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Gold Nanoparticles Catalyzed Synthesis of Ibuprofen Intermediate in Aqueous Ethanol

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ABSTRACT

Ibuprofen was globally consumed drug in huge quantity. It was industrially synthesized by traditional process which generates more waste and used hazardous organic solvents. Hence, it is need to develop environmental benign catalytic synthesis of ibuprofen. We synthesized pearl necklace shaped gold nanostructured material with diameter about 4 nm. Gold nanoparticles (AuNPs) were prepared and tested for the activity in the catalytic reduction of 4-nitrophenol (4-NP) to 4-aminophenol (4-AP) showed excellent catalytic performance. Further, using AuNPs we catalytically synthesized 1-(4-isobutylphenyl)ethanol which is important drug intermediate for the widely used Ibuprofen. The rate constants was determined at room temperature 0.167 ± 0.003 per minute. The recyclability study of AuNPs in the reduction of 1-(4-isobutylphenyl)ethanone (IBPEON) to 1-(4-isobutylphenyl)ethanol (IBPE) in six consecutive reaction cycles found to be (92%), (89%), (86%), (85%), (81%), (77%), respectively. We emphasized, the reported synthesis was smoothly performed in the mild reaction conditions under environmentally benign alternative.

Keywords: Gold nanoparticles, Activation energy, Recyclability, Ibuprofen, 1-(4-isobutylphenyl) ethanol

INTRODUCTION

In the sustainable chemistry of nanoscience and nanotechnology, noble metal nanoparticles have played an important role in the catalytic synthesis of pharmaceutical drugs. Nanotechnology is applicable to most field of science like pharmaceuticals drugs, organic synthesis and is the current focus of researchers. Noble metal particles such as Ag, Pt, Au and Pd have been widely used for catalytic reactions in current research. Gold nanostructured materials have recently gained attention as heterogeneous catalyst in the reduction reactions due to their unique properties like high surface area towards small particle size, high catalytic activity and efficiency to afford high yield of product [1]. AuNPs widely synthesised by several methods including chemical reduction method [2-3], photochemical method using UV [4,5], sonochemical [6,7], biochemical reduction method [8,9], seed-mediated growth method [10,11] and sono-electrochemical method [12,13] etc. Amongst these methods, chemical reduction method is the most easy, safe and clean method for the synthesis of AuNPs. Due to high surface area AuNPs widely used as catalyst in many organic transformations included hydrogenation [14,15], cross coupling reactions [16,17], oxidation [18,19], electron transfer reactions [20].

Nanostructured materials widely used as catalyst is of interest since, catalysis has developed into important technologies in the petroleum, fine chemicals, bulk chemicals and pharmaceutical industries [21]. 1-(4-isobutylphenyl)ehanol (IBPE) is one of the most important drug intermediate used for the synthesis of non-steroidal anti-inflammatory drug (NSAID) Ibuprofen. In the synthesis of 1-(4-isobutylphenyl) ethanol traditionally used hazardous organic solvents [22]. Hence, it is need to develop environmentally benign process for the synthesis of ibuprofen which has very hugely consumed globally.

In the present investigation, we have synthesised spherical necklace shaped AuNPs by chemical reduction method using sodium borhydride. The synthesised AuNPs were tested for determined catalytic activities using the model reaction of the conversion of 4-nitrophenol (4-NP) to 4-aminophenol (4-AP) [23,24]. Further, we used synthesised AuNPs as a catalyst in the synthesis of ibuprofen intermediate 1-(4-isobutylphenyl) ethanol (IBPE) from 1-(4-isobutylphenyl) ethanone (IBPEON) using environmental

benign solvent (Scheme 1). We promisingly not even report benign synthesis of ibuprofen intermediate also proved the six times consecutively recycled AuNPs with high yield of drug against poisoning of catalyst. Also, the reaction was completed within 10 minutes at room temperature.

MATERIALS AND METHODS

Chemicals

All chemicals (4-nitrophenol ($C_6H_5NO_3$, 99%), sodium borohydride ($NaBH_4$, 99%), gold nitrate, ($HAuCl_4$ 50% Au basis) 1-(4-isobutylphenyl) ethanone ($C_{12}H_{16}O$, 98%) and deionized water from Milli-Q system) were purchased from Sigma-Aldrich or Spectrochem or HiMedia and used as received.

Characterizations

The characterizations of AuNPs were collected from various instrumental techniques. The UV-Visible absorption measurement was performed on Shimadzu UV 1800 Spectrophotometer. Water as blank and reference. Transmission electron microscopy was performed on a Philips CM-200 TEM operating at 200 kV, by depositing 20 µL of dispersed sample onto a 300 mesh copper grid coated with carbon layer IR spectra were collected at room temperature from Shimadzu FTIR-Affinity-1instrument in dried KBr pellets in the range 4000 to 400 cm^{-1}. Mass spectra (MS) of 1-(4-isobutylphenyl)ethanol was collected from WATERS, Q-TOF MICROMASS (LC-MS) instrument.

Synthesis of silver nanoparticles (AuNPs)

The AuNPs were synthesized by using chemical reduction method. In brief, 10 mL of 1×10^{-3} M $AgNO_3$ taken in 50 ml of beaker and kept on magnetic stirrer. Then freshly prepared ice cold 30 mL solution of 2×10^{-3} M $NaBH_4$ was hastily added into $AgNO_3$ with vigorous stirring in which the colour change from black to orange and finally pale yellow was observed. Then AuNPs solution was stirred for four hours for good stability and prepared nano-size of AuNPs nanostructured materials. Finally, prepared AuNPs were kept overnight to remove excess hydrogen and used as a catalyst in the model after their characterization.

Typical procedure for catalytic reduction of 4-nitrophenol (4-NP)

The heterogeneous catalytic reduction of 4-NP was performed at room temperature in air. In this typical reaction 1.0 mL of 5×10^{-2} M $NaBH_4$ and 10 µL of AuNPs were mixed for two minutes in 3.0 mL quartz cuvette. To this mixture 1.5 mL of 1×10^{-4} M PNP was added and mixed. The reaction was followed by observing the absorbance spectrum of 4-NP at λ 400 nm. The 4-NP spectrum diminished at every one minute time interval and new spectrum was observed at λ 300 nm is indicates that formation of new product, which was confirmed by isosbestic points [25]. These results were in good agreements with reported literatures [26]. The absorbance spectra were recorded within the wavelength range of 250 – 600 nm. Further, the same experiment were also performed in the temperature range of 298 – 323 K to determine the effect of temperature on the Pseudo first-order rate constant.

Synthesis of 1-(4-isobutylphenyl) ethanol (IBPE)

Aqueous ethanol (3.0 mL) was added in 3.0 mL of AuNPs in round bottom flask, kept in ice bath with constant stirring. This mixture we named as "Alcoholic AuNPs". In the mixture 0.43 g of $NaBH_4$ was slowly added and finally 1.0 g. of IBPEON added with constant stirring. After complete addition, the reaction mixture was removed from the ice bath and stirring was continued at room temperature. The reaction was completed within 5 to 10 minutes and it was preliminary confirmed by thin layer chromatography (TLC). The product was isolated using ethyl acetate as organic layer and AuNPs remained in alcoholic layer. The solvent was removed by rotary evaporator and product was dried at room temperature.

Recycling studies

The recycling study of AuNPs were reported so far, for the catalytic reduction of 4-NP to 4-AP. The above (4-NP to 4-AP) recycling confines towards, used concentration of reactant was low, the reaction was monitor by UV-Vis spectrophotometer. For the first time we have performed the recycling study of AuNPs in the reduction of IBPEON to IBPE. In detail, as discussed above (**2.5**), we synthesized IBPE in first cycle. In second cycle in alcoholic liquor containing AuNPs was added IBPEON and $NaBH_4$ with constant stirring at room temperature. After completion of reaction, the product was isolated from ethyl acetate as organic layer and AuNPs remained in alcoholic layer. Finally the solvent from the product was removed by rotary evaporator. Repeated the similar procedure for next consecutive reaction cycles and recorded the percent yield of product in every cycles. We conclude that the AuNPs showed good catalytic activity against poisoning of catalyst after six consecutive reaction cycles.

RESULTS AND DISCUSSION

The AuNPs synthesised by chemical reduction method at room temperature in the presence of air and the colour changes from black to wine red with continue stirring shown in photographic image of AuNPs (Figure 1). The AuNPs was formed about four hours. The synthesised AuNPs was initially confirmed by UV. Vis Spectrometry. The surface plasmon resonance (SPR) band of AuNPs was at about λ 500 nm.

The morphological behaviour of nanostructured materials plays an important role in the catalytic activity. The synthesised AuNPs was characterized by TEM and HRTEM depicted in Figure 2. The bare AuNPs was formed pearl necklace [27] arrangement of

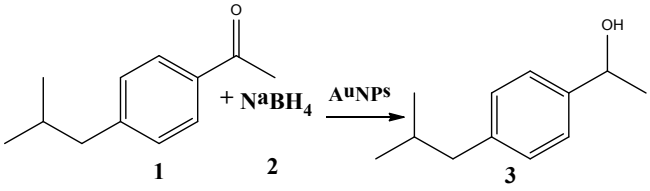
nanostructured material due to simply steady continuous stirring for 4 h (Figure 2). These necklaces of AuNPs were formed by simple chemical reduction method and without addition of stabilizers. The average diameter of necklace was found about 4 nm is very remarkable size resulted high surface area. In the inset of panel a, showed the Selected Area Electron Diffraction (SAED) pattern which confirmed the crystalline nature of particles. The crystalline nature of AuNPs was also confirmed by lattice fringes observed in HRTEM (Figure 2).

The catalytic activity of AuNPs was tested by well-known model reduction reaction of 4-nitrophenol (4-NP) to 4-aminophenol (4-AP) using $NaBH_4$ in the presence of AuNPs. The complete reduction of 4-NP to 4-AP took time of 13 minutes depicted in Figure 3. The isosbestic points confirmed that reduction of 4-NP and formation of 4-AP. Further, kinetics of the reaction was found pseudo-first order and rate constant was 0.167 ± 0.003 per minutes and it is proved the high catalytic activity and fast rate of reaction, this is due to the rigid, small necklace AuNPs was confirm by TEM and HRTEM images.

Table 1 Shows the percent practical yield in every catalytic cycle of AuNPs. The slight decrease in yield was observed. From this cycle count it was proved that the necklace shaped AuNPs showed excellent catalytic activity against poisoning of catalyst.

Spectroscopic characterization of IBPE

Lastly, the synthesized IBPE was characterized by using FTIR, and mass spectroscopy showed in Figure 4. The characterization data of IBPE as given below: 1-(4isobutyl)phenyl ethanol (IBPE) is isolated as viscous oil; b.p. 245-246 ^{0}C; FT-IR (KBr) cm^{-1}:



Scheme 1: Synthesis of IBPE from IBPEON in the presence of AuNPs

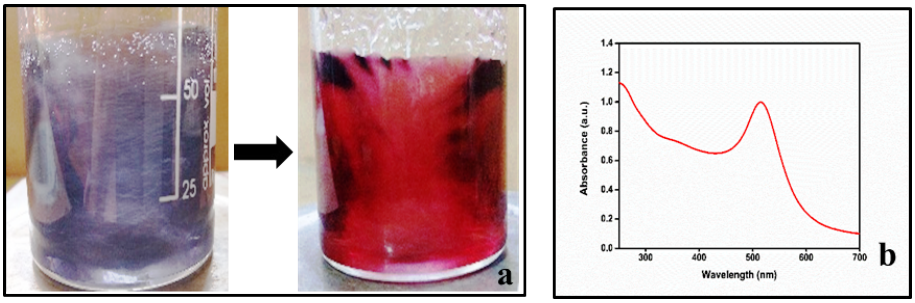


Figure 1: Panel a) synthesis of AuNPs and panel b) surface plasmon resonance (SPR) band of AuNPs

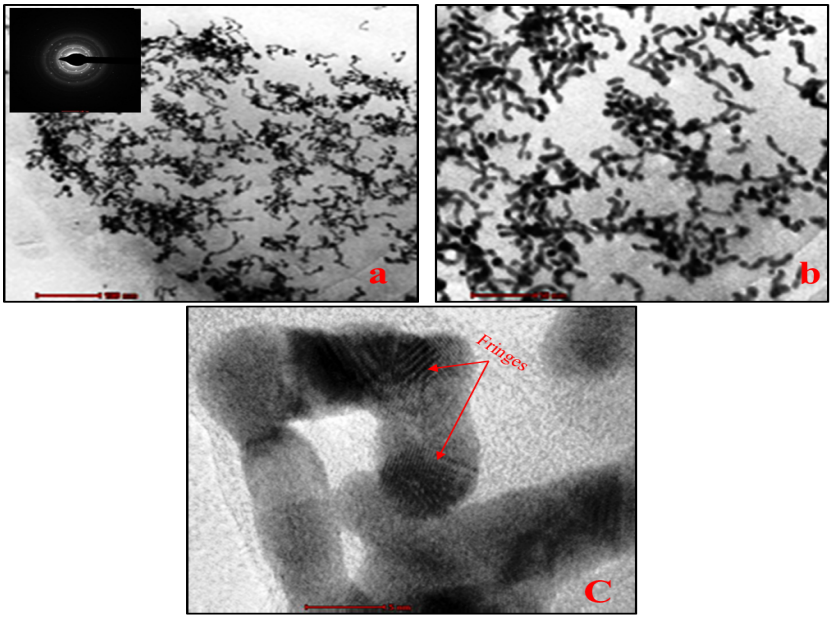


Figure 2: Panel a, b) TEM image of AuNPs and in inset panel a), is the selected area electron diffraction (SAED) pattern and panel c) HRTEM image of AuNPs

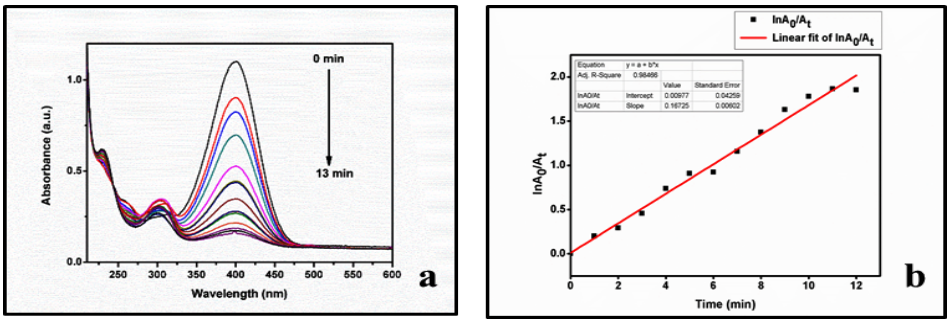


Figure 3: Panel a) Time dependent UV-Vis spectra for the catalytic reduction of 4-NP to 4-AP and panel b) Pseudo first order plot of AuNPs catalysed reduction of 4-NP to 4-AP by $NaBH_4$

Table 1: Percent practical yield of IBPE per cycle count

Cycle count	Percent yield of IBPE
1	92
2	89
3	86
4	85
5	81
6	77

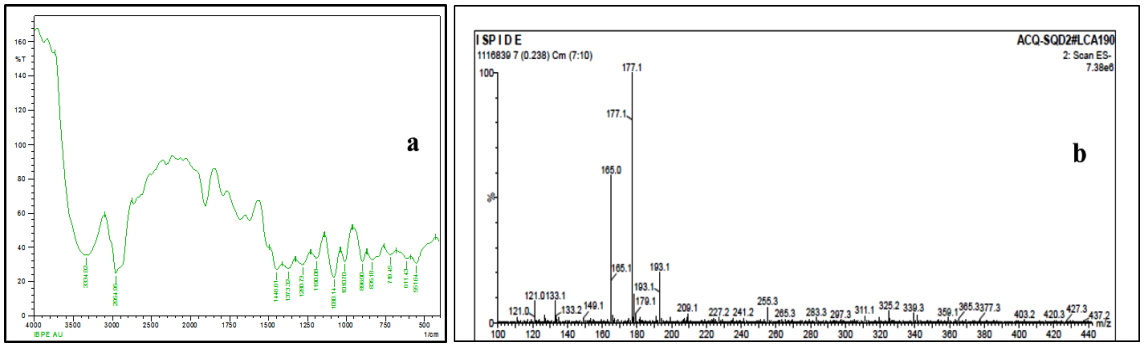


Figure 4: Panel a) FTIR spectra and panel b) mass spectra of IBPE

3334 (OH), 2954 (CH); ESI-MS: m/z = 177.1 $[M - H]^+$. The results were found to be well agreement with the reported literatures to conform the product IBPE.

CONCLUSION

In conclusion, From the TEM and HRTEM reveals necklace shaped gold nanostructured material materials (AuNPs) having excellent nano size thickness about 4 nm conforms large surface area and ultimately huge number of hydrogen was adsorbed on surface of AuNPs. This leads excellent catalytic activity of AuNPs against poison of catalyst. We efficiently evaluated the catalytic activity of AuNPs in the reduction of 4-NP to 4-AP by using $NaBH_4$. The recyclability study of AuNPs has been reported for the first time in the reduction of IBPEON – IBPE by using $NaBH_4$ in "Alcoholic AuNPs" and found very excellent yield of IBPE up to six consecutive reaction cycles. The reaction was completed within 15 minutes at room temperature. The results are first of its kind for using nanotechnology in the conversion of IBPEON to IBPE (Ibuprofen Intermediate) using aqueous Ethanol. The costly and important drug intermediate of Ibuprofen, IBPE was economically synthesized in the laboratory by environmentally benign process. In future, attempts will made to scale up the synthesis of 4-IBPE in pilot plant by collaboration with pharmaceutical industry. These results of the present investigation could be helpful for material chemistry scientists as well as organic researches to design the safer synthesis of important commonly used pharmaceutical drugs.

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