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Hydronium (cycloheptylammonio)-methylene-1,1-bisphosphonate (hydronium incadronate)

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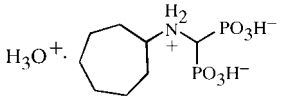
The structure of the title compound, $H_3O^+\cdot C_8H_{18}NO_6P_2^-$, adopts a zwitterionic form containing an alkylammonium group, a hydronium ion, and two negatively charged phosphonate groups. The cycloheptyl side chain adopts a twist-chair conformation. The crystal packing is dominated by an extensive hydrogen-bonding network.

Comment

Incadronate (INC), a patented α-nitrogen-containing bisphosphonate (Yamanouchi Pharmaceutical Co., Bisphonal), is a potent inhibitor of osteoclastic bone resorption. α-Nitrogen bisphosphonates are an unusual type of nitrogen-containing bisphosphonate, since the hydroxyl group found in most clinically used bisphosphonates is replaced by an H atom, and the N atom is located α rather than γ (pamidronate, Aredia) or δ [alendronate (Fosamax) and risedronate (Actonel)] with respect to the backbone C atom.



(I)

Incadronate has been shown to be ten times more potent than alendronate when used to treat patients with malignancy-associated hypercalcemia (Usui *et al.*, 1997) and 50-fold more potent than pamidronate in treating tumor-induced hypercalcemia in rats (Takahashi *et al.*, 1998). In addition to its use in the treatment of bone disorders, incadronate (and other bisphosphonates) has shown potential as a cholesterol-lowering agent. For example, of seven drugs tested, incadronate was the most potent inhibitor of squalene synthase and cholesterol biosynthesis in rats (Amin *et al.*, 1992). In addition, in other related work, it has been shown that incadronate specifically induces apoptosis in human myeloma cells (Shipman *et al.*, 1998).

Incadronate is a low nanomolar inhibitor of farnesyl pyrophosphate (FPP) synthase, and in bone resorption most likely functions by inhibiting this enzyme (van Beek *et al.*, 1999). However, the exact nature of the interaction between FPP synthase and bisphosphates is unknown. One possibility is that they act as azaisoprenoid analogs which can dock in the geranyl pyrophosphate binding site (Martin *et al.*, 1999).

In order to begin to explore these interactions in more detail, it is desirable to obtain high-resolution crystal structures of such bisphosphonates for use in quantitative structure–activity relationship studies and for calibrating the results of other spectroscopic techniques. The crystal structure of hydronium incadronate, (I), is reported herein.

The α-N atom in (I) (Fig. 1) has two H atoms, giving it a +1 charge. The phosphonate groups both have an O atom that is protonated (O3 and O6) [P1—O3 = 1.560 (3) Å and P2—O6 = 1.562 (3) Å] and two O atoms that are unprotonated (O1, O2, O4 and O5) [P1—O1 = 1.509 (3) Å, P1—O2 = 1.496 (3) Å, P2—O4 = 1.528 (3) Å and P2—O5 = 1.479 (3) Å], resulting in both phosphonate groups being negatively charged. With the +1 charge on the α-N atom, the overall 2− charge on the phosphonate groups, and the presence of the hydronium ion, incadronate exists in the zwitterionic form common to many bisphosphonates (Vega *et al.*, 1996, 1998, 2002).

The cycloheptyl side chain of (I) exists in a twist-chair conformation, as determined by inspection of the torsion angles (Table 1) and comparison with the results of Allen *et al.* (1993). The PCP backbone of the bisphosphonate group has a similar conformation to those found in two other bisphosphonates [isozoledronate (ISZ) and three hydrate forms of risedronate, namely monohydrate (RMH), dihydrate (RDH) and 2.5-hydrate (RHP)] studied recently [INC 115.0 (2)°, RHP 112.4 (2)°, RDH 113.30 (15)°, RMH 113.22 (13)° and ISZ 114.8 (1)°] (Gossman *et al.*, 2002, 2003). Examining the orientation of the phosphonate group with respect to the side chain shows that the angle between the bisphosphonate group and the side chain is also very similar [C1—N1—C2 = 119.2 (3)°] to those found in isozoledronate and risedronate (Gossman *et al.*, 2002, 2003), even with the α-N atom substitution.

One major difference in the structure of (I) to those previously examined is the orientation of the phosphonate group with respect to the ring. The cycloheptyl ring is nearly

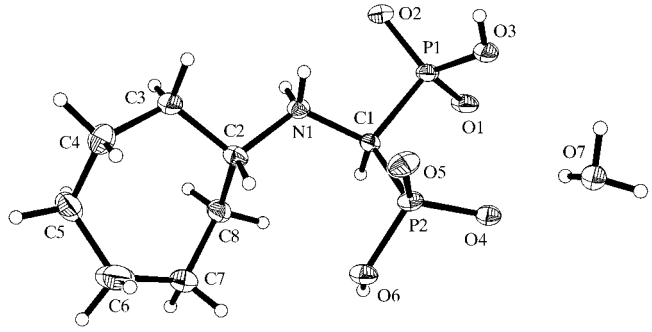


Figure 1
A *SHELXTL* (Bruker, 2001) plot showing the atom-numbering scheme and ellipsoids at the 35% probability level. H atoms are shown as small spheres of arbitrary radii.

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perpendicular to the first phosphonate group [P1—C1—N1—C2 = 178.2 (3)°], whereas in the four previously examined structures, the first phosphonate group adopts a more extended form [ISZ: P1—C5—C6—C7 = 62.0 (2)°; RHP: P1—C1—C2—C3 = 52.8 (6)°, RMH: P1—C1—C2—C3 = 57.8 (3)°; RDH: P1—C1—C2—C3 = 61.7 (3)°]. The crystals of incadronate are held together through an extensive hydrogen-bond network which consist of at least eight hydrogen bonds (Table 2).

Experimental

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

Crystal data

$H_3O^+\cdot C_8H_{18}NO_6P_2^-$
M_r = 305.20
Monoclinic, $P2_1/c$
a = 14.144 (5) Å
b = 10.907 (3) Å
c = 9.052 (3) Å
β = 104.196 (5)°
V = 1353.8 (8) Å^3
Z = 4
D_x = 1.497 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 920 reflections
θ = 3.0–27.3°
μ = 0.35 mm^{-1}
T = 193 (2) K
Tabular, colorless
0.30 × 0.24 × 0.08 mm

Data collection

Siemens Platform/CCD diffractometer
Profile data from ω scans
Absorption correction: by integration (*XPREP*; Bruker, 2001)
T_{min} = 0.912, T_{max} = 0.974
7489 measured reflections
2463 independent reflections
1685 reflections with $I > 2\sigma(I)$
R_{int} = 0.109
θ_{max} = 25.3°
$h = 0 \rightarrow 17$
$k = -13 \rightarrow 0$
$l = -10 \rightarrow 10$
159 standard reflections
frequency: 320 min
intensity decay: 1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.058
$wR(F^2)$ = 0.162
S = 1.05
2463 reflections
186 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0958P)^2 + 0.401P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.47 e Å^{-3}
$\Delta\rho_{min}$ = −0.48 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O1—P1	1.509 (3)	O4—P2	1.528 (3)
O2—P1	1.496 (3)	O5—P2	1.479 (3)
O3—P1	1.560 (3)	O6—P2	1.562 (3)
P2—C1—P1	115.0 (2)	C1—N1—C2	119.2 (3)
C8—C2—C3—C4	71.4 (5)	C5—C6—C7—C8	23.5 (8)
C2—C3—C4—C5	−58.4 (6)	C3—C2—C8—C7	−87.9 (4)
C3—C4—C5—C6	74.5 (6)	C6—C7—C8—C2	49.8 (6)
C4—C5—C6—C7	−77.1 (7)	P1—C1—N1—C2	178.2 (3)

Four frame series were filtered for statistical outliers and corrected for absorption by integration using *SHELXTL*/*XPREP* (Bruker, 2001), then were sorted, merged and scaled using *SAINT*/*SADABS* (Bruker, 2001). 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. The proposed model includes one hydronium ion. Donor H-atom positions were refined under restraint to idealized O—H and N—H distances, with an effective s.u. of 0.03 Å. The remaining H atoms were included as riding idealized contributors [U_{iso} = 1.2U_{eq} (C)]. The highest peaks in the final difference Fourier map were in the vicinity of the bisphosphonate moiety, suggesting possible additional disorder of the H atoms; however, models incorporating a more complex disordered scheme failed to converge with chemically reasonable geometry. A final analysis of variance between observed and calculated structure factors showed no dependence on amplitude or resolution.

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···O4^{i}	0.88 (3)	2.02 (3)	2.893 (4)	176 (4)
N1—H1B···O1^{ii}	0.93 (3)	2.16 (3)	3.066 (5)	166 (4)
O3—H3C···O1^{i}	0.83 (3)	1.75 (3)	2.539 (4)	157 (5)
O6—H6···O5^{iii}	0.81 (3)	1.75 (3)	2.554 (4)	170 (5)
O7—H7C···O4^{iv}	0.85 (3)	1.75 (4)	2.493 (4)	144 (5)
O7—H7E···O2^{v}	0.87 (3)	1.63 (3)	2.503 (4)	179 (5)
O7—H7D···O1^{ii}	0.84 (3)	2.01 (3)	2.760 (5)	148 (5)
O7—H7D···O3^{ii}	0.84 (3)	2.40 (4)	3.117 (5)	144 (4)

Symmetry codes: (i) $x, \frac{3}{2}-y, \frac{1}{2}+z$; (ii) $-x, 1-y, -z$; (iii) $x, \frac{3}{2}-y, z-\frac{1}{2}$; (iv) $x, y-1, z$; (v) $-x, y-\frac{1}{2}, \frac{1}{2}-z$.

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: *CIFTAB* in *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1146). Services for accessing these data are described at the back of the journal.

References

Allen, F. H., Howard, J. A. K. & Pitchford, N. A. (1993). *Acta Cryst.* B**49**, 910–928.
Amin, D., Cornell, S. A., Gustafson, S. K., Needle, S. J., Ullrich, J. W., Bilder, B. E. & Perrone, M. H. (1992). *J. Lipid Res.* **33**, 1657–1663.
Beek, E. van, Pieterman, E., Cohen, L., Lowik, C. & Papapoulos, S. (1999). *Biochem. Biophys. Res. Commun.* **264**, 108–111.
Bruker (2001). *SMART* (Version 5.625), *SAINT* (Version 6.22), *SHELXTL* (Version 6.12) and *XPREP*. Bruker AXS Inc., Madison, Wisconsin, USA.
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.
Martin, M. B., Arnold, W., Heath, H. T. III, Urbina, J. A. & Oldfield, E. (1999). *Biochem. Biophys. Res. Commun.* **263**, 754–758.
Shipman, C. M., Croucher, P. I., Russell, R. G., Helfrich, M. H. & Rogers, M. J. (1998). *Cancer Res.* **58**, 5924–5297.
Takahashi, K., Shirahata, A., Fukushima, S., Satoshi, K., Teramura, K. & Usuda, S. (1998). *Jpn J. Pharmacol.* **76**, 155–163.
Usui, T., Oiso, Y., Tomita, A., Ogata, E., Uchida, T., Ikeda, K., Watanabe, T. & Higuchi, S. (1997). *Int. J. Clin. Pharmacol. Ther.* **35**, 239–244.
Vega, D., Baggio, R. & Garland, M. T. (1996). *Acta Cryst.* C**52**, 2198–2201.
Vega, D., Baggio, R. & Piro, O. (1998). *Acta Cryst.* C**54**, 324–327.
Vega, D., Fernandez, D. & Ellena, J. A. (2002). *Acta Cryst.* C**58**, m77–m80.