Title:

Selective oxidation of glycerol to dihydroxyacetone (DHA): a comparison between neocuproine-Pd(OAc)\(_2\) based catalyst and an its dimeric form

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Abstract

The behaviour of two different organometallic complexes based on Pd were examined in depth with the aim to obtain the selective oxidation of glycerol to 1,3-dihydroxyacetone (DHA). An high glycerol conversion (93.5%) was obtained in a acetonitrile/water mixture in the presence of oxygen as a terminal oxidant.

1. Introduction

Much attention has been given to the transformation of biomass derived chemicals to valuable chemicals [1-4]. In the bio-refinery glycerol is a renewable feedstock because it is the coproduct of triglyceride saponification and biodiesel fuel manufacture. The present demand of glycerol cannot compensate its production and, for this reason, new procedures for the transformation of glycerol into valuable chemicals are highly desired [5-7]. Oxidation with molecular oxygen is one of the most attractive ways to achieve glycerol transformation even considering the low cost of the reactants, their abundance and the only by-product, water, generated by the reaction. Usually in these kind of reaction the main problem is the selectivity, mainly due to the wide list of by-products coming from the oxidation[8-9]. DHA is currently produced in biocatalytic processes using the Gluconobacter Oxydans, a reaction that presents many drawbacks such as yield and DHA purity[10]. This last parameter is fundamental because DHA finds applications in pharmaceutical industry where the purity takes great importance. However, cause its complexity, direct aerobic oxidation of glycerol to DHA has been less studied than that to glyceraldehyde or glyceric acid[11]. In 2010 N.R.Conley and co-workers presented a research about the selective oxidation of glycerol into DHA using an organometallic catalyst based on Pd and 2,9-dimethyl-1,10-phenanthroline (neocuproine), figure 1c, at mild conditions,[12-13]

![Figure 1. The Pd complexes; (a) neocuproine-Pd(OAc)\(_2\), (b) neocuproine-Pd(MeCN)\(_2\)(OTf)\(_2\) and neocuproine-Pd(µ-OH)\(_2\)(OTf)\(_2\)]
In their work Conley and co-worker used benzoquinone (BQ) as main solvent, even if a mixture of water and CH$_2$CN was also proposed. The results presented were not suitable to take into the account the idea to scale-up the reaction. The BQ as main solvent should be avoided and a more environmental friendly one, as water, is highly desired for an industrial application. For the same reason in this study other themes like the catalyst synthesis accessibility or the possibility to reduce oxidation reaction time have been taken into consideration looking for developing an industrial DHA synthesis method.

A comparison between the catalyst proposed by Conley, Painter and co-workers and its monomeric form (figure 1a) is proposed. Indeed, the mandatory step to obtain the dimer form of the catalyst pass from the synthesis of the Pd-Neocuproine in its monomeric structure. This monomer form of palladium was tested for the selective glycerol oxidation because of its relative simplicity in the synthesis and of its lower possible environmental impact due to the fact that two less chemical reactions were required for the preparation.

2. Results and discussion

Monomer and dimer form of the Pd-organometallic catalyst were studied. The monomeric complex (PdNc-C) was synthesized from the reaction between Pd(OAc)$_2$ and Neocuproine [12]. The activation of CH$_2$CN was done using trifluoromethanesulfonic acid (triflic acid) [14-15]. Anhydrous CH$_2$CN and anhydrous reaction condition were necessary to reach the activation (figure 2). Once the CH$_2$CN was activated, its reaction with PdNc-C permitted to obtain Neocuproine-Pd(MeCN)$_2$(OTf)$_2$ (PdNc-A), last intermediate in the preparation of the dimer complex (PdNc-D).

All synthesis and products characterization have been monitored using High Pressure Liquid Chromatography (HPLC), Nuclear Magnetic Resonance (NMR), Inductively Coupled Plasma (ICP), Karl-Fischer (KF) and Matrix Assisted Laser Desorption Ionization (MALDI).

Once characterized the catalysts have been employed to study their activity and selectivity in the reaction of interest. The tests were performed in a batch reactor using pure glycerol (≥99%) and oxygen. Demineralized water, acetonitrile and their mixtures were employed as solvents. Mild conditions were avoided in order to reduce the reaction time. All tests have been performed with the idea to compare the monomer and dimer activity at the same experimental conditions. Two different molar ratios (MR) (mole of substrate/mole of catalyst) were tested with the aim to investigate the possibility to reduce the catalyst amount employed. Many authors in literature, indeed, have presented the catalyst activity but working at not reliable MRs (10%; catalyst weight/reaction substrate weight %) for an industrial application [12,16].
Summarizing the reactions were conducted varying five parameters: oxygen pressure (10 and 30 bar), temperature (40 and 60 °C), nature of the solvent (CH₃CN:water (10:1) mixture, CH₃CN:water (1:1) mixture and pure water), molar ratio (glycerol/catalyst equal to 16, 160 and 1600) and kind of catalyst (PdNc-C or PdNc-D).

It is important to underline how the oxygen, necessary for the re-oxidation of the Pd from Pd(0) to Pd²⁺ [12], has different solubility in water and CH₃CN. In CH₃CN the O₂ has solubility is eight times higher than in water [17].

PdNc-C was first tested in only pure water at different molar ratio (table 1). In this condition the glycerol substrate is highly soluble, overcoming any kind of mass transfer problem which could reduce the reaction efficiency. Of course, the oxidation agent (O₂) has a ten time less solubility comparing to acetonitrile environmental, the only other solvent reported in this article. The MR variation, passing from 16 to 1600, showed, as expected, a strong effect on the substrate oxidation. After a comparable kinetic value at the starting point the catalyst activity seems to reduce soon and quite rapidly (after 50 minutes) its activity reaching a plateau. This behaviour suggested a progressive de-activation of the catalyst as reported by Conley and co-workers [18] too and other authors [19-20].

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Table 1 - Results obtained employing PdNc in its monomeric as catalyst at different reactor conditions and with different solvent. *When the tests were conducted using acetonitrile:water 10:1 as reaction environment, the glycerol conversion could be determined only after reaction ending (final point) when solution was obtained adding the necessary water amount.

Variations in pressure and temperature parameters don’t affect the reaction behaviour. Here we report two oxidations conducted at 60°C and 30 bar versus 40°C and 10 bar respectively: the total glycerol conversion and DHA yield didn’t change (table 1).

Even the glycerol conversion was strictly function of the catalyst content all these tests showed a low selectivity in these conditions.

Recognizing the important role played by the MR (the conversion best results were obtained at high MR), a series of comparative tests (table 1) were performed at different conditions, maintaining unchanged the MR ratio, varying the main solvent with the aim to verify the role played by acetonitrile in the reaction of interest.

At 60°C and 30 bar the conversion level was quite the same using two different reaction solvents (85% in only water; 93% in the mixture acetonitrile and water 10:1). A significant difference was obtained comparing the DHA yield. It became double using acetonitrile as the main solvent. Again the catalytic activity decreased rapidly reaching a deactivated status.

Finally, differences in terms of DHA yield using monomer and dimer have been compared in a final set of trials. Comparing the two catalysts, at 60°C and 30 bar of oxygen, and maintaining constant the MR, the yield remained strictly depend on the acetonitrile presence at higher values of PdNc-D (table 2). Using a mixture 10:1 (CH₃CN:water), with a MR equal to 16 the yield improves from 2 to 2.5 times using dimer instead of monomer catalyst.
Many efforts will be necessary to reduce the catalyst decomposition and recovering. The importance of the solvents, such as CH₃CN and water, pressure and temperature was deeply explored and can offer new suggestion to develop new studies about the scale-up of this reaction. Many efforts will be necessary to reduce the catalyst decomposition and recovering.

3. Experimental and methods

Neocuproine-Pd(OAc)₂[24,25]; 5.28 g (23.52 mmol) of Pd(OAc)₂ (reagent grade 98%, Sigma Aldrich) were dissolved in 250 ml of anhydrous toluene (purity grade 99.8%, Sigma Aldrich). 5.00 g (24.00 mmol) of neocuproine were dissolved in 50 ml of CH₃Cl₂ (purity grade ≥ 99.5%, Sigma Aldrich). The neocuproine solution is added drop wise in 3 hours and the solution obtained was left under mixing for 16 hours to complete the reaction. The solution was used for the next synthesis step without isolation. HPLC analysis has been performed to monitor the reaction. The HPLC employed a C18 column using as mobile phase MeOH and pure water (gradient flow from 5% MeOH - 95% water to 95% MeOH - 5%water in 34 minutes).

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Table 2 - Results comparing activity of PdNc in its monomeric and dimeric form at different conditions.

2. Conclusion

This work underlines new important evidences about the two Pd organometallic complexes employed as catalysts. The effect plays by the CH₃CN is fundamental in terms of DHA yield. The conversion is not influenced by the composition of solvent, temperature and pressure do not influence the catalysts activity, but the yield. Even if the yield obtained with these two catalysts is comparable with the best results in literature [12,13,21-24], decomposition during the reaction remains a big problem and the catalyst cannot be considered a good candidate for industrial applications. Initially O₂ permits the catalysts re-oxidation, but after a brief period, about 50 minutes, decomposition took place and glycerol conversion rapidly moved to zero. At the end of the reaction a residual amount of glycerol remains into the reactor.

The comparison on monomer and dimer has showed how, even obtaining an higher yield, the values were too low to consider a positive result to work at MR=160. On the other hand, at these conditions, the results about the glycerol conversion suggested a low selectivity to DHA. Furthermore the results obtained suggest how the best operative conditions, without using BQ as main solvent, involved a large amount of CH₃CN. The water results to be a bad solvent for the selective oxidation to DHA even the activity does not change. The temperature and oxygen pressure have a smaller influence on the kinetic as showed in figure 11.
the activation was completed and it was possible to use the activated CH\textsubscript{3}CN for the synthesis next step. In three hours the activated CH\textsubscript{3}CN was dropped into the flask containing PdNc-C. H-NMR (600 MHz, Bruker, CD\textsubscript{3}CN): \(\delta 2.16 (d, 6H, J=6.34)\), \(\delta 3.02 (d, 6H, J=6.00)\), \(\delta 7.81 (d, 2H, J=2.00 \text{ Hz})\), \(\delta 8.11 (d, 2H, J=1.97 \text{ Hz})\), \(\delta 8.773 (d, 2H, J=1.98 \text{ Hz})\).

ICP: assay 99.6%; Karl-Fischer: Yield 84.15%.

**Neocuproine-[Pd(μ-OH)](OTf):** 0.800 g of PdNc-[A 1.128 mmol] dissolved in a four necks (capacity 100 ml) with 18 ml of CH\textsubscript{3}CN anhydrous. After the complete dissolution, 0.520 g (1.201 mmol) of PdNc-C were added. The solution was left under stirring for 3 hours and after this time was added 21 ml of diethyl ether (DE, laboratory reagent ≥99.5% by Sigma Aldrich) to obtain a solid precipitation \([9,10]\). The solution is left to decant for 15 minutes and subsequently filtered. The supernatant liquid is put in another one to be recovered.

MALDI 795.961 m/z

ICP: assay 87.9%; Karl-Fischer: Yield 77.5%

1,3-dihydroxy-2-propanone.

**GC-FID.** A volume from the sample was evaporated, frozen and lyophilized before 1 ml trifluoracetic anhydride (TFAA) addition. The TFAA permits the derivatization of the sample necessary for GC injection.

**HPLC-RID and -UV.** The analyses were carried out on an HP liquid chromatograph equipped with binary pump delivery system. The mobile phase was composed by a solution with 65:35 mM H\textsubscript{2}O:CH\textsubscript{3}CN containing 0.5 mM H\textsubscript{2}SO\textsubscript{4}, under isocratic conditions. Flow rate 0.5 ml/min and column temperature set on 25°C.

**References**

[22] Andrew J. Ingram, Dr. Diego Solis-Ibarra, Prof. Richard N. Zare and Prof. Robert M. Waymouth, Volume 53, Issue 22, pages 5648-5652
Supporting information

2.1 Neocuproine-Pd(OAc)\textsubscript{2} synthesis

In accord with Sheldon and co-workers \cite{14, 19} 5.28 g (23.52 mmol) of Pd(OAc)\textsubscript{2} (reagent grade 98%, by Sigma Aldrich) were dissolved in 250 ml of anhydrous toluene (purity grade 99.8%, by Sigma Aldrich). 5.00 g (24.00 mmol) of neocuproine were dissolved in 50 ml of CH\textsubscript{2}Cl\textsubscript{2} (purity grade ≥99.5%, by Sigma Aldrich). The neocuproine solution is added by drop wise in 3 hours and the solution obtained was left under mixing for 16 hours (figure 3).

Figure 3. The three steps for the synthesis of PdNc-C; (a) dissolution of Pd(OAc)\textsubscript{2} in toluene, mixing time = 95'; (b) drop wise of neocuproine solution, dropping time = 3h24'; (c) reaction time equal to 16 h; the guard tube ensures anhydrous conditions during the reaction

After this period the solid was filtered on silica filter and washed two times with acetone. The HPLC method developed to follow the reaction confirmed the complete consumption of neocuproine after 16 h.

Neocuproine-Pd(OAc)\textsubscript{2}

Figure 5. The H-NMR for the neocuproine-Pd(OAc)\textsubscript{2}; CH\textsubscript{3}CN was used as solvent in not saturated conditions; H-NMR (600 MHz, Brucker, CD\textsubscript{3}CN, environmental temperature): δ 1.87 (d, 6H), δ 2.88 (d, 6H), δ 7.64 (d, 2H, J=1.79 Hz), δ 7.97 (d, 2H, J=1.78 Hz), δ 8.53 (d, 2H, J=1.83Hz)

ICP and Karl-Fischer analysis permitted to fix the Pd assay to 95.52 % with a final yield of 87.5 %.
2.2 Neocuproine-Pd(MeCN)$_2$(OTf)$_2$ synthesis

The synthesis of this complex passes from the activation of CH$_3$CN [9,10,14]. The study confirmed the necessity to use the CH$_3$CN anhydrous. Mixing 3.30 mmol of triflic acid (reagent grade 98%, by Sigma Aldrich) with CH$_3$CN (0.33 M solution) after fifteen minutes the activation was completed and it was possible to use the activated CH$_3$CN for the synthesis (figure 4). In three hours the activated CH$_3$CN was dropped into the flask containing PdNc-C.

Figure 4. Triflic acid (TfOH) and CH$_3$CN (0.33 M) reacted together, after 15 minutes activated acetonitrile is used to react with PdNc-C. The PdNc-C was previously dissolved with CH$_3$CN anhydrous (1 ml every 100 mg of PdNc-C). The volume of TfOH:CH$_3$CN must respect the molar ratio between TfOH:PdNc-C equal to 2.5. The guard tube it is necessary to maintain the reaction in anhydrous conditions.

Neocuproine-Pd(MeCN)$_2$(OTf)$_2$.
The activation was confirmed because the product obtained, analysed with H-NMR, correspond to the structure in figure 1b (figure 6).
Figure 6. H-NMR on PdNc-A sample, the signal ratio between the two methyl groups in the theorized structure is equal to 1.055 and confirmed the structure proposed. The same ratio using no-anhydrous CH$_3$CN is equal to 0.5. In this picture a zoom in the chemical shift range related to the two methyl groups; H-NMR (600 MHz, Bruker, CD$_3$CN, environmental temperature): $\delta$ 2.16 (s, 6H, $J$=6.34), $\delta$ 3.02 (s, 6H, $J$=6.00), $\delta$ 7.81 (d, 2H, $J$=2.00 Hz), $\delta$ 8.11 (s, 2H, $J$=1.97 Hz), $\delta$ 8.773 (d, 2H, $J$=1.98Hz).

2.3 Neocuproine-Pd(μ-OH)$_2$(OTf)$_2$ synthesis

The synthesis started with 0.800 g of PdNc-A (1.128 mmol) dissolved in a four necks (capacity 100 ml) with 18 ml of CH$_3$CN anhydrous. After the complete dissolution, 0.520 g (1.201 mmol) of PdNc-C were added. The solution was left under stirring for 3 hours and after this time was added 21 ml of diethyl ether (DE, laboratory reagent ≥99.5%, by Sigma Aldrich) to obtain a solid precipitation [9,10]. The solution is left to decant for 15 minutes and subsequently filtered. The supernatant liquid is put in another one to be recovered.

The NMR analysis was not useful to identify correctly the dimer. In solution, indeed, the complex gave a large amount of by-products reaching a thermodynamic equilibrium between numerous different structures. To avoid this problem and to be sure about the nature of the complex another technique was employed, the MALDI (figure 7). This technique ensured a soft ionization, widely used in mass spectrometry for the organic molecules with a high molecular mass.

Figure 7. The MALDI spectrum shows two structures; the signal with a m/z value lower than 600 comes from the matrix

The ICP and Karl-Fischer analysis on the sample confirmed a Pd assay equal to 87.9% with a yield equal to 77.5% (greater than the results present in literature [9,10]).

In the table in figure 8 are summarized the results about the yield and Pd assay for each complex synthesized.

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Figure 8. The Pd assay and final yield from the synthesis of the complexes