Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

[2-(Dimethylsulfonio)-1-hydroxy-1-phosphonoethyl]phosphonate monohydrate

Yonghui Zhang,[a] Rong Cao,[b] Michael P. Hudock,[b] Scott R. Wilson[c] and Eric Oldfield[a]*

[a]Department of Chemistry, University of Illinois at Urbana-Champaign, 600 South Mathews Avenue, Urbana, Illinois 61801, USA, [b]Center for Biophysics and Computational Biology, University of Illinois at Urbana-Champaign, 607 South Mathews Avenue, Urbana, Illinois 61801, USA, and [c]School of Chemical Sciences, Box 59-1, University of Illinois at Urbana-Champaign, 505 South Mathews Avenue, Urbana, Illinois 61801, USA

Correspondence e-mail: eo@chad.scs.uiuc.edu

Key indicators

Single-crystal X-ray study
T = 273 K
Mean σ(C–C) = 0.001 Å
R factor = 0.024
wR factor = 0.071
Data-to-parameter ratio = 32.1

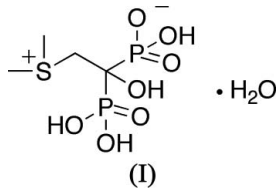
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 17 January 2006
Accepted 6 February 2006

In the title crystal structure, $C_4H_{12}O_7P_2S\cdot H_2O$, the sulfonium groups have a pyramidal geometry and bridging water molecules form a complex three-dimensional hydrogen-bond network involving neighboring phosphonate groups.

Comment

The title compound, (I), belongs to a family of widely used compounds, bisphosphonates, with a characteristic P—C—P linkage that mimics the P—O—P linkage of inorganic diphosphate. Bisphosphonates are used to treat bone resorption diseases such as osteoporosis (Sambrook *et al.*, 2004), and Paget's disease (Vasireddy *et al.*, 2003). In addition, they have been found to have antiparasitic (Yardley *et al.*, 2002; Martin *et al.*, 2001), as well as anticancer activity (*via* γδ T cells) (Sato *et al.*, 2005). They act by targeting the mevalonate pathway enzyme farnesyl diphosphate synthase (FPPS) (EC 2.5.1.10) (Martin *et al.*, 1999). Most bisphosphonates contain positively charged nitrogen-containing (ammonium, pyridinium, imidazolium) side chains, but other isosteres also have activity and we report here the structure of a novel sulfonium bisphosphonate, *viz*. (I).



(I)

The sulfonium bisphosphonate crystallizes as a monohydrate and has one neutral and one monoanionic phosphonate group balancing the +1 charge on the sulfonium group. The PCP backbone of the bisphosphonate group exists in a conformation similar to those reported previously [P1—C1—P2 = 113.87 (4)°] [incadronate (INC), isozoledronate (ISZ) and three hydrate forms of risedronate, namely the monohydrate (RMH), dihydrate (RDH) and 2.5-hydrate (RHP)] [INC 115.0 (2)°, ISZ 114.8 (1)°, RHP 112.4 (2)°, RDH 113.30 (15)° and RMH 113.22 (13)°; Montalvetti *et al.*, 2003; Gossman *et al.*, 2002, 2003]. The P—O distances are given in Table 1.

The dimethylsulfonium group has a distorted tetrahedral geometry with the two methyl groups having very similar C—S—C angles of ∼101° [C4—S1—C3 = 101.04 (5)°, C4—S1—C2 = 102.12 (5)° and C3—S1—C2 = 99.85 (4)°]. The distances of the two phosphate groups to the S atom [S1···P1 = 3.6596 (3) Å and S1···P2 = 4.3143 (3) Å] are consistent with

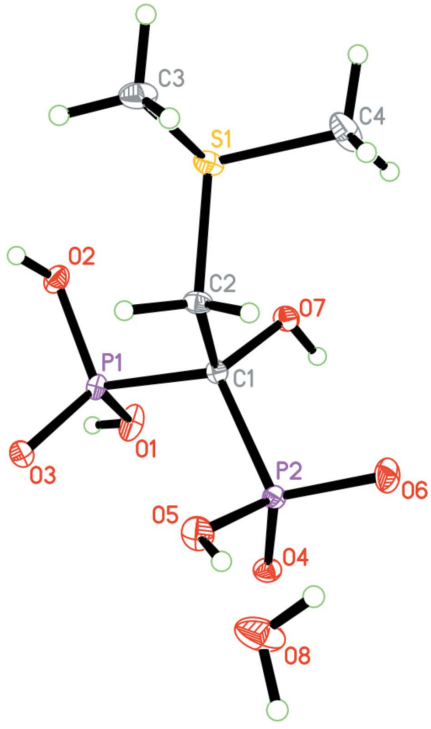


Figure 1
SHELXTL (Bruker, 2001) plot showing 35% probability ellipsoids for non-H atoms and circles of arbitrary size for H atoms.

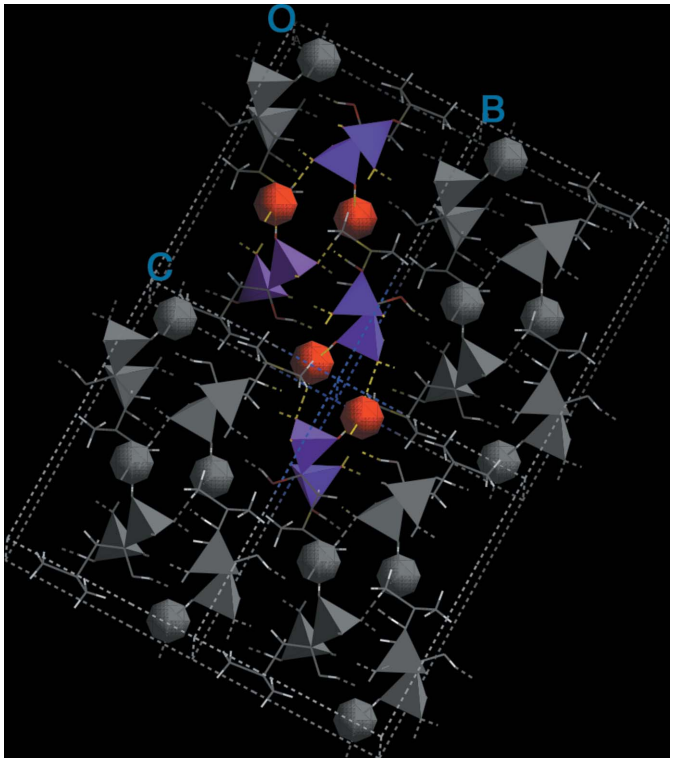


Figure 2
CERIUS^2 (Accelrys, 2005) view of the crystal structure, showing the proposed hydrogen-bond interactions between neighboring molecules. Several such interactions occur by way of 'bridging' water molecules and have been highlighted to 'guide the eye'. Hydrogen bonds are represented by dashed yellow lines, water molecules as red spheres and phosphonate groups as purple polyhedra.

the electrostatic interaction between the positively charged S atom and the anionic phosphonate group. The water molecules form a complex hydrogen bond network with all adjacent phosphonate groups (Fig. 2).

Experimental

Bromoacetic acid (2 mmol) was added to a solution of dimethyl sulfide (2 mmol) in acetone (5 ml) and stirred for 2 h. The white precipitate was filtered off, washed with diethyl ether and dried *in vacuo*. The resulting precipitate was added to a mixture of H_3PO_3 (5 equivalents) and toluene (5 ml) and heated to 353 K until the mixture melted. $POCl_3$ (5 equivalents) was added slowly and the mixture stirred at 353 K for 4 h. Upon cooling, the supernatant was decanted and 4 ml water added. The mixture was refluxed for 1 h. Most of the solvent was then removed *in vacuo* and acetone was added to precipitate the anhydrous sulfonium bisphosphonate. The resulting white powder was collected and crystallized from ethanol–water (2:1). Analysis calculated for $C_4H_{12}O_7P_2S$: C 18.05, H 4.54%; found: C 18.43, H 4.70%. ^{1}H NMR (500 MHz, D_2O): δ 3.50–3.61 (*m*, 2H), 2.65 (*s*, 6H). ^{31}P NMR (162 MHz, D_2O): δ 15.6 (*s*). The final crystals were grown by vapor diffusion of ethanol into an aqueous solution of the bisphosphonate at room temperature, using the sitting-drop method and yielding the monohydrate.

Crystal data

$C_4H_{12}O_7P_2S\cdot H_2O$
M_r = 284.15
Monoclinic, $P2_1/c$
a = 7.1107 (2) Å
b = 10.2149 (3) Å
c = 15.1091 (4) Å
β = 101.653 (10)°
V = 1074.83 (6) Å^3
Z = 4
D_x = 1.756 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 7336 reflections
θ = 2.9–36.3°
μ = 0.62 mm^{-1}
T = 273 (2) K
Column, colorless
0.51 × 0.24 × 0.03 mm

Data collection

Bruker Kappa-APEXII CCD diffractometer
φ and ω scans
Absorption correction: integration (*SHELXTL/XPREP*; Bruker, 2001)
T_{min} = 0.774, T_{max} = 0.955
26896 measured reflections
5196 independent reflections
4605 reflections with $I > 2\sigma(I)$
R_{int} = 0.021
θ_{max} = 36.3°
$h = -11 \rightarrow 11$
$k = -15 \rightarrow 17$
$l = -13 \rightarrow 25$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.024
$wR(F^2)$ = 0.071
S = 1.06
5196 reflections
162 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0343P)^2 + 0.3181P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.68 e Å^{-3}
$\Delta\rho_{min}$ = −0.55 e Å^{-3}

Table 1
Selected bond lengths (Å).

P2—O6	1.5031 (7)	P1—O3	1.4962 (7)
P2—O4	1.5148 (7)	P1—O1	1.5335 (7)
P2—O5	1.5525 (7)	P1—O2	1.5624 (7)
P2—C1	1.8528 (8)	P1—C1	1.8486 (8)

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

D—H···A	D—H	H···A	D···A	D—H···A
O8—H13···O3^{i}	0.859 (14)	1.892 (15)	2.7435 (11)	171.0 (19)
O7—H4···O3^{ii}	0.826 (12)	1.915 (12)	2.7138 (9)	162.6 (14)
O2—H2···O4^{iii}	0.809 (13)	1.721 (13)	2.5287 (10)	176.4 (16)
O1—H1···O6^{iv}	0.814 (13)	1.643 (13)	2.4420 (9)	166.4 (17)
O5—H3···O8	0.781 (13)	1.728 (13)	2.5049 (10)	172.7 (18)
O8—H14···O4^{v}	0.867 (14)	1.959 (15)	2.7975 (11)	162.3 (18)

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

Methyl H atom positions, R—CH_3, were optimized by rotation about R—C bonds with idealized C—H, R—H and H···H distances (methyl C—H = 0.96 Å with AFIX 137). Methylene and hydroxyl H-atom positions were located in late difference Fourier maps and restrained to ideal bond lengths (O—H = 0.84 Å) using an effective standard deviation of 0.02 Å. Methyl and hydroxyl H-atom U_{iso}(H) values were assigned as 1.5 times U_{eq} of the carrier atom; remaining H-atom U_{iso}(H) values were assigned as 1.2 times carrier atom U_{eq}.

Data collection: *APEX2* (Bruker, 2004); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Bruker, 2001); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: XCIF (Bruker, 2001).

This work was supported in part by the United States Public Health Service (grant GM-65307 to EO). YZ is an American Heart Association, Midwest Affiliate, Postdoctoral Fellow. The Materials Chemistry Laboratory at the University of Illinois was supported in part by grants NSF CHE 95–03145 and NSF CHE 03–43032 from the National Science Foundation.

References

Accelrys (2005). *CERIUS*^{2}. Accelrys, Inc., San Diego, CA, USA.
Bruker (2001). *SAINT* (Version 6.22), *SHELXTL* (Version 6.12) and *XCIF*. Bruker AXS Inc., Madison, Wisconsin, USA.
Bruker (2004). *APEX2*. Version 1.0-27. Bruker AXS Inc., Madison, Wisconsin, USA.
Gossman, W. L., Wilson, S. R. & Oldfield, E. (2002). *Acta Cryst.* C**58**, m599–600.
Gossman, W. L., Wilson, S. R. & Oldfield, E. (2003). *Acta Cryst.* C**59**, m33–36.
Martin, M. B., Arnold, W., Heath, H. T., 3rd, Urbina, J. A. & Oldfield, E. (1999). *Biochem. Biophys. Res. Commun.* **263**, 754–758.
Martin, M. B., Grimley, J. S., Lewis, J. C., Heath, H. T., 3rd, Bailey, B. N., Kendrick, H., Yardley, V., Caldera, A., Lira, R., Urbina, J. A., Moreno, S. N., Docampo, R., Croft, S. L. & Oldfield, E. (2001). *J. Med. Chem.* **44**, 909–916.
Montalvetti, A., Fernandez, A., Sanders, J. M., Ghosh, S., Van Brussel, E., Oldfield, E. & Docampo, R. (2003). *J. Biol. Chem.* **278**, 17075–17083.
Sambrook, P. N., Geusens, P., Ribot, C., Solimano, J. A., Ferrer-Barriendos, J., Gaines, K., Verbruggen, N. & Melton, M. E. (2004). *J. Intern. Med.* **255**, 503–511.
Sato, K., Kimura, S., Segawa, H., Yokota, A., Matsumoto, S., Kuroda, J., Nogawa, M., Yuasa, T., Kiyono, Y., Wada, H. & Maekawa, T. (2005). *Int. J. Cancer*, **116**, 94–99.
Vasireddy, S., Talwalkar, A., Miller, H., Mehan, R. & Swinson, D. R. (2003). *Clin. Rheumatol.* **22**, 376–380.
Yardley, V., Khan, A. A., Martin, M. B., Slifer, T. R., Araujo, F. G., Moreno, S. N., Docampo, R., Croft, S. L. & Oldfield, E. (2002). *Antimicrob. Agents Chemother.* **46**, 929–931.