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Asymmetric Addition of Hydrogen Cyanide to Substituted Benzaldehydes Catalyzed by a Synthetic Cyclic Peptide, *Cyclo*((*S*)-phenylalanyl-(*S*)-histidyl)

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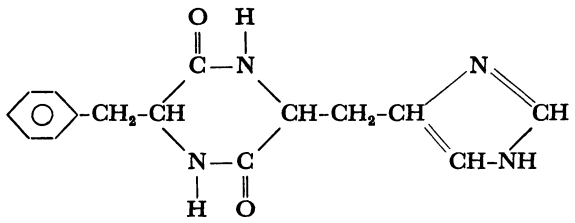
Using *cyclo*((*S*)-phenylalanyl-(*S*)-histidyl) as catalyst, optically active cyanohydrins from substituted benzaldehydes with *p*-methyl, *m*-methyl, *o*-methyl, *m*-methoxyl, or *m*-phenoxyl group were obtained with optical yield of 82—33%. For the asymmetric cyanohydrin synthesis, nonpolar solvent such as benzene or carbon tetrachloride was advantageous, while no asymmetric synthesis took place in methanol or dimethyl sulfoxide.

Enzymatic reactions are characterized by the high degree of specificity and high efficiency under mild conditions. In the application of natural enzyme as catalyst for synthetic reactions, possible shortcomings are the facts that natural enzymes are usually stable under rather limited conditions and that the product obtained is limited only to one of the possible optical isomers. In the asymmetric synthesis catalyzed by synthetic peptides, on the other hand, preferred configuration of the product of the catalyzed reaction can be selected as desired, by the selection of (*R*)- or (*S*)-amino acid in the synthesis of the catalytically active peptides. Therefore, the studies of asymmetric synthesis catalyzed by synthetic peptides are of much interest.

We have studied asymmetric cyanohydrin synthesis catalyzed by synthetic peptides.[1-4] Optically active cyanohydrin is a useful synthetic intermediate which can be readily transformed into optically active α-hydroxy carboxylic acid. More specifically, (*S*)-cyanohydrin of *m*-phenoxybenzaldehyde, for example, is an essential building block for the synthesis of a particularly effective insecticide.[5]



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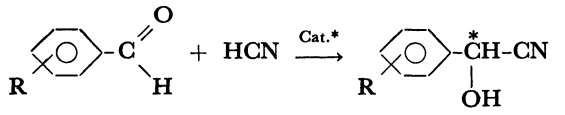
Since it is known that cyanohydrin synthesis is catalyzed by a base, we have used cyclic or linear dipeptides containing (*S*)-histidine as a base catalyst. Among the peptides we examined, *cyclo*((*S*)-phenylalanyl-(*S*)-histidyl) (**1**, *cyclo*(-(*S*)-Phe-(*S*)-His-)) was found to be an effective catalyst for the asymmetric cyanohydrin synthesis from benzaldehyde to give the highest optical yield ever reported (90%) under appropriate conditions.[2,3] This catalyst is applicable also to the asymmetric cyanohydrin synthesis from aliphatic aldehydes with optical yield of 30—40%.[4] In the present study, attempts were made to extend the application of *cyclo*(-(*S*)-Phe-(*S*)-His-) to asymmetric cyanohydrin synthesis from substituted benzaldehydes.

In the asymmetric cyanohydrin synthesis from benzaldehyde with *cyclo*(-(*S*)-Phe-(*S*)-His-) in benzene, the reaction mixture was heterogeneous at first but became homogeneous with the progress of the reaction, and the optical yield of the product was the highest in the early stage but decreased in prolonged reaction.[2,3] Since these phenomena are considered to be due, at least partly, to the change in the polarity of the system with the progress of the reaction by the formation of the product, the effect of the solvent on the reaction was investigated using benzaldehyde as substrate.



2 a-f **3 a-f**

2 a: R=*p*-CH_3- **3 a**: R=*p*-CH_3-
b: R=*m*-CH_3- **b**: R=*m*-CH_3-
c: R=*o*-CH_3- **c**: R=*o*-CH_3-
d: R=*m*-CH_3O- **d**: R=*m*-CH_3O-
e: R=*m*-C_6H_5O- **e**: R=*m*-C_6H_5O-
f: R=H- **f**: R=H-

Results and Discussion

Addition Reaction to Substituted Benzaldehyde. The results obtained in the addition of hydrogen cyanide to substituted benzaldehydes catalyzed by *cyclo*(-(*S*)-Phe-(*S*)-His-) are summarized in Table 1. The reaction conditions employed were the same as those that gave the highest optical yield for benzaldehyde; in benzene at 35 °C for 30 min. All the products obtained from the substituted benzaldehydes examined were of fairly high optical yields. These

Table 1. Asymmetric Addition of Hydrogen Cyanide to Substituted Benzaldehydes Catalyzed by *cyclo*(-(*S*)-Phe-(*S*)-His-)[a]

Run	Aldehyde Substituent	Conv. %	Optical yield of product/ e.e. %[b] by *cyclo*(-(*S*)-Phe-(*S*)-His-)	by D-oxynitrilase[c]
1	*p*-Me (**2a**)	80	33	28
2	*m*-Me (**2b**)	83	82	60
3	*o*-Me (**2c**)	67	70	—
4	*m*-MeO (**2d**)	71	54	51
5	*m*-PhO (**2e**)	70	61[e]	—
6[d]	H (**2f**)	40	90[e]	100

a) Aldehyde: 25 mmol, hydrogen cyanide: 25 mmol, *cyclo*(-(*S*)-Phe-(*S*)-His-): 0.5 mmol, benzene: 10 cm^3, reaction time: 30 min, reaction temperature: 35 °C. b) E.e., enantiomeric excess. c) In 0.05 M† acetate buffer (H_2O:EtOH, 1:1; pH, 5.4); Conv., 94—100%.[6] d) Ref. 2), 3). e) Preferred configuration is *R*.

Table 2. Effect of Solvent on the Asymmetric Addition of Hydrogen Cyanide to Benzaldehyde Catalyzed by *cyclo*(-(*S*)-Phe-(*S*)-His-)[a]

Run	Solvent	React. Time min	Conv. %	Optical yield of product[b] e.e. %
1	Benzene[c]	30	40	90
		60	80	76
		960	90	21
2	Acetonitrile	30	73	30
		840	90	~0
3	Methanol	30	77	0
		660	85	0
4	Carbon Tetrachloride	30	80	58
5	Diethyl Ether	45	80	57
6	Chloroform	30	45	53
7	Dimethyl Sulfoxide	10 s	65	0

a) Benzaldehyde: 25 mmol, hydrogen cyanide: 25 mmol, *cyclo*(-(*S*)-Phe-(*S*)-His-): 0.5 mmol, solvent: 10 cm^3, reaction temperature: 35 °C. b) Preferred configuration is *R*. c) Ref. 2), 3).

optical yields were higher than those reported for D-oxynitrilase, which is a specific enzyme for the addition of hydrogen cyanide to benzaldehyde, although the reaction conditions are not indentical.[6] Using cinnamaldehyde as substrate under the same conditions, the optical yield of the product was 31% at 24% conversion. Thus, *cyclo*(-(*S*)-Phe-(*S*)-His-) is a better catalyst than natural enzyme for asymmetric cyanohydrin synthesis from some aldehydes.

Effect of Solvent on the Reaction of Benzaldehyde. As reported previously,[2] the reaction mixture in the addition of hydrogen cyanide to benzaldehyde in benzene catalyzed by *cyclo*(-(*S*)-Phe-(*S*)-His-) was heterogeneous in the early stage, and became homogeneous after about 30 min. This change from heterogeneity to homogeneity of the reaction mixture is considered to be due to the formation of the product, mandelonitrile. In fact, *cyclo*(-(*S*)-Phe-(*S*)-His-) (0.5 mmol) is soluble in a mixture of racemic mandelonitrile (25 mmol) and benzene (10 cm^3). We attempted to examine the influence of the product on the reaction by adding phenylacetonitrile or benzyl alcohol as the analog of the product to the reaction system. However, the addition of 5 cm^3 of the analog to the reaction mixture, consisting of benzaldehyde (50 mmol), hydrogen cyanide (50 mmol), *cyclo*(-(*S*)-Phe-(*S*)-His-) (1.0 mmol) and benzene (15 cm^3), did not dissolve the peptide, and the optical yield of the product in the asymmetric addition was not much affected. For example, upon addition of phenylacetonitrile the optical yield of the product was 72.5% after 30 min (conv. 60%) and 24.5% after 12 h (conv. 85%), respectively.

† 1 M=1 mol dm^{-3}.

The asymmetric benzaldehyde cyanohydrin synthesis catalyzed by *cyclo*(-(*S*)-Phe-(*S*)-His-) was examined in various solvents, as summarized in Table 2. The reaction in carbon tetrachloride was heterogeneous at first and then became homogeneous similarly to the reaction in benzene. The reaction in other solvents such as chloroform, diethyl ether, acetonitrile, and methanol was heterogeneous. On the other hand, dimethyl sulfoxide dissolved *cyclo*(-(*S*)-Phe-(*S*)-His-), and the reaction proceeded homogeneously and very rapidly to complete within a few minutes.

The reaction in nonpolar solvent such as benzene or carbon tetrachloride, or in solvent with lower polarity such as diethyl ether or chloroform, gave fairly high optical yield of the product. In the reaction using acetonitrile as solvent, the product had a moderate optical activity, while in methanol with almost the same dielectric constant the product exhibited no optical activity. No asymmetric reaction took place in strongly polar solvent such as dimethyl sulfoxide, although the reaction was stopped in a very short time in order to avoid possible decrease in the optical yield with reaction time.

Thus, nonpolar solvent is advantageous for this asymmetric cyanohydrin synthesis, while strongly polar solvent or protic solvent which is considered to weaken the interaction between catalyst and substrates is disadvantageous.

Experimental

Materials. Hydrogen cyanide was prepared from sodium cyanide and sulfuric acid as described previously.[4] All the aldehydes were distilled in nitrogen under reduced pressure. Carbon tetrachloride, diethyl ether, chloroform, and acetonitrile were distilled over calcium hydride in nitrogen. Methanol was distilled over magnesium in nitrogen. Dimethyl sulfoxide was distilled over calcium hydride in nitrogen under reduced pressure. Phenylacetonitrile and benzyl alcohol were distilled in nitrogen under reduced pressure. Commercially available racemic mandelonitrile was dried over Drierite. Other reagents and solvents were commercially purchased and used without futher purification.

Catalyst. *N*-Benzyloxycarbonyl-(*S*)-phenylalanyl-(*S*)-histidine methyl ester [Z-(*S*)-Phe-(*S*)-His-OMe] was prepared by the reaction of benzyloxycarbonyl-(*S*)-phenylalanine with (*S*)-histidine methyl ester as described previously.[4]

Cyclo[(*S*)-phenylalanyl-(*S*)-histidyl][*cyclo*(-(*S*)-Phe-(*S*)-His-)] was prepared from Z-(*S*)-Phe-(*S*)-His-OMe by the removal of benzyloxycarbonyl group by hydrogenation with palladium-black followed by cyclization in refluxing methanol according to the reported procedure.[2] The crude product was recrystallized from water and dried at room temperature under reduced pressure. This product was dissolved in hot ethanol and reprecipitated by adding the ethanol solution to five-fold amount of petroleum ether; mp 251—256 °C; $[\alpha]_D^{r.t.}=-62.1°$ (C=1.95 g/100 cm^3; acetic acid) (lit,[7] mp 267—268 °C; $[\alpha]_D^{20}=-72°$ (C=2.00 g/100 cm^3; acetic acid)).

Addition Reaction. *Cyclo*(-(*S*)-Phe-(*S*)-His-) (0.5 mmol) was placed in a 50 cm^3 round-bottomed flask equipped with a three-way cock, and the atmosphere of the flask was replaced with nitrogen. To this were added the solvent (10 cm^3) and aldehyde (25 mmol) with magnetic stirring, then 1 cm^3 of hydrogen cyanide was added with a chilled syringe. The conversion of aldehyde was determined by infrared spectrum of the reaction mixture using the absorption band due to ν_{C-H} of aldehydic hydrogen at 2735 cm^{-1}. The reaction was stopped by adding 0.5 cm^3 of 2 mol dm^{-3} HCl-CH_3OH. Unreacted hydrogen cyanide and solvent were removed from the reaction mixture through a trap containing aqueous alkali under reduced pressure. Ether was added to the residue, and the supernatant solution containing the product was separated. After washing the residue several times with ether, the combined ether solution and washings were filtered to remove the residual catalyst, then ether was removed under reduced pressure to leave a viscous liquid, which was confirmed to be a mixture of cyanohydrin and unreacted aldehyde by ^{1}H-NMR spectrum in $CDCl_3$. The mole fraction of cyanohydrin in this mixture was determined on the basis of ^{1}H-NMR signals due to C<u>H</u>(O<u>H</u>) (δ=5.5 and 4.5—5.0, respectively) of cyanohydrin and due to the aldehydic hydrogen (δ=9.9).

Determination of Optical Yield. For the determination of the optical purity of the product from *p*-tolualdehyde (**1a**), the product was reacted with (+)-perfluoro-2-propoxypropionyl chloride to give the corresponding ester quantitatively. ^{19}F-NMR spectrum of the ester was measured and the diastereomeric ratio of the ester was calculated from the signals of the trifluoromethyl group bonded to the chiral center.[8] As for *m*-phenoxybenzaldehyde and cinnamaldehyde, the optical purity of the product was calculated from the reported optical rotation of the product; for (*S*)-*m*-phenoxybenzaldehyde cyanohydrin ((*S*)-α-cyano-3-phenoxybenzyl alcohol), $[\alpha]_D^{25}=-24.8°$ (C=1.2 g/100 cm^3; $CHCl_3$)[9]; for (*R*)-cinnamaldehyde cyanohydrin, ((*R*)-α-cyanocinnamyl alcohol), $[\alpha]_D=+77°$ (C=8.4 g/100 cm^3; $CHCl_3$).[10] For the product from other aldehydes, the optical purity was determined by the high-pressure liquid chromatgraph using a chiral column Chiralcel OB (Daicel Chem. Ind., Ltd.); eluent, hexane/isopropyl alcohol (9/1); detecting wavelength, 254 nm.

Measurement. IR spectra were recorded on a Hitachi 260-30 spectrophotometer. NMR spectra were recorded on a Hitachi R-40 spectrometer. The optical rotations of the products at 589 nm were measured using Perkin-Elmer Polarimeter 241 or JASCO DIP-360 Digital Polarimeter. High pressure liquid chromatogram was recorded using Hitachi 638-30 High Pressure Liquid Chromatograph. Melting points were taken on a Yanagimoto Mel-Temp apparatus.

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