MOLECULAR GEOMETRY OF RIBOFURANOSES OBTAINED FROM SEMI-EMPIRICAL MO CALCULATIONS*

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Received November 20th, 1981

Molecular geometry of ribofuranoses *I*– *VIII* has been optimized with respect to all degrees of freedom on the basis of CNDO/2 wave functions. The results obtained are confronted with previous results of partial optimizations.

Biologically fundamental molecules contain frequently ribose molecules bound by nucleosidic bonds exclusively in the corresponding furanose form, although the monosaccharide itself crystallizes in its pyranose form, and the pyranose forms predominate distinctly in its solutions, too[1]. In connection with theoretical studies of molecules of ribonucleosides and with respect to the mentioned non-availability of experimental data on molecular geometry of free ribofuranoses, it appears useful to carry out theoretical calculations of their complete molecular geometry. So far theoretical studies only dealt with optimization of some selected geometrical degrees of freedom with the use of the bicentric potential of the Lennard–Jones type[2–6] and with the use of the quantum-chemical procedures based on the EHT (ref.[7,8]) and PCILO energies[9]. In the present paper we have tried to apply a more perfect semi-empirical approach consisting in an assessment of position of the heavier atoms (C and O) based on X-ray diffraction results for selected nucleosides[10] and in subsequent optimization of positions of all C, O and H atoms with respect to all geometry degrees of freedom with the use of variable metric gradient optimization procedure[11] on the basis of CNDO/2 wave functions. The results are discussed with respect to possible application of this relatively simple optimization procedure to the intended theoretical studies of larger, biologically interresting molecules.

CALCULATIONS

The CNDO/2 wave function necessary for the gradient optimization[11] were obtained by means of standard programs, the used parameters being the same as those used in previous papers of this series. The used program DERIVAL carries out running analysis of the matrix of second

* Part XIX in the series On Calculations of Biologically Important Compounds; Part XVIII: This Journal, in press.

derivatives of energy with respect to coordinates. To verify that the found local minimum is not a saddle point, the calculation was continued after its convergence by carrying out several more variable metric iterations with a prescribed gradient by one order of magnitude lower than that of the previous calculation. In all the cases the results represented local minima at the energy hypersurface.

Each of the four ribose configurational isomers can exist in 4 conformations (Fig. 1). From the point of view of approximation of the isolated molecule in an isotropic field it is sufficient to deal with one series of enantiomers only. We chose the D series. Arnott & Hukins[10] compared results of a large number of X-ray diffraction studies of geometry of furanose cycle of various nucleic acids. On the basis of the compiled data they suggested standard geometry of furanose cycles for β anomers in the conformations C2-*endo*, C3-*endo* and C3-*exo*. We have used them as starting geometries of the molecules *I*—*VIII*. On the basis of ref.[12] the C2-*exo* structure was assigned such position of C(2) and C(3) atoms, that these atoms were located at the same distance on the opposite side of the C(1)—O—C(4) plane as compared with their position in the C2-*endo* structure. Geometries of α anomers were derived from those of β anomers by mutual interchange of hydrogen atom and hydroxyl group at C(1) atom. The following 8 conformers were investigated: C3-*endo* β (*I*), C2-endo β (*II*), C2-*exo* β (*III*), C3-*exo* β (*IV*), C3-*endo* α (*V*), C2-*endo* α (*VI*), C2-*exo* α (*VII*) and C3-*exo* α (*VIII*).

RESULTS AND DISCUSSION

The crystallographic studies dealing with monosaccharides bound to various compounds, especially with nucleic bases[13–17], as well as the previous works from which we have taken the data for assembling the starting geometry[10] give geometry parameters of heavy atoms only. First of all, therefore, it was necessary to find the corresponding positions of hydrogen atoms in the thus chosen rigid skeleton. Hence, we first carried out gradient optimization of the structures *I*—*VIII* with fixed geometry

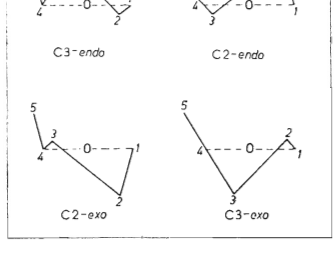

FIG. 1
The studied conformation types of ribofuranoses

degrees of freedom of the heavy atoms except for hydroxyl group at C(5). Having thus established the first approximation of positions of hydrogen atomic centres in space, the structures *I – VIII* were again submitted to variable metric gradient optimization procedure involving, this time, all degrees of freedom. The geometry characteristics of the optimized structures *I – VIII* (after full gradient optimization) are summarized in Tables I, II and III, and the results are compared in Figs 2 and 3. In the series of β riboses, the variable metric gradient optimization procedure found such local minima on the energy hypersurfaces, that the corresponding geometries are very similar to the starting geometry types. In the series of α riboses, deviations were encountered in two cases. For the molecule *VI* the optimization procedure found a geometry whose structural parameters (Fig. 3) could be denoted as V_3 by the notation given in ref.[18]. Similarly optimized geometry of *VII* (Fig. 3) would be assigned ^3V denotation[19]. The local minima on the energy hypersurface corresponding to the optimized structures *VI* and *VII* thus do not correspond strictly to the geometry types C2-*endo* α and C2-*exo* α. Total molecular energies of the optimized structures are compared

Table I

Bond lengths in the individual ribofuranoses after full optimization of geometry

Bond length pm	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*
O—C1()	138·9	138·8	139·0	138·9	139·0	138·9	139·1	138·9
C(1)—C(2)	148·9	148·9	148·8	149·1	148·9	148·8	148·7	148·9
C(3)—C(2)	148·9	148·7	148·9	148·8	148·9	148·9	148·8	148·8
C(4)—C(3)	149·2	149·4	149·2	149·2	149·2	149·2	149·2	149·2
C(5)—C(4)	147·9	148·2	147·9	148·3	147·9	148·3	147·8	148·3
O(1′)—C(1)	138·1	138·1	137·9	138·1	138·0	137·9	137·8	137·9
O(2′)—C(2)	138·4	138·3	138·4	138·3	138·4	138·4	138·4	138·3
O(3′)—C(3)	138·4	138·7	138·3	138·6	138·3	138·6	138·3	138·5
O(5′)—C(5)	137·6	137·6	137·6	137·6	137·6	137·6	137·6	137·6
H—C(1)	113·2	113·3	113·2	113·3	113·2	113·3	113·2	113·4
H—O(1′)	103·2	103·2	103·2	103·2	103·2	103·3	103·2	103·3
H—C(2)	112·8	112·9	112·7	113·0	112·8	112·8	112·9	112·7
H—O(2′)	103·3	103·2	103·3	103·3	103·3	103·2	103·5	103·2
H—C(3)	113·1	112·7	113·1	112·8	113·1	112·8	113·0	112·8
H—O(3′)	103·3	103·1	103·3	103·2	103·3	103·2	103·3	103·2
H—C(4)	113·3	113·2	113·4	113·2	113·2	113·1	113·3	113·1
H—C(5)	112·7	112·6	112·7	112·6	112·7	112·6	112·6	112·6
H′—C(5)	112·6	112·7	112·6	112·7	112·7	112·7	112·7	112·7
H—O(5′)	103·3	103·2	103·2	103·2	103·2	103·2	103·2	103·3

TABLE II

Bond angles in the individual ribofuranoses after full optimization of geometry

Bond angle, (°)	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*
O—C(1)—C(2)	109·1	108·1	109·0	109·1	109·1	109·5	109·9	109·1
C(3)—C(2)—C(1)	101·4	100 0	101·3	101·5	101·7	103·7	102·7	102·2
C(4)—C(3)—C(2)	101·7	102·3	102·0	101·3	101·8	102·9	102·7	101·2
C(5)—C(4)—C(3)	118·0	116·3	117·2	115·7	117·5	115·2	116·5	115·4
O(1′)—C(1)—C(2)	114·1	116·2	110·9	115·1	114·1	115·0	110·6	115·7
O(2′)—C(2)—C(3)	112·5	113·5	112·2	113·4	112·6	111·7	111·9	113·3
O(3′)—C(3)—C(2)	115·2	108·7	115·0	108·8	115·1	109·2	113·8	108·9
O(5′)—C(5)—C(4)	110·3	110·0	108·7	110 4	109·9	109·7	109·2	110·4
H—C(1)—C(2)	112·2	110·7	112·3	111·7	112·2	111·5	112·3	111·5
H—O(1′)—C(1)	106·3	104·8	106·9	105·5	105·9	107·1	107·6	106·9
H—C(2)—C(3)	113·9	109·1	114·2	108·4	113·9	109·0	113·5	108·4
H—O(2′)—C(2)	107·3	105·9	107·3	106·3	107·5	106·5	106·1	106·6
H—C(3)—C(2)	109·4	112·5	109·6	112·5	109·4	111·5	109·9	112·6
H—O(3′)—C(3)	106·1	107·4	106·6	107·1	106·1	106·6	106·7	107·1
H—C(4)—C(3)	108·3	109·2	107·8	110·2	108·2	109·9	108·2	110·4
H—C(5)—C(4)	110·9	111·2	111·6	110·9	111·2	111·3	111·7	111·2
H′—C(5)—C(4)	111·8	112·7	112·5	112·6	112·0	112·7	111·8	112·4
H—O(5′)—C(5)	106·4	106·6	107·0	106·6	106·5	107·3	106·8	106·8

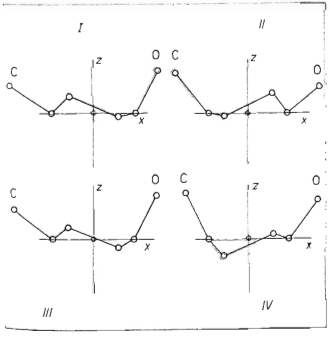

FIG. 2

Geometry representation of β-ribofuranoses after full gradient optimization

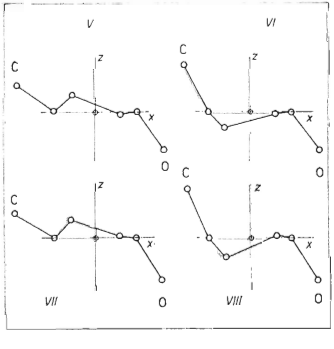

FIG. 3

Geometry representation of α-ribofuranoses after full gradient optimization

in Table IV. Obviously the lowest energy belongs to structure *VII*, but (as it has already been stated) its optimized molecular structure is distinctly deviated from the structural type of the starting approximation. Among the β anomers the energetically most favourable appears to be the C2-*exo* (*III*) structure which is practically not found in nature[13-17] except, perhaps, for ribavirine[18]. Lakshminarayanan & Sasisekharan[2-4] dealt with conformations of ribofuranoses using bicentric potential (analogous to that by Lennard-Jones) for calculation of optimum dihedral angles of the bonding skeleton P—O5′—C5—C4—C3—C3′—P at various conformations of the ribofuranose ring. Similar method was used[5] for constructing energy map corresponding to individual conformations of β D-ribofuranoses and transitions between them, and it was found that the minima at this map belong to the *endo* conformations; no minimum was observed for *exo* conformation. In accordance

TABLE III

Dihedral angles in the individual ribofuranoses after full optimization of geometry

Dihedral angle, (°)	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*
C(3)—C(2)—C(1)—O	−23·8	36·1	−27·6	25·5	−23·5	15·6	−17·2	22·3
C(4)—C(3)—C(2)—C(1)	33·8	−34·5	33·3	−34·1	32·9	−24·8	27·6	−32·8
C(5)—C(4)—C(3)—C(2)	−157·6	−99·3	−155·4	−89·1	−157·0	−96·7	−154·8	−88·7
O(1′)—C(1)—C(2)—C(3)	93·7	154·6	91·8	144·2	−142·2	−106·1	−138·0	−96·6
O(2′)—C(2)—C(3)—C(4)	−81·2	−158·6	−81·2	−159·3	−81·0	−147·6	−89·1	−157·7
O(3′)—C(3)—C(2)—C(1)	156·6	83·8	154·7	84·7	155·5	95·8	149·1	86·3
O(5′)—C(5)—C(4)—C(3)	−82·7	−125·2	−75·9	−137·4	−83·3	−127·9	−70·4	−140·1
H—C(1)—C(2)—C(3)	−142·4	−81·7	−146·6	−92·4	94·1	134·1	100·3	140·4
H—O(1′)—C(1)—C(2)	88·2	63·7	172·4	73·3	−87·3	27·1	−160·0	−43·2
H—C(2)—C(3)—C(4)	155·5	80·2	155·2	80·7	155·3	92·1	149·2	81·9
H—O(2′)—C(2)—C(3)	−63·9	−159·0	−63·9	−164·7	−64·2	−154·8	−37·9	−159·8
H—C(3)—C(2)—C(1)	−81·7	−156·0	−83·4	−155·5	−82·9	−145·3	−89·5	−154·0
H—O(3′)—C(3)—C(2)	73·8	140·2	71·7	154·6	71·2	153·7	70·9	157·3
H—C(4)—C(3)—C(2)	80·3	138·6	84·6	147·9	81·4	141·5	84·5	148·7
H—C(5)—C(4)—C(3)	155·8	113·5	162·9	101·3	155·4	110·7	168·2	98·5
H′—C(5)—C(4)—C(3)	39·2	−3·7	45·6	−15·8	38·5	−6·3	51·1	−18·4
H—O(5′)—C(5)—C(4)	−178·2	−172·8	−178·3	−173·5	−178·2	−175.9	−179·3	−176.4

therewith, an energy barrier was found[6] between the energetically equivalent C2-*endo* and C3-*endo* conformers (about 10·4 kJ mol^{-1}). Govil and Saran[7] used the EHT method for investigation of conformation of the bond skeleton O5′—C5—C4—C3—O3′, and in another report[8] they used the EHT and CNDO/2 methods to examine the changes connected with variation of the dihedral angles C4—O—C1—C2 and O—C1—C2—C3 and found that the energetically most favourable structure corresponds to the dihedral angles −7·5° and 30°, respectively, which is very close to the C3-*endo* conformation of β-ribofuranose optimized by us. The PCILO method was used[9] for variation of torsion angles between all heavy atoms: the most stable conformations found are close to C3-*endo* and C2-*endo* conformations, being separated by an energy barrier of 16·7 kJ mol^{-1}. All the studies cited[2–9] were carried out on ribofuranose fragments bound by glycosidic bond to a simple nitrogen compound. This could be a reason, why our studies of the ribofuranoses themselves found in the β series a different structure – C2-*exo* (*III*) – to be the most favourable. Although the structure C3-*endo* (*I*) has a relatively low energy, it is hardly possible to speak about energetical proximity of the structures C3-*endo* (*I*) and C2-*endo* (*II*). Obviously the energy preference of the individual structural types of ribofuranoses depends considerably on whether the molecule is an isolated one or one involved in glycosidic bond. Geometry of all the eight studied conformations are summarized in Tables I, II and III. From Table III it is seen that dihedral angle at the O(5′)—C(5) bond varies within the limits from −172° to −179° for all β-anomers, which agrees well with the value 180° found by means of bicentric potential in ref.[3] and with the limits of rotations of low energy demands (−210° to −150°) given in ref.[4]. The value of this angle found by the EHT method[7] was 70°. For the dihedral angle O(5′)—C(5)—C(4)—C(3) in the β-conformers C3-*endo* (*I*), C2-*endo* (*II*) C2-*exo* (*III*) and C3-*exo* (*IV*) we have found the values −82·74°, −125·23°, −75·96° and −137·43°, respectively. In ref.[3] several minima of the energy dependence curves were found for each conformer, out of which the values −70°, −60°, −70° and −170°, respectively,

TABLE IV

The CNDO/2 relative energies of the individual ribofuranoses after full gradient optimization

Structure	Energy kJ mol^{-1}	Structure	Energy kJ mol^{-1}
I	12·90	*V*	13·04
II	32·47	*VI*	24·56
III	1·55	*VII*	0·00
IV	28·77	*VIII*	25·77

correspond to the values given by us. The value of this dihedral angle found[7] for planar furanose ring is −135°. The CNDO/2 method found[8] the value −28° for the dihedral angle O—C(1)—C(2)—C(3) of β-ribofuranose, which is very close to the value −23·79° found by us for this dihedral angle in C3-*endo* conformation *I*.

Analysis of quantum-chemical characteristics of the investigated structures revealed that these characteristics are but little affected by conformation.

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Translated by J. Panchartek.