

Zoledronate complexes. II. *catena*-Poly[[tetraaquabis[hemihydrogen μ_3 -1-hydroxy-2-(imidazol-3-ium-1-yl)-ethylidene-1,1-diphosphonato- κ^3 O:O':O'']bis[μ_3 -1-hydroxy-2-(imidazol-3-ium-1-yl)ethylidene-1,1-diphosphonato- κ^4 O:O,O':O'']]trisodium] dihydrate]

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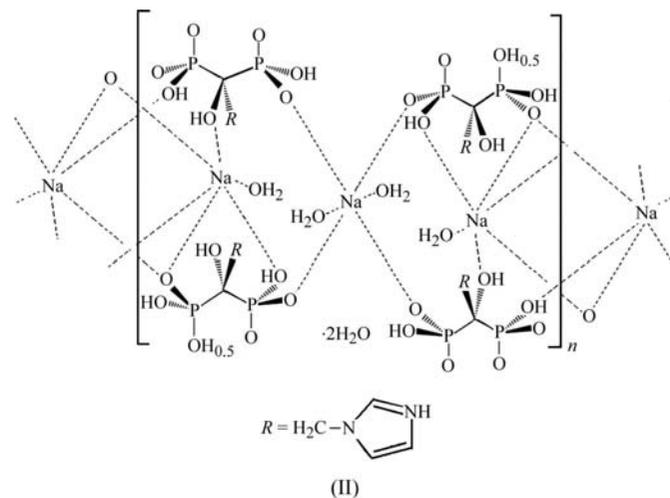
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The title compound, $\{[\text{Na}_3(\text{C}_5\text{H}_9\text{N}_2\text{O}_7\text{P}_2)_2(\text{C}_5\text{H}_9\text{N}_2\text{O}_7\text{P}_2)_2(\text{H}_2\text{O})_4] \cdot 2\text{H}_2\text{O}\}_n$ (II), is polymeric and consists of undulating chains parallel to [011] interconnected by hydrogen-bonding and π - π interactions. There are two independent Na^+ cations in the asymmetric unit (one lying on an inversion centre), two zoledronate anions and three water molecules, two of which are coordinated and one of which is a free solvate. Each cation is surrounded in an octahedral fashion by O atoms from four different zoledronate units and two/one coordinated water molecules. The zoledronate groups present their usual zwitterionic character, with negative charges in the protonated phosphonates and a positive charge at the protonated imidazole N atom. Two symmetry-related phosphonate groups share (in the form of a very strong linear hydrogen bond) an H atom lying on a symmetry centre, midway between the O atoms involved. The zoledronate binding modes present in (II) are both unreported for bisphosphonate anions. Intra- and inter-chain interactions are enhanced by a variety of hydrogen bonds where all the available O—H and N—H donors are involved, in addition to a strong imidazole–phosphonate C—H...O interaction, typical in these kinds of structures.

Comment

Initiating a line of research on mono- and divalent alkaline cation complexes with the zoledronate anion (hereafter

represented by the generic term Zol, irrespective of their different ionic forms), we have recently reported the first structure of this type, *viz.* $\{[\text{K}(\text{Zol})(\text{H}_2\text{O})] \cdot \text{H}_2\text{O}\}_n$ (I) (Freire *et al.*, 2010), where all constituents (cation, anion, coordinated water and solvent water) appeared in a rather simple 1:1:1:1 ratio. A thorough introduction to zoledronate complexes has been included in that report, to which the interested reader is referred.



As a continuation of this line of research, we present herein the sodium counterpart, (II), which shows a quite different formulation (*viz.* 3:4:4:2, or explicitly $\{[\text{Na}_3(\text{Zol})_4(\text{H}_2\text{O})_4] \cdot 2\text{H}_2\text{O}\}_n$), a difference which is readily reflected in important structural differences, to be discussed below.

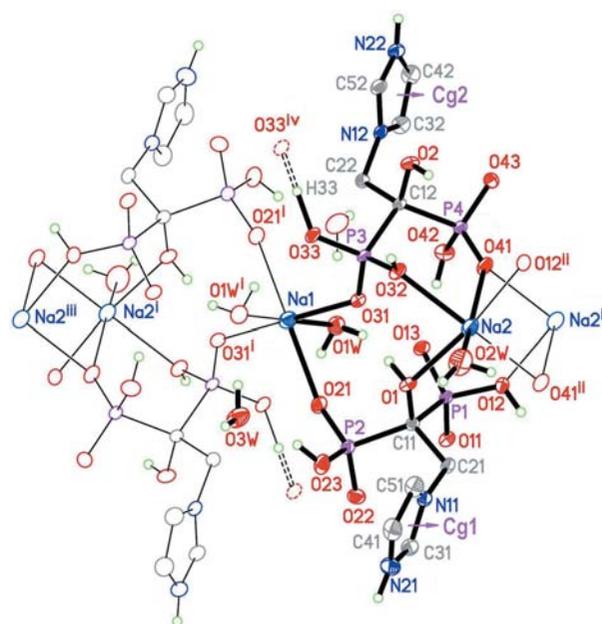
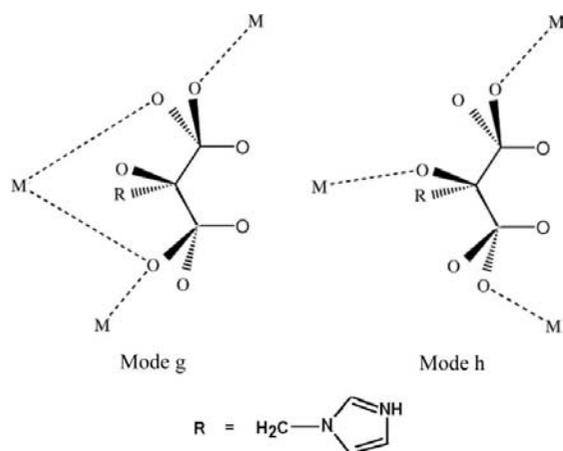


Figure 1
Displacement ellipsoid plot (40% probability level) of (II), showing the asymmetric unit (heavy outline) and the symmetry-related part completing the trinuclear unit (light outline). [Symmetry codes: (i) $1-x, 1-y, 1-z$; (ii) $1-x, 2-y, 2-z$; (iii) $x, -1+y, -1+z$; (iv) $-x, 1-y, 1-z$.]

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**Figure 2**

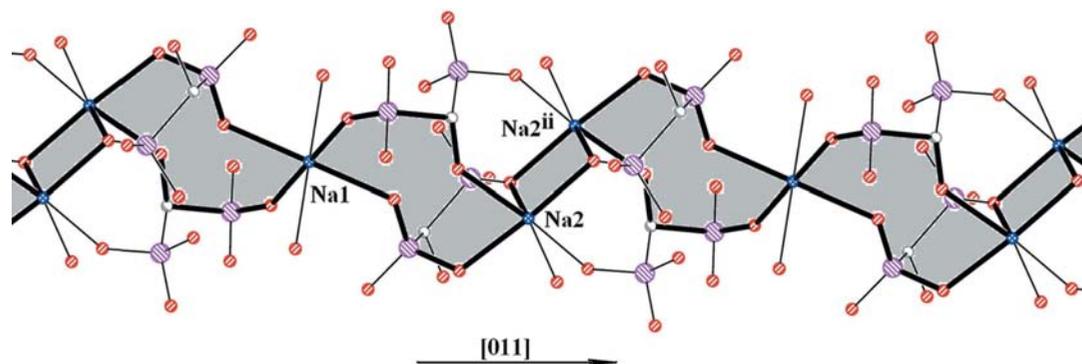
The zoledronate coordination schemes in (II). These should be considered as additional coordination modes to those shown in Fig. 2 in Freire *et al.* (2010).

There are two independent Na^+ cations in the asymmetric unit, one of them lying on an inversion centre (Na1) and the other on a general position (Na2), two zoledronate anions and three water molecules, two of which are coordinated while the remaining one is a free solvate. The centre of symmetry at Na1 transforms the group into a trinuclear unit (see scheme and Fig. 1) which is much simpler to describe and which we shall adopt as our 'molecular formula' ($z = 1$, $z' = 0.5$). The metallic centres present rather distorted NaO_6 octahedral environments, each independent Na1(Na2) cation being connected to four zoledronate anions, and completing the coordination polyhedron with two(one) aqua ligands (Table 1). Coordination parameters are as follows: Na1–O = 2.349 (3)–2.488 (3) Å, O–Na1–O_{opposite} = 180° (due to centrosymmetry); O–Na1–O_{neighbour} = 78.93 (12)–101.07 (12)°; Na2–O = 2.363 (4)–2.554 (4) Å, O–Na2–O_{opposite} = 158.68 (17)–176.02 (14)°; O–Na2–O_{neighbour} = 77.69 (11)–102.25 (15)°. The two independent zoledronate ligands, in turn, bind in a μ_3 -mode to three metal centres each. Unit 1 binds in a simple threefold O:O':O''-monocoordinated fashion through atoms O21, O1 and O12 to atoms Na1, Na2 and Na2($-x + 1, -y + 2, -z + 2$), respectively; unit 2 is a little

more complex with two O atoms (O32 and O41) chelating one metal centre (Na2), with atom O41 also binding Na2($-x + 1, -y + 2, -z + 2$). Finally, there is one mono-coordinated O atom (O31) bound to Na1, all of which leads to an overall O:O,O':O''-chelating bridging mode for the anion.

These coordination schemes are very simple compared to the extremely complex connectivity modes usually displayed by bisphosphonates in general; in fact we could not trace any similar arrangement for any reported bisphosphonate in the Cambridge Structural Database (CSD, Version 5.31; Allen, 2002), and these binding modes are also new for the zoledronate anion (see Fig. 2 in Freire *et al.*, 2010, for the zoledronate binding modes reported so far). The bridging character of both independent anions results in the formation of a chain structure running along [011] consisting of the juxtaposition of the individual three nuclear motifs shown in Fig. 1, linked in a 'slanted' fashion into a rather undulating one-dimensional structure. This is shown schematically in Fig. 3, where the two different types of loops joining metal centres are clearly seen: a very simple Na_2O_2 one, in the form of a rhomboid around an inversion centre joining two symmetry-related Na2 cations through two O41 bridges, and a much more complicated one, joining Na1 and Na2 through both extended zoledronates.

In order to discuss charge balance in (II) we shall first briefly analyse the other related zoledronate complexes in the literature [see Freire *et al.* (2010) for a detailed survey]. The cases reported so far, with the exception of DOGYOO (see Table 3 for details), present one single independent zoledronate group, for which they display a general $M_n^{+x}(\text{Zol}^{-y})_m$ core (M is a metallic cation; x and y are positive numbers accounting for the total charge over each group). Charge balance is achieved within each compound through a set of integer values for the (n, x, m, y) 'quartet' subject to the condition $n \times x = m \times y$ (Table 3, upper block). Different values for the charge in the bisphosphonate units ($-1, -3$) are the result of the different protonation states of the individual phosphonates, where each $\text{PO}_3\text{H}_{n\text{H}}$ group carries a formal negative charge of $(2 - n\text{H})$ electrons, (circumstantially, all these cases present the same number of hydrogens ' $n\text{H}$ ' in both $\text{PO}_3\text{H}_{n\text{H}}$ groups, but this symmetry is obviously not a

**Figure 3**

Schematic packing diagram of (II), showing the undulating chain formed by the two types of loops. The pendant imidazole and hydroxy groups, as well as H atoms, are not shown for clarity.

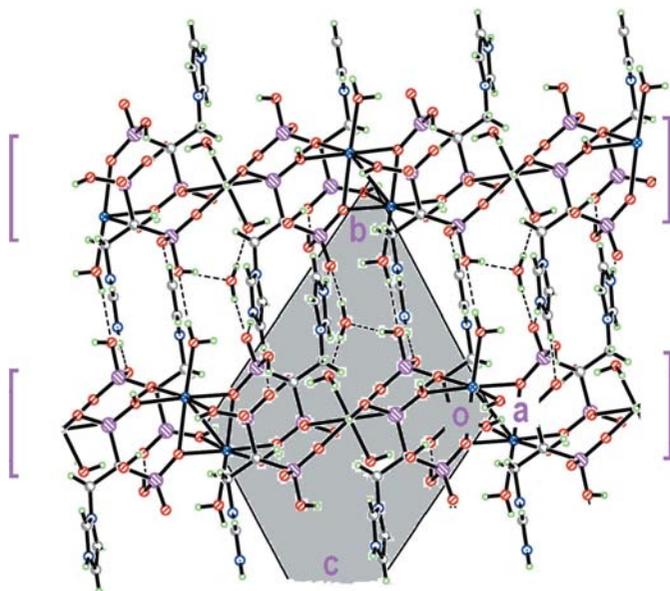


Figure 4
Packing diagram of (II) viewed along *a* and showing the planes in projection. Note the overlap of neighbouring imidazole rings.

necessary condition). The protonated imidazole group adds a positive charge to the total sum. As already stated, the structure DOGYOO is the exception to this, in that it presents two independent zoledronate anions, each one with different charges and thus the compound should be formulated as $M_n^{+x}(\text{Zol}^{-y})_m(\text{Zol}^{-z})_p$, *y* and *z* being the individual (not necessarily equal) number of charges for each Zol group. The charge-balance equation would read, in this case, $n \times x = m \times y + p \times z$ (Table 3, lower block, first entry)

A similar situation is found in (II), where the corresponding ‘sextet’ would be (3, 1, 2, *y*, 2, *z*) and the associated balance equation: $3 \times 1 = 2 \times y + 2 \times z$. It is apparent that there is no possible integer solution for that equation, requiring instead a fractional charge somewhere, which could be achieved, for example, through some half-occupied H-atom site. Instead of that, the structure fulfils this condition by placing one proton at a symmetry centre, midway between two symmetry-related O atoms [O33 and O33^{iv}; symmetry code: (iv) $-x, -y + 1, -z + 1$] in a symmetric O···H···O’ bridge (O···H = 1.21 Å; see Fig. 1, H33 at $0\frac{1}{2}\frac{1}{2}$). The alternative possibility of a disordered H atom with 0.5 occupancy at both sides of the symmetry centre was disregarded after a difference map, calculated through the symmetry-related O atoms, showed a well defined spherical single peak at the centre.

In addition to the key role it plays in the charge-balance equation, this H33 atom is central to the structure packing, since it serves to join parallel chains along the *a* direction to form a two-dimensional structure parallel to (01 $\bar{1}$) (viewed in projection in Fig. 4 as horizontal linear arrays, limited by square brackets). These planes present the imidazole rings protruding outwards (at both sides) so that piling up of planes leads to interdigitation and the concomitant appearance of

π - π contacts between neighbouring layers [viz. $\text{Cg1} \cdots \text{Cg2}^{\text{i}} = 3.791(3)$ Å and $\text{Cg2} \cdots \text{Cg2}^{\text{ii}} = 3.700(2)$ Å, where Cg1 and Cg2 are the centroids of the imidazole rings containing atoms N11 and N12, respectively; symmetry codes: (i) $x + 1, y, z + 1$; (ii) $-x, -y + 2, -z + 1$] (Fig. 1). Both types of interchain interactions are complemented by a number of hydrogen bonds in which all the available O—H and N—H (and some C—H, see below) donors take part (Table 2). Many of these interactions are visible in Fig. 4, in particular as bridging agents between layers.

It has been shown (Freire *et al.*, 2010) that zoledronate compounds very often present unusually short imidazole–phosphonate C—H···O interactions, with H···O distances as short as 2.24 Å, *e.g.* refcode VIMXIZ (Cao *et al.*, 2007). The present structure, (II), is not an exception to the rule, as the last entry in Table 2 confirms (H···O = 2.31 Å).

At this stage it is worth comparing the structure of (II) with two closely related compounds in the literature, with similarities and differences originating for quite different reasons. The first one, Na(isoZol)·4H₂O, (III) (isoZol is isozoledronate, a zoledronate isomer; Gossman *et al.*, 2002), shares with (II) the same Na⁺ cation, while the anion has its imidazole unit ‘rotated’ around its plane and bound to the main frame *via* a C atom instead of an N atom, thus leaving two active amine H atoms free for hydrogen bonding, instead of the single one found in zoledronate. In spite of the obvious molecular similarities, this slight change in the way in which the imidazole group is attached to the ligand seems crucial in defining the way both structures build up, the differences including formulation [in the above-mentioned notation, 3:4:4:2 for (II) and 1:1:3:1 for (III)] and, a direct consequence of the different formulation, charge balance [achieved in a straightforward 1:1 fashion in (III) but in the rather complicated way already discussed in (II)], dimensionality [while (II) is a chain structure, (III) is dimeric], *etc.*

The second analogue is the structure reported under CSD refcode DOGYOO (see Table 3 and the charge-balance discussion); the compound is one of the copper zoledronates reported in Cao *et al.* (2008), *viz.* Cu₃(Zol)₄·4H₂O, (IV), which bears a similar 3:4 cation–anion ratio to (II) and many structural similarities, *viz.* in both structures there is one cation on a symmetry centre and a second cation in a general position, they are joined by the two independent Zol groups into chains formed by two types of links, some in the form of small centrosymmetric M—O—M—O loops, and others larger and more irregular, involving unrelated cations. However, the difference in cation valence (Na^I *versus* Cu^{II}) leads to differences in the way charge balance is achieved (we have already discussed this point), as well as different coordination geometries: there are no coordinated water molecules in (IV). The result is reflected in the formulation, *viz.* 3:4:4:2 for (II) and 3:4:0:4 for (IV)

All three structures coincide in the existence of a complex and extensive hydrogen-bonding scheme, which is the result of a rich provision of hydrogen-bonding donors and acceptors, and which in all cases results in a tightly bound three-dimensional structure.

Experimental

Crystals of (II) were synthesized by neutralization of a solution of zoledronic acid (from GADOR Argentina SA) with a NaOH solution in a 1:1 stoichiometric ratio. The unperturbed solution was allowed to concentrate slowly and, after a few days, large colourless blocks were obtained suitable for X-ray diffraction.

Crystal data

[Na₃(C₅H₉N₂O₇P₂)₂(C₅H_{9.5}N₂-O₇P₂)₂(H₂O)₄]-2H₂O
M_r = 1262.40
 Triclinic, *P* $\bar{1}$
a = 9.0690 (18) Å
b = 11.309 (2) Å
c = 12.594 (3) Å
 α = 115.58 (3)°
 β = 98.86 (3)°
 γ = 99.76 (3)°
V = 1110.1 (6) Å³
Z = 1
 Mo *K* α radiation
 μ = 0.46 mm⁻¹
T = 295 K
 0.36 × 0.22 × 0.20 mm

Data collection

Rigaku AFC-6S diffractometer
 Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.78, *T_{max}* = 0.83
 5236 measured reflections
 4366 independent reflections
 3797 reflections with *I* > 2 σ (*I*)
R_{int} = 0.034
 3 standard reflections every 150 reflections
 intensity decay: 1%

Refinement

R[*F*² > 2 σ (*F*²)] = 0.056
wR(*F*²) = 0.170
S = 1.09
 4366 reflections
 331 parameters
 H-atom parameters constrained
 $\Delta\rho_{\max}$ = 1.05 e Å⁻³
 $\Delta\rho_{\min}$ = -0.78 e Å⁻³

Table 1

Selected interatomic distances (Å).

Na1—O21	2.349 (3)	Na2—O41	2.404 (3)
Na1—O31	2.463 (3)	Na2—O12 ⁱ	2.485 (4)
Na1—O1 <i>W</i>	2.488 (3)	Na2—O2 <i>W</i>	2.502 (5)
Na2—O41 ⁱ	2.363 (4)	Na2—O1	2.554 (4)
Na2—O32	2.389 (4)		
Na2...Na2 ⁱ	3.085 (4)	Na1...Na2	5.943 (4)

Symmetry code: (i) -*x* + 1, -*y* + 2, -*z* + 2.

H atoms attached to O and N atoms were found in a difference Fourier map, further adjusted along the X—H bond to reach ideal values (O—H = 0.85 Å and N—H = 0.88 Å) and finally allowed to ride. The exception to this was atom H33, which was constrained to lie on an inversion centre midway between the donor and acceptor of the hydrogen bond in which it takes part. H atoms attached to C atoms were placed at calculated positions (C—H = 0.93 and 0.97 Å for CH and CH₂ groups, respectively) and allowed to ride. Displacement parameters were taken as *U*_{iso}(H) = 1.2*U*_{eq}(host).

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *MSC/AFC Diffractometer Control Software*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *SHELXTL* and *PLATON* (Spek, 2009).

Table 2

Hydrogen-bond geometry (Å, °).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
O12—H12...O11 ⁱⁱ	0.85	1.71	2.561 (4)	178
O23—H23...O3 <i>W</i>	0.85	1.79	2.628 (5)	167
O32—H32...O22 ⁱⁱⁱ	0.85	1.71	2.559 (4)	174
O33—H33...O33 ^{iv}	1.21	1.21	2.419 (6)	180
O42—H42...O13	0.85	1.73	2.565 (4)	169
O1—H1...O31	0.85	1.80	2.628 (4)	163
O2—H2...O11 ⁱⁱⁱ	0.85	1.87	2.700 (4)	165
N21—H21...O22 ^v	0.88	1.77	2.644 (5)	172
N22—H22...O43 ^{vi}	0.88	1.80	2.669 (5)	171
O1 <i>W</i> —H1 <i>WA</i> ...O33 ^{vii}	0.85	2.15	2.961 (5)	161
O1 <i>W</i> —H1 <i>WB</i> ...O13	0.85	1.89	2.739 (5)	174
O2 <i>W</i> —H2 <i>WA</i> ...O23 ^{viii}	0.85	2.22	3.068 (5)	174
O2 <i>W</i> —H2 <i>WB</i> ...O42 ⁱ	0.85	2.52	3.305 (6)	153
O3 <i>W</i> —H3 <i>WA</i> ...O1 <i>W</i> ^{vii}	0.85	1.94	2.771 (5)	166
O3 <i>W</i> —H3 <i>WB</i> ...O43 ^{ix}	0.85	2.01	2.844 (5)	168
C21—H21 <i>B</i> ...O41 ⁱ	0.97	2.60	3.538 (6)	164
C22—H22 <i>B</i> ...O33 ^{iv}	0.97	2.51	3.370 (6)	147
C31—H31...O2 <i>W</i> ^x	0.93	2.57	3.483 (8)	167
C52—H52...O1 <i>W</i> ⁱⁱⁱ	0.93	2.49	3.404 (6)	167
C42—H42 <i>A</i> ...O13 ^{xi}	0.93	2.31	3.205 (7)	161

Symmetry codes: (i) -*x* + 1, -*y* + 2, -*z* + 2; (ii) -*x* + 2, -*y* + 2, -*z* + 2; (iii) *x* - 1, *y*, *z*; (iv) -*x*, -*y* + 1, -*z* + 1; (v) -*x* + 2, -*y* + 1, -*z* + 2; (vi) -*x*, -*y* + 2, -*z* + 1; (vii) -*x* + 1, -*y* + 1, -*z* + 1; (viii) -*x* + 1, -*y* + 1, -*z* + 2; (ix) *x*, *y* - 1, *z*; (x) *x* + 1, *y*, *z*; (xi) -*x* + 1, -*y* + 2, -*z* + 1.

Table 3

Charge-balance summary in zoledronate complexes.

CSD refcode	Reference	<i>M</i>	<i>n</i>	<i>x</i>	<i>m</i>	<i>y</i>	<i>p</i>	<i>z</i>
VIMXEY	<i>a</i>	Co	3	2	2	3		
VIMXIZ	<i>a</i>	Ni	3	2	2	3		
VIMXOF	<i>a</i>	Co	1	2	2	1		
VIMXUL	<i>a</i>	Ni	1	2	2	1		
DOGYEE	<i>b</i>	Cu	1	2	2	1		
DOGYII	<i>b</i>	Cu	1	2	2	1		
DOGYUU	<i>b</i>	Cu	3	2	2	3		
	<i>c</i>	Zn	1	2	2	1		
	<i>d</i>	Zn	1	2	2	1		
(I)	<i>e</i>	K	1	1	1	1		
DOGYOO	<i>b</i>	Cu	3	2	2	2	2	1
(II)	<i>f</i>	Na	3	1	2	1	2	0.5

References: (a) Cao *et al.* (2007); (b) Cao *et al.* (2008); (c) Freire & Vega (2009a); (d) Freire & Vega (2009b); (e) Freire *et al.* (2010); (f) this work.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN3137). Services for accessing these data are described at the back of the journal.

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