Crystal structure of diaquadisodium [1-(ethoxy-hydroxy-phosphoryl)-1-hydroxy-ethyl]phosphonic acid diethyl ester, $\text{Na}_2(\text{H}_2\text{O})_2[(\text{C}_2\text{H}_5\text{OPO}_2)_2\text{C}(\text{CH}_3)\text{OH}]$, a pro-drug derivative for etidronate

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methanol to the corresponding symmetrical ethylidene bisphosphonate diethyl ester with 95 % yield. The sodium salt crystallizes from a mixture of water and methanol as small colorless cubes.

Discussion

Bisphosphonates compounds containing a stable P–C–P bridge, are widely used either in the treatment of diseases in skeletal pathologies, bone formation and/or resorption disorders [1]. They are also investigated in the treatment of cancer [2,3]. The major drawbacks of these drugs reside in their poor oral bioavailability mainly due to their strong hydrophilicity [4] and their ability to complex biologically important divalent cations [5]. By masking one or several ionisable groups it was anticipated the formation of prodrugs with higher lipophilicity that could facilitate the drug delivery and metabolism [6,7]. The aim of this work is to investigate the structure of 1-hydroxybisphosphonate partial ethyl esters derived from the widely used drug residronate as its disodium salt (figure, top), and to analyze the corresponding hydrogen bond network.

The crystal structure consists of layers of hydrophobic regions that enclose ethyl chains and polar regions where most of the charged oxygens, sodium cations and water molecules are observed as a complicated network (figure, bottom). The two sodium cations are six-coordinated with slightly distorted bi-pyramidal geometries. Na1 is coordinated to one water molecule (O1W) and to five phosphonic oxygens coming from three different symmetry-related molecules whilst Na2 aggregates three water molecules (O1W and two symmetry-related O2W) plus three phosphonic oxygens, also from three symmetry-related mates of diethyl etidronate.

Abstract

$\text{C}_6\text{H}_{18}\text{Na}_2\text{O}_9\text{P}_2$, monoclinic, $P12_1/c1$ (no. 14), $a = 13.27(1)$ Å, $b = 6.226(2)$ Å, $c = 17.84(1)$ Å, $\beta = 102.2(1)^\circ$, $V = 1440.3$ Å³, $Z = 4$, $R_{\text{gt}}(F) = 0.070$, $wR_{\text{ref}}(F^2) = 0.189$, $T = 293$ K.

Source of material

The title compound was prepared from acetyl chloride with two equivalent of ethylbis(trimethylsilyl)phosphite following an Arbuzov mechanism. The resulting product was hydrolyzed with

Table 1. Data collection and handling.

Crystal:	colorless cube, size $0.3 \times 0.3 \times 0.4$ mm
Wavelength:	Cu $K\alpha$ radiation (1.54180 Å)
μ :	37.02 cm^{-1}
Diffractometer, scan mode:	Philips PW 1100, $\theta/2\theta$
$2\theta_{\text{max}}$:	131.82°
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$:	3893, 2337
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 2142
$N(\text{param})_{\text{refined}}$:	177
Programs:	SHELXS-86 [8], SHELXL-97 [9]

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Table 2. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	x	y	z	U _{iso}
H(1)	4e	0.7772	−0.3158	0.9119	0.108
H(2A)	4e	0.8885	0.1384	0.8764	0.065
H(2B)	4e	0.8013	0.2176	0.8084	0.065
H(2C)	4e	0.8658	0.0126	0.7985	0.065
H(3A)	4e	0.8308	0.1221	1.0577	0.158
H(3B)	4e	0.9078	0.1591	1.0031	0.158
H(4A)	4e	0.8954	0.5300	1.0374	0.210
H(4B)	4e	0.9674	0.3765	1.0947	0.210
H(4C)	4e	0.8578	0.4352	1.1081	0.210

Table 2. Continued.

Atom	Site	x	y	z	U _{iso}
H(5A)	4e	0.7568	−0.3721	0.6438	0.074
H(5B)	4e	0.7993	−0.1576	0.6847	0.074
H(6A)	4e	0.9278	−0.3525	0.7635	0.175
H(6B)	4e	0.9337	−0.3696	0.6769	0.175
H(6C)	4e	0.8875	−0.5594	0.7165	0.175
H(1W1)	4e	0.3693	0.9199	0.9143	0.056
H(1W2)	4e	0.4862	1.0005	0.9218	0.056
H(2W1)	4e	0.3643	0.2702	0.9760	0.060
H(2W2)	4e	0.3254	0.5099	0.9788	0.060

Table 3. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	x	y	z	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
Na(1)	4e	0.4145(1)	−0.1324(3)	0.75830(9)	0.050(1)	0.037(1)	0.0329(9)	0.0018(8)	0.0072(7)	0.0018(7)
Na(2)	4e	0.4906(1)	0.5257(3)	0.89315(9)	0.053(1)	0.046(1)	0.0307(9)	0.0060(9)	0.0081(7)	0.0000(7)
P(1)	4e	0.68877(8)	0.1209(2)	0.92152(6)	0.0425(7)	0.0342(8)	0.0277(6)	−0.0003(5)	0.0075(5)	−0.0012(4)
P(2)	4e	0.66728(7)	−0.1575(2)	0.77936(5)	0.0315(6)	0.0332(7)	0.0278(6)	0.0017(4)	0.0056(4)	−0.0017(4)
O(1)	4e	0.8163(3)	−0.2156(8)	0.9091(2)	0.077(3)	0.067(3)	0.061(2)	0.020(2)	−0.008(2)	0.001(2)
O(11)	4e	0.6073(2)	0.2483(6)	0.8712(2)	0.054(2)	0.055(2)	0.041(2)	0.021(2)	0.004(1)	−0.008(2)
O(12)	4e	0.6552(3)	−0.0171(6)	0.9802(2)	0.117(3)	0.044(2)	0.047(2)	−0.001(2)	0.048(2)	0.005(2)
O(13)	4e	0.7704(3)	0.2921(6)	0.9646(2)	0.055(2)	0.050(2)	0.059(2)	−0.007(2)	−0.002(2)	−0.021(2)
O(21)	4e	0.6401(2)	0.0130(5)	0.7205(2)	0.055(2)	0.042(2)	0.029(2)	0.008(2)	0.005(1)	0.004(1)
O(22)	4e	0.5834(2)	−0.2732(5)	0.8066(2)	0.037(2)	0.042(2)	0.046(2)	−0.009(1)	0.011(1)	−0.009(1)
O(23)	4e	0.7315(2)	−0.3459(5)	0.7493(2)	0.047(2)	0.042(2)	0.042(2)	0.009(1)	0.015(1)	−0.007(1)
C(1)	4e	0.7593(3)	−0.0432(8)	0.8624(2)	0.034(2)	0.041(3)	0.030(2)	−0.002(2)	0.003(2)	−0.000(2)
C(2)	4e	0.8355(3)	0.0935(9)	0.8339(3)	0.032(2)	0.055(3)	0.047(2)	−0.018(2)	0.017(2)	−0.012(2)
C(3)	4e	0.8549(3)	0.227(2)	1.0252(6)	0.113(6)	0.120(8)	0.122(7)	0.020(6)	−0.068(6)	−0.050(6)
C(4)	4e	0.8973(8)	0.407(2)	1.0700(6)	0.124(7)	0.15(1)	0.114(7)	−0.015(7)	−0.048(6)	−0.040(7)
C(5)	4e	0.7923(4)	−0.311(1)	0.6922(3)	0.063(3)	0.081(4)	0.049(3)	0.013(3)	0.031(2)	−0.004(3)
C(6)	4e	0.8939(5)	−0.406(2)	0.7141(5)	0.059(4)	0.20(1)	0.097(5)	0.038(5)	0.034(4)	0.015(6)
O(1W)	4e	0.4334(2)	0.9007(6)	0.8971(2)	0.047(2)	0.057(2)	0.038(2)	−0.000(2)	0.011(1)	−0.012(2)
O(2W)	4e	0.3857(3)	0.4191(6)	0.9831(2)	0.061(2)	0.044(2)	0.045(2)	0.001(2)	0.010(2)	−0.002(2)

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