

THEORETICAL STUDIES ON THE CONFORMATIONS OF ACYCLIC ALDITOLS

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ABSTRACT

The conformational analysis by energy calculations is described for some acyclic sugars such as D-glucitol, D-mannitol and galactitol. Planar zig-zag conformation is the most favoured conformation for all the three alditols. However, the energy difference between the 'bent-chain' and 'straight-chain' conformations is less in the case of D-glucitol (0.9 Kcal Mole⁻¹) compared to those of D-mannitol (~2.4 Kcal mole⁻¹) and galactitol (~2.5 Kcal Mole⁻¹). The solvent accessibility studies favour bent-chain conformation for D-glucitol and straight-chain conformations for D-mannitol and galactitol. These conformations, arrived at by theoretical analysis are compared with those observed in the solid state determined by X-ray diffraction technique and their acetylated derivatives in solution by NMR technique. These studies suggest that, when the energy difference between straight and bent conformations is small, lattice energy (in the case of solids) and solvent (in the case of solutions) do play a dominant role on the favoured conformations.

INTRODUCTION

SEVERAL investigators¹⁻³ have reported the favoured conformations of a number of acyclic derivatives of sugar in solution by NMR spectroscopy. The conformations of some of the acyclic sugars such as the alditols, in solid state, have been determined by X-ray diffraction methods⁴. Although theoretical energy calculations have been reported for several cyclic sugars and their derivatives⁵⁻⁷ no attempt has so far been made at calculating energies of various conformations of acyclic sugars. Compared to the cyclic systems, the acyclic forms are more flexible because of the greater freedom of rotation about the single bonds. In such cases, the solvent and the lattice energy may play a significant role in stabilizing a particular conformation. In this paper, the conformational analysis by energy calculations is described for acyclic sugars such as D-glucitol, D-mannitol and galactitol, whose conformations in the solid state by X-ray analysis⁴ and for their derivatives in solution by NMR technique^{8,9} have been reported. Comparison of the results with those from experiments throws light on the importance of the parallel 1,3-interaction, lattice energy and solvent on the favoured conformations.

METHODS

(a) Energy calculations :

Figure 1 shows an extended form of an alditol with the backbone dihedral angles. All the atoms in the molecules were fixed with appropriate bond lengths

(C-H = 1.1 Å ; C-O = 1.42 Å ; C-C = 1.52 Å) and bond angles (H-C-C = 109.5° ; H-C-O = 109.5° ; C-C-O = 109.5° ; H-C-H = 109.5°). For reducing computer time the hydroxyl (OH) group was treated as a united atom and its charge was taken as the net charge of O and H. As indicated in the diagram the conformation of the molecule can be defined by a set of dihedral angles χ_1 to χ_6 .

$\chi_1(\text{O}-1-\text{C}-1-\text{C}-2-\text{C}-3) = 0$ when the bond
O-1-C-1 eclipses
the bond
C-2-C-3

$\chi_2(\text{C}-1-\text{C}-2-\text{C}-3-\text{C}-4) = 0$ when the bond
C-1-C-2 eclipses
the bond
C-3-C-4

$\chi_3(\text{C}-2-\text{C}-3-\text{C}-4-\text{C}-5) = 0$ when the bond
C-2-C-3 eclipses
the bond
C-4-C-5

$\chi_4(\text{C}-3-\text{C}-4-\text{C}-5-\text{C}-6) = 0$ when the bond
C-3-C-4 eclipses
the bond
C-5-C-6

$\chi_6(\text{C}-4-\text{C}-5-\text{C}-6-\text{O}-6) = 0$ when the bond
C-4-C-5 eclipses
the bond
C-6-O-6

Clockwise rotations were considered positive.

The potential energy of the molecule was computed considering the non-bonded, electrostatic and torsional

contributions. The form of the functions and constants used are the same as reported by Momany *et al.*¹⁰. The fractional (σ) charges on the atoms of the molecule were calculated by the molecular orbital method¹¹. The charge distribution in the alditol is shown in Fig. 2.

As the dihedral angles χ_i can theoretically have any value from 0° to 360° , an infinite number of conformations becomes possible for the molecule. It is time consuming to compute energies for all possible conformations in order to arrive at the most probable ones. However, from steric and other restrictions, it is known that χ_i generally favours values around 60° , 180° and -60° . Such a restriction on χ_i leads to 3^5 (or 243) possible conformations. These 243 permutations of the five dihedral angles (χ_i) were used as starting conformations and the energy was minimized following the minimization procedure due to Fletcher-Powell¹² and Davidon¹³. The same procedure has been followed for all the alditols, viz., D-glucitol, D-mannitol and galactitol.

(b) Static Accessibility Calculations :

The method of Lee and Richards¹⁴ was used to estimate the solvent (water) accessibilities, 'S' for different conformations of the three alditols. The procedure described earlier¹⁵ for cyclic sugars has been followed to calculate the 'S' values. Higher solvent accessibility for a conformation indicates only a high probability of association with the solvent molecules and does not imply formation of the best hydrogen

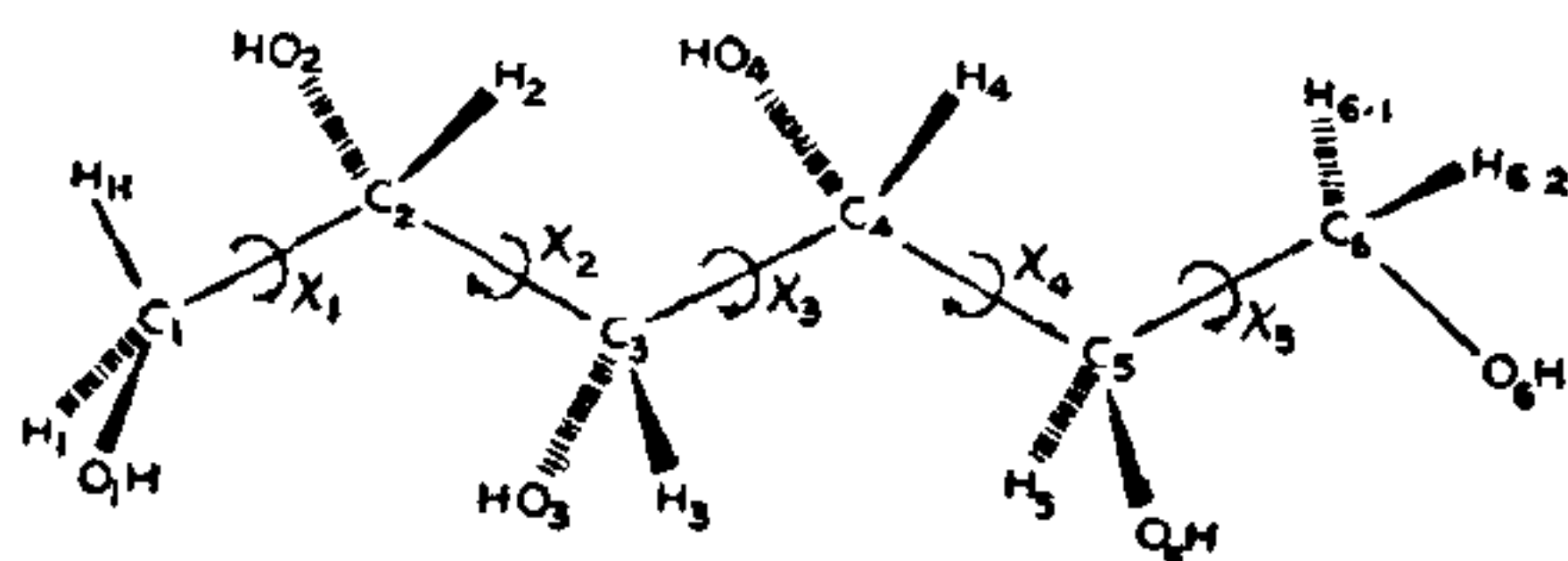


FIG. 1. Schematic representation of an acyclic alditol.

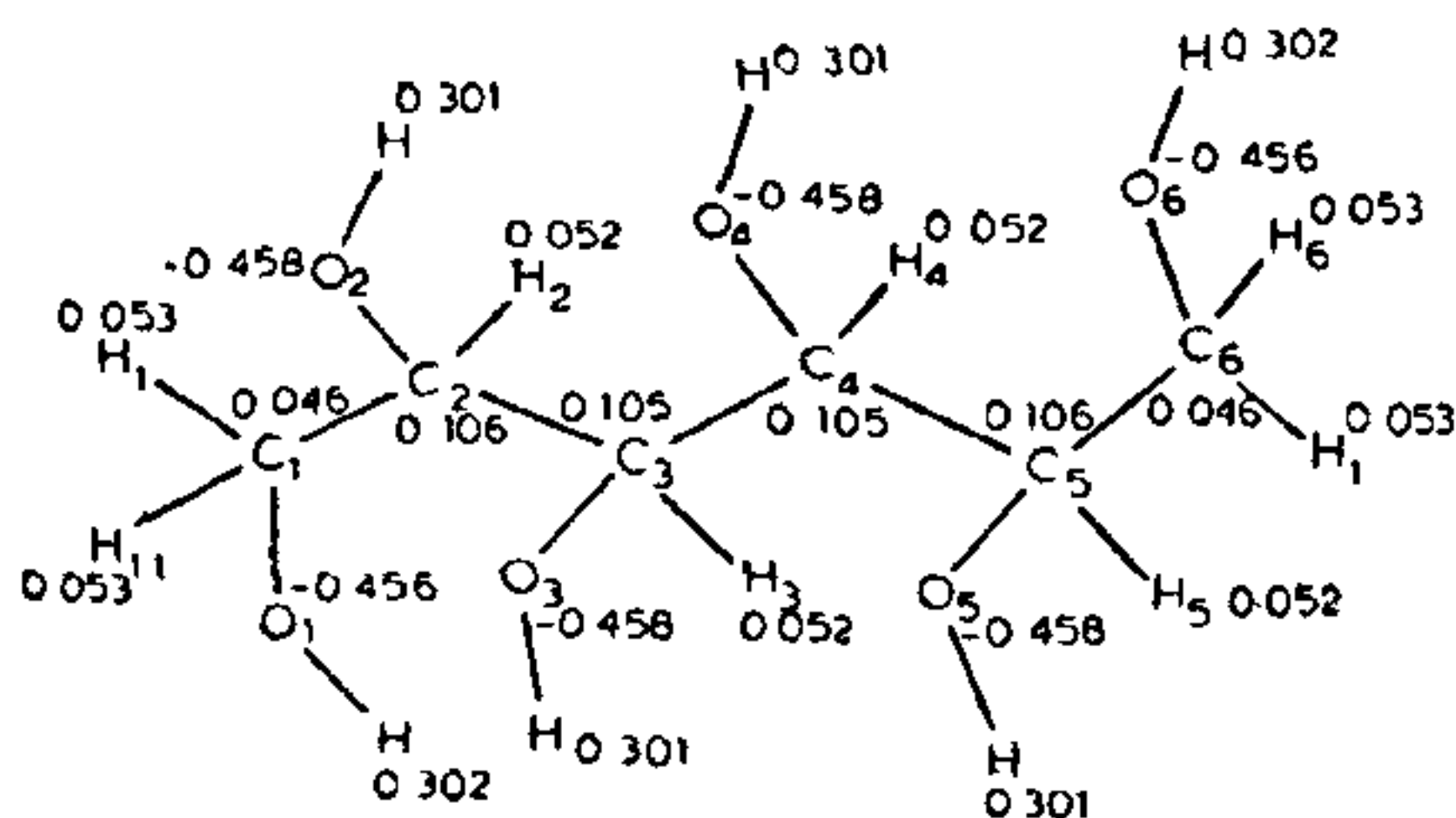


FIG. 2. Charge distribution in an acyclic alditol (in fractions of an electronic charge).

bond, as this requires proper mutual orientations of the polar groups and the solvent molecules.

In the present study, the solvent accessibilities for the polar groups (*viz.*, hydroxyls) of each of the three alditols (*viz.*, D-glucitol, D-mannitol and galactitol) for different minimum energy conformations have been calculated and they are listed in Tables I, II and III.

RESULTS AND DISCUSSION

Tables I, II and III show the lists of calculated low energy conformations within 2-3 Kcal mole⁻¹ from the global minimum energy for D-glucitol, D-mannitol and galactitol. The conformational angles of these molecules in crystalline state, determined by X-ray diffraction technique⁴ are also listed in their respective tables.

It is interesting to note from Tables I, II and III that (i) in all the three alditols studied the dihedral angles χ_3 and χ_4 mostly favour values around 180° and (ii) the dihedral angle χ_2 favours either 180° or $\pm 60^\circ$. Although the dihedral angles χ_1 and χ_5 on either end of the molecule favour all the three staggered orientations, these angles do not affect the general shape of the molecule. Hence the conformation of these molecules are usually classified as straight or bent based on the values of the dihedral angle χ_2 . That is, in the straight chain conformation χ_2 , χ_3 and χ_4 assume values around 180° whereas in the bent chain χ_3 and χ_4 have values around 180° and χ_2 around $\pm 60^\circ$. Or, χ_2 and χ_3 may have values around 180° and χ_4 may have a value around $\pm 60^\circ$ in the bent conformations.

Tables I, II and III show that the potential energy of the molecule favours the straight-chain conformation ($\chi_2 \approx \chi_3 \approx \chi_4 \approx 180^\circ$) for all the three alditols. It is interesting to note that both D-mannitol and galactitol do favour straight-chain conformations in the solid state. The solid state conformation of D-mannitol has the lowest energy whereas those of galactitol and D-glucitol have about 1 Kcal mole⁻¹ and 1.5 Kcal mole⁻¹ higher energy respectively than their global minimum energy conformations. This suggests that the lattice energy does play a significant role in stabilizing the solid state conformations of galactitol and glucitol.

In the case of D-mannitol and galactitol the straight-chain conformations which are favoured by intramolecular interactions have high solvent accessibilities (*vide* Tables II, III). Though the experimental studies on D-mannitol and galactitol (in solution) are not available, the NMR studies on their acetylated derivatives^{8,9} suggest straight-chain conformations. On the other hand, in the case of D-glucitol the intra-

TABLE I
Low Energy Conformations of D-glucitol

No.	χ_1	χ_2	χ_3	χ_4	χ_5	Relative energy Kcal mole ⁻¹	Solvent accessibility S
1	2	3	4	5	6	7	8
1	63	186	175	180	60	-2.18	170.25
2	63	186	174	179	179	-2.02	173.49
3	178	185	174	180	60	-1.56	170.02
4	63	186	176	183	-68	-1.54	163.68
5	177	185	174	179	179	-1.40	173.31
6	-50	-61	185	182	60 ^a	-1.26	174.18
7	-50	-61	186	183	180 ^a	-1.04	177.03
8	189	-65	184	182	60 ^a	-0.95	173.22
9	-61	190	177	180	60	-0.88	170.67
10	177	186	175	183	-68	-0.87	163.95
11	-50	-60	187	186	-66 ^a	-0.84	168.27
12	167	61	164	178	59 ^a	-0.74	163.38
13	169	60	163	178	179 ^a	-0.68	168.67
14	-62	190	176	180	179	-0.65	175.02
15	188	-65	184	182	180 ^a	-0.65	176.53
	186.3	-51.1	181.7	179.9	186.4 ⁺
16	188	-64	186	186	-66 ^a	-0.38	167.45
17	-61	191	178	183	-68	-0.14	166.39

^a Bent conformation.

⁺ Conformational angles of D-glucitol in solid state⁴.

TABLE II
Low Energy Conformations of D-mannitol

No.	χ_1	χ_2	χ_3	χ_4	χ_5	Relative energy Kcal mole ⁻¹	Solvent accessibility S
1	60	179	179	181	60	-2.86	175.36
	56.2	184.7	175.8	180.2	55.5 ⁺
2	60	180	179	182	180	-2.81	179.89
3	180	179	179	181	180	-2.74	179.18
4	-67	182	180	181	60	-2.54	174.39
5	-67	182	180	181	180	-2.44	176.72
6	-67	183	181	184	-67	-2.05	167.87
7	-49	-57	183	182	60 ^a	-0.49	171.70
8	-49	-57	183	182	180 ^a	-0.33	173.98
9	175	74	166	177	58 ^a	-0.17	161.45
10	171	63	163	177	178 ^a	-0.05	165.78

^a Bent conformation.

⁺ Conformational angles of D-mannitol in solid state⁴.

molecular interactions favour straight-chain conformations and the solvent favours bent conformations. Since the energy difference between the most favoured straight and bent conformations is small (~0.9 Kcal

TABLE III
Low Energy Conformations of galactitol

No.	χ_1	χ_2	χ_3	χ_4	χ_5	Relative energy Kcal mole ⁻¹	Solvent accessibility S
1	2	3	4	5	6	7	8
1	62	181	179	178	-62	-3.33	177.35
2	62	181	179	179	183	-2.85	176.08
3	177	181	179	178	-62	-2.82	178.01
4	177	181	179	179	183	-2.39	176.87
	172	-175.1	170.6	172.5	176.4+
5	-64	185	180	178	-61	-2.11	179.21
6	61	181	178	174	65	-1.99	163.45
7	-64	185	180	179	183	-1.67	178.81
8	177	181	179	174	65	-1.50	164.36
9	-61	185	179	174	65	-0.86	166.21
10	167	55	175	177	-62 ^a	-0.75	172.37
11	52	51	172	177	-62 ^a	-0.47	171.51
12	62	183	184	-55	194 ^a	-0.32	170.42
13	184	-85	185	179	-62 ^a	-0.21	169.08
14	58	177	163	70	171 ^a	-0.17	174.58
15	167	55	175	178	184 ^a	-0.12	170.90
16	172	48	-185	169	-64 ^a	-0.08	171.80

^a Bent conformation.

* Conformational angles of galactitol in solid state⁴.

Note: Some of the conformations listed in this table are related by a mirror symmetry; for example, Nos. 2 and 3, 5 and 6, 7 and 8. Their energies are seen to differ very little, within about 0.2 Kcal mole⁻¹ which is within the limits of error involved in the method of calculation.

mole⁻¹), the present studies predict that D-glucitol substantially occurs in bent conformations in solution, in agreement with the NMR studies⁹.

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