Steric Course of the Rhodium-Catalyzed Decarbonylation of Chiral 4-Methyl-[1-^{3}H,2-^{2}H$_1$]pentanal

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Dedicated to Professor Helmut Simon on the occasion of his 60th birthday

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(*R*)- and (*S*)-4-methyl-[1-^{3}H,2-^{2}H$_1$]pentanal were prepared from L- and D-leucine *via* leucic acid and (*S*)- and (*R*)-4-methyl-[2-^{2}H$_1$]pentanoic acid. Decarbonylation of these samples with tris-(triphenylphosphine)rhodium chloride followed by Kuhn-Roth oxidation of the resulting 2-methylbutane gave chiral acetic acid of 35% e.e. *S* and 31% e.e. *R* configuration, respectively. The decarbonylation reaction thus proceeds with net retention of configuration, possibly accompanied by some racemization.

The stereochemistry of the decarbonylation of aldehydes catalyzed by tris-(triphenylphosphine)rhodium chloride has been examined in a few cases [1]. The reaction was found to proceed with high stereoselectivity, except when the α-carbon carried an electron-donating group like $-OCH_3$, and net retention of configuration. However, all the cases studied involved hindered aldehydes in which the formyl group was attached to a quaternary carbon. In the analogous decarbonylation of acid chlorides [2, 3] net retention of configuration was also observed, but these reactions were accompanied by a high degree of racemization. However, the cases studied here also involved less crowded systems in which the carbonyl group was attached to a primary or secondary carbon. These reactions represent the reversal of the so-called carbonyl insertions into transition metal-carbon bonds [4], which, mechanistically, are actually migrations of a metal-bound alkyl group to an adjacent bound carbon monoxide. These, in the cases studied, also proceed with retention of configuration of the alkyl group [5, *cf.* 4, 6, 7].

In the course of studies on stereochemical aspects of the biosynthesis of ergot alkaloids [8] we were faced with the problem of determining the configuration of 4-methylpentanoic acid stereospecifically monodeuterated at C-2 on μg samples obtained in an impure state from complex reaction mixtures. It occurred to us that the limitation of quantity could be overcome by converting the acid to the 1-tritiated alcohol by reduction with tritiated $LiBH_4$, followed by oxidation to the aldehyde and decarbonylation to give 2-methylbutane carrying a chiral methyl group at C-4 (Scheme I). In this sequence the tritiated, deuterated alcohol could be diluted with ample carrier material, allowing the subsequent chemical steps to be carried out on a more manageable scale.

To explore the feasibility of this degradation sequence it was necessary to determine whether the decarbonylation of an uncrowded aldehyde like 4-methylpentanal also proceeds stereospecifically with retention of configuration. The results are reported here because of the current interest in an important biochemical carbonyl insertion reaction, the synthesis of acetic acid in anaerobic organisms [9], and its stereochemistry [10].

Results

To examine the steric course of the transition metal-catalyzed decarbonylation of 4-methylpentanal, we synthesized authentic samples of (2*R*)- and (2*S*)-4-methyl-[2-^{2}H$_1$]pentanoic acid and subjected them to the reaction sequence shown in Scheme I. The synthesis of the two enantiomers of 4-methyl-[2-^{2}H$_1$]pentanoic acid is delineated in Scheme II. *R*- and *S*-leucine were diazotized to give in 70–75% yield *R*- and *S*-leucic acid, respectively, as described by Englard [11]. The reaction proceeds with net retention of configuration, presumably *via* neighboring group participation of the carboxylate anion [12].

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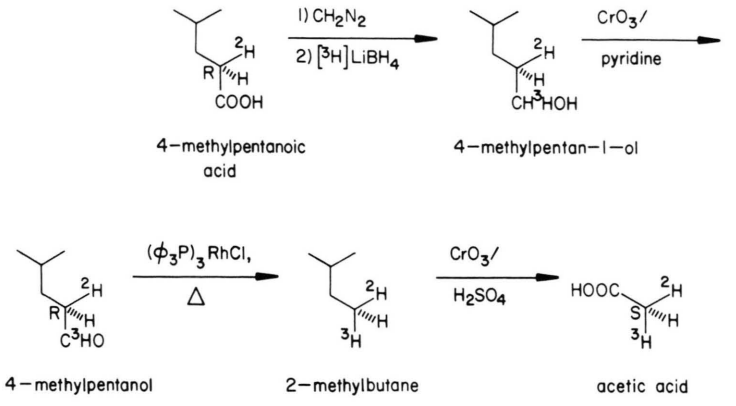
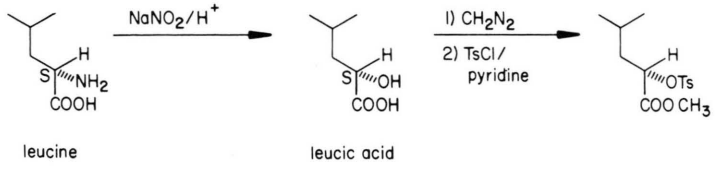
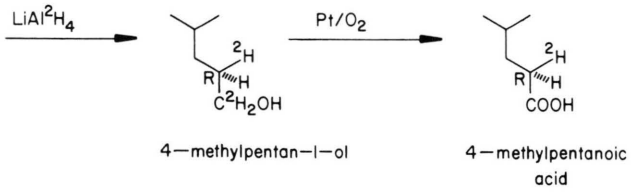


Scheme I.





Scheme II.

Since from the literature [13, 14] the exact value of the specific rotation of optically pure leucic acid is not completely certain, we checked the chiral purity of our samples by conversion to the methyl ester and derivatization with (−)-camphanic acid chloride, followed by GC−MS analysis. The two diastereomeric camphanate derivatives separated cleanly (retention times *R*: 18.01 min, *S*: 18.23 min), and the analysis indicated chiral purities of at least 97% e.e. and 99% e.e. for the *R*- and *S*-leucic acids, respectively. The enantiomeric leucic acid methyl esters were then converted to the *p*-toluenesulfonates, followed by reduction with lithium aluminium deuteride to give two samples of 4-methyl-[1,1,2-$^2H_3$]pentan-1-ol, which were oxidized with oxygen and platinum catalyst to (*S*)- (from (*R*)-leucic acid) and (*R*)-4-methyl-[2-$^2H_1$]pentanoic acid (from (*S*)-leucic acid), respectively. The configuration of the 4-methylpentanoic acid samples follows from the known steric course of hydride displacements of sulfonate esters, inversion of configuration due to an S_N^2 mechanism [15]. The isotopic purity of the (*S*)- and (*R*)-4-methyl-[2-$^2H_1$]pentanoic acid samples was checked by GC−MS analysis of the methyl esters and found to be 97% and 98%, respectively. To assay the chiral purity, aliquots of the two acids were esterified with methyl (*S*)-mandelate and analyzed by proton NMR [16] with decoupling of both deuterium (broadband) and the protons at C-3 (1.6 ppm). The analysis indicated minimum chiral purities of 93% e.e. and 94%

e.e., respectively. These values do not agree well with the specific rotations of −1.98° and +0.398°, respectively, suggesting that the latter reflect contamination with traces of an optically active material of much higher specific rotation.

With these samples at hand we were now ready to embark on the reaction sequence outlined in Scheme I. The esterification of 4-methylpentanoic acid and the subsequent reduction of the ester with tritiated $LiBH_4$ (generated from 100 mCi [^{3}H]$NaBH_4$ and LiCl immediately before use [17]) were carried out on a relatively small scale, 45 mg of acid. A large quantity (2 g) of unlabeled 4-methylpentan-1-ol was added after the reduction and tritiated alcohol was recovered in about 70% yield. The radiochemical yield based on [^{3}H]$NaBH_4$ was, not surprisingly, rather low (3−20%), but the total amount of radioactivity available in each enantiomer (0.95 and 6.6 mCi, respectively) was ample for the subsequent reactions. Collins oxidation of the two alcohol samples gave the aldehyde in 26−36% yield after distillation on a 1 g scale. The decarbonylation of the aldehyde was carried out in CH_2Cl_2 with a slight excess (110% of the stoichiometric amount) of Wilkinson's catalyst at room temperature, and the resulting 2-methylbutane, recovered by lyophilization, was oxidized to acetic acid without purification.

The Kuhn-Roth oxidation of the 2-methylbutane presented a major problem because of the volatility and inertness of the hydrocarbon and because of the fact that it could not be separated from the solvent, CH_2Cl_2. Consequently, the reaction, carried out in a sealed tube, proceeded with very low yield, 0.4−1% based on tritiated aldehyde, but did produce sufficient amounts of acetic acid for configurational analysis. The two acetate samples were isolated and purified by steam distillation and subjected to enzymatic chirality analysis of the methyl group by the method of Cornforth [18] and Arigoni [19], using a procedure routinely employed in our laboratory [20]. This method of analysis involves activation of acetate to acetyl-coenzyme A followed by condensation with glyoxylate, catalyzed by malate synthase, to give malate. A primary deuterium isotope effect in the malate synthase reaction results in an uneven distribution of tritium between the two methylene hydrogens of malate generated from nonracemic, chiral acetate, as revealed by further incubation of the malate with fumarase. The percentage tritium retention in the fumarase reaction, the F value [21], is a measure of the configuration and chiral purity of the methyl group, pure (R)-acetate giving $F=79$ and pure (S)-acetate $F=21$. The chiral purity (enantiomeric excess) is related to the F value as:

$$\text{e.e.} = \frac{|50-F|}{29} \times 100\,[\%].$$

The analysis of the acetate samples from the above reaction sequence gave an F value of 40 for the material derived from (R)-4-methyl-[2-^{2}H$_1$]pentanoic acid, corresponding to 35% e.e. S methyl groups in the acetate. The acetate from the S acid gave $F=59$, corresponding to 31% e.e. R methyl groups. Hence the decarbonylation reaction has proceeded with net retention of configuration at the carbon atom to which the carbonyl group was attached.

Discussion

The observed stereochemistry of the decarbonylation of 4-methyl-[1-^{3}H,2-^{2}H$_1$]pentanal to 2-methyl-[4-^{2}H$_1$,^{3}H]butane, retention of configuration, conforms with that determined for other decarbonylation reactions of, mostly, more crowded systems [1−3]. It also agrees with the stereochemistry of the reverse process, carbonyl insertion reactions [5−7]. This provides further support for the notion [10] that biological carbonyl insertion reactions, even in sterically unhindered cases like the formation of an acetyl group by "carbonyl insertion" into a metal-methyl bond, also proceed with retention of configuration.

The overall conversion of 4-methyl-[2-^{2}H$_1$]pentanoic acid into chiral acetic acid involves a considerable decrease in chiral purity, from 93−94% e.e. to only 31−35% e.e. in the final product. Hence, about 65% of the molecules racemize in the process. The first three steps of the sequence carry no significant risk of racemization, and the chiral purity of the 4-methyl-[1-^{3}H,^{2}H$_1$]pentanal samples should at least approach that of the starting 4-methylpentanoic acid samples. The observed racemization must thus occur in the last two steps, the decarbonylation reaction and the subsequent Kuhn-Roth oxidation. In light of frequent observations of tritium exchange from aromatic [22] and aliphatic [24] methyl groups during Kuhn-Roth oxidations it seems likely that this reaction is responsible for at least some, if not most, of the observed racemization. Thus we think that the degree of stereospecificity of the decarbonylation reaction is much higher than the observed values for enantiomeric purity of starting material and product

would at first glace suggest. Absolutely no racemization was observed in the enzymatic decarbonylation-recarbonylation of acetyl-coenzyme A during the exchange reaction between CO and acetyl-CoA catalyzed by purified CO dehydrogenase from *Clostridium thermoaceticum* [25].

From a practical point of view, the high degree of racemization observed and the low yields encountered made this, conceptually attractive, approach unsuitable as a way of determining the configuration of small samples of 4-methyl-[2-$^2H_1$]pentanoic acid.

Experimental Section

Materials and general methods

Tritiated $NaBH_4$ (5 Ci/mmol) was obtained from Amersham-Searle and $LiAl^2H_4$ (98 atom % ^2H) from Aldrich. All other chemicals were of the highest purity commercially available and were used without further purification.

NMR spectra were recorded on Varian FT-80 JEOL PFT-100 and Bruker WM-300 spectrometers and GC-mass spectra on a Hewlett-Packard 5970A/5790A GC–MS instrument. Radioactive samples were analyzed in a Beckman LS 250 liquid scintillation counter using internal standards of [^{14}C]toluene and [^{3}H]toluene to determine counting efficiencies. The chirality analyses of acetic acid were carried out as previously described [20]; *F* values determined in this way are reproducible to at least ± 2.

Synthesis of (R)- and (S)-4-methyl-[2-$^2H_1$]pentanoic acid

(R)-Leucic acid: To a stirred solution of D-leucine (24.1 g, 180 mmol) in 900 ml of 1 N H_2SO_4 was added 274 ml of 30% aqueous $NaNO_2$ solution during 2 h at 25 °C. Stirring was continued for 19 h, the pH was then adjusted to 1 with 10% H_2SO_4 and the reaction mixture extracted with ether (400 ml, then 2 × 200 ml). The combined ether extracts were washed with water, dried over Na_2SO_4 and evaporated to give an oily residue which crystallized from ether-hexane to yield 17.0 g (71%) of leucic acid as colorless needles. M.p. 72–74 °C; ^{1}H NMR ($CDCl_3$) δ ppm (*J*, Hz) 0.95 (6H, d, $J=5$), 1.7 (3H), 4.39 (1H, t, $J=6$), 7.27 (2H, br s, exchanges with D_2O); $[\alpha]_D^{25}$ +12.6 °C ($c=1.1$, EtOH).

Analogously, L-leucine gave (*S*)-leucic acid, 18.0 g (75%); mp. 72–74 °C; $[\alpha]_D^{25}$ −12.5 °C ($c=1.1$, EtOH).

p-Toluenesulfonyl-(R)-leucic acid methyl ester: Treatment of leucic acid with an ether solution of diazomethane gave the methyl ester in quantitative yield.

R Isomer: b.p.$_{5.5\ Torr}$ 65–66 °C; $[\alpha]_D^{25}$ −3.1 °C ($c=2.5$, $CHCl_3$).

S Isomer: b.p.$_{5.5\ Torr}$ 68 °C; $[\alpha]_D^{25}$ +3.3 °C ($c=4.7$, $CHCl_3$).

A reaction mixture containing (*R*)-leucic acid methyl ester (10.0 g, 68 mmol) and *p*-toluenesulfonyl chloride (15.0 g, 78 mmol) in 120 ml dry pyridine was kept at 0 °C for 24 h and then poured into ice-water (300 ml). The mixture was extracted with ether (250 ml, then 2 × 100 ml) and the combined extracts were washed with 6 N HCl (2 × 100 ml) and water (4 × 100 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the product as an oil which failed to crystallize. Yield 18.4 g (90%); ^{1}H NMR ($CDCl_3$), 0.80 (3H, d, $J=5$), 0.90 (3H, d, $J=5$), 1.4–1.9 (3H, m), 2.48 (3H, s), 3.70 (3H, s), 4.9 (1H, m), 7.49 (2H, d, $J=10$), 7.99 (2H, d, $J=10$); $[\alpha]_D^{25}$ +29.0 °C ($c=1.45$, CCl_4).

The corresponding *S* isomer crystallized from petroleum ether to give 16.6 g (81.2%) colorless crystals; m.p. 26–27 °C; $[\alpha]_D^{25}$ −31.3 °C ($c=0.97$, CCl_4).

(S)-4-Methyl-[1,1,2-$^2H_3$]pentan-1-ol: To a suspension of $LiAl^2H_4$ (3.0 g, 71 mmol) in 120 ml of absolute ether was added dropwise a solution of *p*-toluenesulfonyl-(*R*)-leucic acid methyl ester (16.9 g, 56 mmol) in 30 ml absolute ether over a period of 30 min under gentle reflux. After stirring for an additional hour under reflux, excess $LiAl^2H_4$ was decomposed with water and 150 ml 5% H_2SO_4 was added to hydrolyze the product complex. The ether layer was decanted and the aqueous layer was further extracted with ether (150 ml, then 3 × 100 ml). The combined ether layers were washed with water (2 × 100 ml) and dried over Na_2SO_4. Evaporation of the solvent and fractional distillation gave 3.71 g (63%) of a colorless oil of b.p.$_{5\ Torr}$ 51–53 °C. IR (liq. film), λ_{max} cm^{-1} 3320, 2940, 2900, 2860, 2200, 2090, 1460, 1380, 1120, 970; ^{1}H NMR ($CDCl_3$) 0.91 (6H, d, $J=6$), 1.0–1.8 (4H, m), 2.13 (1H, br s), no signal at 3.70 (unlabeled compound shows triplet, 2H); $[\alpha]_D^{25}$ −1.82 °C ($c=4.68$, $CHCl_3$).

R Isomer: colorless liquid, 4.24 g (72%), b.p.$_{5\ Torr}$ 47–50 °C, $[\alpha]_D^{25}$ +1.03 °C ($c=9.8$, $CHCl_3$).

(S)-4-Methyl-[2-$^2H_1$]pentanoic acid: Platinum oxide (1.1 g) in 40 ml of hexane was reduced with

hydrogen gas for 30 min. After flushing with nitrogen, (*S*)-4-methyl-[1,1,2-$^2H_3$]pentan-1-ol (3.1 g, 30 mmol) was added and oxidized in an atmosphere of O_2 gas for 3 days at 25 °C. The catalyst was removed by filtration, the solvent evaporated under slightly reduced pressure and the residue distilled to give 1.92 g (55%) of a colorless oil of b.p.$_{.5\ Torr}$ 79–83 °C. IR (liq. film) 2940, 2860, 1700, 1460, 1405; ^{1}H NMR ($CDCl_3$) 0.90 (6H, d, $J=6$), 1.4–1.7 (3H, m), 2.33 (1H, tt, $J=8$, $J_{HD}=2$), 9.8 (1H, br s); $[\alpha]_D^{25}$ −1.98 °C ($c=9.8$, $CHCl_3$); MS (methyl ester) *m/z* (% rel intensity) 116 (M^+-1) (2), 100 (18), 88 (45), 75 (100), 73 (23), 56 (57), 44 (61), 43 (65).

(*R*)-4-Methyl-[2-$^2H_1$]pentanoic acid: 1.22 g (35%) colorless oil, b.p.$_{.5\ Torr}$ 78–83 °C; $[\alpha]_D^{25}$ +0.398 °C ($c=2.26$, $CHCl_3$).

Assay of isotopic and/or stereochemical purity

Leucic acid: The methyl esters of (*R*)- and (*S*)-leucic acid (8 mg each) were treated with a slight excess of (−)-camphanic acid chloride (Aldrich) in 1 ml of CH_2Cl_2 containing 3 drops of pyridine overnight at 25 °C. The resulting camphanate esters were analyzed by GC–MS (20 m capillary column SPB-5, temp. gradient 4 min at 60 °C, then 10 °C/min, split ratio 20:1). The derivative of (*R*)-leucate gave a major peak (M^+326) at 18.01 min and a minor one at 18.23 min (ratio 76:1), and the derivative of the *S* isomer gave a major peak at 18.30 min and a minor one at 17.96 min (ratio 230:1).

4-Methyl-[2-$^2H_1$]pentanoic acid: The isotopic enrichment was assayed by esterifying the acids with CH_2N_2 followed by GC–MS analysis of the esters (40 °C isothermal, retention time 3.4 min). Since the molecular ion was very weak, the deuterium content was calculated from the ratio of *m/z* 74:75 of the fragment ion $C_3H_6O_2/C_3H_5{}^2HO_2$ resulting from a McLafferty rearrangement. The isotopic enrichments were 97% (*S* isomer) and 98% (*R* isomer). The chiral purity was assayed by treating the acids (35 mg each) with methyl (*S*)-mandelate (Aldrich) and dicyclohexylcarbodiimide and a catalytic amount of dimethylaminopyridine in 1 ml of CH_2Cl_2 at 25 °C for 22 h [16]. The resulting mandelate esters were purified by preparative layer chromatography (silica gel, ethyl acetate:hexane 1:2) and analyzed by ^{1}H NMR spectroscopy (300 MHz, d_6-benzene) with deuterium broadband and proton single frequency (1.6 ppm, C-3 protons) decoupling. Integration of the signals for the C-2 protons at 2.36 ppm (major signal in *S,S* diastereomer) and 2.26 ppm (major signal in *R,S* diastereomer) indicated stereochemical purities of 93% e.e. and 94% e.e., respectively.

Chiral acetic acid from 4-methyl-[2-$^2H_1$]pentanoic acid

(S)-4-Methyl-[1-^{3}H,2-$^2H_1$]pentan-1-ol: Tritiated $NaBH_4$ (5 Ci/mmol, 100 mCi, 20 μmol) was reacted with LiCl (0.85 mg, 20 μmol) in 0.5 ml of diglyme in a sealed tube, and the supernatant was used as the [^{3}H]$LiBH_4$ solution.

(*S*)-4-Methyl-[2-$^2H_1$]pentanoic acid (45 mg, 390 μmol) was dissolved in 4 ml of dry tetrahydrofuran (THF) and treated with an anhydrous solution of CH_2N_2 in ether until a slight yellow color persisted. To this solution was added 40 μl of a 1 M solution of unlabeled $LiBH_4$ in THF and the mixture was kept for 15 h at 25 °C in a sealed tube. The tube was then opened, approximately one third of the [^{3}H]$LiBH_4$ solution was added and the tube was resealed. After 7 h at 70 °C, 2 g of unlabeled 4-methylpentan-1-ol and 10 ml water were added and the mixture was extracted with ether (2×5 ml). The ether extract was washed with 0.5 N NaOH (3 ml) and water (2×5 ml) and dried over Na_2SO_4. Distillation gave 1.41 g of (*S*)-4-methyl-[1-^{3}H,2-$^{2-}H_1$]pentan-1-ol containing 0.95 mCi of tritium. Analogously, the *R* acid gave 1.44 g of (*R*)-4-methyl-[1-^{3}H,2-$^2H_1$]pentan-1-ol containing 6.6 mCi of tritium.

(S)-4-Methyl-[1-^{3}H,2-$^2H_1$]pentanal: The *S* alcohol (1.02 g, 10 mmol) was oxidized to the aldehyde by treatment with CrO_3 (6.0 g, 60 mmol) and pyridine (9.49 g, 120 mmol) in 125 ml of CH_2Cl_2. After 15 min the organic layer was separated and the residue washed with 50 ml of ether. The combined organic phases were successively washed with 5% NaOH (50 ml), 5% HCl (50 ml), 5% $NaHCO_3$ solution (50 ml) and brine (50 ml) and dried over Na_2SO_4. Distillation gave 357 mg (35.7%) of the *S* aldehyde containing 0.11 mCi of tritium. Analogously, oxidation of the *R* alcohol gave 262 mg (26.2%) of the *R* aldehyde containing 0.66 mCi of tritium.

(R)-[2-$^2H_1$,^{3}H]Acetic acid: (*S*)-4-methyl-[1-^{3}H,2–$^2H_1$]pentanal (25 μl, 0.2 mmol, 6.94 μCi) was dissolved with tris(triphenylphosphine)rhodium chloride (200 mg, 0.22 mmol) in 3 ml of CH_2Cl_2 in a tightly capped 10 ml flask. After 24 h at 25 °C, the

organic layer was distilled into another flask on a vacuum bridge to give about 2 ml of solvent containing 2-methyl-[^{3}H]butane (2.42 μCi). This distillate and an oxidizing solution consisting of 2 ml of water, 0.5 ml of conc. H_2SO_4 and 0.34 g of CrO_3 were sealed in an ampoule and heated, with occasional shaking, first for 10 min at 50 °C and then for 1.5 h at 135 °C. The ampoule was then opened and the acetic acid formed was recovered by steam distillation. Titration of the distillate to pH 8 with 0.1 N NaOH and evaporation in a vacuum gave sodium acetate (0.026 μCi) for chirality analysis.

Analogously, decarbonylation of the *R* aldehyde (64 μCi) gave a solution containing 2-methylbutane (50.5 μCi) which upon Kuhn-Roth oxidation produced 0.66 μCi of sodium acetate.

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