative yields (97−98%: 0.74 mL on average) and purity above 99%. This finding was crucial for the implementation of a model MP procedure for the hydrogenation of **2** in which both the catalyst recycling and the OL recovery and reuse were integrated. A schematic representation is given in Figure 6.

The protocol involved steps 1−7. After the MP hydrogenation of **2** (conditions of Figure 5: first run: 1 → 2), the water phase containing product **2a** was removed from the reactor (2 → 4), while the catalyst was stored in the OL/isooctane mixture (2 → 3). An azeotropic distillation was then carried out (70 °C, 1 bar) without any entrainers, and the distilled THF (>99% pure, ca. 0.74 mL) was added to a fresh aq. solution of the reactant (**2**: 70 mg; H_2O: 5 mL) (4 → 6). The solution of the product was stored for further isolation (4 → 5), while initial conditions were restored by combining the catalyst/THF/isooctane mixture with the THF/H_2O solution of the reagent (3 + 6 → 7). Finally, the first recycling was implemented (7 → 2), and the entire sequence was repeated. The overall arrangement proved perfectly suited to operate in a semicontinuous mode. After five subsequent runs, conversion and selectivity were both >99%, thereby confirming the robustness of the method. From one reaction to another, neither the isolation/purification of the catalyst nor the addition of extra THF or isooctane was required; the only apparent waste was water collected after the product isolation (by rotary evaporation) which in principle could be recycled to prepare fresh solutions of the reagent. If necessary, also the THF/isooctane mixture (box 3) could be rotary-evaporated, to provide a quantitative recovery of the original catalyst as a dry powder.

The E-factor associated with the process was also evaluated after the reaction and the first recycling, respectively, with and without the distillation of THF. Table 2 reports the results given the amount of the isolated product **2a** per cycle (70.12 and 70.08 mg after the reaction and the first recycling).

Table 2. E-Factor of the Semicontinuous Hydrogenation of D-Glucosamine Hydrochloride (2) to 2-Aminosorbitol Hydrochloride (2a)[a]

entry	reaction	waste (mg)		product **2a** (mg)	E-factor
		H_2O	THF		
1	first run[b,c]	5000	660	70.12	80.72
2			660		9.40
3	first recycling	5000	10	70.08	71.44
4			10		0.14

[a]The amounts of the reagent **2a** and the components of the MP system were those of Figure 6 (**2**: 70 mg, 0.32 mmol; 5% Ru/C: 150 mg; H_2O: 5 mL; isooctane: 5 mL; THF = 2.5 mL). [b]Entry 1: water was considered as a waste and THF in the THF/isooctane was not distilled. Entry 2: water was not considered as a waste, and THF was not distilled. [c]Entry 3: water was considered as a waste, but THF was distilled in 97−98% yield (0.74 mL = 650 mg) and recycled. Entry 4: water was not considered as a waste, and THF was distilled in a 97−98% yield and recycled.

Results confirmed that the E-factor was substantially improved with the distillation and the recovery of THF. Water was considered either as a waste (entries 1 and 3) or, as it is more often done, excluded from the calculation (entries 2 and 4). Accordingly, E decreased from 80.72 to 71.44 and even more significantly from 9.40 to 0.14 from the first run to the first recycling, thereby further corroborating the relevance of the semicontinuous hydrogenation.

The last step of this study involved scale-up and optimization of the Ru/substrate molar ratio (Q). Experiments were carried out under the conditions of Figure 5 (run 1), except that the amount of the reagent was progressively increased so that the Q ratio was reduced from 0.22 to 0.03. Results are reported in Table 3 where the reaction-specific

Table 3. Effect of the Ru:Substrate Molar Ratio (Q) on the MP Hydrogenation of D-Glucosamine Hydrochloride[a]

entry	D-glucosamine.HCl (mmol)	Ru:2 (Q, mol:mol)	conv. (%)[b]	select (%)[b]	P[c] (mmol 2a/(g_{cat} h))
1	0.32	0.22	>99	>99	0.18
2	0.47	0.15	>99	>99	0.26
3	0.93	0.075	>99	>99	0.52
4	1.39	0.05	>99	>99	0.78
5	1.86	0.037	86	>99	0.89
6	2.32	0.03	46	>99	0.60

[a]Conditions: **2** (0.32−2.32 mmol), 5% Ru/C (150 mg), H_2O (5 mL), Isooctane (5 mL), THF (2.5 mL), 40 bar H_2, 110 °C, and 12 h. [b]Conversion and selectivity to product **2a** determined by ^{1}H NMR. [c]P was the reaction productivity.

productivity (P) expressed as the mmol of 2-aminosorbitol hydrochloride produced per hour and per mass unit (g) of catalyst (P = mmol **2a**/(g_{cat} h) is also shown.

The hydrogenation of **2** proceeded with unchanged conversion and selectivity to **2a** (both >99%) when the Q ratio was decreased down to a factor of 4.4: the resulting productivity was more than quadrupled (entries 1−4). A further increase of the reagent amount (Q = 0.037) brought caused a drop of the conversion to 86%, but P continued to rise up to 5-fold its initial value [0.89 mmol **2a**/(g_{cat} h): entry 5]. Thereafter, if the concentration of **2** rose further, both the conversion and the productivity decreased (entry 6).

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Results proved that the process could be successfully intensified. Moreover, the catalyst segregation was observed in all cases, confirming the efficiency of the semicontinuous protocol of Figure 6 regardless of the catalyst/substrate molar ratio.

MP Hydrogenation of N-Acetyl-D-Glucosamine (3). The hydrogenation of N-acetyl-D-glucosamine (**3**) was investigated in the MP H_2O/THF/isooctane system optimized for D-glucosamine hydrochloride. Experiments were carried out at different temperatures and times in the range of 90−130 °C and 6−17 h, respectively. The volume of liquid components of the MP was kept unchanged compared to reactions with **2**, and the Ru/substrate molar ratio was set to 0.05, the most effective one reported in Table 2. Accordingly, a mixture of **3** (300 mg, 1.39 mmol), 5% Ru/C (150 mg: 5 mol % with respect to **3**), H_2O (5 mL), isooctane (5 mL), and THF (2.5 mL) was set to react under 40 bar H_2. Results are reported in Table 4.

Table 4. MP Hydrogenation of *N*-Acetyl-D-Glucosamine in a H_2O/THF/Isooctane System[a]

entry	T (°C)	t (h)	conv. (%)[b]	sel. **3a** (%)
1	90	8	32	>99
2		12	52	>99
3		17	76	>99
4	110	8	82	>99
5		12	>99	>99
6	130	6	73	nd[c]
7		12	>99	nd[c]

[a]Reaction conditions: N-Acetyl-D-glucosamine (300 mg, 1.36 mmol), 5% Ru/C (150 mg), H_2O (5 mL), isooctane (5 mL), THF (2.5 mL), and 40 bar H_2. [b]Conversion and selectivity to product **3a** (N-acetamidosorbitol) determined by ^{1}H-NMR. [c]Entries 6 and 7: the selectivity was not determined because of the onset of side-reactions, possibly because of the hydrogenolysis of the reagent.

The H_2O/THF/isooctane system proved suitable also for the hydrogenation of *N*-acetyl-D-glucosamine. The best conditions found for the reaction were the same as for compound **2**: particularly, a quantitative conversion of **3** and selectivity >99% toward N-acetamidosorbitol (**3a**) were achieved at 110 °C after 12 h (entry 5). At a lower temperature (90 °C), the conversion did not exceed 76% even after 17 h (entries 1−3), while at 130 °C, the selectivity was compromised by the onset of side-reactions, presumably because of the hydrogenolysis of the reagent. The observed side-products displayed NMR signals that partially overlapped to those of the product (**3a**), thereby making inaccurate the determination of the products amount and the corresponding selectivity.

The latter process was hypothesized in line with a previously reported paper[26] and was corroborated by the formation of unidentified byproducts. The latter were detected by GC analyses of the water phase collected after tests in entries 6 and 7.

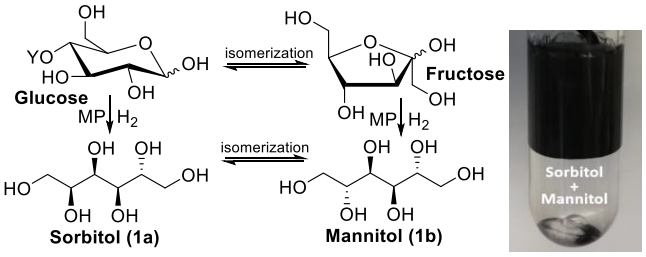
Importantly, the Ru/C appeared perfectly confined out of the aqueous solution in all experiments.

After the reaction of entry 5, water was withdrawn and product **3a** was isolated by rotary evaporation, in a quantitative yield (303 mg). It was fully characterized by NMR (details are in the Supporting Information, Figures S11 and S12).

MP Hydrogenation of Sugars. D-Glucose (1). The hydrogenation of D-glucose (**1**) to D-sorbitol (**1a**) has been extensively investigated because of the high market demand of **1a** mostly for human consumption, from foods to drugs and cosmetic products.[59] This popularity has largely contributed to the classification of sorbitol among the top 10 platform chemicals achieved from renewable feedstocks (biomass).[60,61]

The reaction has been often reported in aqueous solutions with commercial Ru/C catalysts,[27,62−64] but to the best of our knowledge, it was never explored in MP systems. Experimental conditions for the MP hydrogenation of D-glucose were designed in accordance with the protocols described for substrates **2** and **3**. Two procedures, A and B, were used to test the effect of the MP composition, the catalyst amount, the temperature, and the pressure. In the first one (A), a mixture composed of D-Glucose (75 mg, 0.42 mmol), water (5 mL), and isooctane (5 mL) was set to react in the presence of variable quantities of 5% Ru/C (45−150 mg) and at T and p in the range of 100−150 °C and 20−40 bar, respectively.

Table 5. MP Hydrogenation of D-Glucose[a]



entry	MP protocol	T (°C)	p (bar)	conversion (%)	selectivity (%)		
					sorbitol (**1a**)	mannitol (**1b**)	C_4−C_5 derivatives
1	A (w/o THF)	100	20	65	87	12	Trace
2		120		82	85	13	2
3		100	40	90	89	8	3
4		120		>99	87	9	3
5	B (with THF)	100	20	81	85	10	5
6		120		>99	84	11	5

[a]In all cases, a mixture of D-glucose (0.42 mmol, 75 mg), H_2O (5 mL), 5% Ru/C (45 mg: 5 mol % with respect to glucose), and isooctane (5 mL) was set to react for 12 h. Entries 5 and 6, procedure B: THF (2.5 mL) was added.

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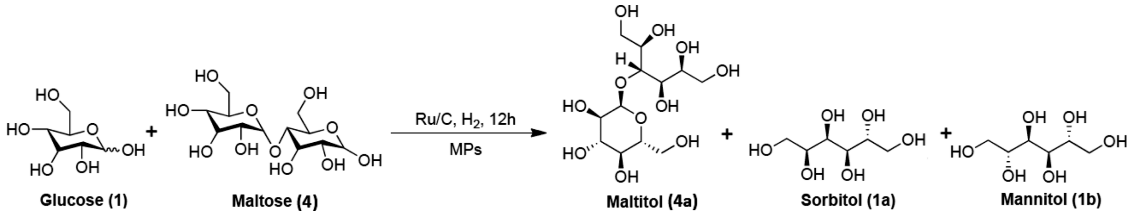
Table 6. MP Hydrogenation of the D-Maltose/D-Glucose Mixture[a]



entry	MP system	T (°C)	p (bar)	conversion (%)[b] 1	conversion (%)[b] 4	product distribution (%)[c] maltitol (**4a**)	sorbitol (**1a**)	mannitol (**1b**)	C_4–C_5 derivatives
1	A (w/o THF)	100	20	>99	93	73	21	6	Trace
2		120			98	70	23	7	Trace
3		150			>99	69	21	6	3
4		120	40		>99	71	21	8	Trace
5		120	60		>99	75	18	7	Trace
6	B (with THF)	120	20		94	74	22	4	Trace
7		150			>99	70	22	5	3
8		120	40		>99	65	20	15	Trace
9		120	60		>99	43	46	6	5

[a]In all cases, a mixture of D-maltose/D-glucose (75 and 25 mg respectively, **4**:**1** mass ratio = 3), 5% Ru/C (45 mg), H_2O (5 mL), and isooctane (5 mL) was set to react for 12 h. Entries 6–9, procedure B: THF (2.5 mL) was added. [b]Conversion of maltose and glucose determined through quantification by HPAEC-MS using the internal standard method. [c]% Amount of maltitol, sorbitol, mannitol, and C_4–C_5 sugars referred to the total of all observed products. This derived from the mass concentration of any product determined through quantification by HPAEC-MS using the internal standard method.

Procedure B was carried out under the same conditions of A, except for the further addition of a constant volume of THF (2.5 mL) in all reactions. Similarly to the behavior observed for compounds **2** and **3**, either without (A) or with (B) THF, the catalyst appeared perfectly segregated out of the water solution in which both glucose and the reaction products were present. The aqueous solution was analyzed by HPAEC-MS to evaluate the conversion and the selectivity of the process.[65] Calibration curves and reference standards of glucose, sorbitol, and mannitol were used to the scope (details are in the Supporting Information). The most representative results of this study are summarized in Table 5. Other details are in Supporting Information (Tables S4 and S5).

Experiments proved that MP conditions could be successfully applied to the hydrogenation of glucose (**1**). Two relevant aspects emerged:

i) the reaction was considerably faster with respect to that of glucosamine hydrochloride (**2**). Tables 1 and 4 showed that in the H_2O/isooctane system, the conversion of **2** reached only 28% after 17 h at 110 °C and 40 bar (Ru/substrate molar ratio of 0.22), while for glucose, an almost quantitative reaction was achieved at 100 °C after 12 h using a far lower Ru/substrate molar ratio of 0.05 (entry 3, Table 4). The same held true for *N*-acetylglucosamine: in the H_2O/isooctane/THF system, the hydrogenation of compound **3** required a higher catalyst amount, and higher T and p compared to glucose (compare, for example, entry 4, Table 4 and entry 5, Table 4). In line with these results, the few available studies on the comparative reactivity of glucose and its amino-substituted derivatives **2** and **3** have reported that also the outcome (rate and yield) of other transformations as the Maillard reaction or the formation of C–C bonds in the sugar derivatization was significantly influenced by the slight differences in the chemical structures of **1** and **2**.[66,67]

ii) the comparison of procedures A and B in Table 5 showed that at 120 °C, the reaction of glucose proceeded up to complete conversion in the H_2O/isooctane biphase (entry 4), but with added THF, the same result was achieved at a lower pressure (20 bar: entry 6). Albeit the effect of the OL was not as pronounced as that observed in the hydrogenation of compounds **2** and **3**, the presence of THF had a positive influence on the reaction kinetics. It should be noted here that a remarkable influence of the H_2 pressure was noticed also in the Ru/C-catalyzed reduction of fructose to a mannitol/sorbitol mixture.[68]

An excellent selectivity, higher than 84%, toward sorbitol (**1a**) was observed in all cases. This matched the best literature results that reported a sorbitol selectivity of 86–88%, at quantitative conversion, for the Ru/C-catalyzed hydrogenation of D-glucose in aqueous solution.[26] Minor amounts of mannitol (**1b**: 9–13%) and light C_4–C_5 sugars and sugars alcohols (trace-to-5%) were also detected. The first byproduct (mannitol) was due to the isomerization of sorbitol and/or glucose-fructose isomerization followed by fructose hydrogenation (Scheme on top of Table 5).[63] The latter path, however, was less plausible because not even traces of fructose were noticed in the final reaction mixtures. C_4–C_5 compounds were derived from side-hydrogenolysis processes. An increase in the formation of such compounds up to 5–10% of the total products was observed by increasing the reaction temperature to 150 °C (Tables S4 and S5).

D-Maltose (4)/D-Glucose (1). The hydrogenation of maltose (**4**) has remarkable synthetic applications because the product maltitol (**4a**) is a common low-calorie sweetener in nutritional programs and diabetic food and a pharmaceutical intermediate.[69] Ru-P and Ru-B amorphous alloys were reported as some of the most effective catalysts for the conversion of pure maltose into **4a**:[70,71] these systems allowed a selectivity >99% notwithstanding the hydrolytic instability of the glycosidic

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bond of the disaccharide could afford undesired products as glucose or its hydrogenated derivatives.[72] Interestingly, the raw materials used in the hydrogenation reactions for the industrial manufacture of maltitol are the so-called high-maltose syrups. These liquids with a maltose content >50% derive from the enzymatic breakdown of starch.[20,73,74]

In this study, a mixture of D-(+)-maltose (**4**) and D-(+)-glucose (**1**) in a 3:1 weight ratio, respectively, was used. The MP experiments were carried out under the same conditions of procedures A and B described in Table 5, except that glucose was replaced by the maltose/glucose mixture (100 mg). As for the case of glucose, the catalyst (Ru/C) was always perfectly confined out of the water solution. The conversion of both maltose and glucose and the distribution of products (from their mass-to-charge ratio) were determined by HPAEC-MS analyses of the aqueous phase. The most representative results are summarized in Table 6, while other analytical and reaction details are in the Supporting Information (Tables S6 and S7).

At 20 bar and in the range of 100−150 °C, both procedures A and B yielded similar results. The conversion of maltose and glucose was substantially quantitative (93− >99%) and the composition of the product mixture showed that maltitol (**4a**, 69−75%) was formed in an amount comparable to that of the reactant maltose, while glucose produced a mixture of sorbitol (**1a**) as the major derivative (21−23%) and mannitol (**1b**) (21−23%). C_4−C_5 sugars and sugar alcohols were detected in trace quantities (<1%) except than at 150 °C (3%) (entries 3 and 7). The results were consistent with: (i) the selective hydrogenation of the primary component of the reactant mixture, maltose, during which the glycosidic bond was preserved from undesired hydrolysis; (ii) the occurrence of both hydrogenation and isomerization processes by which structural isomers as the sugar alcohols sorbitol and mannitol were achieved from the minority reactant glucose; and (iii) the onset of hydrogenolysis reactions to a limited extent, only at high temperature.

As for the case of pure glucose in Table 5, the outcome of the procedures A and B was affected by the H_2 pressure. Exemplificative were the experiments at 120 °C: the increase of p from 20 to 60 bar did not appreciably change conversion and product distribution in the H_2O/isooctane system (A), while with added THF (B), a considerable decrease and increase of maltitol (43%) and sorbitol (46%), respectively, were noticed (entries 4 and 5 and 8 and 9). In other words, procedure B apparently favored the glycosidic bond rupture in maltose. It should be noted that very recent studies have demonstrated that surface weakly acidic groups of carbon-based catalysts are uniquely active for the hydrolysis of cellulose to produce cello-oligosaccharides (C−O) and glucose.[75] It was highlighted that the adsorption of C−O within the micropores of carbon strongly lowered the activation energy for the cleavage of the β-1,4-glycosidic bonds. In our case, albeit the mechanism by which the pressure acted remained unclear, the hypothesis was that the presence of THF improved the contact of Ru/C at the water/organic interphase, thereby facilitating the kinetics of maltose hydrolysis.

The results of Tables 5 and 6 were of immediate practical-synthetic potential. Major advantages of MP hydrogenations, especially in the H_2O/isooctane system, were easily recognized in the preparation of metal-free sugar alcohols which were substantially ready-to-use in aqueous solutions without any further purification, and in the recovery/recycling of a commercial hydrogenation catalyst through a semicontinuous procedure similar but even simpler (without THF distillation) compared to that implemented for aminosugars (glucosamine, Figure 6).

CONCLUSIONS

This paper describes a novel protocol for the selective hydrogenation of sugars and amino-/amido-sugars based on the use of MP systems in which reactants and products are converted and formed, respectively, in an aqueous environment, while the catalyst (Ru/C) acts outside the water in a hydrocarbon or a hydrocarbon/THF suspension. By adjusting the relative proportions of the liquid components, these systems offer unique possibilities compared to conventional procedures. For one thing, products are isolated free of any metal contaminant which is a highly desirable target especially when food and pharma are the final applications (i.e., for sugar alcohols). This is even more important in the case of Ru because its biological activity, mostly in its ionic forms, makes it a highly toxic metal that, if used as part of a catalyst system, must be completely removed from final products.[76] No less significant under MP conditions is the recycling of Ru/C in a semicontinuous mode which improves the efficiency of the downstream reaction processing by avoiding any handling and/or losses of the catalyst through multiple steps of filtration, centrifugation, washing, drying, and restoring in the reactor. This study demonstrates that in the MP system, Ru/C does not alter its hydrogenation performance after nine subsequent runs without ever being removed from the system; however, the upper limit for the catalyst reuse has not been determined and it is certainly far ahead. Moreover, in the semicontinuous mode, more than 97% of the used THF (if necessary) is recovered and reused cycle after cycle, the Ru leaching is negligible, below 0.01 wt %, and water is the only released compound.

The investigated MP procedure achieves significant process intensification which opens new perspectives for scalable applications. As an example, the productivity of 2-amino-sorbitol hydrochloride has been enhanced by a factor of 5, up to 0.5 gram scale, without any variation of the batch reactor size and the volumes of the liquid MP components. The protocol is robust although conditions may need a case-by-case optimization. The analysis of the substrate scope has shown that subtle structural differences between sugars and amino-/amido-sugars imply that the corresponding hydrogenation reactions are conveniently carried out with diverse MP arrangements: to reach a high conversion (>99%) and concurrently achieve the catalyst segregation, glucosamine and *N*-acetylglucosamine do require a H_2O/isooctane/THF system, while sugars are converted to sugar alcohols in a simpler H_2O/isooctane biphase. Further investigations on this aspect, particularly on the catalytic hydrolysis/hydrogenation of disaccharides and cellulose, are ongoing in our laboratories.

From the mechanistic standpoint, the study of MPs composed of a solid catalyst suspended in multiple immiscible and/or partially miscible liquids is extremely challenging. This investigation has highlighted that the presence of THF as a third liquid component of the reaction environment favors the catalyst/reactants contact and the reaction kinetics by plausibly reducing the energy barrier at the water/organic interphase; however, because Ru/C acts anyway out of the water solution where the reaction takes place, MP processes are generally

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slower with respect to those carried out in an aqueous phase only.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.1c08540.

Experiments for: (i) hydrogenations in aqueous solution; (ii) partition of OLs in water and isooctane; (iii) catalyst recycling in MP systems; (iv) ICP analyses; (v) MP hydrogenation of sugars; and (vi) NMR characterization of amino- and amido-sugar alcohols (PDF)

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D.P.: Conceptualization, investigation, methodology, and writing-original draft preparation; A.P.: Writing-reviewing and funding acquisition; E.B.: Analytical methodology and validation; M.F.: Analytical methodology and validation; E.A.: Analytical methodology and validation; M.S.: Conceptualization, supervision, writing-reviewing and editing, and funding acquisition (PDF)

Notes

The authors declare no competing financial interest.

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