Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

1-Hydroxy-1-phosphono-2-(trimethylarsonium-1-yl)ethanephosphonate monohydrate

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

[a]Center for Biophysics and Computational Biology, University of Illinois at Urbana–Champaign, 607 South Mathews Avenue, Urbana, Illinois 61801, USA, [b]Department of Chemistry, University of Illinois at Urbana–Champaign, 600 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 = 193 K
Mean σ(C–C) = 0.004 Å
R factor = 0.033
wR factor = 0.092
Data-to-parameter ratio = 18.8

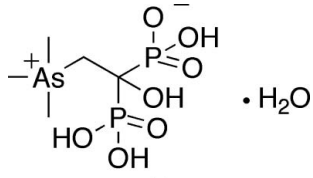
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 6 January 2006
Accepted 17 January 2006

In the crystal structure of the title compound, $C_5H_{15}AsO_7P_2\cdot H_2O$, hydrogen-bonded sheets are formed which contain bisphosphonate(1−) groups and water molecules alternating with trimethylarsonium groups.

Comment

Bisphosphonates, especially N-containing bisphosphonates with positively charged side-chains, are the preferred choice of treatment for bone resorption diseases, such as osteoporosis (Sambrook *et al.*, 2004), osteopenia and Paget's disease (Vasireddy *et al.*, 2003). They act by inhibiting the isoprenoid biosynthesis pathway enzyme farnesyl diphosphate synthase (FPPS; EC No. 2.5.1.10), resulting in the inhibition of protein prenylation. In addition, FPPS inhibition leads to an accumulation of isopentenyl diphosphate which is converted to the strongly pro-apoptotic ATP analog ApppI, the isopentenyl ester of ATP, which inhibits the mitochondrial ADP/ATP transporter (Mönkkönen *et al.*, 2004). Previously, we proposed a possible mechanism of action for FPPS inhibition, suggesting that the N-containing bisphosphonates act as carbocation transition state or reactive intermediate analogs of the FPPS enzyme (Martin *et al.*, 1999). In order to provide additional data for QSAR (quantitative structure–activity relationship) investigations, we now report the synthesis and structure of the title novel As-containing bisphosphonate, (I).



(I)

While arsenicals in general may have limited therapeutic utility, arsenic has been used for the treatment of myelodysplastic syndromes (Faderl & Kantarjian, 2004) and melarsoprol is also the first-line therapy for advanced central nervous system East African trypanosomiasis (Katzung, 2004).

The title compound crystallizes as the zwitterionic monohydrate, with the unprotonated atom O6 balancing the positively charged arsenic As1, resulting in a net zero charge on the molecule. This protonation state is also consistent with the bond lengths observed: P3—O6 = 1.556 (2), P3—O5 = 1.541 (2) and P3—O7 = 1.491 (2) Å. A displacement ellipsoid rendering of the molecule is presented in Fig. 1.

The geometry of the bisphosphonate backbone in (I) is very similar to that seen with other bisphosphonates (Gossman *et*

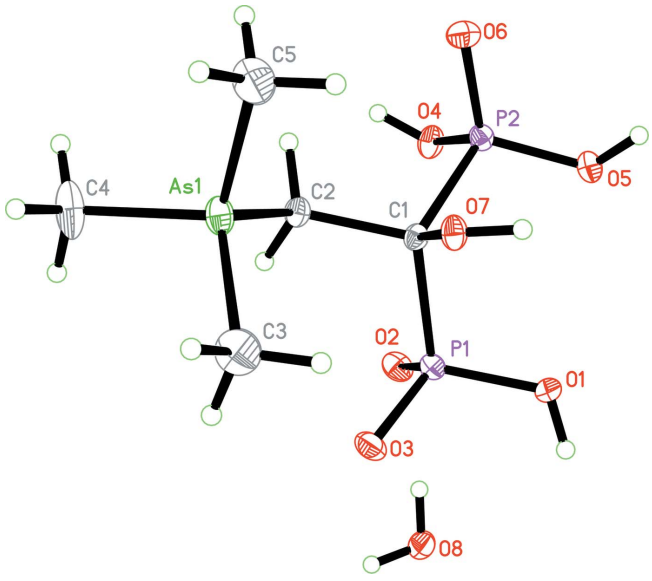


Figure 1
The asymmetric unit of (I), showing 35% probability displacement ellipsoids. H atoms are drawn as circles of arbitrary size.

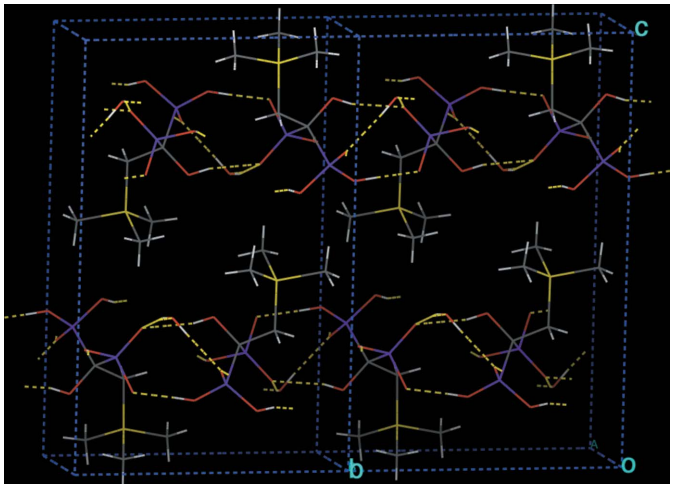


Figure 2
Cerius^2 (Accelrys, 2005) view along the *a* axis, showing the proposed hydrogen-bond interactions (dashed lines) between neighboring molecules of (I). Hydrogen-bonded sheets are perpendicular to the *c* axis.

al., 2002, 2003). The molecules pack in an intercalated sheet-like structure, where the bisphosphonate groups are contained within a plane with the trimethylarsonium groups on alternating sides, represented in Fig. 2.

There is an extensive hydrogen-bond network throughout the bisphosphonate backbone of (I) (Table 1). The unprotonated O atoms from one bisphosphonate form hydrogen bonds with a neighboring bisphosphonate. This interaction is also stabilized by hydrogen bonding with a water molecule located in the bisphosphonate sheet. As expected, the bonding around the As atom is tetrahedral, with angles of 110.41 (17), 108.98 (17) and 107.36 (16)°, and the C—As bond lengths of 1.923 (3), 1.905 (4), 1.905 (3) and 1.901 (4) Å are much larger than those found with the sulfonium [1.8153 (8), 1.7912 (10) and 1.792 (11) Å; Zhang *et al.*, 2006] and phosphonium [1.806 (2) 1.789 (2), 1.779 (2) and 1.1780 (2) Å; Cao *et al.*, 2006] species.

Experimental

Arsenobetaine bromide (2 mmol) 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 then added slowly and the mixture stirred at 353 K for 4 h. Upon cooling, the supernatant was decanted and 4 ml of water added, and the mixture was refluxed for 1 h. Most of the solvent was then removed *in vacuo*, and then acetone was added to precipitate the title compound. The resulting white powder was collected and crystallized from ethanol–H_2O (2:1 *v*/*v*) to afford the pure anhydrous compound. Analysis, calculated for $C_5H_{15}AsO_7P_2$: C 18.53, H 4.67%; found: C 18.30, H 4.65. ^{1}H NMR (400 MHz, D_2O, δ, p.p.m.): 2.82 (*t*, J = 11.8 Hz, 2H), 1.69 (*s*, 9H); ^{31}P NMR (162 MHz, D_2O, δ, p.p.m.): 17.3 (*s*). The final crystals were grown by sitting-drop vapor diffusion of ethanol into an aqueous solution of the compound at room temperature, yielding the monohydrate.

Crystal data

$C_5H_{15}AsO_7P_2\cdot H_2O$
M_r = 342.05
Monoclinic, $P2_1/c$
a = 7.171 (8) Å
b = 10.487 (12) Å
c = 16.849 (19) Å
β = 97.284 (16)°
V = 1257 (2) Å^3
Z = 4
D_x = 1.808 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 897 reflections
θ = 2.3–28.3°
μ = 2.98 mm^{-1}
T = 193 (2) K
Tablet, colorless
0.32 × 0.17 × 0.05 mm

Data collection

Bruker SMART CCD area-detector diffractometer
Profile data from ω scans
Absorption correction: integration (*XPREP* in *SHELXTL*; Bruker, 2001)
T_{min} = 0.442, T_{max} = 0.865
11918 measured reflections
3126 independent reflections
2265 reflections with $I > 2\sigma(I)$
R_{int} = 0.050
θ_{max} = 28.4°
$h = -9 \rightarrow 9$
$k = -13 \rightarrow 14$
$l = -21 \rightarrow 22$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.033
$wR(F^2)$ = 0.092
S = 0.87
3126 reflections
166 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0615P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.005
$\Delta\rho_{max}$ = 0.56 e Å^{-3}
$\Delta\rho_{min}$ = −0.76 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···O6^{i}	0.814 (18)	1.69 (2)	2.486 (4)	165 (4)
O8—H17···O6^{ii}	0.810 (18)	1.951 (19)	2.759 (4)	174 (4)
O7—H4···O2^{iii}	0.827 (17)	1.98 (2)	2.759 (4)	157 (3)
O5—H3···O3^{iii}	0.861 (17)	1.617 (18)	2.471 (4)	171 (3)
O8—H16···O2	0.829 (18)	1.93 (2)	2.747 (4)	169 (4)
O4—H2···O8^{iv}	0.837 (18)	1.69 (2)	2.514 (3)	166 (4)

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

Methylene H atoms are placed geometrically and treated as riding. Methyl H-atom positions were optimized by rotating about R—C bonds with idealized C—H (0.98–0.99 Å), *R*—H and H···H distances. Hydroxyl H atoms were located in a difference Fourier map and restrained to ideal bond lengths using an effective standard uncertainty of 0.02 Å; U_{iso}(H) = 1.5U_{eq}(parent) for methyl and hydroxyl H atoms, or 1.2U_{eq}(parent) for all other H atoms.

Data collection: *SMART* (Bruker, 2001); 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 No. GM-073216 to EO). The Materials Chemistry Laboratory at the University of Illinois was supported in part by grant Nos. NSF CHE 95–03145 and NSF CHE 03–43032 from the National Science Foundation. YZ is an American Heart Association, Midwest Affiliate, Postdoctoral Fellow.

References

Accelrys (2005). *Cerius*^{2}. Accelrys Inc., San Diego, CA, USA.
Bruker (2001). *SAINT* (Version 6.22), *SHELXTL* (Version 6.12), *SMART* (Version 5.625) and XCIF. Bruker AXS Inc., Madison, Wisconsin, USA.
Cao, R., Hudock, M. P., Zhang, Y., Wilson, S. R. & Oldfield, E. (2006). *Acta Cryst. E* . Submitted.
Faderl, S. & Kantarjian, H. M. (2004). *Cancer*, **101**, 226–241.
Gossman, W. L., Wilson, S. R. & Oldfield, E. (2002). *Acta Cryst.* C**58**, m599–m600.
Gossman, W. L., Wilson, S. R. & Oldfield, E. (2003). *Acta Cryst.* C**59**, m33–m36.
Katzung, B. G. (2004). *Basic and Clinical Pharmacology*, 9th edition, pp. 882–884. New York: McGraw–Hill.
Martin, M. B., Arnold, W., Heath, H. T. III, Urbina, J. A. & Oldfield, E. (1999). *Biochem. Biophys. Res. Commun.* **263**, 754–758.
Mönkkönen, H., Lehenkari, P. P., Kellinsalmi, M., Hassinen, I. E., Auriola, S., Vepsalainen, J. & Monkkonen, J. (2004). *Bone*, **34**, S66–S67.
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.
Vasireddy, S., Talwalkar, A., Miller, H., Mehan, R. & Swinson, D. R. (2003). *Clin. Rheumatol.* **22**, 376–380.
Zhang, Y., Cao, R., Hudock, M. P., Wilson, S. R. & Oldfield, E. (2006). *Acta Cryst.* E**62**. Submitted.