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ABSOLUTE CONFIGURATION OF OPTICALLY ACTIVE AMINOPHOSPHONIC ACIDS

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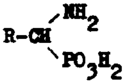
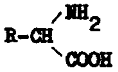
Optically active aminophosphonic acids /I/, interesting as analogs of amino acids II, have received little attention so far. Although there is a large body of information available on the synthesis of racemic aminophosphonic acids[1], only one compound /Ia, R = Ph/ has been obtained optically active by synthesis with asymmetric induction[2] or by resolution of racemate[3]. Both methods yielded pure enantiomers but their absolute configuration has not been established.



$$\text{R-CH}\begin{matrix}\diagup NH_2\\ \diagdown PO_3H_2\end{matrix}$$

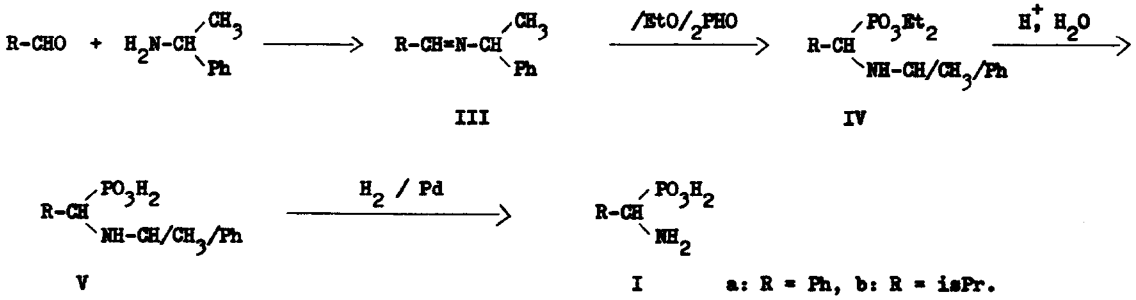
/I/



$$\text{R-CH}\begin{matrix}\diagup NH_2\\ \diagdown COOH\end{matrix}$$

/II/

We now have determined by X-ray crystallographic analysis the absolute configurations of two aminophosphonic acids, Ia and Ib, i. e. of phenylglycine and valine analogs. Optically pure samples of both enantiomers of Ia and Ib were obtained by the asymmetric induction method, described initially by Gilmore and McBride for Ia[2]. The synthesis involved preparation of Schiff's bases III from R/+/ and S/-/-1-phenylethylamine and corresponding aldehydes, addition of diethyl phosphite, hydrolysis and hydrogenolysis.



III IV V I

a: R = Ph, b: R = isPr.

By ^{31}P NMR analysis of crude esters IV we found that diethyl phosphite addition, when carried out

at room temperature without solvent yielded IVa and IVb as mixtures of diastereoisomers formed in ratios of 6:1. At higher temperatures the induction was less pronounced, e. g. heating IIIa with diethyl phosphite at 140° without catalyst, as specified by Gilmore and McBride[2], produced a mixture of diastereoisomeric IVa in a ratio of 2:1. To ensure optical purity of Ia and Ib we purified the N-substituted acids Va and Vb isolating the diastereoisomers formed in larger amounts which upon hydrogenolysis yielded optically active Ia and Ib in total yields of 65-70 %. Final products obtained using R/+/-1-phenylethylamine were levorotatory /Ia: $[\alpha]_D^{20}-18^\circ$, c 2.0, 1N NaOH and Ib: $[\alpha]_D^{20}-10^\circ$, c 2.0, 1N NaOH/, while S/-/-1-phenylethylamine yielded dextrorotatory enantiomers / Ia: $[\alpha]_D^{20}+18^\circ$, c 2.0, 1N NaOH and Ib: $[\alpha]_D^{20}+10^\circ$, c 2.0, 1N NaOH/. Samples for X-ray analysis were crystallized from water.

Direct X-ray analysis of Ia was not possible because of unsuitable properties of crystals and, therefore, the absolute configuration of Ia was determined indirectly from the crystal structure of Va, prepared using S/-/-1-phenylethylamine. Absolute configuration of Ib was determined by measurement of anomalous dispersion on crystals of the levorotatory enantiomer.The crystal structures of Va and Ib were solved by the heavy atom method. The structures were refined using a full-matrix least-squares program with anisotropic thermal parameters for all non-hydrogen atoms.The final values of R were 0.05 /Ib/ and 0.065 /Va/ while the values of R_w were 0.055 /Ib/ and 0.069 /Va/. The intensities were corrected for Lorentz and polarisation factors but not for absorption. Scattering values for neutral atoms, corrected for anomalous dispersion[4] were taken from International Tables for X-Ray Crystallography[5]. All calculations were performed by Syntex XTL Structure Determination System which consists of a Nova 1200 computer and additional external disc memory. The programs were from the Syntex set of programs. The reflections were collected on an automatic Syntex $P2_1$ four-circle diffractometer equipped with a scintillation counter and graphite monochromator.

Compound Ib, $C_4H_{12}NO_3P \cdot H_2O$, is orthorhombic, space group $P2_12_12_1$, with cell dimensions a= 6.596/2/, b = 19.183/4/, c = 6.289/2/ Å as determined from the angular settings of 15 reflections measured using CuK_α radiation /λ= 1.5418 Å/, D_c = 1.428 g/cm^3, D_m = 1.42 g/cm^3, Z = 4, M = 171.13. A total of 657 independent reflections were collected and 624 reflections with $I > 1.96\sigma/I/$ were used for structure determination[6]. Compound Ib has a single asymmetric center at C/1/. The absolute configuration was established by examination of the Friedel pairs of reflections using CuK_α radiation. A group of 49 reflections was chosen with the largest differences between the Friedel pairs. Of 49 unique Friedel pairs examined, 48 indicated the S configuration and only one showed the opposite configuration. Thus, it appears that levorotatory phosphonic valine analog Ib has the configuration S.

Compound Va, $C_{15}H_{18}NO_3P \cdot H_2O$, prepared from S/-/-1-phenylethylamine, is monoclinic, space group $P2_1$ with a = 10.841/4/, b = 6.491/3/, c = 11.846/4/ Å, β = 114.09/5/°, D_c = 1.347 g/cm^3, D_m = 1.35 g/cm^3, Z=2, M = 309.29. A total of 1328 reflections were collected and 1231 reflections with I > 1.96 σ/I/ were used in the analysis. Molecular conformation[7] of Va is shown in Fig. 1.

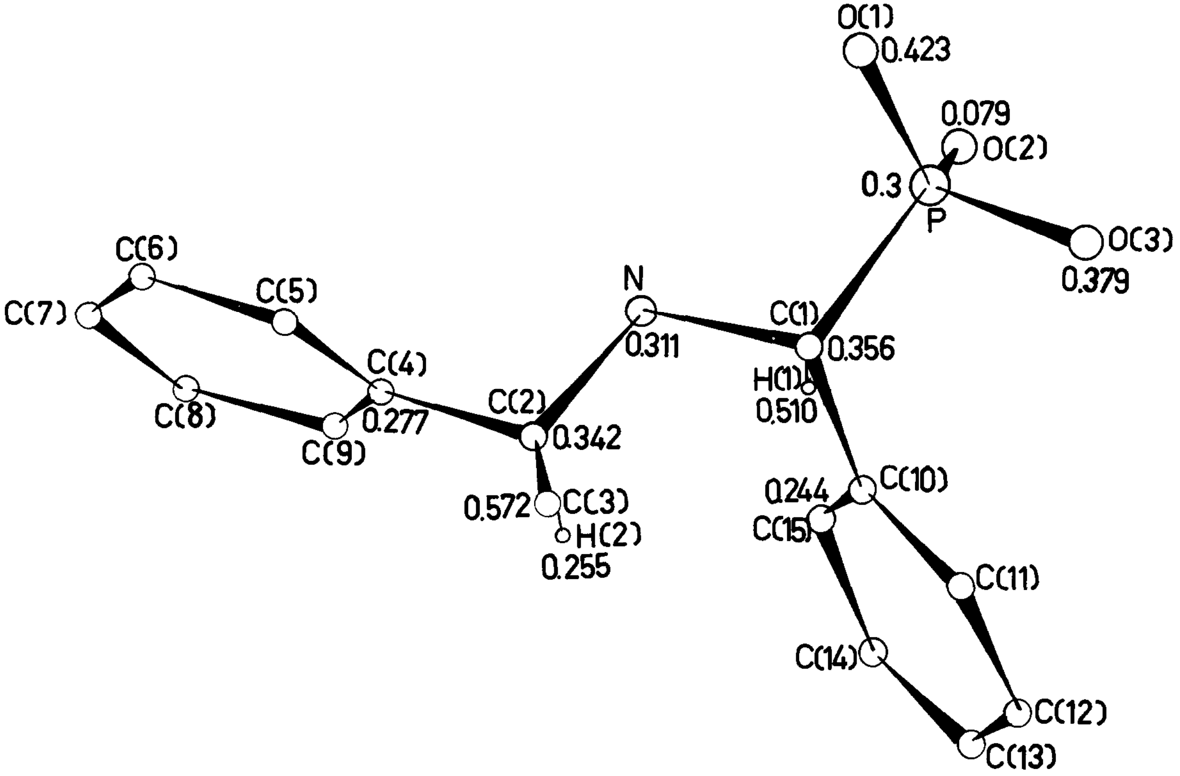
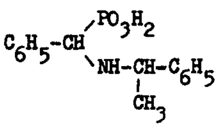


Fig. 1 Molecular conformation of



$$C_6H_5\text{-}CH\begin{matrix}\diagup PO_3H_2\\ \diagdown NH\text{-}\underset{\underset{\displaystyle CH_3}{|}}{CH}\text{-}C_6H_5\end{matrix}$$

The molecule of Va contains two asymmetric carbon atoms at C/1/ and C/2/. Since the compound was prepared from S/-/-1-phenylethylamine and inversion in the process of synthesis is highly unlikely, the conformation shown in Fig. 1 indicates that the configuration at C/1/ is R. Consequently, dextrorotatory Ia, prepared from Va by hydrogenolysis, has the configuration R.

The results indicate that in both examined cases of diethyl phosphite addition to chiral Schiff's bases III, with R in the aldehyde part as different as phenyl and isopropyl, the S amine induces preferentially the configuration R at new asymmetric center. It is interesting to note that, considering the priority rules, the same result was obtained by Harada and Okawara in their studies of hydrogen cyanide addition to chiral Schiff's bases where R aminocarboxylic acids are produced when the bases are prepared from R-α-alkylbenzylamines[8].

Considering that the preferred stereochemistry of diethyl phosphite addition is most probably the same regardless of the structure of R in the aldehyde part of III it should now be possible to establish the absolute configuration of any 1-aminophosphonic acids by synthesis of optically active I as described in this communication.

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