THE CRYSTAL AND MOLECULAR STRUCTURE OF 4-PHOSPHONO-METHYL-2-OXO-1-PIPERAZINYLACETIC ACID

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The structure of the title compound was determined by the method of X-ray diffraction of single crystals. The substance crystallizes in the $P2_1/c$ monoclinic space group. The structure was refined by the least squares method to $R = 0.044$ on the basis of 2 076 observed reflections. It was found that this compound is not a dicarboxylic acid but rather an intramolecularly cyclized lactam. The hydrogen phosphonato functional group participates in the betain form, while the carboxyl group is not ionized. The conformation of the six-membered oxopiperazine ring is similar to that of cyclohexane in which the peptidic group plays a similar role to the double bond.

Aminopolycarboxylic acids are used widely in a great many human activities[1] and modification of these compounds by introduction of an additional functional group is a means by which specialized properties can be attained. Phosphone derivatives can be used, for example, in chelation therapy and medical diagnosis as carriers of radioactive technecium[2].

The studied compound was synthesized by Butvin et al.[3] from ethylenediamine--N,N'-diacetic acid, formaldehyde and phosphonic acid by a Mannisch type reaction in an attempt to prepare ethylenediamine-N,N'-bisphosphonomethyl-N,N'-diacetic acid. Only one compound was always obtained, with a single methylphosphono group, irregardless of the synthesis conditions[4]. This work was carried out to determine the molecular structure of this compound by X-ray structural analysis of the single crystal.

EXPERIMENTAL

A $0.50 \times 0.25 \times 0.15$ mm colourless crystal was prepared by slow cooling of a saturated aqueous solution of the title compound and D_m was found by flotation. The space group was found from Weissenberg photographs (Syntex P2$_1$ diffractometer, graphite monochromator); the lattice parameters were found from 10 reflections $4° < 2\theta < 24°$, $\omega - 2\theta$ technique, scan rate 1·5 to 29·3° 2θ min^{-1}, scan range $2.0° + 2\theta(K\alpha_1) - 2\theta(K\alpha_2)$; the background was measured at each end of the scan for one half of the scan time. Two standards (134) and (210) were monitored after every 98 reflections and did not vary significantly. 3 143 reflections were measured with

$2\theta < 55°$, $h = 0$ to 12, $k = 0$ to 7, $l = -25$ to 24, $(\sin\theta/\lambda)_{max} = 0.651$, 2 655 unique reflections, 579 observed reflections with $I < 1.96\sigma(I)$, $R_{int} = 0.022$. Lorentz and polarization corrections were carried out but no correction was made for absorption and extinction. Crystal data: $C_7H_{13}N_2PO_6.H_2O$, $M_r = 270.2$, monoclinic, $P2_1/c$, $a = 1.0051(3)$, $b = 0.5954(2)$, $c = 1.9790(3)$ nm, $\beta = 103.15(5)°$, $V = 1.1533(5)$ nm^3, $D_m = 1.54(3)$, $D_x = 1.556$ Mg m^{-3}, $Z = 4$, $\lambda(MoK_\alpha) = 0.071069$ nm, $\mu = 0.256$ mm^{-1}, $F(000) = 568$, room temperature.

The structure was solved by the Patterson and Fourier methods. The H-atoms were located by difference synthesis including the water molecule hydrogens, and were refined to $|F_0|$ by block--diagonal least squares; the anisotropic thermal parameters were refined for the heavy atoms and isotropic parameters for the hydrogen atoms; the $w^{-1} = \sigma^2(F) + (0.02|F_0|)^2$, $\sigma(F)$ from counting statistics was employed, yielding $(\Delta/\sigma)_{max} = 0.03$ and $R = 0.044$ and 0.072, $wR = 0.050$ and 0.066 for the observed reflections and all the reflections, respectively, $S = 1.399$. $(\Delta\varrho)_{max} = 0.33 . 10^{30}$ em^{-3} and $(\Delta\varrho)_{min} = -0.21 . 10^{30}$ em^{-3}. The scattering factors for the neutral atoms were taken from the International Tables for X-ray Crystallography[5]. All the calculations were performed with the XRC83 system[6] on an ES-1 033 computer. The final atomic coordinates are given in Table I, the anisotropic thermal parameters in Table II, the H-atom coordinates in Table III, bond lengths and angles in Table IV, selected torsion angles in Table V and characteristics of the hydrogen bonds in Table VI. The values of the observed and calculated structure factors can be obtained on request from the first author.

TABLE I

Final atomic coordinates $(. 10^4)$ with estimated standard deviations in parantheses and equivalent isotropic thermal parameters B_{eq} $(. 10^{-20}$ m$^2)$ defined as $B_{eq} = \frac{4}{3}\sum_i\sum_j B_{ij}\boldsymbol{a}_i\boldsymbol{a}_j$

Atom	z/a	y/b	z/c	B_{eq}
P(1)	2 215(1)	2 427(1)	5 124(1)	1.88
O(1)	3 671(1)	3 027(2)	5 473(1)	2.71
O(2)	1 101(1)	3 152(2)	5 453(1)	2.88
O(3)	2 109(1)	−170(2)	4 987(1)	2.92
O(4)	−1 533(1)	7 518(2)	2 576(1)	3.68
O(5)	−5 223(1)	3 970(2)	1 659(1)	3.39
O(6)	−3 137(1)	2 799(3)	1 633(1)	6.73
O(7)	5 645(1)	2 463(2)	4 683(1)	3.73
N(1)	408(1)	4 074(2)	3 961(1)	1.78
N(2)	−2 127(1)	4 251(2)	3 004(1)	2.40
C(1)	1 900(1)	3 744(2)	4 273(1)	2.28
C(2)	220(1)	5 676(2)	3 369(1)	2.05
C(3)	−1 236(1)	5 880(2)	2 959(1)	2.26
C(4)	−321(1)	1 928(2)	3 726(1)	2.30
C(5)	−1 831(1)	2 370(2)	3 487(1)	2.67
C(6)	−3 545(1)	4 581(3)	2 652(1)	2.93
C(7)	−3 910(1)	3 665(3)	1 924(1)	2.86

TABLE II

Final atomic coordinates (. 10^4) and isotropic temperature factors B (. 10^{-20} m^2) for the hydrogen atoms. Estimated standard deviations given in parentheses

Atom	x/a	y/b	z/c	B
H(1)	2 888(15)	−794(28)	5 041(8)	2·2(4)
H(2)	2 254(14)	2 892(22)	3 962(7)	0·6(3)
H(3)	2 325(14)	5 196(24)	4 324(7)	0·8(3)
H(4)	24(13)	4 762(24)	4 275(7)	0·6(3)
H(5)	796(12)	5 139(22)	3 076(6)	0·1(3)
H(6)	531(14)	7 110(22)	3 552(7)	0·4(3)
H(7)	54(13)	1 328(22)	3 367(6)	0·1(3)
H(8)	−157(15)	867(26)	4 151(8)	1·9(3)
H(9)	−2 232(14)	2 729(24)	3 900(7)	1·1(3)
H(10)	−2 251(15)	1 019(25)	3 268(8)	1·5(3)
H(11)	−4 154(15)	3 844(26)	2 920(8)	2·0(4)
H(12)	−3 756(16)	6 048(28)	2 648(8)	2·6(4)
H(13)	−5 543(22)	3 236(38)	1 145(11)	6·3(6)
H(14)	5 079(22)	2 566(32)	4 922(11)	5·3(5)
H(15)	5 805(19)	4 125(35)	4 606(10)	4·7(5)

TABLE III

Coefficients of the anisotropic temperature factors (. 10^4). Estimated standard deviations given in parentheses. The temperature factor has the form $T = \exp[-(B_{11}h^2 + \ldots + B_{12}hk \ldots)]$

Atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
P(1)	44(1)	151(1)	12(1)	23(1)	6(1)	11(1)
O(1)	57(1)	206(3)	18(1)	5(3)	−7(1)	23(1)
O(2)	71(1)	258(3)	16(1)	83(3)	25(1)	8(1)
O(3)	65(1)	158(3)	26(1)	20(3)	9(1)	9(2)
O(4)	89(1)	274(4)	24(1)	49(4)	11(1)	87(2)
O(5)	59(1)	354(4)	17(1)	33(3)	−7(1)	−19(2)
O(6)	89(1)	835(8)	29(1)	254(6)	−9(1)	−161(3)
O(7)	88(1)	211(3)	34(1)	66(3)	40(1)	−7(2)
N(1)	51(1)	129(3)	10(1)	6(3)	9(1)	3(1)
N(2)	53(1)	210(4)	13(1)	−17(3)	−1(1)	7(2)
C(1)	44(1)	205(4)	15(1)	8(4)	7(1)	21(2)
C(2)	57(1)	140(4)	13(1)	3(4)	14(1)	18(2)
C(3)	63(1)	183(4)	12(1)	39(4)	13(1)	11(2)
C(4)	69(1)	128(4)	16(1)	−14(4)	9(1)	2(2)
C(5)	62(1)	184(4)	19(1)	−61(4)	5(1)	13(2)
C(6)	52(1)	288(5)	17(1)	15(4)	−1(1)	−22(2)
C(7)	61(1)	256(5)	16(1)	39(4)	0(1)	−11(2)

TABLE IV

Interatomic distances (nm) and bond angles (°) with estimated standard deviations in parentheses

Interatomic distances

P(1)—O(1)	0·1512(1)	N(2)—C(5)	0·1458(2)
P(1)—O(2)	0·1482(1)	N(2)—C(6)	0·1450(2)
P(1)—O(3)	0·1569(1)	O(4)—C(3)	0·1230(2)
P(1)—C(1)	0·1820(1)	O(5)—C(7)	0·1317(2)
N(1)—C(1)	0·1500(2)	O(6)—C(7)	0·1185(2)
N(1)—C(2)	0·1488(2)	C(2)—C(3)	0·1508(2)
N(1)—C(4)	0·1493(2)	C(4)—C(5)	0·1506(2)
N(2)—C(3)	0·1337(2)	C(6)—C(7)	0·1505(2)

Bond angles

O(1)—P(1)—O(2)	118·8(1)	P(1)—C(1)—N(1)	112·7(1)
O(1)—P(1)—O(3)	109·4(1)	N(1)—C(2)—C(3)	114·1(1)
O(2)—P(1)—O(3)	109·5(1)	C(2)—C(3)—N(2)	119·2(1)
O(1)—P(1)—C(1)	105·5(1)	O(4)—C(3)—C(2)	117·7(2)
O(2)—P(1)—C(1)	106·9(1)	O(4)—C(3)—N(2)	123·0(1)
O(3)—P(1)—C(1)	105·9(1)	N(1)—C(4)—C(5)	109·6(1)
C(1)—N(1)—C(2)	110·1(1)	N(2)—C(5)—C(4)	112·4(1)
C(1)—N(1)—C(4)	112·9(1)	N(2)—C(6)—C(7)	114·2(1)
C(2)—N(1)—C(4)	109·8(9)	C(6)—C(7)—O(5)	109·7(1)
C(3)—N(2)—C(5)	124·2(1)	C(6)—C(7)—O(6)	125·3(2)
C(3)—N(2)—C(6)	118·0(1)	O(5)—C(7)—O(6)	124·9(1)
C(5)—N(2)—C(6)	116·8(1)		

TABLE V

Selected torsion angles (°) with estimated standard deviations in parentheses

Torsion angles

N(1)—C(2)—C(3)—N(2)	−19·5(2)	C(6)—N(2)—C(3)—C(2)	174·5(1)
C(2)—C(3)—N(2)—C(5)	7·0(2)	C(6)—N(2)—C(3)—O(4)	−8·0(2)
C(3)—N(2)—C(5)—C(4)	−22·1(2)	O(4)—C(3)—N(2)—C(5)	−175·5(1)
N(2)—C(5)—C(4)—N(1)	49·1(1)	O(4)—C(3)—C(2)—N(1)	163·0(1)
C(5)—C(4)—N(1)—C(2)	−62·2(1)	O(1)—P(1)—C(1)—N(1)	−158·5(1)
C(4)—N(1)—C(2)—C(3)	47·0(1)	O(2)—P(1)—C(1)—N(1)	−31·0(1)
O(5)—C(7)—C(6)—N(2)	177·6(1)	O(3)—P(1)—C(1)—N(1)	85·5(1)
O(6)—C(7)—C(6)—N(2)	−2·0(2)	P(1)—C(1)—N(1)—C(2)	165·0(1)
C(7)—C(6)—N(2)—C(5)	−99·5(1)	P(1)—C(1)—N(1)—C(4)	−72·0(1)
C(6)—N(2)—C(5)—C(4)	170·0(1)	C(1)—N(1)—C(2)—C(3)	172·0(1)
C(7)—C(6)—N(2)—C(3)	92·0(2)	C(1)—N(1)—C(4)—C(5)	174·5(1)

DISCUSSION

X-ray structural analysis indicated that the studied substance is not a dicarboxylic acid but a cyclic compound — a piperazine derivative:

$$H_2O_3P-CH_2-N \overset{\displaystyle CH_2-CH_2}{\underset{\displaystyle CH_2 \quad CO}{\Big\langle}} N-CH_2-COOH$$
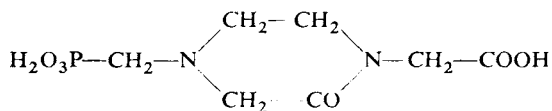
formed by intramolecular condensation. The structure of the compound in solution is not clear as electrophoretic measurements on the complex with metal ions and potentiometric measurements indicate that a tetraprotic acid is present[4].

TABLE VI

Hydrogen bond lengths (nm) and angles (°), estimated standard deviations in parentheses. Symmetry codes: (*i*) x, y, z, (*ii*) $1 - x, 1 - y, 1 - z$, (*iii*) $1 + x, 1/2 - y, 1/2 + z$, (*iv*) $-1 - x$, $1 - y, 1 - z$, (*v*) $1 - x, 1 + y, z$

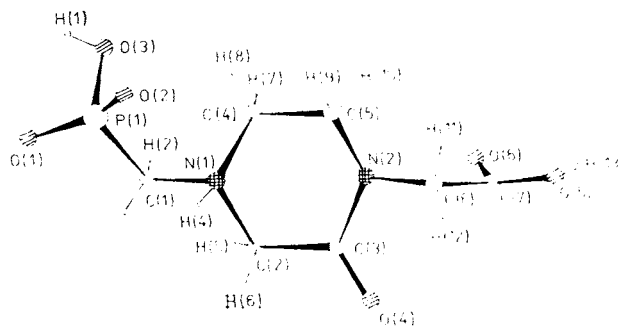| Hydrogen bond X...H—Y	Distance X...Y	Distance X...H	Angle X...H—Y	Symmetry code
O(1)...H(14)—O(7)	0·2806(3)	0·1962(50)	62·75	*i*
O(1)...H(15)—O(7)	0·2806(3)	0·1819(38)	172·11	*ii*
O(1)...H(13)—O(5)	0·2640(2)	0·1660(5)	165·41	*iii*
O(2)...H(4)—N(1)	0·2928(2)	0·2525(24)	107·06	*i*
O(2)...H(4)—N(1)	0·2680(3)	0·1826(25)	153·61	*iv*
O(7)...H(1)—O(3)	0·2590(3)	0·1750(31)	165·47	*v*

FIG. 1

The molecular structure and atom numbering

The crystal structure consists of $C_7H_{13}N_2PO_6$ molecules and molecules of water of crystallization (Fig. 1). The $C_7H_{13}N_2PO_6$ molecule is in the betain form. The phosphono group is ionized; the O(2) atom has a formal negative charge, while the N(1) nitrogen is protonized and has a formal positive charge. On the other hand, the carboxyl group is protonized, as is the O(3) oxygen atom. These unambiguous conclusions followed from precise structural analysis, unambiguously indicating the positions of all the hydrogen atoms, including those in the water molecule. The piperazone ring has a conformation similar to that of the cyclohexene molecule. The partial double character of the peptide bond C(3)—N(2), following from the bond length of 0·1337 nm results in approximate planarity of the fragment consisting of the C(2), C(3), N(2), C(5), O(4) and C(6) atoms. The N(1) and C(4) atoms are symmetrically bent out of this plane in opposite directions. The six-membered ring has approximately C_2 symmetry, where the two-fold axis passes through the centre of the N(2)—C(3) and N(1)—C(4) bonds. This symmetry can be derived from the values of the torsion angles in Table V. The bond lengths have normal values close to those for stanards and do not exhibit anomalies.

The crystal structure is stabilized by a system of hydrogen bonds. The water of crystallization plays a great role in the stabilization; it acts as a proton donor for two different O(1) atoms, and is simultaneously a proton acceptor for the H(1) proton of the phosphono group. The betain proton H(4) also forms a strong hydrogen bond with the O(2) oxygen atom. There is a weak O(2)...H(4) intramolecular bond in the $C_7H_{13}N_2PO_6$ molecule. The system of hydrogen bonds is apparent from Table VI.

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