

# Zeolite screening for the racemization of 1-phenylethanol

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Available online 14 January 2008

## Abstract

To select a suitable system for the racemization of 1-phenylethanol, a commercially relevant chiral alcohol, four acid zeolites and five solvents were screened. Results show that the zeolite/solvent combination influences not only the reaction rate but also the product yield because of their influence on side reactions. As a general rule we can say that the higher the racemization rate, the lower the product yield. The choice of solvent is also important for avoiding catalyst deactivation over time, especially when recycling of the catalyst is envisaged. Kinetic modeling of the results was performed in order to allow a better comparison of the different reaction systems and a more complete analysis of the phenomena underlying their behavior. Of the 20 combinations tested, zeolite H-Beta Si:Al = 75 in ethyl acetate and zeolite H-Beta Si:Al = 12.5 in isooctane, water and vinyl acetate showed the most promising results.

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**Keywords:** Zeolite; Racemization; 1-Phenylethanol; Kinetic modeling

## 1. Introduction

In organic synthesis, racemization is often an undesirable phenomenon. However, the increasing demand for enantiomerically pure compounds led to the development of processes involving the kinetic resolution (KR) of a racemate [1]. In order to circumvent the 50% conversion limitation in a standard KR, it is useful to introduce, *in situ*, a step involving the racemization (or equilibration) of the substrate, thus creating a dynamic kinetic resolution (DKR) process with a theoretical conversion of 100% [2,3].

Enantiopure 1-phenylethanol (1-PE) is a chiral building block in the fine chemical and pharmaceutical industries and has applications as an ophthalmic preservative, a solvatochromic dye, an inhibitor of cholesterol intestinal absorption and a mild floral fragrance [4].

Depending on their nature, different substrates may be racemized in distinct ways [5–7]. For secondary alcohols such as 1-PE, a variety of racemization methods are available. Some of the most popular exploit the reversible oxidation to the corresponding ketone with iridium-, rhodium- or ruthenium-

based catalysts [6]. Their use has been reported both in homogeneous conditions [8] and supported on hydroxyapatite [9] or alumina [10]. For a limited number of *sec*-alcohols and conditions, biocatalytic racemization with mandelate racemase is also possible [11]. Basic catalysis can be used when the substrate presents an acidity-improving substituent adjacent to the chiral center [11].

The racemization of *sec*-alcohols can also be accomplished by acid catalysis. After protonation and water elimination, the chiral identity of the substrate is lost as a result of the reversible formation of a planar carbocation [12]. In the case of 1-PE, the loss of a proton at this stage will yield a styrene molecule as a side product. When using catalysts such as zeolite Beta, the racemization can also occur *via* a redox mechanism [13] (similar to the Meerwein-Ponndorf-Verley reduction and Oppenauer oxidation reactions) with acetophenone as the intermediate (Fig. 1).

Zeolites are extremely versatile heterogeneous catalysts and have a vast number of academic and industrial applications in acid catalysis [14,15]. They have previously been shown to surpass the performance of homogeneous and other heterogeneous acid catalysts in a screen involving the racemization of 1-PE and other benzylic alcohols in aqueous conditions. Wuyts et al. [12] have studied the influence of the zeolite framework type, the zeolite Si:Al ratio, the reaction temperature and the

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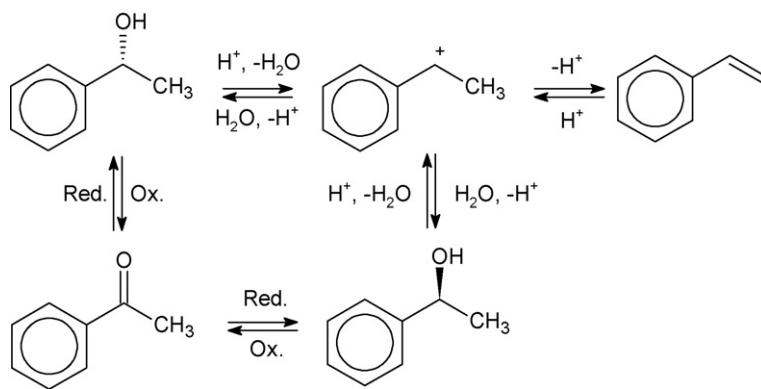


Fig. 1. Two different mechanisms of racemization of 1-phenylethanol catalyzed by zeolite H-Beta [13].

substrate concentration on the reaction rate, but only for racemization occurring in an aqueous medium.

The occurrence of side reactions involving the substrate, the solvent or both can severely impair the development of an adequate system to perform this reaction, as it lowers the product yield. The choice of solvent plays a key role in the analysis of this aspect and it is difficult to theoretically predict the system behavior solely based on the properties of both solvent and zeolite. Therefore, in this work, several acid zeolites were screened in the racemization of 1-PE using aqueous and four organic media.

## 2. Experimental

**Materials.** Zeolites Beta CP814E (Si:Al molar ratio = 12.5), Beta CP811E-150 (Si:Al = 75) and HY CBV 720 (Si:Al = 15, %Na<sub>2</sub>O = 0.03) were from Zeolyst, zeolite LZY-82 (Si:Al = 4.5) was from UOP and zeolite NH<sub>4</sub>Y (Si:Al = 2.5, %Na = 1.6) was from Sigma–Aldrich. All zeolites were calcined at 500 °C for 8 h under 0.5 L<sub>dry air</sub> g<sub>zeo</sub><sup>-1</sup> h<sup>-1</sup> prior to use. Zeolite NaHY (Si:Al = 15, molar %Na = 76) was obtained from calcined HY CBV 720 after two cycles of ion exchange with NaNO<sub>3</sub> 2 M at 100 °C, washing with distilled water and calcination.

(R)-(+)-1-phenylethanol 99% (ee 97+%) was from Alfa Aesar, ethyl acetate (EA) 99.5+% was from Sigma–Aldrich, *tert*-butyl methyl ether (TBME) 98% was from Sigma–Aldrich, isooctane *p.a.* was from Merck and vinyl acetate (VA) 99+% was from Sigma–Aldrich.

**Instrumentation.** Samples were analyzed by gas chromatography on a HP 5890A equipped with a Varian CP-Chirasil-Dex CB (25 m) chiral column and using FID detection. Concentrations were determined using external standards.

**Racemization reactions.** Standard reactions were carried out in closed 10 mL glass reactors containing 2 mL of solvent and 50 mg of zeolite. Reactions started with the addition of 30 mg of (R)-1-PE and took place in an incubator at 30 °C with orbital shaking at 250 rpm.

**Catalyst recycling.** After the first racemization cycle, the reaction mixture was centrifuged, the liquid phase was discarded and the zeolite was washed twice with 2 mL of fresh solvent before being air-dried overnight and reused. Due

to minor losses of catalyst in sampling, the amounts of fresh solvent and reactant were proportionally adjusted.

## 3. Results and discussion

In order to find a suitable system for the racemization of 1-PE, four zeolites – H-Beta Si:Al = 12.5 and 75, HY Si:Al = 15 and ultra stable H-LZY-82 Si:Al = 4.5 – were tested in different media: water and four organic solvents.

Table 1 compares the enantiomeric excess (ee) of the alcohol obtained at 24 h of reaction and at other relevant times for the slowest and quickest reactions. The MB parameter represents the fraction of the initial mass of 1-PE that has disappeared from solution. Ideally, MB should be close to 0% but in some cases it reached 100% (no 1-PE detected), due to the extent of the side reactions. The GC chromatograms did not show an accumulation of acetophenone (a possible intermediate according to Fig. 1) but a peak attributable to styrene was detected in 11 of the 22 experiments, although it represented only negligible amounts and could not explain the reduction in total 1-PE concentration. However, styrene may polymerize in the presence of zeolites [13] and thus elude detection. Other side reactions may breakdown 1-PE, producing compounds that exit the GC column overlapped by the solvent peak, or promote the adsorption of the substrate onto the acid sites, in a process similar to coking, and prevent its detection. Negative MB values mean that no significant transformation occurred *via* side reactions and that solvent evaporation during the experiment (due to the high volatility of some of the solvents used and because the reactor was opened to collect samples) caused an increase in the total concentration of 1-PE.

Zeolite HY showed the poorer results, as it only managed to racemize a small amount of the substrate in TBME and vinyl acetate. Despite having a lower Si:Al ratio, the performance of the ultra stable H-LZY is equal or better than that of HY in every solvent. In isooctane, H-LZY racemizes 1-PE very quickly but its global concentration also decreases very significantly; this decrease in concentration can be due either to secondary reactions that consume the reactant or to 1-PE molecules remaining strongly adsorbed to the zeolite, as a result of the formation of very stable carbocations, which is likely to happen

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