Synthesis, Molecular Structure, and Absolute Configuration of an Optically Active (1-Amino-2-phenylethyl)phosphonic Acid Monohydrate

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Enantiomers of (1-amino-2-phenylethyl)phosphonic acid were obtained by resolution of diethyl (1-amino-2-phenylethyl)phosphonate with dibenzoyl-L-(+)-tartaric acid followed by hydrolysis; *X*-ray analysis shows *S*-(+) configuration for one enantiomer.

Racemic (1-amino-2-phenylethyl)phosphonic acid PheP (**2**), the phosphonic analogue of phenylalanine, strongly inhibits the Phe-t-RNA synthetase[1] and (−)PheP of unknown configuration has been found to interact with rabbit muscle pyruvate kinase, in a mode depending on the pH.[2] Other biochemical interactions of the PheP include transamination with ketoglutarate in mouse tissues[3] and inhibition of one of the key enzymes of plant metabolism, the phenylalanine–ammonia lyase.[4] It is obvious that for biological and biochemical studies it is desirable to know the configuration of optically active enantiomers of (**2**) and the same applies to the phosphonic analogues of other amino acids. So far, only a few optically active (1-aminoalkyl)phosphonic acids have been obtained and the configurations have been unequivocally established only for the phosphonate analogues of valine,[5] alanine,[6] and phenylglycine.[5]

In this study we have synthesized both enantiomers of (**2**) from diethyl (1-oxo-2-phenylethyl)phosphonate, using the reported procedure[7] to obtain racemic (1-amino-2-phenylethyl)phosphonate (**1**).

The resolution of racemic (**1**) (0.7 mol) was easily accomplished with dibenzoyl-L-(+)-tartaric acid (0.35 mol) in an ethanol–methanol mixture. Subsequent partial evaporation of solvent and crystallization of the salt from dioxane, to constant specific rotation,† yielded 122 g (0.2 mol) of a crystalline product $[\alpha]^{20}$ −67.2° (*c* 1.95, MeOH) which was converted to free ester and hydrolysed to afford the dextrorotatory acid (**2**) $[\alpha]^{20}$ +49.9° (*c* 2.0, 1 M NaOH). The residue left after treatment of racemic (**1**) with the resolving agent yielded in the same way the crude levorotatory acid (**2**) $[\alpha]^{20}$ −36.3° (*c* 2.2, 1 M NaOH) and crystallization from water raised the specific rotation to $[\alpha]^{20}$ −49.9° (*c* 1.98, 1 M NaOH). The specific rotation values of these products are closer to the true values than those reported by Stec *et al.*[8]

$PhCH_2CH(NH_2)PO(OR)_2$

(**1**) R = Et
(**2**) R = H

Crystal data‡ for dextrorotatory (**2**): $C_8H_{12}NPO_3 \cdot H_2O$, monoclinic, space group $P2_1$, $a = 6.868(2)$, $b = 5.834(2)$, $c = 13.314(4)$ Å, $\beta = 93.03(3)°$, $Z = 2$, $D_c = 1.37$, $D_m = 1.37$ g cm^{-3}, $\mu(\text{Cu-}K_\alpha) = 22.3$ cm^{-1}. The experimental data were obtained on a Syntex $P2_1$ four-circle diffractometer equipped with a scintillation counter and graphite monochromator. Intensity data were collected by θ—2θ step scans to 2θ = 125°. A total of 951 reflections were collected and 908 reflections with $I > 1.96\,\sigma(I)$ were used in the analysis. The structure was solved by direct methods (MULTAN-78) and refined by a full-matrix least-squares technique with anisotropic thermal parameters for all non-hydrogen atoms. Six of the H atoms were found from the difference Fourier synthesis and the remaining eight were calculated. The intensities were corrected for Lorentz and polarization effects. The scattering factors for the neutral non-hydrogen atoms were corrected for anomalous dispersion.

† All specific rotations quoted were for absorption at 578 nm.

‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

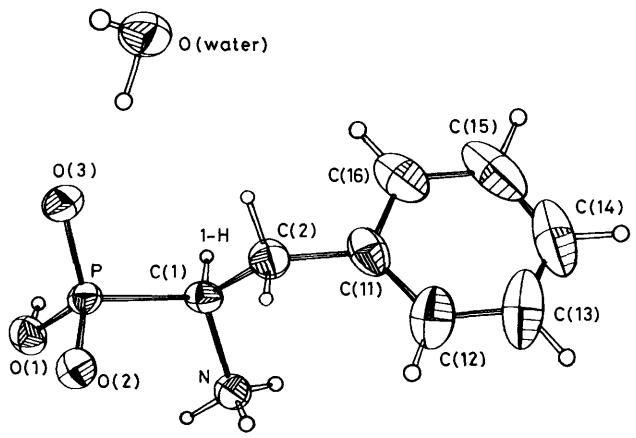

Figure 1. Perspective view of (1-amino-2-phenylethyl)phosphonic acid monohydrate. Important bond distances and angles: P–O(1) 1.573(3), P–O(2) 1.505(3), P–O(3) 1.495(3), P–C(1) 1.826(4), C(1)–N 1.498(3), C(1)–C(2) 1.527(5), C(2)–C(11) 1.501(6), phenyl ring C–C 1.333(13)—1.391(8) Å; O(1)–P–O(2) 106.6(2), –O(3) 112.5(2), –C(1) 104.4(2), O(2)–P–O(3) 117.6(2), –C(1) 109.1(2), O(3)–P–C(1) 105.8(2), P–C(1)–N 110.0(3), P–C(1)–C(2) 111.3(3), N–C(1)–C(2) 111.0(3), C(1)–C(2)–C(11) 115.5(4), phenyl ring C–C–C 121.8(8) —117.5(5)°. Torsion angles: χ^1 [N–C(1)–C(2)–C(11)] 59.1(5), χ^{21} [C(1)–C(2)–C(11)–C(16)] 83.6(5), χ^{22} [C(1)–C(2)–C(11)–C(12)] –99.2(5); ϕ [P–C(1)–C(2)–C(11)] –178.1(3) *trans* configuration; τ [O(1)–P–C(1)–N] –59.0(3)°.

The absolute configuration of (**2**) was established by examination of the Friedel pairs of reflections using Cu-K_α radiation. A group of 87 reflections was chosen with the largest differences between the Friedel pairs. Of 87 unique Friedel pairs examined, 77 indicated the *S* configuration and 10 showed the opposite configuration. The final values of *R* and R_w are 0.038, 0.049, and 0.040, 0.050 for *S* and *R* configuration, respectively. Thus, it appears that dextrorotatory (**2**) has the configuration *S*.

The molecular conformation of PheP (**2**) is shown in Figure 1. No significant deviations from normal values of lengths and angles occur. The conformations about the Cα and Cβ atoms defined by the torsion angles χ^1, χ^{21}, χ^{22} are very close to those found in various phenylalanine derivatives.[9]

An interesting feature of the present structure is the torsion angle τ which has a value [–59.0(3)°] smaller than that in *S*-(+)-AlaP,[10] [–152.3(3)°]. Also, the hydrogen bonding system is different to those observed in other known aminophosphonic acids. It is interesting to note that not all H atoms bound to N and O (water) are involved in hydrogen bond formation. In this structure the molecule exists as a zwitterion.

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