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Structural studies of *O*-sulfated D-glucosamines. The crystal and molecular structures of 2-amino-2-deoxy-α/β-D-glucopyranose 3-sulfate (free acid) and 2-amino-2-deoxy-β-D-glucopyranose 6-sulfate (free base)

William Mackie [a,*], Edwin A. Yates [a], Doriano Lamba [1,b]

[a] *Department of Biochemistry and Molecular Biology, University of Leeds, Leeds LS2 9JT, United Kingdom*

[b] *Max Planck Institut für Biochemie, Abt. Strukturforschung, D-82152 Martinsried bei München, Germany*

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Abstract

The crystal and molecular structures of 2-amino-2-deoxy-α/β-D-glucopyranose 3-sulfate (**1**) and 2-amino-2-deoxy-β-D-glucopyranose 6-sulfate (**2**) have been determined by direct methods. The sugar rings have the expected $^4C_1$ conformation and the geometries of the sulfate groups are comparable with those found in previous investigations except for a significant shortening of the C–O bond and closing of the C–O–S bond angle in **2**.

Keywords: X-ray crystallography; Heparin; 2-Amino-2-deoxy-D-glucopyranose 3-*O*-sulfate; 2-Amino-2-deoxy-D-glucopyranose 6-*O*-sulfate

1. Introduction

Sulfated monosaccharides occur most frequently in plants and animals as building blocks of polysaccharides. These include various polysaccharides from red algae and the proteoglycan and glycosaminoglycan components (chondroitin, dermatan and keratan sulfates, and heparin and heparan sulfates) of the extracellular matrix and cells of many animal tissues [1–3]. Of these only heparin and heparan sulfate preparations have been shown to

* Corresponding author.

[1] On leave from the Istituto di Strutturistica Chimica "Giordano Giacomello", C.N.R, Area della Ricerca di Roma, C.P. 10, I-00016 Monterotondo Stazione (Roma), Italy.

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contain *N*- and *O*-sulfated 2-amino-2-deoxy-D-glucopyranose (D-glucosamine) units. Various biological activities and affinities have been ascribed to heparin and heparin sulfates including anticoagulant activity, angiogenesis, cell adhesion, growth factor, and cell proliferation activity [4–7]. In these, the extent and pattern of sulfation of D-glucosamine residues appears often to be crucial. Effects of this kind are probably best documented in the anticoagulant activity of heparin in which the active sequence has been identified as a pentasaccharide containing three D-glucosamine units of which the nonreducing terminal unit is mono-sulfated (6-sulfate), the central unit is tris-sulfated (2,3,6-sulfate), and the reducing terminal is bis-sulfated (2,6-sulfate) [4,8]. Not surprisingly, in the efforts to determine the precise role of sulfate groups in these biological interactions, much time has been devoted to structural studies of the conformation, cation coordination, and charge distributions of sulfate groups and the influence which these parameters have on the host molecules [4,9]. The present study, in which the crystal and molecular structures of 2-amino-2-deoxy-α/β-D-glucopyranose 3-sulfate (**1**) and 2-amino-2-deoxy-β-D-glucopyranose 6-sulfate (**2**) are reported, forms part of our ongoing studies of sulfated monosaccharides by X-ray crystallography [10–12]. The results provide structural data which may help to give some insight into the structural factors which determine the important biological functions of heparin and heparan sulfate.

2. Experimental

X-ray crystallography.—D-Glucosamine 3-sulfate as the free acid (**1**), $[\alpha]_D^{20}$ +54° (*c* 2.0, H_2O) and D-glucosamine 6-sulfate as the free base (**2**), $[\alpha]_D^{20}$ +66° (*c* 2.0, H_2O) were obtained from the Sigma Chemical Co. and were crystallised by slow concentration of ethanol–water and 2-propanol–water solutions, respectively. The space group and approximate unit-cell parameters were determined from oscillation and Weissenberg photographs. The intensity data were collected at room temperature and were corrected for the average change in the intensities of the reference reflections. Lorentz and polarisation corrections were applied, but no absorption corrections were made. Crystal data and details of the structure analysis for compounds **1** and **2** are presented in Table 1. The structures were solved by direct methods, SHELXTL-Plus [13], and refined by full matrix least-squares methods. The atomic scattering factors used were taken from the International Tables for X-ray Crystallography [14]. The PARST program [15] was used for the molecular geometry calculations. The positional parameters of the nonhydrogen atoms and U_{eq} values for **1** and **2** are listed in Tables 2 and 3, respectively.

The accuracy of the present analysis for compound **1** is poor, due to the presence in the crystal of both the α and β anomers at C-1, the ratio being 65:35. Furthermore, ca. 30% of the molecules showed in the crystal a *gauche–trans* conformation for the primary hydroxymethyl group, whereas the remaining 70% of the molecules had a *gauche*$^-$*–gauche* conformation. The hydrogen atoms for the free acid **1** could not be located from difference Fourier syntheses. Thus, only those H–C attached to the glucopyranose ring were included in the later refinements in their geometrically calculated positions and allowed to ride with fixed $U_{iso} = 0.08$ Å^2. Two large difference peaks of $\simeq 1.77$ e/Å^3 showed in the final difference Fourier map very close to the sulfur atomic position indicating the presence of further

Table 1
Crystal data and details of the structure analysis for **1** and **2**

Crystal data	**1**	**2**
Formula	$C_6H_{13}NO_8S \cdot H_2O$	$C_6H_{13}NO_8S$
Crystal size (mm)	$0.02 \times 0.04 \times 0.10$	$0.03 \times 0.10 \times 0.10$
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$
Unit cell dimensions (Å,°)		
a	7.318(2)	6.1005(5)
b	7.804(2)	10.803(2)
c	9.371(2)	7.7649(7)
β	98.20(2)	90.94(1)
Volume (Å^3)	529.7(2)	511.7(1)
Z	2	2
Formula weight	277.25	259.23
D_c (mg/m^3)	1.74	1.68
Absorption coefficient (mm^{-1})	0.332	0.311
$F(000)$	292	272
Data collection		
Diffractometer used	Siemens R3m/V	Enraf–Nonius CAD-4
Radiation (Å)	Mo$K\alpha$ ($\lambda = 0.71069$)	Cu$K\alpha$ ($\lambda = 1.54182$)
Temperature (K)	298	298
Orienting reflections, range (°)	15, $7 \le \theta \le 18$	52, $28 \le \theta \le 45$
Data collection range (°)	$3.0 \le 2\theta \le 70.0$	$2.0 \le 2\theta \le 120.0$
Scan type	$2\theta - \theta$	$\omega - 2\theta$
Index ranges		
	$0 \le h \le 13$	$-6 \le h \le 6$
	$0 \le k \le 14$	$0 \le k \le 9$
	$-18 \le l \le 17$	$-8 \le l \le 8$
Reflections collected	4375	1388
Independent reflections	4018 ($R_{int} = 0.016$)	848 ($R_{int} = 0.013$)
Observed reflections	1723 ($F_o \ge 8.0\sigma(F_o)$)	730 ($F_o \ge 4.0\sigma(F_o)$)
Refinement		
Quantity minimised	$\Sigma w(F_o - F_c)^2$	$\Sigma w(F_o - F_c)^2$
Weighting scheme $w^{-1} = \sigma^2(F_o) + a \cdot F_o^2$	0.0184	0.0035
Number of parameters refined	171	180
Final R indices (obsd data)		
R	0.091	0.041
wR	0.113	0.056
Goodness-of-fit	0.82	0.96
Largest shift/esd	0.001	0.022
Largest difference peak (e/Å^3)	1.77	0.25
Largest difference hole (e/Å^3)	−1.97	0.33

disorder but no model could be fitted to the electron density. All of these factors contributed to the observed high R and wR values.

For the free base **2**, all hydrogen atoms except the H–OS were located in subsequent difference Fourier maps and included in the later refinement with fixed U_{iso} values equal to

Table 2
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients [a] ($Å^2 \times 10^3$) for **1**

Atom	x/a	y/b	z/c	U_{eq}
S	−6803(2)	901	331(2)	22(1)
O-1S	−8227(6)	−407(7)	283(7)	38(2)
O-2S	−5686(7)	735(12)	−823(6)	46(2)
O-3S	−7485(7)	2579(7)	535(7)	38(1)
O-1A	−674(9)	3397(10)	2726(8)	28(2)
O-1B	987(17)	693(19)	2931(14)	29(3)
N	−1879(6)	1041(8)	586(5)	24(1)
O-3	−5466(5)	345(6)	1755(5)	24(1)
O-4	−5752(6)	2494(8)	4182(5)	33(1)
O-5	−833(5)	1366(7)	4575(5)	26(1)
O-6A	−2354(9)	389(10)	7071(8)	30(2)
O-6B	−909(26)	2108(29)	7449(18)	39(5)
C-1	−568(7)	1652(8)	3108(6)	22(1)
C-2	−2144(6)	771(8)	2121(5)	20(1)
C-3	−4008(6)	1473(7)	2419(5)	19(1)
C-4	−4179(6)	1472(8)	4017(6)	21(1)
C-5	−2445(7)	2217(9)	4953(6)	25(1)
C-6	−2479(10)	2040(13)	6527(7)	38(2)
O-W	−7347(8)	1700(11)	6451(6)	45(2)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.

the U_{eq} of the carrier atoms. The two prochiral hydrogen atoms at C-6, HS-C6, and HR-C6, are differentiated using the rule proposed by Hanson [16][2].

3. Results and discussion

Molecular geometry.—Perspective views of **1** and **2**, together with the atom numbering scheme, are shown in Figs. 1 and 2, respectively. Selected molecular geometry parameters are listed in Table 4. The free acid **1** has a zwitterionic character with the amino N atom protonated and the sulfate moiety ionised. In the crystal and molecular structure of **1**, both α and β anomers are present in a ratio of 65:35. The pattern of the bond lengths and valence angles of the sulfate group allows recognition of the bond S–O-3S (1.423(6) Å) as an S=O bond type [17] with the negative charge distributed between the other oxygens O-1S and O-2S. In the free base **2**, the molecular geometry of the sulfate moiety indicates that S–O-1S and S–O-3S are double bonds (1.433(5) and 1.424(5) Å, respectively) while the S–O-2S (1.450(5) Å) is an S–OH bond type.

The observed geometries of the pyranose rings conform to the stereochemical and conformational classification of hexopyranose sugars [18]. The values of the bond lengths and

[2] The vibrational parameters U_{ij} of the heavy atoms, the coordinates, and U_{iso} values of the H atoms, tables of bond lengths and valence angles, and lists of F_o and F_c structure factors have been deposited with, and may be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, United Kingdom.

Table 3
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients [a] ($Å^2 \times 10^3$) for **2**

Atom	x/a	y/b	z/c	U_{eq}
S	−1245(2)	340	809(1)	35(1)
O-1S	−3432(7)	135(6)	1391(6)	59(2)
O-2S	96(8)	−768(5)	777(6)	58(2)
O-3S	−1150(7)	1054(5)	−729(6)	52(2)
O-1	2940(8)	1052(5)	7878(5)	49(2)
N	5963(9)	3008(6)	8349(6)	42(2)
O-3	7817(7)	3836(5)	5221(6)	45(2)
O-4	4815(9)	3748(7)	2150(7)	65(2)
O-5	2583(7)	1441(5)	5031(5)	39(1)
O-6	−271(6)	1195(5)	2305(5)	49(2)
C-1	3041(10)	1965(7)	6684(7)	38(2)
C-2	5410(10)	2482(7)	6637(7)	37(2)
C-3	5628(9)	3459(7)	5221(7)	40(2)
C-4	4855(11)	2885(7)	3513(7)	39(2)
C-5	2588(10)	2347(6)	3682(7)	38(2)
C-6	1853(9)	1722(8)	2015(6)	41(2)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.

valence angles of the sulfate moieties in **1** and **2** are well within the range of values observed in the crystal and molecular structures of the sulfated carbohydrates known so far: methyl α-D-galactopyranoside 2-(sodium sulfate) [10], methyl α-D-galactopyranoside 3-(sodium sulfate) [10,19], methyl α-D-galactopyranoside 4-(sodium sulfate) [10,20], methyl α-D-galactopyranoside 4-(potassium sulfate) [10], methyl α-D-galactopyranoside 6-(potassium sulfate) [10], β-D-glucopyranose 6-(potassium sulfate) [11], methyl α-D-galactopyranoside 2,6-bis(sodium sulfate) [12], and sucrose octakis (potassium sulfate) [21]. It is worth noting that the averaged values for the seven *O*-sulfate groups in the

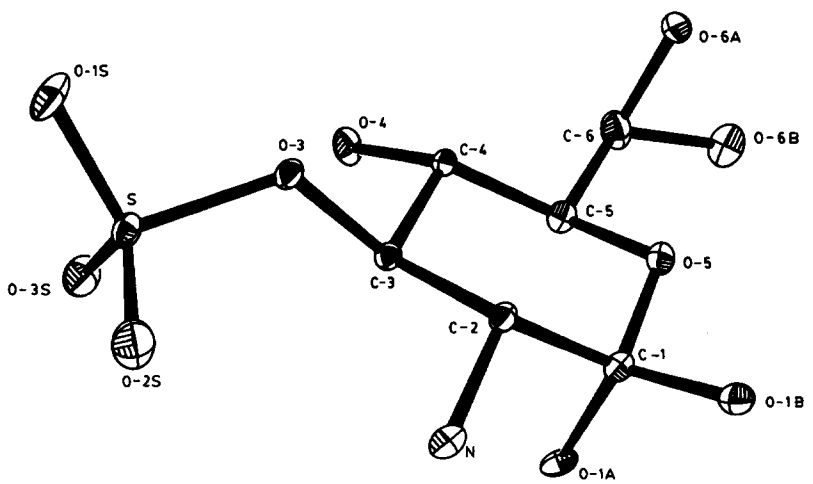

Fig. 1. Perspective view and atom labelling of 2-amino-2-deoxy-α/β-D-glucopyranose 3-sulfate (**1**). Thermal ellipsoids are drawn at 50% probability.

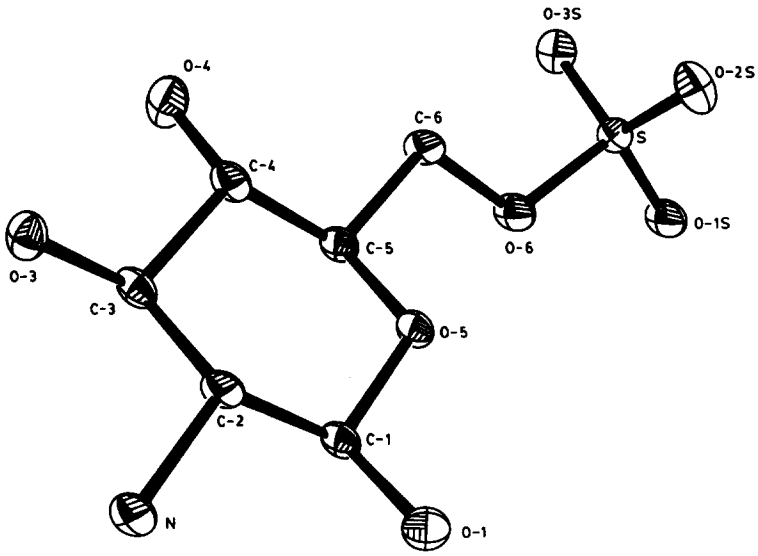

Fig. 2. Perspective view and atom labelling of 2-amino-2-deoxy-β-D-glucopyranose 6-sulfate (**2**). Thermal ellipsoids are drawn at 50% probability level.

monosaccharides [10–12] show a remarkable agreement with values recently obtained by *ab initio* SCF (self consistent field) $6-31+G^{**}$ calculations on methyl and ethyl sulfate anions [22]. The only large discrepancy is between the experimental C–O bond length (1.461(7) Å) found in carbohydrate sulfates and the calculated values (shorter by 0.06 Å). This difference is likely to arise from the further substitution at the carbon atoms in the carbohydrates. In the free acid **1**, it seems that substitution with sulfate at position 3 results in a lengthening of the C–O bond (1.454(6) Å), and in the opening of the C–O–S angle at the point of attachment of the sulfate moiety (121.2(4)°), whereas in the free base **2**, there is a surprising shortening of the C–O bond (1.437(7) Å) and closing of the C–O–S angle (116.3(3)°) as compared, for example, with the corresponding values of 1.472(7) Å and 118.0(4)° observed in the crystal and molecular structure of β-D-glucopyranose 6-(potassium sulfate) [11]. In **1**, steric repulsions with neighbours are diminished due to eclipsing of the bridging S–O bond at position 3 with the C–H bond. In **2**, the sulfate group at position 6 is in a staggered conformation with respect to the ester bond. The conformation along the C-5–C-6–O-6 sequence is *gauche–trans–trans*–, the values of the torsion angles O-5–C-5–C-6–O-6, C-4–C-5–C-6–O-6, and C-5–C-6–O-6–S being 57.2(6), 177.7(5), and −172.4(4)°, respectively. In **1** the primary hydroxyl group adopts the *gauche–trans* and *gauche*$^-$*–gauche* conformations in a 30:70 ratio and the torsion angle values are 37.3(1.0), 158.9(1.0), and −53.9(8), 67.7(8)°, respectively. These are the two preferred noneclipsed orientations found in the solid state for monosaccharides having the gluco configuration [23]. The protonation of the amino moiety at position 2 in the free acid **1** is consistent with the observed lengthening of the C–N bond, 1.493(7) Å, as compared with the value of 1.480(8) Å observed in the free base **2** and that of 1.470(3) Å observed in the crystal and molecular structure of 3-amino-1,6-anhydro-3-deoxy-β-D-glucopyranose [24]. A similar lengthening also occurs in the crystal and molecular structure of β-D-galactosamine hydrochloride [25], α-D-glucosamine hydrochloride [26,27], α-D-glucosamine hydrobromide

Table 4
Selected geometric parameters for amino and sulfate moeties in **1** and **2**

	1	**2**
Bond lengths (Å)		
S–O	1.598(4)	1.591(5)
S–O-1S	1.455(5)	1.433(5)
S–O-2S	1.452(6)	1.450(5)
S–O-3S	1.423(6)	1.424(5)
N–C	1.493(7)	1.480(8)
O–C	1.454(6)	1.437(7)
Bond angles (°)		
O–S–O-1S	100.7(3)	101.4(3)
O–S–O-2S	104.8(3)	106.7(3)
O–S–O-3S	108.8(3)	106.1(3)
O-1S–S–O-2S	113.0(4)	114.0(3)
O-1S–S–O-3S	112.8(3)	113.5(3)
O-2S–S–O-3S	115.3(4)	113.7(3)
S–O–C	121.2(4)	116.3(3)
N–C-2–C-1	109.1(4)	108.4(5)
N–C-2–C-3	111.5(4)	111.0(6)
O-3–C-3–C-2	108.9(4)	
O-3–C-3–C-4	105.2(4)	
O-6–C-6–C-5		107.3(4)
Torsion angles (°)		
C–O–S–O-1S	−167.7(4)	−171.8(4)
C–O–S–O-2S	74.9(5)	68.6(5)
C–O–S–O-3S	−49.0(5)	−53.0(5)
C-2–C-3–O-3–S	−106.7(4)	
C-4–C-3–O-3–S	132.7(4)	
C-5–C-6–O-6–S		−172.4(4)
Puckering parameters for the pyranose ring		
Total puckering amplitude (Å)	0.568(6)	0.597(6)
ϕ (°)	27(4)	30(11)
θ (°)	9.7(7)	3.5(6)

[26,27], and chondrosine [28] (1.50(2) Å), and of 2-amino-2,6-dideoxy-α-D-glucopyranose-6-sulfonic acid [29] (1.495(7) Å) and of methyl 2-amino-2,6-dideoxy-α-D-glucopyranoside-6-sulfonic acid [30] (1.502(4) Å). The puckering parameters for the pyranose rings (see Table 4) are in accordance with a $^4C_1$ (D) conformation [31,32]. In **1**, the substitution pattern at adjacent positions (namely 2 and 3) causes a flattening of the chair conformation. The asymmetry parameters [33] are $\Delta C_s(O\text{-}5) = 0.031(3)$, $\Delta C_2(C\text{-}1\text{–}O\text{-}5) = 0.006(3)$, and $\Delta C_S(O\text{-}5) = 0.011(4)$, $\Delta C_2(C\text{-}1\text{–}O\text{-}5) = 0.006(3)$ for **1** and **2**, respectively.

Hydrogen bonding and packing features.—The molecular packing of **1** and **2**, projected along the *a* axis, are shown in Figs. 3 and 4, respectively. The poor accuracy of the structural determination of the free acid **1** does not provide enough information (hydrogen atoms have been not localised in the final difference Fourier map) to characterise unambiguously the hydrogen bonding scheme of the structure. Only interatomic distances (<3.2 Å) between atoms belonging to putative hydrogen bond donors or acceptors are listed in Table

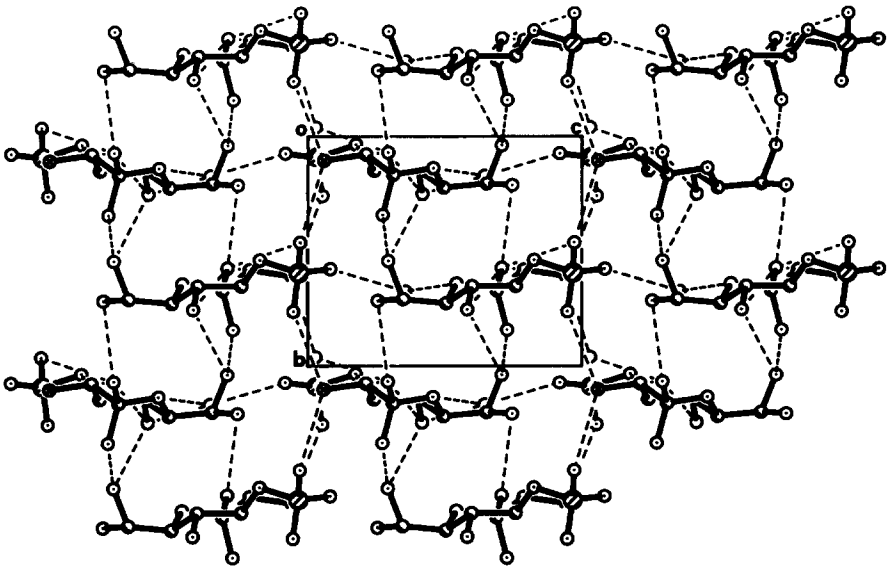

Fig. 3. View of unit cell of 2-amino-2-deoxy-α/β-D-glucopyranose 3-sulfate (**1**) along the *a* axis.

5. The α and β anomeric hydroxyls O-1A and O-1B and the two orientations O-6A and O-6B for the primary hydroxyl oxygen give rise to an intricate network of short contacts involving the water molecule O-W and the sulfate oxygens. The charged amino group

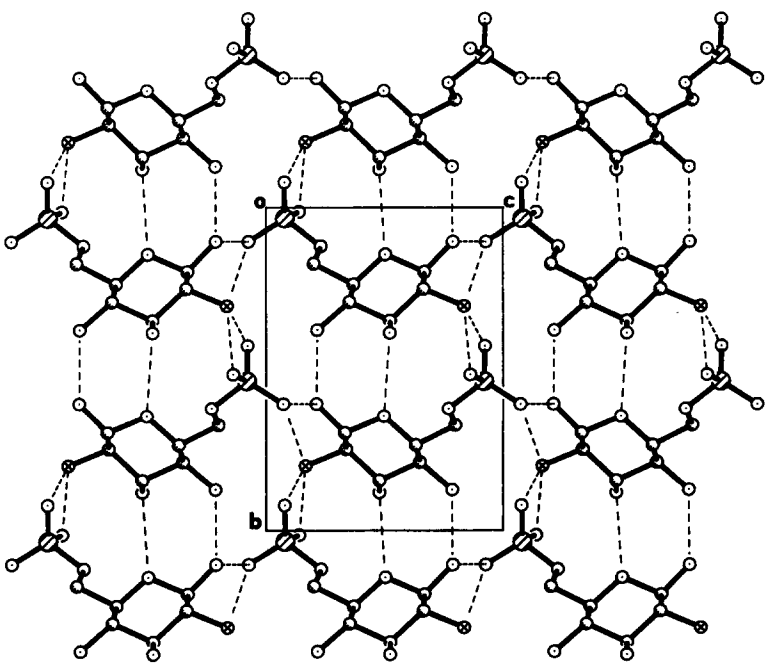

Fig. 4. View of unit cell of 2-amino-2-deoxy-β-D-glucopyranose 6-sulfate (**2**) along the *a* axis.

Table 5
Molecular interactions

Short contacts (Å) for **1**					
O-2S···O-W(I−c)	2.77(1)		O-1B···O-3(I+a)	2.97(1)	
N···O-1S(I+a)	2.95(1)		O-1B···O-4(I+a)	2.87(1)	
N···O-1S(II−a)	2.89(1)		O-1B···O-6B(II+c)	2.82(3)	
N···O-3S(II−a−b)	2.91(1)		O-4···O-6A(II−a+c)	2.82(1)	
O-1A···O-1S(II−a)	2.97(1)		O-4···O-W(I)	2.64(1)	
O-1A···O-6A(II+c)	2.69(1)		O-5···O-W(I+a)	2.90(1)	
O-1A···O-6B(II+c)	3.13(2)		O-6A···O-3S(II−a−b+c)	3.15(1)	
O-1A···O-W(II−a+c)	3.11(1)		O-6B···O-1S(II−a+c)	3.01(2)	
O-1B···O-1S(I+a)	2.76(1)		O-6B···O-W(I+a)	2.91(2)	
O-1B···O-3S(I+a)	3.03(2)				
Geometry of the hydrogen-bonding system for **2**					
Donor H	Acceptor	D··· (Å)	D–H (Å)	H···A (Å)	DH···A (°)
H-1–N	O-2S(II+a+c)	2.817(8)	0.86(8)	1.99(7)	161(6)
H–O-1	O-3S(I+c)	2.735(6)	0.78(7)	2.03(7)	150(8)
H–O-3	O-5(II+a+c)	2.831(8)	0.70(9)	2.19(9)	153(9)
H–O-4	O-1(II+a+c)	2.841(9)	0.85(10)	2.14(10)	140(8)
Short contacts (Å) for **2**					
N···O-1S(II+c)	2.777(9)	N···O-4(I+c)	3.147(7)		
N···O-3S(I+a+c)	2.834(8)				
Symmetry code					
(I) *x,y,z*					
(II) $-x,1/2+y,-z$					

interacts only with the sulfate oxygens O-1S and O-3S, belonging to three symmetry-related molecules. The water molecule O-W is involved in a very short intramolecular contact (2.64(1) Å) with the hydroxyl oxygen O-4. Overall, the molecules are arranged in an anti-parallel sheet manner extending in the $a \cdot c$ plane. A similar packing arrangement has been found for the free base **2**, but with the anti-parallel sheets extending in the $b \cdot c$ plane. The amino group N and the hydroxyl oxygens O-3 and O-4 act as hydrogen bonding donors to the sulfate oxygen O-2S, the ring oxygen O-5, and the hydroxyl oxygen O-1, respectively, all belonging to the same symmetry related molecule, and serving as intersheet cohesive elements. The hydroxyl oxygen O-1 donates a hydrogen atom to the sulfate oxygen O-3S which, together with the short contact N···O-4 (3.147(7) Å), constitute the cohesive elements within the sheets.

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