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The Crystal Structure of β-D-*N*-Acetylneuraminic Acid Dihydrate (Sialic Acid), $C_{11}H_{19}NO_9.2H_2O$

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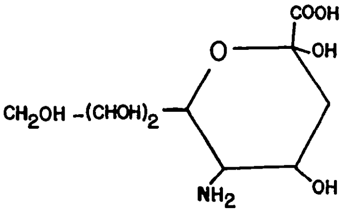
Sialic acid, $C_{11}H_{19}NO_9$, is a naturally occurring amino sugar which has been shown to participate in many areas of body chemistry. It crystallizes as a dihydrate in the monoclinic space group $P2_1$ with $a=8·306$ (4), $b=12·708$ (7), $c=8·237$ (4) Å and $\beta=112·3$ (1)°. There are two molecules per unit cell. The 1400 independent X-ray intensities were collected on an automatic diffractometer and refined by least-squares methods on F values to a final R index of 4·9%. The structure was solved by the symbolic addition procedure for non-centrosymmetric crystals. From chemical studies the molecule is assumed to be the D-isomer and the X-ray analysis establishes it to be the β-anomer. The molecules are held together by an extensive network of hydrogen bonds.

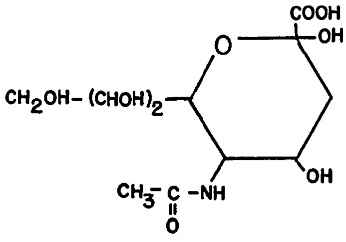
Introduction

Sialic acids are naturally occurring amino sugars which are derivatives of neuraminic acid (I).



(I)

They are formed when the parent substances are acylated at the amino group with an acetyl or glycoyl moiety. They are widely distributed, occurring in glycoproteins, mucoproteins, oligosaccharides and glycolipids, and play an important role in many different biological processes. A great deal of interest has centered on the conformation of sialic acid (II) (*N*-acetylneuraminic acid)



(II)

since its stereochemistry may well affect its activity. It has been established that the molecule is the D-isomer (Kuhn & Brossmer, 1957; Comb & Roseman, 1958). The anomeric (α or β) configuration of the molecule is determined, for sialic acid, by the position of the hydroxyl group on the carbon atom adjacent to the ring oxygen. The anomeric configuration of the molecule has been investigated chemically (Comb, Watson & Roseman, 1966; Yu & Ledeen, 1969; Liu, Gotschlich, Dunne & Jonssen, 1971) with material obtained from various sources. The crystals used in the present study were obtained from human blood and purified by repeated recrystallization from various solvents. The X-ray results show this molecule to be the β-anomer.

Experimental

The crystals used in the X-ray analysis were supplied by Dr S. Roseman of the McCollum-Pratt Institute of Johns Hopkins University. Pertinent physical data for the crystal and a summary of the data collection are presented in Table 1. Lorentz and polarization corrections were applied and normalized structure factor magnitudes $|E|$ as well as structure factor magnitudes $|F|$ were derived.

Table 1. *Crystal data*

Molecular formula	$C_{11}H_{19}NO_9$ $2H_2O$
Crystal size	~(0·22 × 0·60 × 0·13 mm)
Space group	$P2_1$
a	8·306 (4) Å
b	12·708 (7)
c	8·237 (4)
β	112·3 (1)°
Z	2
Density (calc.)	$1·42$ g cm^{-3}
Source of data	Picker FACS-I
Radiation	Cu $K\alpha$ (Ni filter) $\lambda=1·54178$ Å
Collection technique	θ–2θ scan
Scan width (°)	$2·0+2\theta(\alpha_2)-2\theta(\alpha_1)$
Scanning speed	2 °min^{-1}
Background time	10 s
Maximum sin θ/λ	0·567 $Å^{-1}$
No. of independent reflections	1400

The structure was solved by the symbolic addition procedure for non-centrosymmetric crystals (Karle & Karle, 1966) and phase determining formulas which are based on inequality (34) of Karle & Hauptman (1950), and its probability implications. One E map led to a partial structure which was expanded to a reasonable molecule, in view of the expected structure, by recycling with the tangent formula (Karle, 1968). However, the molecule would not refine properly and it soon became apparent that it was misplaced with respect to a true origin for space group $P2_1$. The data set was then expanded from a monoclinic set to a triclinic set by generating $|F_{h\bar{k}l}| = |F_{hkl}|$ and $|F_{h\bar{k}\bar{l}}| = |F_{hk\bar{l}}|$. It was then possible to use the molecule obtained in the original tangent formula recycling procedure as a partial structure for the same procedure in space group $P1$. In this way, the second molecule and the H_2O molecules appeared and the shift of the origin necessary to place the molecules correctly in space group $P2_1$ was easily determined. Two of the 21 atoms used as a partial structure in $P1$ were incorrect (see Fig. 1).

Full-matrix least-squares methods (Busing, Martin & Levy, 1962) were used to refine the structure. The function minimized was $W(|F_o| - |F_c|)^2$. The weighting function W is calculated according to the following equation:

$$W^{-1} = \sigma_{|F|}{}^2 = \frac{Q}{4 \cdot \mathrm{Lp}} \times \left[\frac{P + C^2P^2 + (t_f)^2(B_1 + B_2 + C^2B_1^2 + C^2B_2^2)}{P - (t_f)\,(B_1 + B_2)} \right]$$

where

Q = attenuator factor

P = peak scan counts

B_1B_2 = background counts

C = instrumental stability ($\sim$0·01)

t_f = time factor to put background on same scale as peak scan.

For a more detailed account of the weighting scheme, see Gilardi (1973). The atomic scattering factors used were those listed in *International Tables for X-ray Crystallography* (1962). 17 of the 23 hydrogen atoms were located in a difference map and their positional coordinates were refined. The hydrogen atoms were assigned temperature factors equal to those of their adjoining atoms. A difference map computed after the final cycle of refinement did not reveal the positions of the remaining hydrogen atoms. Table 2 lists the coordinates and thermal parameters of the heavy atoms and the coordinates of the hydrogen atoms. The observed and calculated structure factors are compared in Table 3. The final R index, $R = \sum||F_o| - |F_c||/\sum|F_o|$, for the full set of 1400 reflections is 0·049. The final weighted R index, $R_W = (\sum W(|F_o| - |F_c|)^2/\sum WF_o^2)^{1/2}$, is 0·053.

Discussion

The stereoconfiguration of the molecule is illustrated in Fig. 2. All substituent groups except O(20) are equatorial to the best plane through the pyranoid ring. The molecule has been labeled the β-anomer according to the rules of nomenclature set forth by the IUPAC (1972). For sialic acid, C(5) is the anomeric carbon and C(9) is the reference carbon. The ring is in a slightly flattened chair conformation as can be seen from the torsion angles (see Table 4 for pertinent torsion angles) which are close to 60° and alternate in sign. The overall configuration of the sialic acid molecule agrees with that found for a related molecule; methoxyneuraminic acid (Biedl, 1971). The *N*-acetyl group is *gauche* to both the hydroxyl group on C(3) and the alcohol moiety on C(1). The conformation along the alcohol chain is such that O(10) is *trans* to O(8) and *gauche* with respect

Table 2. *Fractional coordinates and thermal parameters with standard deviations*

The temperature factor is of the form $T = \exp[-\frac{1}{4}(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)]$. Standard deviations are based solely on least-squares parameters.

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(1)	0·5838 (5)	0·1986 (4)	0·2375 (5)	1·6 (1)	2·1 (2)	2·4 (2)	0·1 (1)	0·6 (1)	0·2 (1)
C(2)	0·5209 (5)	0·1910 (4)	0·0374 (5)	1·7 (2)	1·9 (2)	2·4 (2)	0·0 (1)	0·6 (1)	0·1 (1)
C(3)	0·5954 (5)	0·0926 (4)	−0·0118 (5)	2·6 (2)	2·0 (2)	2·2 (2)	−0·2 (1)	1·1 (1)	−0·0 (1)
C(4)	0·7924 (5)	0·0926 (5)	0·0790 (6)	2·3 (2)	2·5 (2)	3·9 (2)	−0·4 (2)	1·3 (1)	−0·5 (2)
C(5)	0·8496 (5)	0·1075 (4)	0·2780 (6)	2·2 (2)	2·1 (2)	3·1 (2)	0·2 (1)	0·6 (1)	−0·4 (1)
O(6)	0·7711 (3)	0·1992 (0)	0·3136 (4)	1·3 (1)	1·7 (1)	2·9 (1)	0·1 (1)	0·3 (1)	−0·5 (1)
C(7)	0·5272 (5)	0·2986 (4)	0·3016 (5)	1·8 (1)	2·3 (2)	2·4 (2)	0·0 (1)	0·7 (1)	0·1 (1)
O(8)	0·6002 (5)	0·3901 (3)	0·2554 (4)	3·3 (1)	1·7 (1)	3·0 (1)	0·1 (1)	1·4 (1)	0·2 (1)
C(9)	0·5653 (5)	0·2940 (4)	0·4987 (6)	1·6 (2)	2·6 (2)	2·7 (2)	−0·4 (2)	0·7 (1)	0·1 (2)
O(10)	0·4439 (4)	0·2198 (3)	0·5176 (4)	3·0 (1)	3·7 (2)	2·7 (1)	−1·3 (1)	1·0 (1)	0·4 (1)
C(11)	0·5443 (8)	0·3999 (5)	0·5722 (6)	4·1 (2)	3·6 (2)	3·1 (2)	−0·7 (2)	1·7 (2)	−0·7 (2)
O(12)	0·5889 (5)	0·3920 (4)	0·7571 (4)	4·0 (2)	5·4 (2)	2·7 (1)	−1·7 (1)	1·7 (1)	−1·3 (1)
N(13)	0·3320 (4)	0·1899 (3)	−0·0391 (4)	1·8 (1)	2·0 (1)	2·3 (1)	−0·4 (1)	0·3 (1)	0·2 (1)
C(14)	0·2362 (5)	0·2666 (4)	−0·1395 (6)	2·3 (2)	2·7 (2)	2·5 (2)	0·4 (1)	1·0 (1)	0·0 (1)
O(15)	0·3009 (4)	0·3468 (3)	−0·1750 (4)	2·7 (1)	2·8 (1)	4·6 (2)	0·8 (1)	1·5 (1)	1·5 (1)
C(16)	0·0434 (6)	0·2529 (6)	−0·2055 (8)	2·1 (2)	4·9 (3)	5·3 (3)	0·7 (2)	1·0 (2)	1·1 (2)
C(17)	1·0462 (6)	0·1236 (4)	0·3697 (7)	3·0 (2)	3·1 (2)	4·6 (3)	−0·0 (2)	1·4 (2)	−0·4 (2)
O(18)	1·1024 (4)	0·2115 (4)	0·3332 (6)	2·7 (1)	4·0 (2)	8·4 (2)	−0·1 (1)	1·6 (1)	0·7 (2)
O(19)	1·1403 (5)	0·0598 (5)	0·4671 (7)	2·6 (1)	6·9 (3)	9·2 (3)	1·0 (2)	0·5 (2)	3·3 (2)
O(20)	0·8060 (4)	0·0211 (3)	0·3588 (4)	3·1 (1)	2·2 (1)	2·9 (1)	0·0 (1)	0·3 (1)	0·3 (1)
O(21)	0·5487 (4)	0·0881 (3)	−0·1980 (4)	3·7 (1)	2·4 (1)	2·4 (1)	−0·6 (1)	1·2 (1)	−0·4 (1)
O(22)	0·1509 (5)	0·0116 (4)	0·0137 (6)	3·5 (1)	3·8 (2)	4·7 (2)	0·4 (1)	1·3 (1)	0·8 (2)
O(23)	0·9501 (6)	0·4162 (4)	0·3194 (6)	4·9 (2)	3·2 (2)	5·0 (2)	−0·2 (1)	0·6 (2)	−0·8 (2)

Table 2 (*cont.*)

	x	*y*	*z*
H(1)	0·533 (7)	0·133 (5)	0·276 (8)
H(2)	0·553 (7)	0·260 (5)	0·002 (8)
H(3)	0·545 (7)	0·033 (5)	0·022 (7)
H(4*A*)	0·841 (7)	0·032 (5)	0·043 (7)
H(4*B*)	0·827 (8)	0·135 (5)	0·041 (8)
H(7)	0·388 (8)	0·309 (5)	0·234 (7)
H(8)	0·735 (9)	0·388 (5)	0·291 (8)
H(9)	0·702 (8)	0·263 (5)	0·572 (8)
H(10)	0·464 (7)	0·193 (5)	0·606 (8)
H(11*A*)	0·418 (9)	0·414 (6)	0·510 (9)
H(11*B*)	0·657 (9)	0·445 (5)	0·563 (8)
H(12)	0·488 (9)	0·376 (6)	0·771 (8)
H(13)	0·278 (7)	0·140 (5)	−0·016 (7)
H(16*A*)	1·007 (9)	0·297 (7)	0·807 (10)
H(16*B*)	0·010 (8)	0·193 (6)	0·826 (9)
H(21)	0·484 (8)	0·039 (5)	−0·241 (8)
H(22*A*)	0·766 (9)	0·475 (6)	0·901 (10)
H(22*B*)	0·884 (10)	0·481 (6)	0·091 (11)
H(23*A*)	0·019 (10)	0·353 (7)	0·340 (10)
H(23*B*)	0·971 (10)	0·457 (6)	0·401 (10)

to O(12). The hydroxyl group on C(5) is *cis* to the carbonyl group on C(17) and *trans* to O(18).

Table 4. *Selected torsion angles for sialic acid*

C(2)—C(1)–O(6)—C(5)	−60·8 (5)°	Pyranoid ring
C(1)—O(6)–C(5)—C(4)	58·2 (5)	
O(6)—C(5)–C(4)—C(3)	−53·9 (6)	
C(5)—C(4)–C(3)—C(2)	53·7 (6)	
C(4)—C(3)–C(2)—C(1)	−55·2 (5)	
C(3)—C(2)–C(1)—O(6)	57·6 (5)	
N(13)–C(2)–C(3)—O(21)	63·0 (5)	
N(13)–C(2)–C(1)—C(7)	−62·1 (5)	
O(8)—C(7)–C(9)—O(10)	162·7 (4)	
O(10)–C(9)–C(11)–O(12)	64·9 (5)	
O(20)–C(5)–C(17)–O(19)	12·4 (8)	
O(20)–C(5)–C(17)–O(18)	−167·7 (5)	

Standard deviations are given in parentheses.

The torsion angles were calculated according to the sign convention of Klyne & Prelog (1960).

Table 3. *Observed and calculated structure factors for sialic acid*

The columns are the index *h*, $10|F_o|$ and $10|F_c|$.

-9	K	1
0	44	46
1	6	14
2	86	78
3	71	69
-9	K	2
0	57	60
1	80	74
2	80	82
3	35	27
4	45	45
-9	K	3
0	11	3
1	30	29
2	9	4
3	21	25
4	4	12
5	56	55
-9	K	4
0	93	96
1	54	48
2	23	16
3	34	35
4	36	40
5	49	49
-9	K	5
0	70	75
1	66	64
2	47	45
3	41	46
4	12	16
-9	K	6
0	87	82
1	70	75
2	63	72
3	23	24
-8	K	1
0	20	19
1	49	59
2	40	40
3	29	23
4	63	67
5	22	22
6	73	63
7	45	45
-8	K	2
0	21	17
1	11	18
2	79	82
3	46	44
4	30	30
5	85	81
6	54	45
7	60	56
8	13	7
-8	K	3
0	190	192
1	32	29
2	134	134
3	45	50
4	10	14
5	15	12
6	45	43
7	86	79
8	107	104
-8	K	4
0	100	101
1	48	48
2	68	64
3	90	92
4	64	65
5	79	83
6	59	57
7	27	29
8	28	23
-8	K	5
0	24	21
1	34	42
2	10	2
3	23	19
4	28	28
5	29	29
6	27	25
7	15	16
-8	K	6
0	9	14
1	19	26
2	96	86
3	35	35
4	82	88
5	85	86
6	19	24
-8	K	7
0	152	156
1	119	112
2	101	106
3	43	47
4	57	55
-7	K	1
0	105	112
1	79	73
2	107	105
3	106	111
4	67	67
5	56	50
6	37	34
7	35	38
8	47	47
9	44	40
-7	K	2
0	51	51
1	109	115
2	19	15
3	72	70
4	233	232
5	172	164
6	42	41
7	40	37
8	68	72
9	89	91
10	44	43
-7	K	3
0	195	197
1	102	100
2	118	124
3	113	111
4	86	81
5	90	89
6	162	162
7	78	79
8	158	157
9	38	38
10	79	80
-7	K	4
0	110	108
1	127	124
2	13	6
3	40	36
4	60	54
5	164	165
6	27	26
7	35	41
8	76	84
9	69	65
-7	K	5
0	15	32
1	63	58
2	130	130
3	41	48
4	36	32
5	106	100
6	65	72
7	88	83
8	0	10
9	16	12
-7	K	6
0	41	37
1	82	75
2	56	59
3	75	76
4	155	148
5	93	97
6	112	112
7	32	35
8	59	61
-7	K	7
0	80	85
1	55	55
2	148	145
3	26	26
4	65	66
5	7	12
6	25	31
7	79	81
-7	K	8
0	66	67
1	53	47
2	46	43
3	63	60
4	47	48
-6	K	1
0	29	28
1	112	99
2	143	143
3	228	227
4	49	47
5	273	268
6	203	206
7	194	191
8	38	36
9	39	43
10	35	29
11	25	28
-6	K	2
0	230	228
1	187	186
2	96	98
3	79	77
4	279	278
5	182	182
6	374	376
7	84	86
8	117	116
9	45	51
10	58	61
11	46	37
-6	K	3
0	73	74
1	107	105
2	99	94
3	32	33
4	134	131
5	188	194
6	29	33
7	16	14
8	41	52
9	36	40
10	34	29
11	54	51
-6	K	4
0	75	76
1	45	46
2	131	123
3	76	83
4	103	106
5	50	51
6	112	128
7	60	60
8	54	47
9	34	47
10	51	47
11	14	14
-6	K	5
0	86	83
1	71	70
2	106	113
3	125	122
4	216	226
5	96	104
6	110	115
7	76	69
8	41	47
9	59	55
10	42	37
-6	K	6
0	11	3
1	24	18
2	113	113
3	46	49
4	135	135
5	134	137
6	111	119
7	48	53
8	52	51
9	49	54
-6	K	7
0	45	43
1	42	46
2	71	75
3	17	9
4	7	9
5	47	46
6	43	42
7	18	10
8	12	19
-6	K	8
0	32	43
1	48	43
2	101	97
3	34	28
4	21	32
5	33	29
6	26	31
-6	K	9
0	0	7
1	38	40
2	22	19
-5	K	1
0	115	115
1	213	212
2	280	286
3	95	94
4	277	278
5	213	212
6	192	194
7	132	128
8	122	124
9	144	142
10	18	21
11	102	100
12	63	58
-5	K	2
0	72	72
1	108	110
2	61	61
3	111	107
4	168	160
5	122	127
6	113	107
7	8	6
8	160	165
9	23	23
10	46	34
11	43	50
12	37	45
-5	K	3
0	39	22
1	140	130
2	122	130
3	158	155
4	98	98
5	198	196
6	100	99
7	66	68
8	30	26
9	34	28
10	29	35
11	13	19
12	34	32
-5	K	4
0	42	45
1	167	172
2	125	128
3	61	66
4	51	46
5	65	67
6	70	74
7	87	91
8	82	97
9	60	61
10	38	43
11	59	71
12	50	47
-5	K	5
0	19	17
1	83	80
2	54	54
3	84	93
4	36	35
5	60	60
6	69	76
7	103	112
8	62	64
9	44	47
10	53	50
11	41	36
-5	K	6
0	29	29
1	83	84
2	133	135
3	81	76
4	117	114
5	69	74
6	81	84
7	98	95
8	45	46
9	25	28
10	8	8
-5	K	7
0	128	128
1	62	54
2	40	43
3	34	34
4	37	34
5	98	102
6	25	28
7	26	32
8	55	50
9	71	66
-5	K	8
0	156	154
1	104	108
2	52	54
3	60	58
4	49	53
5	28	32
6	67	65
7	6	11
-5	K	9
0	0	17
1	12	14
2	20	15
3	25	24
4	35	36
-4	K	1
0	57	55
1	292	284
2	331	340
3	188	183
4	153	144
5	75	74
6	23	37
7	275	280
8	33	36
9	69	65
10	8	27
11	84	93
12	113	117
13	54	55
-4	K	2
0	368	388
1	198	194
2	237	242
3	60	60
4	342	342
5	190	190
6	159	151
7	210	209
8	76	76
9	84	79
10	62	63
11	54	83
12	69	77
13	42	47
-4	K	3
0	20	8
1	180	173
2	38	45
3	228	225
4	61	63
5	159	163
6	57	57
7	87	88
8	59	49
9	35	26
10	50	56
11	86	85
12	19	16
13	46	47
-4	K	4
0	36	35
1	198	204
2	102	114
3	36	38
4	95	103
5	74	78
6	61	45
7	114	112
8	119	122
9	77	77
10	25	25
11	15	13
12	0	7
-4	K	5
0	107	101
1	85	83
2	45	54
3	182	185
4	112	112
5	91	87
6	58	64
7	102	102
8	81	90
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8	118	116
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10	96	107
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7	113	119
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3	205	203
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10	80	77
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3	16	24
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5	54	59
7	K	0
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2	54	59
3	56	52
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5	99	98
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7	75	85
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9	34	31
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3	33	28
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7	19	28
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2	21	20
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2	66	66
3	20	17
8	K	0
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1	52	50
2	18	19
3	48	49
4	28	23
5	48	49
6	21	15
8	K	1
0	40	40
1	25	30
2	40	35
3	22	21
4	28	21

Bond distances and angles are illustrated in Fig. 3. The estimated standard deviations, based solely on least-squares parameters, are of the order of 0·006 Å for the bonds and 0·4° for the angles. The mean C–C bond length in the pyranoid ring is 1·526 (6) Å and the mean C–OH [excluding C(17)–O(18) which is shortened due to its proximity to the C(17)=O(19) double bond] distance is 1·424 (6) Å. The C(5)–O(20) distance at 1·400 (6) Å is 0·03 Å shorter than the average value of 1·430 (6) Å of the other C–OH bonds [excluding C(17)–O(18)]. This shortening of the anomeric C–O bond has been noted in several investigations of sugar molecules (*e.g.* Johnson, 1966; Chu & Jeffrey, 1967, 1968; Beevers & Hansen, 1971; Takai, Watanabe, Ashida & Kakudo, 1972). Valence angles both within and outside the pyranoid ring are well within the range commonly found for similar rings in other sugar molecules (Jeffrey & Rosenstein, 1964). In the *N*-acetyl moiety both the N(13)–C(14) and C(14)–C(16) bond lengths are shorter than normal N–C and C–C single bonds due to the conjugative effects of the C(14)=O(15) double bond.

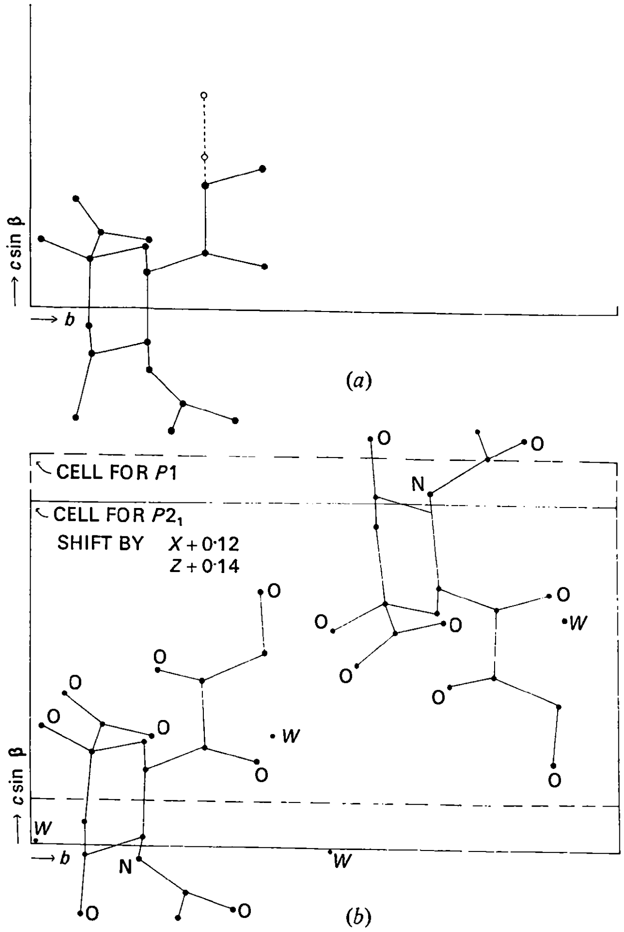

Fig. 1. (*a*) Molecule obtained from original phase determination which was used as a partial structure in $P1$. Atoms connected by dotted lines were incorrect. (*b*) Final molecule showing correct placement in the $P2_1$ cell as well as position with respect to $P1$ cell.

The packing, which is illustrated in Fig. 4, is dominated by an extensive system of hydrogen bonds (Table 5). There are 11 independent hydrogen bonds which link the molecules in all directions and make use of all the hydrogen atoms available on the hydroxyl oxygens, the water molecules, and N(13). Two of the hydroxyl hydrogens, on O(18) and O(20), were not located in the difference map. However, owing to the angles and distances involved, they should probably still be considered as donors in hydrogen bonds. Of the two carbonyl oxygen atoms O(15) is the acceptor in two hydrogen bonds and O(19) is the acceptor in one. Even though the O(19)–O(20) intramolecular separation of 2·62 Å is quite small, the angles involved between the two atoms preclude the presence of an intramolecular hydrogen bond. All the hydroxyl oxygen atoms act as acceptors as well as donors in hydrogen bonds. One of the water oxygen atoms, O(22), participates in three hydrogen bonds. The other water oxygen, O(23), participates in four hydrogen bonds which involve five other oxygen atoms. It is the acceptor from O(8) and O(22) and the donor to O(18). The fourth hydrogen bond is bifurcated, and involves both O(19) and O(20). Both O(19) and O(20) are at reasonable hydrogen bond distances from O(23) and the hydrogen atom was found to lie along the bisector of the O(19)–O(23)–O(20) angle (see Fig. 5). Other examples of bifurcated hydrogen bonds have been presented (*e.g.*Donohue, 1968; Keefe & Stewart, 1972). HN(13) is also within hydrogen bond distance of two possible acceptor oxygen atoms, O(22) at 2·84 Å and O(21) at 2·90 Å. How-

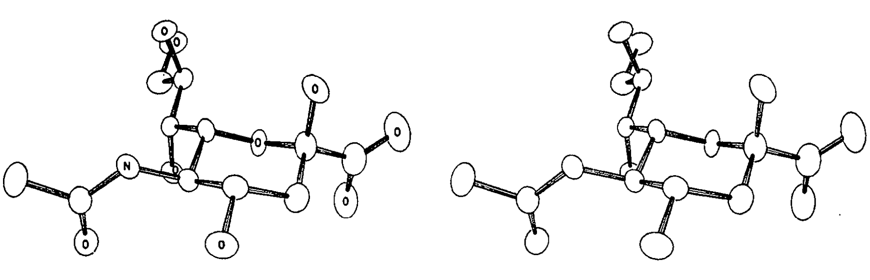

Fig. 2. Stereodiagram of a molecule of sialic acid. The figure was drawn using the *ORTEP* program of Johnson (1965).

ever, in this case the hydrogen atom is directed solely at O(22) (see Fig. 5) and the N(13)· · ·O(21) separation is then a close, but not unusual, intramolecular distance. Other than the hydrogen bonds, the closest intermolecular approach is O(23)· · ·O(6) at 3·12 Å.

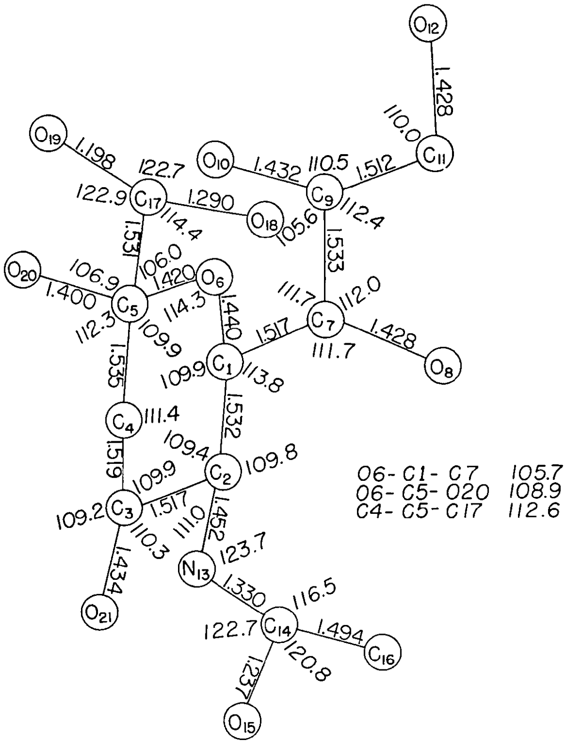

Fig. 3. Bond distances and angles for sialic acid.

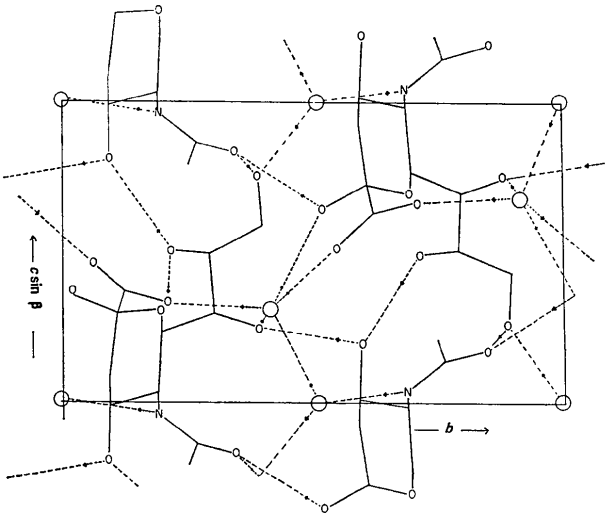

Fig. 4. Contents of one unit cell. Water molecules are shown as ○ and hydrogen bonds are indicated by dashed lines.

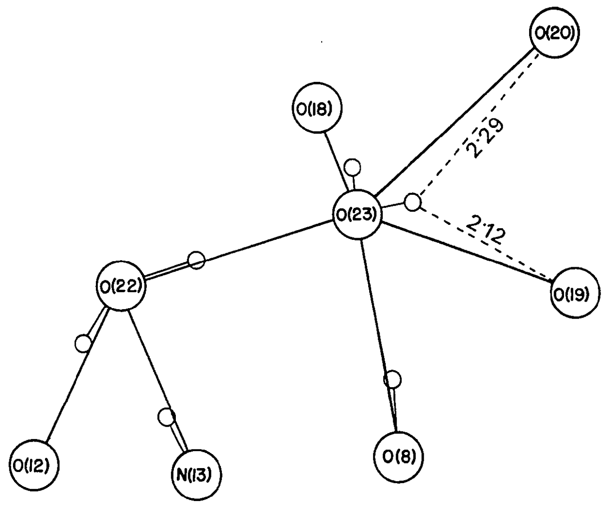

Fig. 5. Hydrogen bonding environment of the water oxygen atoms [O(22) and O(23)] showing the bifurcated hydrogen bond and the hydrogen atoms at their refined positions. See Table 5 for symmetry operations on acceptor atoms.

Table 5. *Hydrogen bond lengths and other close approaches for sialic acid*

Donor	Acceptor	Distance (Å)	Symmetry operation on acceptor			
O(8)	$H_2O(23)$	2·77	x	y	z	
O(10)	O(21)	2·74	x	y	$1+z$	
O(12)	O(15)	2·72	x	y	$1+z$	
N(13)	$H_2O(22)$	2·84	x	y	z	
O(18)	O(10)	2·66	$1+x$	y	z	
O(20)	O(15)	2·64	$1-x$	$-\frac{1}{2}+y$	$\bar{z}$	
O(21)	O(8)	2·76	$1-x$	$-\frac{1}{2}+y$	$\bar{z}$	
$H_2O(22)$	O(12)	2·73	$1-x$	$-\frac{1}{2}+y$	$1-z$	
$H_2O(22)$	$H_2O(23)$	2·82	$1-x$	$-\frac{1}{2}+y$	$\bar{z}$	
$H_2O(23)$	O(19)	2·83	$2-x$	$\frac{1}{2}+y$	$1-z$	Bifurcated
$H_2O(23)$	O(20)	2·97	$2-x$	$\frac{1}{2}+y$	$1-z$	
Close approaches						
N(13)	O(21)	2·90				intramolecular
O(19)	O(20)	2·62				
O(8)	C(11)	2·82				
O(18)	O(6)	2·70				
$H_2O(23)$	O(6)	3·12				

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The Crystal and Molecular Structure of Haloperidol, a Potent Psychotropic Drug

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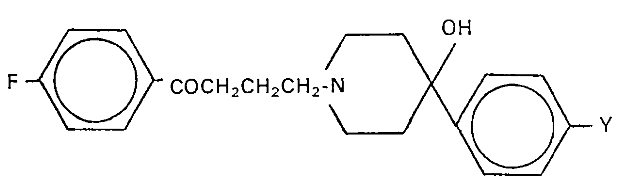
The crystal and molecular structure of haloperidol has been determined using single-crystal X-ray diffraction techniques. The molecule crystallizes in the space group $P2_1/c$ in a cell of dimensions $a=7{\cdot}816$ (5), $b=8{\cdot}995$ (6), $c=28{\cdot}344$ (20) Å, $\beta=106{\cdot}34$ (4)° with $Z=4$. The structure was solved by direct methods and refined by full-matrix least-squares calculations to a final residual of 0·077.

Haloperidol [4-(4-hydroxy-4-*p*-chlorophenylpiperidino) 4′-fluorobutyrophenone, I*a*] is an extremely potent member of the butyrophenone based psychotropic drugs. The recent structure determinations of two very similar compounds, I*b* and I*b*.HCl (Koch & Germain, 1972), prompt us to report our findings for haloperidol. This structure was determined in connection with our general interest in psychotropic drugs including molecules of the thioxanthene structural type (Schaefer, 1967).



(I*a*), Y=Cl
(I*b*), Y=F

Experimental

A sample of haloperidol (HALDOL®, McNeil Laboratories) was recrystallized from ethanol–ethyl acetate.

Preliminary photographic studies showed the crystals to be monoclinic (2/*m*). The space group $P2_1/c$ was determined from the observed extinctions. Unit-cell parameters, $a=7{\cdot}816$ (5), $b=8{\cdot}995$ (6), $c=28{\cdot}344$ (20) Å, $\beta=106{\cdot}34$ (4)° were obtained by least-squares, refinement of the angular parameters of several reflections accurately aligned on a Picker FACS-I four-circle diffractometer.

The calculated crystal density 1·24 g cm^{-3} based on four molecules per unit cell is in good agreement with the observed density of 1·23 g cm^{-3} determined by flotation.

Intensity data were collected on a Picker FACS-I diffractometer using monochromatic Cu $K\alpha$ radiation ($\lambda=1{\cdot}5418$ Å, graphite single-crystal monochromator) and a crystal of approximate dimensions $0{\cdot}5\times0{\cdot}2\times0{\cdot}1$ mm. The θ–2θ scanning technique involved a scan rate of 2·0° min^{-1}, covering a minimum interval width of 2·0° in 2θ (automatically adjusted to correct for dispersion). Stationary-crystal stationary-counter background measurements of 10 s duration were made at each end of the scan interval. To minimize counter coincidence losses, aluminum foil attenuators were automatically inserted in the diffracted beam whenever the counting rate exceeded $\sim10^4$ counts s^{-1}. Monitoring of equipment stability and crystal movement or decomposition was provided by the periodic collection of two standard reflections. Subsequent analysis of these standards revealed only minor fluctua-