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trans-(4-Methylcyclohexylcarbamoyl)phosphonic acid: a representative matrix metalloproteinase (MMP) inhibitor

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Key indicators

Single-crystal X-ray study
T = 173 K
Mean σ(C–C) = 0.004 Å
R factor = 0.048
wR factor = 0.105
Data-to-parameter ratio = 13.6

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

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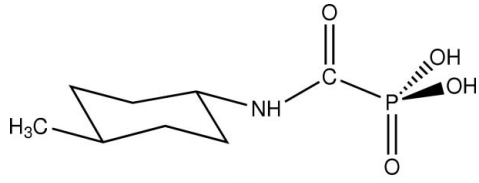
Carbamoylphosphonate MMP inhibitors. V.

The title compound, $C_8H_{16}NO_4P$, is the first carbamoylphosphonic acid for which the crystal structure has been solved. The $-PO_3H_2$ group has three distinct P—O bond distances of 1.483 (1), 1.506 (1) and 1.545 (2) Å. Hydrogen bonds of types P—O—H···O=C and N—H···O=P [2.416 (2) and 2.954 (2) Å, respectively] connect the molecules to form a chain of condensed ten-membered hydrogen-bonded rings. The second P—O—H group of each phosphonic acid is hydrogen-bonded to an O=P group of the next chain, so serving to link adjacent chains together.

Comment

Matrix metalloproteinases (MMPs) are enzymes that, if overexpressed, are involved in a wide range of harmful biological activities. Therefore, over the last two decades or so, there has been a worldwide research effort directed at the development of clinically useful inhibitors of these enzymes [for recent reviews, see Matter & Schudok (2004), Skiles *et al.* (2004) and Breuer *et al.* (2005)].



(I)

We have recently reported that some classes of carbamoylphosphonates act as potent non-toxic MMP inhibitors which are active *in vivo* (Breuer, Salomon *et al.*, 2004; Reich *et al.*, 2005). In the course of structure–activity relationship studies of our novel inhibitors for various medically important MMP subtypes, we required stereochemically defined *cis*- and *trans*-4-methylcyclohexylcarbamoylphosphonic acids (Breuer, Katz *et al.*, 2004). The title

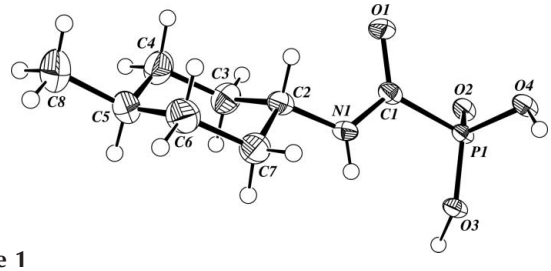


Figure 1
The molecular structure of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

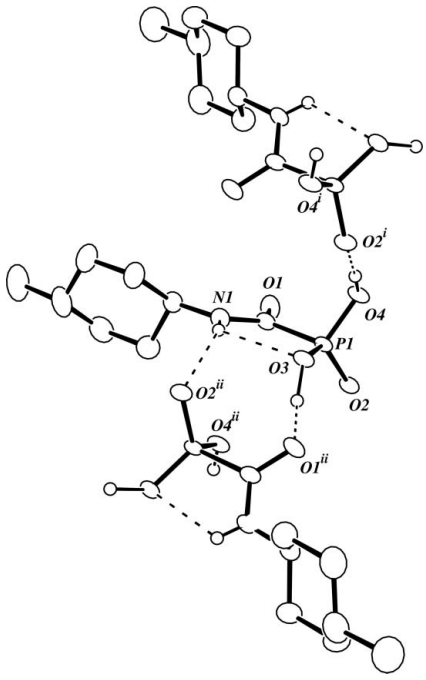


Figure 2
Part of the crystal structure of (I), showing the different types of hydrogen bonding. Most H atoms have been omitted for the sake of clarity. [Symmetry codes: (i) $x, \frac{3}{2} - y, \frac{1}{2} + z$; (ii) $1 - x, -\frac{1}{2} + y, \frac{1}{2} - z$.]

compound, (I), is the first carbamoylphosphonic acid for which the X-ray structure has been determined (Fig. 1).

More than a quarter of a century ago, Jones & Kennard (1978) reported the X-ray crystal structure of monosodium acetylphosphonate acetic acid solvate, which can be considered the parent compound of the class of acylphosphonic acids. Gibson & Karaman (1989) later reported the structures of the related (*Z*)- and (*E*)-oxyiminophosphonates, which were derived from the related acylphosphonates.

The crystal structure of (I) consists of a rather simple net of hydrogen bonds (Fig. 2 and Table 2). In each molecule there are three donors, namely one N—H and two P—O—H, and two acceptors, namely P═O and C═O. The amine H atom is involved in a trifurcated hydrogen bond, one intramolecular [N1···O3 2.916 (2) Å] and two intermolecular [N1···O2($1 - x, y - \frac{1}{2}, \frac{1}{2} - z$) 2.954 (2) Å and N1···O3($1 - x, 1 - y, 1 - z$) 3.118 Å]. The same O3 atom of the first molecule also acts as a donor to the C═O group of the second molecule [O3···O1($1 - x, y - \frac{1}{2}, \frac{1}{2} - z$) 2.416 (2) Å], thus forming a ten-membered ring with graph-set notation $R_2^2(10)$ (Bernstein *et al.*, 1995). Rings of this type condense together to form an infinite chain parallel to the *b* axis. Finally, adjacent chains link each other *via* O4···O2($x, \frac{3}{2} - y, z + \frac{1}{2}$) [2.518 (2) Å] hydrogen bonds.

The very short P—O3—H···O1═C1 [2.416 (2) Å] hydrogen bond is worthy of further consideration. A survey of the Cambridge Structural Database (Version 5.26, February 2005 release; Allen, 2002) for structures containing this type of phosphoryl–carbonyl interaction revealed 14 examples. Only one structure has a value (2.426 Å; Sawka-Dobrowolska *et al.*, 1987) close to that of (I), while the average value is 2.529 Å. On the other hand, the geometrical parameters of the C—PO_3 group in (I) (Table 1) are similar to those of acetylphosphonate (P—O 1.489, 1.505 and 1.563 Å, and C—P 1.859 Å; Jones & Kennard, 1978).

The refined position of atom H3 requires additional attention. Its relatively high thermal motion (0.08 Å^2), the rather long O3—H3 distance (1.13 Å) and the long C1═O1 bond (1.275 Å) demand a more careful examination of the difference Fourier map along the O3···O1 line. Two maxima were found, one at (0.595, 0.413, 0.325), 1.06 Å away from atom O1 of an adjacent molecule, and the second at (0.582, 0.502, 0.328), 0.73 Å from atom O3. Averaging these two positons gives a point very close to the coordinates of the refined atom H3. The atom H3 in Fig. 2 represents its average position.

Experimental

The synthesis and separation of *cis*- and *trans*-4-methylcyclohexylcarbamoylphosphonic acids were described recently by us (Breuer, Katz *et al.*, 2004). Crystals of the *trans*-isomer, (I) (m.p. 442–444 K), suitable for single-crystal X-ray diffraction, were obtained by slow evaporation of an ethanol solution.

Crystal data

$C_8H_{16}NO_4P$
$M_r = 221.19$
Monoclinic, $P2_1/c$
$a = 15.0959$ (15) Å
$b = 8.2686$ (8) Å
$c = 9.3397$ (9) Å
$\beta = 94.812$ (2)°
$V = 1161.7$ (2) Å^3
$Z = 4$
$D_x = 1.265$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 1967 reflections
$\theta = 2.7$–$27.9°$
$\mu = 0.23$ mm^{-1}
$T = 173$ (1) K
Plate, colourless
0.17 × 0.15 × 0.09 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: integration [face-indexed; *XPREP* (Bruker, 2003)]
$T_{min} = 0.730$, $T_{max} = 0.982$
6852 measured reflections
2522 independent reflections
2029 reflections with $I > 2\sigma(I)$
$R_{int} = 0.037$
$\theta_{max} = 27.0°$
$h = -19 \rightarrow 18$
$k = -9 \rightarrow 10$
$l = -10 \rightarrow 11$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.048$
$wR(F^2) = 0.105$
$S = 1.07$
2522 reflections
185 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0492P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.55$ e Å^{-3}
$\Delta\rho_{min} = -0.26$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

C1—P1	1.842 (2)	O3—P1	1.5060 (13)
O2—P1	1.4833 (14)	O4—P1	1.5454 (14)
O2—P1—O3	118.53 (8)	O2—P1—C1	107.80 (8)
O2—P1—O4	109.69 (8)	O3—P1—C1	106.13 (8)
O3—P1—O4	110.95 (8)	O4—P1—C1	102.40 (9)
O1—C1—P1—O2	−50.87 (18)	N1—C1—P1—O3	2.50 (19)
O1—C1—P1—O3	−178.82 (15)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O4—H4···O2^{i}	0.80 (3)	1.72 (3)	2.5184 (19)	173 (3)
O3—H3···O1^{ii}	1.13 (3)	1.29 (3)	2.4156 (18)	173 (3)
N1—H1···O3	0.80 (2)	2.46 (2)	2.916 (2)	117 (2)
N1—H1···O2^{ii}	0.80 (2)	2.25 (2)	2.954 (2)	146 (2)
N1—H1···O3^{iii}	0.80 (2)	2.57 (2)	3.118 (2)	127 (2)

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

All H atoms were located in difference Fourier maps and were refined isotropically.

Data collection: *SMART* (Bruker, 2003); cell refinement: *SAINT-Plus* (Bruker, 2003); data reduction: *SAINT-Plus*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 2000); software used to prepare material for publication: *SHELXTL*.

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