Pt/C catalyst and its use in the hydrogenation of 6,9-Imino ether for at least ten cycles are also disclosed herein.

**Title:** A PROCESS OF RECOVERY OF Pt/C CATALYST IN THE PREPARATION OF AZITHROMYCIN DIHYDRATE

**Abstract:** A process of recovery of Pt/C catalyst from the hydrogenation of 6,9-Imino ether is carried out by isolating spent Pt/C by filtration, reactivating the wet spent Pt/C catalyst by treating the spent Pt/C with strong acid like perchloric acid and recycling the reactivated catalyst along with fresh catalyst in the weight ratio of 98:2 in next cycle of hydrogenation of 6,9-Imino ether. The regenerated catalyst and its use in the hydrogenation of 6,9-Imino ether for at least ten cycles are also disclosed herein.
FIELD OF THE INVENTION

The invention relates to a process of recovery of Pt/C catalyst from the hydrogenation of 6,9-Imino ether of formula (II)

Formula (II)

in the preparation of Azithromycin dihydrate of formula (I)

Formula (I)

BACKGROUND OF THE INVENTION

Azithromycin is a semi-synthetic macrolide antibiotic chemically related to Erythromycin. Azithromycin is a broad-spectrum bactericide and effective against a wide variety of microorganisms,
such as Hemophilus influenzae, Streptococcus pneumoniae, Mycoplasma pneumoniae, Staphylococcus aureus, and Mycobacterium avium, and many others.

The transformation of Erythromycin A into Azithromycin comprises the conversion of Erythromycin into its oxime; Beckmann's rearrangement of the Erythromycin oxime into 6,9-Imino ether; hydrogenation of the 6,9-Imino ether to 9-deoxo-9a-aza-9a-homoerythromycin A and further reductive methylation to obtain Azithromycin.

The hydrogenation of 6,9-Imino ether to a secondary amine, 9-Deoxo-9a-aza-9a-homoerythromycin A, is carried out by using Sodium borohydride in Methanol which is disclosed in J. Chem. Soc. Perkin Trans. 1, 1986, 1881; J. Org. Chem. 1997, 62, 7479-7481; US 4,328,334; US 5,869,629; International publications WO 01/00640; WO 03/082889 and WO 03/102009; or by catalytic hydrogenation in the presence of platinum dioxide and acetic acid as solvent, which is disclosed in Tetrahedron left. 1994, 35, 3025; International publications WO 94/26758 and WO 03/102009; or by catalytic hydrogenation in the presence of platinum over carbon (Pt/C) or rhodium over carbon (Rh/C) at 3-10 atm in solvent consisting of water-acetic acid-methanol mixture, which is disclosed in US 4,328,334; US 5,869,629; and EP 0,879,823. International publication WO 03/102009 describes hydrogenation of 6,9-Imino ether with platinum / carbon in water as solvent to which acid is added to adjust the pH till 4 followed by crystallization to obtain 9-Deoxo-9a-aza-9a-homoerythromycin A in crystalline form.

Further EP 0,879,823 discloses preparation of Azithromycin from 6,9-Imino ether by carrying out the hydrogenation and reductive methylation sequentially with the noble catalyst and hydrogen in the presence of formaldehyde. In this patent, the preferred catalyst is 5% rhodium over carbon but platinum, palladium or rhuthenium, can also be used. It is stated at page 3 line 20 of this patent that if so desired, the catalyst can be recycled and reused several times thus rendering the process more economic. It does not, however, give any procedure for recycling and reusing the catalyst.

WO 96/02323 discloses a catalyst containing platinum metal in at least two bond energy states deposited on titanium or vanadium silicalite for liquid phase olefin hydro oxidation where the oxidation catalyst is regenerated by burning off carbon coatings in a controlled manner at temperature from 350° to 650° C, followed by reduction with hydrogen.

WO 01/41926 describes the activation and regeneration of a hydro oxidation catalyst where the catalyst comprises of at least one metal selected from gold, silver, platinum group metal. The activation or
regeneration process involves contacting the catalyst with ozone. The regeneration stream contains ozone, oxygen, water, and helium; temperature for regeneration is 140°C and the processing time is 3 to 6 hours.

Chemical abstract 1976, 85, 37659C (Akimoto, Yumi Kuroda; Yaso, Kobayashi; Mitsubishi metal corporation) discloses the regeneration of spent catalyst Pt, Pd or Pu supported by various carriers such as SiO₂, Al₂O₃, C by treating the spent catalyst in chlorine atmosphere at 350°C to 750°C and subsequently treating in an inert gas containing ≥ 5%, heating at 150°C to 850°C.

All the above described activation and regeneration methods consume valuable time to heat up the catalyst to activation or regeneration temperature and cooling down to operating temperature. Further, high input of heat energy is required to effect the activation or regeneration process. Further, the reported activation and regeneration methods require treatment in which catalyst is heated in presence of ozone or chlorine atmosphere or inert gas, which needs special instrument.

The reported activation or regeneration methods will be time consuming, need special instrument and expensive. Further the activation or regeneration at high temperature may deteriorate or degrade the properties of Pt metal as catalyst, thereby affecting the catalyst lifetime.

OBJECTS OF THE INVENTION

An object of the invention is to provide a process of recovery of spent Pt/C catalyst by reactivation and recycling of the reactivated Pt/C catalyst in the hydrogenation of 6,9-Imino ether to 9-deoxo-9a-aza-9a-homoerythromycin A in the preparation of Azithromycin dihydrate.

Another object of the invention is to provide the process of recovery of Pt/C catalyst where reactivation of spent catalyst is carried out at room temperature and atmospheric pressure, which minimizes deterioration of the Pt/C catalyst, thereby prolonging the catalyst’s lifetime.

Yet another object of the invention is to provide the process of recovery of spent Pt/C catalyst where reactivation of spent Pt/C catalyst can be performed in a short period of time.

Yet another object of the invention is to provide the reactivated Pt/C catalyst, which is used in hydrogenation of 6,9-Imino ether in the preparation of Azithromycin without affecting yield and purity.
Yet another object of the invention is to provide the process for recycling of reactivated Pt/C where the recycling of reactivated catalyst can be done for at least ten cycles of hydrogenation of 6,9-Imino ether.

Yet another object of the invention is to provide the recovery process of the spent Pt/C catalyst which is a simple and economical.

Yet another object of the invention is to provide the process for recycling of Pt/C where the reactivation of spent Pt/C catalyst is carried out without need of regeneration of spent Pt/C catalyst for at least ten cycles of hydrogenation of 6,9-Imino ether.

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention discloses a process of recovery of Pt/C catalyst from the hydrogenation of the 6,9-Imino ether in preparation of Azithromycin dihydrate comprising isolating spent Pt/C catalyst from the hydrogenation of 6,9-Imino ether by filtration; reactivating the wet spent Pt/C catalyst by treating the same with strong acid till pH 3-6 while stirring; washing the treated catalyst with aqueous sodium carbonate solution followed by washing with hot water (55°C) till the pH of washing is neutral, to obtain reactivated catalyst; and recycling the reactivated catalyst along with fresh catalyst in the weight ratio of 98: 2 in the hydrogenation of 6,9-Imino ether.

The strong acid is selected from the group consisting of perchloric acid; halogenated acid like hydrochloric acid, hydroiodic acid, or hydrobromic acid; percarboxylic acid like peracetic acid or perbenzoic acid; or nitric acid.

The preferred strong acid is perchloric acid. Particularly, the perchloric acid used in reactivation of the spent Pt/C catalyst is 50% perchloric acid. The aqueous sodium carbonate used in the reactivation of spent Pt/C catalyst is 10% aqueous sodium carbonate.

The reactivation of catalyst (Pt/C) is carried out at room temperature, particularly 25 to 35°C and atmospheric pressure.

In the present invention, the spent Pt/C catalyst is treated with acid like perchloric acid or any above mentioned acid or with any other suitable reagents to oxidize the impurities present on the catalyst; washed with aqueous sodium carbonate solution to remove the oxidized impurities which goes into the
filtrate; further washed with water to remove sodium carbonate and thus obtained is the reactivated Pt/C catalyst with the free active sites, ready to use in new cycle of hydrogenation.

In the present invention the 6,9-Imino ether of formula (II)

![Formula II](image)

is hydrogenated by dissolving the 6,9-Imino ether in methanol, cooling the reaction mixture at temperature 5-6° C; adjusting the pH of the reaction mixture to 5.5 with 70 % perchloric acid; hydrogenating the reaction mixture with 20 % Pt/C catalyst with respect to 6,9-Imino ether, at temperature 30-50° C and pressure 10-14 kg/cm²; filtering the reaction mass to isolate wet spent catalyst; distilling out the methanol from the reaction mass to obtain residue, adding water to the residue, adjusting the pH of the reaction mass by adding 5 % aqueous sodium hydroxide solution; and filtering out the 9-deoxo-9a-aza-9a-homoerythromycin A, followed by washing 9-deoxo-9a-aza-9a-homoerythromycin A with water and drying at 65° C. The isolated wet spent catalyst is reactivate'd according to the invention and the reactivated Pt/C catalyst is recycled along with the fresh catalyst in the weight ratio of 98:2 in the hydrogenation of 6,9-Imino ether.

The reactivated Pt/C catalyst is recycled in the hydrogenation of 6,9-Imino ether for atleast ten times with subsequent reactivation by the above mentioned reactivation process at the end of the each cycle of hydrogenation.

The use of reactivated Pt/C catalyst or recyclization of the reactivated catalyst did not find any adverse affect on yield and purity of Azithromycin dihydrate.

The spent Pt/C catalyst is given out for regeneration only after the recycling the reactivated Pt/C catalyst for at least ten cycle of the hydrogenation of 6,9-Imino ether.
Further, 9-deoxo-9a-aza-9a-homoerythromycin A obtained from hydrogenation of 6,9-Imino ether is converted to Azithromycin dihydrate of formula (I);

![Diagram of Azithromycin dihydrate](image)

Formula (I)

by

a) methylating the 9-deoxo-9a-aza-9a-homoerythromycin A of formula (III);

![Diagram of Azithromycin dihydrate](image)

Formula III

with formaldehyde and formic acid in presence of lower chain alcohol /acetone to obtain Azithromycin dihydrate of formula (I);
b) isolating the Azithromycin dihydrate of formula (I);

by separating acetone/alcohol layer from the methylation of 9-deoxo-9a-aza-9a-homoerythromycin A mixture followed by adding water to the acetone/alcohol layer within 12 hours while stirring, further stirring the mixture at 20°C for 12 hours; filtering the Azithromycin dihydrate of formula (I);
washing the Azithromycin dihydrate with water and drying Azithromycin dihydrate at 65°C; and

c) purifying the Azithromycin dihydrate by dissolving it in a solvent like acetone or lower chain alcohol with stirring, adding charcoal to the solution with stirring, filtering the solution to obtain filtrate, adding water to filtrate at 50°-55°C, cooling aqueous filtrate to room temperature, chilling the aqueous filtrate to 0° to 5°C, filtering Azithromycin dihydrate from the aqueous filtrate; washing Azithromycin dihydrate with chilled water and drying Azithromycin dihydrate at 65°C.

Thus the invention provides the recovery process of the spent Pt/C catalyst where the reactivation of spent Pt/C catalyst is efficiently accomplished in a short period of time at room temperature and atmospheric pressure. Further, the reactivation of the spent Pt/C catalyst is carried out at room temperature and thus minimizing deterioration to the catalytic metal, thereby prolonged catalyst lifetime, which is an added advantage of the present invention. The process of recovery of spent Pt/C catalyst of the present invention is very simple to carry out, as it does not require any special instruments. The present invention provides a process for recyclization of the reactivated Pt/C catalyst along with the fresh catalyst in the hydrogenation of 6,9-Imino ether, which drastically cuts down the requirement of fresh platinum without affecting the output and the catalyst need to be sent for regeneration only after atleast ten cycles of hydrogenation making overall process of hydrogenation of 6,9-Imino ether efficient and economical.

The invention is further illustrated by the following examples, which should not construe the effective scope of the claims.

**Example 1A**

**Preparation of 6,9-Imino ether**

To 100 gm of Erythromycin thiocynate, 450 ml of methylene chloride was added at 25°C. To this, 100 ml of Liquid ammonia was added and reaction mixture was stirred till it gets cleared solution. Once the reaction mixture was cleared, the layers were separated and organic layer was collected. Methylene chloride of organic layer was completely distilled off to obtain residue. To the residue, 100 ml of
methanol was added followed by addition of 32 ml of triethylamine and 43.7 gm of hydroxyl amine hydrochloride. The reaction mixture was stirred at room temperature for 10 minutes and then the reaction mixture was refluxed for 25 hours. The reaction mixture was cooled to 55°C and the solvent was distilled off from the reaction mixture. The reaction mixture was further cooled to room temperature and 460 ml of methylene chloride was added to it. The pH of the reaction mixture was adjusted to 9.8 to 10.0 by adding ammonia. Organic layer was separated from the reaction mixture and washed the organic layer with water. The organic layer was cooled to 0° to 3°C. Chilled Sodium bicarbonate solution (1.24 % w/v) was added to the reaction mixture followed by addition of p-toluene sulfonyl chloride solution (50 gm of p-toluene sulfonyl chloride + 100 ml methylene chloride) at 0° ib 3°C and then reaction mixture was stirred for 2 hours at the same temperature. The pH of the reaction mixture was adjusted 5.4 to 5.5 by adding acetic acid. Organic layer was separated from the reaction mixture. The pH of aqueous layer of the reaction mixture was adjusted to 12 to 13 by adding Sodium hydroxide solution at 30° C. 6,9-Imino ether was filtered from the reaction mixture. The 6,9-Imino ether was washed with water and dried at 50° to 60°C. The yield and purity of 6,9-imino ether was 90 % and 95 %.

Example IB(A)

Hydrogenation of 6,9-Imino ether to 9-Deoxo-9a-aza-9a-homoerythromycin A

(Using Fresh Catalyst)

To the 650 ml of methanol, 100 gm of 6,9-Imino ether (prepared according to example IA) was added. The methanolic solution of 6,9-Imino ether was filtered after Charcoal treatment. The filtrate was chilled to 5° to 6°C. To this mixture, 70% perchloric acid solution was added to adjust the pH of the reaction mixture to 5.5. 20 gm of Pt/C catalyst was added to the reaction mixture. The reaction mixture was flushed with N₂ and then with H₂. The hydrogenation was carried out at temperature 42° C and 14 kg/cm² of pressure with stirring for 3 hours. The reaction was monitored by HPLC. The spent wet catalyst was filtered from the reaction mixture. Methanol was distilled out from the reaction mixture to obtain residue. 700 ml of water was added to the residue. The pH of the residue was adjusted with 5 % aqueous sodium hydroxide solution to 12-12.5. The precipitated 9-deoxo-9a-aza-9a-homoerythromycin A was filtered and washed with water. The product thus obtained was dried at 65° C. The yield and purity of 9-deoxo-9a-aza-9a-homoerythromycin A was 86.6 and 91%.

The spent wet catalyst, which was filtered during the hydrogenation of 6,9-Imino ether, was reactivated as per the example 2.
Example IB(B)

Hydrogenation of 6,9-Imino ether

(Using Reactivated Catalyst)

To the 650 ml of methanol, 100 gm of 6,9-Imino ether (prepared according to example IA) was added. The methanolic solution of 6,9-Imino ether was filtered after Charcoal treatment. The filtrate was chilled to 5° to 6°C. To this mixture, 70% perchloric acid solution was added to adjust the pH of the reaction mixture to 5.5. 20 gm of Pt/C catalyst comprising reactivated catalyst along with fresh catalyst in the ratio of 98:2 was added to the reaction mixture. The reaction mixture was flushed with N₂ and then with H₂. The hydrogenation was carried out at temperature of 42° C and pressure of 14 kg/cm² with stirring for 3 hours. The reaction was monitored by HPLC. The spent wet catalyst was filtered from the reaction mixture. Methanol was distilled out from the reaction mixture to obtain residue. 700 ml of water was added to the residue. The pH of the residue was adjusted with 5% aqueous sodium hydroxide solution to 12-12.5. The precipitated 9-deoxo-9a-aza-9a-homoerythromycin A was filtered and washed with water. The product thus obtained was dried at 65° C. The yield and purity of 9-deoxo-9a-aza-9a-homoerythromycin A was 91.5% and 91%.

The reactivated catalyst used in this example is prepared according to the Example 2. Further the spent wet catalyst, which was filtered during the hydrogenation of 6,9-Imino ether, was reactivated as per the example 2.

Example 1C

Preparation of Azithromycin dihydrate

To the 300 ml of acetone, 100 gm 9-deoxo-9a-aza-9a-homoerythromycin A (prepared according to Example IB) was added. The mixture of 17.49 ml of formic acid and 17.49 ml of formaldehyde was prepared. This mixture was added to 9-deoxo-9a-aza-9a-homoerythromycin A solution within 5 to 6 hours at 40° C. The reaction was monitored for 2 hours at 40° to 45° C. The pH of the reaction mixture was adjusted to 11 to 11.5 by adding sodium hydroxide solution. The charcoal treatment was given to reaction mixture. The acetone layer was separated from the reaction mixture. To the acetone layer, 650 ml water was added within 12 hour while stirring. The mixture was stirred at 20° C for 12 hours. After the completion of reaction, Azithromycin dihydrate was filtered and washed with water. Azithromycin dihydrate was dried at 65° C. The yield and purity of the Azithromycin dihydrate was 87% and 98%.
Example ID

Purification of Azithromycin dihydrate

To 10 g of Azithromycin dihydrate, 30 ml acetone was added for 30 minutes with stirring till the clear solution obtained. 0.3 g charcoal was added to this solution and the mixture was stirred for 30 minutes and subsequently filtered. To the filtrate, 180 ml of water was added at 50° to 55° C within 12 hour. The aqueous filtrate was cooled to room temperature and then chilled to 0° to 5° C. Azithromycin dihydrate was filtered from the aqueous filtrate and washed with chilled water (0° to 5° C). Azithromycin dihydrate was dried at 65° C. The yield and purity of Azithromycin dihydrate was 95% and 100%.

Azithromycin dihydrate was characterized with IR (Refer Figure 1 of the Accompanying drawing).

Example 2

The spent wet Pt/C catalyst obtained from the hydrogenation process of 6,9-Imino ether by filtration (according to Example IB) was treated with 50% of perchloric acid till the pH of the catalyst solution was adjusted to 5.1 to 5.3 while stirring. The catalyst was filtered off while the pH of the catalyst solution was acidic i.e. 5.1 to 5.3. The reactivated catalyst was washed with 10% of aqueous sodium-bicarbonate solution followed by washing the catalyst with hot water (55° C) till the pH of the filtrate was neutral.

Example 3

Azithromycin dihydrate was prepared by the procedure as described in the Example IB to ID where Pt/C catalyst was reactivated according to the Example 2 and further the reactivated Pt/C catalyst was recycled along with the fresh catalyst in weight ratio of 98:2 in the hydrogenation of 6,9-Imino ether to 9-deoxo-9a-aza-9a-homoerythromycin A, for nine times in the preparation of Azithromycin dihydrate. The percentage yield and purity of 9-deoxo-9a-aza-9a-homoerythromycin A and subsequently Azithromycin dihydrate by recycling the reactivated Pt/C catalysts in the hydrogenation of 6,9-Imino ether till nine cycles are reported in table 1.
Table 1: Yield and purity of 9-deoxo-9a-aza-9a-homoerythromycin A and Azithromycin dihydrate

<table>
<thead>
<tr>
<th>Cycle</th>
<th>9-deoxo-9a-aza-9a-homoerythromycin A</th>
<th>Azithromycin dihydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Yield</td>
<td>% Purity</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>91.2-91.5</td>
<td>92.87</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>90</td>
<td>90.6-91</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>89</td>
<td>90.46</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt;</td>
<td>83</td>
<td>89.9</td>
</tr>
<tr>
<td>5&lt;sup&gt;th&lt;/sup&gt;</td>
<td>90</td>
<td>86.96</td>
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<td>85</td>
<td>86.12</td>
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<tr>
<td>8&lt;sup&gt;th&lt;/sup&gt;</td>
<td>87</td>
<td>89</td>
</tr>
<tr>
<td>9&lt;sup&gt;th&lt;/sup&gt;</td>
<td>85</td>
<td>85</td>
</tr>
</tbody>
</table>

The % yield and % purity of 9-deoxo-9a-aza-9a-homoerythromycin A by using fresh catalyst was found to be 86.6 and 91 respectively. The % yield and % purity of Azithromycin dihydrate by using fresh catalyst was found to be 95 and 100 respectively. The yield and purity of Azithromycin dihydrate as obtained in Example IB (A) and ID and Table 1 by recycling the reactivated catalyst was found to be more or less same as compared to fresh catalyst. The experimental finding further supports, the reactivation method by the invention did not deteriorate or degenerate the catalytic metal.
1. A process of recovery of Pt/C catalyst from the hydrogenation of the 6,9-Imino ether in preparation of Azithromycin dihydrate comprising isolating spent Pt/C catalyst from the hydrogenation of 6,9-Imino ether by filtration; reactivating the wet spent Pt/C catalyst by treating the same with strong acid till pH 3-6 while stirring; washing the treated catalyst with aqueous sodium carbonate solution followed by washing with hot water till the pH of washing is neutral, to obtain reactivated catalyst; and recycling the reactivated catalyst along with fresh catalyst in the weight ratio of 98:2 in the hydrogenation of 6,9-Imino ether.

2. The process as claimed in claim 1, wherein the strong acid is selected from the group consisting of perchloric acid; halogenated acid like hydrochloric acid, hydroiodic acid, or hydrobromic acid; percarboxylic acid like peracetic acid or perbenzoic acid; or nitric acid.

3. The process as claimed in claim 1, wherein the preferred strong acid is perchloric acid.

4. A reactivated catalyst prepared by the process as claimed in any one of claims 1 to 3.

5. The reactivated catalyst as claimed in claim 4, which is recycled into the hydrogenation of 6,9-Imino ether at least ten times.