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Three hydrates of the bisphosphonate risedronate, consisting of one molecular and two ionic structures

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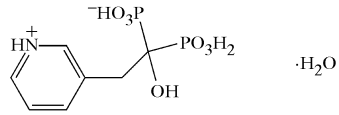
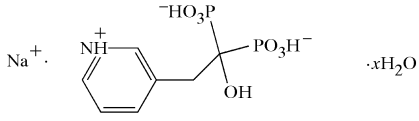
Three different hydrates of risedronate were obtained by varying the pH of a solution containing the compound. At the pH values used, the N atom of the pyridine group is protonated and the compounds are zwitterionic. Crystals obtained directly from the synthesis resulted in risedronate monohydrate, or [1-hydroxy-1-phosphono-2-(pyridinium-3-yl)ethyl]phosphonate monohydrate, $C_7H_{11}NO_7P_2\cdot H_2O$, (I), in which just one phosphonate group is negatively charged. Recrystallizations at pH values of 2 and 4 yielded risedronate dihydrate, or sodium [1-hydroxy-2-(pyridinium-3-yl)ethane-1,2-diyl]bis(phosphonate) dihydrate, $Na^+\cdot C_7H_{10}NO_7P_2^-\cdot 2H_2O$, (II). Finally, recrystallizations at pH values of 7 and 8 produced risedronate 2.5-hydrate, or sodium [1-hydroxy-2-(pyridinium-3-yl)ethane-1,2-diyl]bis(phosphonate) 2.5-hydrate, $Na^+\cdot C_7H_{10}NO_7P_2^-\cdot 2.5H_2O$, (III). At these four pH values, both phosphonate groups in (II) and (III) are negatively charged and coordinated to an Na^+ ion. Crystals of (II), *i.e.* those grown at pH values of 2 and 4, have isomorphous polymeric ion aggregate structures with geminal phosphonate and alcohol groups coordinated to the same Na^+ ion. On the other hand, crystals of (III), *i.e.* those grown at pH values of 7 and 8, have isomorphism polymeric ion aggregate structures with geminal phosphonate and alcohol groups coordinated to different Na^+ ions.

Comment

Risedronate (Actonel; Procter & Gamble) is a potent inhibitor of osteoclast-mediated bone resorption and has found widespread use in the treatment of osteoporosis. More recently, risedronate has also been shown to have antiparasitic properties, in particular against the organisms which cause sleeping sickness, Chagas' disease, leishmanasis, toxoplasmosis and cryptosporidiosis (Martin *et al.*, 2001; Urbina *et al.*, 1999; Moreno *et al.*, 2001). With the knowledge that several million people contract these diseases worldwide each year, it is important to explore the structural origins of bisphosphonate activity against these parasites. Only one structural form of risedronate, one of the most potent antiparasitic and antiresorptive agents, has been published to date (Barbey & Lecouvey, 2002). Here, the structures of three different forms of risedronate, *viz.* (I), (II) and (III), are reported.



(I)



(II) $x = 2$
(III) $x = 2.5$

All three hydrates exist as zwitterions, a common characteristic of bisphosphonates (Vega *et al.*, 1996, 1998). The monohydrate, (I) (Fig. 1), has an overall charge of zero, with one positively charged N atom and one negatively charged phosphonate group (Barbey & Lecouvey, 2002). The dihydrate, (II) (Fig. 2), and the 2.5-hydrate, (III) (Fig. 3), both have an overall charge of −1, again with a positively charged N atom but with two negatively charged phosphonate groups. These protonation states are correlated with the P—O bond lengths.

Fig. 4 shows a histogram of the P—O bond distances observed in these three hydrates, along with those in two other bisphosphonate structures explored recently (isozoledronate and incadronate; Gossman *et al.*, 2002; Van Brussel *et al.*, 2003), together with values found in 62 three-dimensional X-ray crystal structures of similar phosphonate-containing compounds that are listed in the Cambridge Structural Database (Version 1.4; Allen, 2002). The two histograms are very similar and show a clear bimodal distribution. P—O bonds in which the O atom is unprotonated are between 1.47 and 1.53 Å long, but this increases to 1.54–1.60 Å if the O atom is protonated.

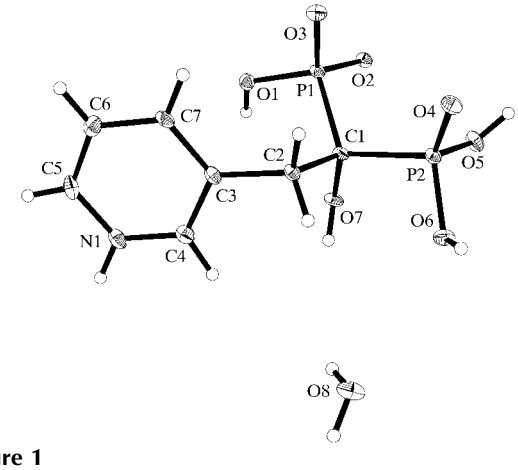


Figure 1
A view of the molecule of (I), showing 35% probability displacement ellipsoids and the atom-numbering scheme. H atoms are shown as small spheres of arbitrary radii. Secondary sites for the disordered water molecule, O9, have been omitted for clarity.

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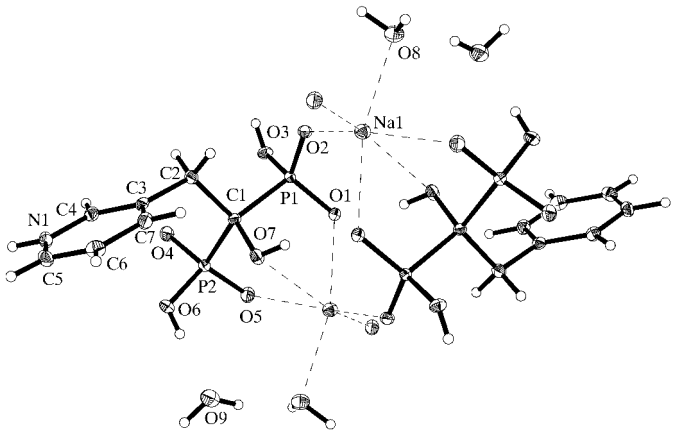

Figure 2
A view of the molecule of (II), showing 35% probability displacement ellipsoids and the atom-numbering scheme. H atoms are shown as small spheres of arbitrary radii.

Using this description to inspect the P—O bond lengths in the three hydrates studied here (Tables 1, 3 and 5), compound (I), with P1—O1 = 1.548 (2), P1—O2 = 1.524 (2) and P1—O3 = 1.494 (2) Å, and P2—O4 = 1.479 (2), P2—O5 = 1.555 (2) and P2—O6 = 1.562 (2) Å, shows three protonated O atoms on the phosphonate groups, namely O1, O5 and O6, and three unprotonated O atoms, namely O2, O3, and O4, leading to the conclusion that atom P1 is negatively charged, while atom P2 is neutral. Inspection of (II), with P1—O1 = 1.513 (2), P1—O2 = 1.514 (2) and P1—O3 = 1.579 (2) Å, and P2—O4 = 1.515 (2), P2—O5 = 1.495 (2) and P2—O6 = 1.600 (2) Å, results in only two protonated O atoms, namely O3 and O6, and four unprotonated O atoms, namely O1, O2, O4 and O5, showing that both phosphonate groups in (II) carry a −1 charge, unlike (I). Analysis of (III), with P1—O1 = 1.510 (1), P1—O2 = 1.510 (1) and P1—O3 = 1.566 (1) Å, and P2—O4 = 1.498 (1), P2—O5 = 1.509 (1) and P2—O6 = 1.581 (1) Å, shows that the phosphonate groups have the same protonation state as in (II).

The conformation of risedronate in all three hydrates is very similar. The P1—C1—P2 angles are nearly identical [113.2 (2), 113.2 (2) and 111.8 (1)° in (I), (II) and (III), respectively], and the P1—C1—C2—C3 torsion angles between the phosphonate group and the ring are also similar [57.6 (3), 61.8 (3) and 53.8 (1)° in (I), (II) and (III), respectively]. One noticeable difference found in the structures is a rotation of almost 180° of the ring in the dihydrate compared with the mono- and 2.5-hydrates, as reflected in the C1—C2—C3—C4 torsion angles of the C atom closest to the N atom [82.9 (4), −97.2 (3) and 68.2 (1)° in (I), (II) and (III), respectively].

The main distinguishing structural feature between these three hydrates lies in their ion aggregate propagation. In the monohydrate, only the hydrogen-bonding network interconnects the host bisphosphonate molecules (Table 2). In the dihydrate, (II), atoms O1, O5 and O7 coordinate to Na1, atom O5 coordinates to a site on an inversion-related Na1, and atom O2 bridges another Na1 through a different inversion centre (Table 4). The ion aggregate propagates along the *a* axis. In the 2.5-hydrate, (III), atoms O1 and O5 coordinate to Na1, atom O7 coordinates to the terminal site on a *c*-glide-related Na atom, and water molecule O8 bridges two Na atoms related by an inversion centre (Table 6). The ion aggregate propagates parallel to the *bc* plane. All three conformations show an extensive hydrogen-bonding network, with each structure having at least ten hydrogen bonds.

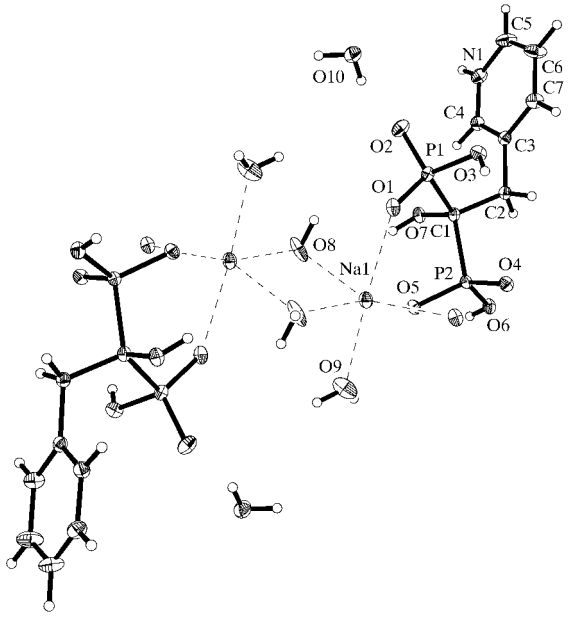

Figure 3
A view of the molecule of (III), showing 35% probability displacement ellipsoids and the atom-numbering scheme. H atoms are shown as small spheres of arbitrary radii. Secondary sites for the disordered positions O10, O11, O12 and Na2 have been omitted for clarity.

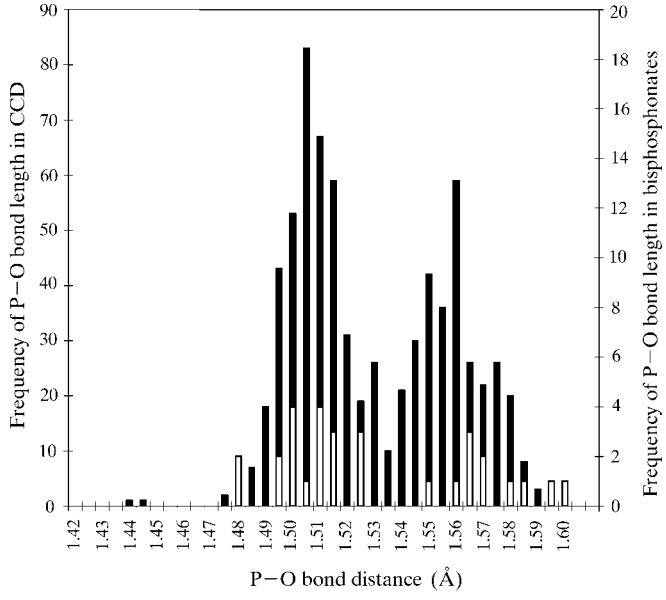

Figure 4
Histograms of P—O bond lengths in compounds in the Cambridge Structural Database (black; see text for details), and those measured in bisphosphonates (white).

Experimental

For (I), crystals were obtained directly from the synthesis mixture. For (II), crystals of (I) were recrystallized by vapour diffusion of ethanol into a buffered (glycine–HCl, pH = 2 or 4) aqueous solution. For (III), crystals of (I) were recrystallized by vapour diffusion of ethanol into a buffered [Tris–HCl, pH = 7 or 8; Tris is 2-amino-2-(hydroxymethyl)-1,3-propanediol] aqueous solution.

Compound (I)

Crystal data

$C_7H_{11}NO_7P_2\cdot H_2O$
M_r = 301.12
Monoclinic, $P2_1/n$
a = 7.1219 (15) Å
b = 10.694 (2) Å
c = 14.710 (3) Å
β = 101.996 (4)°
V = 1095.9 (4) Å^3
Z = 4
D_x = 1.825 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 940 reflections
θ = 3.4–27.4°
μ = 0.43 mm^{-1}
T = 193 (2) K
Plate, colorless
0.15 × 0.08 × 0.02 mm

Data collection

Bruker Platform CCD area-detector diffractometer
Profile data from ω scans
Absorption correction: by integration (*XPREP* in *SHELXTL*; Bruker, 2001)
T_{min} = 0.936, T_{max} = 0.991
8978 measured reflections
2236 independent reflections
1534 reflections with $I > 2\sigma(I)$
R_{int} = 0.079
θ_{max} = 26.4°
$h = -8 \rightarrow 8$
$k = -13 \rightarrow 13$
$l = -18 \rightarrow 18$
100 standard reflections
frequency: 731 min
intensity decay: 1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.043
$wR(F^2)$ = 0.108
S = 1.01
2236 reflections
200 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0469P)^2 + 0.5123P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.46 e Å^{-3}
$\Delta\rho_{min}$ = −0.37 e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (I).

O1—P1	1.548 (2)	O4—P2	1.479 (2)
O2—P1	1.524 (2)	O5—P2	1.555 (2)
O3—P1	1.494 (2)	O6—P2	1.562 (2)
P1—C1—P2	113.20 (15)	C1—C2—C3	117.6 (2)
P1—C1—C2—C3	57.6 (3)	C1—C2—C3—C4	82.9 (4)

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O2^{i}	0.91 (3)	1.94 (4)	2.847 (4)	172 (3)
O1—H1A···O8^{ii}	0.84 (3)	1.66 (4)	2.496 (6)	172 (4)
O1—H1A···O9^{ii}	0.84 (3)	1.61 (4)	2.355 (18)	147 (4)
O5—H5A···O2^{iii}	0.80 (4)	1.84 (4)	2.634 (3)	174 (4)
O6—H6A···O2^{iv}	0.76 (4)	1.91 (4)	2.661 (3)	172 (4)
O7—H7A···O3^{v}	0.78 (3)	1.96 (4)	2.730 (3)	168 (3)
O8—H8A···O3^{v}	0.84 (3)	1.87 (3)	2.704 (5)	170 (5)
O8—H8B···O4^{vi}	0.85 (3)	1.83 (3)	2.675 (5)	174 (5)

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

Compound (II)

Crystal data

$Na^+\cdot C_7H_{10}NO_7P_2^-\cdot 2H_2O$
M_r = 341.12
Triclinic, $P\overline{1}$
a = 7.663 (4) Å
b = 8.039 (4) Å
c = 10.770 (5) Å
α = 93.655 (8)°
β = 95.277 (9)°
γ = 96.017 (8)°
V = 655.2 (6) Å^3
Z = 2
D_x = 1.729 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 914 reflections
θ = 3.1–27.5°
μ = 0.41 mm^{-1}
T = 193 (2) K
Tabular, colorless
0.20 × 0.16 × 0.06 mm

Data collection

Bruker Platform CCD area-detector diffractometer
Profile data from ω scans
Absorption correction: by integration (*XPREP* in *SHELXTL*; Bruker, 2001)
T_{min} = 0.935, T_{max} = 0.976
4297 measured reflections
2586 independent reflections
2007 reflections with $I > 2\sigma(I)$
R_{int} = 0.027
θ_{max} = 26.3°
$h = -9 \rightarrow 9$
$k = -9 \rightarrow 9$
$l = -13 \rightarrow 12$
104 standard reflections
frequency: 490 min
intensity decay: 2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.100
S = 1.02
2586 reflections
237 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0513P)^2 + 0.2778P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.50 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}

Table 3
Selected geometric parameters (Å, °) for (II).

O1—P1	1.5134 (19)	O4—P2	1.515 (2)
O2—P1	1.514 (2)	O5—P2	1.495 (2)
O3—P1	1.579 (2)	O6—P2	1.600 (2)
P1—C1—P2	113.21 (14)	C3—C2—C1	114.8 (2)
P2—C1—C2—C3	61.8 (3)	C1—C2—C3—C4	−97.2 (3)

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3···O2^{i}	0.79 (3)	1.82 (3)	2.613 (3)	177 (4)
N1—H1···O4^{ii}	0.97 (4)	1.63 (4)	2.592 (3)	173 (3)
O6—H6A···O9	0.80 (3)	1.86 (3)	2.656 (3)	178 (4)
O7—H7A···O1^{iii}	0.81 (3)	2.00 (3)	2.791 (3)	166 (3)
O8—H8A···O1^{iv}	0.89 (3)	2.03 (3)	2.902 (3)	165 (3)
O8—H8A···O3^{iv}	0.89 (3)	2.63 (4)	3.124 (3)	116 (3)
O8—H8B···O4^{i}	0.93 (3)	2.25 (4)	2.797 (3)	116 (4)
O8—H8B···O3^{i}	0.93 (3)	2.55 (4)	3.283 (3)	136 (4)
O9—H9A···O8^{iii}	0.90 (3)	1.81 (3)	2.696 (3)	165 (5)
O9—H9B···O6^{v}	0.84 (3)	2.13 (3)	2.914 (3)	156 (4)

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

Compound (III)

Crystal data

$Na^+ \cdot C_7H_{10}NO_7P_2^- \cdot 2.5H_2O$
$M_r = 350.13$
Monoclinic, $C2/c$
$a = 21.664$ (7) Å
$b = 8.930$ (3) Å
$c = 15.123$ (5) Å
$\beta = 114.692$ (5)°
$V = 2658.3$ (14) Å^3
$Z = 8$
$D_x = 1.750$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 963 reflections
$\theta = 2.5$–28.2°
$\mu = 0.41$ mm^{-1}
$T = 193$ (2) K
Plate, colorless
0.30 × 0.20 × 0.06 mm

Data collection

Bruker Platform CCD area-detector diffractometer
Profile data from ω scans
Absorption correction: by integration (*XPREP* in *SHELXTL*; Bruker, 2001)
$T_{min} = 0.886$, $T_{max} = 0.977$
13 009 measured reflections
2435 independent reflections
2142 reflections with $I > 2\sigma(I)$
$R_{int} = 0.035$
$\theta_{max} = 25.4°$
$h = -26 \rightarrow 26$
$k = -10 \rightarrow 10$
$l = -18 \rightarrow 18$
161 standard reflections
frequency: 458 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.030$
$wR(F^2) = 0.082$
$S = 1.05$
2435 reflections
298 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0468P)^2 + 2.8440P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.043$
$\Delta\rho_{max} = 0.37$ e Å^{-3}
$\Delta\rho_{min} = -0.35$ e Å^{-3}

Table 5
Selected geometric parameters (Å, °) for (III).

O1—P1	1.5098 (6)	O4—P2	1.4983 (7)
O2—P1	1.5104 (7)	O5—P2	1.5089 (7)
O3—P1	1.5657 (6)	O6—P2	1.5808 (6)
P2—C1—P1	111.84 (4)	C3—C2—C1	116.69 (7)
P1—C1—C2—C3	−53.84 (7)	C1—C2—C3—C4	−68.20 (10)

Table 6
Hydrogen-bonding geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O2^{i}	0.880 (9)	1.765 (9)	2.6440 (11)	177.7 (8)
O3—H3···O5^{ii}	0.765 (9)	1.745 (9)	2.5002 (8)	168.9 (9)
O6—H6A···O1^{iii}	0.736 (9)	1.922 (9)	2.6538 (10)	172.5 (9)
O7—H7A···O4^{iii}	0.827 (9)	1.954 (9)	2.7487 (10)	161.0 (9)
O8—H8B···O4^{iii}	0.846 (11)	1.957 (13)	2.7671 (13)	160.1 (17)
O8—H8A···O1	0.868 (11)	2.106 (15)	2.7339 (13)	128.7 (14)
O9—H9A···O3^{iii}	0.822 (13)	2.253 (12)	2.9671 (15)	145.4 (11)
O9—H9B···O10^{iv}	0.832 (10)	2.013 (11)	2.7596 (16)	149.1 (17)
O10—H10A···O2	0.841 (13)	1.879 (14)	2.6914 (15)	161.9 (15)
O10—H10B···O2^{v}	0.848 (13)	2.081 (14)	2.9097 (15)	165.5 (11)
O11—H11A···O4^{iii}	0.841 (14)	2.017 (13)	2.7575 (18)	146.4 (11)
O11—H11B···O1	0.863 (12)	1.946 (13)	2.7972 (17)	168.6 (16)
O12—H12A···O3^{iii}	0.867 (14)	2.130 (12)	2.9219 (15)	151.7 (17)
O12—H12B···O2^{iv}	0.845 (11)	2.167 (11)	2.9804 (15)	161.4 (17)

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

In (I), the solvate water molecule was disordered over two general positions. Owing to high correlations, donor H-atom positions were refined under restraint to idealized O—H and N—H distances, with an s.u. of 0.03 Å, and H—R distances for the water molecules were also restrained (s.u. = 0.06 Å). The remaining C—H H atoms were included as riding atoms, with $U_{iso}(H) = 1.2U_{eq}$ of their parent atoms. Disordered O—H distances were restrained to equivalent idealized values, with an effective s.u. of 0.03 Å..

For (II), owing to high correlations, O—H distances were restrained to equivalent idealized values, with an s.u. of 0.04 Å, and H—R distances for the water molecules were also restrained (s.u. = 0.04 Å). The remaining H-atom parameters were refined independently.

For (III), the uncoordinated solvate water molecule was disordered about the twofold axis. The proposed model also included two disordered positions for the Na^+ ion, in addition to the bridging and terminal water ligands. Owing to high correlations, O—H distances and angles for the disordered water molecules were restrained to equivalent idealized values, with s.u. values of 0.03 Å and 0.04°, respectively. Displacement parameters for H atoms bound to the same disordered O atom were restrained to be similar (s.u. = 0.01 Å^2). The remaining H-atom parameters were refined independently without restraints. The highest peaks in the final difference Fourier maps for all three compounds were located along the C—P bonds.

For all compounds, 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 *SHELXL*97-2 (Sheldrick, 2001).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1145). Services for accessing these data are described at the back of the journal.

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