Synthesis and Characterization of γ-Fe_2O_3@HAp@β-CD Core-Shell Nanoparticles As a Novel Magnetic Nanoreactor and Its Application in the One-Pot Preparation of β-azido Alcohols, β-nitro Alcohols, and β-cyanohydrins

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ABSTRACT: *In this study, β-cyclodextrin(β-CD) supported, hydroxyapatite encapsulated γ-Fe_2O_3 (γ-Fe_2O_3@HAp@β-CD) was successfully prepared and evaluated as a solid–liquid phase transfer catalyst and also a molecular host system and nanoreactor for the nucleophilic ring opening of epoxides in water for the preparation of β-azido alcohols, β-nitro alcohols, and β-cyanohydrins. The catalyst was characterized with FT-IR, XRD, TGA and SEM. This procedure offers several advantages including excellent regioselectivity, high yields, short reaction times, recyclable catalyst, easy separation of the catalyst through external magnet, and easy work-up.*

KEYWORDS: *Hydroxyapatite-encapsulated-γ-Fe_2O_3; β-cyclodextrin; Epoxides; β-azido alcohols; β-nitro alcohols; β-cyanohydrins.*

INTRODUCTION

Magnetic iron oxide nanoparticles have attracted extensive interest in modern chemistry due to their unique properties such as optical, electronic, magnetic, and catalytic effects. These catalysts' superiority is due to their simple separation through an external magnet and their reuse [1-5].

Developing novel materials for immobilizing a catalyst with the ability of maintaining its activity is a task of great economic and environmental importance in chemical and pharmaceutical industries, especially when expensive and/or toxic homogenous materials are employed [6].

In this regard, Magnetic NanoParticles (MNPs) have emerged as new catalyst supports because of their specific characteristics. These nanoparticles, owing to their high surface area, non-toxicity, and unique magnetic properties, have a broad range of potential use in biomedical and catalyst support applications [4-7]. A distinct advantage of this technology is that magnetic materials can be readily isolated from sample solutions by an external magnetic field.

Iron oxides, magnetite (Fe_3O_4), and maghemite (γ-Fe_2O_3) are by far the most widely used MNPs,

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1021-9986/2019/3/61-68 *8/$/5.08*

because they are much less toxic than their metallic counterparts and still have high saturation magnetization and superparamagnetic behavior. MNPs can be easily formed at low temperatures under mild conditions and modified in terms of hydrophilicity/hydrophobicity to tune their dispersion stability in organic or aqueous media. For this purpose, surface of the particles should be modified by a biocompatible and stable compound such as polyethylene glycol, polyvinyl alcohol, silica, gold, and hydroxyapatite (HAp) [8-10]. These surface modifications shield magnetic particles from the surrounding environment, prevent their aggregation in solutions, and improve their chemical stability. In these conditions, the surfaces of these metal oxides are readily modified by desired molecules which can be very useful for biological and catalytic applications.

Hydroxyapatite, the main component of bone and teeth, is of considerable interest in many areas because of its adsorption capacity, ion-exchange ability, acid–base properties, and many P–OH functional groups. Hydroxyapatite as a surface modifier produces new properties, such as acidity and basicity, affinity and catalytic activity. In general, due to good chemical stability, high surface area, and easy synthesis, hydroxyapatite-coated magnetic nanoparticles have been recently used as heterogonous catalytic supports [11-13].

β-Cyclodextrin as one of the phase-transfer catalysts is known as a remarkable natural macrocyclic host with hydrophobic cavity, which forms inclusion complexes with a large variety of guest molecules. Such molecular guest–host systems have been attracting enormous interest by researchers in recent years and widely used in various fields, including pharmacy, food, cosmetics, chemical production, and catalysts [14-17]. Practical utility of β-CD in aqueous media could be extended further if it could be made water insoluble, for which some methods such as immobilization of β-CD on solid supports or conversion into insoluble polymeric derivatives have been already suggested [18-19]. Immobilization of phase transfer catalyst on MNPs has considerable advantages such as increase catalyst recovery and decrease time of this process also product isolation be greatly simplified.

Considering all the above-mentioned points and in continuation of our interest for the preparation of novel nanocatalysts and molecular host–guest systems [20, 21], herein, β-CD grafted onto magnetic nanoparticle (γ-Fe_2O_3@HAp@β-CD) was successfully prepared and its performance as solid–liquid phase-transfer catalyst was investigated for the nucleophilic ring opening of epoxides in water (Scheme 1).

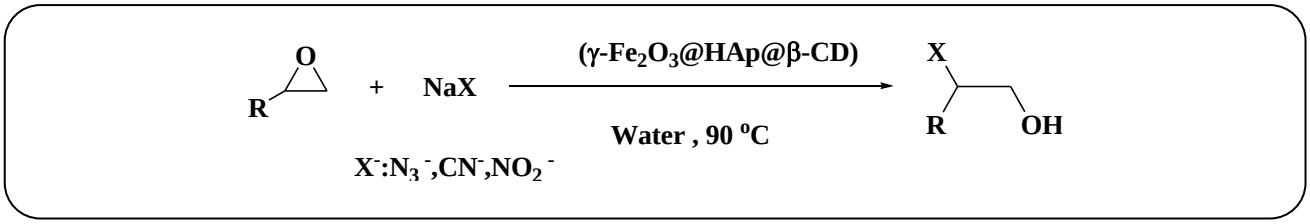
EXPERIMENTAL SECTION

General

Chemicals were purchased from Fluka, Merck, and Aldrich Chemical Companies. β-cyclodextrin was heated at 80°C under vacuum for 30 min before use to remove the moisture trace. Yields refer to the isolated crude products. NMR spectra were recorded in $CDCl_3$ on a Bruker Advance DPX 400 MHz instrument spectrometer using TMS as internal standard. Purity determination of the products and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates. The FT-IR spectra of β-cyclodextrin were measured as a potassium bromide disc on a BOMEM MB-Series1998 FT-IR spectrophotometer. X-Ray Diffraction (XRD) patterns of the samples were taken by a Philips X-ray diffractometer, model PW1840 (Bragg–Brentano configuration), at room temperature using Cu K_α radiation with the wavelength of 1.5418 Å. The peak position and intensities were obtained between 10 and 80° with the velocity of 0.02 °C/s. The TGA curve of the β-CD grafted onto Fe_2O_3@HAp was recorded on a BAHR, SPA 503 in the heating rates of 10 °C/min. The thermal behavior was studied by heating 1–3 mg of the samples in aluminum crimped pans under nitrogen gas flow within the temperature range of 25–600 °C. The particle morphology was performed by measuring SEM using a Philips XL30 Scanning Electron Microscope (SEM) operating at 20 kV.

General procedure for the preparation of γ-Fe2O3@HAp

Preparing γ-Fe_2O_3@HAp was according to the previously reported method [10]. For this purpose, $FeCl_2.4H_2O$ (1.85 mmol) and $FeCl_3.6H_2O$ (3.7 mmol) were dissolved in deionized water (DW) (30 mL) under N_2 atmosphere at room temperature and the resulting solution was added to the 25% NH_4OH solution (10 mL) under vigorous mechanical stirring (700 rpm). Black precipitate of Fe_3O_4 was produced instantly. In order to obtain small and uniform Fe_3O_4 particles, the drop rate of



Scheme 1: Ring opening reaction of epoxides with azide, cyanide and nitrite in the presence of γ-Fe_2O_3@HAp@β-CD.

NH_4OH was controlled precisely by a constant dropper and the drop rate was 1 mL min^{-1}. After 15 min, 100 mL of $Ca(NO_3)_2.4H_2O$ (33.7 mmol, 0.5 M) and $(NH_4)_2HPO_4$ (20 mmol, 3.0 M) solutions adjusted to pH 11 were added drop-wise to the obtained precipitate over 30 min under mechanical stirring. The resultant milky solution was heated to 90°C. After 2 h, the mixture was cooled to the room temperature and aged overnight. The dark brown precipitated form was filtered, washed repeatedly using DW until neutral, and air-dried under vacuum at room temperature. The as-synthesized sample was calcined at 300°C for 3 h which produced a reddish-brown powder.

General procedure for the preparation of γ-Fe_2O_3@HAp@β-CD

For introducing isocyanate groups into the surface of MNPS, γ-Fe_2O_3@HAp-NCO, the obtained MNPs powder (0.2 g) was dispersed in DMF (15 mL) by sonication. Then, hexamethylene diisocyanate (HMDI) (1.36 mL) in 5 mL of dry DMF was added drop-wise to the mixture. After mechanical agitation for 3 h, the suspended substance was separated by an external magnetic field. For removing the unreacted HMDI, the settlement product was re-dispersed in dry DMF by sonication and isolated by magnetic decantation for three times. The precipitated product (γ-Fe_2O_3@HAp-NCO) was used in the next step.

To graft β-CD onto the surface of MNPs, the synthesized (γ-Fe_2O_3@HAp-NCO) was suspended in dry DMF (7.5 mL) and then 1 g of β-CD (1.76 mmol) was dissolved in 7.5 mL of dry DMF and added drop-wise to the mixture. The reaction mixture was stirred at 70°C for 3 h. The precipitate was separated by magnetic decantation and washed with water and acetone for several times.γ-Fe_2O_3@HAp@β-CD was dried in vacuum for 24 h (Fig. 1). All the procedures in which γ-Fe_2O_3 was involved were carried out under N_2 protection to avoid possible oxidization during reaction.

General procedure for the ring opening of epoxides

A mixture of epoxide (1 mmol), anion [NaN_3 (1mmol) or NaCN (3mmol) or $NaNO_2$ (7 mmol)], and γ-Fe_2O_3@HAp@β-CD (0.15 g) was heated at 90°C. After satisfactory completion of the reaction and cooling, the product was extracted by chloroform and the catalyst was removed by an external magnet. Formation of the products was related to each other by comparing the IR and NMR data using authentic samples and literature data.

RESULTS AND DISCUSSION

Synthesis of β-CD grafted onto Fe_2O_3@HAp and its structural and morphological analysis

Magnetic nano-phase transfer catalysts have the advantages of both magnetic separation techniques and nano-sized materials, which can be easily recovered or manipulated by an external magnetic field. As the catalysts are usually immobilized on the surface of the MNPs, easy access of reactants to the active sites of the nano-complex can be also achieved. In the present study, hydroxyapatite encapsulated γ-Fe_2O_3, Fe_2O_3@HAp@HAp was synthesized according to the procedure shown in Fig. 1.

As shown in Fig. 1, MNPs were prepared by a coprecipitation method from ferrous and ferric ion solutions in the basic media. The MNPs prepared by this method had significant numbers of hydroxyl groups on the surface from contact with the aqueous phase. Because of the sensitivity of γ-Fe_2O_3, its surface was first coated with hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$, HAp).

For grafting β-CD, the isocyanate groups were preliminarily bonded onto the surface of γ-Fe_2O_3@HAp by the reaction of hydroxyl groups of MNPs with hexamethylene diisocyanate. After removing the unreacted hexamethylene diisocyanate, β-CD was reacted with the modified γ-Fe_2O_3@HAp.

Chemical structure of the synthesized material was characterized using FT-IR, XRD, SEM, and TGA analyses.

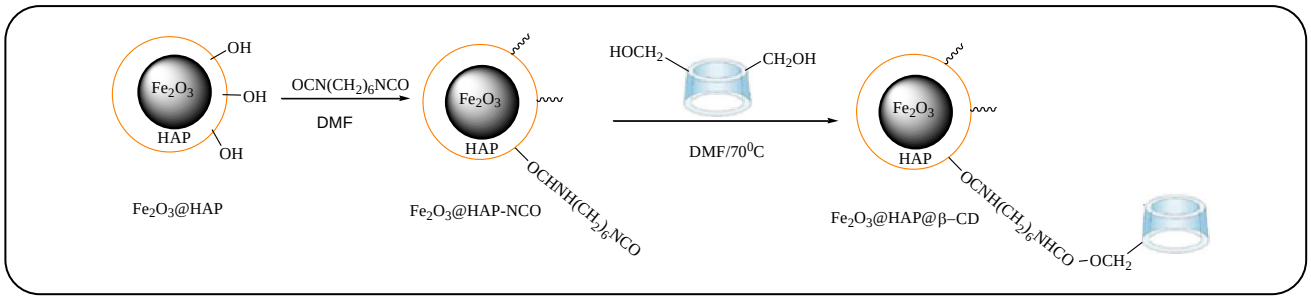


Fig. 1: Synthesis of β-CD grafted onto γ-Fe_2O_3 magnetic nanoparticles (γ-Fe_2O_3@HAp@β-CD).

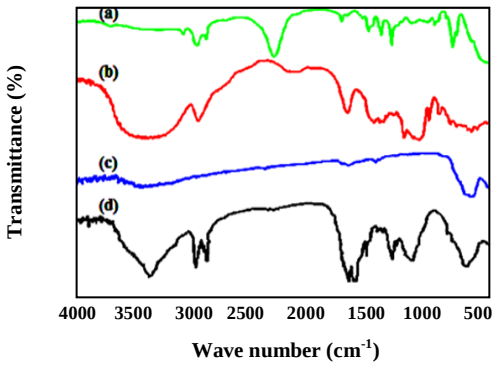


Fig. 2: FT-IR spectra of (a) hexamethylene diisocyanate (HMDI), (b) β-CD, (c)γ-Fe_2O_3@HAp, and (d)γ-Fe_2O_3@HAp@β-CD.

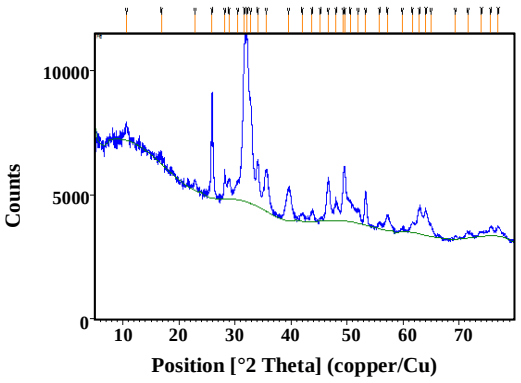


Fig. 3: XRD pattern of γ-Fe_2O_3@HAp@β-CD.

IR spectrum (Fig. 2) of the γ-Fe_2O_3@HAp@β-CD shows characteristic adsorption bands at 3330 and 1630 cm^{-1} corresponding to NH and C=O groups. The NHCO stretching was also observed at 1570 cm^{-1}. In addition, all the significant peaks of β-CD in the range of 900–1200 cm^{-1} were present in the spectrum of Fe_2O_3@HAp@β-CD with a small shift. It is worth noting that the isocyanate peak in the IR spectrum at about 2280 cm^{-1} was disappeared. The infrared band at 575 cm^{-1} was associated with the stretching vibration modes of the magnetite Fe–O bonds in tetrahedral sites [4], which was shifted to 594 cm^{-1} after surface modification by β-CD.

Thus, all of the above results indicated that β-CD was successfully grafted onto γ-Fe_2O_3@HAp. Fig. 3 shows the powder XRD patterns of γ-Fe_2O_3@HAp. The pattern of γ-Fe_2O_3 was at the most intense state at 2θ = 36.56. This line was in correspondence to that of pure γ-Fe_2O_3, confirming the presence of γ-Fe_2O_3 [5]. The characteristic peaks of β-CD [20] and Hydroxyapatite [26] are evident as we have reported previously.

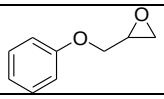
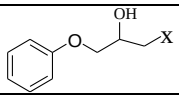
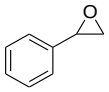
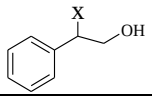
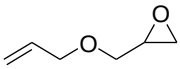
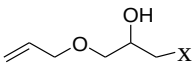
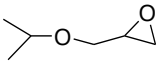
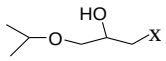
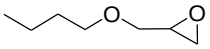
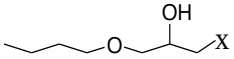
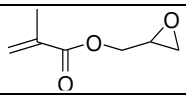
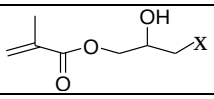
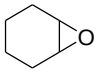
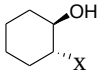
Fig. 4 shows the TGA analysis of γ-Fe_2O_3@HAp@βCD. TGA thermogram exhibited the first weight loss of 5 % below 120°C which might be due to the loss of residual water adhering to the sample surface and adsorbing in the β-CD cavities. The second weight loss step of about 35 % in the region of 190–380°C was due to the breakdown and decomposition of β-CD moieties [4]. Thus, the TGA curves also conveyed the obvious information that the β-CD molecules were successfully grafted onto the magnetic surface.

The morphology and particle size distribution of γ-Fe_2O_3@HAp@β-CD nanostructure were performed by measuring SEM using a Philips XL30 scanning electron microscope. As shown in the images (Fig. 5), the nanoparticles in all the samples had spherical shapes, indicating that γ-Fe_2O_3@HAp@β-CD had large surface area.

Applying γ-Fe_2O_3@HAp@β-CD as nanomagnetic phase transfer catalyst for nucleophilic substitution reactions in water

To evaluate the catalytic activity of γ-Fe_2O_3@HAp@β-CD as a phase transfer catalyst in the nucleophilic substitution reaction, the ring opening of the epoxides with azide, cyanide, and nitrite anions in water was examined to determine whether the use of β-CD

Table 1: Ring opening of epoxides with different anions catalyzed by γ-Fe_2O_3@HAp@β-CD in water.

Entry	Reactant	Product	X	Time (min)	Yield (%)
1			X: CN X:N_3 X:NO_2	75 55 80	66 89 66
2			X: CN X:N_3 X:NO_2	65 35 5	85 89 83
3			X: CN X:N_3 X:NO_2	25 60 5	77 88 66
4			X: CN X:N_3 X:NO_2	18 20 9	91 88 93
5			X: CN X:N_3 X:NO_2	22 30 8	75 90 71
6			X: CN X:N_3 X:NO_2	5 20 18	71 91 84
7			X: CN X:N_3 X:NO_2	21 25 10	94 87 75

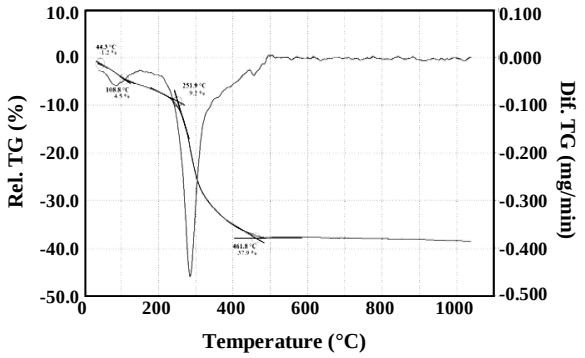


Fig. 4: TGA curve of γ-Fe_2O_3@HAp@β-CD.

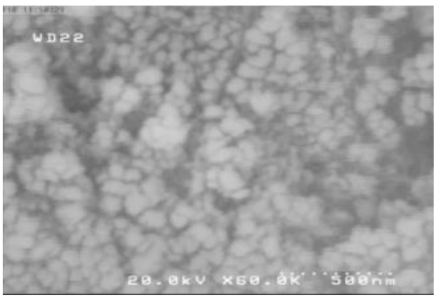


Fig. 5: SEM image of γ-Fe_2O_3@HAp@β-CD.

conjugated magnetic nanoparticles was efficient or not and to investigate the optimized conditions.

In order to examine the efficiency of the immobilized β-CD onto γ-Fe_2O_3@HAp as a solid–liquid phase transfer catalyst, 2,3-epoxypropyl methacrylate was chosen as a model compound and reacted with azide anion in the presence of γ-Fe_2O_3@HAp@β-CD, in water. After some experiments, it was found that efficient conversion can be obtained in the presence of 0.15 g of catalyst in water at 90 °C as the best condition. This method was found to be applicable to a series of epoxides under similarly experimental reaction conditions and the results are illustrated in Table 1.

The catalytic property of γ-Fe_2O_3@HAp@β-CD is due to the inclusion complex formation of epoxides via the hydrogen bonding of the epoxide oxygen to the outer OH groups of the β-CD (Fig. 6).

It is worth noting that γ-Fe_2O_3@HAp@β-CD did not suffer from extensive mechanical degradation after operating and could be quantitatively recovered by external magnetic field and washing with water and ethanol. The recovered catalyst was reused for four times for the ring opening reactions. The results clearly showed that the catalyst did not demonstrate any loss in its activity even after four runs.

Table 2: Comparison of the reported methods in the literature with γ-Fe_2O_3@HAp@β-CD for the azidolysis of phenyl glycidyl ether.

Entry	Catalyst/ Condition	Time (h)	Yield (%)	Ref.
1	PEG-Dowex/ H_2O reflux	0.75	96	15
2	Fe_3O_4@SiO_2/BNC/ H_2O 90°C	0.5	95	21
3	PEG–silica hybrid/ H_2O reflux	0.5-2.5	89	22
4	SiO_2-OPEG/ H_2O reflux	2	83	23
5	cross-linked polyacrylamide/ H_2O R.T.	12	94	24
6	$(Bu)_3SnN_3$/ 60°C solvent-free	6	95	25
7	γ-Fe_2O_3 @HAp @β-CD/ H_2O reflux	0.92	89	This work

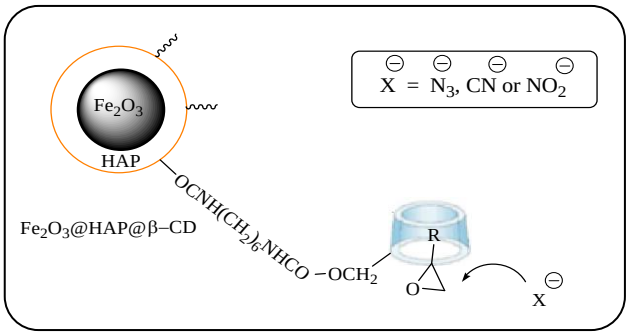


Fig 6: Postulated inclusion complex formation of γ-Fe_2O_3@HAp@β-CD with epoxides to facilitate the nucleophilic ring opening.

The advantage of utilizing γ-Fe_2O_3 @HAp@β-CD as catalyst for the ring-opening of phenyl glycidyl ether using sodium azide is shown by comparing our results with those previously reported in the literature (Table 2). Some procedures require long reaction time (Table 2, Entry 4, 5, 6) or lower yield of the product has been obtained (Table 2, Entry 4). Accordingly these results clearly demonstrate that the γ-Fe_2O_3 @HAp@β-CD is equal to and in some cases more efficient for this reaction than the other catalysts.

CONCLUSIONS

In the present work, β-CD grafted onto γ-Fe_2O_3@HAp magnetic nanoparticles was successfully prepared and the performance as solid–liquid phase-transfer catalyst for nucleophilic ring opening of epoxides with azide, cyanide, and nitrite anions in water. The catalyst was characterized with FT-IR, XRD, TGA and SEM. This procedure offers several advantages including excellent regioselectivity, high yields, short reaction times, recyclable catalyst, easy separation of the catalyst through external magnet, and easy work-up.

Acknowledgments

We are grateful to the Research Council of Shahid Chamran University for financial support.

Received : Apr. 12, 2017 ; Accepted : Jun. 18, 2018

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