THEORETICAL STUDIES ON THE CONFORMATION OF ALDOHEXOPYRANOSES*

V. S. R. RAO, K. S. VIJAYALAKSHMI, AND P. R. SUNDARARAJAN
Centre of Advanced Study in Biophysics, University of Madras, Madras-25 (India)

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ABSTRACT

The σ-charges on various atoms in aldohexopyranoses have been computed by using the MO-LCAO method of Del Re. The potential energy of sixteen aldohexopyranoses in the *C1* (D) and *1C* (D) conformations have also been calculated. Minimization of the energies of these conformations have been studied by suitably tilting the axial substituents. Considerable release of strain is achieved when tilts of about 4.5° and 3° are given for the axial CH_2OH and the axial OH groups, respectively, involved in the Hassel–Ottar effect. The calculated energy-values not only explain the favored conformations assigned from n.m.r. studies but are also found to be in fairly good agreement with the energy values assigned by Angyal.

INTRODUCTION

The conformation of aldohexopyranoses in solution has been discussed theoretically by many workers[1–5] by considering various factors such as the Hassel–Ottar effect[1], the $\Delta 2$ effect[2,3], the anomeric effect[4–9], and so on. Angyal[4,5] assigned interaction energies for various aldohexopyranoses in aqueous solutions from experimental data obtained from the equilibria of cyclitols with their borate complexes and from equilibria of sugars. Very few attempts[10,11] have been made to determine these energies theoretically, but the results obtained from those theoretical calculations made have been found to be at variance with experiment, mainly because only ideal models were considered in the calculations. Hence, an attempt has been made to compute the potential energy of these molecules for ideal and distorted forms by taking into account the nonbonded and electrostatic interactions, to afford a better understanding of the conformations of the simple sugars in solution.

THEORETICAL TREATMENT

A. Expression for energy. — The nonbonded interaction-energy between a pair of atoms can be expressed as[12]:

$$V_{nb}(i,j) = 3.5\,(8{,}600 \exp(-13Z) - 0.04/Z^6) \qquad (1)$$

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where $Z = r_{ij}/r_0$, r_{ij} being the distance between the interacting atoms i and j and r_0 is the equilibrium distance between them. The values of r_0 used in these calculations are the same as those described earlier[13].

The electrostatic interactions can be incorporated by adding pair-wise, coulombic contributions to the potential energy. The electrostatic term can be expressed as:

$$V_{es}(i,j) = \frac{332\, Q_i Q_j}{\varepsilon' r_{i,j}} \tag{2}$$

where Q_i and Q_j are the charges (expressed as fractions of the charge on an electron) of a pair of interacting atoms i and j, r_{ij} is the distance between them, ε' is the effective dielectric constant of the medium, and 332 is the conversion factor to express the result in kcal.mole^{-1}. Hence the total energy is expressed as:

$$V = \sum_{i,j} V_{nb}(i,j) + \sum_{i,j} V_{es}(i,j) \tag{3}$$

The torsional potential was not treated as a separate function, for reasons stated earlier[11].

B. Calculation of σ-charges. — Since the sugar molecules are fully saturated σ-systems, the MO-LCAO (molecular orbital–linear combination of atomic orbitals) method of Del Re[14] has been followed to calculate the σ-charges.

C. Bond angle strain. — Under certain circumstances it is likely that an axial substituent will be forced out to approach a more equatorial orientation in order to free itself of nonbonded interactions, although at the expense of increased angle strains in the ring itself. The energy associated with distorting a single bond-angle θ from the tetrahedral angle (109.5°) may be computed by using the expression:

$$V_\theta = K_\theta(\theta - 109.5°)^2 \tag{4}$$

K_θ (in kcal.mole^{-1}.rad^{-2}) is taken as 40 for H–C–C; 58 for C–C–C, and 50 for O–C–O angles[15,16]. In the absence of any available data, we have used a value of 58 for K_θ for the O–C–C angle (the same as that of the C–C–C angle) and about 40 for H–C–O (the same as that for the H–C–C bond angle). The deviations in the O–C–C and H–C–O bond angles are found to be much less than 4.5° in most of the cases in the present study. Hence, the energy involved in bond-angle strain is small, and a variation of as much as 20% in the K_θ values for the angles O–C–C and H–C–O may not affect the results significantly. The change of one angle at a tetrahedral carbon atom is accompanied by changes in other angles, whenever an axial substituent is tilted. Accordingly, the other angles at the tetrahedral carbon atom are also adjusted, such that the total energy of angle-strain in the five angles involved (since the ring angle θ is not altered), is at a minimum. These strain energies were also computed separately and added to the total energy.

D. Choice of the value for the effective dielectric constant. — Most of the experimental data on free sugars available in the literature were obtained from studies in aqueous solutions. To compare the theoretical results with the experimental values, proper account must be taken of solvent effects.

It is generally accepted that the value of the effective dielectric constant to be used in expression *2* should be much less than the actual dielectric constant of the medium[17–20]. In the treatment of unperturbed dimensions of polypeptides, Flory has used a value of $\varepsilon' = 3.5$. Scheraga preferred a value of 4.0. Each of these were adjusted to obtain better agreement with experimental observations. It is also noted that these small differences in the dielectric constant do not affect the results, since we are interested in the relative energies of various possible conformations. In the present calculation a value of 3.5 is used for ε'.

E. Energy calculations. — The atoms in the ring (Fig. 1), and the atoms directly connected to the ring of these molecules, were fixed in the *C1* (D) and *1C* (D) conformations, with the same bond lengths and angles used earlier[10].

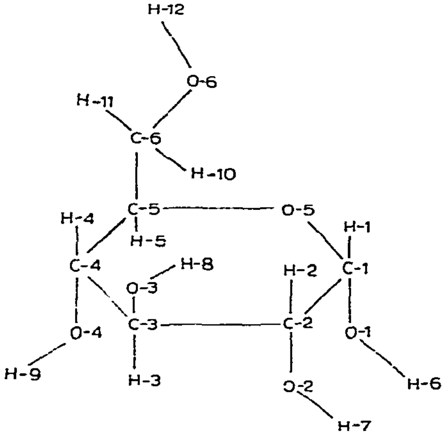

Fig. 1. Schematic diagram of an aldohexopyranose.

To introduce distortion in the molecule, the axial CH_2OH or OH group was tilted, by following the method of Hendrickson[21]. The CH_2OH group is tilted by varying symmetrically the angles C-6–C-5–O-5(ϕ) and C-6–C-5–C-4(ϕ) (Fig. 2). This operation changes the C-6–C-5–H-5 bond angle considerably, and in turn increases the strain energy. Hence, to decrease the bond-angle strain-energy, the angular distortion is distributed evenly over the three angles (ψ), namely, C-6–C-5–H-5, C-4–C-5–H-5, and O-5–C-5–H-5. These angles were then adjusted for minimum bond-angle strain by using the expression:

$$\tan\psi = \frac{2(\cos\phi - 1)}{2(\cos\theta + 1) - 4\cos^2\phi} \tag{5}$$

After tilting the CH_2OH to the required angle ϕ, the H-5 atom was re-fixed with the corresponding value of ψ. Hence, the angle strain of the CH_2OH group is given by $2V(\phi)+3V(\psi)$. The energy of angle strain was thus minimized over the five angles shown in Fig. 2, the ring angle θ being unaltered. Thus, H-5 was re-fixed at the position of minimum energy by using Eqn. 5 for the corresponding tilts of the CH_2OH group. Whenever the axial hydroxyl groups were tilted, the same procedure was also followed to re-fix the corresponding hydrogen atoms of the ring.

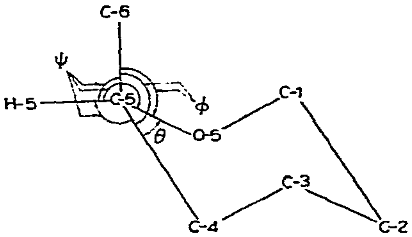

Fig. 2. Schematic diagram showing the tilted orientation of the CH_2OH group, in the *1C* (D) conformation.

The remaining atoms (O-6 and H-6 to H-12) in the pyranose ring were fixed at the positions of minimum energy by using the iterative process given below. The O–H bonds, O-1–H-6 to O-6–H-12, were initially fixed so as to be *cis* to each preceding bond in the ring. For example O-1–H-6 was initially fixed *cis* to the C-1–O-5 bond and then rotated from its *cis* position about the C-1–O-1 bond from 0° to 360° at intervals of 5°. At each position the potential energy of interaction with all the rest of the atoms was computed by using Eqn. 3, and a search was made for the position of the minimum energy. After thus fixing O-1–H-6 in its minimum-energy position, the bond O-2–H-7 was rotated about the C-2–O-2 bond at intervals of 5°, and the interaction of H-7 with the rest of the atoms (including H-6 in its position of minimum energy) was computed. This process was repeated to fix the remaining atoms. These coordinates of the atoms were fed in the computer to perform a series of iterations. For the nth hydrogen atom in the ith cycle, the interaction of $H_{j,i}(j = 6$ to $n-1)$, $H_{k,i-1}$ $(k = n+1$ to $12)$, and O-6 (besides other fixed atoms) were considered[11]. Convergence was observed in all of these cases within five cycles. Having thus obtained the positions of minimum energy for the different side groups, the nonbonded and electrostatic interaction energies were computed. To these energies the total bond-angle strain-energies were added, wherever necessary. Since it is known from n.m.r. studies[22-32] of free sugars in solution that the pyranose ring exists in a chair conformation, the relative stability of the *C1* (D) and *1C* (D) conformations were alone considered here.

RESULTS AND DISCUSSION

The σ-charges calculated by using the method of Del Re *et al.*[14], are given in Table I. Similar calculations on pentoses have been reported by Sundararajan[33] and by Zhdanov *et al.*[34]. Since hexoses and pentoses differ only in the nature of the C-5 substituent (Fig. 1) the values of the fractional charges assigned for various

TABLE I

CHARGES ON THE ATOMS OF THE ALDOHEXOPYRANOSE SUGARS (IN FRACTIONS OF AN ELECTRONIC CHARGE) CALCULATED BY THE MO-LCAO METHOD[14]

Atom name[a]	*Fractional charge*	*Atom name*[a]	*Fractional charge*
H-6	0.303	C-5	0.086
H-7	0.301	O-5	−0.262
H-8	0.301	O-1	−0.446
H-9	0.301	O-2	−0.458
H-10	0.053	O-3	−0.458
H-11	0.053	O-4	−0.458
O-6	−0.457	C-6	0.053
H-12	0.302	H-1	0.061
C-1	0.189	H-2	0.052
C-2	0.120	H-3	0.052
C-3	0.105	H-4	0.052
C-4	0.105	H-5	0.051

[a]Numbered as given in Fig. 1.

atoms of similar environment (C-1 to C-4, O-1 to O-5, H-1 to H-4, and H-6 to H-9) agree well with those assigned by Sundararajan on pentoses[33], but differ slightly from those assigned by Zhdanov *et al.*[34]. On the other hand, the values assigned by Zhdanov *et al.*, on pentoses agree well with those assigned by Sundararajan if the original method described by Del Re in the earlier paper[35] is followed, but differ slightly from the values assigned by following the slightly modified procedure of Del Re *et al.*[14].

The results of energy calculations based on ideal models for aldohexoses are given in Columns 2 and 3 of Table II. The excess of energy of a particular conformation above that of β-D-glucopyranose in the *C1* conformation is given. The energy values assigned by Angyal[4,5] also are shown in Columns 6 and 7 of Table II. These are also the excess values above that of β-D-glucose in the *C1* conformation. The favored conformations, assigned from n.m.r. studies, are also shown in Table II (Column 8). It can be seen from Table II that, except in the case of α-D-altropyranose and α-D-idopyranose, the favored conformations assigned from n.m.r. studies have the lower energy (Columns 2 and 3 of Table II). From n.m.r. studies, a *C1*$\rightleftharpoons$*1C* equilibrium appears to exist with α-D-altropyranose and α-D-idopyranose. In contrast (and in disagreement with experimental results), the calculations would suggest large energy differences (of the order 3–5 kcal.mole^{-1}) that would rule out the possibility of the *1C* (D) conformation for these molecules, at least based on the ideal models. The calculated energy values, based on ideal models, seem to agree with the values assigned by Angyal only in the case of the *C1* (D) conformations, considering the approximations involved in both procedures for assigning the energy values. While comparing the calculated energy values with those assigned by Angyal, it should be kept in mind that the calculated energies do not include the entropy con-

TABLE II

CALCULATED ENERGIES OF D-ALDOHEXOPYRANOSES[a]

Aldose	*Calculated energy values (kcal.mole^{-1})*						*Favored conformation from n.m.r. spectroscopy (Refs. 5, 22, and 29)*
	Ideal		*Distorted*		*Angyal's*[4,5] *values*		
	C1	1C	C1	1C	C1	1C	
α-D-Allose	2.13	9.75	1.80	3.90	1.85	3.30	*C1*
β-D-Allose	0.47	11.32	0.47	3.85	0.90	4.0	*C1*
α-D-Altrose	1.63	6.44	1.28	2.18	1.60	1.80	*C1, 1C*
β-D-Altrose	0.81	10.88	0.79	3.07	1.30	3.30	*C1*
α-D-Galactose	0.86	10.35	0.78	2.76	0.80	4.25	*C1*
β-D-Galactose	0.48	21.44	0.47	4.26	0.45	5.7	*C1*
α-D-Glucose	0.53	11.77	0.44	3.77	0.35	4.5	*C1*
β-D-Glucose	0.0	21.99	0.0	5.16	0.0	5.95	*C1*
α-D-Gulose	1.80	6.52	1.49	2.75	1.95	2.7	
β-D-Gulose	0.38	10.59	0.35	3.37	1.00	3.4	*C1*
α-D-Idose	2.57	5.55	1.57	1.87	2.30	1.80	*C1, 1C*
β-D-Idose	1.78	10.12	1.40	2.94	2.00	3.30	
α-D-Mannose	0.90	10.12	0.81	2.67	0.45	3.50	*C1*
β-D-Mannose	0.93	20.66	0.93	4.48	0.90	5.60	*C1*
α-D-Talose	1.83	10.88	1.57	3.35	1.50	3.85	*C1*
β-D-Talose	2.38	22.32	2.18	5.60	1.95	5.95	

[a] The excess of energy of a particular conformation in each set, over that of β-D-glucopyranose in the *C1* (D) conformation in that set, is given here.

tribution, that is, the calculated values yield potential energies (enthalpies) whereas the experimental values are free energies. Nevertheless, the calculated energy values for the *1C* (D) conformations remain very high compared with the values assigned by Angyal. This can be ascribed to the fact that, in ideal models, the axially oriented CH_2OH group in the *1C* conformation is placed in close proximity to the other axially oriented atoms and groups on the same side of the ring. Such close proximity of atoms gives rise to large interaction energies. To relieve such unfavorable interactions the bulky, axially oriented CH_2OH group will, in fact, be forced out into a more equatorial orientation. Such distortions of the *1C* (D) conformation at C-5 can be treated in the model by tilting the axial CH_2OH group. Axial OH groups were also tilted wherever necessary, in both the *C1* (D) and *1C* (D) conformations, to relieve the strain. The calculations were performed by varying the angles of tilt for the axially oriented groups in each of the conformations, in such a way that the total energy passes through a minimum. In order to reduce the computer time required for calculating the *1C* (D) conformations, the calculations were first performed for α-D-idopyranose, which has only the bulky (CH_2OH) substituent axial. When the axial CH_2OH group is tilted somewhat (the side groups were re-fixed at the minimum-energy positions by following the iterative process described earlier whenever angles of tilt were given), a considerably release of strain is achieved. The total energy passes through a minimum at a tilt angle of 4.5°, corresponding to a bond angle of 114° for

TABLE III

BOND ANGLES AT THE RING ATOM HAVING AXIAL SUBSTITUENT IN THE MINIMUM-ENERGY CONFORMATION[a]

Aldopyranose	*Bond-angle deviations from ideal values in the minimum-energy conformation (in degrees)*			
	C1		1C	
	Bond angle	*Value*	*Bond angle*	*Value*
α-D-Allose	O-5–C-1–O-1 C-2–C-1–O-1	111	O-5–C-5–C-6 C-4–C-5–C-6	114
	C-2–C-3–O-3 C-4–C-3–O-3	111	C-1–C-2–O-2 C-3–C-2–O-2	112
			C-3–C-4–O-4 C-5–C-4–O-4	112
β-D-Allose			O-5–C-5–C-6 C-4–C-5–C-6	114
			O-5–C-1–O-1 C-2–C-1–O-1	112
			C-1–C-2–O-2 C-3–C-2–O-2	112
			C-3–C-4–O-4 C-5–C-4–O-4	112
α-D-Altrose	O-5–C-1–O-1 C-2–C-1–O-1	111	O-5–C-5–C-6 C-4–C-5–C-6	114
	C-2–C-3–O-3 C-4–C-3–O-3	111		
β-D-Altrose	C-1–C-2–O-2 C-3–C-2–O-2	111	O-5–C-5–C-6 C-4–C-5–C-6	114
	C-2–C-3–O-3 C-4–C-3–O-3	111	O-5–C-1–O-1 C-2–C-1–O-1	112
α-D-Galactose	O-5–C-1–O-1 C-2–C-1–O-1	111	O-5–C-5–C-6 C-4–C-5–C-6	114
	C-3–C-4–O-4 C-5–C-4–O-4	111	C-2–C-3–O-3 C-4–C-3–O-3	112
β-D-Galactose	C-3–C-4–O-4 C-5–C-4–O-4	111	O-5–C-5–C-6 C-4–C-5–C-6	114
			O-5–C-1–O-1 C-2–C-1–O-1	113
			C-4–C-3–O-3 C-2–C-3–O-3	113
α-D-Glucose	O-5–C-1–O-1 C-2–C-1–O-1	111	O-5–C-5–C-6 C-4–C-5–C-6	114
			C-1–C-2–O-2 C-3–C-2–O-2	112
			C-2–C-3–O-3 C-4–C-3–O-3	112
			C-3–C-4–O-4 C-5–C-4–O-4	112

TABLE III (*continued*)

Aldopyranose	*Bond-angle deviations from ideal values in the minimum-energy conformation (in degrees)*			
	C1		1C	
	Bond angle	*Values*	*Bond angle*	*Value*
β-D-Glucose			O-5–C-5–C-6 C-4–C-5–C-6	114
			O-5–C-1–O-1 C-2–C-1–O-1	112
			C-1–C-2–O-2 C-3–C-2–O-2	112
			C-2–C-3–O-3 C-4–C-3–O-3	112
			C-3–C-4–O-4 C-5–C-4–O-4	112
α-D-Gulose	O-5–C-1–O-1 C-2–C-1–O-1	111	O-5–C-5–C-6 C-4–C-5–C-6	114
	C-2–C-3–O-3 C-4–C-3–O-3	111		
β-D-Gulose	C-2–C-3–O-3 C-4–C-3–O-3	111	O-5–C-5–C-6 C-4–C-5–C-6	114
	C-3–C-4–O-4 C-5–C-4–O-4	111	O-5–C-1–O-1 C-2–C-1–O-1	111
α-D-Idose	O-5–C-1–O-1 C-2–C-1–O-1	111	O-5–C-5–C-6 C-4–C-5–C-6	114
	C-1–C-2–O-2 C-3–C-2–O-2	111		
	C-2–C-3–O-3 C-4–C-3–O-3	111		
	C-3–C-4–O-4 C-5–C-4–O-4	111		
β-D-Idose	C-1–C-2–O-2 C-3–C-2–O-2	111	O-5–C-5–C-6 C-4–C-5–C-6	114
	C-2–C-3–O-3 C-4–C-3–O-3	111	O-5–C-1–O-1 C-2–C-1–O-1	112
	C-3–C-4–O-4 C-5–C-4–O-4	111		
α-D-Mannose	O-5–C-1–O-1 C-2–C-1–O-1	111	O-5–C-5–C-6 C-4–C-5–C-6	114
	C-1–C-2–O-2 C-3–C-2–O-2	111	C-2–C-3–O-3 C-4–C-3–O-3	112
β-D-Mannose			O-5–C-5–C-6 C-4–C-5–C-6	114
			O-5–C-1–O-1 C-2–C-1–O-1	113
			C-2–C-3–O-3 C-4–C-3–O-3	113

TABLE III (*continued*)

Aldopyranose	*Bond-angle deviations from ideal values in the minimum-energy conformation (in degrees)*			
	C1		*1C*	
	Bond angle	*Value*	*Bond angle*	*Value*
α-D-Talose	C-1–C-2–O-2 C-3–C-2–O-2	112	O-5–C-5–C-6 C-4–C-5–C-6	114
	C-3–C-4–O-4 C-5–C-4–O-4	112	C-2–C-3–O-3 C-4–C-3–O-3	112
β-D-Talose	C-1–C-2–O-2 C-3–C-2–O-2	111	O-5–C-5–C-6 C-4–C-5–C-6	114
	C-3–C-4–O-4 C-5–C-4–O-4	111	O-5–C-1–O-1 C-2–C-1–O-1	113
			C-2–C-3–O-3 C-4–C-3–O-3	113

[a] When the axial substituents are tilted, the hydrogen atoms attached at these ring-carbon atoms were re-fixed by using the expression (*5*) to minimize the total energy of angle strain in the five angles involved. These bond angles are not shown in the Table.

the angles C-6–C-5–C-4 and C-6–C-5–O-5. For the other molecules in the *1C* (D) conformation, the axial CH_2OH group was fixed by using this value of 114° for the above bond angles, and the energy calculations were performed by varying the tilt angles at the other axially oriented OH groups. In this way, a conformation of over-all minimum energy was found for the *1C* (D) forms. The energies of these minimum-energy conformations, so obtained, are shown in Columns 4 and 5 of Table II. The angles that deviate from ideal values in the minimum-energy conformations are shown in Table III. It is seen from Table III that tilting the axial CH_2OH group through about 4.5° and the axial OH group (when it is placed on the same side of axially oriented CH_2OH group) through about 3° releases considerable strain-energy. Such deviations from the tetrahedral angle in overcrowed molecules are quite well established in the solid state[36–38]. Table III also shows that in most of the *C1* (D) conformations, the axial hydroxyl groups have to be tilted through about 1.5°. Deviations of this magnitude from tetrahedral angles have also been reported in the angle O-1–C-1–O-5 when O-1 is axial in the solid state[39].

Table II shows that, in all examples, the interaction energies in the *1C* (D) conformation are decreased considerably after giving the appropriate tilts to the axial groups. In few cases, for those *C1* (D) conformations where two *syn*-diaxial OH groups are present, the energy is also decreased to a small extent by introducing distortion.

It is seen from Columns 4 and 5 of Table II that the favored conformations assigned from n.m.r. studies have the lowest energy. For those molecules, conformationally homogeneous by n.m.r. studies, the calculated energy-difference of 1.7–4.0

kcal.mole^{-1} between the *C1* (D) and *1C* (D) forms also indicates that these molecules exist preponderantly in the *C1* (D) conformation. The low values of the calculated energy-differences between the *C1* and *1C* conformations (about 0.3 and 0.9 kcal.mole^{-1}) obtained for α-D-idopyranose and α-D-altropyranose, respectively, indicate the existence of substantial proportions of both chair forms in equilibrium, in agreement with the n.m.r. results.

Interestingly (Table II), the calculated energy values, after introducing the distortions, agree fairly well with the values assigned by Angyal, considering the uncertainty in the energy parameters and also the errors arising from omision of entropy effects. It should also be kept in mind that the calculated values correspond to conformations of minimum energy, and the experimental values to the average conformations in solution. Due to the possible rotations of the hydroxyl groups about the corresponding C–O bonds, the hydroxyl hydrogen atom may take various positions in solution, but the favored conformation is the one having the minimum energy. Any change in the orientation of one of the O–H bonds may affect the orientation of others such that the molecule adopts those conformations (differing in the orientations of O–H bonds) whose energies are not much different from the minimum-energy conformation. In fact, after two iterations of the energy-minimization procedure we observed (when all of the O–H bonds have become staggered) that even a large change in the orientation of one of the O–H bonds (shifting from one staggered position to another) affected only the orientation of neighboring O–H bonds, keeping the total potential energy of the molecule in a particular chair-form nearly the same. Hence, the experimental energy values (for the averaged conformations differing in the orientation of O–H bonds) may not be much different from the theoretical values calculated for the minimum-energy conformation. Since the restrictions on the possible orientations of O–H bonds around C–O bonds, and the hydroxymethyl group around the C-5–C-6 bond, are about the same in all molecules, the entropy contribution due to different possible orientations of these groups might nearly cancel out, when we consider the excess energies. Whilst assigning energy values, Angyal[4,5] added to the interaction energies energy values for the anomeric effect of about 0.55 kcal.mole^{-1} or 1.0 kcal.mole^{-1}, depending upon the orientation of the hydroxyl group at C-2 atom, to afford agreement with the experimental results. It is seen from the results with the distorted forms (Table II) that the α, β difference for D-glucopyranose and D-galactopyranose in the *C1* (D) conformation indicate that the anomeric effect appears to be an automatic consequence of the calculations. On the other hand, considering the energy values of α- and β-D-mannopyranose (Column 4 of Table II), the α-D form has a lower energy by about 0.12 kcal.mole^{-1} than β-D-mannose; but the difference is small compared with the value of 0.45 kcal.mole^{-1} assigned by Angyal. This shows that the so-called $\Delta 2$ effect is not explicitly revealed in the present energy calculations. However, in view of the approximations involved in these calculations, an agreement better than this cannot be anticipated at this stage. Angyal[4] derived the energy values assigned for various interactions in sugars from the equilibria of cyclitols with their borate complexes. The agreement between the calculated values and those assigned by Angyal seems to indicate that the experimental observations in aqueous solution can be explained by taking into account both non-bonded and electrostatic interactions.

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