Optical Resolution of 1-Hydroxyethylphosphinic Acid and Its Esters

Mitsuru Sasaki

Pesticides Research Laboratory, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., Takatsukasa 4-2-1, Takarazuka, Hyogo 665, Japan

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1-Hydroxyethylphosphinic acid (1) is of interest in a study of biological activity as it is perhaps the closest phosphorus analog of lactic acid. Although the synthesis of racemic 1 has been achieved in several ways, no report has yet appeared on resolution of the optical isomers at the C-1 position. This paper deals with the optical resolution of 1 and its esters.

Both enantiomers of 1-hydroxyethylphosphinic acid were obtained by resolution of the racemic acid using (+) and (-)-l-(1-naphthyl)ethylamine as the resolving agents, and the (+)-isomer was assigned to be (S)-configuration. The four diastereomers of butyl 1-hydroxyethylphosphinates were prepared in an optically pure state by reacting the resolved acid with 1-butanol in benzene and then separating the diastereomeric products by chromatographic means.

1-Hydroxyethylphosphinic acid (1) is of interest in a study of biological activity as it is perhaps the closest phosphorus analog of lactic acid. Although the synthesis of racemic 1 has been achieved in several ways, no report has yet appeared on resolution of the optical isomers at the C-1 position. This paper deals with the optical resolution of 1 and its esters.

The diastereomeric salt prepared by mixing (±)-1 and optically active l-(1-naphthyl)ethylamine in methanol was recrystallized three times from methanol-acetonitrile to give the resolved salt in a 20~30% yield. The salt was transformed to the free acid in a high yield by using a cation exchange resin in methanol. The attempted resolution using 1-phenylethylamine as a chiral base was not achieved because crystallization of the diastereomeric salt was not possible.

The absolute configuration of the resolved acid was determined by employing the partial resolution method. The (+)-phosphinic acid, (+)-1, was converted by successive oxidation with bromine and esterification with diazomethane to (+)-dimethyl 1-hydroxyethylphosphonate (+)-3. The phosphonate was then esterified with (+)-2-phenylbutanoic anhydride in pyridine. The 2-phenylbutanoic acid recovered in a 75.6% optical yield was found to be dextrorotatory. This enabled us to assign a (S)-configuration to (+)-1, (+)-2 and (+)-3, as previously established with (−)-dimethyl 1-hydroxypropylphosphonate (6), the ethyl homolog of (−)-3 derived from phosphonomycin (5). It is worth noting that although the phosphoryl group of (R)-(−)-3 is placed on the same side as the carbonyl group of (S)-(−)-4, both groups may contribute to levorotatory power.

The partially resolved acids 1 [(+) rich, $\left[\alpha\right]_D^{23} + 8.8^\circ$, and (−)-rich, $\left[\alpha\right]_D^{23} - 6.4^\circ$] were con-

![Fig. 1. Determination of the Absolute Configuration at C-1.](image-url)
verted to the corresponding (+)-enriched 3 ([z]_D^{23} + 3.0°) and (−)-enriched 3 ([z]_D^{23} - 2.2°) by the method already described. Their NMR spectra were recorded at 200 MHz in the presence of the chiral shift reagent, tris-3-(trifluoromethylhydroxymethylene)-d-camphorato europium(III) [Eu(tfc)_3]. The optical purities of these enantiomers were then calculated from the ratio of well-separated NMR signals for the P-OCH_3 protons, as illustrated in Fig. 2. Interestingly, the methoxy signals of (R)-(−)-3 were observed between those of (−)-(+)−3. During the conversion of 1 to 3, racemization should not occur at C-1. Based on this assumption, the optical purity of the initial (+)-1 showing [z]_D^{23} + 8.8° was calculated as 82% from A, with that of (−)-1 showing [z]_D^{23} - 6.4° as 47% from B. Because no extra peak in the P-OCH_3 regions was detected when measuring its NMR spectrum under the same conditions as those already described, the optical purity of 1 having the highest specific rotation (12) was approximated to be over 95%. In order to estimate the optical purity of 1 more precisely, the resolved acid was esterified with diazomethane to give a diastereomeric mixture of methyl 1-hydroxyethylphosphinate (7) in a 95% yield. Comparison between the 60 MHz NMR spectra of (+)-7 with (−)-7 and that of (±)-7 enabled us to estimate the optical purity of 1, as shown in Fig. 3. The racemate showed three peaks at δ 11.30, 11.40 and 11.50 ppm with a 1:1:2 ratio (Fig. 3a). Upon the addition of Eu(tfc)_3, one of the signals shifted in the lower field and separated cleanly into two peaks (δ 12.90 and 13.10 ppm) with a 1:1 ratio (Fig. 3b). This observation implies the lanthanide-induced separation of signals due to the 1/2 protons of one pair of diastereomers (7). Also, the unshifted signals due to the 1/2 protons of another pair of diastereomers appeared as a doublet centered at δ 11.45 ppm (J = 3.0 Hz), which were hard to separate by adding the chiral shift reagent. The ratio of the shifted
to the unshifted signals was found to be ca. 1:1. In contrast, a singlet peak was observed at δ 13.10 ppm in the case of (+)-7, and at δ 12.90 ppm in the case of (-)-7 by measuring the NMR spectrum of the optically active diastereomers under the same conditions as those for the racemate (7), (Figs. 3c and 3d). When the NMR spectrum of an equimolar mixture of the racemate and (+)-7 was recorded under the same conditions, the ratio of the signal at δ 13.10 ppm to the signal at δ 12.90 ppm was found to be 3:1 (Fig. 3e). These observations led us to believe that the diastereomeric ratio of 7 was ca. 1:1, and that the resolved acid 1 was in an optically pure state. It was impossible to separate each diastereomer of 7 by chromatographic means, possibly due to high polarity of the methyl ester.

To increase the lipophilicity of the ester, (+)-butyl 1-hydroxyethylphosphinate [(+)-8] was prepared as a diastereomeric mixture in a 95% yield by reacting (S)-(+)-1 with 1-butanol in benzene. The diastereomeric ratio of (+)-8 was estimated to be ca. 1:1 by measuring its 1H-NMR in the same manner as that for the methyl ester (7). These diastereomers were cleanly separated by using column chromatography over silica gel to give (-)-8A and (+)-8B. The absolute configuration of the resolved (-)-8A and (+)-8B was tentatively assigned by comparing their IR and 1H-NMR spectra, the IR spectra of both diastereomers exhibiting the presence of intramolecular hydrogen bonding between the P=O and OH functions. The coupling constants of the vicinal protons (HCPH) differed significantly between the diastereomers: (-)-8A (0.3 Hz) eluted in the earlier fraction had a smaller J value than (+)-8B (3.0 Hz) eluted in the later fraction. These facts enabled us to deduce the steric structure of the product. As shown in the Newman projection of Fig. 4, there exists a diastereomer which can easily form intramolecular hydrogen bonding between the P=O and OH functions. Its strong hydrogen bonding makes it easy to maintain nearly 90° of dihedral angle between the PH and CH planes. This corresponds to (-)-8A having a smaller J value (0.3 Hz), and therefore its absolute configuration is assigned to be (S)c(R)p. On the other hand, there exists another diastereomer which cannot easily form intramolecular hydrogen bonding between the P=O and OH functions because of steric repulsion between the methyl group and the butoxy group. This corresponds to (+)-8B having a larger J value (3.0 Hz) and (S)c(S)p stereochemistry. In a similar manner, (+)-8C and (-)-8D were prepared by using (R)-(-)-1 as the starting material in place of (+)-1 with the results summarized in Table I. The data in Table I show that (-)-8A and (+)-8C are one pair of enantiomers, while (+)-8B and (-)-8D are another. A further study on the biological evaluation of 1 and related compounds is in progress and the results will be reported elsewhere.
EXPERIMENTAL

IR spectra were measured with a Hitachi 270-30 spectrophotometer. 1H-NMR spectra were recorded with tetramethylsilane as an internal standard on a Hitachi R-24 A spectrometer (60 MHz) or on a JOEL JNM-ML 200 spectrometer (200 MHz). 31P-NMR were recorded on a Hitachi R-90 spectrometer using 85% phosphoric acid as an external standard at 36.5 MHz. Optical rotations were measured with a JASCO DIP-181 digital polarimeter.

Optical resolution of 1-hydroxyethylphosphinic acid. The racemic 1 (160.8 g, 1.46 mol) and (R)-(+) -1-(1-naphthyl)ethylamine (250 g, 1.46 mol) were mixed in MeOH (500 ml). After evaporating the MeOH, the product (410.0 g) was recrystallized from water-MeCN (1:1, each 300 ml) to give the dextrorotatory salt (43.6 g, 21.3% yield of the theoretical amount of the optical isomer, mp 180~181°C, [α]D25 +13.2° (c=2.0, ethanol)). The salt (40 g) was treated with a cation exchange resin (Dowex 50 W, H+ form, 100 g) in MeOH (300 ml) for 3 hr. After removing the resin, the solution was concentrated in vacuo to give 15.3 g (+)-1 in a 97.7% yield, nD25 1.4765, [α]D25 +12.0° (c=2.0, H2O).

In a similar manner, (−)-1 [nD25 1.4760, [α]D25 -12.0° (c=2.0, H2O)] was prepared from the salt [mp 180~181°C, [α]D25 -13.3° (c=2.0, ethanol)] which was obtained by mixing (+)-1 and (S)-(+)-1-(1-naphthyl)ethylamine. The partially resolved acids ((+)-1, [α]D25 +8.8° (c=2.0, H2O) and (−)-1, [α]D25 -6.4° (c=2.0, H2O)) were converted by the method described later to dimethyl 1-hydroxyethylphosphonate (3). 1H-NMR spectra of the esters in the presence of a chiral shift reagent were measured at 200 MHz, as illustrated in Fig. 2. In the case of (+)-1 and (−)-1 having the highest specific rotation value (12), no extra peak in the P-OCH3 regions was detected under the conditions already described.

Determination of the absolute configuration at C-1. Bromine (1.6 g, 10 mmol) was added to a ice-cooled solution of (+)-1 (1.10 g, 10 mmol, [α]D25 +12° (c=2.0, H2O)) in water (10 ml). The mixture was stirred overnight at room temperature and concentrated in vacuo to give 1.25 g of (+)-1-hydroxyethylphosphonic acid (2) in a 99.7% yield, [α]D25 +4.0° (c=0.5, H2O). The phosphonic acid (1.25 g) was esterified with CH2N2 in ether-THF to give 1.28 g of (+)-dimethyl 1-hydroxyethylphosphonate (3) in a 90% yield, [α]D25 +4.2° (c=0.5, MeOH). The phosphonate (154 mg) was added to a stirred and ice-cooled (0~2°C) solution of (+)-2-phenylbutanoic anhydride (620 mg) in dry pyridine (5 ml). After 16 hrs, 0.5 ml of water was added in one portion and the resulting mixture was gradually warmed to room temperature. The mixture was diluted with benzene (5 ml) and neutralized with 1.N NaOH (3.40 ml). The aqueous layer was separated, acidified with 10% HCl and extracted with benzene. The benzene layer was dried (MgSO4), filtered and concentrated in vacuo to give 166 mg of (+)-2-phenylbutanoic acid in a 75.6% optical yield, [α]D25 +14.6° (c=1.66, benzene). According to Horeau and Kagan, (+)-1 was assigned to be of (S)-configuration.

Esterification of 1 with CH2N2. The racemic 1 (5.5 g, 50 mmol) was esterified with CH2N2 in ether-THF to give 5.9 g of methyl 1-hydroxyethylphosphinate (7) in a 95% yield, bp 98~100°C/0.15mmHg; nD25 1.4563; IR νmax (cm-1): 3300 (OH), 2510 (P=O); 1H-NMR δ (MeCl4): 1.20~1.75 (3H, m, CH3), 3.90~4.20 (1H, m), 3.90 (3H, d, J=12 Hz, CH3O), 4.40 (1H, bs, CH2), 6.50 (1H, dd, J=6.0 Hz, J=5.0 Hz, CH3), 7.10 (1H, d, J=8.0 Hz, CH3). In a similar manner, 1.1 g of (+)-1 gave 1.13 g of (+)-7, [α]D25 +6.9° (c=0.5, CHCl3), while 1.1 g of (−)-1 gave 1.2 g of (−)-7, [α]D25 -7.1° (c=0.5, CHCl3). The esters obtained were used for a direct estimation of optical purity as shown in Fig. 3.

Esterification of 1 with 1-butanol. A mixture of (+)-1 (2.20 g, 20 mmol) and 1-butanol (5 ml) in benzene (20 ml) was heated under reflux for 5 hr. The cooled solution was washed with water, dried (MgSO4) and concentrated in vacuo to give a diastereomeric mixture of 8 (2.63 g, 95%, [α]D25 +10.3° (c=0.5, CHCl3)). This was chromatographed over SiO2 (Merck Kieselgel 60, 70~230 mesh, 100 g) in ethyl acetate, the eluent being monitored by measuring its NMR spectrum. The unresolved fractions were rechromatographed on the same column. The first major fraction to be eluted was (−)-8A, 0.43 g, [α]D25 1.4490, [α]D25 -2.6° (c=0.5, CHCl3); IR ν(CH3) cm-1: 3304 (OH), 3160, 2254 (P=O); 1H-NMR δ (MeCl4): 1.20-1.75 (3H, m, CH3), 3.90~4.25 (2H, m), 7.00 (1H, d, J=5.0 Hz, CH3). In a similar manner, 1.1 g of (−)-1 gave 1.2 g of (−)-7, [α]D25 -7.1° (c=0.5, CHCl3). The esters obtained were used for a direct estimation of optical purity as shown in Fig. 3.

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REFERENCES
1-Hydroxyethylphosphinic Acid


