

[(5-Bromopyridinium-2-ylamino)-
(phosphono)methyl]phosphonateEwa Matczak-Jon,^{a*} Katarzyna Ślepokura^b and Paweł Kafarski^a^aDepartment of Chemistry, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland, and ^bFaculty of Chemistry, University of Wrocław, 14 Joliot-Curie St., 50-383 Wrocław, Poland
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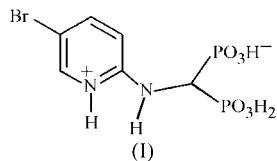
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The title compound, C₆H₉BrN₂O₆P₂, a micromolar inhibitor of the farnesyl pyrophosphate synthase, is a *Z*-isomer zwitterion with one negative phosphonate group and a protonated pyridine N atom. Two types of ribbons, both parallel to the *a* axis, formed by several centrosymmetrically related O—H···O and N—H···O hydrogen bonds are generated in the crystal structure. The resulting two-dimensional (001) 'double-layered' networks are joined into a three-dimensional network *via* inversion-related halogen–oxygen interactions.

Comment

Nitrogen-containing bisphosphonates are the subject of considerable interest because they have a wide range of potential applications, ranging from agriculture to medicine. It was only recently found that their mode of action in humans, parasites and plants relies on inhibition of the same enzyme of the mevalonate/isoprenoid pathway, namely the farnesyl pyrophosphate synthase (FPPS) (van Beek *et al.*, 1999; Martin *et al.*, 1999; Cheng & Oldfield, 2004; Sanders *et al.*, 2005; Ling *et al.*, 2005; Cromartie *et al.*, 1999).



The title compound, (I), is a member of the *N*-(2-pyridyl)-aminomethane-1,1-diphosphonic acid family. These compounds, first developed by Nissan as herbicides (Suzuki *et al.*, 1979), have recently been shown to rank among highly active inhibitors of FPPS (Ghosh *et al.*, 2004; Sanders *et al.*, 2003). Spectroscopic and X-ray studies have revealed an interesting relationship between the topology of a substituent on the pyridyl ring and conformational preferences of this subclass of acids (Matczak-Jon *et al.*, 2001, 2006; Matczak-Jon, 2005; Szabo *et al.*, 2002; Sanders *et al.*, 2003). The placement of the

substituent at the 4- or 5-position of the ring results in the predominance of the *Z* over the *E* geometrical isomer in solution and, as a result, the predominant form crystallizes in the solid state. By contrast, the 3-pyridyl-substituted compounds prefer the opposite *E* geometry in both solution and the solid state (Matczak-Jon *et al.*, 2001; Szabo *et al.*, 2002).

We report here the results of our single-crystal X-ray study of (I), and compare the results with those previously obtained for the *N*-(5-methyl-2-pyridyl)- [Cambridge Structural Database (CSD; Allen, 2002) refcode QURYEH (Matczak-Jon *et al.*, 2001)] and *N*-(5-chloro-2-pyridyl)- (Sanders *et al.*, 2003; CSD refcode BEKCAW) derivatives, which unlike (I) contain two instead of one crystallographically independent zwitterion in the asymmetric unit.

Compound (I) is a zwitterion with one of the phosphonic acid groups deprotonated and pyridyl atom N2 protonated (Fig. 1); this situation is common for this subclass of acids (Matczak-Jon *et al.*, 2001, 2006; Sanders *et al.*, 2003; Szabo *et al.*, 2002). Atoms N1 and C1 are both coplanar with the pyridyl ring because of the formal *sp*² hybridization of atom N1. This results in a partial double-bond character of the C2–N1 linkage, which is reflected in the difference between its length and the length of the C1–N1 bond, which is typical for a single C–N bond (Table 1). The C1–N1–C2–N2 torsion angle indicates that atom C1 is only slightly displaced from the pyridyl ring plane [the distance of atom C1 from that plane is 0.09 (2) Å]. As expected, (I) adopts the same *Z* geometry as the related 5-methyl and 5-chloro derivatives. This is reflected in the C1–N1–C2–C3 torsion angle (see Table 1), which can be compared with values of 3.7 (12) and 5.9 (12)°, and 6.5 (11) and 13.4 (11)°, respectively, in the two crystallographically independent molecules of the 5-methyl- and 5-chloro-substituted compounds.

The geometry of the diphosphonate fragment is similar to that observed previously (Matczak-Jon *et al.*, 2001, 2006). The O1–P1–C1–P2–O5 sequence with one protonated and one deprotonated O atom reveals a typical almost planar *W* conformation. Accordingly, every P atom is oriented antiperiplanar (*ap*) to one of the O atoms from the adjacent phosphonic/phosphonate group and synclinal to the remaining O atoms from that group. The orientation of the diphosphonate group in relation to the rest of the molecule is additionally stabilized by an intramolecular N1–H2···O3 hydrogen bond. The formation of such an intramolecular

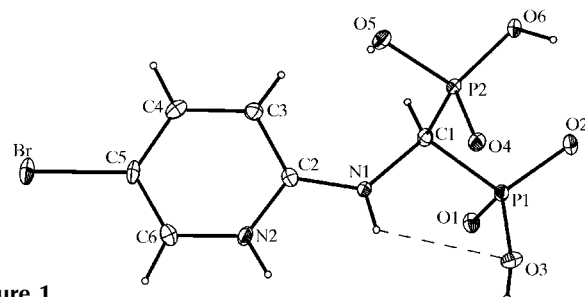


Figure 1
The molecular structure of (I) showing the atom-numbering scheme and the intramolecular N—H···O hydrogen bond. Displacement ellipsoids are drawn at the 50% probability level.

hydrogen bond, observed also in the *Z*-isomeric 4-methyl derivative (Maczak-Jon *et al.*, 2006) and the *E*-isomeric 3-methyl (Szabo *et al.*, 2002) and 3-carboxy derivatives (Maczak-Jon *et al.*, 2001), is a common feature of most of the aminomethane-1,1-diphosphonic acids studied to date (Maczak-Jon *et al.*, 2005). As shown by the values of the C2—N1—C1—P1 and C2—N1—C1—P2 torsion angles, both P atoms have an *ac* orientation with respect to the pyridyl C2 atom.

The geometry of both the phosphonic acid (PO₃H₂) and the phosphonate (PO₃H[−]) groups deviates significantly from an ideal tetrahedron (Table 1). This deviation is reflected in the values of the phosphonate O1—P1—O2 angles, in which the unprotonated O atoms are involved, and in the phosphonic acid O4—P2—O6 angles, involving the formal double P=O bond. This configuration is consistent with what was previously observed for other members of this class of compounds (Maczak-Jon *et al.*, 2001; Szabo *et al.*, 2002; Sanders *et al.*, 2003; Maczak-Jon & Videnova-Adrabińska, 2005; Maczak-Jon *et al.*, 2006).

The crystal packing in (I) is determined mainly by hydrogen bonds involving the phosphonic acid and phosphonate groups, which is a common feature of all the related compounds. The

W conformation of the O1—P1—C1—P2—O5 sequence enables atoms O5 and O1 from adjacent molecules to participate in strong O5—H5···O1ⁱⁱ hydrogen bonds (the geometry and symmetry codes are listed in Table 2). Such direct *a*-axis translation generates infinite chains of zwitterions (Fig. 2*a*), which is a common structural phenomenon for *N*-(5-methyl-2-pyridyl)-, (Maczak-Jon *et al.*, 2001), *N*-(5-chloro-2-pyridyl)- (Sanders *et al.*, 2003), *N*-(4-methyl-2-pyridyl)- and non-substituted *N*-(2-pyridyl)aminomethane-1,1-diphosphonic acid (Maczak-Jon *et al.*, 2006), but not for the 3-methyl and 3-carboxyl derivatives and the sodium salt of the 5-chloro-substituted compound (Sanders *et al.*, 2003).

The head-to-head arrangement of the molecules in adjacent chains enables the diphosphonate and diphosphonic acid groups to interact with each other to form ribbons (Fig. 2). Two different types of ribbons, both parallel to the *a* axis, can be distinguished in the crystal structure of (I). Each zwitterion from one chain interacts with two others from an adjacent chain *via* several different hydrogen bonds. The centrosymmetric O3—H3···O1ⁱ contact with one zwitterion generates an $R_2^2(8)$ ring motif. Additional $R_2^2(10)$ and $R_2^2(6)$ rings are formed along the ribbon by bifurcated centrosymmetric N1—H2···O4^{iv} and N2—H4···O4^{iv} contacts to the same O4 atom of another zwitterion. Such ribbons (Fig. 2*a*) are also observed in *N*-(4-methyl-2-pyridyl)aminomethane-1,1-diphosphonic acid (Maczak-Jon *et al.*, 2006). On the other hand, pairs of zwitterions from adjacent chains are linked to each other by strong phosphonic–phosphonate O6—H6···O2ⁱⁱⁱ hydrogen bonds. These, in combination with the O5—H5···O1ⁱⁱ chain-forming interactions, give rise to $R_2^2(12)$ and $R_4^4(16)$ rings and another type of ribbon, shown in Fig. 2*b*. The arrangement of the molecules within these ribbons is almost identical to that observed in *N*-(2-pyridyl)aminomethane-1,1-diphosphonic acid (Maczak-Jon *et al.*, 2006).

As a result, a two-dimensional (001) ‘double-layered’ network is formed, which in turn interacts with the others *via* short halogen–oxygen interactions about inversion centres,

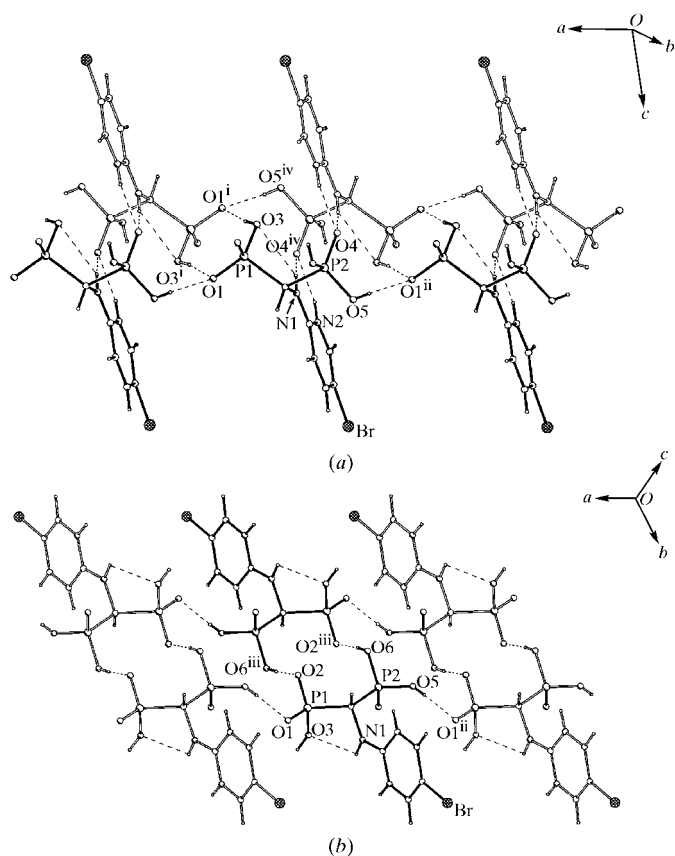


Figure 2

The arrangement of the zwitterions in (I) within two types of ribbons (both along the *a* axis) formed by adjacent chains interacting with each other *via* (a) centrosymmetric O3—H3···O1ⁱ, N1—H2···O4^{iv} and N2—H4···O4^{iv} or (b) O6—H6···O2ⁱⁱⁱ hydrogen bonds. The stabilizing N1—H2···O3 interactions are also shown. Symmetry codes are given in Table 2.

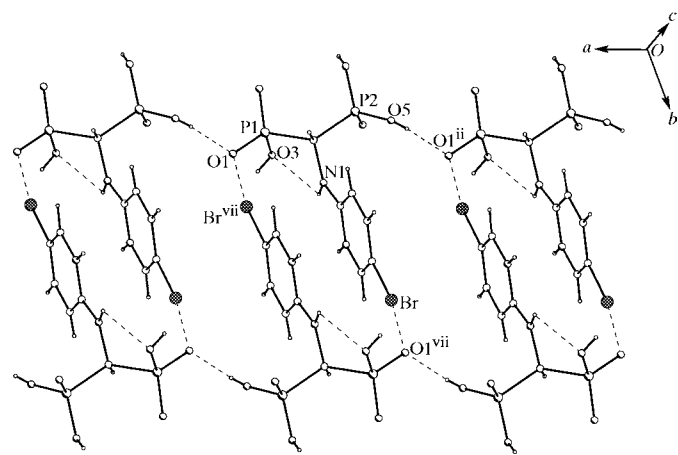


Figure 3

Adjacent chains from two different ribbons joined by Br···O1^{vii} interactions (dashed lines) [Br···O1^{vii} = 2.967 (2) Å, C5—Br···O1^{vii} = 165.6 (1)° and Br···O1^{vii}—P1^{vii} = 126.8 (1)°; symmetry code: (vii) $-x + 2, -y + 2, -z + 2$].

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