Acceleration of transfer-hydrogenation of cyclohexene with palladium catalysts in the presence of polysaccharides

Oshrat Levy-Ontman[ID], Bar Tabibian[ID], Stanislav Shaklein[ID], Eyal Tzur[ID] and Adi Wolfson[ID]*

Department of Chemical Engineering, Sami Shamoon College of Engineering, Basel/Bialik Sts.,

Beer-Sheva 8410001, Israel

Abstract: Transfer hydrogenation of alkenes is a very attractive reduction pathway, as it does not involve hazardous metal hydrides or high pressure hydrogen. It can be easily performed with isopropanol as a solvent and hydrogen donor, using a homogenous or heterogeneous palladium catalyst. We present here, for the first time, that the addition of a xerogel composed of natural polysaccharides to the transfer hydrogenation of cyclohexene with palladium salts or Pd/C in isopropanol tremendously increased the reaction activity rate. The Carrageenans forms, and especially iota, were found to be the most useful additives in two scales that were tested.

1. Introduction

Reduction reactions are part of basic living pathways and very common transformations in organic chemistry. These reactions can be accomplished via removal of oxygen, addition of hydrogen, or gain of electrons[1]. One of the most widespread reduction reaction is saturation of unsaturated bonds, which can be achieved via three main different routes, using different reducing agents; (1) reduction with metal hydrides, (2) hydrogenation with molecular hydrogen, or (3) transfer hydrogenation (TH) that uses an organic compound as the hydrogen source[2].

While the use of metal hydrides requires special conditions and produces hazardous waste, and gaseous hydrogen necessitates precautions and special high pressure equipment, TH, in which hydrogen is usually transferred from an alcohol to an unsaturated bond, is a cheaper and more environmentally benign reduction method[3-6]. It proceeds in the presence of a variety of homogeneous and heterogeneous catalysts, from salts and complexes of transition metals[7,8] and their supported heterogeneous analogs[9,10] to supported pure metals[11,12]. Moreover, in many of these catalytic systems, an addition of catalytic amounts of an organic or inorganic base is also required to activate the metal

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* Corresponding author: E-Mail: adiw@sce.ac.il, Phone: + 972547733805; Fax: + 972 86475636..

complex and/or to assist in proton dissociation from the hydroxyl group of the alcohol. Finally, although different alcohols can be used as solvent and hydrogen donor, isopropanol, i.e., 2-propanol (IPA), a commonly used solvent for many industrial processes, is frequently used due to its low price and low toxicity as well as high activity rate and availability.

Reduction of alkenes is a fundamental organic transformation, yielding useful alkanes[13,14] and cycloalkanes[15,16]. While a variety of methods are now available for the reduction of alkenes, catalytic hydrogenation is still the most widely used technique, while the TH of alkenes is much less studied. Nevertheless, different noble-metal catalysts, and especially palladium-based catalysts were employed in the TH of alkenes, using alcohols, formic acid, or hydroaromatic compounds as hydrogen donors[17,18]. Furthermore, earth metals were also recently successfully used for this purpose[19].

Cycloalkanes are saturated hydrocarbons that contain one ring, among which cyclohexane is the most studied and most important one[20,21]. They naturally appear in petrochemical feedstocks and renewable sources, but can also be synthesized by ring closing or ring forming reactions, using dihalogen compounds or Clemmensen reduction, or by reduction of cycloalkenes or aromatic rings. They are usually used as solvents in different paints and as blowing agents, as well as building blocks for other molecules in synthetic organic chemistry, and as an intermediate in the Nylon industry[22,23]. Finally, cycloalkanes are very similar to alkanes in reactivity, and they can be oxidized or halogenated.

As noted above, one route to produce cycloalkanes is via TH of the corresponding cycloalkenes, using both homogeneous and heterogeneous catalysts[24-28]. Yet, as homogeneous catalysts are difficult to separate from the reaction mixture and to be recycled, heterogeneous catalysts are more desirable for use in industrial processes.

The simplest and most straight forward catalysts for reduction or TH reactions are supported metal catalysts, using inorganic supports, such as activated carbon or oxides, or organic supports - mainly polymers[28]. Alternatively, heterogenization of homogeneous transition metal complexes, thereby combining the advantages of homogeneous and heterogeneous catalysis, e.g., high activity and selectivity and easy separation and stability, respectively, is also often used, employing both organic and inorganic supports[29,30].

Polysaccharides that are produced from various natural sources are emerging as very attractive and versatile materials. Most of these renewable and biodegradable organic polymers are very soluble in water and less soluble in organic solvents[31,32]. Moreover, their diverse functional groups, unique structure and physicochemical behavior are the main reasons for their growing use in many areas, such as food[33,34], pharmaceutical[35,36], and biomedical[37] industries, and they have also drawn a lot of attention to be used as supports for heterogeneous catalysis[38,39].

We recently synthesized polysaccharide-based supported palladium and rhodium catalysts that were tested in Suzuki[40-44] and Heck couplings and in TH of alkenes[45]. In all these catalysts, the metal center was immobilized to the polysaccharide with or without the assistance of a ligand, and the resulting catalysts were recyclable. Moreover, when $Pd(OAc)_2(TPPTS)_2$ or $PdCl_2(TPPTS)_2$, which were prepared from the corresponding palladium salts and the ligand TPPTS (sodium triphenylphosphine trisulfonate ligand), were heterogenized to iota carrageenan polysaccharide and employed in a Suzuki cross coupling reaction, the heterogeneous system yielded a higher activity rate than the homogeneous reaction with the parent salt or complex[40,41].

In this paper, we report for the first time, acceleration of the TH of cyclohexene by addition of pure polysaccharide xerogel to palladium catalysts. The effects of the catalyst type and the amount and the type of the polysaccharide on the reaction performances were also tested, using TH of cyclohexene as a reaction model (Figure 1).
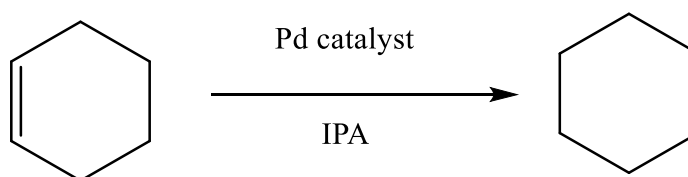
Figure 1. TH of cyclohexene in IPA

2. Experimental

Reagents: All polysaccharides and other chemicals (analytical grades) were purchased from Sigma-Aldrich Israel.

Preparation of xerogels: A xerogel was prepared as follows: First, 1 g of polysaccharide was dissolved in 100 mL DDW by heating the solution to 50 °C. The mixture was then stirred for several hours until a homogeneous solution was obtained. Then, 3 mL of 1% wt/v of the polysaccharide solution, was added together with 3 mL DDW to a 15 mL polypropylene tube that was sealed and then vortexed for homogenization. The next step was to deep-freeze the tube at −20°C for 24 h until all the liquid was frozen. The seal was removed, and the tube was then covered with a paraffin sheet pierced by a disposable toothpick and lyophilized for 48 h. At the end of this process, the dried 'sponge-like' xerogel was cut into pieces measuring ~ 1 cm × 1 cm and added to the reaction mixture.

Transfer hydrogenation of cyclohexene-small scale: An amount of 10 μmol of palladium, in homogeneous or heterogeneous form, was added to a vial with 5 mL isopropanol (IPA), which serves as a solvent and hydrogen source, together with 1.2 mmol cyclohexene, with or without addition of the xerogel polysaccharide. Then, the vial was placed in a preheated oil bath at 60 °C and magnetically stirred for 1-24 h. At the end of the reaction, the mixture was cooled. For cases in which a heterogeneous catalyst was used, the catalyst was removed by filtration of the reaction mixture through a paper filter. To determine the reaction conversion, the organic phase was then analyzed by gas chromatography (GC) by a HP-5 column.

Transfer hydrogenation of cyclohexane-Large scale: A corresponding amount of 600 μmol of palladium (5% wt. Pd/C) was added to a 1 L Buchi glass reactor with propeller stirrer, having 300 mL isopropanol (IPA), which serves as a solvent and hydrogen source, together with 72 mmol cyclohexene, with or without addition of iota xerogel. Then, the reactor was heated to 60 °C, using a jacket and an oil bath. Samples were obtained every 15 min to determine the reaction conversion, and the organic phase was then analyzed by gas chromatography (GC) by a HP-5 column.

3. Present Study

As previously mentioned, TH is an advantageous reduction route, being free from hazardous metallic hydrides or explosive pressurized hydrogen gas. Herein, the solvent also serves as a hydrogen donor, where IPA, a safe, non-toxic and relatively environmentally friendly alcoholic solvent, was widely employed. Thus, the investigation began with performing the homogenous TH reaction of cyclohexene with two commercially available palladium salts, $PdCl_2$ and $Pd(OAc)_2$, (Table 1 entries 1 and 2). As can be seen from the results in Table 2, $PdCl_2$ was much more active than $Pd(OAc)_2$ and reached a very high conversion after 4 h.

As noted before, our previous work in Suzuki cross coupling of halobenzenes and phenylboronic acids derivatives, showed that both palladium salts, $PdCl_2$ and $Pd(OAc)_2$, as well as their complexes with TPP, $PdCl_2(TPP)_2$ and $Pd(OAc)2(TPP)2$, could not be immobilized on polysaccharides[40-42]. On the contrary, addition of a sulfuric acid group to the ligand, yielding TPPTS, allowed the complex immobilization to the polysaccharide. Moreover, the new palladium-based polysaccharide catalysts, *i*-$PdCl_2(TPPTS)_2$ and *i*-$Pd(OAc)_2(TPPTS)_2$, showed superior performance when compared to the homogeneous parent salt or complex. In addition, it was found that addition of water to the Suzuki homogeneous reaction with both palladium salts accelerated the reaction, as reported before in the literature[46,47]. Thus it was assumed that the polysaccharide matrix offered a water-like surrounding, hence activating the reaction. Finally, $PdCl_2(TPPTS)_2$ and $Pd(OAc)_2(TPPTS)_2$ supported on iota xerogel or hydrogel that was prepared with chitosan, were also successfully used in the TH of cyclohexene[45].

Addition of water to IPA in the homogenous TH reaction of cyclohexene with $PdCl_2$ (Table 1, entry 3) yielded a lower conversion rate than the reaction without water (entry 1). Yet, when water was mixed with IPA solution of $Pd(OAc)_2$, it resulted in a much higher conversion rate in comparison to the reaction without water (Table 1, entries 4 and 2, respectively). In addition, performing a blank TH reaction, where neat iota xerogel (Figure 2) was added to the reaction mixture in the absence of palladium catalyst, did not yield any product. However, when neat iota xerogel was added to the reaction mixture with both palladium salts, a very high activity rate was observed (entries 5 and 6).

Figure 2. Iota carrageenan xerogel

As the addition of iota xerogel accelerated the reaction, it was suggested that this might be attributed to an interaction between the polysaccharide and the catalyst, yielding active palladium species. In addition, as the aim of the study was to obtain a heterogeneous catalytic system, it was suggested to perform the reaction also by adding xerogel to a reaction with commercially available and commonly used heterogeneous 5 wt.% Pd/C catalyst (Table 1, entries 7 and 8). As illustrated in Table 1, using Pd/C yielded a very high conversion rate, higher than those observed using the palladium salts (entry 7), whereas addition of iota xerogel to Pd/C also increased the reaction conversion, which reached almost 100% conversion after one hour (entry 8). Finally, using i-Pd/C composite, which was prepared by mixing Pd/C in aqueous solution of iota and freeze drying yielding Pd/C embedded in the polysaccharide xerogel, resulted in negligible conversion even after 24 h, probably as the polysaccharide was adsorbed on the carbon surface, and therefore blocked the palladium catalyst. Thereby, it was decided to use commercial available and heterogeneous Pd/C catalyst together with polysaccharide xerogel in the following experiments.

Table 1. TH of cyclohexene with different homogeneous and heterogeneous palladium catalysts[a]

Entry	Catalyst	Conversion (%)		
		1h	4h	24h
1	$PdCl_2$	52.4	90.6	100
2	$Pd(OAc)_2$	28.7	53.6	100
3	$PdCl_2$[b]	27.2	78	100
4	$Pd(OAc)_2$[b]	71.0	91.0	100
5	$PdCl_2$[c]	81.0	98.2	100
6	$Pd(OAc)_2$[c]	86.1	94.0	100
7	(5 wt%)Pd/C	83.4	100	-
8	(5 wt%)Pd/C[c]	98.7	100	-

[a]Reaction conditions: 1.2 mmol cyclohexene, 10 µmol Pd, 60 °C, 5 mL IPA.
[b]4 mL IPA and 1 mL water.
[c]Addition of 0.03 g iota xerogel.

As the addition of iota xerogel to the reaction mixture increased the activity rate, the next step was to check the effect of polysaccharide type on the conversion with Pd/C as catalysts (Table 2). Various representative polysaccharides with different functional groups on their backbone were tested, and the conversion was extremely affected by their characteristics. First, three forms of carrageenans were used: kappa, iota and lambda, which are all linear polysaccharides that differ in the amount of ester sulfate groups on the polysaccharide, one, two or three, correspondingly, and in their sulfate positions. In addition, the basic building block of lambda is not composed of the 3,6-anhydro-galactose as in the other forms. As illustrated in Table 2 (entries 2-4), the three carrageenans accelerated the reaction compared to the reaction without polysaccharide (entry 1), and yielded a higher conversion rate after 60 min, whereas iota yielded the highest conversions from the beginning

(entry 3). Although both iota and kappa have a similar basic building block of D-Gal-4-sulfate, 3,6-anhydro-D-Gal-2-sulfate and D-Gal-4-sulfate, 3,6-anhydro-D-Gal, respectively, it seems that the additional sulfate ester group in the iota further enhanced the reaction rate. However, employing lambda that bears higher sulfate ester, did not yield a higher conversion rate than those observed with iota. Therefore, it seems that the number of sulfate ester groups is not the only parameter responsible for the enhancement of the catalytic activity (e.g., the sulfate positions and monosaccharide blocks also have impact on the catalyst performances), or alternatively an optimal amount of sulfate groups is required. Alginate and xanthan, which besides hydroxyl groups also have a carboxylic group on their polymer chain, where alginate is linear and xanthan is branched, were also used. From the results in Table 2, it can be seen that alginate (entry 5) accelerated the reaction to a much higher extent than xanthan, yet less than the reaction with iota (entry 3). Furthermore, addition of xanthan yielded an even lower conversion rate than the reaction with only Pd/C (entry 6). The same phenomenon was observed also when guar-gum, which besides hydroxyl groups has no functional group on its backbone, was used (entry 7). Thus, it was concluded that the presence of a strong acid like sulfate ester groups on the polysaccharide accelerated the reaction, and iota was found to be the best additive among all tested polysaccharides.

Table 2. Effect of polysaccharide type on TH reaction conversion with Pd/C[a]

Entry	Polysaccharide	Functional Groups	Conversion (%)			
			15 min	30 min	45 min	60 min
1	none	-	5.3	13.0	41.6	83.4
2	Kappa	-OH, -OSO$_3$-	3.9	12.0	61.0	81.1
3	Iota	-OH, -OSO$_3$-	10.1	82.1	97.1	98.7
4	Lambda	-OH, -OSO$_3$-	6.3	41.0	79.2	90.8
5	Alginate	-OH -COO-	4.8	40.2	78.4	82.9
6	Xanthan	-OH -CH$_2$OCOCH$_3$ -COO-	5.0	6.3	11.0	34.9
7	Guar-Gum	-OH	2.2	2.5	2.9	6.7

[a]Reaction conditions: 1.2 mmol cyclohexene, 10 µmol Pd, 60 °C, 5 mL IPA, 0.03g xerogel

Finally, the effect of polysaccharides xerogel amount on the reaction conversion was also tested. For this purpose, we used two different systems, a vial with a magnetic stirrer containing 5 mL IPA (Table 3) and a glass Buchi reactor with a volume of 300 mL (Table 4). In addition, as the concentrations of cyclohexene and Pd/C in both systems were similar throughout the study, and only the amount of iota xerogel was changed, we calculated the progress in the reaction by a normalized yield, which reflects this change. As such, the normalized yield was calculated by the amount of the substrate that was reacted, i.e., multiplying the conversion by the initial amount of the substrate in moles, divided by the amount of the iota in grams and the reaction time in minutes. This measure is similar to the well-known and used measure of turn over frequency (TOF), yet, instead of measuring the specific activity of a catalytic center for a certain reaction it expresses the contribution of the polysaccharide addition to the activity of the reaction.

As illustrated in Table 3, increasing the amount of iota xerogel increased the conversion rate. Yet the reaction was fast even with a low amount of polysaccharide, yielding 100% after 1 h with all the iota loadings.

Table 3. Effect of iota xerogel amount on TH reaction normalized yield with Pd/C in small scale[a]

Entry	Amount of iota (g)	Normalized yield (mmol cyclohexane/g iota/min)		
		15 min	30 min	60 min
1	0.0075	0.427	3.947	2.640
2	0.015	0.320	2.133	1.320
3	0.03	0.267	1.093	0.660

[a]Reaction conditions: 1.2 mmol cyclohexene, 10 µmol Pd, 60 ºC, 5 mL IPA.

In addition, increasing the amount of the polysaccharide decreased the normalized yield (Table 3). This reveals that every amount of iota which was added has a much lower effect on the reaction, and it is enough to add a small amount of polysaccharide to accelerate the reaction. Moreover, when the normalized yield increased from 15 min to 30 min, it was decreased from 30 min to 60 min. This might be attributed to the fact that the reaction rate is fast at the beginning when the substrate concentration is high, and the rate decreases with time and almost reaches a plateau.

As the reaction was proceeded in a small amount using a magnetic stirrer, which also crushed the xerogel to powder, it can be postulated that using more controlled and efficient stirring will allow to explore the real contribution of the xerogel on the reaction. In the next stage, the TH of cyclohexene was also performed in a glass Buchi reactor, in a volume of 300 mL IPA, using Pd/C as the catalyst, where both the concentration of the catalyst and the substrate were comparable to those in the vial (Table 4). It is worth mentioning that the results in the table were noted until the time that the reaction reached almost 100% conversion.

Table 4. Effect of iota xerogel amount on TH reaction normalized yield with Pd/C in large scale[a]

Entry	Amount of iota (g)	Normalized yield (mmol cyclohexane/g iota/min)						
		15 min	30 min	45 min	60 min	75 min	90 min	120 min
1	0.03	6.40	11.20	16.00	24.00	112.00	139.20	160.00
2	0.06	9.60	56.00	69.60	76.00	-	-	-
3	0.15	2.88	19.20	25.92	28.48	30.08	-	-
4	0.30	1.12	9.12	12.32	13.92	14.88	-	-

[a]Reaction conditions: 72 mmol cyclohexene, 600 µmol Pd, 60 ºC, 300 mL IPA.

A control reaction with no polysaccharide reached 96% conversion after 120 min (not shown in the table). Addition of iota xerogel in a small amount (0.03 g) resulted in almost comparable conversions, and yielded 100% conversion after 120 min. However, doubling the amount of the polysaccharide to 0.06 g, tremendously increased the reaction rate, yielding 95% after 60 min. Nonetheless, further increase in the amount of the polysaccharide, to 0.15 g and 0.3 g, yielded 94% and 93% conversions after 75 min. As illustrated in Table 4, the normalized yield increases with the progress of the reaction. In addition, maximum normalized yield was detected when 0.06 g of iota was used, where a further increase in the polysaccharide amount decreased the normalized yield, revealing that it is not necessary to add extra polysaccharide. Hence, it was found that addition of a very small amount of iota xerogel can tremendously increase the TH reaction.

5. Conclusion

Transfer hydrogenation of cyclohexane over Pd/C was strongly accelerated by a simple addition of a renewable and commercially available polysaccharide xerogel to the reaction mixture. Both the type and the amount of the xerogel affected the activity. Among all the tested polysaccharides, carrageenans, which bare sulfate groups on their backbone, were the most useful additives, and among them iota carrageenan was the best. Finally, performing the reaction in a controlled and well stirred Buchi reactor allowed the use of a very small amount of polysaccharide.

ORCID 🆔
Oshrat Levy-Ontman: 0000-0002-3977-7066
Bar Tabibian: 0000-0003-0405-0120
Stanislav Shaklein: 0000-0002-5764-3862
Eyal Tzur: 0000-0002-0384-1919
Adi Wolfson: 0000-0002-8013-0846

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