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Streptidinium sulfate monohydrate

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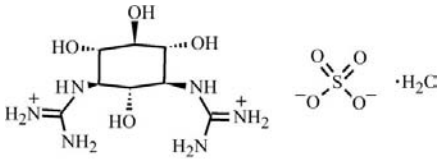
In streptidinium sulfate monohydrate {systematic name: 1,1′-[(1*S*,3*R*,4*S*,6*R*)-2,4,5,6-tetrahydroxycyclohexane-1,3-diyl]diguanidinium sulfate monohydrate}, $C_8H_{20}N_6O_4^{2+}\cdot SO_4^{2-}\cdot H_2O$, at 100 (2) K, the components are arranged in double helices based on hydrogen bonds. One helix contains streptidinium cations and the other contains disordered sulfate anions and solvent water molecules. The helices are linked into a three-dimensional hydrogen-bonded network by O—H···O and N—H···O hydrogen bonds.

Comment

Streptidine {*N*,*N*‴-[(1*S*,3*R*,4*S*,6*R*)-2,4,5,6-tetrahydroxycyclohexane-1,3-diyl]diguanidine} is a substrate in the biosynthesis of aminoglycosides as streptomycin, dihydrostreptomycin and bluensomycin. Streptidine is a derivative of cyclohexane which is substituted with four hydroxyl groups and two basic guanidine groups, and it has been shown to be one of the eight *meso* forms of 1,3-diguanido-2,4,5,6-tetrahydroxycyclohexane (Carter *et al.*, 1947). Streptidine is responsible for the Sakaguchi reaction given by streptomycin, whereby guanidines in alkaline solution develop an intense red colour when treated with α-naphthol and sodium hypochlorite; this is a qualitative test for arginine, whether free or combined within a protein. Electrometric titration of streptidine dihydrochloride showed it to be a very strong base (Fried *et al.*, 1946).



(I)

Streptidine is a 'decoy acceptor' which allows the antibiotic activity of streptomycin to recover against the *Escherichia coli* strain overexpressing the aminoglycoside-modifying enzyme 6-*O*-adenyltransferase. It could be a good starting compound for the design of more efficient 'decoy acceptors' of aminoglycoside-modifying enzymes (Latorre *et al.*, 2007). Streptidine is a metabolite but not the antibiotic itself. It is a potential contributor to ototoxicity after prolonged antibiotic administration since it acts as a damaging agent for the inner ear (Meza & Granados, 2005). The only previous structural study of this compound employed X-ray powder diffraction (Rose, 1954). We report here a single-crystal study of the title compound, (I) (Fig. 1), at 100 K.

The sulfate anions of (I) are doubly charged but the water molecule is not protonated. The stoichoimetry of the crystal structure requires the streptidinium cation to carry two positive charges, which are located on the guanidine groups. The planarity of these groups and their relative closeness to the sulfate anions suggest that they must in fact be protonated. The sulfate anion is disordered over two sets of atomic sites, with occupancies of 0.786 (3) and 0.214 (3).

The central cyclohexane ring adopts a classical chair conformation. All H atoms occupy axial positions, while hydroxyl groups and protonated guanidine groups occupy equatorial positions. Streptidine is present in a cationic form and the protonation is on the C=NH N atom in both guanidine fragments. The same type of protonation was found in the crystal structure of streptomycin oxime selenate tetrahydrate (Neidle *et al.*, 1978). From this result, the protonation on the $C-NH_2$ group of streptidine, as proposed by Latorre *et al.* (2007), seems to be incorrect.

In both guanidinium groups, the N atoms have a planar geometry. The C—N bond lengths are in the range 1.318 (5)–1.355 (5) Å, intermediate between double (1.28 Å; *International Tables for Crystallography*, 1999, Vol. C) and single (1.47 Å) bonds, indicating delocalization of the double C=N bond over all three C—N bonds. The guanidinium groups, N1–

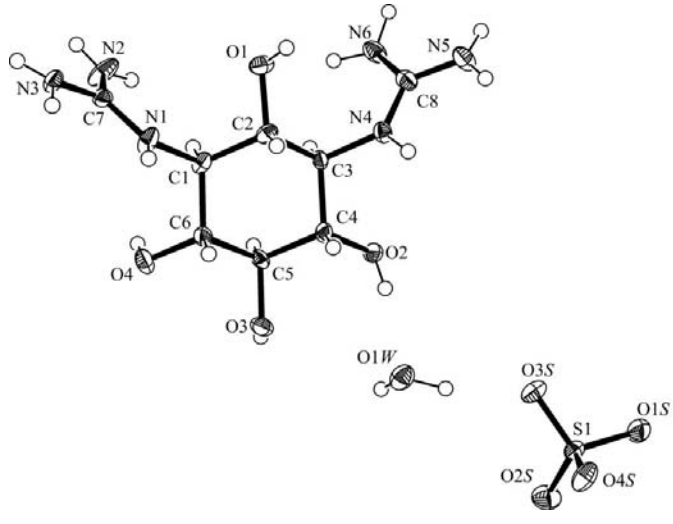


Figure 1
The molecular structure of (I), showing the atom-labelling scheme. Only the major component of the sulfate anion is shown. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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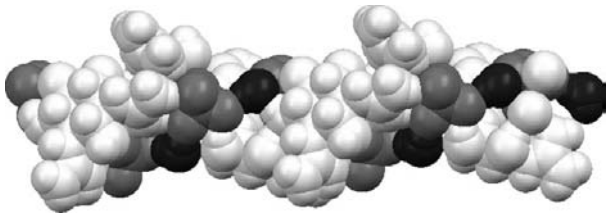

Figure 2
The double helical arrangement of streptidinium cations (white), sulfate anions (grey) and water molecules (black) around the 3_2 crystallographic axis.

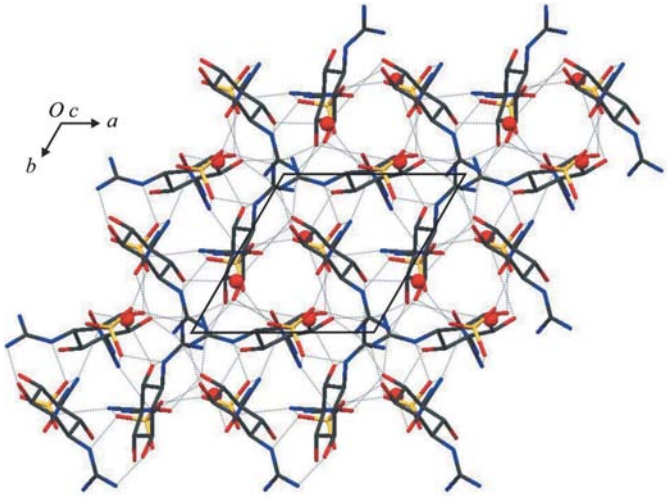

Figure 3
The packing of (I) along the *c* axis, with hydrogen bonds shown as dashed lines. Water molecules are represented as spheres.

N3/C7 and N4–N6/C8, are planar to within 0.003 (4) and 0.006 (5) Å, respectively. The dihedral angles between the plane of the central cyclohexane ring (C1–C6) and those of the guanidinium groups are 100.4 (3) (plane of N1–N3/C7) and 113.0 (2)° (plane of N4–N6/C8). For comparison, the respective dihedral angles in streptomycin oxime selenate tetrahydrate are 97.5 and 109.2° (Neidle *et al.*, 1978).

The crystal structure of (I) is stabilized by N—H···O and O—H···O hydrogen bonds and electrostatic interactions. The molecules are arranged in double helices based on hydrogen bonds, one of streptidinium cations and the second of sulfate anions and water molecules (Fig. 2). Between the helices, O—H···O and N—H···O hydrogen bonds occur, and a three-dimensional hydrogen-bonding network is built up through the entire crystal structure. Hydrogen bonds linking the sulfate anion, the streptidinium cation and the water molecule are summarized in Table 1 and shown in Fig. 3. The geometries of all the hydrogen bonds are within accepted limits (Desiraju & Steiner, 1999). The streptidinium cation is involved in 15 hydrogen bonds of O—H···O and N—H···O types with adjacent streptidinium cations (three bonds), water molecules (two bonds) and sulfate ions (ten bonds). The sulfate anion accepts eight hydrogen bonds from the streptidinium cation and one from the water molecule. Finally, the water molecule is involved in four O—H···O bonds, two to a streptidinium cation as an acceptor and two to a sulfate anion as a donor. There are no intramolecular hydrogen bonds in the streptidinium cation.

Experimental

Streptidine crystals were obtained while attempting to crystallize a molecular complex of streptomycin sulfate with *p*-sulfonatocalix[4]-arene. The calixarene (100 mg) was dissolved in a 1:1 water–ethanol mixture (2 ml) and mixed in a 1:1 molar ratio with streptomycin sulfate dissolved in a 1:1 water–ethanol mixture (1 ml). Due to acidic hydrolysis of streptomycin to streptidine and dihydrostreptobiosaminidine, instead of the desired complex, crystals of streptidinium sulfate monohydrate, (I), were obtained.

Crystal data

$C_8H_{20}N_6O_4^{2+}\cdot SO_4^{2-}\cdot H_2O$
M_r = 378.38
Trigonal, $P3_2$
a = 9.1105 (5) Å
c = 16.2506 (7) Å
V = 1168.1 (1) Å^3
Z = 3
Mo $K\alpha$ radiation
μ = 0.27 mm^{-1}
T = 100 K
0.50 × 0.40 × 0.35 mm

Data collection

Bruker–Nonius Kappa-APEXII diffractometer
4125 measured reflections
2645 independent reflections
2547 reflections with $I > 2\sigma(I)$
R_{int} = 0.028

Table 1
Hydrogen-bond geometry (Å, °).

O*nS*′ labels represent the minor component of the disordered sulfate anion.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1*O*···O1*W*^{i}	0.78 (6)	2.00 (6)	2.775 (4)	170 (5)
O2—H2*O*···O1*W*	0.85 (5)	1.90 (5)	2.748 (4)	171 (5)
O3—H3*O*···O3*S*′^{ii}	0.83 (5)	1.79 (5)	2.590 (12)	162 (5)
O3—H3*O*···O3*S*^{ii}	0.83 (5)	2.00 (5)	2.801 (5)	160 (5)
O3—H3*O*···O1*S*^{ii}	0.83 (5)	2.56 (5)	3.155 (5)	130 (4)
O4—H4*O*···O2^{ii}	0.76 (6)	2.15 (6)	2.876 (4)	158 (5)
N1—H1*A*···O3*S*′^{iii}	1.00 (5)	2.07 (5)	2.863 (12)	135 (4)
N1—H1*A*···O4*S*^{iii}	1.00 (5)	2.27 (5)	3.136 (5)	145 (4)
N2—H2*B*···O1*S*^{iv}	0.92 (6)	1.87 (6)	2.782 (5)	174 (5)
N2—H2*B*···O1*S*′^{iv}	0.92 (6)	1.99 (6)	2.805 (14)	147 (5)
N2—H2*A*···O2*S*′^{v}	1.01 (6)	1.85 (6)	2.811 (8)	158 (4)
N2—H2*A*···O2*S*^{v}	1.01 (6)	2.25 (6)	3.220 (6)	161 (4)
N3—H3*A*···O3*S*′^{iii}	0.85 (5)	2.00 (5)	2.774 (12)	150 (4)
N3—H3*A*···O3*S*^{iii}	0.85 (5)	2.12 (5)	2.978 (5)	176 (4)
N3—H3*B*···O4*S*^{iv}	0.93 (5)	2.02 (5)	2.949 (5)	174 (4)
N3—H3*B*···O4*S*′^{iv}	0.93 (5)	2.05 (5)	2.952 (14)	161 (4)
N4—H4*A*···O4*S*′^{i}	0.86 (5)	2.02 (5)	2.865 (14)	168 (4)
N4—H4*A*···O4*S*^{i}	0.86 (5)	2.14 (5)	2.976 (5)	167 (4)
N5—H5*A*···O3^{vi}	0.95 (5)	1.90 (5)	2.831 (5)	169 (4)
N5—H5*B*···O2*S*^{i}	0.84 (5)	2.22 (5)	3.009 (5)	157 (5)
N5—H5*B*···O2*S*′^{i}	0.84 (5)	2.43 (5)	3.019 (14)	127 (4)
N5—H5*B*···O4*S*′^{i}	0.84 (5)	2.54 (6)	3.258 (15)	144 (5)
N6—H6*B*···O4^{vi}	0.99 (5)	1.94 (5)	2.884 (4)	159 (4)
N6—H6*B*···O3^{vi}	0.99 (5)	2.66 (5)	3.284 (4)	122 (3)
N6—H6*A*···O4*S*′^{v}	0.91 (5)	2.40 (5)	3.021 (13)	125 (4)
N6—H6*A*···O2*S*^{v}	0.91 (5)	2.45 (5)	3.358 (5)	170 (4)
O1*W*—H1*W*···O1*S*^{ii}	0.85 (6)	1.95 (6)	2.784 (5)	166 (5)
O1*W*—H1*W*···O1*S*′^{ii}	0.85 (6)	2.25 (6)	2.894 (12)	133 (5)
O1*W*—H2*W*···O3*S*	0.95 (6)	1.84 (6)	2.772 (5)	166 (5)
O1*W*—H2*W*···O2*S*′	0.95 (6)	2.06 (6)	2.884 (12)	144 (5)

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

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.046$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.100$	$\Delta\rho_{max} = 0.67$ e Å^{-3}
$S = 1.05$	$\Delta\rho_{min} = -0.59$ e Å^{-3}
2645 reflections	Absolute structure: Flack (1983), with 882 Friedel pairs
279 parameters	Flack parameter: 0.08 (12)
29 restraints	

Due to the unsatisfactory geometry of the sulfate anion, all S—O bonds were restrained to have similar lengths with a restraint s.u. of 0.002 Å. The anisotropic displacement parameters of the O atoms of the minor component in the disordered anion were kept the same as the corresponding atoms of the major component. H atoms attached to C atoms were then treated as riding atoms in geometrically calculated positions, with C—H distances of 1.00 Å and U_{iso}(H) values of $1.2U_{eq}$(C). For H atoms bonded to N or O atoms, the atomic corrdinates were refined with U_{iso}(H) values of $1.2U_{eq}$(N) and $1.5U_{eq}$(O), to give N—H distances in the range 0.84 (5)–1.01 (6) Å and O—H distances in the range 0.78 (6)–0.95 (6) Å. Friedel opposites were kept unmerged, and the value of the Flack *x* parameter (Flack, 1983) confirmed that the space group was $P3_2$.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* and *SCALEPACK*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996); software used to prepare material for publication: *publCIF* (Westrip, 2009).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD3283). Services for accessing these data are described at the back of the journal.

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