

Gas-phase Catalytic Asymmetric Reaction using Chirally Modified Microporous Catalysts

Saskia Feast,^a Donald Bethell,^a Philip C. Bulman Page,^a Frank King,^b Colin H. Rochester,^c M. Rafiq H. Siddiqui,^a David J. Willock^a and Graham J. Hutchings^a

^a Leverhulme Centre for Innovative Catalysis, Robert Robinson Laboratories, Department of Chemistry, University of Liverpool, Oxford Street, Liverpool, UK L69 3BX

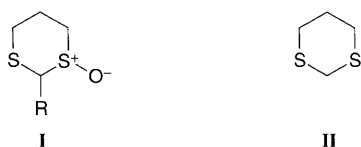
^b ICI Katalco, Research and Technology Group, PO Box 1, Billingham, Cleveland, UK TS23 1LB

^c Department of Chemistry, University of Dundee, Dundee, UK DD1 4HN

The first example of an enantioselective gas-phase reaction heterogeneously catalysed by a zeolite is demonstrated using as catalyst a zeolite modified with a non-racemic chiral mediator.

Many pharmaceuticals, agrochemicals and food additives are chiral and are often normally available only as a racemic mixture of the two enantiomers. These enantiomers may show different biological activities, and in recent years the synthesis of such materials as pure enantiomers has gained new impetus as a result of the increasing awareness among legislative bodies of the relationship between absolute stereochemistry and activity. To date, such asymmetric syntheses have been mostly carried out in the liquid phase, often with the use of an homogeneous catalyst. This approach can lead to difficulties in product recovery and catalyst separation. The design of heterogeneous asymmetric catalysts has therefore become a subject of intensive research, and recently considerable progress has been made using immobilized homogeneous systems.¹ A number of examples of heterogeneously catalysed asymmetric reactions involve the modification of an active surface by an enantiomerically pure compound, as typified by the hydrogenation of methyl pyruvate.^{2,3} Chiral modification of zeolite catalysts has also been used for heterogeneous enantioselective catalysis using liquid reagents.⁴⁻⁶ Herein we describe a method by which zeolite supercages can be made enantiomerically discriminating by including within them a chiral species, and we use this approach to demonstrate the first example of a gas-phase enantioselective reaction heterogeneously catalysed by a zeolite.

In this study we have used zeolite Y as an example of a well studied microporous material.⁷ A modifier within the zeolite supercages creates the chiral environment required to favour the formation of one of a pair of diastereoisomeric transition states, necessary for an enantioselective reaction. Chiral dithiane oxides **I** (R = H, phenyl) were selected as modifiers for study.



The acid-catalysed dehydration of butan-2-ol was chosen as a reaction capable of demonstrating both enantioselectivity [differentiation between (*R*)- and (*S*)-butan-2-ol] and chemoselectivity (evidenced by variation of the butene isomers as products).

Zeolite Y (2.0 g, LZY 82, Union Carbide) was treated with a solution of 1,3-dithiane 1-oxide (0.144 g) in deionised water (30 ml) at 50 °C for two hours to achieve a loading of one modifier molecule per supercage. The modified zeolite was filtered and dried (100 °C), pelleted and sieved to give particles with a diameter of ca. 0.6–1 mm. Characterization by X-ray diffraction demonstrated that the modifier did not affect the crystallinity of the zeolite, and studies using ¹³C MAS NMR spectroscopy showed that the dithiane oxide had been molecularly adsorbed into the zeolite. The dithiane oxide was remarkably stable inside the acidic zeolite: it did not undergo acid-catalysed elimination, hydrolysis or rearrangement. Heating the modified zeolite in flowing nitrogen at 180 °C did not lead to any decomposition, and the dithiane oxide could be recovered intact in high yield by solvent extraction. Of particular importance is that such treatment of enantiomerically enriched (*R*)-dithiane oxide did not result in racemization. Decomposition of compound **I** (R = H) adsorbed on the zeolite was only observed at temperatures well in excess of 400 °C.

The initial experiments were carried out using zeolite Y modified with racemic 1,3-dithiane 1-oxide, and this was compared as a catalyst for the dehydration of racemic butan-2-ol with a control sample of zeolite Y prepared by an analogous method but without the modifier. The results (Table 1) demonstrate that the dithiane oxide modified catalyst was considerably more active than the control sample by several orders of magnitude, and that this activity was maintained over several days of testing without significant loss of the enhanced activity. Under the reaction conditions studied, the control sample only became active at temperatures above 150 °C and required a reaction temperature of 225 °C to achieve 90% conversion, whereas the modified zeolite gave 90% conversion at 115 °C. For the modified zeolite, the distribution of butene isomers is close to that expected for equilibrium;⁸ subsequent

Table 1 Reaction of racemic butan-2-ol over modified catalysts^a

	Catalyst								
	Y ^b		Y-SO ^c	Y-S ^d	SiO ₂ /Al ₂ O ₃ ^e		SiO ₂ /Al ₂ O ₃ ^f	BN-SO ^g	
<i>T</i> /°C	115	225	115	110	175	200	200	115	225
Conv. (%)	0	90	90	3.6	35.6	31.5	24.5	0	0
Selectivity (%)									
but-1-ene	—	17.7	8.3	15.4	14.7	16.5	21.6	—	—
<i>E</i> -but-2-ene	—	40.6	53.8	53.8	46.5	31.7	33.9	—	—
<i>Z</i> -but-2-ene	—	41.6	37.8	30.7	38.8	51.8	46.5	—	—

^a Catalyst (0.3 g) tested in a conventional glass microreactor using on-line GC analysis with butan-2-ol (3.3×10^{-3} mol h⁻¹) prevaporized in a nitrogen diluent (3.7×10^{-2} mol h⁻¹). ^b Zeolite Y (ultrastabilized LZY 82, Union Carbide). ^c Zeolite Y modified with (±)-1,3-dithiane 1-oxide, 1 molecule per supercage (7.6 mass%). ^d Zeolite Y modified with 1,3-dithiane, 1 molecule per supercage (7.2 mass%). ^e Non-microporous silica alumina, SiO₂/Al₂O₃ = 5.7. ^f Non-microporous silica alumina, SiO₂/Al₂O₃ = 5.7, modified with 1,3-dithiane 1-oxide (6.9 mass%). ^g Boron nitride modified with 1,3-dithiane 1-oxide (7.4 mass%).

experiments revealed that the modified zeolite was also an active catalyst for butene isomerization. To confirm that the rate enhancement observed was due to an interaction between the modified zeolite and the substrate, a number of control experiments were carried out (Table 1). Zeolite Y was modified using 1,3-dithiane **II**, and, under the same conditions used for the sulfoxide-modified zeolite, no rate enhancement was observed, indicating that the sulfoxide oxygen atom is a vital feature of this catalyst system. Investigation of a non-microporous silica/alumina catalyst that had an Si:Al ratio identical to that of the zeolite Y studied indicated that modification by the dithiane oxide acted as a poison. The microporous aluminosilicate framework is therefore also important. In addition, 1,3-dithiane 1-oxide supported on the inert material boron nitride was found to be totally inactive for butan-2-ol dehydration, indicating that it is the combination of the dithiane oxide with the zeolite which is essential.

To understand the origin of this high catalytic activity, a series of computer simulation studies was carried out to determine the most favourable locations for 1,3-dithiane 1-oxide within the zeolite framework. The Biosym docking package⁹ was used to generate a random set of ten energetically favourable arrangements of the (*R*)-dithiane oxide molecule in a host zeolite Y structure with an Si:Al ratio of 1:1. Each structure was energy minimized and the lowest energy conformation taken as the most likely dithiane position in the zeolite. Within this structure, the framework proton nearest to the dithiane oxygen was transferred to form the 1-hydroxy-1,3-dithiane cation, and the cation position re-optimized (Fig. 1). Molecular dynamics simulations at the experimental temperature revealed that the 1-hydroxydithiane cation was considerably more stable than the physisorbed 1,3-dithiane molecule.¹⁰ We consider that the 1-hydroxydithiane cation may act as a proton transfer agent and this may account for the enhanced reactivity of this system. The structure shown in Fig. 1 was used as the host for further docking calculations to introduce each of the enantiomers of butan-2-ol; the docked structures were energy minimized and the lowest energy structures selected as the most likely butan-2-ol binding positions; these are shown in Fig. 2.

Since the active sites in the modified zeolite are considerably more active than those of the unmodified zeolite, we considered that the modified zeolite could form the basis of an enantioselective catalyst. A catalyst was therefore prepared using enantiomerically enriched (*R*)-1,3-dithiane-1-oxide (enantiomeric excess 83%),¹¹ and a series of control experiments was carried to show that enantiomerically pure (*R*)- and (*S*)-butan-2-ol were not racemized under the reaction conditions used in this study. The results for the independent reactions of (*R*)- and (*S*)-butan-2-ol over a wide temperature range are shown in Fig. 3, and it is apparent that the (*S*)-butan-2-ol is more reactive than the (*R*)-enantiomer over the entire temperature range investigated, suggesting that this catalyst system should be able to discriminate between the two enantiomers of racemic butan-2-ol. Our initial experiments confirm that this can be observed, and the results are given in Table 2. For example, at 110 °C, when a total butan-2-ol conversion of 0.5% is observed, (*S*)-butan-2-ol reacts more than 17 times faster than the (*R*)-enantiomer. Similar results were obtained at 120 °C at a total conversion of 1.3% and, under the same conditions at the higher temperature of 150 °C, an improved effect is observed at a higher conversion of 9.9%, although the effect is short lived. It is interesting that the enantiomeric discrimination obtained

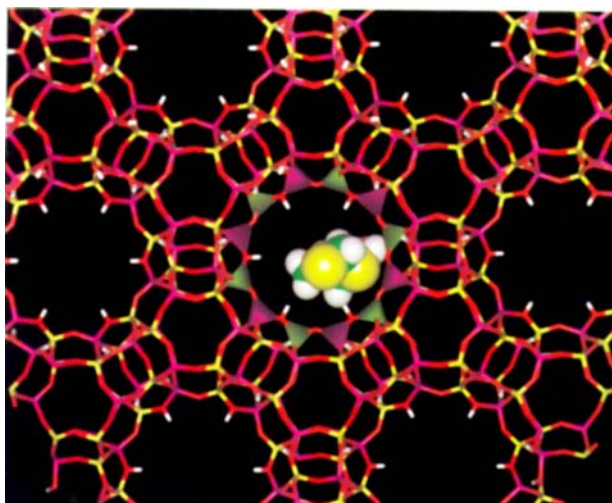


Fig. 1 Calculated low energy conformations of the protonated dithiane oxide cation in zeolite Y (Si/Al = 1).^{8,9} The bridging oxygen atom which donated the proton is highlighted as a small red sphere. The purple tetrahedra are centred on aluminium atoms and the green tetrahedra on silicon atoms.

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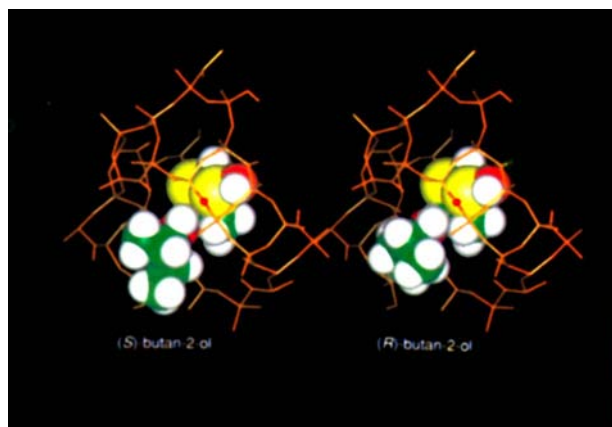


Fig. 2 Calculated low energy conformations for enantiomers of butan-2-ol in dithiane oxide loaded zeolite Y (Si/Al = 1).⁹ Each of the two butan-2-ol enantiomers was docked into the zeolite Y/dithiane hydroxide cation system, and the lowest energy structures are shown here. Binding energies for butan-2-ol: (*S*)-form, $-64.7 \text{ kJ mol}^{-1}$; (*R*)-form, $-48.3 \text{ kJ mol}^{-1}$. Two views of each structure are shown, with most of the zeolite framework cut away for clarity; the bridging oxygen atom which donated the proton is highlighted as a small red sphere.

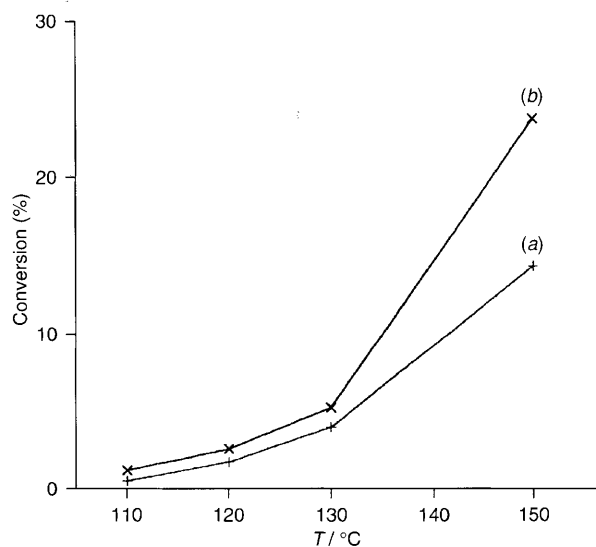


Fig. 3 Effect of temperature on the conversion of (*R*)-butan-2-ol (a) and (*S*)-butan-2-ol (b) over zeolite Y (Crosfield NaY ion-exchanged with NH_4NO_3 and calcined at 550 °C) modified with one molecule per supercage of (*R*)-1,3-dithiane 1-oxide and treated with $1.77 \times 10^{-3} \text{ mol h}^{-1}$ of enantiomerically pure alcohol pre-vaporized in diluent nitrogen ($5.6 \times 10^{-2} \text{ mol h}^{-1}$).

Table 2 Reaction of racemic butan-2-ol over zeolite Y modified by enantiomerically enriched dithiane oxides

Catalyst		$T/^\circ\text{C}$	Conv. ^a /%	10^3 Product composition ^b /mol h ⁻¹				Butan-2-ol conversion/%		
Zeolite	Modifier			but-1-ene	but-2-ene	(<i>R</i>)-butan-2-ol	(<i>S</i>)-butan-2-ol	(<i>R</i>)	(<i>S</i>)	Relative rate
Y ^c	(<i>R</i>)-I, R = H	110	0.5	—	0.037	3.673	3.640	0.002	0.035	1 : 17.5
Y ^c	(<i>R</i>)-I, R = H	120	1.3	0.015	0.085	3.669	3.581	0.006	0.094	1 : 15.7
Y ^c	(<i>R</i>)-I, R = H	150	9.9	0.105	0.620	3.657	2.968	0.018	0.707	1 : 39.3
Y ^d	(<i>S</i>)-I, R = Ph	110	4.2	0.020	0.271	3.399	3.660	0.276	0.015	18.4 : 1
Y ^d	(<i>S</i>)-I, R = Ph	120	7.5	0.044	0.507	3.260	3.594	0.415	0.081	5.1 : 1

^a Total conversion of (*R*)- and (*S*)-butan-2-ol. ^b Flow rate 10^{-3} mol h⁻¹. Products were analysed using on-line GC with a 40 m capillary γ -cyclodextrin column with trifluoroacetyl stationary phase, temperature programmed from 25–70 °C with a split ratio of 120 : 1. Error on response factors for (*R*)- and (*S*)-butan-2-ol $\pm 0.5\%$. ^c Zeolite Y (Crosfield NaY, ion exchanged with NH₄NO₃ and calcined at 550 °C), modified with (*R*)-1,3-dithiane 1-oxide, 1 molecule per supercage. (0.1 g), tested in a conventional glass microreactor with racemic butan-2-ol (7.35×10^{-3} mol h⁻¹), prevaporized in a nitrogen diluent (6.7×10^{-3} mol h⁻¹). ^d Zeolite Y (ultrastabilized LZY 82, Union Carbide) modified with (*S*)-2-phenyl-1,3-dithiane, 1 molecule per supercage (0.1 g), tested in a conventional glass microreactor with racemic butan-2-ol (7.35×10^{-3} mol h⁻¹), prevaporized in a nitrogen diluent (6.2×10^{-3} mol h⁻¹).

from reaction of the racemate is higher than that expected on the basis of the results of the conversion of the separate pure enantiomers, suggesting that preferential adsorption of the (*S*)-butan-2-ol over the (*R*)-butan-2-ol occurs at the chiral active site.

The simulation work suggests that both enantiomers of butan-2-ol adsorb on the opposite side of the 12-ring containing the donor oxygen atom from the 1-hydroxydithiane cation. These structures involve the framework and the 1-hydroxydithiane cation acting in concert to bind the butan-2-ol molecules, and calculations indicate that the (*S*)-enantiomer is bound more tightly than the (*R*)-form (by 16.4 kJ mol⁻¹).

In a further set of experiments, the same reaction was investigated for zeolite Y modified with (*S*)-2-phenyl-1,3-dithiane 1-oxide (99% ee).¹¹ The results, shown in Table 2, confirm that the same effect is observed, but that in this case the (*R*)-butan-2-ol reacts in preference to the (*S*)-enantiomer.

Taken together, these results provide the first example of a gas-phase enantioselective reaction heterogeneously catalysed by a zeolite. Although the initial approach has been to design a catalyst that consumes chiral molecules, we have demonstrated that a catalyst can be designed that is capable of discriminating between enantiomers and preferentially transforming one of them. This important effect is achieved by enantioselective rate enhancement, *i.e.* both enantiomers react faster in the chiral environment than in the absence of the chiral modifier, but one reacts faster than the other. In view of the vast range of microporous materials and potential enantiomerically pure modifiers available, together with the recent advances in theoretical methods, we believe that this approach will provide the basis for a general advance in the design of ultrasensitive chiral catalysts.

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