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The Catalytically Active Conformation of Cyclo-[(*S*)-His-(*S*)-Phe] as Determined by Solid State NMR

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Abstract: *The solid state conformation of the amorphous catalyst cyclo-[(S)-His-(S)-Phe] is determined by a combination of solid state ^{1}H and ^{13}C NMR techniques. The results provide strong evidence in support of the previously proposed mechanism for the asymmetric addition of HCN to aldehydes catalysed by this dipeptide.*

The cyclic dipeptide (diketopiperazine) *cyclo*-[(*S*)-His-(*S*)-Phe] **1** is well known to catalyse the asymmetric addition of hydrogen cyanide to aldehydes, producing the (*R*)-enantiomer of cyanohydrins with enantiomeric excesses and yield of up to 99% or greater in favourable cases.[1] This simple catalyst is unusual in a number of respects, since it is a very good mimic of the enzyme D-oxynitrilase[1,2] (E.C. 4.1.2.10), and the catalyst is active in the solid state rather than in solution.[3] The synthetic applications of this catalyst have been well studied,[1] however little is known about the mechanism of asymmetric induction although a number of possible transition state structures have been put forward.[4-6] Recently, we[7] and others,[4] have shown using variable temperature nmr that in DMSO or methanol solution, the minimum energy conformation of catalyst **1** is as shown in Figure 1. In this conformation the phenyl ring is bent over the diketopiperazine ring, shielding one of the histidine β-protons, though at ambient temperatures the phenyl ring is free to rotate about the α–β bond, and all three staggered conformations are appreciably populated. Our mechanistic proposal[6] for the mode of action of catalyst **1** is based upon the conformation shown in Figure 1. However, the structure shown in Figure 1 has only been shown to represent the conformation present in solution, and in the catalytically active solid state it is quite possible that a different conformation would be adopted by catalyst **1**. Previous attempts to study the solid state conformation of compound **1** using X-ray crystallography have been unsuccessful due to the amorphous nature of the catalyst,[8] and solid state infra-red and ^{13}C nmr spectra also failed to give a definitive structure.[9] In this communication therefore, we report for the first time, solid state nmr studies which show that the solid state conformation of catalyst **1** resembles the conformation found in solution.

By far the most characteristic feature of the *solution* state proton nmr spectrum of compound **1**, is the unusually low frequency chemical shift observed for one of the histidine β-protons (1.5ppm at 20°C, 0.7ppm at -80°C). This shielding is caused by the phenyl ring in the conformation shown in Figure 1, in which one of

the histidine β-protons lies within the region of aromatic ring current of the phenyl ring. The solid state proton nmr spectrum of compound **1** acquired at 200MHz using the CRAMPS technique[10] is shown in Figure 2. The spectrum was aquired using the BR24 pulse sequence, and was referenced indirectly to an external sample of TMS.

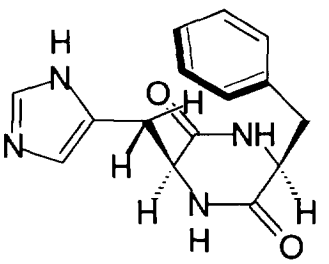

Figure 1: Compound **1** drawn in its minimum energy conformation

The spectrum is generally similar to the solution state spectrum,[6] with the peak at 6.4ppm being assignable to the aromatic protons, that at 2.5ppm to the α-protons and that at 1.5 to the β-protons. Two other resonances are observed, that at 4.7ppm does not match the solution state spectrum and is most likely due to the NH's, and finally a very low frequency resonance is observed at -1.0ppm, which could be due to a highly shielded histidine β-proton. In order to confirm these peak assignments, a solid state 2D ^{1}H-^{13}C correlation experiment[11] was undertaken, the result of which is shown in Figure 3. This spectrum was aquired in phase sensitive mode at 300MHz (for protons), using a MAS probe and a spin rate of 5200Hz. The scaling factor for the ^{1}H axis was determined by varying the ^{1}H offset, and both axes are referenced to TMS, in the case of the ^{1}H axis indirectly *via* a sample of poly(methyl methacrylate). The solid state 75MHz ^{13}C nmr spectrum of compound **1** showed resonances at the same chemical shifts as those previously reported for the solution state spectrum,[6] some of the peak assignments were confirmed by a protonated carbon suppression experiment.[12] The key correlation in the 2D experiment is between the proton resonance at -1ppm, and the carbon resonance at 31.9ppm which can be assigned to the histidine β-carbon based on the spectral editing and the known assignments for the solution state ^{13}C nmr spectrum. Thus the proton resonance at -1ppm is confirmed as being due to one of the histidine β-protons. The other histidine β-proton appears to occur at a 'normal' chemical shift of 2ppm, as the carbon correlation shown in Figure 3 is rather broad, suggesting a correlation to two separate proton resonances.

Thus the solid state and solution proton nmr spectra of catalyst **1**, closely resemble one another. As the solution state proton nmr spectrum is known to be characteristic of the folded conformation (Figure 1) adopted by this compound, these results suggest that the same conformation is adopted in the solid state. In solution state spectra, there is evidence for an intramolecular hydrogen bond between the imidazole NH and carbonyl, it is not apparent from the solid state spectrum whether or not this hydrogen bond is retained in the solid state. The very highly shielded nature of the His-β-proton, the chemical shift of which is comparable to the chemical shift observed in solution spectra at very low temperatures, suggests that in the solid state, the phenyl ring is not free to rotate about the α–β bond, but is constrained into the conformation shown in Figure

1. Attempts to study any conformational changes in compound **1** using variable temperature solid state ^{13}C nmr, failed to show any significant changes in chemical shift with temperature. Hence it can be concluded that the structure shown in Figure 1 represents the conformation adopted by compound **1** in its catalytically active form.

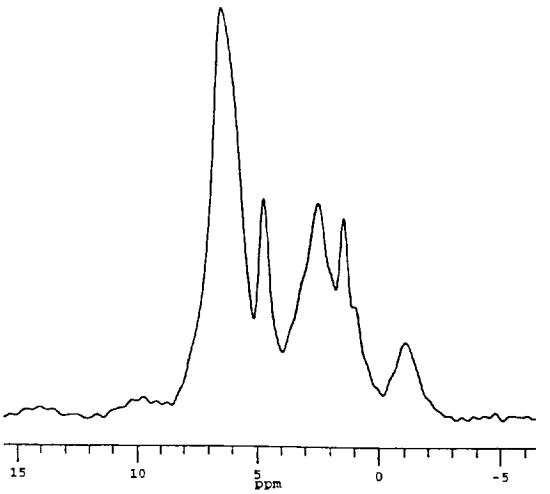

Figure 2: Solid state 200MHz ^{1}H nmr spectrum of compound **1**

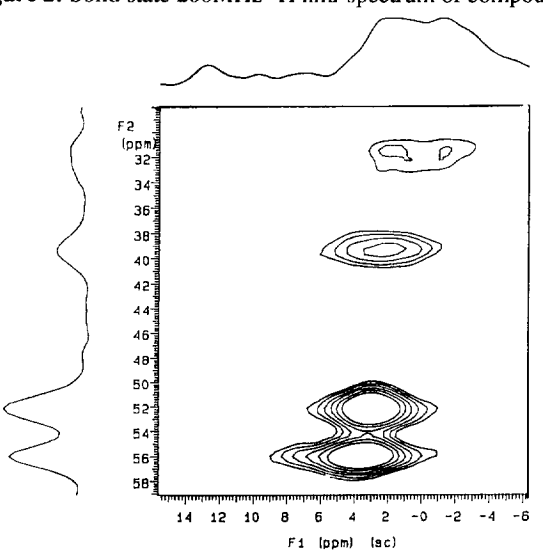

Figure 3: ^{1}H-^{13}C correlation experiment on compound **1**. An extract of the ^{13}C spectrum is shown along the ^{13}C axis, and no spinning side bands are present in this region of the spectrum. Along the proton axis is shown a slice through the 2D-spectrum at δ_C=32ppm.

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