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Monosodium [1-hydroxy-2-(1*H*-imidazol-3-ium-4-yl)ethane-1,1-diyl]-bis(phosphonate) tetrahydrate (monosodium isozoledronate)

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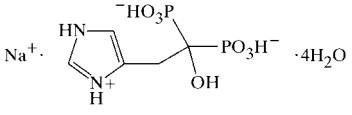
The title compound, $Na^+\cdot C_5H_9N_2O_7P_2^-\cdot 4H_2O$, is an isomer of zoledronate, a potent bone antiresorptive bisphosphonate drug having significant activity against several parasitic protozoa. The crystal structure of isozoledronate consists of bisphosphonate dimers coordinated by two Na^+ ions. The dimers are held together through an extensive hydrogen-bonding network. The crystals exhibit non-merohedral twinning that roughly superimposes the *a* and *b* axes, and inverts the *c* axis.

Comment

The title compound, (I), is an isomer of zoledronate, a potent bone antiresorptive bisphosphonate drug. Isozoledronate, as well as a series of other bisphosphonates, has recently been shown to have significant activity against *Trypanosoma cruzi*, a parasitic protozoan which is the causative agent of Chagas' disease, and *Trypanosoma brucei*, the causative agent of African sleeping sickness (Martin *et al.*, 2001). It is important to understand the key structural features of bisphosphonates that lead to their activity. In order to develop good quantitative structure–activity relationship (QSAR) methods, information is needed on the patterns of protonation and charge



(I)

distribution, since these influence the predictive power of the QSAR method. Isozoledronate has a wide range of possible protonation states and charge distributions, arising from the phosphonate groups and the imidazole ring, so in order to gain a better understanding of these charge distributions, the crystal structure of monosodium [1-hydroxy-2-(1*H*-imidazol-3-ium-4-yl)ethane-1,1-diyl]bis(phosphonate) tetrahydrate, also known as monosodium isozoledronate, (I), is reported herein.

In the crystal structure of (I), both N atoms (N1 and N3) of the imidazole ring are protonated, leading to a +1 charge in the ring, while both phosphonate groups have only one protonated O atom, leading to a −1 charge on each phosphonate group. The isozoledronate anion is also coordinated to one Na^+ ion, leading to the zwitterionic character found in many bisphosphonates (Vega *et al.*, 1996, 1998). Inspection of the bond distances in the imidazole ring shows two short [N1—C2 = 1.327 (3) and N3—C2 = 1.315 (3) Å] and two long [N1—C5 = 1.384 (2) and N3—C4 = 1.370 (3) Å] N—C bonds, implying partial double-bond character between atoms C2 and N1/N3, but essentially single-bond character at N1—C5 and N3—C4, consistent with an approximately equal charge distribution on the two N atoms. The other double bond in the ring is found at C4═C5.

Analysis of the bond distances in the phosphonate groups [P1—O2 = 1.506 (1), P1—O3 = 1.498 (1) and P1—O4 = 1.591 (1) Å, and P2—O5 = 1.499 (1), P2—O6 = 1.524 (1) and P2—O7 = 1.569 (2) Å] reveals one protonated O atom on each phosphonate group, namely O4 and O7, and two non-protonated O atoms on each, namely O2 and O3, and O5 and O6, resulting in a −1 charge on each phosphonate group. The orientation of the phosphonate groups with respect to the ring is very similar to that recently found in risedronate, both with respect to the backbone C—C—C angles [C5—C6—C7 = 113.4 (2)° in (I), C3—C2—C1 = 117.4 (4)° in RHP, C3—C2—C1 = 117.5 (3)° in RMH and C3—C2—C1 = 114.8 (2)° in RDH] and to the torsion angles between the phosphonate groups and the ring [P1—C5—C6—C7 = 62.0 (2)° in (I), P1—C1—C2—C3 = 52.6 (5)° in RHP, P1—C1—C2—C3 = 57.7 (3)° in RMH and P1—C1—C2—C3 = 61.8 (3)° in RDH], where RHP, RMH and RDH are analogues of (I) (Gossman *et al.*, 2002).

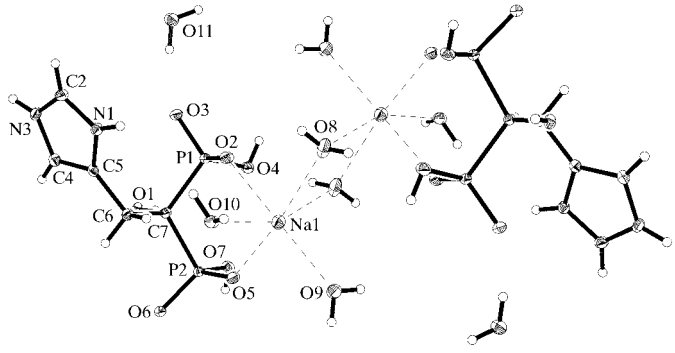


Figure 1
A view of the molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 35% probability level and H atoms are shown as small spheres of arbitrary radii.

Compound (I) consists of anionic dimers coordinated by two Na^+ ions, as shown in Fig. 1. These dimers are held together through an extensive hydrogen-bonding network, consisting of at least 13 hydrogen bonds (Table 2).

Experimental

Crystals of (I) were grown by vapour diffusion of ethanol into water.

Crystal data

$Na^{+}\cdot C_5H_9N_2O_7P_2^{-}\cdot 4H_2O$
M_r = 366.14
Triclinic, $P\bar{1}$
a = 6.6664 (19) Å
b = 6.6765 (19) Å
c = 15.5711 (18) Å
α = 84.075 (4)°
β = 82.803 (5)°
γ = 85.776 (5)°
V = 682.6 (3) Å^3
Z = 2
D_x = 1.781 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 864 reflections
θ = 2.6–28.1°
μ = 0.41 mm^{-1}
T = 193 (2) K
Prism, colourless
0.22 × 0.22 × 0.10 mm

Data collection

Siemens Platform CCD area-detector diffractometer
Profile data from ω scans
Absorption correction: multi-scan (*SAINT* and *SADABS*; Bruker, 2001)
T_{min} = 0.915, T_{max} = 0.960
3252 measured reflections
3252 independent reflections
2769 reflections with $I > 2\sigma(I)$
θ_{max} = 25.4°
$h = -7 \rightarrow 8$
$k = -7 \rightarrow 8$
$l = 0 \rightarrow 18$
118 standard reflections
frequency: 399 min
intensity decay: 0.3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.029
$wR(F^2)$ = 0.077
S = 1.04
3252 reflections
259 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0460P)^2 + 0.0847P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ < 0.001
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N1—C2	1.327 (3)	O3—P1	1.4983 (14)
N1—C5	1.384 (2)	O4—P1	1.5912 (14)
C2—N3	1.315 (3)	O6—P2	1.5235 (13)
N3—C4	1.370 (3)	O5—P2	1.4991 (13)
C4—C5	1.353 (3)	O7—P2	1.5687 (15)
O2—P1	1.5060 (14)		
C5—C6—C7	113.37 (16)	P2—C7—P1	114.75 (9)
C5—C6—C7—P1	61.98 (18)		

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O6^{i}	0.865 (19)	1.898 (19)	2.751 (2)	168.5 (19)
N3—H3···O3^{ii}	0.857 (18)	1.91 (2)	2.678 (2)	148 (2)
O1—H1A···O11^{iii}	0.85 (3)	1.87 (3)	2.667 (2)	156 (3)
O4—H4A···O10^{iv}	0.83 (2)	1.88 (2)	2.672 (2)	157 (2)
O7—H7A···O2^{iii}	0.83 (2)	1.66 (2)	2.492 (2)	179 (3)
O8—H8A···O4^{v}	0.85 (3)	2.22 (2)	3.061 (2)	170 (3)
O8—H8B···O5^{i}	0.84 (3)	2.12 (3)	2.960 (2)	173 (3)
O9—H9A···O7^{vi}	0.82 (2)	2.06 (2)	2.826 (2)	157 (2)
O9—H9B···O5^{vii}	0.83 (2)	2.09 (2)	2.907 (2)	171 (2)
O10—H10A···O9^{viii}	0.83 (2)	2.02 (2)	2.817 (2)	160 (2)
O10—H10B···O6^{i}	0.85 (2)	1.95 (2)	2.774 (2)	163.5 (19)
O11—H11A···O3	0.84 (2)	1.87 (2)	2.708 (2)	171 (3)
O11—H11B···O6^{ix}	0.84 (2)	1.98 (2)	2.793 (2)	165 (3)

Symmetry codes: (i) $1+x, y, z$; (ii) $2-x, -y, -z$; (iii) $x-1, y, z$; (iv) $x, y-1, z$; (v) $2-x, -y, 1-z$; (vi) $1-x, -y, 1-z$; (vii) $1-x, 1-y, 1-z$; (viii) $2-x, 1-y, 1-z$; (ix) $1+x, y-1, z$.

All crystals examined exhibited non-merohedral twinning, which roughly superimposed the a and b axes, and inverted the c axis. Two distinct triclinic cells were identified using *SMART* (Bruker, 2001) and integrated using *SAINT* (Bruker, 2001). Unit-cell parameters were determined from both components using *SAINT*. The twin law by rows was (0/1/0, 1/0/0, $\frac{1}{2}/\frac{1}{2}/-1$). Non-overlapping reflections from the primary orientation were used for phasing. Four frame series were filtered for statistical outliers, and then sorted, merged, scaled and corrected for absorption using *TWINABS*, an unpublished upgrade of *SADABS* (Bruker, 2001) written for non-merohedral twins. A unique section of reciprocal space was measured. However, owing to the close proximity of the non-merohedral twins, reflections filtered as statistical outliers left the fraction of data measured at full θ slightly less than ideal (0.88). Combined data with complete or no overlap were used for refinement. Crystal decay was monitored by collecting identical frames at the beginning and end of the experiment. No correction for decay as a function of X-ray exposure time was applied.

Space group $P\bar{1}$ was chosen for the system and confirmed by the successful refinement; the hydrogen-bonded dimer lies about an inversion centre, as shown in Fig. 1. R—H distances were restrained to ideal values, with an effective s.u. of 0.02 Å, and H—O—H angles were also restrained to ideal values (s.u. = 0.04°). The remaining H-atom parameters were refined independently without restraints. The relative volume of the secondary orientation converged at 0.2687 (7). The highest peaks in the final difference Fourier map were located along the C—P bonds; the final map had no other significant features. A final analysis of the variance between observed and calculated structure factors showed no dependence on amplitude or resolution.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; structure solution: *SHELXTL* (Bruker, 2001); structure refinement: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *CIFTAB* in *SHELXL*97 (Sheldrick, 2001) and *PLATON* (Spek, 2002).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1144). Services for accessing these data are described at the back of the journal.

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