

Chirality Inversion in HZSM-5 and Nafion-H Solid Acid-catalysed Synthesis of Ethers from Alcohols via Surface S_N2 Reaction

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A surface-catalysed S_N2 reaction is demonstrated for the dehydrative coupling of alcohols to form ethers over heterogeneous acid catalysts, HZSM-5 and Nafion-H, with shape-selectivity playing a major role in the case of HZSM-5 catalyst.

Solution phase S_N2 reactions have been extensively studied, and the first gas phase S_N2 experiment was reported in the early 1970s.¹ Recently, a comprehensive theoretical account of solution and gas-phase S_N2 reactions was provided.² The dehydrative coupling of alcohols to form ethers is practiced on an industrial scale for symmetric ethers with small alkyl groups. In solution phase with an acid catalyst such as H₂SO₄, it is generally believed that the synthesis of ethers from secondary and tertiary alcohols follows the S_N1 pattern, while synthesis from primary alcohols follows the S_N2 pathway.³

So far, however, no evidence for *surface-catalysed* S_N2 reactions has been reported. We report herein the first evidence for heterogeneous acid-catalysed S_N2 reactions in coupling of chiral alcohols to form ethers with a very high degree of chiral inversion, 97% over the zeolite HZSM-5 vs. 77–80% over the fluorocarbon sulfonic acid resin Nafion-H and liquid H₂SO₄. Chiral pentan-2-ol was reacted with a light alcohol, *e.g.* [¹⁸O]ethanol, to form ethoxy pentanes, and the products were examined for chirality using a Chirasil-CD column (fused silica column coated with β-cyclodextrin) and, in the case of [¹⁸O]ethanol, for the source of the ether oxygen by GC-MS. The reference compound (*R*)-2-ethoxypentane was synthesized using the Williamson method starting with (*R*)-pentan-2-ol and sodium metal.

The present heterogeneous acid-catalysed experiments were carried out at 90–100 °C and 1 MPa total pressure⁴ in a gas-phase downflow stainless steel tubular reactor provided with a liquid injection metering pump and with on-line GC analysis to determine alcohol conversion and product selectivities. The injected liquid mixture was vaporized in a preheater section before it reached the catalyst bed. The [¹⁸O]ethanol employed in this study contained 98% atom% ¹⁸O, while (*R*)-pentan-2-ol and (*S*)-pentan-2-ol of 98% chiral purity (Aldrich) were used for the chirality studies. Two kinds of solid acid catalysts, HZSM-5 (with Si:Al ratio = 34:1) and Nafion-H (with ion exchange capacity of 0.9 mequiv g⁻¹), were employed. Typically, 30 μl min⁻¹ liquid alcohol mixture was injected into a 88 ml (STP)/min He and 12 ml (STP)/min N₂ carrier gas, while the reactant conversion was limited to less than 5%. The condensable products were trapped in a glass bubbler, cooled with liquid nitrogen and then analysed by GC-MS for quantitative isotope analysis. For comparison, similar experiments were also carried out in liquid phase at 100 °C and ambient pressure for 1 h, with concentrated H₂SO₄ as the catalyst and the molar ratio of ethanol: pentan-2-ol: H₂SO₄ = 4.0:1.0:0.4.

Under these reaction conditions, the dehydrative coupling of ethanol and pentan-2-ol produced diethyl ether and di-2-amylyl ether as self-coupling products, 2- and 3-ethoxypentane as cross-coupling products, and the dehydration product pent-2-ene but not ethene. For acid-catalysed cross-coupling of ethanol and pentan-2-ol via an S_N2 process, the 2-ethoxypentane product can in principle be formed either by ethanol attacking the activated pentan-2-ol or *vice versa*, where the attacking alcohol would retain its oxygen. The experiment with [¹⁸O]ethanol was designed to determine the relative contributions from these two distinct routes, and the ¹⁸O content and chirality of the cross-coupling products are presented in Table 1. The true configuration inversion (*I*) for the ether formation due to S_N2 attack of the activated pentan-2-ol by ethanol (Table 1, col. 5) was calculated from the oxygen isotope fraction *Z* (Table 1, col. 4) and the ratio *X/Y* of the (*R*)- and (*S*)-isomers of 2-ethoxypentane (Table 1, col. 3) using the relations, $X = ZI$ and $Y = Z(1 - I) + (1 - Z) = (1 - ZI)$, that yield eqn. (1).

$$I (\%) = 100/[Z(1 + Y/X)] \quad (1)$$

The unconverted ethanol and diethyl ether retained more than 98% of ¹⁸O from the starting ethanol, indicating that there was no isotope scrambling during the dehydrative coupling reactions. The data in Table 1 demonstrate that ¹⁸O was retained in the product ether, and ethanol attack of the acid activated pentan-2-ol was the predominant synthesis pathway in all the cases here. On the other hand, for pentan-2-ol attacking activated ethanol, the product ether retained the ¹⁶O from pentan-2-ol and the chirality of the starting (*S*)-pentan-2-ol.

The combined ¹⁸O retention and the (*R*)/(*S*)-chirality results demonstrate that the axial rear-attack S_N2 mechanism dominates (97% over HZSM-5 and 77% over Nafion-H) in this heterogeneous acid-catalysed dehydrative coupling of alcohols. Evidently, the shape selectivity induced by the ZSM-5 zeolite channel structure (Fig. 1) plays an important role in achieving markedly higher configuration inversion than either Nafion-H resin or liquid H₂SO₄. The ZSM-5 framework contains two channel systems, *i.e.* straight-type channels with elliptical cross section (5.4 × 5.6 Å) that are intersected by sinusoidal channels with cross section of (5.1 × 5.4 Å).⁵ The cross coupling of ethanol and pentan-2-ol could not proceed inside either channel because once the pentan-2-ol is adsorbed at the acid site, there is not enough space for ethanol to attack the activated pentan-2-ol from the rear end of the asymmetric carbon. However, the intersection of the channels could accommodate the transition

Table 1 Product selectivities (±2 mol%) (taking into account 2- and 3-ethoxypentane only) from the reaction of [¹⁸O]ethanol and *S*-pentan-2-ol (¹⁶O) over Nafion-H and HZSM-5 catalysts at 100 °C and 1 MPa, and in concentrated H₂SO₄ solution at 100 °C and ambient pressure, where the true inversion (*I*) was calculated by using eqn. (1)

Acid catalyst	Product selectivity(%) ^a			Ratio for (<i>R</i>)-2-EP/ (<i>S</i>)-2-EP (<i>X/Y</i>)	¹⁸ O/(¹⁶ O + ¹⁸ O) (%) (<i>Z</i>)	Inversion (%) (<i>I</i>)
	(<i>S</i>)-2-EP	(<i>R</i>)-2-EP	3-EP			
HZSM-5	14.0	86.0	0.0	86.0/14.0	89	97
Nafion-H	32.9	60.9	6.2	60.9/32.9	84	77
H ₂ SO ₄	33.6	64.0	2.4	64.0/33.6	82	80

^a Where (*S*)-2-EP stands for (*S*)-2-ethoxypentane, (*R*)-2-EP for (*R*)-2-ethoxypentane, and 3-EP for 3-ethoxypentane.

state (TS) as illustrated in Fig. 1. The TS geometry was optimized by using the SPARTAN program⁶ (at the RHF/STO-3G level) with the constraints that the O–C–O angle at the activated asymmetric carbon atom was equal to 180° and the two C–O bond distances (represented by dashed lines between the asymmetric carbon atom and the oxygen atoms from the attacking ethanol and the leaving water molecules, respectively) were 2.0 Å.⁷ This result indicates that the proton-donating acid sites of HZSM-5 zeolite that catalyse the coupling of ethanol and pentan-2-ol are located at the intersection of the two channels.

In contrast, the Nafion-H resin catalyst bears similarity to acid solution, possibly due to its flexible fluorocarbon backbone carrying the sulfonic acid groups. The OH group of pentan-2-ol is the preferred leaving group, after being activated by the

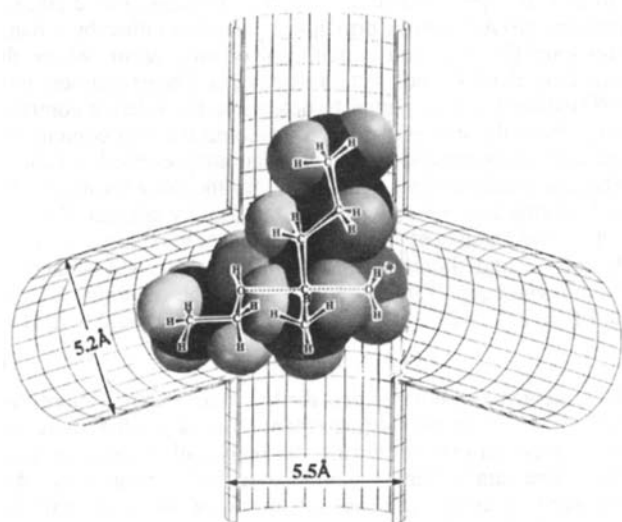


Fig. 1 Transition complex in the EtOH + pentan-2-ol S_N2 reaction activated by the proton at the channel intersection of HZSM-5. The zeolite pore structure is represented as a wire-frame section of the intersecting channels.⁸ The zeolite proton that activates the pentan-2-ol molecule is marked with an asterisk (*).

Table 2 Product selectivities (taking into account 2- and 3-ethoxypentane only) from the reaction of EtOH + pent-2-ene and EtOH + pentan-3-ol over the HZSM-5 catalyst at 110 °C and 1 MPa total pressure and in concentrated H_2SO_4 solution at 100 °C and 0.1 MPa

Reaction and catalyst	(S)-2-Ethoxy-pentane	(R)-2-Ethoxy-pentane	3-Ethoxy-pentane
EtOH + Pent-2-ene: over HZSM-5	47.0	47.0	6.0
	with H_2SO_4	28.2	43.6
EtOH + Pentan-3-ol: over HZSM-5	36.5	36.5	27.0
	with H_2SO_4	2.2	95.6

Table 3 Product selectivities (taking into account 2-methoxypentane and 3-methoxypentane only) from the reactions of MeOH + pent-2-ene at 120 °C and MeOH + pentan-3-ol at 110 °C and 1 MPa total pressure over the HZSM-5 catalyst

Reaction	(S)-2-Methoxy-pentane	(R)-2-Methoxy-pentane	3-Methoxy-pentane
MeOH + Pent-2-ene	32.5	32.5	35.0
MeOH + Pentan-3-ol	8.5	8.5	83.0

surface H^+ and subjected to concerted nucleophilic attack by the light alcohol. The minor paths (23% over Nafion-H and 3% over HZSM-5) can be accounted for by a less efficient carbenium ion (C^+) or olefin ($C=$) intermediate mechanism. These minor paths are corroborated by observations of the 3-ethoxypentane side product, which could only be formed *via* carbenium ion or olefinic intermediates, over Nafion-H and in the liquid phase with H_2SO_4 . However, 3-ethoxypentane was not observed with the HZSM-5 catalyst, indicating that its formation was suppressed by shape selectivity. The 3-ethoxypentane is more branched and is expected to pass through the HZSM-5 channel at a slower rate than 2-ethoxypentane, even if formed by the carbenium ion or the olefin reactions at the channel intersections.

Shape selectivity of HZSM-5 favouring the 2-isomer over the 3-isomer of ethoxypentane was also displayed in syntheses utilizing pent-2-ene + ethanol and pentan-3-ol + ethanol mixtures, which were carried out with HZSM-5 and H_2SO_4 as catalysts, as shown in Table 2. These experiments were performed under similar conditions as those for the ethanol coupling with pentan-2-ol (Table 1), except that the temperature was 10 °C higher for ethanol coupling with pent-2-ene because at 100 °C the amounts of products formed were negligible.

The ethanol coupling with pent-2-ene is likely to proceed *via* a carbenium ion pathway, and the present experiment indicated that this coupling reaction was less efficient than the alcohol coupling *via* the S_N2 pathway. Under the normal acid catalysis condition (with H_2SO_4), the 3-isomer is expected to be preferred over the 2-isomer. The liquid phase H_2SO_4 -catalysed reaction produced the 3-isomer almost exclusively when pentan-3-ol was reacted with ethanol. In contrast, significant amounts of the 2-isomer were obtained as a racemic mixture over HZSM-5 in both cases. It is evident that 2-ethoxypentane was preferred over 3-ethoxypentane inside the zeolite pores. On the other hand, when methanol was treated with pent-2-ene and pentan-3-ol over the HZSM-5 catalyst, the shape selectivity was not pronounced owing to the smaller size of the methoxy group (Table 3).

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