CHEMISTRY LETTERS, pp. 1415-1418, 1974. Published by the Chemical Society of Japan

STRUCTURAL STUDY OF MUCOPOLYSACCHARIDE, CRYSTAL STRUCTURE OF CHONDROSINE MONOHYDRATE

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The structure of chondrosine monohydrate was determined by an X-ray study. The zwitter-ionic character of the molecule and the intermolecular hydrogen bondings stabilize the crystal structure. An intramolecular hydrogen bond is found between the axial oxygen O(4') and the ring oxygen O(5). The galactosamine moiety has α-configuration in the crystalline state.

Chondrosine (2-amino-2-deoxy-3-O-β-D-glucopyranurosyl-D-galactose) is a unit disaccharide obtained by partial hydrolysis of mucopolysaccharide chondroitin sulfates extracted from animal connective tissues. The present X-ray study of chondrosine crystals was performed to investigate the feature of the specific β(1→3) linkage in chondroitin sulfates. Since chondrosine has a zwitter-ionic character, the molecular arrangement in the crystal was also interesting with relation to the interaction between the amino and carboxyl groups.

Rod-shaped small single crystals, elongated along the c-axis, were obtained by slow evaporation of an aqueous solution. Crystal data are: $C_{12}H_{21}NO_{11}\cdot H_2O$; space group $P2_12_12_1$; four formula units per unit cell with dimensions a=19.395(5), b=17.221(5), c=4.718(9) Å; D_x=1.57gcm^{-3}. Reflections (hk0∼hk3) were recorded on equi-inclination Weissenberg photographs using Ni-filtered Cu-Kα radiation. Intensities of 1201 independent reflections were measured visually, and the inter-layer scales were corrected by the double slit method. All non-hydrogen atoms were found by direct methods based on 275 reflections with $|E|>1.30$, using the program MULTAN.[1] The structure was refined by the block-diagonal and full-matrix least-squares methods. Two cycles of anisotropic refinement for carbon, nitrogen, and oxygen atoms reduced the R index to 0.094. All hydrogen atoms located from a difference Fourier map were included in the structure factor calculation. The final atomic coordinates are given in Table, and the bond lengths and angles in the molecule are shown in Fig.1.

Both rings of the glucuronic acid and galactosamine residues have the chair C1 form. The mean values of the torsion angles about the C-C and C-O bonds within the pyranose rings are 56.5° and 60.0° for the glucuronic acid and galactosamine moieties, respectively. These rings are linked together by a β(1→3) glucuronidic linkage in the manner in which the mean planes of each ring are almost coplanar. The torsion angles O(5)-C(1)-O(1)-C(3') and C(1)-O(1)-C(3')-C(4') are -87.1° and 55.4°, respectively. The carboxyl group in the glucuronic acid moiety is nearly

coplanar with the mean plane of the pyranose ring attached to it. The torsion angle C(4)-C(5)-C(6)-O(7) is -45.6°, which differs from -86.0° found in potassium glucuronate dihydrate.[2] The conformation about the exocyclic C(5')-C(6') in the galactosamine moiety is gauche-trans, which is one of the two preferable conformations reported by Fries et al.[3]; the torsion angles O(5')-C(5')-C(6')-O(6') and C(4')-C(5')-C(6')-O(6') are 62.9° and -178.5°, respectively.

An unknown configuration at carbon C(1') in the galactosamine moiety was assigned as α-configuration, because the oxygen O(1') is located at the axial position. Since the galactosamine moiety in the chondroitin sulfates is known to have β-configuration, the anomeric inversion must occur during the hydrolysis or in the crystallizing processes.

The mean values of the C-C and C-O bond lengths within the rings are 1.54Å and 1.40Å, respectively. The mean value of the C-OH bond length, except for C(1')-O(1'), is 1.43Å. These C-C and C-O values are normal. The anomeric C(1')-O(1') bond length 1.35Å is significantly short. Such shortening of the axial anomeric C-O bond has been found in several monosaccharides in which the hydrogen atom on O(1) is unsubstituted.[4,5,6,7,8] The C-O bond lengths, 1.40Å and 1.45Å, and the C-O-C bond angle, 116.5°, at the bridge oxygen will be comparable with those found in β(1→4) linkages of other disaccharides.[3,9,10]

The molecular arrangement and hydrogen-bond networks in the crystal are shown in Figs.2 and 3. The crystal structure is composed of almost planar molecules packed along the c-axis. The molecule has a zwitter-ionic character, and the charged groups $-NH_3^+$ and $-COO^-$ of neighboring molecules approach each other. All oxygen and nitrogen atoms participate in the hydrogen bond formation, except for the bridge oxygen O(1) and the ring oxygen O(5'). There are three intermolecular hydrogen-bonded chains running along the c-axis. One chain is formed through the N(2')···O(7) type of hydrogen bonds. Another is formed between O(W) of the water molecule and O(6') of the hydroxymethyl group. The other chain links O(3) and O(4) belonging to the neighboring molecules related by a screw axis. The crystal structure is stabilized by these hydrogen bondings and the ionic interactions mentioned above.

An intramolecular hydrogen bond is formed between the axial oxygen O(4') and the ring oxygen O(5) on one side of the molecule. O(2) and N(2') on the other side of the same molecule form hydrogen bonds with a water molecule located at their mid point. These hydrogen bonds will stabilize the conformation of β(1→3) linkage in the chondrosine molecule. Similar intramolecular hydrogen bonds have been found in disaccharides linked by β(1→4), in which the equatorial oxygen O(3') forms a hydrogen bond with the ring oxygen O(5).[3,9,10]

Table. Atomic parameters of chondrosine monohydrate ($\times 10^4$)

Atom	x	y	z	Atom	x	y	z
C(1)	3741(5)	2905(5)	4610(27)	C(1')	5181(5)	557(6)	4010(33)
C(2)	3904(5)	3767(5)	4428(29)	C(2')	5038(5)	1401(5)	3137(30)
C(3)	3220(5)	4212(5)	5125(30)	C(3')	4410(5)	1715(5)	4785(30)
C(4)	2606(4)	3922(5)	3324(26)	C(4')	3769(5)	1192(6)	4134(29)
C(5)	2544(4)	3037(5)	3339(27)	C(5')	3983(5)	361(6)	5054(32)
C(6)	2054(5)	2702(6)	1211(28)	C(6')	3408(5)	-223(6)	4336(33)
O(1)	4328(3)	2501(4)	3711(18)	O(1')	5387(4)	542(4)	6753(19)
O(2)	4377(3)	4011(4)	6542(22)	N(2')	5654(4)	1895(5)	3840(23)
O(3)	3341(3)	5031(4)	4607(19)	O(4')	3572(3)	1197(4)	1256(20)
O(4)	1966(3)	4266(4)	4503(21)	O(5')	4567(3)	100(4)	3428(19)
O(5)	3212(3)	2714(3)	2658(18)	O(6')	3620(4)	-961(4)	5276(26)
O(6)	2236(3)	2135(4)	-283(21)				
O(7)	1478(3)	3045(4)	1074(20)	O(W)	5648(4)	3541(4)	4940(24)

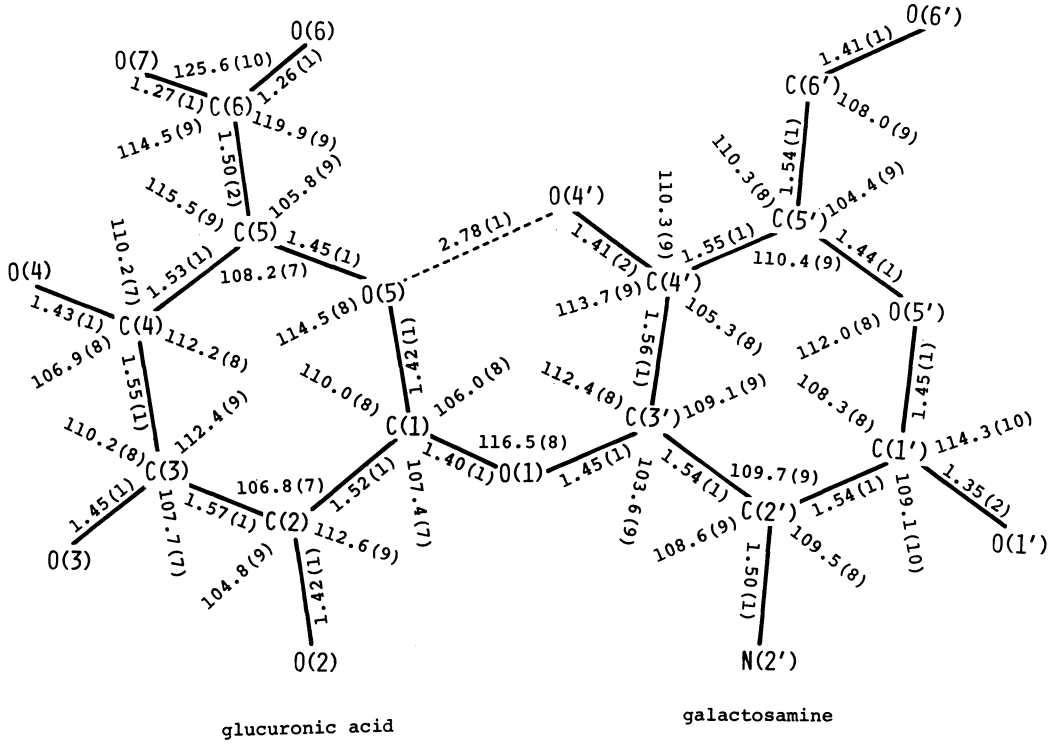

Fig. 1. Bond lengths and angles in chondrosine molecule. Estimated standard deviations are given in parentheses referred to the last decimal places of the respective values.

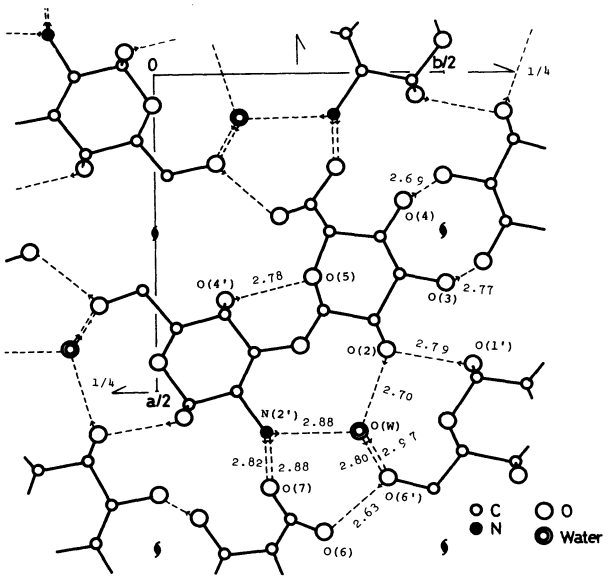

Fig. 2. Projection of chondrosine monohydrate viewed along the c-axis. Hydrogen bonds are shown by dotted lines.

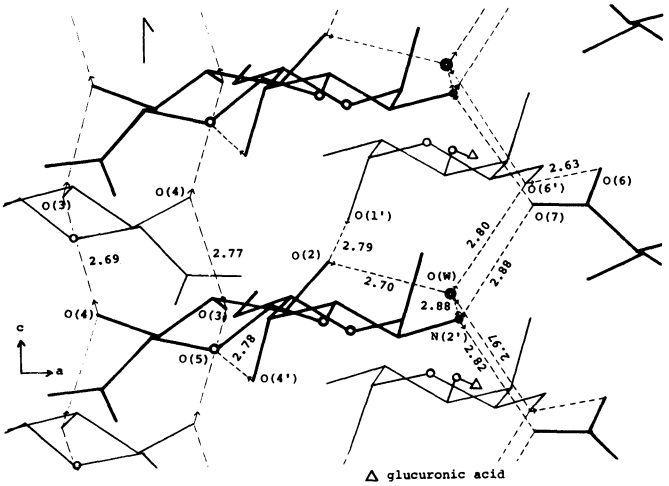

Fig. 3. Drawing of the schematic hydrogen bond networks viewed along the b-axis.

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(Received September 24, 1974)