Tetrahedron Letters,Vol.30,No.34,pp 4535-4538,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

Asymmetric Syntheses of Amino Acids by Addition of Cyanide to the Schiff Bases in the Presence of Cyanide-Modified Hemin-Copolymer

Kiyoshi Saito and Kaoru Harada*

Department of Chemistry, University of Tsukuba
Tsukuba, Ibaraki, 305 Japan

Summary : Sterically controlled addition reactions of CN group to the Schiff bases by using CN-modified hemin-copolymer were carried out, and the optical yields (80-95 e.e.) of the resulting amino acids were much higher than that obtained without hemin-copolymer.

Iron-porphyrin complex is a kind of tetrapyrrole derivatives containing a large π electron system and shows aromatic property. The axial coordination site of porphyrin could be a possible reaction field for various organic reactions. In the study from this laboratory, hemin containing copolymers were synthesized in order to prevant the stacking of hemin[1)], and various ligands combined with hemin in the copolymer have been used as nucleophilic reagents in several substitution reactions[2)]. The results obtained indicated that the chemical reactions using the reagent-copolymer were strongly sterically controlled.

In this study, by the use of a CN-modified hemin-copolymer, addition reactions to the Schiff bases prepared from optically active benzylic amines and aliphatic aldehydes were carried out. It was found that the asymmetric induction in the addition reaction of cyanide with hemin-copolymer was much more effective than in the absence of the hemin-copolymer[3),4)].

Hemin-copolymer was prepared by suspension copolymerization of hemin, divinylbenzene and 2-methyl-5-vinylpyridine in aqueous organic solvent[5)]. The hemin-copolymer was controlled to form beads of uniform size (average diameter=250μm). The measurement of the surface of the beeds showed that the hemin copolymer was macroporous with a hemin content of 0.1 mmol/g, and a 50% degree of crosslinkage. The hemin-copolymer (1eq) was treated with an aqueous solutin of potassium cyanide (20 eq) at pH 9.0 at room temperature overnight, and the CN-modified hemin-copolymer was filtered off and dried. The CN content of the polymer was determined by the method described in the previous study5). Schiff bases were prepared by mixing freshly distilled optically active amines (1eq) and aldehyde (1 eq) in benzene in the presence of anhydrous sodium sulfate at room temperature for overnight. After the desiccant was removed off by filtration, the solvent was evaporated under reduced pressure and the Schiff base was obtained as an oil.

The addition reaction was carried out as follows : CN-bound hemin-copolymer (1 mmol as CN^-) and Schiff base (0.5 mmol) dissolved in ethanol (30 ml) and was kept at 20°C for 20 h in the presence of ammonium chloride (1 mmol). The progress of the addition reaction was checked by thin layer chromatography. After the reaction was over, hemin-copolymer was removed by filtration and was washed with ether. The combined organic solution was evaporated under reduced pressure. The residue was hydrolyzed with 6N HCl for 24 h under refluxing. The hydrolyzed solution was extracted with ether in order to remove colored material. After evaporation of hydrochloric acid in vacuo, the resulting N-alkylamino acids were subjected to hydrogenolysis, using palladium hydroxide on charcoal for 24 h. Amino acids synthesized were converted to N-trifluoroacetyl amino acid isopropyl ester, and the enantiomeric excess (e.e.) was determined by gas chromatography using chiral stationary phase (Chirasil-Val III)6).

Three kinds of amines were used as chiral source in the asymmetric addition reactions. These were (R)-and (S)-1-phenyl-1-ethylamine (R-1, S-2) ,(R)-1-phenyl-1-propylamine (R-2) and (R)-1-α-naphthyl-1-ethylamine (R-3). When the R-, and S-1 were used the e.e. were in the range of 74-91%, while R-2 gave an e.e. of 91-99%, and R-3, gave an e.e. of 79-95%. The results are summerized in Table 1. The chemical yields are in the range 29-59% which are similar to those obtained without hemin-copolymer3), and the yields decreased with the increse in the bulkiness of the alkyl group of the amino acids. Thus the e.e. of amino acids prepared by the present method were much higher than that of amino acids (40-50% e.e.) prepared by the same addition reaction without hemin-copolymer3,4). The results indicate that hemin in the copolymer provides strong steric control in the asymmetric addition of CN group. The experimental results indicate that the difference of bulkiness between alkyl group and hydrogen attached to the chiral center of amines is important to yield higher e.e. A possible explanation of the steric course could be shown as in Fig. 1, and the use of R-2 gave the highest e.e. among the three amines.

The addition reaction in the presence of CN-modified hemin-copolymer demonstrated higher steric control in the asymmetric syntheses of amino

Table 1. Asymmetric Syntheses by Addition to the Schiff Bases with CN Modified Hemin-copolymer$^{a)}$.

	(R)-PhCH(Me)NH$_2$$^{b)}$			(S)-PhCH(Me)NH$_2$$^{b)}$		
Aldehyde	Product	e.e. (%)$^{c)}$	Overall Yield(%)$^{d)}$	Product	e.e. (%)$^{c)}$	Overall Yield(%)$^{d)}$
CH_3CHO	(S)-Ala	74	59	(R)-Ala	76	56
C_2H_5CHO	(S)-But	77	53	(R)-But	79	50
$PhCH_2CHO$	(S)-Phe	85	44	(R)-Phe	84	46
$(CH_3)_2CHCHO$	(S)-Val	87	32	(R)-Val	91	29
	(R)-PhCH(Et)NH$_2$$^{b)}$			(R)-NaphCH(Me)NH$_2$$^{b)}$		
CH_3CHO	(S)-Ala	92	57	(S)-Ala	79	50
C_2H_5CHO	(S)-But	96	46	(S)-But	82	44
$PhCH_2CHO$	(S)-Phe	99	41	(S)-Phe	89	42
$(CH_3)_2CHCHO$	(S)-Val	91	34	(S)-Val	95	36

a) CN$^-$:Schiff Base=2:1mmol/30ml 95%EtOH, 20°C, 20h, in the presence of 1mmol NH_4Cl.

b) (R)-(+)-1-Phenyl-1-ethylamine, $[\alpha]_D^{25}$+39.3°(c=5,benzene),95%e.e.,lit. $[\alpha]_D^{25}$+41.5°(benzene)$^{7)}$;(S)-(-)-1-phenyl-1-ethylamine, $[\alpha]_D^{25}$-38.7°(c=5, benzene),93%e.e.,lit.$[\alpha]_D^{25}$-41.5°(benzene)$^{7)}$; (R)-(+)-1-phenyl-1-propylamine, $[\alpha]_D^{22}$+19.8°(c=6,benzene),94%e.e.,lit.$[\alpha]_D^{25}$+21.1°(c=6,benzene)$^{3)}$; (R)-(+)-1-α-naphthyl-1-ethylamine, $[\alpha]_D^{22}$+83.4°(c=7,benzene),95%e.e.,lit. $[\alpha]_D^{25}$+88.0°(benzene)$^{8)}$.

c) The e.e. of the synthesized amino acids were corrected by using the e.e. of the amines used in the reactions.

d) The chemical yields are calculated from amines.

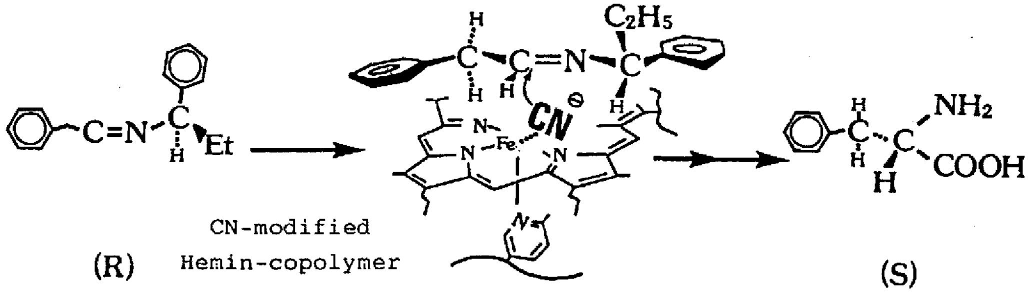

Fig.1. A Possible Steric Course of the Asymmetric Addition Reaction by Using CN-modified Hemin-copolymer

acids. Another applications of the modified hemin-copolymer as a reaction field for various organic reactions are under way.

References and Note

1) I.A.Cohen, Ann.N.Y.Acad.Sci.,206,453 (1973).; J.P.Collman and C.A.Reed, J.Am.Chem.Soc.,95,2048 (1973).; T.G.Traylor, M.J.Mitchell, J.P.Ciccon, S.Nelson, J.Am.Chem.Soc.,104, 4986 (1982).
2) Manuscript in preparation.
3) K.Harada and T.Okawara, J.Org.Chem.,38,707 (1973).
4) Following results are obtained in this laboratory by using CN-bound Amberlyst A26 (commercial anion exchange resin) under the same reaction conditions.

Aldehyde=$PhCH_2CHO$ Amine	Product	e.e. (%)	Overall Yield(%)
(R)-$PhCHMeNH_2$	(S)-Phe	32	14
(S)-$PhCHMeNH_2$	(R)-Phe	33	17
(R)-$PhCHEtNH_2$	(S)-Phe	46	18
(R)-$NaphCHMeNH_2$	(S)-Phe	40	15

5) E.Kokufuta and K.Saito, J.Appl.Polym.Sci.,34,517 (1987).
6) H.Frank, G.J.Nicolson and E.Bayer, J.Chromatogr.,146,197 (1978).
7) K.Harada and K.Matsumoto, J.Org.Chem.,32,1794 (1967).
8) K.Harada and K.Matsumoto, J.Org.Chem.,33,4467 (1968).

(Received in Japan 19 June 1989)