COMMUNICATION

Surfactant-templated zeolites for the production of active pharmaceutical intermediates

Received 00th January 20xx,
Accepted 00th January 20xx

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DOI: 10.1039/x0xx00000x

A hierarchical USY zeolite has been produced using the surfactant-templating method and used as catalyst for the production of two important active pharmaceutical ingredients. The presence of intracrystalline mesoporosity in the zeolite results in a significant increase in both the activity (up to 30 fold increase in TOF) and reusability for Friedel-Crafts alkylation and aldol condensation steps.

The production of active pharmaceutical ingredients (APIs) has traditionally relied on the use of homogeneous soluble catalysts.¹ Soluble acids and bases are very effective catalysts for key reactions but suffer from important drawbacks such as corrosion, toxicity, moderate selectivity and complicated product purification.¹ On the other hand, the use of solid acids, such as zeolites, which can be easily recovered and reused, is widespread in different catalytic applications (mainly in petrochemistry).² However, their use in the fine chemicals and pharmaceutical industries is more limited.^{2–6} Recently, some of us reported the use of USY zeolite as a very attractive option both in terms of catalytic performance and price, for this type of reactions.⁷ However, despite the adequate acidity of this widely used zeolite, the small size of its micropores often results in diffusion limitations, especially for the synthesis of the bulky organic molecules involved in the production of APIs. The access of the reactants and exit of the products in and out the zeolite structure can be highly restricted.⁸ In the last years, hierarchical zeolites featuring intracrystalline mesoporosity system have been investigated as an alternative to overcome the drawbacks related to the limited accessibility of conventional zeolites.⁸ The post-synthetic treatment with cationic surfactants, known as surfactant-templating, is an

effective tool to introduce tunable intracrystalline mesoporosity while maintaining the key features of the zeolite.⁹ However, in spite of the numerous reports dealing with the preparation of hierarchical zeolites by this method,^{9–12} their application has been limited to petrochemistry-related process.^{13,14} Herein, we provide compelling evidence of the effectiveness of these novel materials as solid catalysts in the production of two related APIs (C-H functionalized indoles and steroids) through C-C bond formation steps, i.e. alkylations and aldol condensations (see Figure 1).^{15,16} Indole scaffolds and steroidal analogues demonstrate diverse pharmacological applications, the former for the treatment of neuropathic pain, glaucoma, migraine headaches or Alzheimer's and Parkinson's diseases, among others;¹⁷ and the latter for their effects on sex hormones, immune response, cell proliferation, and their neuroactive properties.¹⁸

Previous works:

Glucagon receptor antagonist

Leukemia cells inhibitor

This work:

Figure 1. Reported preparation of APIs involving some of the reactions performed in this work (A) Friedel-Crafts alkylation of indole using alcohols as alkylating agents, and (B) Aldol condensation of ketones with benzaldehyde.^{15,16}

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

For the preparation of the mesoporous zeolite,⁹ cetyltrimethylammonium bromide (0.7 g) was dissolved in 63.6 mL of a 0.36 M aqueous NH_4OH solution. To this solution, 1 g of USY zeolite (CBV 720, Si/Al = 15) was added. The mixture was subsequently stirred at room temperature for 20 min, and transferred to a Teflon® lined stainless steel autoclave. The hydrothermal treatment was carried out at 150 °C under static conditions for 6 h. Autoclaves were cooled-down to room temperature, solid products were filtered off, washed thoroughly with distilled water, and dried overnight at 70 °C. The calcination of the samples was carried out at 550 °C for 5 h ($1.5\text{ }^\circ\text{C min}^{-1}$); being the recovery yield close to 100%. As shown in Figure 2, the surfactant-templating treatment allows for the development of a high amount of intracrystalline mesoporosity homogeneously distributed through the crystal, see TEM micrographs of ultramicrotomed samples before (A) and after (B, C and D) the treatment. The formation of mesoporosity in the zeolite was also studied by N_2 physisorption at 77 K. As shown in Figure 2C, the parent zeolite (CBV 720) produces a type I isotherm with some contribution of large mesopores, which are due to the steaming process performed by the supplier.¹² After the surfactant-templating

treatment, the obtained zeolite displays a type I+IV isotherm, with a sharp N_2 uptake at a relative pressure of approximately 0.4, indicating the presence of very narrow and well-defined mesoporosity (see inset in Figure 2).^{10,11} The incorporation of mesoporosity does not compromise the microporous volume neither the crystallinity of the zeolite (see Figure 2D for the XRD patterns). Additionally, most of the key properties of the original zeolite, including strong acidity, were preserved after the surfactant-templating treatment (Table S1).

Both the original and hierarchical zeolites were tested as catalysts for the transformation of bulky compounds under solvent-free conditions, in order to minimize the environmental footprint of the processes (see SI for details).⁷ Two reactions related to the synthesis of steroidal analogs and indole scaffolds were selected (see Figure S1). In all cases, the surfactant-templated zeolite exhibited higher catalytic activity than the original zeolite (see Figure 3 and Figures S1-S2). The better accessibility of the hierarchical catalyst resulted in Turn-Over-Frequencies (TOFs calculated as the initial reaction rate per mole of total acid sites (including both Brønsted and Lewis)) 4 to 30 times higher than in the microporous catalyst. The different enhancements in the performance are related to the bulkiness of the reactants and products involved in every specific reaction. Thus, for the alkylation of indoles with bulky alcohols, such as benzoin (α -hydroxy- α -phenylacetophenone), which generates a very bulky indole derivative, the mesoporous zeolite presents an enhancement of ca. 30 times in TOF in comparison to the microporous USY zeolite. Moreover, when comparing with other solid acid catalysts namely, Al-MCM-41 and Amberlyst resin (Figure 3A) in the same reaction conditions, our mesoporous zeolite shows the highest TOF. However, it is worth noting that the Al-MCM-41 performs better than the original USY for the alkylation of indole with benzoin. In this case, the use of a relatively activated alcohol as the benzoin for the alkylation, while requiring much space, does not need strong acid sites for the generation of an electrophile at the benzylic position (despite the electron-withdrawing carbonyl group).¹⁹ For this reason, the acid sites of Al-MCM-41, numerous but weaker than the USY zeolite, are still sufficiently effective for this reaction.^{20,21} Amberlyst sulphonic resin, on the other hand, shows similar substrate conversion than the mesoporous zeolite, however, because of the very high number of acid sites present in this solid, its activity per acid site (TOF) is the lowest of all catalysts (Figure 3A). Taking all these observations into account, our results indicate that surfactant-templated zeolites with their combination of well-defined mesoporosity and strong acidity are ideal catalysts for the different transformations of bulky molecules involved in fine-chemistry applications.

It is worth noting that the incorporation of mesoporosity in the USY zeolite not only increases the activity of the catalyst but also its lifetime for the aldol condensation reaction. Figure 3B presents the conversion over the microporous and hierarchical zeolites during 3 catalytic cycles in the aldol condensation of estrone and benzaldehyde. After each reaction cycle was finished, the catalysts were recovered by centrifugation,

Figure 2. TEM micrographs of the ultramicrotomed (A) original USY zeolite, and (B) after surfactant-templating, scale bar represents 50 nm in both cases. (C) Magnified TEM image of the ultramicrotomed surfactant-templated USY zeolite (scale bar = 5 nm) and its corresponding fast Fourier transform (FFT) pattern (inset), (D) reconstruction of the image produced by masking the halo (mesoporous structure) and the spots (crystalline structure) of the FFT pattern (inset). (E) N_2 sorption isotherms at 77 K; the corresponding pore size distributions (NL-DFT adsorption branch) are shown in the inset. (F) Low and wide angle XRD patterns of the original (black) and surfactant-templated (blue) zeolites.

Figure 3. (A) Activity of the different catalysts in the a) Friedel-Crafts alkylation of indole with benzoin and b) Aldol condensation of estrone and benzaldehyde. (B) Increased lifetime of the surfactant-templated zeolite (blue) regarding the original USY zeolite (black), for the aldol condensation of estrone and benzaldehyde. (C) Conversion in the a) Friedel-Crafts alkylation of indole with different alcohols and, b) Aldol condensation of different ketones and benzaldehyde; catalyzed by the original USY zeolite (black), and the surfactant-templated zeolite (blue). The alcohols and ketones used are shown in the figure. (D) Ratio between the activity of the hierarchical and microporous zeolites versus the critical diameter of the reactants involved in the different reactions.

thoroughly washed with ethanol/acetone and reused by addition of new reaction mixture. As shown, the activities of the catalysts decrease with the number of cycles in both cases. It is well-known that the blocking of the microporosity of zeolites during reaction can limit the access of new reactants to the catalytic sites, which may explain the drop in the conversion. However, on hierarchical catalysts, the shorter diffusional path length improves desorption of products outside the zeolite micropores increasing its lifetime.²² As observed in Figure 3B, the mesoporous zeolite retains more of the initial activity after 3 catalytic cycles (82% of the initial conversion) than the microporous zeolite (66% of the initial conversion). The amount of the organics trapped on the different catalysts was investigated by TG-DTG/MS analyses while the accessibility was analyzed by N_2 adsorption in the zeolites after the 3 catalytic cycles (see Figure S3). The results indicate that, while the amount of organics in the hierarchical catalyst and in the parent zeolite is fairly similar (20 wt%), the mesoporous zeolite is able to convert a much larger amount of substrate. The fraction of organic deposition per substrate converted is significantly decreased (by about 1.4 times) with the introduction of mesoporosity in the zeolitic structure (Table S2). The accessibility of the reactants to the used catalysts is greatly affected by the organic deposits. As shown in the N_2 isotherms of the used catalysts presented in Figure S3, there is a partial pore blocking of the catalysts after 3 cycles of reaction which is, however, more pronounced in the microporous zeolite, explaining the higher deactivation rate (63% of total pore blocking in the USY vs 48% in the MesoUSY, Table S2). After the calcination of both catalysts a new catalytic cycle was carried out (Figure 3B) resulting in the recovery of most of the initial activity (90% of the initial conversion for the hierarchical catalyst vs 83% for the original USY).

In order to determine the impact of the size of the reactants on the performance, the bulky compounds (benzoin and estrone) were replaced by other molecules that do not present steric limitations, namely 3,4-dimethoxybenzyl alcohol in the case of the Friedel-Crafts alkylation of indole, and cyclopentanone for the aldol condensation with benzaldehyde. As observed in Figure 3C, when the reactants do not experience diffusion limitations, both catalysts perform similarly.²³ However, when the critical diameter²⁴ of the compound exceeds the pore window size of the zeolite ($d_{\text{crit}} = 0.76$ nm for benzoin vs 0.74 nm for the pore opening of FAU), the differences between the activity of both catalysts are clear. To better visualize the effect of the reactant size in the activity of both catalysts, in Figure 3D the ratio between the TOFs of the hierarchical and microporous zeolites is plotted against the critical diameter of the reactants involved in the different reactions. The incorporation of mesoporosity in the zeolite has a tremendous impact on the reaction when molecules with excluded sizes are present and much higher yields can be obtained using the hierarchical zeolite. When the compounds used have free access to the microporosity the ratio between the activities of both zeolites is very close to 1, as the catalysts have the same activity. The better diffusion of the bulky

compounds in the hierarchical material was also evaluated by adsorption experiments. In Figure S4 the adsorption of estrone and cyclopentanone on the porous catalysts included in this work is presented. The incorporation of mesoporosity in the zeolite results in a 50% increase of estrone uptake for the same mass of catalyst; however, similar adsorption results were found for the smaller ketone. The increased access of the steroid at the active sites of the hierarchical zeolite makes those sites more available for the conversion of the bulky reactant than in the original microporous zeolite.

In conclusion, the incorporation of mesoporosity in USY zeolite by surfactant-templating enhances its activity in the conversion of bulky compounds. This has been studied in two different acid-catalyzed reactions, namely Friedel-Crafts alkylation and aldol condensation. While USY zeolite is a very active acid catalyst, as confirmed using smaller analogs for the same reactions, the narrow size of its microporous system greatly limits its use in the synthesis of important pharmaceutical molecules, as they involved the transformation/production of bulky intermediates. Furthermore, surfactant-templated USY zeolites present better recyclability and lower pore blocking due to undesired products, emerging as a very attractive option as a catalyst, both in terms of catalytic performance and lifetime for the synthesis of important APIs.

Acknowledgments

N. L. wishes to thank the Generalitat Valenciana for financial support under the project *BEST/2018/039* and the University of Alicante, through the “Programa de captación y retención de talento” (UATALENTO17-05). F.G.C. kindly acknowledges the European Commission-Horizon 2020 under the Marie Skłodowska-Curie Individual Fellowship grant agreement number 750391 (Project acronym SINMOF) for financial support.

Conflicts of interest

There are no conflicts to declare.

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