

## Influence of Hydrogen Bonds on Molecular Conformation. Molecular-Mechanics Calculations on $\alpha$ -D-Glucose

BY L. M. J. KROON-BATENBURG AND J. A. KANTERS

*Structural Chemistry Group, Rijksuniversiteit Utrecht, Transitorium 3, Padualaan 8, 3508 TB Utrecht, The Netherlands*

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### Abstract

To study the effect of the crystal environment on the molecular conformation of saccharides a model is developed in which the surroundings of a single molecule are represented by a limited number of water molecules. This model is tested on the molecular conformation of  $\alpha$ -D-glucose in two different crystal modifications, that of  $\alpha$ -D-glucose and of  $\alpha$ -D-glucose monohydrate. The molecular-mechanics force field *MM2* is used to cover *intramolecular* interactions and a previously described hydrogen-bond potential for *intermolecular* hydrogen-bond interactions. The results are most pronounced for the conformation of hydroxyl groups; r.m.s. deviations of 16.4 and 17.2° for the isolated molecules diminish to 4.8 and 6.7° for the water-surrounded model of  $\alpha$ -D-glucose and  $\alpha$ -D-glucose monohydrate respectively. Energetical considerations are given for the conformation of the hydroxymethyl group.

### Introduction

In a previous paper (Kroon-Batenburg & Kanters, 1983), a modified version (*MM2HB*) of the molecular-mechanics program *MM2* (Allinger, Tribble, Miller & Wertz, 1971; Allinger & Chung, 1976; Allinger & Yuh, 1980) was presented. In order to be able to treat hydrogen-bond interactions of the O–H...O class, it was necessary to implement an empirical potential which was derived using the configuration-interaction water-dimer calculations of Matsuoka, Clementi & Yoshimine (1976). The chief aim, to modify and to extend *MM2*, was the application of this force field in studies of environmental effects on the conformation of saccharides. Di- and higher oligosaccharides can form pronounced *intramolecular* hydrogen bonds, whereas in monosaccharides weak hydrogen bonds are possible in principle between adjacent hydroxyl groups. However, in the solid state the weaker bonds will be overruled by stronger *intermolecular* bonds and only the stronger *intramolecular* bonds will be preserved.

To study the influence of both *intra*- and *inter*-molecular hydrogen bonds on the molecular conformation of saccharides, a model has been developed in which the crystal environment of a single molecule is simulated by rigid water molecules at positions corresponding to those of hydrogen-bond donors and acceptors in the actual crystal structures. In this paper the newly developed O–H...O potential is tested with the simulation model on the crystal modifications of  $\alpha$ -D-glucose and its monohydrate.

### Method

Among the *intermolecular* forces affecting the molecular conformation of saccharides in crystal structures, the hydrogen bond is by far the most important interaction. Therefore only this type of interaction will be considered in this study.

The method consists of molecular-mechanics calculations of the conformation of the monosaccharide comprising *intermolecular* hydrogen-bond interactions. The force field *MM2HB* is described in a previous paper (Kroon-Batenburg & Kanters, 1983). Additional modifications to the force field had to be made to account for the so-called anomeric effect (Eliel, Allinger, Angyal & Morrison, 1965) which influences geometries of the hemiacetal sequence O(1)–C(1)–O(5)–C(5) of saccharides (see Fig. 1 for atomic numbering). The relevant parameters in the force field were changed according to the proposal of Jeffrey & Taylor (1980).\* The crystal environment is represented in such a way that the preponderant hydrogen-bond interactions are preserved without having to include all neighbouring molecules. When the hydrogen-bond criterion is set at an intermolecular O...O distance of 3.30 Å the central molecule is hydrogen-bonded to 12 glucose molecules in the crystal structure of  $\alpha$ -D-glucose (Brown & Levy, 1979) and to

\* The  $r_o$  values of C(1)–O(1), C(1)–O(5) and C(5)–O(5) become 1.384, 1.396 and 1.412 Å, respectively. The  $\theta_o$  values for O(5)–C(1)–O(1) and C(5)–O(5)–C(1) become 109.3 and 107.5° respectively.

six glucose molecules and four water molecules in the monohydrate (Hough, Neidle, Rogers & Troughton, 1973). The limiting distance was chosen so as to cover all interactions within the range that is normal for hydrogen bonds (Jeffrey, 1982). The relevant hydroxyl and ring ether groups of the neighbouring molecules were replaced by water molecules in such a way that C—O—H(1) is replaced by H(2)—O—H(1), with the same bond angle but with the H(2)—O distance set at 0.96 Å and C—O—C was similarly replaced by H—O—H. Because the geometry of  $\alpha$ -D-glucose monohydrate was derived from X-ray data, the O—H(1) distance was corrected to 0.96 Å in all cases; for  $\alpha$ -D-glucose the neutron-diffraction-derived O—H(1) distance was used.

The glucose residue caged within this rigid framework of water molecules was then allowed to relax to its minimum-energy geometry. In this process the formation of *intramolecular* hydrogen bonds between O atoms that are not bonded to the same C atom is allowed.

O atoms in the molecular-mechanics force field are parametrized with having two lone pairs attached that act as pseudo atoms in the calculations. So at every O two lone pairs were placed in the bisecting plane of R—O—R' at distances of 0.6 Å and a lone pair—O—lone pair angle of 133° (Kroon-Batenburg & Kanters, 1983; Allinger & Yuh, 1980).

### Calculations

We have performed three types of calculations; the resulting geometries are compared with those observed in the crystal structure (*A*). The first type of calculation is that of a minimum-energy conformation of the isolated molecule (*B*). When starting from the crystal molecular conformation, this calculated conformation does not necessarily have to correspond to the global minimum, but it is a local minimum-energy conformation of the isolated molecule that will not be very

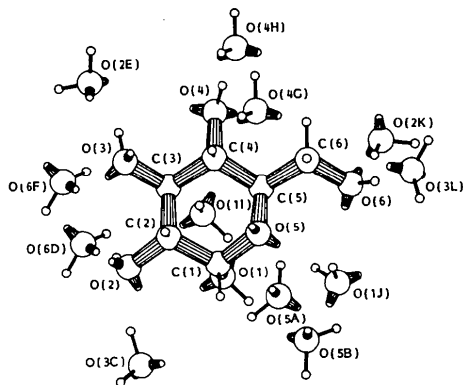


Fig. 1. The  $\alpha$ -D-glucose—water complex for  $\alpha$ -D-glucose. The lone-pair atoms are represented by small spheres with thick bonds attached to them.

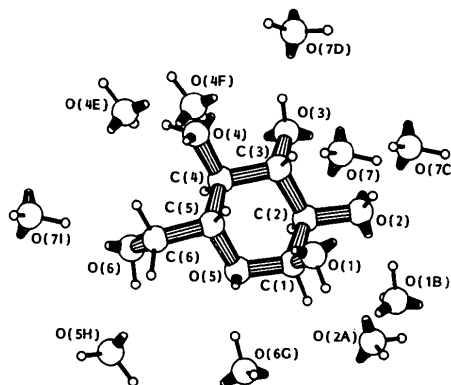


Fig. 2. The  $\alpha$ -D-glucose—water complex for  $\alpha$ -D-glucose monohydrate. The lone-pair atoms are represented by small spheres with thick bonds attached to them.

Table 1.  $\alpha$ -D-Glucose: hydrogen bonds for  $O \cdots O \leq 3.3 \text{ \AA}$

$$d_{OO} \equiv O \cdots O, d_{HO} \equiv H \cdots O, \theta \equiv \angle O-H \cdots O.$$

	Crystal ( <i>A</i> )			Surrounded ( <i>C</i> )		
	$d_{OO}$ (Å)	$d_{HO}$ (Å)	$\theta$ (°)	$d_{OO}$ (Å)	$d_{HO}$ (Å)	$\theta$ (°)
O(1)—H...O(5 <i>B</i> )	2.85	1.92	161	2.89	1.97	157
O(2)—H...O(6 <i>D</i> )	2.78	1.82	170	2.79	1.84	168
O(3)—H...O(2 <i>E</i> )	2.71	1.76	165	2.68	1.77	156
O(4)—H...O(4 <i>H</i> )	2.78	1.82	168	2.74	1.79	165
O(6)—H...O(3 <i>L</i> )	2.71	1.76	170	2.64	1.67	170
O(7)—H...O(5 <i>A</i> )	3.29	2.92	104	3.27	2.80	111
O(3 <i>C</i> )—H...O(2)	2.71	1.77	165	2.73	1.79	166
O(6 <i>F</i> )—H...O(3)	2.71	1.76	170	2.73	1.78	170
O(4 <i>G</i> )—H...O(4)	2.78	1.83	168	2.81	1.86	168
O(1 <i>J</i> )—H...O(5)	2.85	1.92	161	2.87	1.95	161
O(2 <i>K</i> )—H...O(6)	2.78	1.83	170	2.93	1.98	171
O(1 <i>I</i> )—H...O(5)	3.29	2.92	104	3.30	2.93	104
$A_{r.m.s.}$				0.03	0.07	4
$A_{mean}$				-0.02	-0.02	2

$A_{r.m.s.} = [\sum (p_A - p_C)^2/N]^{1/2}$ ;  $A_{mean} = [\sum (p_A - p_C)/N]$ . Characters in the atomic numbering refer to symmetry operations: *A* 564.4, *B* 565.4, *C* 465.2, *D* 655.3, *E* 665.4, *F* 664.4, *G* 645.3, *H* 644.3, *I* 654.3, *J* 565.2, *K* 554.1, *L* 556.1. The last digit indicates one of the following symmetry operations: (1)  $x, y, z$ ; (2)  $x + \frac{1}{2}, -y + \frac{1}{2}, -z$ ; (3)  $-x, y + \frac{1}{2}, -z + \frac{1}{2}$ ; (4)  $-x + \frac{1}{2}, -y, z + \frac{1}{2}$ . The first three digits specify the lattice translation (e.g. 564.4 is  $+b - c$  from 555.4).

different from that in the crystal. Secondly, starting from the crystal-structure geometries, the conformation of the molecules surrounded by the rigid cage of water molecules was calculated (*C*). This calculation was repeated for the isolated molecule (*B*), which was placed in the cage in a position as closely as possible to that in the crystal structure (*D*). In all cases the central molecule was allowed to relax to its minimum-energy conformation.

The  $\alpha$ -D-glucose and  $\alpha$ -D-glucose monohydrate molecules with the simulated surroundings are illustrated in Figs. 1 and 2 respectively. For  $\alpha$ -D-glucose the selected 12  $O \cdots O$  contacts within 3.3 Å are given in Table 1. Table 2 lists the data for 11  $O \cdots O$  contacts for the monohydrate.

Table 2.  $\alpha$ -D-Glucose monohydrate: hydrogen bonds for  $O \cdots O \leq 3.3 \text{ \AA}$ 

Corrected positions have been used for H atoms.  $d_{OO} \equiv O \cdots O$ ,  $d_{HO} \equiv H \cdots O$ ,  $\theta \equiv \angle O-H \cdots O$ .

	Crystal (A)			Surrounded (C)		
	$d_{OO}$ ( $\text{\AA}$ )	$d_{HO}$ ( $\text{\AA}$ )	$\theta$ ( $^\circ$ )	$d_{OO}$ ( $\text{\AA}$ )	$d_{HO}$ ( $\text{\AA}$ )	$\theta$ ( $^\circ$ )
O(1)—H...O(2A)	2.73	1.84	155	2.83	1.92	156
O(2)—H...O(7C)	2.81	1.90	158	2.86	1.92	165
O(3)—H...O(7D)	2.74	1.81	161	2.79	1.93	147
O(4)—H...O(4E)	2.81	1.89	160	2.74	1.81	160
O(6)—H...O(5H)	2.84	1.95	153	2.91	2.09	141
O(7)—H...O(2)	3.30	2.69	91	3.09	2.46	123
O(7)—H...O(3)	2.76	1.83	161	2.74	1.84	155
O(1B)—H...O(2)	2.73	1.83	155	2.81	1.91	156
O(4F)—H...O(4)	2.81	1.89	160	2.86	1.94	158
O(6G)—H...O(5)	2.84	1.95	153	2.86	1.97	153
O(7I)—H...O(6)	2.79	1.84	171	2.80	1.85	171
$\Delta_{r.m.s.}$				0.08	0.07	11
$\Delta_{mean}$				-0.01	-0.02	-1

Characters in the atomic numbering refer to symmetry operations: A 555.2, B 545.2, C 565.1, D 556.2, E 646.2, F 656.2, G 655.2, H 645.2, I 655.2. The last digit indicates one of the following symmetry operations: (1)  $x, y, z$ ; (2)  $-x, y + \frac{1}{2}, -z$ . The first three digits specify the lattice translations (e.g. 645.2 is  $+a -b$  from 555.2).

### Results and discussion

Only the results of two calculated structures are given in the tables, that of the isolated molecule (B) and the structure obtained by including the environment (C). Calculations performed on (C) and (D) systems gave practically the same results, so only one of them is listed.

#### Hydrogen bonds

The calculated hydrogen-bond geometries for  $\alpha$ -D-glucose and  $\alpha$ -D-glucose monohydrate (C) are listed, together with the observed geometries (A), in Tables 1 and 2 respectively. For the monohydrate corrected O—H distances were applied. From the r.m.s. deviations it can be seen that the calculated  $O \cdots O$  and  $H \cdots O$  distances and the  $O-H \cdots O$  angles are well in agreement with the observed values for  $\alpha$ -D-glucose. The r.m.s. deviations for the monohydrate are larger. This is mainly caused by shortening of the  $O(7) \cdots O(2)$  hydrogen bond, which illustrates the overestimation of the strength of longer  $O \cdots O$  bonds due to the simulation by water molecules, with large dipole moments, instead of aliphatic hydroxyl groups. Comparison of the mean with the r.m.s. deviation shows that there is no distinct systematic deviation to longer or shorter bonds, or to larger or smaller angles.

#### Bond distances

Results for the calculations (B) and (C) are compared with the observed crystal structures (A) in Table 3. The r.m.s. deviation is not very dependent on

inclusion of the surroundings. The r.m.s. deviation of the surrounded molecule (C) is  $0.012 \text{ \AA}$  for  $\alpha$ -D-glucose and  $0.019 \text{ \AA}$  for the hydrate. The mean

Table 3. Bond distances ( $\text{\AA}$ ) for  $\alpha$ -D-glucose and  $\alpha$ -D-glucose monohydrate

	$\alpha$ -D-Glucose			$\alpha$ -D-Glucose monohydrate		
	Crystal (A)	Free (B)	Surrounded (C)	Crystal (A)	Free (B)	Surrounded (C)
C(1)—C(2)	1.535	1.536	1.538	1.509	1.538	1.535
C(2)—C(3)	1.525	1.535	1.534	1.522	1.536	1.534
C(3)—C(4)	1.520	1.539	1.537	1.521	1.538	1.535
C(4)—C(5)	1.530	1.540	1.539	1.513	1.538	1.537
C(5)—C(6)	1.511	1.538	1.538	1.510	1.539	1.539
$\Delta_{r.m.s.}$		0.013	0.012		0.024	0.022
$\Delta_{mean}$		-0.011	-0.011		-0.023	-0.021
C(1)—O(1)	1.390	1.385	1.387	1.412	1.386	1.386
C(2)—O(2)	1.416	1.412	1.412	1.422	1.412	1.414
C(3)—O(3)	1.417	1.412	1.411	1.422	1.412	1.410
C(4)—O(4)	1.426	1.412	1.412	1.435	1.410	1.413
C(6)—O(6)	1.414	1.410	1.411	1.438	1.408	1.407
$\Delta_{r.m.s.}$		0.007	0.007		0.022	0.019
$\Delta_{mean}$		0.006	0.006		0.020	0.018
C(1)—O(5)	1.427	1.406	1.409	1.427	1.407	1.409
C(5)—O(5)	1.428	1.428	1.428	1.451	1.423	1.425
$\Delta_{r.m.s.}$		0.015	0.013		0.024	0.022
$\Delta_{mean}$		0.010	0.009		0.024	0.022
Total						
$\Delta_{r.m.s.}$		0.013	0.012		0.023	0.019
$\Delta_{mean}$		0.000	-0.001		0.003	0.002

Table 4. Bond angles ( $^\circ$ ) for  $\alpha$ -D-glucose and  $\alpha$ -D-glucose monohydrate

	$\alpha$ -D-Glucose			$\alpha$ -D-Glucose monohydrate		
	Crystal (A)	Free (B)	Surrounded (C)	Crystal (A)	Free (B)	Surrounded (C)
C(1)—C(2)—C(3)	111.1	110.1	110.8	112.7	110.9	111.9
C(2)—C(3)—C(4)	109.8	108.1	108.5	109.0	107.6	108.7
C(3)—C(4)—C(5)	111.1	111.1	110.7	111.4	110.8	110.7
C(4)—C(5)—O(5)	108.7	110.0	109.1	108.9	110.2	110.4
C(5)—O(5)—C(1)	113.8	114.7	114.5	113.1	114.3	115.0
O(5)—C(1)—C(2)	110.1	110.1	109.6	110.9	110.5	110.1
$\Delta_{r.m.s.}$		1.0	0.7		1.2	1.1
$\Delta_{mean}$		0.3	0.2		0.3	-0.1
C(2)—C(1)—O(1)	109.3	111.1	110.7	110.2	111.0	111.0
O(1)—C(1)—O(5)	111.5	110.2	111.1	110.2	110.4	111.3
C(1)—C(2)—O(2)	110.9	109.9	111.6	110.9	109.9	111.7
C(3)—C(2)—O(2)	112.3	112.4	112.1	112.6	112.2	110.9
C(2)—C(3)—O(3)	108.1	109.7	108.6	106.8	109.6	107.5
C(4)—C(3)—O(3)	110.6	109.7	109.9	110.5	109.7	109.0
C(3)—C(4)—O(4)	108.3	108.7	109.3	108.7	109.6	109.1
C(5)—C(4)—O(4)	110.9	109.0	109.5	109.2	108.7	109.4
C(4)—C(5)—C(6)	111.6	111.8	111.6	114.0	112.9	113.1
O(5)—C(5)—C(6)	108.1	107.7	108.2	106.6	108.5	108.3
$\Delta_{r.m.s.}$		1.2	0.8		1.3	1.1
$\Delta_{mean}$		0.1	-0.1		-0.3	-0.2
C(5)—C(6)—O(6)	110.5	109.3	109.7	112.2	110.4	111.4
$\Delta_{r.m.s.}$		1.2	0.8		1.8	0.8
Total						
$\Delta_{r.m.s.}$		1.1	0.8		1.3	1.1
$\Delta_{mean}$		0.1	0.1		0.0	-0.1

difference for the C—C bonds shows that they are calculated systematically too long. The shortening of the bonds in the crystal structure may well be caused by a crystal-compression effect. This effect could be reproduced by inclusion of many more glucose molecules in the calculation instead of a limited number of water molecules, but that would complicate the calculations too much and is beyond our goal. The C—O bonds are, though to a lesser extent, systematically too short. This was already noticed by Allinger & Chung (1976) who found that in contrast to ether-like C—O bonds, methanol-like C—O bonds are calculated too short. Compared with the neutron data of  $\alpha$ -D-glucose, the calculated C—H distances are systematically (0.02 Å) too long. Inclusion of the surroundings has practically no effect on bond distances involving H atoms.

### Bond angles

The results for endocyclic and exocyclic angles and for the angle of the hydroxymethyl group are listed separately in Table 4. There is little difference in agreement between these categories. The mean devia-

tions are always smaller than the r.m.s. deviations, indicative of the absence of systematic deviations. The r.m.s. deviations of calculation (C) are smaller than those of calculation (B) for all categories. In most of the cases the individual deviations between (A) and (C) are smaller than between (A) and (B). The overall improvement by including the surroundings is 0.2° for both  $\alpha$ -D-glucose and the hydrate. For angles involving H atoms, compared with the neutron data of  $\alpha$ -D-glucose, the results are similar.

### Torsion angles

The results for endocyclic, hybrid, exocyclic and hydroxymethyl group torsion angles involving C and O atoms are listed in Table 5. The endocyclic torsion angles show the largest r.m.s. deviation for the free molecule (B). The deviations of all categories are diminished when going from the free (B) to the surrounded molecule (C) except for the hydroxymethyl group in the structure of  $\alpha$ -D-glucose. This may be due to the flexibility of this group and the absence of a direct restraint on the —CH<sub>2</sub> group by an intermolecular interaction. The conformation of this par-

Table 5. Torsion angles (°) involving non-H atoms for  $\alpha$ -D-glucose and  $\alpha$ -D-glucose monohydrate

	$\alpha$ -D-Glucose			$\alpha$ -D-Glucose monohydrate		
	Crystal (A)	Free (B)	Surrounded (C)	Crystal (A)	Free (B)	Surrounded (C)
<b>Endocyclic</b>						
C(1)—C(2)—C(3)—C(4)	-51.3	-55.2	-54.5	-50.5	-54.7	-52.2
C(2)—C(3)—C(4)—C(5)	53.3	54.0	54.7	53.5	55.0	52.5
C(3)—C(4)—C(5)—O(5)	-57.5	-54.7	-56.6	-58.5	-56.8	-55.7
C(4)—C(5)—O(5)—C(1)	62.3	58.8	61.1	61.4	59.4	60.1
C(5)—O(5)—C(1)—C(2)	-60.9	-60.8	-61.2	-58.7	-59.2	-59.1
O(5)—C(1)—C(2)—C(3)	54.1	58.2	56.8	53.0	56.6	54.6
$\Delta_{r.m.s.}$		3.0	1.9		2.6	1.6
<b>Hybrid</b>						
C(5)—O(5)—C(1)—O(1)	60.6	62.6	61.2	63.5	63.7	63.5
O(1)—C(1)—C(2)—C(3)	-68.7	-64.3	-65.9	-69.3	-66.2	-69.2
O(5)—C(1)—C(2)—O(2)	179.7	-177.4	-177.9	-179.8	-179.1	179.3
O(2)—C(2)—C(3)—C(4)	-176.1	-178.1	-179.7	-176.7	-177.7	-176.9
C(1)—C(2)—C(3)—O(3)	-172.0	-174.7	-173.7	-169.8	-173.8	-169.5
O(3)—C(3)—C(4)—C(5)	172.5	173.5	173.0	170.5	174.1	169.4
C(2)—C(3)—C(4)—O(4)	175.3	173.9	175.3	173.8	175.0	172.8
O(4)—C(4)—C(5)—O(5)	-178.0	-174.4	-176.8	-178.5	-177.2	-175.5
C(3)—C(4)—C(5)—C(6)	-176.6	-174.3	-176.0	-177.3	-178.1	-175.5
C(6)—C(5)—O(5)—C(1)	-176.5	-179.0	-177.3	-175.2	-176.8	-176.3
$\Delta_{r.m.s.}$		2.7	1.9		2.3	1.2
<b>Exocyclic</b>						
O(1)—C(1)—C(2)—O(2)	56.9	60.1	59.3	57.9	58.1	55.4
O(2)—C(2)—C(3)—O(3)	63.2	62.3	61.2	63.9	63.2	65.7
O(3)—C(3)—C(4)—O(4)	-65.5	-66.6	-66.4	-69.2	-65.9	-70.3
O(4)—C(4)—C(5)—C(6)	62.9	66.0	63.8	62.7	61.6	63.5
$\Delta_{r.m.s.}$		2.3	1.7		1.8	1.7
<b>Hydroxymethyl group</b>						
C(4)—C(5)—C(6)—O(6)	-170.3	-169.8	-173.5	52.5	47.0	47.2
O(5)—C(5)—C(6)—O(6)	70.2	69.2	66.5	-67.9	-75.2	-75.0
$\Delta_{r.m.s.}$		0.8	3.5		6.5	6.3
<b>Total</b>						
$\Delta_{r.m.s.}$		2.6	2.1		2.9	2.4

Table 6. Torsion angles ( $^{\circ}$ ) of hydroxyl groups for  $\alpha$ -D-glucose and  $\alpha$ -D-glucose monohydrate

	$\alpha$ -D-Glucose			$\alpha$ -D-Glucose monohydrate		
	Crystal (A)	Free (B)	Surrounded (C)	Crystal (A)	Free (B)	Surrounded (C)
O(5)-C(1)-O(1)-H	74.9	64.6	67.4	96.6	76.0	93.3
C(1)-C(2)-O(2)-H	-100.6	-75.3	-101.0	-75.2	-68.1	-73.3
C(2)-C(3)-O(3)-H	-166.0	-177.1	-169.3	-156.5	179.1	-164.1
C(3)-C(4)-O(4)-H	134.2	141.5	139.1	129.4	149.5	127.6
C(5)-C(6)-O(6)-H	-143.9	-164.8	-148.7	90.0	70.0	77.9
r.m.s.		16.4	4.8		17.2	6.7

ticular group is discussed in the next section. The r.m.s. deviation for all torsion angles is reduced by  $0.5^{\circ}$  upon inclusion of the surroundings in the calculations.

The largest differences between the crystal structure molecule (A) and the isolated molecule (B) are those of the torsion angles of the hydroxyl groups (Table 6), which are most directly influenced by hydrogen bonding. Here the effect of our method is expected to be most pronounced. For  $\alpha$ -D-glucose the r.m.s. deviation between the crystal molecular structure (A) and the free molecular structure (B) is  $16.4^{\circ}$ , and for the hydrate  $17.2^{\circ}$ . Similar values have been found by Kildeby, Melberg & Rasmussen (1977). These deviations are reduced to  $4.8$  and  $6.7^{\circ}$  respectively in the water-surrounded complex (C). These results indicate that the model reproduces a molecular structure in a crystal in a satisfactory way.

#### Conformation of the hydroxymethyl group

The local minimum-energy conformations of the free molecules (B), derived from the two different crystal structures, mainly differ in the conformation of the hydroxymethyl group caused by rotation about C(5)-C(6) and C(6)-O(6) (see Table 5). The torsion angle relative to the bond C(5)-C(6) is approximately *gt* for  $\alpha$ -D-glucose [*gauche* for O(5)-C(5)-C(6)-O(6) and *trans* for C(4)-C(5)-C(6)-O(6)] and *gg* for the hydrate.

The energies for the free glucose molecules (B) are referred to as  $E_g^{\text{free}}$  in Table 7; the difference in energy between the structure derived from  $\alpha$ -D-glucose and that from  $\alpha$ -D-glucose monohydrate is  $13.0 \text{ kJ mol}^{-1}$  in favour of the latter. The energies of the free molecules should be compared with gas-phase data, but as these are not available it will be most proper to compare them with data from solutions. From NMR studies of  $\alpha$ -D-glucose in acetone a ratio of 77:23 for *gg*:*gt* conformations was found (Streefkerk, de Bie & Vliegthart, 1973), corresponding to an energy difference of  $3.3 \text{ kJ mol}^{-1}$  at room temperature, obviously much smaller than the calculated  $\Delta E_g^{\text{free}}$  of  $13.0 \text{ kJ mol}^{-1}$ .

In the crystal structures the calculated energy difference between the two glucose molecules (A) is

Table 7. Energies ( $\text{kJ mol}^{-1}$ ) for the water complexes of  $\alpha$ -D-glucose and  $\alpha$ -D-glucose monohydrate

	$\alpha$ -D-Glucose	$\Delta$	$\alpha$ -D-Glucose monohydrate
	<i>gt</i>	<i>gt</i> - <i>gg</i>	<i>gg</i>
$E_{\text{tot}}$			
$E_w$			
$E_g$			
$E_{g/w}$			
$E_{g/w}^{\text{free}}$			
$E_g^{\text{free}}$			
$E_{g/w}^{\text{free}}$			
$E_g^{\text{free}} + \frac{1}{2}E_{g/w}^{\text{free}}$			
$E_g^{\text{free}}$			
$E_g^{\text{free}} (\epsilon = 3)$			
	-268.6	-28.4	-240.2
	40.6	11.7	28.9
	-93.7	-2.5	-91.2
	34.6	13.0	21.6
	33.2	2.9	30.2

$11.7 \text{ kJ mol}^{-1}$  ( $\Delta E_g$  in Table 7). From crystal-structure data of saccharides containing glucose moieties it appears that *gg* and *gt* conformations occur in a ratio of 60:40 (Marchessault & Pérez, 1979) which would correspond to an energy difference of  $1.3 \text{ kJ mol}^{-1}$  at room temperature.

The relative stabilities of the two molecules (A) will be influenced by the crystal-packing energies, represented in the model calculations by hydrogen-bond energies. If the interaction energy of glucose with the water cage is included ( $E_g + \frac{1}{2}E_{g/w}$  in Table 7), the energy difference between the two molecules (A) becomes  $-2.5 \text{ kJ mol}^{-1}$ , the *gt* conformation in the homomolecular structure now being lower in energy than the *gg* conformation in the heteromolecular structure. Whether these values of  $\frac{1}{2}E_{g/w}$  are representative for the environments of all *gg* and *gt* conformations observed is yet unknown. However, it is obvious that this contribution will influence their relative occurrence in dense polar media.

It should be noted that the relative energies of the *gg* and *gt* conformations are dependent on the value of the dielectric constant ( $\epsilon$ ) that is used in the calculation of the dipole energies. In all calculations the value of  $\epsilon$  was taken equal to unity. It turned out that the conformations of the free molecules (B) hardly changed with  $\epsilon = 3$ , whereas the energy difference between *gg* and *gt* conformations becomes  $2.9 \text{ kJ mol}^{-1}$ , *gg* being lower in

energy. This result is more in agreement with the previously mentioned NMR data than the results from the calculations with  $\epsilon = 1$ . Future calculations on saccharides will decide whether  $\epsilon = 3$  should be used in the case of intramolecular energies, or that the apparent disagreement between experimental and theoretical results is due to the packing effects described above.

#### References

- ALLINGER, N. L. & CHUNG, D. Y. (1976). *J. Am. Chem. Soc.* **98**, 6798–6803.  
 ALLINGER, N. L., TRIBBLE, M. T., MILLER, M. A. & WERTZ, D. H. (1971). *J. Am. Chem. Soc.* **93**, 1637–1648.  
 ALLINGER, N. L. & YUH, Y. H. (1980). *Quantum Chemistry Program Exchange*, No. 423. Chemistry Department, Indiana Univ., Bloomington, IN.  
 BROWN, G. M. & LEVY, H. A. (1979). *Acta Cryst.* **B35**, 656–659.

- ELIEL, E. L., ALLINGER, N. L., ANGYAL, S. J. & MORRISON, G. A. (1965). In *Conformational Analysis*, Ch. 6. New York: Wiley Interscience.  
 HOUGH, E., NEIDLE, S., ROGERS, D. & TROUGHTON, P. G. H. (1973). *Acta Cryst.* **B29**, 365–367.  
 JEFFREY, G. A. (1982). In *Molecular Structure and Biological Activity*, edited by J. F. GRIFFIN & W. L. DUAX. New York: Elsevier Biomedical.  
 JEFFREY, G. A. & TAYLOR, R. (1980). *J. Comput. Chem.* **1**, 99–109.  
 KILDEBY, K., MELBERG, S. & RASMUSSEN, K. (1977). *Acta Chem. Scand. Ser. A*, **31**, 1–13.  
 KROON-BATENBURG, L. M. J. & KANTERS, J. A. (1983). *J. Mol. Struct.* Submitted.  
 MARCHESSAULT, R. H. & PÉREZ, S. (1979). *Biopolymers*, **18**, 2369–2374.  
 MATSUOKA, O., CLEMENTI, E. & YOSHIMINE, M. (1976). *J. Chem. Phys.* **64**, 1351–1361.  
 STREEFKERK, D. G., DE BIE, M. J. A. & Vliegenthart, J. F. G. (1973). *Tetrahedron*, **29**, 833–844.

*Acta Cryst.* (1983). **B39**, 754–760

## Etude Conformationnelle par Diffraction des Rayons X et Calcul Théorique du Fragment 23–26 de l'ACTH: Ac-Tyr-Pro-Asn-Gly-OH, C<sub>22</sub>H<sub>29</sub>N<sub>5</sub>O<sub>8</sub> · 0,7C<sub>2</sub>H<sub>6</sub>OS

PAR M. COTRAIT, S. GEOFFRE, M. HOSPITAL ET G. PRÉCIGOUX

Laboratoire de Cristallographie associé au CNRS, LA 144, 351 avenue de la Libération, 33405 Talence CEDEX, France

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#### Abstract

A conformational study of Ac-Tyr-Pro-Asn-Gly-OH, the 23–26 ACTH fragment, is presented, in the solid state using X-ray analysis (Cu K $\alpha$ ) and in the isolated state by empirical calculations. Monoclinic,  $P2_1$ ,  $a = 9.574$  (3),  $b = 9.831$  (3),  $c = 15.707$  (4) Å,  $\beta = 103.06$  (1)°,  $V = 1440$  Å<sup>3</sup>,  $Z = 2$ . In the crystal, the tetrapeptide has an approximately stretched conformation and is involved in numerous intermolecular hydrogen bonds; this conformation is rather close to those of its zwitterionic form. Theoretical calculations show that the most stable conformation (by 11–25 kJ mol<sup>-1</sup>) is the (Pro<sub>2</sub>-Tyr<sub>3</sub>)  $\beta$  turn III. It is followed by numerous partially or fully stretched structures as well as the (Pro<sub>2</sub>-Tyr<sub>3</sub>)  $\beta$  turns II and I. It appears that such a short peptide may adopt various conformations in a limited range of energy, some of which may be stabilized by surrounding molecules.

L'hormone adrénocorticotrope (ACTH) est un peptide linéaire, constitué de 39 acides aminés, produit par l'hypophyse antérieure. Son action biologique prin-

cipale est la stimulation et la régulation de la sécrétion des corticostéroïdes (Sayers, Beall & Seelig, 1974). De nombreuses études ont montré que l'ACTH et certains de ses fragments sont aussi impliqués dans le processus comportemental chez l'animal (de Wied, 1974).

Les études physicochimiques les plus récentes: par dichroïsme circulaire, RMN et prédictions conformationnelles (Toma, Greff, Fermandjian, Löw & Kisfaludy, 1976; Toma, Fermandjian, Löw & Kisfaludy, 1978; Mutter, Mutter & Bayer, 1979) sont plus ou moins en faveur d'une structure non ordonnée pour l'ACTH 16–22 ou 17–24 mais sont en désaccord en ce qui concerne la partie C-terminale. Par exemple, Jibson & Li (1979) concluent à la formation d'un ' $\beta$  turn' pour le fragment 23–26 suivi d'une hélice  $\alpha$  pour la séquence 27–35 tandis que Mutter *et al.* (1979) inclinent pour une structure non ordonnée suivie par une structure en feuillet  $\beta_p$ .

Pour apporter un éclairage nouveau à ce problème, nous avons synthétisé, cristallisé, établi la structure cristalline du fragment 23–26 et calculé les conformations les plus probables du térapeptide.