Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

[Hydroxy(aryl)methylene]diphosphonic acids, a class of drugs in bone pathology treatments, crystallize as head-to-head dimers

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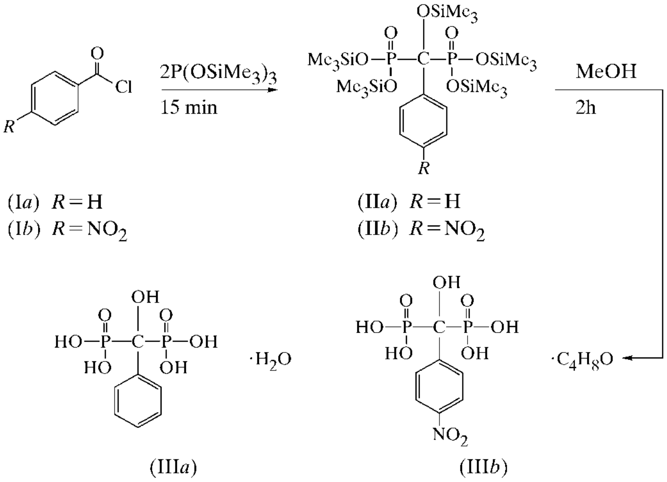
Received 10 June 2002
Accepted 10 July 2002
Online 31 July 2002

Two [hydroxy(aryl)methylene]diphosphonic acids have been crystallized as dimers. The first compound, [hydroxy(phenyl)-methylene]diphosphonic acid monohydrate, $C_7H_{10}O_7P_2 \cdot H_2O$, crystallizes in the non-centrosymmetric space group $P2_1$, with the two enantiomers related by a non-crystallographic centre of inversion, while the second compound, [hydroxy(4-nitrophenyl)methylene]diphosphonic acid tetrahydrofuran disolvate, $C_7H_9NO_9P_2 \cdot 2C_4H_8O$, crystallizes in the centrosymmetric space group $P2_1/c$ and uses the centre of symmetry to form the same dimer.

Comment

Bisphosphonates belong to a relatively new class of drugs developed for the treatment of various pathologies in bone (Fleisch, 1999), and also for the treatment of cancer (Mundy, 1999; Brown & Coleman, 2002). We have previously described a one-pot method for the synthesis of aromatic 1-hydroxymethane-1,1-bisphosphonic acid compounds (Lecouvey *et al.*, 2001). The aim of this paper is to analyze the structure of two new 1-hydroxymethane-1,1-bisphosphonic acids, namely hydroxy(phenyl)methylene]diphosphonic acid monohydrate, (III*a*), and [hydroxy(4-nitrophenyl)methylene]diphosphonic acid tetrahydrofuran disolvate, (III*b*), with an aromatic ring attached to the functional C atom. These structures were also investigated to confirm the presence of the bisphosphonic acid group, because of a possible phosphono–phosphate rearrangement as a by-product of the synthesis, as previously mentioned by Fitch & Moedritzer (1962) and Kanaan & Burgada (1988).

Hydroxy bisphosphonic acids are compounds with super-acid properties, and they are able to complex with a large number of cations. As such, they have been widely investigated as detoxifying agents in heavy-metal poisoning and also as carrier molecules for $^{99\text{m}}$Tc delivery in scintillography. They are very difficult to crystallize as free dehydrated acids and only one example has been reported for the crystal structure of an anhydrous hydroxybisphosphonic compound (Ohanessian *et al.*, 1997). These acids are more easily crystallized as mono salts of sodium or potassium (Sylvestre *et al.*, 2001), or better, dimethylammonium salts using the vapour-diffusion technique (Neuman *et al.*, 2002). When crystals are obtained, they generally include solvent, and give well characterized solvates, as is the case for the two title compounds, (III*a*) and (III*b*).



Although (III*a*) is a racemic monohydrate, it crystallizes in the non-centrosymmetric space group $P2_1$ with the two (+)- and (−)enantiomers facing each other, building a tight dimer around a local non-crystallographic centre of symmetry at $(x, y, z) = (0.609, 0.255, 0.354)$. The content of the asymmetric unit corresponds to two molecules of (III*a*) and two molecules of water. The centrosymmetry is only broken by the hydration network.

Phosphonic acids are usually diprotonated in their free acid form. In (III*a*), the phosphonic H atoms are observed, but those of the two solvate water molecules are not (Fig. 1); these are probably in a disordered exchange within the hydrogen-

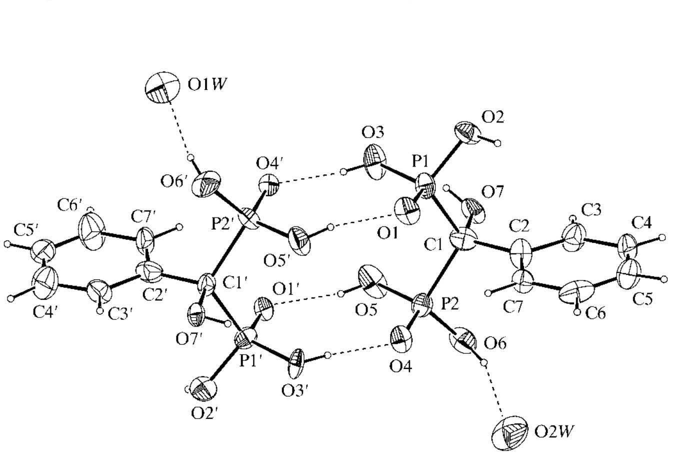


Figure 1
A view of the dimer of (III*a*) (asymmetric unit), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

DOI: 10.1107/S0108270102012386

bond network. Nevertheless, atom O1W is 3.02 Å from symmetry-related atom O2W and is certainly hydrogen bonded to it.

Details of the four hydrogen bonds responsible for the pairing are given in Table 2. In addition, infinite intermolecular hydrogen-bond networks are present along the a and c directions. Firstly, dimers are connected side-by-side, building infinite ribbons along the c direction (Fig. 2), and secondly, these ribbons are crosslinked perpendicularly (along **a**) through their O2/O1′ and O2′/O1 atoms. The most significant distances are given in Table 2.

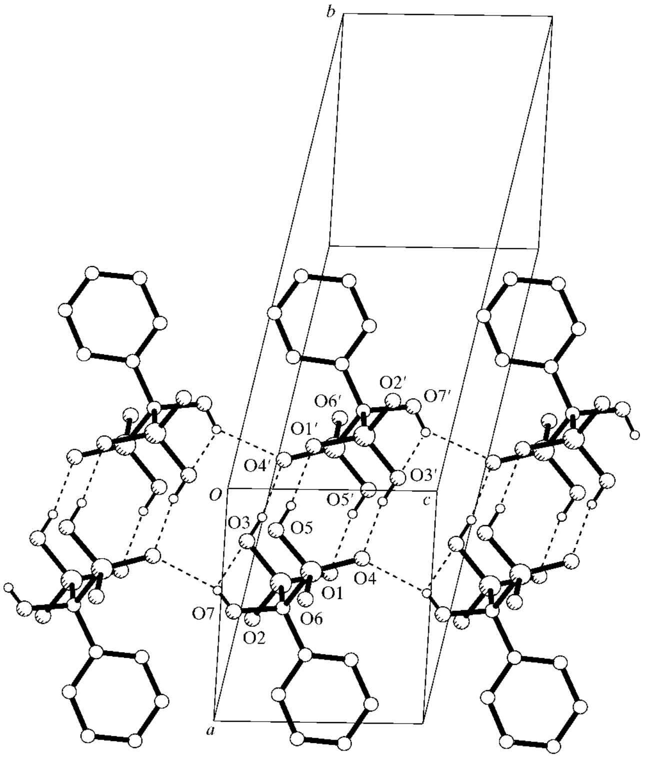


Figure 2
The hydrogen bonding between dimers of (IIIa), viewed along the c axis. Only H atoms involved in the bonding are shown and the solvate water molecules have been omitted for clarity.

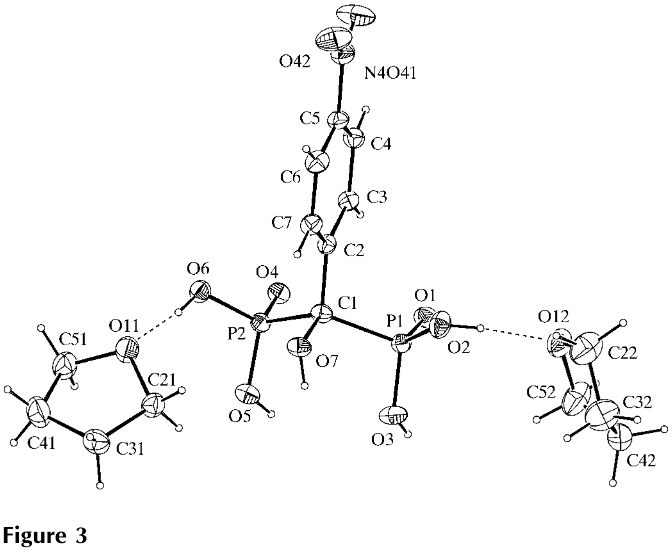


Figure 3
A view of the asymmetric unit of (IIIb), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

The crystals of (IIIb) are less stable than those of (IIIa), with a tendency to bleach and turn to powder upon standing in air at room temperature. The present data were therefore recorded at 132 K. The structure is a tetrahydrofuran disolvate which crystallizes in the $P2_1/c$ space group (Fig. 3). The bis-hydroxyphosphonate molecules also form strong dimers, linked by four hydrogen bonds, as in (IIIa). However, the local centre of inversion in the dimer corresponds to a crystallographic centre of symmetry of the space group. All the phosphonic acid H atoms were located in difference maps. The hydrogen-bond network in (IIIb) also involves dimers, building β-sheet-like ribbons (Fig. 4) similar to those observed in (IIIa) but running along the b axis. The two solvated tetrahydrofuran molecules form part of the network through their ring O atoms (Fig. 3). They connect locally those phosphonate O atoms that are not involved in the pairing (O2 and O6; Table 4). In a similar way, molecules of water connect the dimers in (IIIa). However, the tetrahydrofuran molecules are more bulky than the water molecules and fill more space between the ribbons, preventing them from coming close enough for crosslinking. This leads to weaker crystal cohesion in the direction perpendicular to the ribbons.

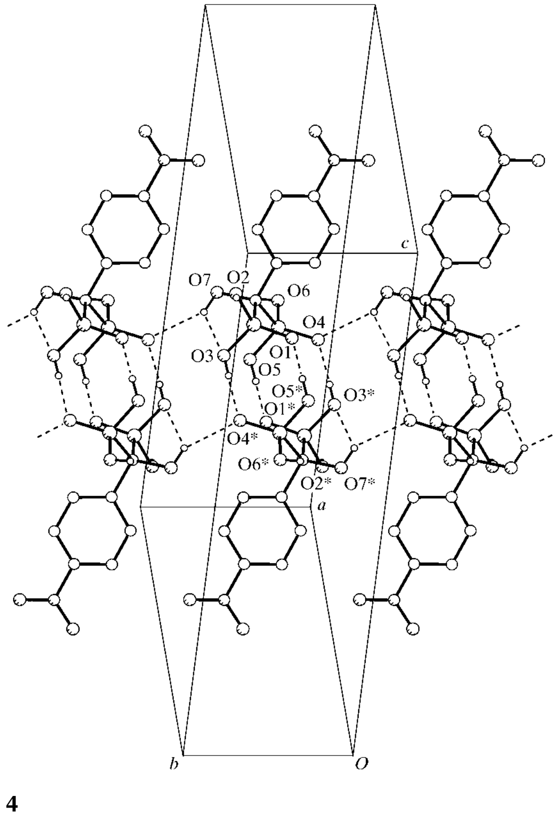


Figure 4
The supramolecular arrangement of (IIIb) dimers along the b direction; tetrahydrofuran solvate molecules have been omitted for clarity. Atoms labelled with an asterisk (*) are at symmetry position $(1 - x, 1 - y, 1 - z)$.

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Experimental

The syntheses of the title compounds were based on the addition of two equivalents of tris(trimethylsilyl)phosphite to the corresponding acid chlorides, (I), to yield the tetrakis(trimethylsilyl) ester of 1-aryl-1-trimethylsiloxymethane-1,1-bisphosphonic acid, (II) (not isolated). Direct methanolysis afforded the title substituted [hydroxy(aryl)-methylene]diphosphonic acids, (III*a*) with aryl = phenyl and (III*b*) with aryl = 4-nitrophenyl, in nearly quantitative yields (see *Scheme*). Compound (III*a*) was obtained as a white powder in 91% yield, and was crystallized by slow evaporation of a solution in a mixture of ethanol and water (90:10) at room temperature. Spectroscopic analysis, ^{31}P NMR (D_2O, δ, p.p.m.): 16.0 (*s*); ^{1}H NMR (D_2O, δ, p.p.m.): 7.08–7.13 (*m*, 4H, C_6H_5), 7.46 (*t*, ^{3}J = 5 Hz, 1H, C_6H_5); ^{13}C NMR (D_2O, δ, p.p.m.): 78.76 (*t*, ^{1}J = 145.75 Hz, COH), 128.9, 130.8, 131.2, 138.6 (C_6H_5). Compound (III*b*) was obtained as a yellow powder in 85% yield, and was crystallized by slow evaporation of a solution in tetrahydrofuran at room temperature. Spectroscopic analysis, ^{31}P NMR (D_2O, δ, p.p.m.): 15.3 (*s*); ^{1}H NMR (D_2O, δ, p.p.m.): 7.89 (*d*, 2H, ^{3}J = 8.5 Hz, C_6H_4), 8.15 (*d*, 2H, ^{3}J = 8.5 Hz, C_6H_4); ^{13}C NMR (D_2O, δ, p.p.m.): 75.28 (*t*, ^{1}J = 149 Hz, COH), 124.67, 128.15, 146.13, 148.35 (C_6H_4).

Compound (III*a*)

Crystal data

$C_7H_{10}O_7P_2 \cdot H_2O$
M_r = 286.10
Monoclinic, $P2_1$
a = 8.42 (2) Å
b = 23.05 (1) Å
c = 5.91 (2) Å
β = 97.7 (2)°
V = 1137 (6) Å^3
Z = 4

D_x = 1.668 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 8–25°
μ = 3.81 mm^{-1}
T = 293 (2) K
Rod-shaped prism, colourless
0.5 × 0.2 × 0.2 mm

Data collection

Philips PW1100 diffractometer
$\theta/2\theta$ scans
3430 measured reflections
3430 independent reflections
2875 reflections with $I > 2\sigma(I)$
θ_{max} = 65.8°
$h = -9 \rightarrow 9$

$k = -23 \rightarrow 24$
$l = 0 \rightarrow 6$
3 standard reflections every 130 reflections frequency: 120 min intensity decay: 3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.096
S = 1.12
3430 reflections
311 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0356P)^2 + 1.8431P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.098
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}

Table 1
Selected interatomic distances (Å) for (III*a*).

P1—O1	1.502 (6)	P1′—O1′	1.520 (7)
P1—O2	1.554 (5)	P1′—O2′	1.511 (5)
P1—O3	1.539 (6)	P1′—O3′	1.527 (6)
P1—C1	1.824 (5)	P1′—C1′	1.866 (5)
P2—O4	1.497 (7)	P2′—O4′	1.478 (7)
P2—O5	1.552 (6)	P2′—O5′	1.547 (6)
P2—O6	1.558 (4)	P2′—O6′	1.561 (4)
P2—C1	1.840 (7)	P2′—C1′	1.836 (7)

Table 2
Hydrogen-bonding geometry (Å, °) for (III*a*).

D—H···A	D—H	H···A	D···A	D—H···A
O2—H21···O1′^{i}	0.82	1.92	2.583 (9)	137
O2′—H2P···O1^{ii}	0.82	1.80	2.602 (9)	164
O3—H31···O4′	0.82	1.78	2.592 (9)	169
O3′—H3P···O4	0.82	1.75	2.549 (9)	165
O5—H51···O1′	0.82	1.84	2.647 (9)	169
O5′—H5P···O1	0.82	1.83	2.637 (9)	167
O6—H61···O2*W*	0.82	1.83	2.609 (9)	160
O6′—H6P···O1*W*	0.82	1.80	2.594 (9)	163
O7—H71···O4^{iii}	0.82	2.07	2.805 (9)	149
O7—H71···O3	0.82	2.36	2.894 (10)	123
O7′—H72···O4′^{iv}	0.82	2.12	2.789 (9)	138

Symmetry codes: (i) $1 + x, y, z$; (ii) $x - 1, y, z$; (iii) $x, y, z - 1$; (iv) $x, y, 1 + z$.

Compound (III*b*)

Crystal data

$C_7H_9NO_9P_2 \cdot 2C_4H_8O$
M_r = 457.30
Monoclinic, $P2_1/c$
a = 14.0005 (9) Å
b = 6.0243 (2) Å
c = 24.4427 (6) Å
β = 91.903 (3)°
V = 2060.44 (16) Å^3
Z = 4

D_x = 1.474 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 78 reflections
θ = 8–40°
μ = 0.27 mm^{-1}
T = 132 (1) K
Plate, pale yellow
0.20 × 0.20 × 0.05 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans
3734 measured reflections
3734 independent reflections

2986 reflections with $I > 2\sigma(I)$
θ_{max} = 25.5°
$h = 0 \rightarrow 16$
$k = 0 \rightarrow 7$
$l = -29 \rightarrow 29$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.045
$wR(F^2)$ = 0.096
S = 1.02
3734 reflections
329 parameters
All H-atom parameters refined

$w = 1/[\sigma^2(F_o^2) + (0.025P)^2 + 2.62P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.046
$\Delta\rho_{max}$ = 0.39 e Å^{-3}
$\Delta\rho_{min}$ = −0.37 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0017 (6)

For compound (III*a*), all H atoms apart from four (on the O1*W* and O2*W* solvent water molecules) were located in difference Fourier

Table 3
Selected interatomic distances (Å) for (III*b*).

P1—O1	1.5034 (17)	P2—O4	1.5044 (16)
P1—O2	1.5637 (18)	P2—O5	1.5615 (17)
P1—O3	1.5553 (18)	P2—O6	1.5881 (18)
P1—C1	1.889 (2)	P2—C1	1.870 (2)

Table 4
Hydrogen-bonding geometry (Å, °) for (III*b*).

D—H···A	D—H	H···A	D···A	D—H···A
O2—H21···O12	0.87 (4)	1.73 (3)	2.594 (3)	173 (3)
O3—H31···O4^{i}	0.80 (4)	1.85 (3)	2.645 (3)	175 (4)
O5—H51···O1^{i}	0.94 (4)	1.63 (3)	2.564 (3)	171 (4)
O6—H61···O11	0.84 (4)	1.74 (3)	2.579 (3)	174 (4)
O7—H71···O4^{ii}	0.86 (4)	2.21 (3)	2.981 (3)	150 (3)
O7—H71···O3	0.86 (4)	2.51 (3)	2.993 (3)	117 (3)

Symmetry codes: (i) $1 - x, 1 - y, 1 - z$; (ii) $x, 1 + y, z$.

maps. They were placed in geometrically idealized positions and were constrained to ride on their parent atoms, with C—H = 0.93 and O—H = 0.82 Å, and $U_{\rm iso}$(H) = 1.2$U_{\rm eq}$(C). For compound (III*b*), all H atoms were located in successive difference Fourier maps and freely refined, except for those on atoms C22 and C23 of one of the tetrahydrofuran molecules; the C—H distances were in the range 0.92 (3)–1.06 (3) Å.

For compound (III*a*), data collection: *PHIL* [local program; adapted from Riche (1980)]; cell refinement: *PARAM* (local program; Prangé, 1995); data reduction: *PHIL*. For compound (III*b*), data collection: *KappaCCD Server Software* (Nonius, 1997); cell refinement: *DENZO–SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO–SMN*. For both compounds, program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2002); software used to prepare material for publication: *SHELXL*97 and *PLATON*.

The authors thank M. Nierlich (Saclay, France) for access to the KappaCCD diffractometer.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1653). Services for accessing these data are described at the back of the journal.

References

Brown, J. E. & Coleman, R. E. (2002). *Breast Cancer Res.* **4**, 24–29.
Fitch, S. J. & Moedritzer, K. (1962). *J. Am. Chem. Soc.* **84**, 1876–1879.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Fleisch, H. (1999). *Prog. Mol. Subcell. Biol.* **23**, 197–216.
Kanaan, K. & Burgada, R. (1988). *Phosphorus Sulfur Silicon*, **37**, 217–230.
Lecouvey, M., Mallard, I., Bailly, T., Burgada, R. & Leroux, Y. (2001). *Tetrahedron Lett.* **42**, 8475–8478.
Mundy, G. R. (1999). *Expert Opin. Investig. Drugs*, **8**, 2009–2015.
Neuman, A., Coindet-Benramdane, M., Gillier, H., Leroux, Y., El Manouni, D. & Prangé, T. (2002). *Z. Kristallogr. New Cryst. Struct.* **217**, 154–156.
Nonius (1997). *KappaCCD Server Software*. Windows 3.11 Version. Nonius BV, Delft, The Netherlands.
Ohanessian, J., Avenel, D., El Manouni, D. & Benramdane, M. (1997). *Phosphorus Sulfur Silicon*, **129**, 99–110.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Prangé, T. (1995). *PARAM*. University of Bobigny, France.
Riche, C. (1980). *PHIL*. CNRS, 91190 Gif-sur-Yvette, France.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.
Spek, A. L. (2002). *PLATON*. Version of January 2002. University of Utrecht, The Netherlands.
Sylvestre, J. P., Nguyen, Q. D. & Leroux, Y. (2001). *Heteroatom Chem.* **12**, 73–90.