Tetrahedron: Asymmetry Vol. 4, No. 7, pp. 1553-1558, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

The Oxidation of Benzaldehyde to Benzoic Acid Catalysed by *Cyclo*-[(S)-His-(S)-Phe], and its Implications for the Catalytic Asymmetric Addition of HCN to Aldehydes.

David J.P. Hogg, Michael North*, Robert B. Stokoe, and William G. Teasdale

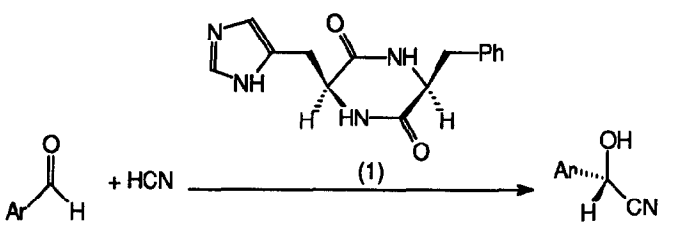
Department of Chemistry, University of Wales, Bangor, Gwynedd, LL57 2UW

(*Received in UK* 16 *March* 1993)

Key Words: cyclo-[(S)-His-(S)-Phe]; Benzaldehyde; Oxidation; Asymmetric Hydrocyanation; Mechanism

Abstract: *The cyclic dipeptide cyclo-[(S)-His-(S)-Phe] is found to catalyse the oxidation of benzaldehyde to benzoic acid. A mechanism is proposed both for this reaction, and for the asymmetric addition of HCN to aldehydes catalysed by this peptide based on a common intermediate for both reactions.*

There is much current interest in the asymmetric synthesis of natural and unnatural products[1]. Of the various methodologies available to accomplish this goal, the use of homochiral catalysts to catalyse reactions occuring at prochiral centres is attractive, as in principle, high optical and synthetic yields can be obtained at low cost. Although a number of asymmetric catalysts are known[2], very few catalyse the asymmetric formation of carbon-carbon bonds[3]. However, the cyclic dipeptide *cyclo*-[(S)-His-(S)-Phe] (1) is known to catalyse the asymmetric addition of hydrogen cyanide to aromatic aldehydes, giving (R)-cyanohydrins of high optical purity[4] as shown in Scheme 1. Although a number of synthetic investigations using this catalyst have been carried out[4], very little is known about the mechanism of the reaction. Recently, we have reported on the conformations adopted by the catalyst, and the nature of the interaction between catalyst (1) and HCN[5]. The nature of the complex formed between compound (1) and HCN has also been reported by de Vries *et al.*[6].



Scheme 1

Although our work on this reaction has been mainly mechanistic, a number of synthetic reactions were carried out to prove that the catalyst was in an active form. Throughout this work, ether was used as the reaction solvent, benzaldehyde as the substrate, and mandelonitrile was obtained in good yield and high optical purity. Unlike the literature work carried out using benzene as the solvent[7], we observed that the catalyst appeared to be totally insoluble in the reaction medium, and no gel formation occured during the reaction. Indeed the catalyst could be recoved from the reaction mixture simply by filtration and reused

without loss of catalytic activity, indicating that gel formation is incidental and not essential to the reaction. These results prompted us to investigate whether the reaction is actually catalysed by a very small amount of catalyst dissolved in the solvent, or whether it is a solid state reaction in which case conformational results obtained in solution may not be relevent.

In order to investigate this, the catalyst was placed in a soxhlet thimble and continuously extracted with either ether or benzene for 24 hours. The resulting solvent was then used in a cyanohydrin forming reaction to which no catalyst was added, and was found to be catalytically inactive. In addition, no evidence for the presence of catalyst (1) in the solvent could be found by nmr. The catalyst from the soxhlet thimble however, was still catalytically active, showing that the catalyst had not been decomposed or denatured by the extended contact to hot solvent. These results clearly indicated, that the catalyst (1) has no solubility in ether or benzene.

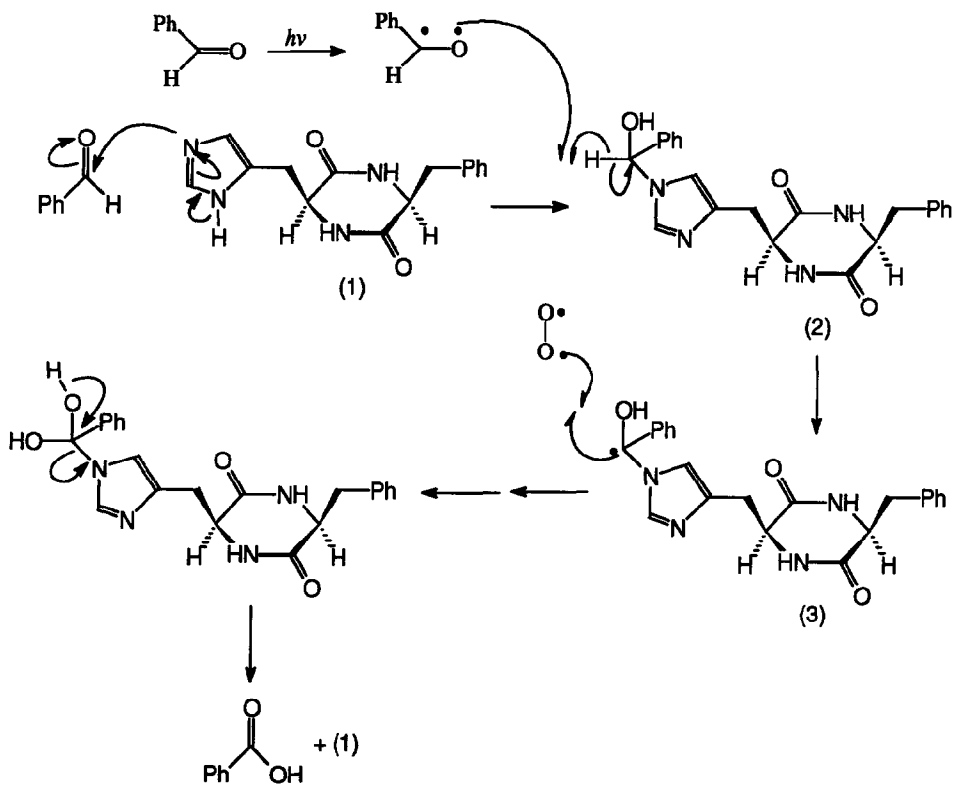
However, during an asymmetric cyanohydrin formation reaction, benzaldehyde and mandelonitrile (or another aldehyde and cyanohydrin) are also present in the reaction mixture, and their presence could affect the solubility of the catalyst. (However, over 50 different aldehydes have been successfully used as substrates for this reaction, so the catalyst would have to dissolve in each of them.) It is known that the catalyst is soluble in pure mandelonitrile, and in benzene containing more than 10% mandelonitrile[6], however mandelonitrile is not present at the start of the reaction, so we investigated the solubility of the catalyst in benzaldehyde.

When, in a typical reaction (one of over twenty such reactions carried out by us to date), catalyst (1) (50 mg) was added to freshly distilled benzaldehyde (5 ml), and the mixture allowed to stir at room temperature for 48 hours, approximately half of the solution solidified. The solid was isolated, purified by acid/base extraction, and identified as benzoic acid (2.8 g) on the basis of its mp, mixed mp, ir spectrum, and ^{1}H nmr spectrum. The remainder of the benzaldehyde was recovered unchanged, and no benzyl alcohol was detected in the products. It is well known, that benzaldehyde is readily oxidised to benzoic acid in a photochemical reaction without the need for a catalyst[8], so a control experiment was carried out as above, but without adding catalyst (1). Under these conditions, only 1.2 g of benzoic acid was formed, thus confirming that catalyst (1) was catalysing the oxidation of benzaldehyde to benzoic acid. That the catalysed reaction was also photochemical was shown by reactions carried out in the dark, the yield of benzoic acid from both the catalysed and uncatalysed reactions was substantially reduced under these conditions (1.07 and 0.48g respectively). A number of other catalysts have previously been reported for this oxidation[9], however to the best of our knowledge no basic catalyst has been reported, and bases have been reported to inhibit the oxidation[10].

The source of the oxygen required for this reaction was found to be molecular oxygen from the atmosphere, as when the reaction was carried under a nitrogen atmosphere using degassed benzaldehyde, no reaction occurred. This enabled the kinetics of the oxidation reaction to be determined by conducting the reaction within a standard atmospheric pressure hydrogenator filled with air, and monitoring the rate of oxygen absoption. In order to eliminate the effect of factors such as light intensity, and temperature two reactions were conducted side by side, differing only in that one of the reactions had peptide (1) (50mg for 5ml of benzaldehyde) added, and the other did not. The initial rate of the catalysed reaction was found to be double the rate of the uncatalysed reaction (reproducable over three such experiments), showing that peptide (1) exerts a genuine catalytic effect. The above reactions were all conducted in the absence of solvent, adding

a solvent (toluene, dichloromethane, or methanol) to either a catalysed or uncatalysed oxidation reaction resulted in suppression of the reaction, and formation of less then 20mg of benzoic acid.

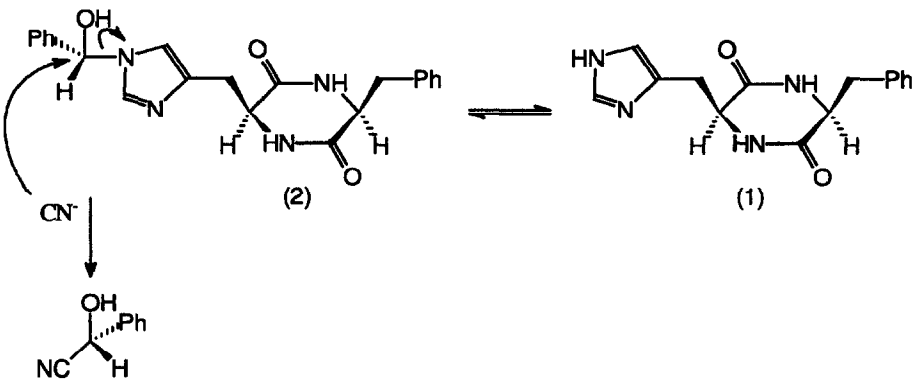
The accepted mechanism for the uncatalysed oxidation of benzaldehyde, involves the photochemical excitation of benzaldehyde, to the triplet excited state which then abstracts a hydrogen atom from another molecule of benzaldehyde, giving a carbonyl radical[8]. These react with molecular oxygen, giving initially the peracid which decomposes to benzoic acid. The catalyst may be acting by forming an aminol intermediate (2), as shown in Scheme 2, which on hydrogen atom abstraction by photochemically excited benzaldehyde would give the radical (3) which is a much more stable equivalent than the carbonyl radical. This radical would then be oxidised as in the uncatalysed reaction, before the catalyst was finally regenerated by its elimination from a carboxylic acid derivative. This catalytic cycle depends upon the imidazole ring in catalyst (1), to actually carry out the chemistry. Imidazole itself was found not to be a catalyst for this oxidation, indeed it acts as an inhibitor. This difference may be due to differences in the solid state structures of compound (1) and imidazole, or to differences in their nucleophilicities due to the formation of an intramolecular hydrogen bond in catalyst (1) as previously proposed[5]. Support for the later suggestion comes from experiments in which 1,2,4-triazole (a better nucleophile than imidazole) was found to be as effective a catalyst as compound (1) for this oxidation, giving a 43% yield of benzoic acid under the same conditions described above.



Scheme 2

These results also provide evidence to support a mechanism for the formation of chiral cyanohydrins catalysed by compound (1). Conversion of benzaldehyde to aminol (2) results in formation of the required new chiral centre whilst the benzaldehyde is attached to the catalyst, thus it is not unreasonable to suppose that a single diastereomer of compound (2) will be generated, or that the two diastereomers will be formed in unequal amounts. Displacement of the imidazole leaving group by cyanide in an SN_2 reaction would then result in the formation of optically pure cyanohydrins as shown in Scheme 3. Should both diastereomers of compound (2) be formed under the reaction conditions, it is possible that the substitution reaction with cyanide will occur at different rates with the two diastereomers, resulting in the observed enantiomeric excess, as the two diastereomers will be in equilibrium. It has not proven possible to detect the aminol intermediate (2) spectroscopically[6,11].

This is the first mechanism to be proposed for this asymmetric cyanohydrin forming reaction that relies upon formation of such an aminol intermediate. Previous mechanistic suggestions[6,12], have emphasised the formation of an imidazole/ cyanide salt, and suggested that the aldehyde forms a hydrogen bond to one of the amide NH's, which whilst not unreasonable, has not been supported experimentally. However, we have recently shown that the interaction between catalyst (1) and HCN is of a covalent hydrogen bonded nature rather than formation of ionic species[5], and the oxidation of benzaldehyde to benzoic acid catalysed by peptide (1) is best explained by an imidazole/ aldehyde complex. Thus the mechanism shown in Scheme 3 appears to be more consistent with the experimental observations concerning catalyst (1) than previous suggestions.



Scheme 3

In order to provide evidence for the above mechanism, a molecular modelling study of the aminol intermediate (2) was carried out. We have recently reported details of a molecular mechanics study of catalyst (1)[5], and the same methods were used in this study. Thus starting from the structure shown in Figure 1 which was determined by both molecular mechanics and nmr to be the minimum energy conformation of catalyst (1), the structure was modified by incorporation of the aminol unit in which the new chiral centre was set to both **R** and **S** configurations. This introduced two new rotatable bonds, and a grid search (conducted at 30° resolution with the Macromodel package[13], followed by energy minimisation using the MM+ forcefield

within the Hyperchem modelling package[14]) was carried out to find the minimum energy conformation of both diastereomers. The global minimum energy conformation of the aminol diastereomer with the (S)-configuration at the aminol centre was found to be 5KJmol^{-1} more stable than the minimum energy conformation of the diastereomer with the (R)-configuration. This is consistent with the mechanism shown in Scheme 3, as the (S)-isomer of the aminol would give the experimentally observed (R)-enantiomer of the cyanohydrin. The same energy difference between the minimum energies of the two diastereomers was found when the energies were calculated using semi empirical methods at the CNDO level.

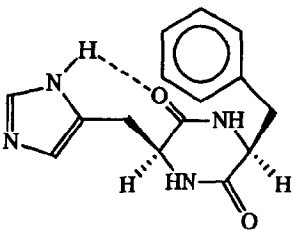


Figure 1

Preliminary experiments suggest that the oxidation reaction is not limited to benzaldehyde, as *p*-methoxybenzaldehyde is also oxidised by this catalyst. Our synthetic and mechanistic efforts on reactions catalysed by dipeptide (1) are continuing, and will be reported in due course.

Acknowledgements

The authors thank Peboc Ltd. for generous financial support, and for a research studentship to D.J.P.H. R.S. thanks the E.E.C. Social Fund for a studentship. The Silicon Graphics workstation used for the molecular modelling was purchased with a grant from the Wolfson Foundation.

References

1) G.M. Coppola, and H.F. Schuster, 'Asymmetric Synthesis: The Construction of Chiral Molecules using Amino Acids', Wiley, Chichester, 1987; J.D. Morrison (Ed.), 'Asymmetric Synthesis Volumes 1-4', Academic Press, London, 1985

2) J.D. Morrison (Ed.), 'Asymmetric Synthesis Volume 5: Chiral Catalysis', Academic Press, London, 1985.

3) N. Oguni, Y. Matsuda, and T. Kaneko, *J. Am. Chem. Soc.*, **1988**, 110, 7877; M. Kitamura, S. Okada, S. Suga, and R. Noyori, *J. Am. Chem. Soc.*, **1989**, 111, 4028; and references therein.

4) J. Oku, and S. Inoue, *J. Chem. Soc., Chem. Commun.*, **1981**, 229; J. Oku, N. Ito, and S. Inoue, *Makromol. Chem.*, **1982**, 183, 579; S. Asada, Y. Kobayashi, and S. Inoue, *Makromol. Chem.*, **1985**, 186, 1755; Y. Kobayashi, S. Asada, I. Watanabe, H. Hayashi, Y. Motoo, and S. Inoue, *Bull. Chem. Soc.*

Jpn., **1986**, 59, 893; B.R. Matthews, W.R. Jackson, G.S. Jayatilake, C. Wilshire, and H.A. Jacobs, *Aust. J. Chem.*, **1988**, 41, 1697; H. Danda, H. Nishikawa, and K. Otaka, *J. Org. Chem.*, **1991**, 56, 6740; H. Danda, *Synlett.*, **1991**, 263; J. Oku, N. Ito, and S. Inoue, *Makromol. Chem.*, **1979**, 180, 1089; A. Mori, Y. Ikeda, K. Kinoshita, and S. Inoue, *Chem. Lett.*, **1989**, 2119.

5) M. North, *Tetrahedron*, **1992**, 48, 5509; D.J.P. Hogg, and M. North, *Tetrahedron*, **1993**, 49, 1079.

6) D. Callant, B. Coussens, T.V.D. Maten, J.G. de Vries, and N.K. de Vries, *Tetrahedron Asymmetry*, **1992**, 3, 401.

7) H. Danda, *Synlett*, **1991**, 263.

8) H.L.J. Backstrom, and U. Riiner, *Acta Chemica Scand.*, **1966**, 20, 630.

9) A. Sobkowiak, and D.T. Sawyer, *J. Am. Chem. Soc.*, **1991**, 113, 9520; T. Yamada, O. Rhode, T. Takai, and T. Mukaiyama, *Chem. Lett.*, **1991**, 5;

10) Z. Csuros, I. Geczy, J. Morgos, and B. Losonczi, *Periodica Polytech.*, **1961**, 5, 123.

11) D.J.P. Hogg and M. North unpublished results.

12) W.R. Jackson, G.S. Jayatilake, B.R. Matthews, and C. Wilshire, *Aust. J. Chem.*, **1988**, 41, 203; K. Tanaka, A. Mori, and S. Inoue, *J. Org. Chem.*, **1990**, 55, 181;

13) W.C. Still, F. Mohmadi, N.G.J. Richards, W.C. Guida, M. Lipton, R. Liskamp, G. Chang, T. Hendrickson, F. DeGunst, and W. Hasel. *Macromodel 3D.*, Version 3.1, Columbia University, New York, NY, **1991**.

14) Hyperchem, Release 2 for UNIX/ MOTIF Workstations, **1992**, Autodesk Inc.