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Key indicators

Single-crystal X-ray study T = 173 KMean $\sigma(C-C) = 0.004 \text{ Å}$ R factor = 0.048 wR factor = 0.105Data-to-parameter ratio = 13.6

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

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

The $C_8H_{16}NO_4P$ title compound. is the first carbamoylphosphonic acid for which the crystal structure has been solved. The -PO₃H₂ 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- $H \cdot \cdot \cdot O = P [2.416 (2) \text{ and } 2.954 (2) \text{ Å, respectively}] \text{ connect}$ 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.

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Carbamoylphosphonate MMP inhibitors. V.

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)].

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

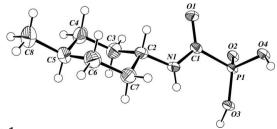


Figure 1

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 arbritary radii.

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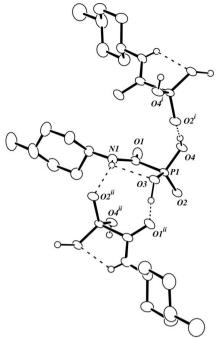


Figure 2 Part of the crystal structure of (I), showing the different types of hydrogen bonding. Most H atoms have been omitted for the sake of clarity. [Symmetry codes: (i) $x, \frac{3}{2} - y, \frac{1}{2} + z$; (ii) $1 - x, -\frac{1}{2} + y, \frac{1}{2} - z$.]

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 $[N1\cdots O2(1-x, y-\frac{1}{2}, \frac{1}{2}-z) \ 2.954 \ (2) \ \text{Å} \ \text{and} \ N1\cdots O3(1-x,$ 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 $[O3 \cdots O1(1-x, y-\frac{1}{2}, \frac{1}{2}-z) \ 2.416 \ (2) \ \mathring{A}]$, thus forming a tenmembered 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

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

Data collection

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

Refinement

Refinement on F^2	All H-atom parameters refined
$R[F^2 > 2\sigma(F^2)] = 0.048$	$w = 1/[\sigma^2(F_0^2) + (0.0492P)^2]$
$wR(F^2) = 0.105$	where $P = (F_0^2 + 2F_c^2)/3$
S = 1.07	$(\Delta/\sigma)_{\rm max} = 0.001$
2522 reflections	$\Delta \rho_{\text{max}} = 0.55 \text{ e Å}^{-3}$
185 parameters	$\Delta \rho_{\min} = -0.26 \text{ e Å}^{-3}$

Table 1Selected 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)		,

organic papers

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

D $ H$ $\cdot \cdot \cdot A$	D-H	$H \cdot \cdot \cdot A$	$D \cdot \cdot \cdot A$	$D-\mathrm{H}\cdots A$
$\begin{matrix} O4{-}H4{\cdot}\cdot\cdot O2^{i} \\ O3{-}H3{\cdot}\cdot\cdot O1^{ii} \\ N1{-}H1{\cdot}\cdot\cdot O3 \\ N1{-}H1{\cdot}\cdot\cdot O2^{ii} \\ N1{-}H1{\cdot}\cdot\cdot O3^{iii} \end{matrix}$	0.80 (3)	1.72 (3)	2.5184 (19)	173 (3)
	1.13 (3)	1.29 (3)	2.4156 (18)	173 (3)
	0.80 (2)	2.46 (2)	2.916 (2)	117 (2)
	0.80 (2)	2.25 (2)	2.954 (2)	146 (2)
	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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