Towards molecular sieve inorganic catalysts that are akin to enzymes: studies of a selective cyclo-dimerization over ferrierite at ambient temperature

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The solid-acid (Brønsted)-catalyzed cyclo-dimerization of 3-hydroxy-3-methylbutan-2-one (HMB) over a synthetic ferrierite molecular sieve is reported. HMB is a stable liquid at ambient temperatures but in acidic solutions it readily undergoes reaction to generate a variety of products. However, in the acidic molecular sieve catalyst studied here, only one product – the cyclic dimer (proven by *in situ* solid state ^{13}C NMR and other evidence) – is observed, together with some unreacted HMB. A plausible, proton-catalyzed mechanism is proposed, and prompts comparison between the cyclo-dimerization of HMB within ferrierite and the mode of action of certain enzymes.

KEY WORDS: Brønsted acid catalysis; zeolites; solid-state NMR spectroscopy; enzyme analogues

1. Introduction

The analogy between the mode of action of enzymes on the one hand, and molecular sieve catalysts such as zeolites and metal-substituted aluminophosphates on the other, has frequently been drawn [1–7].[1] In each case, cavities in the catalysts impose shape selectivity that governs the "choice" of reactant species (substrate) which is to be transformed, and the molecular complementarity of the microenvironment at the active site facilitates ensuing chemical conversion. In designing new catalysts, whether they are enzymes or high-area, microporous inorganic catalysts, the desiderata are the same: high activity coupled with high selectivity and an ability to function at ambient temperatures and pressures.

At first sight, the prospects of achieving more than mere superficial kinship between these two quite different types of structure seem discouraging. None of the delicate techniques of structural variation in the world of enzymes – site-directed mutagenesis [8], chemically modified mutant enzymes [9], design by directed (Darwinian) evolution [10] and the exploitation of non-natural amino acids in an expanded genetic code [11] – are likely ever to be incorporated into the inorganic world based on microporous solids. Even so, thanks to recent progress in the preparation, modification and characterization of myriad new types of open-structure inorganic solids [4,12,13], there are several distinct advantages to be gained in pursuing the analogy between enzymes and microporous inorganic catalysts. The latter are in general thermally, mechanically and otherwise much more robust and are usually readily capable of being regenerated when (through "poisoning" of active sites, for example) their performance diminishes. Moreover, much is now known about ways of designing the molecular dimensions [4,12,13], degree of hydrophobicity [14] and other features [15] of microporous inorganic catalysts. In addition, a range of highly refined techniques has been evolved to probe, under operating conditions, the behaviour of reactant species and the active sites inside the cavities of high-area solids [4b,16,17] and in other model systems with high porosity [18]. Finally, there is already adequate evidence that the performance of certain designed molecular sieve inorganic catalysts rivals [19,20] that of enzymes, such as the α,ω-hydroxylases in the aerobic regioselective oxidation of alkanes.

2. Results and discussion

For the reasons discussed above, we have embarked on a programme of research in which we propose to explore how far the analogies between enzymes and inorganic catalysts hold. The first step, described herein, is to identify a reaction which may be shape-selectively catalyzed under ambient conditions within an appropriate inorganic analogue of a proteolytic enzyme such as chymotrypsin. Ideally, the model system chosen for study should have the potential to undergo a variety of competing reaction pathways under ambient conditions, allowing selectivity to be probed, and should also be directly relevant to known enzymatic systems. Only a very small number of reactions

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[1] In a historical context, it is interesting to note that Willstätter in his Faraday Lecture, given at the Royal Institution on 18 May 1927 [5], drew parallels between enzymes and artificial inorganic catalysts.

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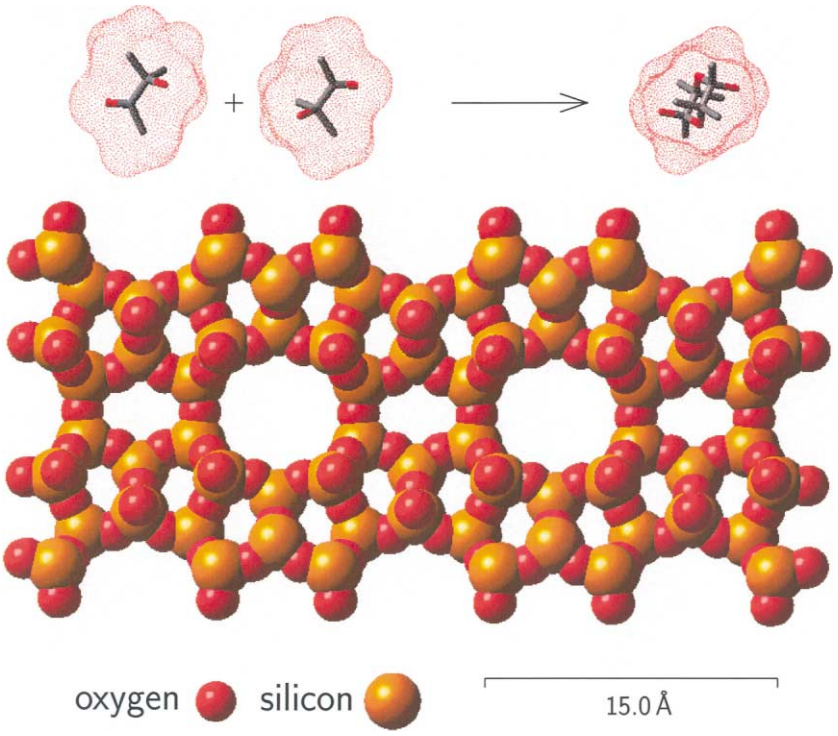
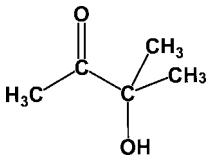
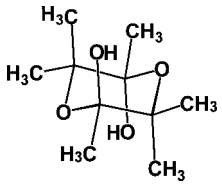


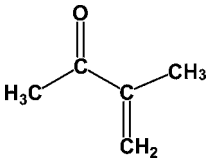
Figure 1. Computer graphic picture showing the structure of ferrierite viewed along the direction of the main tunnel. Two molecules of HMB and one molecule of the cyclic dimer **P** are shown, with molecular surfaces represented (hydrogen atoms are not shown, but were included in the determination of the molecular surfaces).



Scheme 1.



Scheme 2.



Scheme 3.

comply with these conditions. Examples include the rearrangement of allyl benzyl ethers to 4-arylbutanals [21], the dimerization of alkenes [22–24] and the cyclization of unsaturated alcohols [25]. Another example, reported here, is the acid-catalyzed oligomerization or cyclo-dimerization of 3-hydroxy-3-methylbutan-2-one (scheme 1), hereafter abbreviated as HMB.

HMB is a stable liquid at ambient temperature. In acidic solutions (for example, in *p*-toluenesulfonic acid/benzene), however, HMB readily undergoes reaction to generate a variety of products (together with unreacted HMB) including the cyclic dimer (denoted **P**, scheme 2) and the dehydrated reactant shown in scheme 3. The precise nature and distribution of the products varies significantly depending on the solvent and conditions used for the proton-catalysed solution-state reaction. However, when HMB is incorporated within the channels of the synthetic zeolite ferrierite [26] (figure 1), only one product is observed together with some unreacted HMB.[2] The identity of this product is seen from *in situ* high-resolution solid-state ^{13}C NMR (figure 2) to be the cyclic dimer **P** (see appendix). A plausible mechanism for the Brønsted acid-catalysed cyclo-dimerization is shown in scheme 4. In principle, linear oligomers $\{O–C(CH_3)_2–C(CH_3)(OH)\}_n$ could arise if intermediate **A** in scheme 4 were to react with another monomer of HMB. However, our mass spectrometric analyses of the products extracted from the reaction in ferrierite rule out the presence of any species possessing a mass higher than that of the cyclic dimer **P**.[3]

[2] The ratio of **P** to unreacted HMB established from figure 2 (confirmed from solution-state ^{1}H NMR data of the extracted products) represents a percentage conversion in the region of about 30–40%. This value is essentially constant for repeated measurements on other samples of HMB/ferrierite (prepared using the same batch of ferrierite), and no significant variation with temperature is evident from our *in situ* solid-state ^{13}C NMR studies carried out between −80 and 80 °C. Further experiments (for example, involving different loadings of HMB on ferrierite, and samples of ferrierite with different Si/Al ratios) are required to establish the underlying reasons, which might include the establishment of an equilibrium distribution of HMB and **P** (consistent with the mechanism shown in scheme 4), inaccessibility of all reactant HMB molecules to the active sites for the reaction, or statistical constraints imposed on the maximum attainable conversion for dimerization reactions in one-dimensional systems (see reference [27]).

[3] While the ^{1}H and ^{13}C chemical shifts in **P** may be difficult to distinguish from those in linear oligomers $\{O–C(CH_3)_2–C(CH_3)(OH)\}_n$, the signals

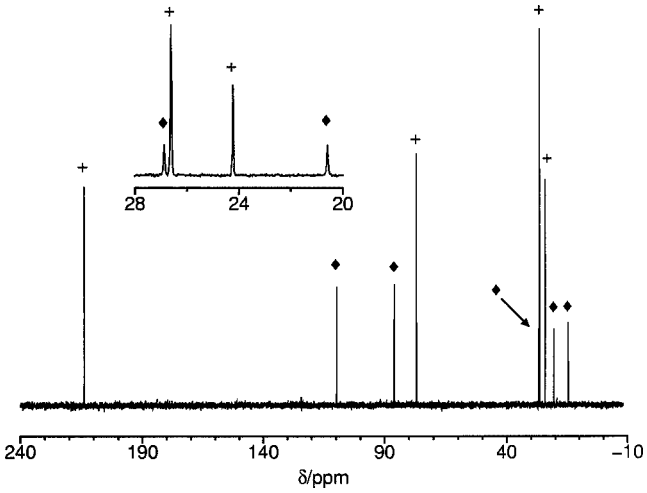
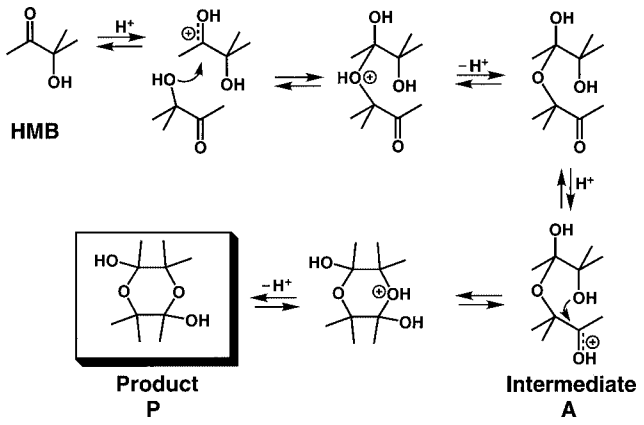


Figure 2. *In situ* high-resolution solid-state ^{13}C NMR spectrum recorded at ambient temperature for a sealed ampoule of HMB/ferrierite ((+) symbols represent peaks due to unreacted HMB, (♦) symbols represent peaks due to the product **P**). The detection level in this spectrum is better than ca. 5%, and thus any other products, if present, represent less than this amount. *In situ* solid-state ^{1}H NMR studies on the sealed ampoules of HMB/ferrierite and solution-state ^{13}C and ^{1}H NMR studies on the extracted products confirm that the cyclic dimer **P** is the only product of the reaction of HMB inside ferrierite.



Scheme 4. Proposed mechanism for the Brønsted acid-catalysed cyclo-dimerization of HMB to produce **P**.

In this preliminary exploration of the kinship between molecular sieve catalysts and enzymes, we have identified a reaction which proceeds smoothly under ambient conditions, and which exhibits the product specificity expected of a reaction that proceeds within a well-defined microenvironment. It is instructive to contrast the nature of the proton-catalysed bimolecular reaction (scheme 4) observed in the cyclo-dimerization of HMB in ferrierite with the mode of action of triosephosphate isomerase, which catalyses the chemically simple interconversion of the two triose phosphates, dihydroxyacetone phosphate and R-glyceraldehyde 3-phosphate, studied by Knowles [28]. Triosephosphate isomerase can accommodate only one molecule in its active site (and thus catalyses a unimolecular reaction), whereas here the cavity where the active site resides in the ferrierite acid catalyst may facilitate bimolecular reactions. There is clearly scope in inorganic molecular sieve catalysts to "tune" the siting of the active sites, as has been demonstrated elsewhere [19,29] in the regioselective oxidation of alkanes, so as to facilitate a desirable organic reaction.

due to the end-groups in any oligomeric species would nevertheless be expected to be observable in both the solid-state and solution-state NMR spectra (provided that the number of monomer units *n* is not sufficiently high).

3. Experimental

A sample of ferrierite (idealized formula $Na_2Mg_2[Al_6Si_{30}O_{72}]\cdot 18H_2O$) with actual Si/Al ratio of 40 was calcined in air at 550 °C for 12 h and dehydrated under vacuum at 500 °C for 1 h. Using standard vacuum line techniques, HMB was adsorbed from the gas phase into the dehydrated ferrierite, which was contained in a 7.5 mm diameter quartz tube. The temperature of the HMB/ferrierite sample was not raised above ambient temperature during this procedure. Following the adsorption, the quartz tube was sealed to form an ampoule of appropriate length for solid-state NMR experiments. The quartz tube was wrapped in PTFE tape to give a good fit inside the NMR rotor. In a separate series of thermogravimetric analysis experiments, the loading of HMB in the ferrierite was estimated to represent approximately 2.3 molecules of HMB per unit cell of ferrierite.

Solid-state ^{13}C and ^{1}H NMR experiments on the sealed ampoules of HMB/ferrierite were carried out at ambient temperature (20 °C) on a Chemagnetics CMX Infinity 300 spectrometer using a Chemagnetics 7.5 mm magic angle spinning probe (typical spinning frequency 4 kHz). High-power ^{1}H decoupling ($\nu_1 \approx 20$ kHz) was applied for the ^{13}C NMR measurements, which were carried out using a spin-echo sequence (to suppress the signal from the PTFE tape around the sample). Solid-state ^{13}C NMR experiments were also recorded between −80 and 80 °C. Following the solid-state NMR experiments, the ampoules were broken in an atmosphere of dry nitrogen (glove box) and the species adsorbed in the ferrierite were extracted in DMSO. These extracts were analysed by gas chromatography, mass spectrometry and solution-state ^{1}H and ^{13}C NMR spectroscopy, confirming the assignment of the cyclic dimer **P** as the only reaction product (in addition to unreacted HMB).

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Appendix

Note that molecule **P** can exist as different configurational isomers, denoted *cis* (with the two OH groups on the same face of the six-membered ring) and *trans* (with the two OH groups on opposite faces of the six-membered ring, as illustrated in scheme 2). These configurational isomers also represent different stereoisomers, recalling that the molecule contains two chiral centres. Thus, the *cis* isomer comprises either {R,R} or {S,S} chiral centres and the *trans* isomer comprises either {R,S} or {S,R} chiral centres. The *cis* and *trans* isomers therefore have a diastereoisomeric relationship. For the *cis* isomer, ring inversion interconverts two conformations of equal energy (each containing one *axial* OH group and one *equatorial* OH group), whereas for the *trans* isomer, ring inversion interconverts conformations of unequal energy (with the two OH groups either *diaxial*, as shown in scheme 2, or *diequatorial*). The fact that the *geminal* CH_3 carbons in **P** have different chemical shifts (see figure 2) arises from the non-equivalent geometric relationships of these CH_3 groups to the adjacent chiral centre (even when averaged over the ring inversion process). The observation of only five distinguishable ^{13}C resonances for **P** (both in the solid-state and solution-state ^{13}C NMR spectra, and also consistent with the solution-state ^{1}H NMR spectra) suggests either: (i) that only one configurational isomer is present, or (ii) if both configurational isomers are present, that their ^{13}C chemical shifts are indistinguishable. Situation (ii) would be justifiable if the ^{13}C chemical shifts are only influenced significantly by the neighbouring groups (and their substituents) on the ring, and not by interactions across the ring. On the other hand, considering situation (i), we note that *for the isolated molecule* the *trans* isomer is substantially favoured energetically on the basis of the steric and anomeric advantages conferred upon the conformation in which the OH groups are *diaxial* (indeed, this conformation should significantly predominate over that in which the OH groups are *diequatorial*). Thus, while caution is required before assuming that the energetically preferred isomer of **P** in the isolated state is also the preferred isomer of **P** produced by the cyclo-dimerization of HMB inside the ferrierite host structure, it is nevertheless likely that the *trans* isomer of **P** in the conformation with the OH groups *diaxial* should also predominate (i.e., situation (i)) as the product of the reaction in ferrierite. Finally, we note that solution-state ^{1}H NMR experiments on the extracted product also cannot directly distinguish the *cis* and *trans* isomers of **P** due to the absence of any significant J-coupling (distinguishable ^{1}H nuclei in **P** are separated by at least four bonds).

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