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A synchrotron radiation study of the one-dimensional complex of sodium with (1*S*)-*N*-carboxylato-1-(9-deaza-adenin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol, a member of the 'immucillin' family

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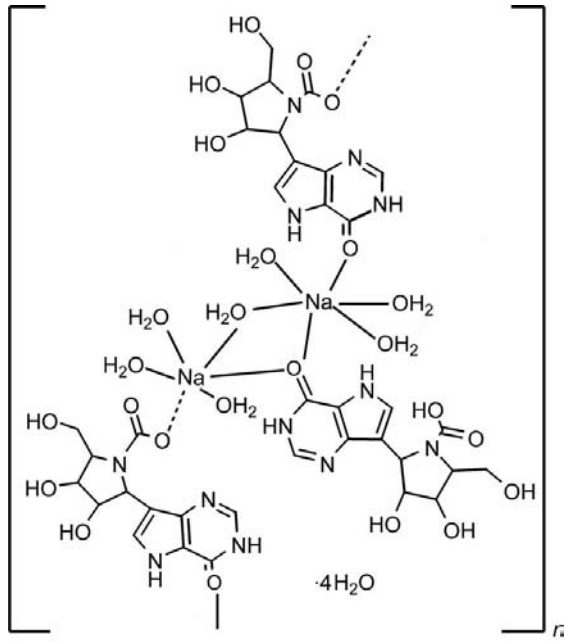
The sodium salt of [immucillin-A–CO_2H]$^-$ (Imm-A), namely *catena*-poly[[[triaquadisodium(I)](μ-aqua)[μ-(1*S*)-*N*-carboxylato-1-(9-deazaadenin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol][triaquadisodium(I)][μ-(1*S*)-*N*-carboxylato-1-(9-deazaadenin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol]] tetrahydrate], {[$Na_2(C_{12}H_{13}N_4O_6)_2(H_2O)_7]\cdot 4H_2O$}$_n$, (I), forms a polymeric chain *via* Na^+—O interactions involving the carboxylate and keto O atoms of two independent Imm-A molecules. Extensive N,O—H$\cdots$O hydrogen bonding utilizing all water H atoms, including four waters of crystallization, provides crystal packing. The structural definition of this novel compound was made possible through the use of synchrotron radiation utilizing a minute fragment (volume $\sim 2.4 \times 10^{-5}$ mm^{-3}) on a beamline optimized for protein data collection. A summary of intra-ring conformations for immucillin structures indicates considerable flexibility while retaining similar intra-ring orientations.

Comment

The title compound, (I), was prepared as part of continuing studies of the so-called 'immucillin' family of compounds which are potent aza-C-nucleoside inhibitors of purine nucleoside phosphorylase (Evans *et al.*, 2003). The immucillin compounds do not usually form adequate-quality crystals, and only adducts protonated on the aza-ribitol sugar (N1) positions have been reported (MILMAV: Federov *et al.*, 2001; MEFZOM: Evans *et al.*, 2000) (alphabetic codes used herein are those used in the Cambridge Structural Database, 2009). A related compound, with oxygen replacing NH in the saturated five-membered ring, is VOVJIZ (Otter *et al.*, 1992), while compound VILHON (Ikegami *et al.*, 1990) has been re-assigned as a related 6′-amino compound by Otter *et al.* (1992). Some of these compounds have been successfully defined 'in action' as inhibitors in sites within the enzymes (*e.g.* MT-Imm-A; Singh *et al.*, 2004). The size of the crystal fragment used here meant that both the superb power and resolution of synchrotron radiation were essential even when used in the less than optimum settings at the end of a protein data collection. We are thus able to present the first anionic derivative of this family.



(I)

The asymmetric unit contents of the title compound, (I), are shown in Fig. 1; the polymer linking bonds (Na1*—O16, Na1—O16*) are shown at the top and bottom of the figure (see also Fig. 2 and the scheme above). The two independent Imm-A–CO_2^- molecules, which are label-related by adding 10 to the number of the first (*i.e.* N1 and N11), are almost superimposable. The absolute configurations at C1′ (*S*), C2′ (*S*), C3′ (*R*) and C4′ (*R*) indicated by a Flack parameter of 0.0 (3) agree with the stereochemistry known from the synthesis. There is a slight difference in tilt angle, $\sim$10°, between the two rings (see the dihedral angles around C1′—C9 and C11′—C19 in Table 1), and ring comparisons (Spek, 2009) give r.m.s. bond and angle fits of 0.016 Å and 1.25°, respectively. The 1,9-deazaadenin-9-yl nine-membered rings (*e.g.* N1/C2/N3/C4/C9/C8/N7/C5/C6) are made up of two rigidly planar five- and six-membered rings, with the planes at an average angle of 1.8 (3)° with respect to each other. The five-membered (imino-ribitol) rings (*e.g.* N1′/C1′–C4′) are puckered on C2′ and C3′ [Cremer & Pople (1975) parameters $Q(2)$ = 0.342 (6) Å and $\varphi(2)$ = 272.3 (9)°] in molecule 1 and twisted on C12′—C13′ [$Q(2)$ = 0.307 (6) Å and $\varphi(2)$ = 268.2 (10)°] in the other. Such variations are normal, as shown by the pyrrolidine-1-carboxylate adduct FISNUR (Zukerman-Schpector *et al.*, 2005) which also twists along C2′—C3′ [$Q(2)$ = 0.426 Å and $\varphi(2)$ = 266.4 (3)°].

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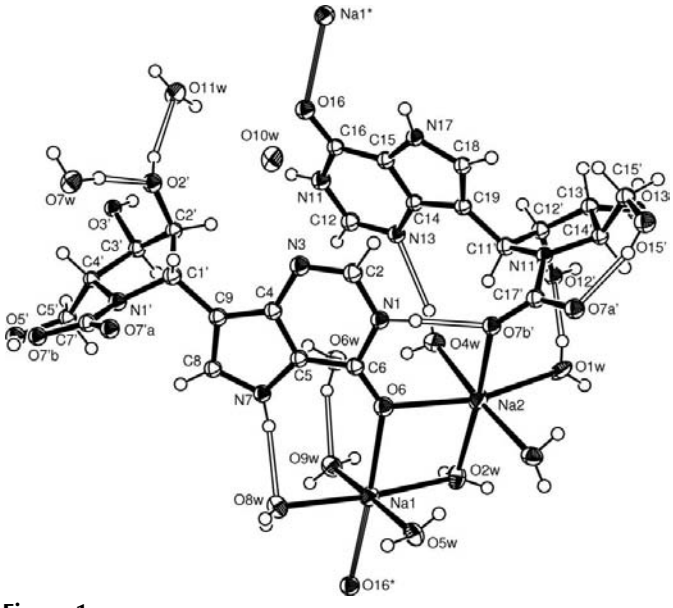

Figure 1
Diagram of the asymmetric unit and two extra atoms of (I), shown with 50% displacement ellipsoids (Farrugia, 1997). Atoms Na1* (at $x-1$, $y-1$, z) and O16* (at $x+1$, $y+1$, z) are included and linked by three-line bonds to show the polymeric linkages. H atoms have arbitrary radii. Identified hydrogen bonds within the asymmetric unit are shown as dashed lines. The H atoms on water atom O10*W* were not located.

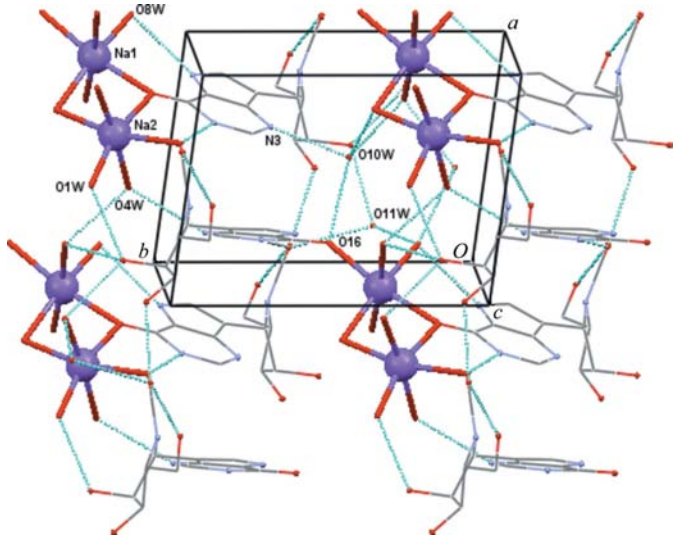

Figure 2
Packing diagram of the cell of (I) (Bruno *et al.*, 2002), viewed approximately down the *c* axis. Representative atom labels are given (see *Comment* and Table 2) and H atoms have been omitted for clarity. Hydrogen bonds are shown as dashed lines. (Key in the electronic version of the paper: N, blue sticks; Na, purple balls; O, red sticks; C, grey wires.)

For completeness, we note that other pyrimidin-4-one structures have been reported: FOYWIZ (Girgis *et al.*, 1987) and QINBOE (Jukic *et al.*, 2000); the former has (fortuitously) similar relative orientations of the two rings to molecule 1 here.

One of the Imm-A–CO_2^- molecules provides a bridging oxygen (O6) to the two independent cations, while the other bonds to only Na2 through carboxylate atom O7*b*′ (Fig. 1). The Na cations are further bridged by one water molecule (O2*W*) and both have the usual approximate octahedral binding stereochemistry, with variation in Na—O distances depending on the *trans* donor atoms. Finally, the packing cohesion is provided by extensive hydrogen bonds involving all the waters of crystallization, the aqua molecules and the Imm-A–CO_2^- N-bound H atoms as donors (Table 2, and scheme). Overall, the structure can be described as a polymeric chain parallel to the $(1\bar{1}1)$ plane crosslinked by hydrogen bonds to the water molecules that lie between the chains (Fig. 2).

It is of interest to compare the relative conformations of the two independent Imm-A–CO_2^- molecules here with the previously reported (free) Imm-H cationic molecules and Imm-H as found bound in a human purine nucleoside phosphorylase mutant (Table 3). There is quite a wide variation of relative conformations of the ten-membered 9-deazaadenin-9-yl and the 4-aza-ribitol rings with respect to the linking bond (*e.g.* C1—C9′), with the two independent molecules here being closely related both in intra-ring orientations and in the 4-aza-ribitol ring descriptions. This is rather remarkable given the variation that might be expected in the strongly hydrogen-bonded network and with each molecule involved in different interactions with the cations. Agreement between the two free Imm-H studies (entries 4 and 6 in Table 3) is also notable. It is also apparent that the protein-bound molecule (entry 5) has been twisted about the link bond in response to close interactions, but still retains a similar intraplanar angle (between the two rings) to that in the free ligand structures. The linking factor in these determinations is that the variable conformations retain a similar intraplanar angle with only minor variations in the attachment angles [*e.g.* C1′—C9—C8 = 126.3 (5)° and C11′—C19—C18 = 129.1 (5)° here, compared with 130.2° in the bound molecule (Murkin *et al.*, 2007)].

Experimental

The title compound (immucillin-A–CO_2H) was made by incubation of the Imm-A–HCl salt (50 mg, 0.165 mmol) (Evans *et al.*, 2003) dissolved in water (2 ml). The compound was deprotonated with sodium hydroxide (0.165 mmol, 6.6 mg) dissolved in water (100 µl), which caused precipitation, but the addition of more sodium hydroxide (0.165 mmol, 6.6 mg) dissolved in water (100 µl) caused the compound to redissolve. The aqueous mixture was left open to the atmosphere to allow evaporation of the solvent (and absorption of CO_2) and for crystallization. The described material crystallized after a week.

Crystal data

$[Na_2(C_{12}H_{13}N_4O_6)_2(H_2O)_7]\cdot 4H_2O$
M_r = 862.68
Triclinic, *P*1
a = 7.6620 (15) Å
b = 10.488 (2) Å
c = 11.606 (2) Å
α = 98.24 (3)°
β = 91.07 (3)°
γ = 98.49 (3)°
V = 912.1 (3) Å^3
Z = 1
Synchrotron radiation
λ = 0.98000 Å
μ = 0.16 mm^{-1}
T = 100 K
0.08 × 0.06 × 0.01 mm

Table 1
Selected geometric parameters (Å, °).

Na1—O9*W*	2.382 (5)	Na2—O1*W*	2.340 (5)
Na1—O5*W*	2.391 (5)	Na2—O2*W*	2.419 (5)
Na1—O16^{i}	2.396 (4)	Na2—O3*W*	2.436 (5)
Na1—O8*W*	2.398 (5)	Na2—O6	2.454 (4)
Na1—O6	2.426 (4)	Na2—O7*B*′	2.513 (4)
Na1—O2*W*	2.504 (5)	Na2—O4*W*	2.518 (5)
O16^{i}—Na1—O8*W*	77.40 (15)	O2*W*—Na2—O7*B*′	167.45 (16)
O16^{i}—Na1—O6	172.39 (15)	O6—Na2—O7*B*′	88.54 (14)
O1*W*—Na2—O2*W*	106.58 (16)	Na2—O2*W*—Na1	95.78 (15)
O1*W*—Na2—O7*B*′	83.68 (16)	Na1—O6—Na2	96.92 (15)
C2—N1—C6—O6	179.6 (5)	C14′—N11′—C17′—O7*B*′	−156.8 (5)
N1′—C1′—C9—C8	11.0 (7)	N11′—C11′—C19—C18	21.7 (8)
N1′—C1′—C9—C4	−167.6 (5)	N11′—C11′—C19—C14	−159.3 (5)

Symmetry code: (i) $x+1, y+1, z$.

Data collection

MAR CCD detector diffractometer
2357 measured reflections
2357 independent reflections
2330 reflections with $I > 2\sigma(I)$
$R_{int} = 0.034$
$\theta_{max} = 25.5°$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.035$
$wR(F^2) = 0.092$
$S = 1.07$
2357 reflections
360 parameters
27 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.22$ e Å^{-3}
$\Delta\rho_{min} = -0.21$ e Å^{-3}
Absolute structure: Flack (1983), with 1161 Friedel pairs
Flack parameter: 0.0 (3)

One low-angle reflection ($\bar{1}10$) and eight high-angle reflections ($\Delta(F^2)$/e.s.d. > 3.8) were omitted. A total of 44 non-H atoms were refined with isotropic displacement parameters (some being unstable to anisotropic refinement) thereby improving the data/parameter value. The number of Friedel pairs was 1161. All H atoms were constrained, with U_{iso} values of 1.2 times the U_{eq} of the parent atom for C, N and hydroxy O atoms, and with U_{iso} values of 1.2 times the U_{eq} of the parent atom for water O atoms. Most water H atoms were located on difference Fourier maps; other water H atoms were positioned from stereochemical considerations and confirmed by improved agreement factors and Fourier maps. The O10*W* water H atoms could not be resolved from difference Fourier maps and their placement lead to unacceptably close contacts with other water H atoms (<1.5 Å); they were thus excluded from the final refinement. In the final refinements, all water O—H distances were constrained to 0.82 (3) Å, with a minimum H···H distance of 1.35 (3) Å. In the final model, there are some close water H···H distances reflecting the model and data limitations. All other H atoms were geometrically constrained (riding model) to C—H, N—H and O—H bond lengths of 0.99, 0.88 and 0.84 Å, respectively.

Data collection: *DENZO* (Otwinowski & Minor, 1997); cell refinement: *DENZO*; data reduction: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP* in *WinGX* (Farrugia, 1997) and *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXL97*, *PLATON* and *Mercury* (Bruno *et al.*, 2002).

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1*W*—H1*W*1···O3′^{ii}	0.82 (5)	2.00 (5)	2.815 (5)	175 (7)
O1*W*—H1*W*2···O12′	0.78 (5)	1.99 (5)	2.735 (5)	160 (8)
O2′—H2′O···O11*W*	0.84	1.92	2.745 (5)	168
O2*W*—H2*W*1···O10*W*^{iii}	0.83 (5)	2.02 (5)	2.849 (6)	178 (7)
O3′—H3′O···O7′*B*^{iv}	0.84	1.87	2.683 (4)	163
O2*W*—H2*W*2···O5′^{ii}	0.83 (5)	2.07 (5)	2.878 (6)	163 (6)
O3*W*—H3*W*1···O7′*B*^{ii}	0.80 (5)	2.08 (5)	2.839 (5)	159 (5)
O5′—H5′O···O7′*B*	0.84	1.93	2.701 (6)	152
O3*W*—H3*W*2···O7*W*^{ii}	0.84 (5)	1.99 (5)	2.785 (6)	158 (5)
O4*W*—H4*W*1···O6*W*	0.85 (4)	1.93 (4)	2.748 (7)	163 (5)
N7—H7N···O8*W*	0.88	2.06	2.833 (6)	145
O4*W*—H4*W*2···N13	0.82 (4)	2.15 (5)	2.952 (6)	165 (5)
O5*W*—H5*W*1···O4*W*^{v}	0.85 (6)	2.06 (6)	2.821 (6)	150 (6)
O5*W*—H5*W*2···O12′^{v}	0.80 (5)	2.24 (6)	2.951 (6)	148 (6)
O6*W*—H6*W*1···O15′^{vi}	0.84 (5)	1.89 (6)	2.717 (6)	168 (6)
O11*W*—H11*A*···O13′^{vii}	0.82 (5)	2.19 (5)	2.968 (5)	158 (5)
O11*W*—H11*B*···O7′*A*^{iv}	0.84 (6)	2.09 (5)	2.846 (5)	150 (6)
N11—H11N···O7′*A*^{iv}	0.88	1.85	2.729 (6)	175
O6*W*—H6*W*2···O9*W*	0.82 (6)	1.98 (5)	2.778 (6)	164 (7)
O12′—H2O′···O3*W*^{iv}	0.84	1.93	2.704 (5)	153
O7*W*—H7*W*1···O7*A*′^{vii}	0.81 (4)	1.98 (5)	2.773 (5)	165 (5)
O13′—H3O′···O7*A*′^{viii}	0.84	1.84	2.667 (5)	166
O7*W*—H7*W*2···O2′	0.83 (5)	1.86 (5)	2.685 (6)	170 (7)
O8*W*—H8*W*1···O11*W*^{i}	0.84 (5)	1.99 (6)	2.795 (6)	160 (5)
O15′—H5O′···O7*A*′	0.84	1.85	2.650 (6)	159
O8*W*—H8*W*2···O6*W*^{v}	0.81 (4)	2.01 (4)	2.818 (6)	175 (6)
O9*W*—H9*W*1···O10*W*^{iii}	0.84 (5)	1.96 (5)	2.780 (6)	165 (5)
N17—H17N···O5*W*^{ix}	0.88	2.06	2.919 (6)	166
O9*W*—H9*W*2···O7*W*^{iii}	0.83 (4)	2.08 (3)	2.861 (7)	156 (6)
N1—H1N···O7*B*′	0.88	1.86	2.733 (6)	175

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

Table 3
Comparison of immucillin ring conformations (angles in °).

Compound	φ_1 (N1′–C1′–C9–C8′)	φ_2 (C2′–C1′–C9–C4)	Intraplanar angle†	4-Aza-ribitol ring description (Spek, 2009)
Molecule_1, (I)	11.0 (7)	72.5 (8)	70.5 (3)	Twist on C2′,C3′
Molecule_10, (I)	21.7 (8)	81.2 (7)	77.8 (3)	Twist on C2′,C3′
Federov *et al.* (2001)	66 (3)	129 (2)	89.5 (11)	Envelope on C2′
Evans *et al.* (2003) (average)	−88 (3)	−30 (4)	75.3 (11)	Twist on C2′,C3′
Bound in 2oc4 (Murkin *et al.*, 2007)	−45.3	17	61	Envelope on C3′
Evans *et al.* (2010) (average)	−88.7 (4)	−26.5 (5)	66.7 (2)	Envelope on C2′

† Between the mean planes through N1/C2/N3/C4/C5/C6/N7/C8/C9 and C1′/C2′/C3′/C4′/N1′.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3359). Services for accessing these data are described at the back of the journal.

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