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Structure of 6-Amino-1-hydroxyhexylidenebis(phosphonic acid)

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Abstract. $C_6H_{17}NO_7P_2$, $M_r = 277\cdot1$, monoclinic, $P2_1/c$, $a = 6\cdot960\ (2)$, $b = 13\cdot127\ (5)$, $c = 12\cdot056\ (3)$ Å, $\beta = 95\cdot89\ (2)°$, $V = 1095\cdot6\ (6)$ Å^3, $Z = 4$, $D_x = 1\cdot68$ Mg m^{-3}, Mo $K\alpha$, $\lambda = 0\cdot71069$ Å, $\mu = 4\cdot24$ cm^{-1}, $F(000) = 584$, $T = 293$ K, final $R = 0\cdot043$ ($wR = 0\cdot065$) for 2798 observed reflections. The title compound exists as a zwitterion and the alkylamino side chain adopts a *trans–trans–trans–gauche$^-$–gauche$^-$* backbone conformation. The phosphonate O atoms form a nearly planar W configuration. There are seven independent hydrogen bonds in the structure, three bifurcated of type N—H···O and four of type O—H···O.

Introduction. Diphosphonate compounds, owing to their ability to inhibit either dissolution or formation of crystals of hydroxyapatite (King, Francis & Michael, 1971), find therapeutic use in diseases related to the metabolism of calcium and phosphates (Francis & Centner, 1978). Among them, *gem*-diphosphonates, in which the linkage P—C(R')R—P′ simulates the linkage P—O—P present in pyrophosphates, are particularly important, due to an increased resistance to the hydrolysis. Different substitution patterns of groups R and R' might modify their chemical and biological properties. The structure determination of the title compound was undertaken to characterize a new series of compounds, exhibiting calcium binding properties, in which R = OH and R' = an alkyl chain with a terminal amino group.

Experimental. Colourless prismatic-shaped crystals of the title compound were grown from water. Preliminary oscillation and Weissenberg photographs indicated crystals to be monoclinic, $P2_1/c$. A crystal *ca* $0\cdot2 \times 0\cdot3 \times 0\cdot5$ mm was selected for the data collection and set on a Nicolet $R3$ diffractometer equipped with Mo $K\alpha$ radiation and graphite monochromator.

Intensity data were collected at room temperature, the experimental conditions being: $2\theta_{max} \leq 73°$, *hkl* ranges h −11→11, k 0→20, l 0→21, θ–2θ scan mode, scan range 1·2°, scan rate 2·0–29·3° min^{-1} (depending on the reflection intensity), background-count time equal to the scan time. Accurate unit-cell parameters were determined by least-squares fit of the setting angles of 15 selected reflections with $10 \leq 2\theta \leq 42°$.

Four control reflections monitored every hundred indicated a smooth variation (crystal decay of *ca* 1%) of intensity during data collection. The data were processed and corrected for the average change in the intensity of the reference reflections. Lorentz and polarization corrections were applied but no absorption or extinction corrections were made.

Merging equivalents gave 5423 unique reflections ($R_{int} = 0\cdot027$), of which 2798 with $I \geq 3\sigma(I)$ were used for the structure refinement.

The structure was solved by Patterson and Fourier methods and refined by full-matrix least-squares procedures minimizing the function $\sum w|\Delta F|^2$ with $w = (a + |F_o| + b|F_o|^2)^{-1}$. The parameters a and b were given values of $2 \times F_{o\min}$ and $2/F_{o\max}$ in order to obtain $\langle w|\Delta F|^2\rangle$ nearly constant in ranges of F_o and $\sin\theta/\lambda$.

The H atoms were located by difference Fourier syntheses. Non-H atoms were refined anisotropically and H atoms refined with isotropic temperature factors. The final R value is 0·043 ($wR = 0\cdot065$). At convergence, the maximum shift-to-e.s.d. ratio was 2·60, which corresponds to B_{iso} of H(41), meanwhile the other parameters have shift-to-e.s.d. ratios less than 0·2; $S = 0\cdot31$. Maximum and minimum $\Delta\rho$ in the final difference Fourier synthesis were 0·3 and −0·5 e Å^{-3}. All calculations were performed on a Data General

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Table 1. *Atomic coordinates of non-*H *atoms and isotropic thermal parameters with their e.s.d.'s in parentheses*

$$B_{eq} = \tfrac{4}{3}\textstyle\sum_i \sum_j \beta_{ij} \mathbf{a}_i . \mathbf{a}_j.$$

	x	y	z	B_{eq}(Å^2)
O(11)	−0·2334 (3)	0·0749 (1)	0·0742 (2)	1·80 (4)
O(12)	−0·2456 (3)	0·2251 (2)	0·2037 (2)	2·19 (5)
O(13)	−0·3329 (3)	0·2498 (2)	0·0003 (2)	2·29 (5)
P(1)	−0·2023 (1)	0·1871 (1)	0·0863 (1)	1·32 (1)
C(1)	0·0467 (3)	0·2260 (2)	0·0707 (2)	1·17 (4)
O(1)	0·1629 (3)	0·1666 (2)	0·1520 (2)	1·64 (4)
C(2)	0·0695 (4)	0·3416 (2)	0·0935 (2)	1·57 (5)
C(3)	0·2784 (4)	0·3767 (2)	0·1070 (3)	2·1 (1)
C(4)	0·2991 (5)	0·4868 (2)	0·1466 (3)	2·2 (1)
C(5)	0·5064 (5)	0·5244 (3)	0·1599 (3)	2·7 (1)
C(6)	0·6384 (5)	0·4692 (3)	0·2464 (3)	2·7 (1)
N	0·6000 (4)	0·4972 (3)	0·3608 (2)	2·5 (1)
P(2)	0·1271 (1)	0·1927 (1)	−0·0673 (1)	1·31 (1)
O(21)	0·0531 (3)	0·2743 (2)	−0·1477 (2)	2·10 (4)
O(22)	0·0203 (3)	0·0904 (2)	−0·1038 (2)	1·89 (4)
O(23)	0·3406 (3)	0·1724 (2)	−0·0529 (2)	2·06 (4)

Eclipse MV8000 II with the *SIR-CAOS* package (Camalli, Capitani, Cascarano, Cerrini, Giacovazzo & Spagna, 1986). The atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974). Final atomic parameters are given in Table 1.*

Discussion. A perspective view of the molecule is shown in Fig. 1. Bond distances and angles are in Table 2.

The title compound exists as a zwitterion with the amino N atom protonated and the P(2) phosphonyl group ionized. The locations of H(12), H(13) and H(22) near O(12), O(13) and O(22) respectively, in addition to the pattern of the bond lengths and angles, indicate P(1)—O(12), P(1)—O(13) and P(2)—O(22) to be P—OH bond types and P(1)—O(11) to be a double bond. The negative charge is distributed between O(21) and O(23) as indicated by the lengths of the bonds P(2)—O(21) and P(2)—O(23), 1·500 (2) and 1·502 (2) Å respectively. The coordination around both P(1) and P(2) atoms departs significantly from regular tetrahedral, the angles varying from 106·1 (1)° O(12)—P(1)—C(1) to 113·0 (1)° O(11)—P(1)—O(13) and from 105·9 (1)° C(1)—P(2)—O(22) to 118·1 (1)° O(21)—P(2)—O(23). The protonated O atoms influence the bond angles at the P atoms. The two smallest angles involve the protonated O(12) and O(22), while the two largest O—P—O angles involve the unprotonated O(11), O(21), O(23) and the protonated O(13). The orientations of the phosphonate O atoms form a nearly planar W configuration O(12), P(1), C(1), P(2) and O(23).

Table 2. *Bond lengths* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

C(1)—C(2)	1·547 (4)	O(11)—P(1)	1·493 (2)
C(1)—O(1)	1·436 (3)	O(12)—P(1)	1·558 (2)
C(1)—P(2)	1·861 (2)	O(13)—P(1)	1·545 (3)
C(2)—C(3)	1·518 (4)	P(1)—C(1)	1·835 (2)
C(3)—C(4)	1·525 (4)	P(2)—O(21)	1·500 (2)
C(4)—C(5)	1·518 (5)	P(2)—O(22)	1·575 (2)
C(5)—C(6)	1·503 (5)	P(2)—O(23)	1·502 (2)
C(6)—N	1·478 (5)		

C(2)—C(1)—P(2)	110·8 (2)	O(11)—P(1)—O(12)	111·5 (1)
O(1)—C(1)—C(2)	111·8 (2)	O(11)—P(1)—O(13)	113·0 (1)
O(1)—C(1)—P(2)	106·4 (2)	O(12)—P(1)—C(1)	106·1 (1)
P(1)—C(1)—C(2)	109·6 (2)	O(12)—P(1)—O(13)	106·5 (1)
P(1)—C(1)—O(1)	104·5 (2)	O(13)—P(1)—C(1)	106·2 (1)
P(1)—C(1)—P(2)	113·6 (1)	C(1)—P(2)—O(21)	107·1 (1)
C(1)—C(2)—C(3)	113·3 (2)	C(1)—P(2)—O(22)	105·9 (1)
C(2)—C(3)—C(4)	112·3 (2)	C(1)—P(2)—O(23)	108·8 (1)
C(3)—C(4)—C(5)	113·5 (3)	O(21)—P(2)—O(22)	107·9 (1)
C(4)—C(5)—C(6)	115·0 (3)	O(21)—P(2)—O(23)	118·1 (1)
C(5)—C(6)—N	111·8 (3)	O(22)—P(2)—O(23)	108·3 (1)
O(11)—P(1)—C(1)	113·2 (1)		

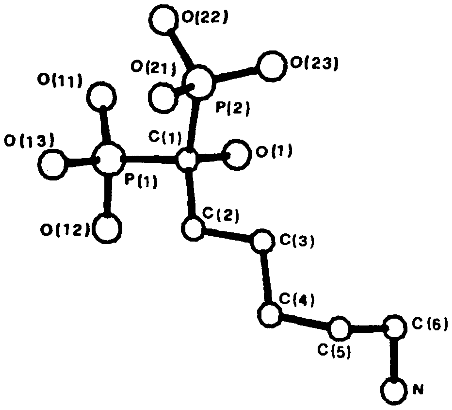

Fig. 1. Perspective view of 6-amino-1-hydroxyhexylidenebis(phosphonic acid) showing the atomic labelling.

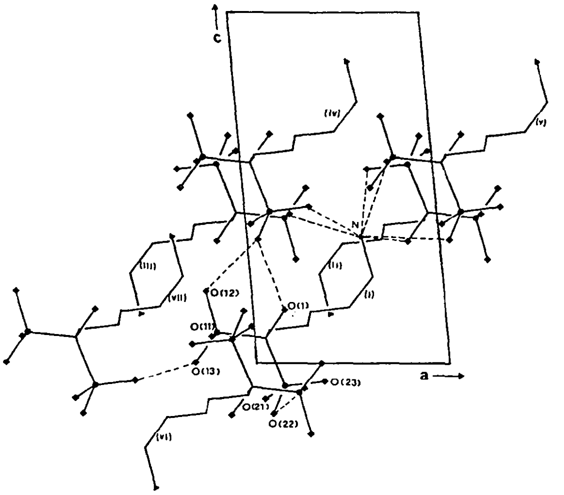

Fig. 2. Geometry of the hydrogen-bonding system.

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* Lists of structure factors, H-atom coordinates and anisotropic thermal parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51433 (20 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Hydrogen bonds (e.s.d.'s are in parentheses)*

D—H···*A*	*D*···*A* (Å)	*D*—H (Å)	H···*A* (Å)	*D*—H···*A* (°)
N—H(101)$^{\rm i}$···O(1)$^{\rm ii}$	2·782 (4)	0·89 (5)	2·02 (5)	143 (3)
···O(23)$^{\rm ii}$	3·259 (4)		2·63 (5)	129 (3)
N—H(102)$^{\rm i}$···O(11)$^{\rm iii}$	2·929 (4)	0·81 (8)	2·23 (8)	144 (5)
···O(23)$^{\rm iv}$	3·112 (4)		2·59 (8)	123 (5)
N—H(103)$^{\rm i}$···O(11)$^{\rm v}$	2·871 (4)	0·92 (5)	2·01 (5)	155 (3)
···O(22)$^{\rm v}$	3·132 (4)		2·57 (5)	120 (3)
O(1)—H(1)$^{\rm i}$···O(21)$^{\rm iv}$	2·720 (3)	0·82 (4)	1·90 (4)	174 (3)
O(22)—H(221)$^{\rm i}$···O(11)$^{\rm vi}$	2·632 (3)	0·83 (5)	1·81 (5)	175 (3)
O(12)—H(12)$^{\rm i}$···O(21)$^{\rm iv}$	2·602 (3)	0·75 (6)	1·86 (6)	170 (4)
O(13)—H(13)$^{\rm i}$···O(23)$^{\rm vii}$	2·511 (3)	0·78 (6)	1·73 (6)	173 (4)

Symmetry code: (i) x, y, z; (ii) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$; (iii) $-x, \frac{1}{2}+y, \frac{1}{2}-z$; (iv) $x, \frac{1}{2}-y, \frac{1}{2}+z$; (v) $1+x, \frac{1}{2}-y, \frac{1}{2}+z$; (vi) $-x, -y, -z$; (vii) $-1+x, y, z$.

The torsion angles for O(12)—P(1)—C(1)—P(2) and P(1)—C(1)—P(2)—O(23) are −177·7 (1) and −148·9 (1)° respectively. Overall the molecular geometry of the diphosphonate moiety compares well with those found in analogous compounds (Nardelli, Pelizzi, Staibano & Zucchi, 1983, and references therein).

The alkylamino side chain adopts a *trans–trans–gauche$^-$–gauche$^-$* backbone conformation, with the torsion angles around C(2)—C(3), C(3)—C(4), C(4)—C(5) and C(5)—C(6) bonds being −171·3 (2), −179·5 (3), −63·0 (4) and −73·5 (4)° respectively. The O(1) hydroxyl group is (+)synclinal with respect to the C(3) methylene group, the torsional angle O(1)—C(1)—C(2)—C(3) being 52·3 (3)°.

The crystal structure is stabilized by seven hydrogen bonds involving the N amino, the O(1) hydroxyl and both phosphonyl groups (Fig. 2), three (bifurcated) of type N—H···O and four of type O—H···O. Details of these are given in Table 3.

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Structure of 1-(4-Chlorophenacyl)-2-methyl-5-morpholino-4-nitroimidazole

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Abstract. $C_{16}H_{17}ClN_4O_4$, $M_r = 364·5$, monoclinic, $P2_1/n$, $a = 14·333\,(3)$, $b = 11·398\,(2)$, $c = 10·663\,(2)$ Å, $\beta = 102·90\,(2)°$, $V = 1698·1\,(6)$ Å^3, $Z = 4$, $D_m = 1·40$, $D_x = 1·43$ g cm^{-3}, $\lambda(\mathrm{Cu}\,K\alpha) = 1·54178$ Å, $\mu = 21·47$ cm^{-1}, $F(000) = 760$, room temperature, $R = 0·049$ for 1883 unique observed reflections. The molecule is highly overcrowded, the imidazole ring is planar. The presence of the NO_2 group in position 4 of the imidazole makes the protonation of N(3) impossible. The lone pair of the morpholine N atom takes part, to some extent, in the p–π overlap.

Introduction. *N*-Alkylnitroimidazoles are chemotherapeutically important as antiprotozoal and antibacterial agents (Hoffer & Rachlin, 1972), *e.g.* metronidazole, 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, is both an amoebicide and a trichomonacide (Powell, McLeod & Wilmot, 1966), while azomycine, 2-nitroimidazole, exhibits antibiotic properties (Maeda, Osato & Umezawa, 1953). Moreover, metronidazole has been reported to sensitize tumour hypoxic cells both *in vitro* and *in vivo* (Chapman, Reuvers & Borsa, 1973; Asquith, Foster & Willson, 1973). 1-(2-Hydroxy-3-methoxypropyl)-2-nitroimidazole (misonidazole) is the most effective radiosensitizing agent, but its toxicity is

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