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The first separation and stereochemical determination of bis(α-hydroxyalkyl) phosphinic acids diastereoisomers

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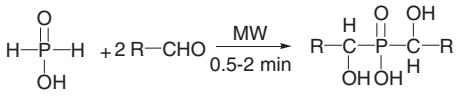
Abstract—A separation of bis(α-hydroxyalkyl) phosphinic acid diastereoisomers is described. A novel method for the determination stereochemistry of bis(α-hydroxyalkyl) phosphinic acid diastereoisomers has been developed. The stereochemistry of one diastereoisomer was confirmed after converting to the corresponding methyl ester using trimethyl orthoformate.

α-Functionalized phosphinic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates.[1–4] Among the α-functional phosphinic acids, α-hydroxyphosphinic acids are an important class of compounds that exhibit a variety of interesting and useful properties.[5–10] In recent years, the preparation of α-hydroxyphosphinic acids has attracted attention due to their biological activities with broad applications as enzyme inhibitors or as dinucleotide analogues having antiviral properties.[11] In addition, they are useful intermediates in the synthesis of other phosphorus compounds.[12,13] These compounds may also be used as precursors for the synthesis of organophosphorus polymers possessing flame-resistant, corrosion-resistant and ion-exchange properties.[14,15] Indeed, α-hydroxyphosphinic acids are used as extractants for the recovery or separation of some metal ions.[16] As part of our efforts to explore the use of microwave-assisted reactions for the synthesis of organophosphorus compounds,[17] we recently described a new method for the preparation of bis(α-hydroxyalkyl) phosphinic acids from the reactions of hypophosphorous acid with aldehydes using microwave irradiation, which produces high yields of bis(α-hydroxyalkyl) phosphinic acids.[18] In contrast to the widely studied separation and stereochemical determination of α-hydroxyphosphonic acid diastereomers,[19] we did not find any report on the separation and structure determination of bis(α-hydroxyalkyl) phosphinic acid diastereoisomers. Herein, we report the first method for the separation and determination of stereochemistry of bis(α-hydroxyalkyl) phosphinic acid diastereoisomers.

We carried out the reaction of benzaldehyde with hypophosphorus acid under microwave irradiation to afford bis(α-hydroxyphenylmethyl) phosphinic acid in 82% yield after 0.5 min. ^{31}P NMR spectrum of **2a** exhibited two peaks at δ 38.74 and 36.59 ppm due to the diastereoisomers. ^{1}H NMR spectrum of **2a** exhibited two doublets at δ 5.14 and 4.84 ppm indicative of HC-P coupling ($J_{HP} = 7.4$ Hz). Due to the presence of two stereogenic carbons bonded to the phosphorus atom, and the phosphorus atom itself being a pseudo-asymmetric center,[20] these compounds exist as three diastereomeric forms: two meso (*syn*) and one racemic pair (*anti*). However, ^{31}P and ^{1}H NMR spectra exhibit degeneracies due to the rapid prototopic transfer of the acidic proton between the phosphoryl (P=O) and acidic (P–OH) sites and only two signals are observed, corresponding to the racemic form *R*,*R*/*S*,*S* and the meso (*R*,*S*). We found that when the reaction mixture was subjected to washing with nonpolar and polar solvents, only one diastereomer was extracted using methanol (Schemes 1 and 2).



1 2

Scheme 1.

Keywords: Phosphinic acids; Stereochemistry; Microwave; Trimethyl orthoformate.
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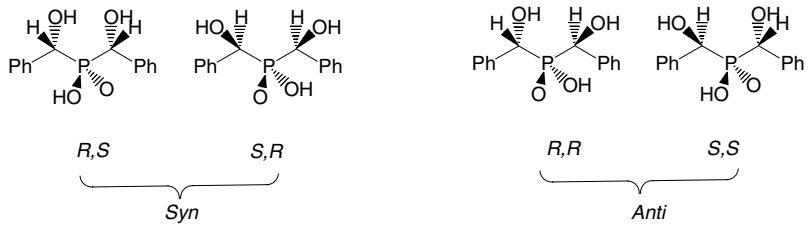
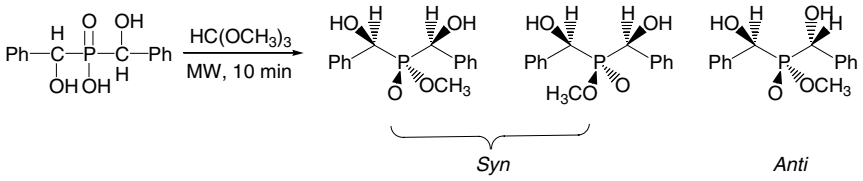


Scheme 2.



Scheme 3.

The stereochemistry of this diastereoisomer was confirmed after converting to the corresponding methyl ester using trimethyl orthoformate under microwave irradiation for 10 min.[21] This reaction failed after 24 h without microwave irradiation. The *syn* methyl ester would be formed as a mixture of two diastereoisomers, due to the new stereogenic center at the phosphorus atom, whilst the *anti* as a *dl* pair would have only one stereoisomer. ^{31}P NMR spectrum of the methyl ester exhibited only one major peak at δ 44.98 ppm (Scheme 3). On the other hand, ^{13}C NMR of the methyl ester exhibited two doublet peaks at 68.3 and 69.0 for two C–P groups. On the basis of these results, the diastereoisomer assigned as the *anti*. On the other hand, methylation of a mixture of the two diastereomeric bis(α-hydroxyphenylmethyl) phosphinic acids showed three peaks in ^{31}P NMR spectrum due to the three diastereomeric forms, the *syn* and *anti* diastereomers (Scheme 3).

Further investigations on this reaction are now in progress.

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20. Hypophosphorus acid 10 mmol (50%) was added to 30 mmol of benzaldehyde and the mixture irradiated with microwaves for 0.5 min at 180 W (a kitchen-type microwave was used in all experiments). After irradiation, 50 ml of ethyl acetate was added and the reaction mixture was stirred for 5 min. *n*-Hexane (50 ml) was added to this mixture and a white powder precipitated. The precipitated bis(α-hydroxyalkyl)phosphinic acid was filtered. For the separation of diastereoisomers, a simple washing with nonpolar to polar solvents (*n*-hexane to EtOAc) then washing with methanol (300 mL), gave the *anti*-diastereoisomer as major diastereoisomer.
21. New procedure for the synthesis of methyl bis(α-hydroxyphenylmethyl) phosphinate: A suspension of bis(α-hydroxyphenylmethyll)phosphinic acid (0.556 g, 0.002 mol) and trimethyl orthoformate (5 ml excess) was irradiated with microwaves for 10 min (step-by-step) at 180 W. The mixture became homogeneous as it was irradiated by microwaves. Volatile compounds were removed in vacuo and then 5 ml of acetone was added to the reaction mixture and stirred for 5 min. *n*-Hexane (50 ml) was added to this mixture and white powder was precipitated. The precipitated methyl bis(α-hydroxyphenylmethyll)phosphinate was filtered and chromatography on a plug of silica gel with *n*-hexane-ethyl acetate (9:1 to 1:9) and evaporation of the solvent under reduced pressure gave the pure product as white crystals in a 65% (0.38 g) yield. Methyl bis(α-hydroxyphenylmethyl) phosphinate: mp 172–174 °C (*n*-hexane–dichloromethane); ^{1}H NMR (CD_3SOCD_3/TMS-500 MHz): 2.95 (d, 3H, $J = 9.4$ Hz), 5.21 (2H, d, $J = 6.9$ Hz), 6.21–6.42 (br, OH), 7.2–7.45 (10H, m); ^{31}P-NMR (CD_3SOCD_3/H_3PO_4): 44.98 ppm; ^{13}C NMR (CD_3SOCD_3/TMS-125.7 MHz): 52.2 (d, $J_{PC} = 7.5$ Hz), 68.3 (d, $J_{PC} = 65.7$ Hz), 69.0 (d, $J_{PC} = 72.3$ Hz), 127.4, 127.6, 127.8, 128.1, 128.2, 138.2 (d, $J_{PC} = 2.9$ Hz), 138.3 (d, $J_{PC} = 2.9$ Hz). Anal. Calcd for $C_{15}H_{17}O_4P$. C, 61.64; H, 5.82. Found: C, 61.38; H, 5.73.