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ACKNOWLEDGMENTS AND ADDRESSES

Received May 29, 1967 from *Revlon Research Center, Inc., Bronx, NY 10473*
Accepted for publication June 25, 1969.

Stereospecific Hydrogenations IV: Palladium-on-Poly-*S*-Valine and Palladium-on-Poly-*S*-Leucine

ROBERT L. BEAMER, ROBERT H. BELDING, and CAROLYN S. FICKLING

Abstract □ Studies concerning the influence of helical conformation on the enantioselective hydrogenations catalyzed by palladium-on-poly-*S*-amino acids are described. Poly-*S*-valine which does not normally form a helical conformation and poly-*S*-leucine which forms a right-handed helix were chosen as carriers for this study. Hydrogenations of α-methylcinnamic acid and α-acetamidocinnamic acid using palladium-on-poly-*S*-valine produced predominantly *S*(+)-dihydro-α-methylcinnamic acid and R(+)-phenylalanine (after hydrolysis), respectively. The hydrogenations catalyzed by palladium-on-poly-*S*-leucine produced predominantly R(−)-dihydro-α-methylcinnamic acid and *S*(−)-phenylalanine (after hydrolysis), respectively. These results indicate that the helical conformation of the polyamino acid carriers does influence the asymmetric induction observed. The asymmetric induction arising from the chirality of the screw sense of the polyamino acid appears to have a stronger influence on the configuration of the products than does the asymmetric induction arising from the configurations of the amino acid residues. The asymmetric induction arising from the helical conformation appears to mask any influence arising from the asymmetric carbon atoms of the amino acid residues.

Keyphrases □ Palladium-on-poly-*S*-valine—α-methylcinnamic and α-acetamidocinnamic acid hydrogenation □ Palladium-on-poly-*S*-leucine—α-methylcinnamic and α-acetamidocinnamic acid hydrogenation □ Asymmetric induction—polyamino acid, helical conformation.

Stereospecific hydrogenations using palladium-on-poly-*S*-leucine, palladium-on-poly-γ-benzyl-*S*-glutamate and palladium-on-poly-β-benzyl-*S*-aspartate were described in earlier papers (1, 2). The substrates used in these hydrogenations were α-methylcinnamic acid and α-acetamidocinnamic acid, both of which produce asymmetric carbon atoms on hydrogenation.

Predominantly R(−)dihydro-α-methylcinnamic acid was formed when α-methylcinnamic acid was hydrogenated using either palladium-on-poly-*S*-leucine or palladium-on-poly-γ-benzyl-*S*-glutamate. *S*(−)-Phenylalanine was formed when α-acetamidocinnamic acid was hydrogenated using these same catalysts and the hydrogenation product hydrolyzed with dilute aqueous hydrochloric acid. Catalysts prepared from poly-β-benzyl-*S*-aspartate induced the formation of predominantly *S*(−)-dihydro-α-methylcinnamic acid and predominantly R(−)-phenylalanine, respectively, when the same substrates were used. Since both poly-*S*-leucine and poly-γ-benzyl-*S*-glutamate form stable helices having a right-handed screw sense and poly-β-benzyl-*S*-aspartate forms an anomalous left-handed helix (3–6), the helical sense of the poly-*S*-amino acid carrier must influence the asymmetric induction observed.

The present paper describes studies made to compare the influence of the chirality of the secondary structure (helix) *versus* the chirality arising from the asymmetric carbon atoms of the *S*-amino acid residues on the steric course of the enantioselective hydrogenations.

The carrier polyamino acids chosen for these studies were poly-*S*-valine and poly-*S*-leucine. As noted above, poly-*S*-leucine possesses a right-handed helix. Poly-*S*-valine, a lower homolog of poly-*S*-leucine differing from poly-*S*-leucine by one methylene group per amino acid residue, does not normally form a helical conformation, but forms a random β structure because of steric hindrance (7).

EXPERIMENTAL[1]

Reagents—*N*-Carbobenzyloxy-*S*-valine (Nutritional Biochemicals), α-methylcinnamic acid (Aldrich), α-acetamidocinnamic acid (Aldrich), leucine (Mann Biochemical Corp.)., and carbobenzyloxy chloride (Nutritional Biochemicals).

N-Carboxy-S-valine Anhydride (I)—This compound was prepared according to the Leuchs procedure (8). Twelve grams (0.1 mole) of glass-distilled thionyl chloride were added to 12.5 g. (0.05 mole) of *N*-carbobenzyloxy-*S*-valine. The mixture was warmed gently to 40° until evolution of gas diminished and heated on a

[1] All temperatures are uncorrected. Elemental analyses were determined using a Hewlett-Packard model 185 C, H, and N analyzer. Optical rotation measurements were made using a Rhudolph model 200S polarimeter. A Perkin-Elmer Infracord model 137B spectrophotometer was used to obtain the IR spectra.

Table I—Hydrogenation Studies Using Palladium-on-Poly-*S*-Valine and Palladium-on-Poly-*S*-Leucine

Substrate	Catalyst: Poly-*S*-Valine % Yield (overall)	Poly-*S*-Valine $[\alpha]_D^{23}$	Poly-*S*-Valine % Optical Yield	Poly-*S*-Leucine % Yield (overall)	Poly-*S*-Leucine $[\alpha]_D^{23}$	Poly-*S*-Leucine % Optical Yield
α-Methylcinnamic acid	87.0	+0.245	0.90	77.7	−0.300	1.10
		+0.220	0.81		−0.305	1.12
		+0.205	0.75		−0.320	1.18
		+0.218	0.80			
		+0.223	0.82			
		+0.223	0.82			
α-Acetamidocinnamic acid	68.0	+2.060	4.25	92.3	−2.50	5.16
		+2.010	4.15		−2.46	5.08
		+2.030	4.19		−2.54	5.24

water bath at 50–60° for 15 min. The excess thionyl chloride was removed under reduced pressure and the oily residue was titrated with petroleum ether until solidification occurred. Throughout the procedure precautions were taken to keep reagents and apparatus dry. Calcium chloride drying tubes were employed wherever possible. The product was recrystallized from a dry ether–acetone mixture. It melted from 63–65° (with evolution of gas). The literature value is 65° [with decomposition (7)]. The yield was 6.1 g. or 84.7% of theory.

Poly-S-valine (II)—*N*-Carboxy-*S*-valine anhydride (I) (6.1 g., 0.042 mole) was placed in a 100-ml. round-bottom flask and evacuated for 2 hr. at 32° and 10^{-2} torr. The temperature was raised gradually over a 1-hr. period to 63°. The product was observed to melt with a rapid evolution of gas. The pressure was reestablished at 10^{-2} torr after 15 min., and the reaction then was considered to be complete. The contents of the flask were stirred with petroleum ether. Following stirring, the petroleum ether was removed under reduced pressure and the product was washed with ethanol. The finely divided powdery residue was collected by suction filtration. The product was soluble in dimethylformamide but insoluble in water. The IR spectrum (mineral oil mull) conformed to that of Bloom *et al.* (7). A yield of 4.1 g. (96.2% of theory) was obtained.

Anal.—Calcd. for C_5H_9NO: C, 60.57; H, 9.15; N, 14.13. Found: C, 60.66; H, 9.52; N, 14.12.

Poly-S-leucine (III)—This polypeptide was prepared by the procedure of Beamer *et al.* (1) starting with *S*-leucine and carbobenzyloxy chloride.

Preparation of the Catalysts—The catalysts were prepared by depositing palladium (from a solution of palladous chloride, 2.5%) upon the respective polyamino acids according to Method II of Beamer *et al.* (1). The catalyst concentration was 200 mg. of palladous chloride per gram of carrier.

Hydrogenation Studies—The substrates used were α-methylcinnamic acid and α-acetamidocinnamic acid. The catalysts employed were palladium-on-poly-*S*-valine and palladium-on-poly-*S*-leucine. A Parr low-pressure hydrogenator was used with an initial hydrogen pressure of 4.2 kg./cm.^{2}. The usual time allowed for complete hydrogenation was 8 hr. (for 0.05 mole of α-methylcinnamic acid or 0.023 mole of α-acetamidocinnamic acid).

1. Hydrogenations Using Palladium-on-poly-S-valine—a. Hydrogenation of α-methylcinnamic Acid—The hydrogenations were performed using 8.10 g. (0.05 mole) of α-methylcinnamic acid in 100 ml. of absolute ethanol and 1.0 g. of catalyst.

Following hydrogenation, the catalyst was removed by filtration and the ethanol was removed by evaporation under reduced pressure. The residue was vacuum-distilled. The yield of dihydro-α-methylcinnamic acid was 6.82 g. or 87.0% of theory. The boiling point was 136°/0.75 torr [lit. val. 160°/13 torr (9)]. The IR spectrum was identical with that given by Beamer and Lawson (10). The neutralization equivalent agreed with that calculated for dihydro-α-methylcinnamic acid. The average $[\alpha]_D^{23}$ was +0.227° (c = 40 in benzene). The specific rotation represented 0.82% of the literature value of 27.06° (9).

b. Hydrogenation of α-acetamidocinnamic Acid—Hydrogenation of 4.8 g. (0.023 mole) of α-acetamidocinnamic acid was carried out in 100 ml. of absolute ethanol using 1.0 g. of catalyst.

Following hydrogenation, the catalyst was removed and the solvent was evaporated leaving a white, crystalline residue. The residue was treated according to the directions of Akabori (11) by refluxing with 30 ml. of 10% hydrochloric acid.

After acid hydrolysis, the solution was concentrated under vacuum to approximately one-half its original volume and treated with acetone to precipitate the amino acid hydrochloride. The phenylalanine was obtained by adjusting a hydromethanolic (50% v/v) solution of the hydrochloride to the isoelectric point of phenylalanine (pH 5.4) and collecting the resulting precipitate by suction filtration.

The product weighed 2.4 g. representing a yield that was 68.0% of theory. The product melted from 268–270° [lit. 271–273° dec. (12)]. TLC on alumina using 50% v/v methanol-water by the microscope slide method of Peifer (13) showed the R_f value of the product to be identical with that of known phenylalanine. The IR spectrum of the product was identical with an authentic sample of phenylalanine.

The phenylalanine was dissolved in 2 *N* sodium hydroxide and placed in a 100-mm. polarimeter tube and the optical rotation was determined. The average $[\alpha]_D^{23}$ was +2.033° (c = 20 in 2 *N* NaOH). [The literature value is 48.4° (14).] From these data an optical yield of 4.20% was calculated.

2. Hydrogenations Using Palladium-on-poly-S-leucine—a. Hydrogenation of α-methylcinnamic Acid—The procedure followed was the same as that already described for the polyvaline catalyst. The weight of the product was 6.3 g. representing a percent yield of 77.7%. The average $[\alpha]_D^{23}$ was −0.308° (c = 20 in benzene) representing an optical yield of 1.13%.

b. Hydrogenation of α-acetamidocinnamic Acid—The procedure followed was the same as that already described under the polyvaline catalyst. The product weighed 3.5 g. which was 92.3% of theory. The average $[\alpha]_D^{23}$ was −2.50° (c = 10 in 2 *N* NaOH) representing an optical yield of 5.16%.

RESULTS

The results of the hydrogenation studies were reproducible for a series of experiments using a single batch of catalyst preparation, but slight variations were seen between batches of catalyst. Although some variations were observed between different catalyst preparations, the sign of optical rotation of the hydrogenation products was always the same when the same catalyst type was used. Typical results are given in Table I.

DISCUSSION OF RESULTS

As can be seen from Table I, conformation influences the configurations of the products of stereoselective hydrogenations catalyzed by palladium-on-poly-*S*-amino acids. The results of this study may be better understood by referring to the current ways of looking at protein structure (15).

The structure of proteins is generally considered to be developed from a series of superimposed levels of higher complexities. The peptide chain is called the primary structure of the protein. The secondary structure is the α-helix or the β-pleated sheet and is superimposed upon the primary structure. The tertiary structure consists of folding the protein's helical peptide chains into a spherical or elliptical shape in the case of albumins or globulins or not folding the peptide chains as in the fibrous or scleroproteins.

A similar treatment can be considered in discussing the results of the studies presented in this paper. Poly-*S*-valine for steric

reasons does not assume a helical conformation (7). Therefore, the asymmetric induction observed using a catalyst employing poly-*S*-valine as a carrier may be considered to arise from the asymmetric carbon atoms of the amino acid residues of the peptide chain (primary structure) only. When α-methylcinnamic acid or α-acetamidocinnamic acid are used as substrates, the enantioselection of this non-helical catalyst leads to dextrorotatory products.

When the helical poly-*S*-leucine is used as the carrier for palladium, the primary structure is superimposed by a helical secondary structure (3, 15). Apparently the helical secondary structure has a greater asymmetric inductive influence on the enantioselection since palladium-on-poly-*s*-leucine catalyzed hydrogenations of the same substrates as those employed with the poly-*S*-valine catalyst lead to levorotatory products at a higher optical yield.

Thus one may conclude that the secondary structure of the polyamino acid carrier does influence the steric course of the asymmetric hydrogenations catalyzed by these palladium-on-poly-*S*-amino acid catalysts and that the superimposition of the helical conformation upon the peptide chain brings a stronger influence of the chirality of the helix on the enantioselection and masks that of the asymmetric carbon atoms of the amino acid residues of the peptide chain.

The absolute configurations of the enantiomers of dihydro-α-methylcinnamic acid and of phenylalanine have been determined by Schrecker and by Karrer, respectively (16, 17).

The observation that hydrogenations of α-methylcinnamic acid catalyzed by palladium-on-poly-*S*-leucine lead to predominantly R(−)-dihydro-α-methylcinnamic acid while those of α-actamidocinnamic acid using the same catalyst lead to predominantly *S*(−)-phenylalanine (after hydrolysis) has been reported earlier (1). As noted in Table I, hydrogenations of the above substrates using palladium-on-poly-*S*-valine also lead to respective products of opposite configuration. Similar results were reported with catalysts using poly-α-benzyl-*S*-glutamate and poly-β-benzyl-*S*-aspartate as carriers (2). With all the polyamino acid catalysts studied thus far, the two substrates (α-methylcinnamic acid and α-acetamidocinnamic acid) must occupy at least in part different sites on the catalyst surface.

SUMMARY

1. Palladium-on-poly-*S*-valine and palladium-on-poly-*S*-leucine both catalyze asymmetric hydrogenations of α-methylcinnamic acid and α-acetamidocinnamic acid.

2. Hydrogenations of α-methylcinnamic acid and of α-acetamidocinnamic acid using palladium-on-poly-*S*-valine lead to *S*(+)-dihydro-α-methylcinnamic acid and to R(+)-phenylalanine (after hydrolysis), respectively.

3. Hydrogenations of α-methylcinnamic acid and of α-acetamidocinnamic acid using palladium-on-poly-*S*-leucine produced R(−)-dihydro-α-methylcinnamic acid and *S*(−)-phenylalanine (after hydrolysis of the hydrogenation product), respectively.

4. Results of these experiments indicate participation of the helical structure in a manner which is superimposed upon the primary structure of the polyamino acid carrier. Greater influence on the enantioselectivity is observed with the helical conformation and masks that of the asymmetric carbons of the amino acid residues of the carrier polyamino acids.

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ACKNOWLEDGMENTS AND ADDRESSES

Received July 7, 1969 from the *School of Pharmacy, University of South Carolina, Columbia, SC 29208*

Accepted for publication July 31, 1969.