# Asymmetric Cyanohydrin Synthesis catalysed by a Synthetic Cyclic Dipeptide

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*Summary* Asymmetric addition of hydrogen cyanide to benzaldehyde catalysed by *cyclo*(L-phenylalanyl-L-histidine) gave the highest optical yield ever obtained.

ASYMMETRIC syntheses catalysed by synthetic peptides are of much interest in connection with the high stereospecificity of enzymatic reactions. However, there are few reported examples and the optical yields obtained are low.[1] In the present communication, we report an asymmetric synthesis catalysed by a synthetic cyclic dipeptide which yields the highest optical yield ever obtained.

The reaction examined is the addition of hydrogen cyanide to benzaldehyde to give the corresponding cyanohydrin [HO–CH(Ph)–CN]. The enzyme oxynitrilase is

known to catalyse this reaction to give only the (*R*)-isomer of the cyanohydrin. As for non-enzymatic catalysts, alkaloids,[2] poly(L-iminoisobutylethylene),[3] and linear or cyclic dipeptides from histidine and alanine[4] have also been examined, but the highest optical yield was *ca.* 20%[3,5]

In the present study, we used as the catalyst a synthetic cyclic dipeptide *cyclo*(L-phenylalanyl-L-histidine) [*cyclo*(L-Phe-L-His)] in which the imidazole group of the histidine residue is catalytically active as a base. *cyclo*(L-Phe-L-His), recrystallized from water, is a white powder, m.p. 262—264 °C, $[\alpha]_D^{21}$ −66·4° (*c* 2·00, $CH_3CO_2H$), containing half a molecule of water {lit. m.p. 267—268 °C, $[\alpha]_D^{23}$ −72° (*c* 2·00, $CH_3CO_2H$)}.[6] I.r. ν(C=O) 1662 $cm^{-1}$ (amide I); no amide II. $^1H$ N.m.r. ($CF_3CO_2H$) δ 8·16 (1H, s, Im), 7·91 and 7·84 (2H, 2 s, Im), 6·7—7·1 (*ca.* 6H, m, Im and Phe $C_6H_5$), 4·38 (1H, s, His $C_\alpha H$), 3·99 (1H, t, Phe $C_\alpha H$), 2·7—3·2 (2H, m, His $C_\beta H_2$), 1·3—2·1 (2H, m, Phe $C_\beta H_2$).

The addition reaction was carried out using equimolar amounts of hydrogen cyanide and benzaldehyde in benzene under a nitrogen atmosphere at 35 ± 1 °C with stirring. At first, the reaction mixture was heterogeneous, but it became homogeneous after *ca.* half an hour. The isolation and the determination of the enantiomeric excess (e.e.) of the product were carried out by a procedure similar to that described previously.[4]

The results of the asymmetric synthesis are summarized in the Table. In the half-hour reaction (run 1), the e.e. of the product was as high as 90% and rich in the (*R*)-antipode. This value is the highest ever reported not only in this asymmetric cyanohydrin synthesis but also for all asymmetric syntheses catalysed by synthetic oligo- or polypeptides. When the reaction time was longer, the e.e. of the product was reduced (runs 2—5), indicating that racemization of the product takes place under the reaction conditions. In fact, when a mixture of optically active (90% e.e.) cyanohydrin (4·8 mmol) and benzaldehyde (3·9 mmol) was kept with *cyclo*(L-Phe-L-His) (0·17 mmol) for 3·5 h, the e.e. of the recovered cyanohydrin was 35%. Consequently, in this reaction, the 'real' enantioselectivity of *cyclo*(L-Phe-L-His) is considered to be higher than 90%.

TABLE. Asymmetric addition of HCN to benzaldehyde catalysed by *cyclo* (L-Phe-L-His).[a]

| Run No. | Time/h | % Conversion | E.e.[b] of product/% |
|---|---|---|---|
| 1 | 0·5 | 40 | 90 |
| 2 | 1 | 80 | 76 |
| 3 | 4 | 80 | 69 |
| 4 | 16 | 90 | 21 |
| 5 | 72 | 90 | 12 |

[a] Benzaldehyde (50 mmol); hydrogen cyanide (50 mmol); *cyclo*(L-Phe-L-His) (0·97 mmol); benzene, 20 ml; 35 °C. [b] In all cases, the (*R*)-antipodes were preferred.

(*Received*, 11*th August* 1980; *Com.* 887.)

[1] For a review see S. Inoue, *Adv. Polym. Sci.*, 1976, **21**, 78.
[2] G. Bredig and P. S. Fiske, *Biochem. Z.*, 1912, **46**, 7; V. Prelog and M. Wilhelm, *Helv. Chim. Acta*, 1954, **37**, 1634.
[3] S. Tsuboyama, *Bull. Chem. Soc. Jpn.*, 1962, **35**, 1004.
[4] J. Oku, N. Ito, and S. Inoue, *Makromol. Chem.*, 1979, **180**, 1089.
[5] J. D. Morrison and H. S. Mosher, 'Asymmetric Organic Reactions,' Prentice-Hall, Englewood Cliffs, New Jersey, 1971, p. 131.
[6] F. Schneider, *Hoppe-Seyler's Z. Physiol. Chem.*, 1964, **338**, 131.