

# Surfactant-templated zeolites for the production of active pharmaceutical intermediates

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## Table of Contents

<b>1. Experimental Procedures</b>	<b>1</b>
<b>1.1 Materials</b>	<b>1</b>
<b>1.2 Sample characterization</b>	<b>1</b>
<b>1.3 Catalytic evaluation</b>	<b>2</b>
<b>1.4 Adsorption experiments</b>	<b>2</b>
<b>2. Results and Discussion</b>	<b>2</b>
<b>2.1 Characterization of the catalysts before reaction</b>	<b>2</b>
<b>2.2 Catalytic results</b>	<b>3</b>
<b>2.3 Characterization of the catalysts after 3 consecutive reaction cycles</b>	<b>3</b>
<b>2.4 Adsorption experiments</b>	<b>4</b>
<b>3. References</b>	<b>4</b>

## 1. Experimental Procedures

**1.1 Materials.** USY zeolite (CBV720 with molar ratio Si/Al = 15, as indicated by the supplier), was provided by Zeolyst®. Hexadecyltrimethylammonium bromide (98%) (CTAB) and ammonium hydroxide (28-30%) were purchased from Sigma-Aldrich. The substrates and reactants employed in the catalytic tests, i.e. testosterone, estrone, indole, benzoin, benzyl alcohol, octanoic acid, and benzaldehyde were used as received from Sigma-Aldrich without further purification. The catalyst Amberlyst 15 was obtained from Sigma-Aldrich while the Al-MCM-41 (Si/Al = 15) was synthesized as described in Martin *et al.* [1].

**1.2 Sample characterization.** The morphology of the catalysts was investigated by transmission electron microscopy (TEM) using a JEM-2010 microscope (JEOL, 200 kV, 0.14 nm of resolution). The samples were embedded in a Spurr resin and cut into slices 80 nm thin using RMC-MTXL ultramicrotome (Boeckeler Instruments, Tucson, AZ). These slices were then displayed on a grid to observe by TEM the cross sections of the zeolites before and after the introduction of the mesoporosity. The digital analysis of the TEM micrographs was performed using Gatam DigitalMicrograph™ 1.80.70 for GMS 1.8.

Porous texture was characterized by N<sub>2</sub> gas adsorption at 77 K in an AUTOSORB-6 apparatus. The samples were previously degassed for 8 h at 250 °C at 5x10<sup>-5</sup> bars. Adsorption data were analyzed using the software QuadraWin™ (version 6.0) of Quantachrome Instruments. Cumulative pore volumes and pore-size distribution curves were calculated using DFT method (NL-DFT adsorption branch model). The total pore volume was obtained at the plateau of the cumulative adsorption pore volume plot at a relative pressure (P/P<sub>0</sub>) of 0.95. Micropore volume was determined by NL-DFT from the adsorption branch of the isotherms, and mesopore volume was calculated by subtracting the micropore volume from the total pore volume.

The materials were also characterized by X-ray powder diffraction (XRD) in the: (i) low angle region from 1 to 8 degrees  $2\theta$  at a scanning velocity of 0.01 degrees  $\text{min}^{-1}$ , and (ii) wide angle region from 5 to 50 degrees  $2\theta$  range using a scanning velocity of 1 degree  $\text{min}^{-1}$ ; in a SEIFERT 2002 apparatus using a  $\text{CuK}\alpha$  (1.5418 Å) radiation.

In order to study the amount of organics trapped within the pores of the zeolite, thermogravimetry (TG) in combination with differential thermal analysis (DTA) experiments were carried out using a TGA/SDTA851/LF/1600 from METTLER TOLEDO from 25 to 1000 °C at a heating rate of 10 °C  $\text{min}^{-1}$  under a  $\text{O}_2:\text{N}_2$  4:1 atmosphere. The amount of coke formed was calculated by the weight loss above 300 °C.

**1.3 Catalytic evaluation.** The reactions were performed as follows: ca. 0.04 mmol of substrate (10 mg estrone or 5 mg of indole) was stirred with a) 50  $\mu\text{l}$  of benzaldehyde and b) 30 mg of benzoin, respectively, in a glass vessel containing 10 mg of the catalyst for reaction a) and 5 mg for reaction b). The vials were closed and transferred into an aluminum heating block preheated to 100 °C. The mixture was stirred (400 rpm) at this temperature for different reaction times. After reaction the reaction mixture was cooled down, washed with acetone and centrifuged. Products were identified by comparing the retention time with that of pure samples and by using gas chromatography coupled to mass spectrometry (GC-MS).

**1.4 Adsorption experiments.** The experiments related to the adsorption of estrone on the zeolites were carried out in the following way: A solution of 10 mg of estrone 5 ml of acetone was added to each porous solid (10 mg) in a glass vial. The slurry was stirred (400 rpm) at room temperature for 1 h. After this time, the liquid supernatant was isolated by centrifugation and the estrone was analyzed by GC-FID using n-tetradecane as the external standard for the analysis with gas chromatography. The amount of testosterone adsorbed in the porous solids was calculated by comparison with the initial estrone concentration. For the small ketone (cyclopentanone), a similar procedure but using 50 mg of substrate was performed.

## 2. Results and Discussion

### 2.1 Characterization of the catalysts before reaction

Table S1. Properties of the catalysts used in this study.

Samples	Brønsted acidity ( $\mu\text{mol g}^{-1}$ )	Lewis acidity ( $\mu\text{mol g}^{-1}$ )	B/L	$V_{\text{micro}}$ ( $\text{cm}^3 \text{g}^{-1}$ )	$V_{\text{meso}}$ ( $\text{cm}^3 \text{g}^{-1}$ )	$V_{\text{tot}}$ ( $\text{cm}^3 \text{g}^{-1}$ )	Reference
CBV 720	190.4 <sup>a</sup>	84.6 <sup>a</sup>	2.25	0.30 <sup>b</sup>	0.26 <sup>b</sup>	0.56 <sup>b</sup>	[2]
Meso-USY	130.8 <sup>a</sup>	91.9 <sup>a</sup>	1.42	0.24 <sup>b</sup>	0.34 <sup>b</sup>	0.58 <sup>b</sup>	[2]
Al-MCM-41	157 <sup>a</sup>	527 <sup>a</sup>	0.53	0	0.85 <sup>c</sup>	0.85 <sup>c</sup>	[1,3]
Amberlyst-15	4700	-	-	-	-	-	[4]

<sup>a</sup> Concentration of Brønsted (B) and Lewis (L) acid sites in  $\mu\text{mol}$  of adsorbed pyridine per gram of zeolite after evacuation at 150 °C. As described in references [2,3].

<sup>b</sup> Volume of micropores (pore size < 2 nm) and surfactant-templated mesopores (pore size from 2 to 8 nm) for the different samples were calculated applying the NL-DFT method to the adsorption branch of the  $\text{N}_2$  isotherms.

<sup>c</sup> Volume of mesopores calculated from the adsorption branch of the  $\text{N}_2$  isotherm at a  $P/P_0 = 0.95$ .

## 2.2 Catalytic results

### a) Aldol condensation of estrone and benzaldehyde:

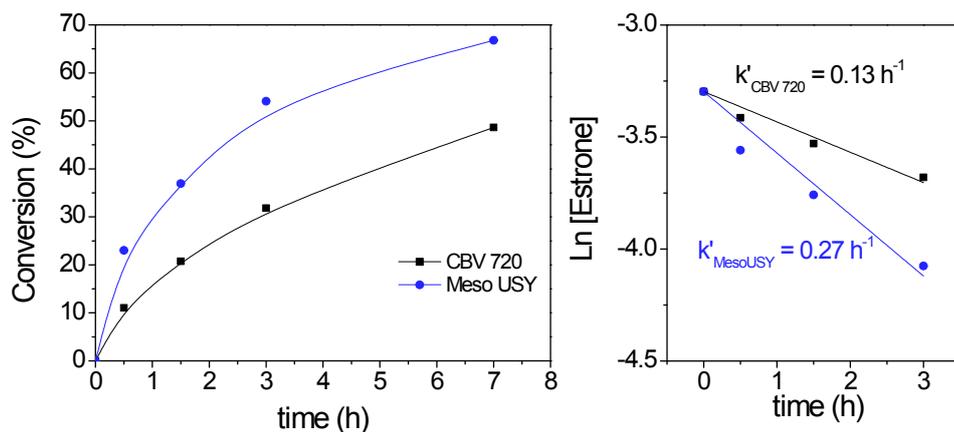


Figure S1. Kinetic plot for estrone and benzaldehyde condensation (left) and calculation of the pseudo-first order kinetic rate constant (right),  $k'$ , from the slope of the  $\ln[\text{estrone}]$  vs time plot for both catalysts, the original USY zeolite (black) and the surfactant-templated zeolite (cyan).

### b) Friedel-Crafts alkylation of indole with benzoin:

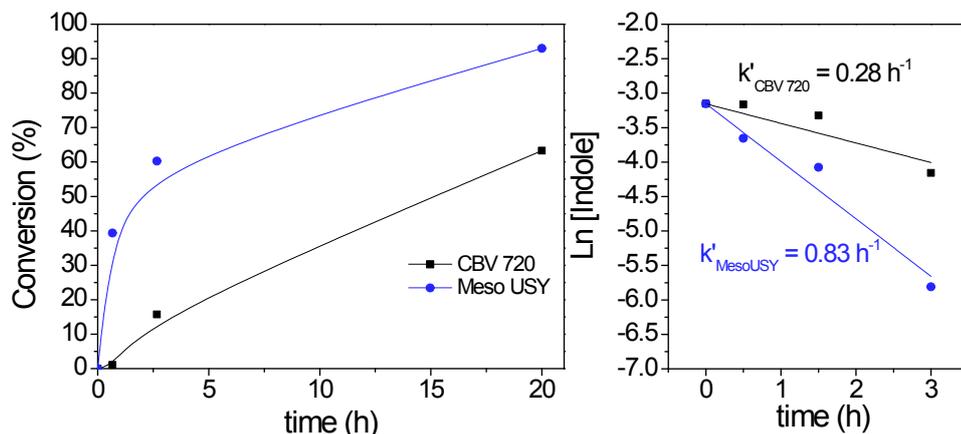


Figure S2. Kinetic plot for the indole alkylation with benzoin (left) and calculation of the pseudo-first order kinetic rate constant (right),  $k'$ , from the slope of the  $\ln[\text{indole}]$  vs time plot for both catalysts, the original USY zeolite (black) and the surfactant-templated zeolite (cyan).

## 2.3 Characterization of the catalysts after 3 consecutive reaction cycles

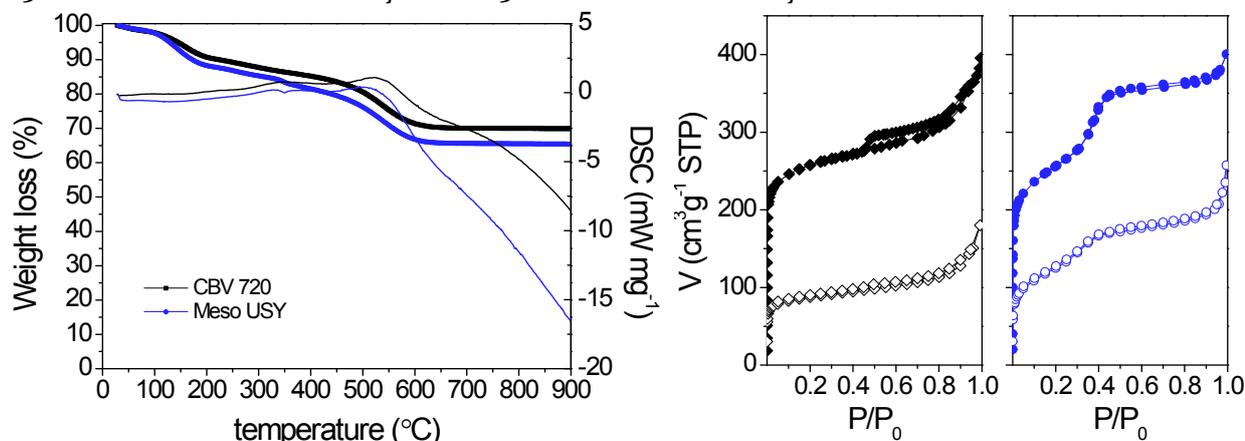


Figure S3. TG-DSC measurements (left) and  $\text{N}_2$  adsorption/desorption isotherms at 77 K (right) for both catalysts after three catalytic cycles, original USY zeolite (black) and surfactant-templated zeolite (cyan). The TGA (solid line) is presented along with the DSC data (dashed line).

Table S2. Properties of the catalysts after 3 catalytic cycles.

Samples	Substrate converted (mg)	TG wt% loss	Fraction of organic deposited ( $\text{mg}_{\text{org}}/\text{g}_{\text{cat}} \cdot \text{mg}_{\text{subs}}$ )	$V_{\text{tot}}$ before ( $\text{cm}^3 \text{g}^{-1}$ )	$V_{\text{tot}}$ after ( $\text{cm}^3 \text{g}^{-1}$ )	% $V_{\text{blocked}}$ ( $\text{cm}^3 \text{g}^{-1}$ )
CBV 720	60.4	18	3.0	0.56	0.21	63%
Meso-USY	92.1	20	2.2	0.58	0.30	48%

#### 2.4 Adsorption experiments

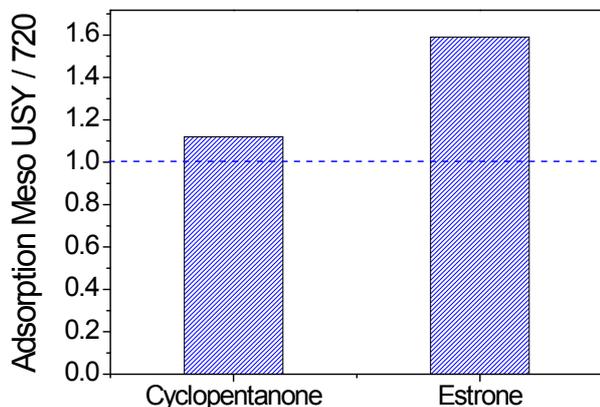


Figure S4. Ratio between the amount of cyclopentanone and estrone adsorbed in the surfactant-templated zeolite and the original USY zeolite. The dashed blue line indicates equal adsorption.

#### References

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