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CeZSM-5—a designer's catalyst for selective synthesis of octahydroacridine†

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High activity of cyclohexanone, formaldehyde and ammonia to form 1,2,3,4,5,6,7,8-octahydroacridine (OHA) is observed over different classes of zeolites and molecular modeling studies confirm the suitability of HZSM-5 catalyst for selective synthesis of OHA.

Octahydroacridine and its derivatives are of great interest as they play an important role in the preparation of alkaloids, dyes, drugs and other biologically active compounds with intriguing pharmacological and therapeutic properties.[1–3] Conventional methods so far reported in literature[4–6] for the synthesis of octahydroacridines are multistep, homogeneous and require tedious work-up procedures. The present investigation brings out a unique, eco-friendly and simple method for the synthesis of OHA for the first time using the low cost raw materials cyclohexanone, formaldehyde and ammonia.

Demand to design heterogeneous catalysts is increasing to make processes clean, viable and selective. In particular, molecules of fine chemicals being large, poly-functional and less stable, impose requirements for activity under milder conditions and higher selectivity on catalysts. Such demands are met by the many novel catalytic materials now becoming available.[7] When a catalytic process takes place in a porous system in the range 3–12 Å the reaction pathway is strongly influenced by the framework geometry and steric constraints, driving the reaction towards the desired products. Zeolites are often preferred due to their well-defined geometry, shape selectivity, catalytic properties (variable acidity) and ability to exchange metal cations in the porous system. The present paper describes an attempt to identify a porous catalyst of a definite geometry with high activity and selectivity for OHA. The formation of OHA resulting *via* the cyclization of the intermediates is expected in large pore zeolites with minimum constraints. However, the experiments highlight the suitability of medium pore (5.6 Å) HZSM-5 compared to large pore (>7 Å) HY, Hβ and mesoporous (>20 Å) Al-MCM-41. This observation is further supported by molecular modeling studies.

The vapor phase cyclization reaction was carried out using a fixed-bed tubular down-flow glass reactor (i.d 20 mm and length 45 cm) at atmospheric pressure. The reaction mixture was fed from the top of the reactor by using a syringe pump (Profuse, B. Braun Germany) to the catalyst placed in the middle of the reactor and the products collected at regular intervals were analyzed by gas chromatography with a 10% SE-30 column. The analysis was confirmed by GC-MS, MS and NMR. The zeolites HY (5.6), HZSM-5 (30) and Hβ (40) were commercially available and Al-MCM-41 (31) was prepared in the laboratory using a sol–gel method as reported earlier.[8]

The cyclization reaction of cyclohexanone, formaldehyde and ammonia (2:1:3 molar ratio) was carried out at a WHSV of 1 in the temperature range of 250–400 °C at 1 atm over the zeolites mentioned above. The observed product distribution shows OHA as a major product and methyloctahydroacridine (MOHA) and dicyclohexylamine (DCA) as by-products. At lower conversion, side products are predominant and at higher conversions steady activities are observed forming major products of the cyclization reaction.

Product distributions of the cyclization reaction over HY, HZSM-5, Hβ and Al-MCM-41 in the temperature range of 250–350 °C are shown in Table 1. All the zeolite catalysts show activity at 250 °C independent of the zeolite used and the activity increased with increasing temperature on HY, HZSM-5 and Hβ, reaching a maximum around 350 °C. Such an increase in activity is not observed on Al-MCM-41. This may be seen as due to low acidity of Al-MCM-41 compared to HY, HZSM-5 and Hβ (Table 1) that might be affecting the activity. On all the catalysts, reaction at 400 °C leads to coke formation resulting in deactivation. The main products of the reaction in the temperature range studied are DCA, OHA and MOHA. In general a high selectivity towards OHA is predominantly seen on all the zeolites indicating the suitability of zeolite systems for selective synthesis of OHA. However, this selectivity is affected to a considerable extent by the formation of DCA and MOHA. It may be seen from Table 1 that the formation of DCA is temperature dependent and the formation of MOHA is dependent on temperature, number and type of acid sites and the geometry of the pores. Thus MOHA formation is seen decreasing in the order Al-MCM-41 (mesopore, week/medium acid sites) > Hβ (large pore, weak/medium/strong acid sites) > HY (large pore, weak/medium/strong acid sites) > HZSM-5 (30) (medium pore, medium/strong acid sites). The possible reaction mechanism for the formation of products is shown in Scheme 1. The reactant cyclohexanone initially forms an imine with ammonia, which isomerises to an amine. When two mol of this imine ↔ amine intermediate condense in the presence of formaldehyde, this gives a product, which on further deamination and dehydrocyclization and aromatisation leads to a larger cyclised product, OHA. Simultaneous deamination and dehydrocyclization results in OHA while deamination results in DCA. MOHA might be resulting by the reaction of OHA with *in situ*-generated methylamine. The main reaction is not devoid of side products. Such a distribution might be resulting either due to acid site density, temperature, or the framework geometry that governs the relative adsorption/desorption of the reactants and products. A critical examination of the product distribution shows that of all the zeolites studied, HZSM-5 and Hβ show maximum activity and selectivity for OHA. Such a high selectivity of OHA is resulting when the conversions are high. It may be further highlighted that medium pore HZSM-5 has more suitable acid sites and framework geometry to give maximum activity and OHA selectivity. When the reactants are totally consumed in the main reaction, the side reactions are also minimized. HZSM-5 is modified by doping several metal ions such as V, Mn, Fe, Cu, Zn, Zr, La, Ce and Pb to obtain acid sites of uniform strength. The activity and modified acidity of few typical examples are given in Table 1. The modification by Ce^{3+}ion increased the total acidity and maximum increase in acidity is seen in the range of 200–350 °C by TPD of ammonia (0.41–0.67 mmol g^{-1}). The cyclization reaction on CeZSM-5 (30) is improved to 100% giving OHA selectivity as high as ≈ 92% without DCA and MOHA, thus highlighting the suitability of Ce-ZSM-5 (30). By contrast such a modification by V and La does not improve the conversion and selectivity. The steady

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† Electronic supplementary information (ESI) available: Details of molecular modeling studies. See http://www.rsc.org/suppdata/cc/b4/b409413a/

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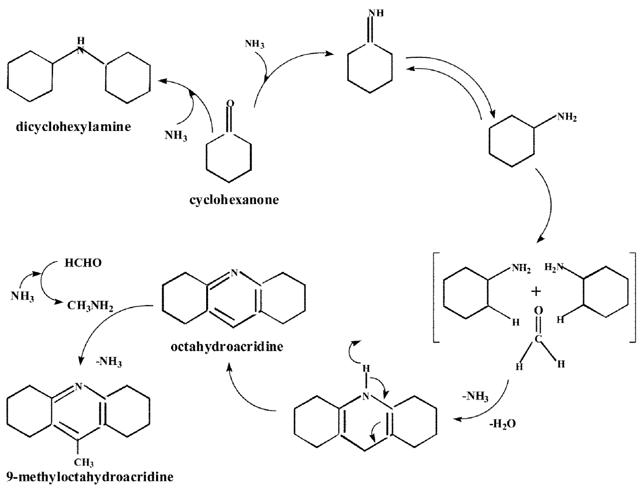
Table 1 Synthesis of octahydroacridines over various zeolite catalysts[a]

Catalyst (pore size/Å)	T/°C	Cyclohexanone conv. (%)	Selectivity (%) DCA	OHA	MOHA	Others	Acidity[b]/ mmol g^{-1}	Surface area[c]/ m^2 g^{-1}	Acid site density/ μmol m^{-2}
HY (7.4)	250	63.3	15.2	28.6	17.8	38.3	0.709	457	1.55
	300	73.9	21.9	44.2	8.4	25.3			
	350	88.6	4.4	68.4	5.8	21.3			
HZSM-5 (5.6)	250	54.0	11.0	43.1	17.7	28.1	0.53	350	1.51
	300	68.8	14.3	56.0	5.2	24.4			
	350	**95.8**	1.0	**81.8**	5.4	11.7			
Hβ (7.6 × 6.4)	250	69.5	7.8	33.5	29.8	28.7	0.52	406	1.28
	300	88.8	2.0	71.8	5.2	20.8			
	350	95.6	4.0	70.4	13.4	11.5			
Al-MCM-41 (30)	250	47.8	9.9	39.0	33.4	17.5		920	0.23
	300	55.7	2.1	48.0	20.9	28.8			
	350	67.6	14.0	52.0	5.2	28.2			
[d]**CeZSM-5**	250	33.2	—	59.0	—	41.0	0.79	297	2.65
	300	62.3	—	78.3	—	21.7			
	350	**100**	—	**91.7**	—	8.3			
[d]VZSM-5	350	75.2	—	76.1	1	23.8	0.54	290	1.86
[d]LaZSM-5	350	69.5	—	62.8	3	37.1	0.61	310	1.96

[a] Feed: cyclohexanone: formaldehyde: ammonia = 2:1:3; WHSV = 1; time on stream = 2 h; DCA = dicyclohexylamine OHA = octahydroacridine, MOHA = methyloctahydroacridine; others = cyclohexylamine, traces of aminooctahydroacridines and other unidentified products. [b] Acidities measured by stepwise thermal desorption of ammonia. [c] Surface areas measured by BET method. [d] 3 wt% metals impregnated on HZSM-5 (30).



Scheme 1 Reaction mechanism for the synthesis of OHA.

activity of CeZSM-5 observed for 10 h shows minimum deactivation compared to HZSM-5 maintaining high selectivity of OHA. The activity of the catalyst is restored by intermittent oxidative regeneration. These observations further confirm that modification of HZSM-5 by Ce^{3+} ion resulted in acid sites of uniform strength.

Computational modeling has been shown to be an efficient method of screening the possible catalysts for shape-selective reactions.[9] To support our experimental results Monte Carlo simulations (see ESI†) were performed for 100 000 runs at temperatures of 250, 300, 350 and 400 °C at 1 atm considering all the reactants involved in the reaction and products formed by cyclization reaction. The sorption studies given in Table 2, involving HY, HZSM-5 and Hβ show selectivity towards OHA, compared to DCA and MOHA, which is comparable with our experimental results (Table 1). Among the reactants cyclohexanone has high average loading compared to ammonia and formaldehyde. In the cyclization products OHA has high average loading compared to DCA and MOHA. In the case of Al-MCM-41 having pore size of *ca.* 30 Å, the molecular simulations carried out for two million simulations show the average loading very low for reactants and it is almost nil in the case of products indicating free translational and rotational motion along the channels of Al-MCM-41. The zeolite HZSM-5 (30) shows significant average loading after two million Monte Carlo simulations. The stabilization energy of OHA is lower than all other reactants and products.

Table 2 Average loading and average energy (kcal mol^{-1}) at the end of the Monte Carlo simulations at 1 atm and 350 °C

Reactants/ products	HY Av. load.	HY Av. energy	HZSM-5 Av. load.	HZSM-5 Av. energy	Hβ Av. load.	Hβ Av. energy
Cyclohexanone	1.4	−9.2	0.2	−7.4	1.4	−8.8
Formaldehyde	0.2	−4.8	0.03	−2.2	0.2	−4.0
Ammonia	0.2	−1.2	0.02	−0.6	0.05	−1.0
DCA	1.6	−13.7	1.5	−12.9	2.1	−14.2
OHA	4.6	−14.0	2.7	−15.1	2.9	−14.8
MOHA	1.0	−14.6	2.3	−13.8	1.8	−15.2

In conclusion, we have succeeded in identifying a suitable zeolite catalyst, namely HZSM-5, to convert cyclohexanone, formaldehyde and ammonia for the synthesis of 1,2,3,4,5,6,7,8-octahydracridine. HZSM-5 is further modified with Ce^{3+} ion to produce acid sites of uniform strength that could form OHA with selectivity as high as 92% without byproducts at 100% cyclohexanone conversion. The high activity and selectivity of HZSM-5 are supported by molecular modeling studies.

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