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## Activity and selectivity of different base catalysts in synthesis of guaifenesin from guaiacol and glycidol of biomass origin

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### ABSTRACT

Guaiacol and glycidol can be obtained from biomass valorization. Guaiacol (2-methoxyphenol) and glycidol (2,3-epoxy-1-propanol) have been used for the efficient synthesis of guaifenesin ((RS)-3-(2-methoxyphenoxy) propane-1,2-diol). Different catalysts such as hydrotalcite (HT), calcined hydrotalcite (CHT), calcinated hydrotalcite supported on hexagonal mesoporous silica, magnesium oxide, alumina and, potassium promoted zirconium oxide were synthesized, out of which CHT was found to be the most active, selective and reusable catalyst. The catalyst characterization was done by different techniques. Both Oxide and hydroxide phases were observed on calcination of HT in air at 450 °C for 6 h. CHT possess both acidic and basic sites and basicity of CHT was the highest. Crystallite size, surface area and pore size of CHT play important role in catalytic activity and selectivity. Reaction was carried out in a batch reactor and influence of different parameters was systematically studied. The reaction mechanism involving two sites, acidic and basic, was proposed. A suitable kinetic model was developed and fitted against experimental data. A second order rate equation was derived on the basis of Langmuir–Hinshelwood–Hougen–Watson mechanism with weak adsorption of reactants, intermediates and products. Kinetics was used to predict reaction conditions to obtain guaifenesin selectively. Guaifenesin was efficiently obtained with 94.8% selectivity at guaiacol conversion of 38.2% over CHT at 80 °C after 4 h.

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### 1. Introduction

In the foreseeable future, the stocks of fossil fuels would have been exhausted and it would be necessary to derive chemicals and fuels from renewable resources [1–3]. A variety of fresh and waste biomass ought to be subjected to chemical, biological and extractive technologies to derive platform chemicals, fuels and materials [4]. Lignin is abundantly available as a waste from the paper and pulp industries. In this regard, lignin will be an important source for conversion into a spectrum of intermediates which could be further valorized [5]. Similarly, glycerol, a co-product of biodiesel production, can be catalytically transformed into a number of bulk chemicals such as acrolein, acrylic acid, 1,2-propanediol, 1,3-propanediol, etc. [6–8]. Guaiacol (2-methoxyphenol) and glycidol (2,3-epoxy-1-propanol) have been obtained from biomass from lignin and glycerol, respectively [9,10].

Synthesis of guaifenesin from renewable sources should result in a greener and more sustainable process. One of the possible

paths to produce guaifenesin is based on biomass-derived guaiacol and glycidol by using heterogeneous catalysis which has been at the hub of green chemistry leading to waste reduction, process intensification and profitability. Hydrotalcites (for instance,  $Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O$ ) have been used as solid base catalysts for various reactions [11–17] and can be used for the production of guaifenesin. Hydrotalcite is a bifunctional catalyst having both base (major) and acid (minor) sites. It has a layered double hydroxide structure in which positively charged magnesium-aluminum layers are formed due to defects in the structure. Defects are formed by replacement of magnesium by aluminum. Anions such as carbonate, nitrate, hydroxide and chloride are present at the interlayer. On calcination at 500–800 °C, mixed magnesium-aluminum oxides are formed with large surface area with basic and acidic sites. Acid and basic properties can be adjusted with change in metal and metal composition [18,19].

Guaifenesin is an expectorant drug used in racemic form for the treatment of cough, asthma, gout, fibromyalgia, to facilitate conception and to improve voice [20]. Generally, guaifenesin is synthesized by Williamson's etherification reaction in which nucleophile of guaiacol attacks on glycidol, epichlorohydrin, 1-chloroglycerol, glycerol carbonate, 3-bromo-1-propene and isopropylidene glycerol [21–26]. Homogeneous bases such as triethyl

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amine, sodium hydroxide, potassium carbonate are used in stoichiometric quantities and neutralized at the end of reaction causing environmental pollution problems. The literature review suggests that guaifenesin synthesis has not been so far reported using heterogeneous catalysis. In this work, we report a novel protocol for the synthesis of guaifenesin using guaiacol and glycidol catalyzed by calcined hydrotalcite (CHT). The reaction is additive and 100% atom economical. Influences of different parameters are studied including reaction mechanism and kinetics.

## 2. Experimental

Following catalysts were prepared and further characterized by various techniques, details of which are included in supporting information.

### 2.1. Preparation of catalysts

#### 2.1.1. Hydrotalcite (HT)

The synthesis process is different and modified from that reported in literature [27]. HT of Mg: Al ratio 3:1 was prepared by co-precipitation method. Solution of magnesium nitrate (7.66 g, 0.03 mol) and aluminium nitrate (3.79 g, 0.01 mol) in 30 mL distilled water was prepared. Solution of sodium hydroxide (3.6 g, 0.09 mol) and sodium carbonate (2.8 g, 0.027 mol) in 30 mL distilled water was prepared. At constant pH (9), both the solutions were added simultaneously to a round bottom flask (500 mL) with overhead stirrer at a speed of 300 rpm immersed in oil bath at temperature 30 °C. White precipitate of HT was obtained and further digested at 60 °C for 12 h. HT obtained was washed with distilled water to get neutral pH to the supernatant solution. HT was filtered and then dried at 100 °C for 24 h to obtain dry lumps. HT lumps were crushed in mortar to get fine powder of weight 2.8 g. HT powder was calcined at 450 °C for 6 h to get calcined HT (CHT) [27].

#### 2.1.2. Hexagonal mesoporous silica supported hydrotalcite (HMSSH)

Hexagonal mesoporous silica (HMS) was prepared by a known procedure [28]. HMSSH (10% w/w) of Mg: Al ratio 3:1 was prepared by co-precipitation method. In a conical flask, solution of magnesium nitrate (2.29 g, 0.009 mol) and aluminium nitrate (1.14 g, 0.003 mol) in 50 mL distilled water was prepared. In another conical flask, solution of sodium hydroxide (1.08 g, 0.027 mol) and sodium carbonate (0.85 g, 0.008 mol) in 50 mL distilled water was prepared. Five g of HMS was added to a round bottom flask (250 mL) with overhead stirrer at a speed of 300 rpm immersed in oil bath at temperature 30 °C. At constant pH (9), both the solutions were added simultaneously to the round bottom flask, white precipitate of HT was obtained, which further was digested at 60 °C for 12 h. Material so obtained was washed with distilled water to get neutral pH to the supernatant solution. Then material was filtered and dried at 100 °C for 12 h to obtain dry powder. It was crushed in mortar to get fine powder which was calcined at 450 °C for 6 h [11,29].

#### 2.1.3. Potassium modified zirconium hydroxide (PMZH)

PMZH (8.8% w/w) was prepared by wet impregnation method. Zirconium hydroxide was synthesized by a known procedure [30,31]. 0.25 g of potassium nitrate was dissolved in 1.5 mL of distilled water. This solution was added to 1 g of zirconium hydroxide under stirring to get wet material which was dried in oven at 100 °C for 12 h. It was crushed in mortar to get fine powder which was calcined at 600 °C for 3 h [32].

#### 2.1.4. Aluminium oxide

Aluminium hydroxide was synthesized by co-precipitation method from aluminium nitrate by following the same procedure

**Table 1**

TPD analysis of catalysts, PMZH, MgO, CHT, HMSSH, and Al<sub>2</sub>O<sub>3</sub>.

Catalyst	PMZH	MgO	CHT	HMSSH	Al <sub>2</sub> O <sub>3</sub>
Acidity (mmol g <sup>-1</sup> )	0.09	0.41	0.68	0.63	0.76
Basicity (mmol g <sup>-1</sup> )	0.49	0.75	1.53	0.48	0.32

described in preparation of hydrotalcite (Section 2.1.1). Aluminium hydroxide was calcined at 450 °C in a furnace for 6 h to get aluminium oxide (Al<sub>2</sub>O<sub>3</sub>).

#### 2.1.5. Magnesium oxide

Magnesium hydroxide was synthesized by co-precipitation method from magnesium nitrate. The same procedure described in preparation of hydrotalcite (Section 2.1.1) was followed. Magnesium hydroxide was calcined at 450 °C in a furnace for 6 h to get magnesium oxide (MgO).

### 2.2. Reaction procedure

In a typical reaction, autoclave reactor (details included in supporting information) was charged with guaiacol (0.0081 mol), glycidol (0.020 mol), tetrahydrofuran (THF) (10 mL) and 0.03 g mL<sup>-1</sup> (0.9 g) of the catalyst. The total organic phase volume was made to 30 mL with THF. An initial sample was taken at the desired temperature. The reaction mixture was stirred with mechanical stirrer at the desired speed, and samples were collected periodically. For control reaction, speed of agitation was 1000 rpm and temperature was 120 °C at self-generated pressure. Reaction samples were analyzed by HPLC (details included in supporting information). Synthesis of guaifenesin (3-(2-methoxyphenoxy)propane-1,2-diol) and byproduct (2-(2-methoxyphenoxy)propane-1,3-diol) from condensation reaction of guaiacol and glycidol is shown in Scheme 1.

## 3. Results and discussions

### 3.1. Catalyst characterization

TPD (temperature programmed desorption) analysis of the catalysts PMZH, MgO, CHT, HMSSH, and Al<sub>2</sub>O<sub>3</sub> was carried out to find out the strength of acidic and basic sites (Table 1). Acidity (except Al<sub>2</sub>O<sub>3</sub>) and basicity of CHT was the highest. In the case of CHT, NH<sub>3</sub> desorption peak was observed at 123 °C corresponding to weak as well as strong acidic sites of concentration 0.68 mmol g<sup>-1</sup> (Fig. S1). Two CO<sub>2</sub> desorption peaks were observed, first peak at 116 °C corresponding to weak basic sites of concentration 0.95 mmol g<sup>-1</sup> and second peak at 264 °C corresponding to strong basic sites of concentration 0.58 mmol g<sup>-1</sup> (Fig. S2) [12,17,33].

All the catalysts were analyzed for surface area analysis. All showed, type IV adsorption-desorption isotherm with hysteresis loop of type H1, which is a characteristic of a mesoporous solid (Fig. 1). The Brunauer-Emmett-Teller (BET) surface area, Langmuir surface area, pore size, and pore volume of all the catalysts are shown in Table 2. Surface area of PMZH was the lowest. Surface area of HMSSH was the highest while pore size was the lowest. After calcination, surface area of hydrotalcite increases due to formation of mixed Mg-Al metal oxides. On calcination, due to evolution of CO<sub>2</sub> and H<sub>2</sub>O, more porous material is formed by the formation of pores through the layers. Hydrotalcites containing carbonates and showing such behavior have been reported [27]. BET surface area of CHT was measured to be 240.5 m<sup>2</sup> g<sup>-1</sup>. The pore volume and pore diameter were 0.97 mL g<sup>-1</sup> and 159.2 Å, respectively. Pore width of CHT was in range of 100–600 Å (Fig. S3).

The XRD (X-ray diffraction) pattern of HT have sharp reflections at 11.2°, 22.5°, 34.2°, 38.2°, 45.0°, 60.0°, and 61.3° (JCPDS 22-700) corresponding to (003), (006), (012), (015), (018), (110),

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