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Structure of 2-Amino-3-phosphonopropionic Acid, $C_3H_8NO_5P$

BY W. SAWKA-DOBROWOLSKA, T. GŁOWIAK AND Z. SIATECKI

Institute of Chemistry, University of Wrocław, F. Joliot-Curie 14, 50-383 *Wrocław, Poland*

AND M. SOROKA

Institute of Organic and Physical Chemistry, Polytechnical University, 50-370 *Wrocław, Poland*

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Abstract. $M_r = 169{\cdot}1$, monoclinic, $C2/c$, $a = 19{\cdot}976\ (7)$, $b = 7{\cdot}028\ (3)$, $c = 10{\cdot}786\ (4)$ Å, $\beta = 121{\cdot}42\ (4)°$, $V = 1292{\cdot}2\ (10)$ Å^3, $Z = 8$, $D_m = 1{\cdot}74\ (1)$, $D_x = 1{\cdot}74$ Mg m^{-3}, $\bar{\lambda}(\text{Cu } K\alpha) = 1{\cdot}5418$ Å, $\mu = 3{\cdot}59$ mm^{-1}, $F(000) = 704$, $T = 293$ K, final $R = 0{\cdot}039$ for 786 observed reflexions. The molecule exists as a zwitterion, $HOOC{-}CH(NH_3^+)CH_2{-}PO_3H^-$. The conformation about the $C^\beta{-}C^\alpha$ bond is *gauche–gauche*, angles φ[P—C—C—C] and φ'[P—C—C—N] 60·1 (4) and −62·1 (4)° respectively. The NMR results show, however, that in aqueous solution the most stable rotamer is that with the phosphonic and carboxyl groups *trans* relative to each other. The crystal structure is stabilized by five intermolecular and one intramolecular hydrogen bond.

Introduction. Replacement of the β-carboxyl group of aspartate by phosphonate (PO_3^{2-}) yields 2-amino-3-phosphonopropionic acid (β-PAsp).

β-PAsp has been found in living organisms (*Zoanthus sociatus, Tetrahymena pyriformis*) and plays an important role not only as a building unit in proteins but also as a precursor in the biosynthesis of 2-aminoethylphosphonic acid (2-AEP) (Hilderbrand, Curley-Joseph, Lubansky & Henderson, 1982).

Furthermore, Roberts, Foster, Sharif & Collins (1982) reported that the phosphonate analogues of the amino acids aspartate and glutamate interact with excitatory amino-acid receptors as excitatory transmitters in the brain in a manner similar to that of aspartate.

The present structural investigation was undertaken as part of our study of the conformation and hydrogen bonding of this biologically important molecule.

Experimental. Synthesis described by Soroka & Mastalerz (1976). Clear, colourless crystals from water at room temperature, dimensions 0·15 × 0·2 × 0·3 mm; density by flotation in carbon tetrachloride/ethylene bromide; monoclinic Cc or $C2/c$ from Weissenberg photographs, $C2/c$ confirmed by refinement; Syntex $P2_1$ computer-controlled four-circle diffractometer, Cu $K\alpha$ radiation, scintillation counter, graphite monochromator; cell parameters by least squares from setting angles of 15 reflexions with $25 \le 2\theta \le 36°$ measured on the diffractometer; 803 independent reflexions; $2\theta_{max} = 114°$; variable θ–2θ scans, scan rate

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2·0–29·3° min^{-1}, depending on intensity; two standards (22$\bar{2}$, 511) measured every 50 reflexions, variation in intensities ±2%; data corrected for Lorentz and polarization, not for absorption; 786 with $I > 1{\cdot}96\sigma(I)$ used for structure determination; index range h 0 to 21, k 0 to 7, l −11 to 9; calculations performed with Syntex (1976) *XTL/XTLE* system; neutral-atom scattering factors from *International Tables for X-ray Crystallography* (1974); direct methods, Syntex (1976) version of *MULTAN* (Germain, Main & Woolfson, 1971); full-matrix least-squares refinement, minimizing $\sum w(|F_o| - |F_c|)^2$, $w = 1/\sigma^2(F)$; difference synthesis revealed H atoms; non-H atoms refined with anisotropic and H atoms with isotropic temperature factors; 123 variables; max. parameter shift in final LS cycle for non-H atoms $0{\cdot}06\sigma$, for H atoms $0{\cdot}12\sigma$; residual electron density in final difference map within −0·14 and +0·15 e $Å^{-3}$; $R = 0{\cdot}039$, $R_w = 0{\cdot}044$, $S = 5{\cdot}13$.

The NMR spectra of the aqueous (D_2O) solutions of β-PAsp and its methylphosphinic analogue (β-PCH_3Asp) were recorded on a 100 MHz JEOL PS 100 spectrometer at 298 K. The proton spectra were analysed as *ABCX* ($X = {}^{31}P$) systems using LAOCN3 (Siatecki & Kozłowski, 1980, 1981).

Discussion. Final atomic parameters are given in Table 1.* The molecular structure and atom numbering are shown in Fig. 1. Bond distances and angles are in Table 2.

The β-PAsp molecule occurs as a zwitterion. The phosphonic group is negatively charged, the charge being equally distributed between O(1) and O(2), P–O lengths being 1·503 (3) and 1·501 (3) Å. The P–O(3) bond length of 1·583 (3) Å indicates a single bond. All P–O lengths agree within the limits of error with similar bonds in 2-aminoethylphosphonic acid (β-ciliatine) (Okaya, 1966), aminomethylphosphonic acid (β-AMPh) (Darriet, Darriet, Cassaigne & Neuzil, 1975) and (1-amino-2-phenylethyl) phosphonic acid (PheP) (Kowalik, Sawka-Dobrowolska & Głowiak, 1984). The P–C length is 1·809 (4) Å which is identical to the P–C bond length of 1·807 (4) Å in the biological compound β-ciliatine.

The O–P–O and O–P–C angles in β-PAsp range from 105·5 (2) to 117·3 (2)°. The smallest angle involves the protonated O(3) and C(1), while the largest angle involves the unsubstituted O(1) and O(2). The above values agree well with those of the corresponding angles in other aminophosphonic acids.

The C(2)–C(3) bond distance of 1·533 (5) Å involving the sp^2-hybridized C atom is significantly longer than the value (1·50 Å) normally associated with a C_{sp^2}–C_{sp^3} single bond, and is similar to the $C(1)_{sp^3}$–$C(2)_{sp^3}$ bond distance of 1·536 (6) Å.

The P–C(1)–C(2) bond angle of 116·4 (3)° is considerably greater than the tetrahedral value. Furthermore, it is about 4° larger than that found in 3-amino-3-phosphonopropionic acid [α-PAsp; 112·5 (3)°] (Sawka-Dobrowolska, Głowiak, Siatecki & Kowalik, 1984).

Table 1. *Positional parameters and isotropic temperature factors with e.s.d.'s in parentheses*

For non-H atoms $B_{eq} = \frac{1}{3}\sum B_{ii}$.

	x	y	z	B_{eq}/B_{iso}(Å²)
P	0·1408 (1)	0·3991 (1)	0·3463 (1)	2·4 (1)
O(1)	0·2211 (1)	0·4129 (3)	0·3669 (2)	2·7 (2)
O(2)	0·1052 (1)	0·5791 (3)	0·3613 (2)	3·2 (2)
O(3)	0·1419 (2)	0·2457 (3)	0·4549 (3)	3·1 (2)
O(4)	0·0654 (2)	−0·1258 (4)	0·1958 (3)	3·4 (2)
O(5)	0·1939 (1)	−0·0750 (4)	0·3052 (3)	3·4 (2)
N	0·1762 (2)	0·2027 (5)	0·1142 (3)	2·7 (2)
C(1)	0·0752 (2)	0·3051 (5)	0·1663 (4)	2·8 (3)
C(2)	0·1066 (2)	0·1394 (5)	0·1181 (4)	2·6 (2)
C(3)	0·1280 (2)	−0·0338 (5)	0·2183 (4)	2·6 (3)
H(1)	0·1187 (21)	0·2163 (51)	0·5070 (37)	2·7 (8)
H(2)	0·0605 (22)	0·4049 (56)	0·0980 (41)	4·0 (9)
H(3)	0·0262 (23)	0·2612 (50)	0·1588 (36)	3·6 (9)
H(4)	0·0648 (21)	0·1111 (49)	0·0188 (40)	3·4 (8)
H(5)	0·2077 (22)	0·2710 (55)	0·1904 (42)	3·6 (9)
H(6)	0·2106 (31)	0·0940 (76)	0·1103 (53)	7·4 (13)
H(7)	0·1568 (29)	0·2920 (76)	0·0270 (54)	7·3 (13)
H(8)	0·0856 (32)	−0·2391 (76)	0·2607 (57)	8·6 (15)

Table 2. *Bond distances* (Å) *and bond angles* (°)

P–O(1)	1·503 (3)	C(1)–C(2)	1·536 (6)
P–O(2)	1·501 (3)	C(2)–N	1·483 (6)
P–O(3)	1·583 (3)	C(2)–C(3)	1·533 (5)
P–C(1)	1·809 (4)	C(3)–O(4)	1·313 (5)
		C(3)–O(5)	1·186 (5)
O(1)–P–O(2)	117·3 (2)	C(1)–C(2)–C(3)	112·2 (3)
O(1)–P–O(3)	109·4 (2)	C(1)–C(2)–N	109·7 (3)
O(1)–P–C(1)	107·6 (2)	C(3)–C(2)–N	109·7 (3)
O(2)–P–O(3)	108·6 (2)	O(4)–C(3)–O(5)	125·6 (4)
O(2)–P–C(1)	107·7 (2)	O(4)–C(3)–C(2)	111·8 (3)
O(3)–P–C(1)	105·5 (2)	O(5)–C(3)–C(2)	122·6 (3)
P–C(1)–C(2)	116·4 (3)		

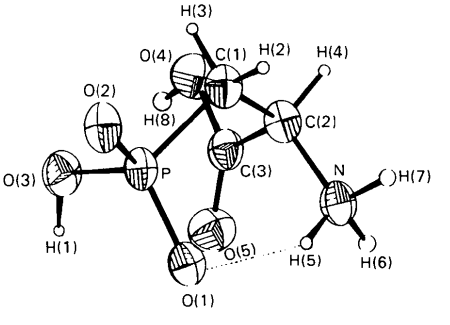

Fig. 1. Perspective view of the title molecule (β-PAsp).

* Lists of structure amplitudes, anisotropic thermal parameters, bond distances and angles involving H, hydrogen-bond distances and angles, torsion angles and ^1H NMR spectroscopic parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39835 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

The carboxyl group is planar and protonated. The two C—O lengths corresponding to C=O and C—OH bonds are 1·186 (5) and 1·313 (5) Å respectively. They are within 3σ of the average values of 1·221 (3) and 1·304 (3) Å in DL and L-aspartic acid (Rao, 1973; Derissen, Endeman & Peerdeman, 1968). The two O—C—C angles differ from each other, being 122·6 (3) and 111·8 (3)° (Marsh & Donohue, 1967). The angle O—C—O of 125·6 (4)° compares well with those found in amino acids.

The maximum deviation from the least-squares plane through the carboxyl group, O(4), O(5), C(3) and C(2), is 0·003 (4) Å. The distance of N from this plane is 0·417 (3) Å.

The conformation of the alanine residue is defined by the torsion angles O(5)—C(3)—C(2)—N (ψ_1) and O(4)—C(3)—C(2)—N (ψ_2), describing the orientation of the two C′—O bonds about C^{α}—C′. The values of ψ_1 and ψ_2 are 17·8 (5) and −162·8 (4)°. The side-chain conformation is given by the torsion angles P—C(1)—C(2)—C(3) (φ) and P—C(1)—C(2)—N (φ'); these values are 60·1 (4) and −62·1 (4)°. The conformation is such that the amino and carboxyl groups are both *gauche* with respect to the phosphonic acid group. Thus, the conformation about C^{β}—C^{α} is different from that found in α-PAsp where the phosphonic acid group is *trans* to the carboxyl group. The torsion angle HO(3)—P—C(1)—C(2) of −74·1 (4)° is, however, within about 17·0° of that observed in α-PAsp [91·1 (3)°].

One of the most important aspects of this structure is the hydrogen-bonding pattern. The conformation of the molecule is stabilized by the formation of an intramolecular hydrogen bond between the amino group and the O atom of the phosphonic group. The intramolecular distance between H(5) and O(1) is 2·04 (4) Å and between N and O(1) 2·805 (4) Å. The angle N—H(5)···O(1) is 145 (4)°. In addition, H(5) participates in a second hydrogen bond involving O(5) of the carboxyl group from a neighbouring molecule {N[H(5)]···O(5)($\frac{1}{2}-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$) 2·753 (5), H(5)···O(5) 2·22 (5) Å, N—H(5)···O(5) 119 (4)°}. Two other hydrogen bonds link the molecules into zigzag chains along the *b* axis {O(4)[H(8)]···O(2)(x, $y-1$, z) 2·577 (3), H(8)···O(2) 1·58 (5) Å, O(4)—H(8)···O(2) 171 (6)° and N[H(6)]···O(1)($\frac{1}{2}-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$) 2·821 (4), H(6)···O(1) 1·79 (6) Å, N—H(6)···O(1) 171 (5)°}. Two further hydrogen bonds link molecules in the **c** direction {O(3)[H(1)]···O(1)($\frac{1}{2}-x$, $\frac{1}{2}-y$, $1-z$) 2·636 (4), H(1)···O(1) 1·84 (4) Å, O(3)—H(1)···O(1) 162 (4)° and N[H(7)]···O(2)(x, $1-y$, $-\frac{1}{2}+z$) 2·788 (4), H(7)···O(2) 1·78 (5) Å, N—H(7)···O(2) 169 (5)°}.

NMR results. The conformational analysis of β-PAsp in aqueous solution (Table 3)* shows that the rotational isomerism in this molecule is similar to that found for α-PAsp (Siatecki & Kozłowski, 1980, 1981). The most stable rotamer is the one with carboxyl and phosphonic groups *trans* relative to each other (rotamer 2 in Fig. 2). The population of rotamer 3 in β-PAsp is slightly but distinctly higher than in α-PAsp. The latter result is consistent with the X-ray data which show that α-PAsp crystallized as rotamer 2 and β-PAsp as rotamer 3 (see above). In the case of β-PAsp the hydrogen bond between N and O(1) (Fig. 1) could stabilize rotamer 3 also in solution. Rotamer 3 is even more stable in β-PCH_3Asp (Table 4)* suggesting that intramolecular hydrogen bonding may play a critical role in the conformation of this molecule.

* Tables of the ^{1}H NMR spectroscopic parameters have been deposited. See deposition footnote.

Table 3. *Rotamer populations of the* β-PAsp *molecule at different* pH

Rotamer populations were calculated according to the modified Pachler method described earlier (Siatecki & Kozłowski, 1981) for the rotamer notation as in Fig. 2.

pH	p_1	p_2	p_3
0·6	0·19	0·54	0·27
1·5	0·19	0·58	0·23
3·2	0·11	0·67	0·22
4·2	0·11	0·76	0·13
5·2	0·10	0·78	0·12
6·2	0·05	0·83	0·12
8·0	0·00	0·94	0·06
9·3	0·00	0·94	0·06
10·5	0·00	0·91	0·09
11·3	0·00	0·88	0·12
12·5	0·00	0·80	0·20

Table 4. *Rotamer populations of the* β-PCH_3Asp *molecule at different* pH

Rotamer populations as described in Table 3.

pH	p_1	p_2	p_3
0·5	0·30	0·46	0·24
1·7	0·24	0·55	0·21
3·0	0·11	0·67	0·22
4·2	0·08	0·73	0·19
5·3	0·05	0·74	0·21
6·7	0·06	0·74	0·20
8·1	0·07	0·70	0·23
9·3	0·07	0·72	0·21
13·0	0·11	0·66	0·23

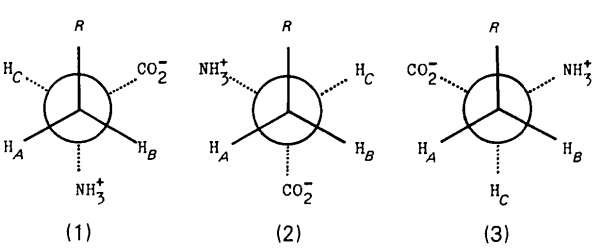

Fig. 2. Rotamer notation for β-PAsp ($R = PO_3H^-$) and β-PCH_3Asp ($R = PCH_3O_2^-$).

* Tables of the ^{1}H NMR spectroscopic parameters have been deposited. See deposition footnote.

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Methyl 3-Phenyl-4a,7,8,8a-tetrahydropyrido[4,3-*e*][1,4,2]dioxazine-7-carboxylate, $C_{14}H_{14}N_2O_4$

BY RICHARD G. BALL

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

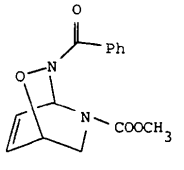
AND EDWARD E. KNAUS AND SUSHIL K. DUBEY

Department of Pharmacy, University of Alberta, Edmonton, Alberta, Canada T6G 2N8

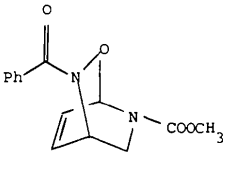
(*Received* 5 *July* 1984; *accepted* 24 *October* 1984)

Abstract. $M_r = 274{\cdot}28$, monoclinic, $P2_1/c$, $a = 14{\cdot}304\ (5)$, $b = 10{\cdot}297\ (2)$, $c = 9{\cdot}092\ (3)$ Å, $\beta = 102{\cdot}09\ (3)°$, $V = 1309$ Å^3, $Z = 4$, $D_x = 1{\cdot}39$ Mg m^{-3}, λ(Mo $K\alpha$) $= 0{\cdot}71069$ Å, μ(Mo $K\alpha$) $= 0{\cdot}097$ mm^{-1}, $F(000) = 576$, $T = 294$ K, $R = 0{\cdot}061$ for 769 observed reflections. The title compound was prepared by the rearrangement of the product from the reaction of nitrosocarbonylbenzene with methyl 1,2-dihydro-1-pyridinecarboxylate. The pyrido and dioxazine rings are fused in an *endo* conformation.

Introduction. The title compound is a rearrangement product arising from one of two possible regioisomers, (1) and (2), formed by the ($\pi 2 + \pi 4$) cycloaddition reaction of nitrosocarbonylbenzene with methyl 1,2-dihydro-1-pyridinecarboxylate. The crystal structure of this rearrangement product was investigated to determine from which regioisomer it was derived.



(1)



(2)

Experimental. A solution of tetraethylammonium periodate (5 mmol) in 20 mL dry methylene chloride was added dropwise with stirring to a solution of methyl 1,2-dihydro-1-pyridinecarboxylate (5 mmol) and *N*-benzoylhydroxylamine (5 mmol) in 100 mL dry methylene chloride under nitrogen at 195 K. The reaction mixture was allowed to warm to 298 K followed by continued stirring for an additional 6 h. The solvent was removed *in vacuo* and the residue was chromatographed on a silica-gel column using ether as the eluant to yield the ($\pi 2 + \pi 4$) adduct as a viscous oil. The viscous oil was allowed to stand at room temperature for 14 d during which time it rearranged completely. Trituration of this product with hexane and then ether afforded a white solid, m.p. 401–403 K (methanol).

Crystal $0{\cdot}07 \times 0{\cdot}09 \times 0{\cdot}31$ mm. CAD-4 diffractometer. Lattice parameters determined using 17 reflections with $9 < 2\theta < 20°$. Lp correction applied. No absorption correction. Intensity measurements in range $0 < 2\theta < 54°$ (index limits: $h \pm 18$; k 13; l 11). Intensity standards: $\bar{2}\bar{1}2$ 11864 (117); $0\bar{2}\bar{1}$ 21098 (403). 3206 reflections measured, 2846 unique, 2077 unobserved [$I < 3\sigma(I)$]. R factor for merging equivalent reflections 0·027. Structure solved by direct methods using *MULTAN*11/82 (Main, 1982). Full-

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