Stereospecific Hydrogenations III: Palladium-on-Poly-γ-benzyl-S-glutamate and Palladium-on-Poly-β-benzyl-S-aspartate

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Abstract □ Stereospecific hydrogenations were demonstrated using palladium-on-poly-γ-benzyl-*S*-glutamate and palladium-on-poly-β-benzyl-*S*-aspartate. The results of the hydrogenation experiments indicate that the helical conformations of the poly-*S*-amino acid carriers influence the asymmetric induction observed. Hydrogenations using palladium-on-poly-γ-benzyl-*S*-glutamate produced R(−)-dihydro-α-methylcinnamic acid and *S*(−)-phenylalanine (after hydrolysis of the hydrogenation product) when α-methylcinnamic acid and α-acetamidocinnamic acid, respectively, were used as substrates. When hydrogenations were carried out using palladium-on-poly-β-benzyl-*S*-aspartate as the catalyst and the same substrates, *S*(+)-dihydro-α-methylcinnamic acid or R(+)-phenylalanine (after hydrolysis of the hydrogenation product were produced).

Keyphrases □ Hydrogenation—stereospecific □ Palladium-on-poly-γ-benzyl-*S*-glutamate and poly-β-benzyl-*S*-aspartate—synthesis □ Catalysts—stereospecific hydrogenation □ IR spectrophotometry—identity □ Optical rotation—identity

The stereospecificity of catalysts prepared from silica gels precipitated in the presence of cinchona alkaloids has been shown by Padgett and Beamer (1). Beamer and Lawson have presented evidence of substrate specificity with catalysts prepared from similarly prepared gels (2). A more recent report described stereospecific hydrogenations using palladium-on-poly-*S*-leucine (3).

These studies were based on prior evidence indicating the existence of stereospecific and substrate-specific centers in palladium-on-charcoal catalysts (4). Also, Akabori *et al.* have demonstrated the stereospecificity of palladium-on-silk fibroin (5) and Beckett *et al.* have shown stereospecific adsorption upon specially prepared silica gels (6–8).

The present work is a continuation of investigations into the stereospecific hydrogenations observed using palladium-on-poly-*S*-amino acids. The poly-*S*-amino acids chosen for study were poly-γ-benzyl-*S*-glutamate and poly-β-benzyl-*S*-aspartate. These two poly-*S*-amino acids were chosen because of recent reports showing a tendency for poly-*S*-aspartates and poly-*S*-glutamates to form helical conformations of opposite senses (9–11).

The poly-*S*-amino acids were prepared by polymerization of their *N*-carboxy-α-amino acid anhydrides *in vacuo* (12).

The substrates used in the hydrogenation studies were α-methylcinnamic acid and α-acetamidocinnamic acid.

EXPERIMENTAL

Reagents—α-Methylcinnamic acid (Aldrich), carbobenzyloxychloride (Nutritional Biochemicals), *S*-glutamic acid (Columbia Organic Chemicals Co.), *S*-aspartic acid (Columbia Organic Chemicals Co.), benzyl alcohol (Fisher Scientific Co.).

All temperatures are uncorrected. Elemental analyses were determined using a C, H, and N analyzer (Hewlett-Packard model 185).

N-Carbobenzyloxy-S-aspartic Acid (I)—This compound was prepared according to the Bergmann procedure starting with 13.3 g. of *S*-aspartic acid (12). The yield was 14.1 g. representing 53% of theory. The product melted from 115–117° [lit. value 116° (13)].

Dibenzyl-N-carbobenzyloxy-S-aspartate (II)—The dibenzyl ester of *N*-carbobenzyloxy-*S*-aspartic acid was prepared from the acid (I) by the method of Berger and Katchalski (14). When 26.7 g. of (I) was used, the yield was 32.6 g. representing 73% of theory. The product melted from 65–67° [lit. value 66.5° (14)].

β-Benzyl-N-carbobenzyl-S-aspartate (III)—The monobenzyl ester of *N*-carbobenzyloxy-L-aspartic acid was prepared by partial hydrolysis of 4.56 g. of the dibenzyl ester (II) according to the directions of Berger and Katchalski (14). The yield was 2.5 g. representing 78.3% of theory, m.p. 106–108° [lit. value 108° (14)].

β-Benzyl-N-carboxy-S-aspartate Anhydride (IV)—This compound was prepared by treating the carbobenzyloxyamino acid (III) with phosphorus pentachloride (14). The yield was 22.5 g. or 90% of theory when 35.7 g. of III was used in the preparation. The melting point was 121–125° (with evolution of gas). The literature value was 121° (with evolution of carbon dioxide) (14).

Poly-β-benzyl-S-aspartate (V)—The polymerization of the anhydride (IV) was performed *in vacuo* (10^{-2} mm. Hg) according to the procedure of Katchalski (14). The anhydride (15.0 g.) was melted and the polymerization conducted at an oil bath temperature of 125°. A rapid evolution of gas was observed. The hot residue was treated with ether with stirring. The residue became a finely divided solid which was soluble in dimethylformamide but insoluble in water. The resulting compound had $[\alpha]_D^{23.5}$ −19.1° [c = 10 in 3% dichloroacetic acid), which corresponds to a literature value of −18° (15)].

The IR spectrum of the product conformed to that given by Bradbury *et al.* for poly-β-benzyl-*S*-aspartate (9). The yield was 8.0 g. or 64.7% of theory. The compound softened from 150–155° and melted from 207–208°. The literature gives no melting point but reports softening at 160° (14).

Anal.—Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.38; N, 6.87. Found: C, 63.93; H, 5.32; N, 6.70.

γ-Benzyl-S-glutamate (VI)—The preparation of this monobenzyl ester of *S*-glutamic acid followed the procedure of Hanby *et al.* (16). The yield was 159.0 g. which was 67.0% of theory based on 147.0 g. of *S*-glutamic acid. The melting point was 169–170° [lit. value 170° (16)].

γ-Benzyl-N-carbobenzyloxy-S-glutamate (VII)—This compound was prepared from 23.7 g. of the monobenzyl ester of *S*-glutamic acid (VI) (16). The product melted from 75–78° [lit. value 76–78° (16)]. The yield was 25.0 g. (67.5% of theory).

γ-Benzyl-N-carboxy-S-glutamate Anhydride (VIII)—The anhydride was prepared by treating 37.1 g. of the amino acid (VII) with phosphorus pentachloride according to the procedure of Hanby *et al.* (16). The melting point of the product was from 94–95° (in an open tube with gas evolution). The literature value was 96–97° [in a sealed tube with decomposition (16)]. The yield was 20.1 g. which was 76.5% of theory.

Poly-γ-benzyl-S-glutamate (IX)—The polymerization of the anhydride (VIII) was carried out using the procedure of Hanby *et al.* (16). The anhydride (VIII) (15.2 g.) was melted *in vacuo* (10^{-2} mm. Hg) with evolution of gas. The hot residue was covered with 100 ml. of ether and the mixture was stirred vigorously until a finely divided solid formed. The solid was collected by filtration and

Table I—Hydrogenation Studies Using Palladium-on-Poly-γ-benzyl-*S*-glutamate and Palladium-on-Poly-β-benzyl-*S*-aspartate

Substrate	Catalyst: Polyglutamate % Yield (overall)	Polyglutamate $[\alpha]_D^{23.5}$	Polyglutamate % Optical Yield	Catalyst: Polyaspartate % Yield (overall)	Polyaspartate $[\alpha]_D^{23.5}$	Polyaspartate % Optical Yield
α-Methylcinnamic acid	80.4	−1.116	4.12	54.5	+0.300	1.11
		−1.112	4.11		+0.236	0.87
		−1.116	4.12		+0.300	1.11
		−1.124	4.15		+0.388	1.43
					+0.313	1.16
					+0.312	1.15
α-Acetamidocinnamic acid	56.5	−2.881	5.95	56.5	+0.450	0.93
		−2.863	5.92		+0.430	0.89
		−2.863	5.92		+0.450	0.93
		−2.900	5.99		+0.460	0.95

the powder was taken up in dimethylformamide and precipitated with water. The product exhibited a $[\alpha]_D^{23.5}$ +13.94° (c = 0.954 in chloroform) corresponding to a literature value of +14° (c = 0.954 in chloroform). The yield was 10.1 g. representing 79.5% of theory. The IR spectrum of the product conformed to that given by Bradbury *et al.* (9). No melting point has been reported for poly-γ-benzyl-*S*-glutamate. The poly-*S*-amino acid was found to soften from 150–155° and melted from 207–208°.

Anal.—Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.99; N, 6.39. Found: C, 65.97; H, 6.09; N, 6.35.

α-Acetamidocinnamic Acid (X)—This compound was prepared by hydrolysis of 47.0 g. of the azlactone, 2-methyl-4-benzilidene-1,3-oxazoline-5-one, by the method of Herbst and Shemin (17). The yield was 25.5 g. or 49.8% of theory. The product melted from 190–191.5° [lit. value 191–192° (17)].

Preparation of the Catalysts—The catalysts were prepared by depositing palladium (from a solution of palladous chloride) upon the respective poly-*S*-amino acids according to Method II of Beamer *et al.* (3). The catalyst concentration employed was 144 mg. of palladous chloride per gram of carrier.

Hydrogenation Studies—The substrates used in the hydrogenation studies were α-methylcinnamic acid and α-acetamidocinnamic acid. The catalysts employed were palladium-on-poly-γ-benzyl-*S*-glutamate and palladium-on-poly-β-benzyl-*S*-aspartate. A Parr low-pressure hydrogenator was used with an initial hydrogen pressure of 4.2 kg./cm.^{2}. The usual time for complete hydrogenation was 48 hr. (for 0.05 mole of α-methylcinnamic acid or 0.023 mole of α-acetamidocinnamic acid). Optical rotation measurements were made using a polarimeter (Rhudolph model 200S).

Hydrogenations using Palladium-on-poly-γ-benzyl-S-glutamate—*Hydrogenations 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 removed by evaporation under reduced pressure. The residue was vacuum distilled. The yield of dihydro-α-methylcinnamic acid was 6.80 g. or 43.0% of theory. The boiling point was 114°/0.25 mm. Hg [lit. value 160°/13 mm. Hg (18)]. The average $[\alpha]_D^{23.5}$ was −1.117° (c = 25 in benzene). The specific rotation represented 4.13% of the literature value of 27.06° (18). The IR spectrum was identical to that given by Beamer and Lawson (2). The neutralization equivalent agreed with that calculated for dihydro-α-methylcinnamic acid.

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 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 (5) 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 2.6 g. representing a yield that was 73.7% of the theoretical. The product melted from 269–271° [lit. value 271–273° decomposed (19)]. TLC on alumina using 50% v/v methanol-water showed the R_f value of the product to be identical with that of known phenylalanine.[1] The IR spectra of known phenylalanine and the product were identical.

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 $[\alpha]_D^{23.5}$ was −2.876° (c = 7.52 in 2 *N* NaOH). The literature value is −48.4 for the specific rotation of phenylalanine (21). From these data an optical yield of 5.94% was calculated.

Hydrogenations using Palladium-on-Poly-β-benzyl-S-aspartate—*Hydrogenation of α-Methylcinnamic Acid*—The procedure followed was the same as that already described for the polyglutamate catalyst. The average $[\alpha]_D^{23.5}$ was +0.316 (c = 25 in benzene) representing an optical yield of 1.16%.

Hydrogenation of α-Acetamidocinnamic Acid—The procedure followed was the same as that which has already been described under the polyglutamate catalyst. The $[\alpha]_D^{23.5}$ of the phenylalanine obtained was +0.450 (c = 4.7 in 2 *N* NaOH) representing an optical yield of 0.93%.

RESULTS

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

DISCUSSION AND CONCLUSIONS

The results indicate that the enantioselective hydrogenations using palladium-on-poly-γ-benzyl-*S*-glutamate and palladium-on-poly-β-benzyl-*S*-aspartate arise from the chirality (the helical sense) of the carrier polyamino acids (secondary structure). The poly-γ-benzyl-*S*-glutamate and the poly-β-benzyl-*S*-aspartate possess opposite helical senses (9–11) and the catalysts prepared from them induce the formation of products possessing predominantly opposing configurations.

Poly-γ-benzyl-*S*-glutamate possesses the normal right-handed helix of *S*-amino acids (9). The induced formation of predominantly levorotatory dihydro-α-methylcinnamic acid and phenylalanine when α-methylcinnamic acid and α-acetamidocinnamic acid were used as substrates is the same result reported by Beamer *et al.* (3) who studied a catalyst prepared from poly-*S*-leucine, a polyamino acid possessing the same helical sense as that of poly-γ-benzyl-*S*-glutamate (22).

[1] The method used was adapted from that of Peifer (20). Microscope slides were sprayed with an aluminum oxide (Brinkman Instruments) slurry in water. Following chromatography, the plates were treated with iodine vapors in a closed jar for visualization at the phenylalanine spots.

The helical sense of poly-β-benzyl-*S*-aspartate is left-handed and is considered an anomalous helical conformation (9–11). The opposing helical sense of poly-β-benzyl-*S*-aspartate from that of poly-γ-benzyl-*S*-glutamate apparently arises from the steric interactions resulting from one less methylene group in the side chain of the aspartate residues (9). The poly-*S*-aspartate catalyst induced the formation of predominantly dextrorotatory products when α-methylcinnamic acid and α-acetamidocinnamic acid were used as substrates.

One would not expect respective hydrogenation products of equal but opposite rotations with these catalysts for two reasons: 1. There should be some contribution to asymmetric induction arising from the asymmetric centers in the individual amino acid residues (primary structure). 2. The anomalous helical sense of the poly-β-benzyl-*S*-aspartate opposes the normal helical sense of a poly-*S*-amino acid and should cause the polyaspartate carrier to possess a lower degree of helical formation than the polyglutamate carrier. A lower degree of helical formation should result in lower optical yields of the products from the asymmetric hydrogenations catalyzed by the polyaspartate catalyst than the products resulting from the reactions catalyzed by the polyglutamate catalyst. As may be seen from Table I, higher optical yields of products are obtained from the polyglutamate catalyst than from polyaspartate catalyst (a ratio of about 5:1).

The absolute configuration of levorotatory dihydro-α-methylcinnamic acid is R (23) while the absolute configuration of levorotatory phenylalanine is S (24, 25). In the enantioselective hydrogenations using the polyglutamate catalyst, predominantly R(−)-dihydro-α-methylcinnamic acid and S(−)-phenylalanine were produced. The polyaspartate catalyst produced a similar result except that predominantly S(+)-dihydro-α-methylcinnamic acid and R(+)-phenylalanine were formed. Palladium-on-poly-*S*-leucine catalyzes the formation of predominantly R(−)-dihydro-α-methylcinnamic acid and predominantly S(−)-phenylalanine (3).

These results indicate that the α-methylcinnamic acid and the α-acetamidocinnamic acid are occupying (at least in part) different sites on the catalysts prepared from these three polyamino acids.

SUMMARY

Palladium-on-poly-γ-benzyl-*S*-glutamate and palladium-on-poly-β-benzyl-*S*-aspartate both catalyze asymmetric hydrogenations of α-methylcinnamic acid and α-acetamidocinnamic acid.

The hydrogenations of α-methylcinnamic acid and α-acetamidocinnamic acid using palladium-on-poly-γ-benzyl-*S*-glutamate produces R(−)-dihydro-α-methylcinnamic acid and *S*(−)-phenylalanine (after hydrolysis of the hydrogenation product), respectively.

The hydrogenations of α-methylcinnamic acid and α-acetamidocinnamic acid using palladium-on-poly-β-benzyl-S-aspartate produced S(+)-dihydro-α-methylcinnamic acid and R(+)-phenylalanine (after hydrolysis), respectively.

Results of the hydrogenation experiments indicate participation of the helical conformation or secondary structure of the poly-*S*-amino acid carrier in the asymmetric induction catalyzed by palladium-on-poly-*S*-amino acids.

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