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THEORETICAL STUDIES ON THE CONFORMATION OF ALDOPYRANOSES

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Abstract—The potential energy of non-bonded interactions for sixteen aldohexopyranoses and eight aldopentopyranoses have been calculated using the Kitaigorodsky type functions. It has been shown that the C1 (chair) conformation has the lowest energy for all the aldohexoses and most aldopentoses. Only for α-D-arabinose and α-D-ribose does the 1C conformation have the lowest energy. The energy difference between C1 and 1C conformations of β-D-arabinose and α-D-lyxose is small and it is likely that these molecules exist in C1 ⇄ 1C equilibrium. The differences in the preferred conformations assigned by the earlier instability schemes and the present energy calculations are also discussed.

INTRODUCTION

THE study of pyranose ring conformation of aldoses was first undertaken by Hassel and Ottar[1] who suggested that the pyranose ring can exist in two possible conformations, C1 and 1C. In considering the relative stability of these conformations, it was assumed that the conformation placing both the $-CH_2OH$ group and a OH group in axial orientations on the same side of the ring is energetically unfavourable. (Hassel-Ottar effect).

Reeves[2] proposed six boat forms in addition to the two chair forms as possible ring conformations for the pyranose ring. It was pointed out, that, although the chair forms are generally of lower energy, in certain circumstances, the difference may be offset, when a boat conformation allows all bulky substituents to be equatorial. In fact, from optical rotation and other chemical studies it was suggested[3,4] that the non-reducing residue in maltose and all the residues in amylose exist in boat forms. However, the recent theoretical[5] and NMR results[6,7] ruled out the boat forms as possible ring forms for the glucose unit either in maltose or amylose. The X-ray crystal structure[8–10] and the NMR studies[11–16] on free sugars and their derivatives also indicate that the chair conformation is the most probable one. Reeves also supplemented the investigations of Hassel and Ottar by introducing different ratings for various factors causing instability in the ring conformation. Additive instability units of arbitrary value was assigned for the following features:

(i) An axial group other than hydrogen imparts an instability of one unit to the molecule.

(ii) An axial OH group at C_2 atom which is involved in the Δ2 effect described by Reeves[2] is assigned an instability rating of 2·5 units.

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(iii) An axial $-CH_2OH$ group on the same side of the ring as another bulky axial substituent imparts an additional instability of 0·5 units (Hassel-Ottar effect).

The conformations thus predicted based on the assigned instability units are found to be in agreement with the conformations deduced from complex-forming reactions of cuprammonium reagent with the sugar, except in a few cases like methyl β-D-mannopyranoside and methyl α-ö-gulopyranoside. In order to bring these in line with experimental results, Kelly[17] supplemented Reeves'[2] ideas by modifying the instability factor assigned to an axial $-CH_2OH$ group. An instability factor of 2 units is assigned to the axial $-CH_2OH$ group not involved in Hassel-Ottar effect and 2·5 units for the axial $-CH_2OH$ group with Hassel-Ottar effect.

The knowledge of pyranose ring conformation is important not only to understand its physical and chemical properties, but also in the study of polysaccharide conformation. Hence the present study is undertaken to find out the preferred conformations for hexoses and pentoses and also to examine the validity of the various instability factors proposed by different workers.

Potential energy calculations. The position of the atoms (Fig. 1) in the ring and the atoms bonded directly to the ring (C_1 to C_6, O_1 to O_5, H_1 to H_5) in a particular conformation were fixed taking the bond angles at a tetrahedrally bonded carbon atom to be 109·47°, the divalent oxygen angle to be 114° and the bond lengths C—C = 1·53Å, C—O = 1·42Å, C—H = 1·1Å and O—H = 1Å. This conformation was fixed in a cartesian coordinate system chosen with respect to an arbitrary origin in the molecule. The remaining atoms were fixed, using an additional parameter χ, the dihedral angle of rotation about the neighbouring single bond, corresponding to the minimum energy position.

This was done by an iterative process, similar to that described earlier.[5] However, a slightly different method was adopted to reduce the computer time. First, the position of H_6 corresponding to minimum energy was obtained by rotating the bond O_1—H_6 about the C_1—O_1 single bond at intervals of 30° and calculating the interaction energy of this atom with the rest of the atoms using the expression II described later. Then O_2—H_7 was rotated about the bond C_2—O_2 and the interaction energy of H_7 with the rest of the atoms including H_6 in its minimum position was determined. The same process was then repeated to fix the remaining atoms. A series of iterations were performed, until there was no change in the minimum positions from one cycle to the next. Let these temporary minimum positions be denoted by $H_{6,0}$, $H_{7,0}$ . . . . $H_{12,0}$, and the corresponding angles be denoted as ω_i $(i = 1,6)$. These coordinates were again fed into the computer to perform a second series of iterations, the angles of rotation being $(\omega - 30)°$ to $(\omega + 30)°$ at the intervals of 5°. In these cases also for a rotation of the nth hydrogen in the ith cycle, the interactions of $H_{j,i}$ from $J = 6$ to $n - 1$ and of $H_{k,i-1}$ $(K = n + 1$ to $12)$ were considered besides the other atoms.

The actual convergence was obtained in these cases, within four cycles. The same procedure was adopted to fix the atoms of the other molecules in the two conformations (C1 and 1C). (Fig. 2).

In the present study since we are interested only in the relative stability of C1 and 1C forms of aldopyranoses, the absolute energy of the molecule is not calculated. Only the non-bonded interaction (van der Waals type) energies are considered.

Generally various types of potential functions have been used by different workers to obtain the non-bonded interaction energy. Hendrickson[18] used the Buckingham type potential functions for calculating the non-bonded interactions energies of cyclohexane, namely

$$V(r_{ij}) = -\frac{a}{r_{ij}^6} + c\exp(-\mu r_{ij}) \qquad \text{I}$$

where $V(r_{ij})$ is the interaction energy between a pair of non-bonded atoms i and j at a distance r_{ij} and a and c are constants for the particular pairs of atoms. The first term can be evaluated from theory. If μ is known, the constant c can be obtained by making $\delta V/\delta r = 0$ at $r = r_0$, the equilibrium distance between the two atoms. This is usually taken to be $(r_1 + r_2)$ where r_1 and r_2 are the van der Waals radii of the interacting atoms.

However, as reported in the earlier paper, the Kitaigorodsky type of functions[19]

$$v(r_{ij}) = 3{\cdot}5\,(8{\cdot}6 \times 10^3 \times \exp(-13\,Z) - 0{\cdot}04/Z^6) \qquad \text{II}$$

(Here $Z = r_{ij}/r_0$ where r_0 is again the equilibrium distance between the interacting atoms) is found to be very satisfactory for carbohydrates. Hence, in the present calculations only the above type of functions is used to calculate the non-bonded interaction energy. The constants used in the above expression for different pairs of interacting atoms are the same as reported by the authors earlier.[5] In computing these energies only the distance between third and higher neighbours were considered, since the distance between second neighbours remains the same in both the conformations. The energy values, thus obtained, are shown in Tables 1 and 2.

DISCUSSION

From Table 1 it is clear that for the aldohexopyranoses, the C1 conformation has the lowest energy. The energetically favoured conformations proposed by various workers from different instability schemes are also shown in Table 1. The molecules β-D-allose, β-D-altrose, α- and β-D-galactose, α- and β-D-glucose, β-D-gulose, β-D-idose, α- and β-D-mannose, α- and β-D-talose which are involved in Hassel-Ottar effect in the 1C conformation may be divided into two distinct classes for stability considerations. Those having

(i) One axially oriented OH group (H-1)

(ii) two axially oriented OH groups (H-2)

placed on the same side of the ring in addition to the axially oriented $-CH_2OH$ group. It is seen from Table 1 that the energy difference between C1 and 1C forms for these molecules is 10 to 12 kcal/mole for case (i) and 25 to 28 kcal/mole for case (ii). These differences are so large that the possibility of these molecules existing in 1C conformation is completely ruled out. This is in agreement with the conclusion of Hassel and Ottar, that the conformation having both the $-CH_2OH$ group and a hydroxyl group in axial orientation on the same side of the ring is energetically unfavourable. It is noticed from Table 1 that for these molecules the preferred conformations proposed by Hassel and Ottar is of the lowest energy.

It is also interesting to note from the Table that the compounds whose α,β-anomers are not involved in Δ2 instability effect of Reeves, the β-anomer has the lower energy than the corresponding α-anomer in C1 conformation. This is in agreement with the conclusion of Reeves that the β anomer of these compounds have lower instability factors than the corresponding α anomer.

The instability factors, estimated for these molecules by taking the energy difference between α and β-D-glucose in C1 conformation as one unit are also shown in Table 1. (Only the excess energy of a particular molecule above that of β-D-glucose in C1 conformation is considered in estimating the instability factors).

These instability factors are in general agreement with that of Reeves except in cases where a Δ2 instability factor is involved. The Δ2 effect of Reeves is not seen in the present calculations. This might be due to omission of dipolar interactions, which might be significant in Δ2 condition.

C1 ⇄ 1C conformational equilibrium for α and β-D-altrose and α and β-D-talose and 1C conformation for α and β-D-idose have been assigned from the instability scheme of Kelly. Since α and β-D-talose, β-D-altrose and β-D-idose are involved in Hassel-Ottar effect in 1C conformation, the energy difference between C1 and 1C forms is very large for these molecules. Kelly has assigned an instability rating of 2·5 units for the axial-CH_2OH group involved in Hassel-Ottar effect. Taking the energy difference of about 0·8 kcal/mole for one instability unit, the non-bonded interaction energy expected due to Hassel-Ottar effect, according to Kelly is about 2·0 kcal/mole. This is very small compared to 10-12 kcal/mole obtained from the energy calculations. Hence, the disagreement in preferred conformations assigned

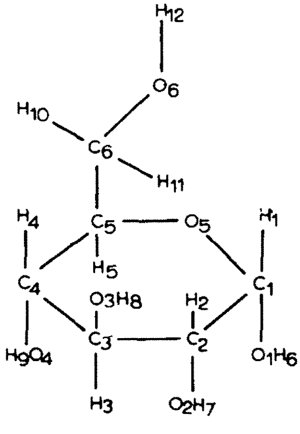
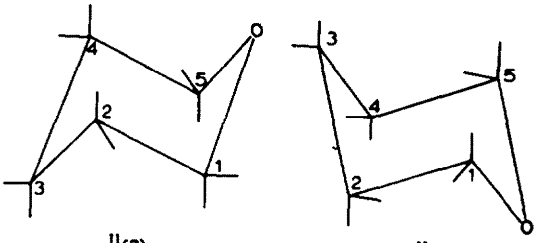


FIG. 1 Schematic representation of α-D-glucose.



II(a) II(b)

FIG. 2 II(a) and II(b) 1C conformations of Reeves.

for these molecules according the earlier instability schemes and the present energy calculations appears to be due to the low instability rating assigned by Kelly for the axial $-CH_2OH$ group involved in Hassel-Ottar effect.

The preferred conformation assigned for α-D-idose from energy calculations (C1) and from the rating scheme of Kelly (1C) are different. This may be due to the fact that the instability rating units of 2·0 assigned by Kelly for an axial $-CH_2OH$ group is an underestimation.

It is interesting in some cases to consider the boat forms having all the substituents in the equatorial orientation as possible ring conformation as suggested by Reeves. α-D-Mannose in B1 form has all the substituents in equatorial orientation; on the other hand, it has two OH groups in axial orientation in C1 form. Surprisingly, the non-bonded interaction energy for B1 form is about 4·8 kcal/mole higher than the C1 form. Hence it is very unlikely that this molecule exists in B1 form.

The instability factors, estimated for aldopentoses, by taking the energy difference between α and β-D-xylose, in C1 conformation as one unit are shown in Table 2. (Only the excess energy of a particular molecule above that of β-D-xylose in C1 form is considered in estimating the instability factors). These instability factors are in fairly good agreement with values assigned by Reeves except in cases where $\Delta 2$ instability factor is involved. The energetically favoured conformations proposed for the aldopentoses from the energy calculations are in agreement with the predictions of the earlier instability scheme; except in the cases of β-D-arabinose, β-D-lyxose, and α-D-ribose. The reason for the disagreement in these cases is mainly due to the $\Delta 2$

TABLE 1

Name of compound	Energy (kcal/mole)		Instability factors estimated from			Preferred conformation from		
	C1	1C	Energy calculation for C1*	*Reeves-Kelly scheme* C1	*Reeves-Kelly scheme* 1C	Energy calculation	Reeves-Kelly	Hassel-Ottar
α-D-allose	2·07	6·45	2	2	6·5 (Δ)	C1	C1	—
β-D-allose	0·81	12·85	0·5	1	5·5 (H-1)	C1	C1	C1
α-D-altrose	2·20	5·74	2·5	3	3·0	C1	C1 ⇄ 1C	—
β-D-altrose	0·99	12·10	1	4·5 (Δ)	4·5 (H-1)	C1	C1 ⇄ 1C	C1
α-D-galactose	1·51	12·91	1·5	2	7 (Δ, H-1)	C1	C1	C1
β-D-galactose	0·73	27·90	0·5	1	5·5 (H-2)	C1	C1	C1
α-D-glucose	1·13	12·89	1	1	8 (Δ, H-1)	C1	C1	C1
β-D-glucose	0·31	28·17	0	0	6·5 (H-2)	C1	C1	C1
α-D-gulose	2·35	6·1	2·5	3	5·5 (Δ)	C1	C1	—
β-D-gulose	1·08	12·39	1	2	4·5 (H-1)	C1	C1	C1
α-D-idose	2·94	5·74	3	4	2·0	C1	1C	—
β-D-idose	1·72	12·13	2	5·5 (Δ)	3·5 (H-1)	C1	1C	C1
α-D-mannose	1·40	12·16	1·5	2	4·5 (H-1)	C1	C1	C1
β-D-mannose	0·62	27·6	0·5	3·5 (Δ)	5·5 (H-2)	C1	C1	C1
α-D-talose	2·21	12·67	2·5	3	3·5 (H-1)	C1	C1 ⇄ 1C	C1
β-D-talose	1·44	27·6	1·5	4·5 (Δ)	4·5 (H-2)	C1	C1 ⇄ 1C	C1

* The values have been rounded off to the nearest 0·5

H-1: One OH group involved in Hassel-Ottar effect

H-2: Two OH groups involved in Hassel-Ottar effect

Δ: Conformation involved in $\Delta 2$ condition of Reeves.

TABLE 2

Name of compound	Energy calculated		Instability factor estimated from				Preferred conformation from		
	C1	1C	energy calculation**		Reeves scheme		Energy calculation	Reeves Scheme	NMR* Studies
	kcal/mole	kcal/mole	C1	1C	C1	1C			
α-D-arabinose	2·68	0·99	2·5	0·5	3	1	1C	1C	1C
β-D-arabinose	1·43	1·78	1	1·5	4·5 (Δ)	2	C1 ⇄ 1C	1C	1C
α-D-lyxose	1·74	1·43	1·5	1	2	2	C1 ⇄ 1C	C1 ⇄ 1C	C1 ⇄ 1C
β-D-lyxose	0·94	2·73	0·5	2·5	3·5 (Δ)	3	C1	C1 ⇄ 1C	C1
α-D-ribose	2·53	1·75	2·5	1·5	2	4·5 (Δ)	1C	C1	1C
β-D-ribose	1·25	2·52	1	2·5	1	3	C1	C1	C1 ⇄ 1C
α-D-xylose	1·50	2·11	1	2	1	5·5 (Δ)	C1	C1	C1
β-D-xylose	0·66	3·36	0	3·5	0	4	C1	C1	C1

Δ Conformation involved in Δ2 condition of Reeves

** The values have been rounded off to nearest 0·5

* From the Ref. 14

C1 ⇄ 1C Conformation equilibrium is assigned when the energy difference between those conformations is less than 0·4 kcal/mole.

effect of Reeves, which is not observed in the present calculations. The preferred conformations assigned from the NMR studies[14] are also shown in Table 2. It is clear from the table that there is a better agreement between the NMR studies and energy calculations.

In all these calculations, only ideal models are considered. It might be possible that in some of the cases the distorted chair form may have a lower energy than either of the ideal chair forms. Work in this direction is in progress.

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