

CONFORMATION OF OXYGEN-CONTAINING HETEROCYCLES: SEARCH OF THE ISOMERIZATION PATHS

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(Received in the UK 13 June 1972; Accepted for publication 19 September 1972)

Abstract—A method is proposed for the search of the conformational isomerization paths and barriers to interconversion. Use of this method in the study of the ring interconversion of α -D-glucose gives the minimal barrier for $1C \rightleftharpoons C1$ isomerization, which is in agreement with the experimental data.

The problems of elucidating the equilibrium conformations and estimating their relative stabilities are readily solved by the methods of local search for the potential function minima if the starting approximations for geometric parameters are known with some accuracy. More complicated is the search for conformational isomerization paths (energetically favourable transitions between local minima) and transition barriers. This can be explained by the fact that isomerization paths cannot be sought with the local search methods (the two-dimensional search which is usually made by the calculation of conformational maps presents a limiting case).

Of all the known nonlocal search methods Gel'fand and Tsetlin's approach (the valley method) is used throughout.^{1,2} Unfortunately this method is not sufficiently accurate for the search but gives only the regions of small changes of the function. This specificity being advantageous in the search of absolute minimum in the multiextremal problems is however rather unfavourable for an automatic search of an exact position of the saddle points. When accuracy of the search increases the Gel'fand method loses its nonlocal features and behaves as a common local search.

In the present paper an automatic search method is proposed which provides high accuracy of the search and might be efficient in the solution of some conformational problems (search of the isomerization paths, transition barriers etc.). The paper also presents an example of the search for the equilibrium conformations and estimating their relative stabilities, transition barriers and isomerization paths for α -D-glucose.

The search of conformational isomerization paths

Let x_1, x_2, \dots, x_n be the independent geometric parameters and $f(x_1, x_2, \dots, x_n)$ —the value of function which is calculated using the formulas for the potential energy. If in the region of the search there is such an ensemble of the points

which (i) belong to continuous and monotonous curves, (ii) the first derivatives along the tangents at any point of each such curve are nonzero (or equal to zero at the extremum) while those along the normals to tangents always vanish, then we shall discuss the function $f(x_1, x_2, \dots, x_n)$ as that having the valley behaviour.

It is natural to assume that (i) the valleys go over all local minima and (ii) the attraction region of the global minimum is larger than that of some other minimum. Probably a rigorous proof of the assumption (i) can be found at least for some classes of functions. As far as condition (ii) is concerned a check can be made by computing the systems interesting for the conformational analysis.

If the two assumptions mentioned above are true then from (i) it would follow that proceeding along the bottom of the valley one may find all the minima of the system, determine possible isomerization paths, transition barriers and relative conformational energies. From (ii) it follows that a probability to get into a global minimum is higher than that of arriving to some other minimum. That is if a considerable number of the minima is found then one can choose from them the global minimum with a great deal of confidence.

In the general case the search is begun at a random point A_0 in the space of geometric parameters then a subsequent local minimization is performed to arrive at the point A_0 with coordinates $(x_1^{(0)}, x_2^{(0)}, \dots, x_n^{(0)})$ at which the value of function is equal to $f^{(0)}$. In order to make a choice of the first step let us explore the function behaviour in the vicinity of A_0 and give increment h to such a variable in which the function changes least of all, e.g. the absolute value of the derivative df/dx_i is minimal. After the first step we reach the point a_1 with coordinates $(x_1^{(0)} + h, x_2, \dots, x_n^{(0)})$. Starting from this point we apply local minimization by all other $n-1$ independent variables at the fixed value of $x_1^{(1)} = x_1^{(0)} + h$. If high accuracy is required to find the bottom of the valley then the most efficient would

be a quadratic minimization procedure.⁷ Let the point A_1 with coordinates $(x_1^{(1)}, x_2^{(1)}, \dots, x_n^{(1)})$ and the value of function $f^{(1)}$ corresponds to a local minimum in $n-1$ variables.

A relative change of the function after one iteration step along the axes x_1, x_2, \dots, x_n can be written as follows:

$$\begin{aligned} \Delta_1 &= \Delta f/h, \Delta_2 = \Delta f/\Delta x_2, \\ \Delta_3 &= \Delta f/\Delta x_3, \dots, \Delta_n = \Delta f/\Delta x_n, \end{aligned} \quad (1)$$

where

$$\begin{aligned} \Delta f &= f(x_1^{(0)} + h, x_2^{(1)}, \dots, x_n^{(1)}) - f(x_1^{(0)}, x_2^{(0)}, \dots, x_n^{(0)}); \\ \Delta x_i &= x_i^{(1)} - x_i^{(0)}, (i = 1, 2, \dots, n). \end{aligned}$$

A subsequent step is analogous to a preceding one and made in the direction of the least change in Δ_i . Then follow both the minimization procedure and repetition of the process.

Fig 1 shows an example of the search of the valley bottom for a two-dimensional case at $h = 0.5$ and 1.0 . At $h = 0.5$ the local minimization starts from the points a_1, a_2, \dots , while at $h = 1.0$ —from the primed points a'_1, a'_2, \dots . As seen from Fig 1, an efficiency of the search depends essentially upon the choice of step h . In the general case the smaller the value of h the greater the accuracy would be attained in the search of the valley bottom and saddle point (and hence transition barrier). But a decrease of h leads to the greater number of iteration steps. Thus it would be reasonable to employ optimal values of h .

An experience of the calculation with the given potential functions of the conformational problems indicates that for any part of the valley optimal

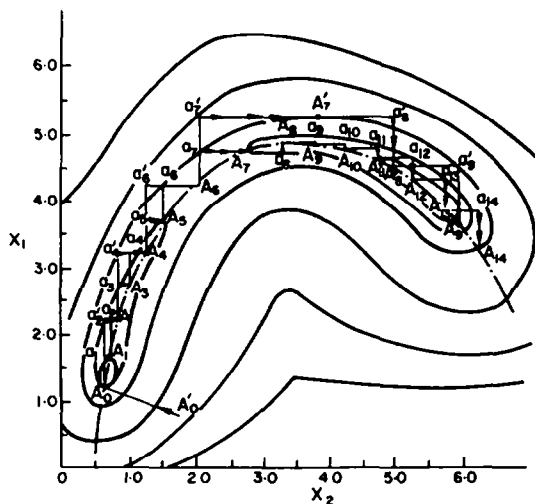


Fig 1. An example of a two-dimensional search by the modified valley method with fixation of essential variables.

values should satisfy the following condition

$$0.7 \leq \Delta x_i/h \leq 2.0 \quad (2)$$

where x_i is a maximal change of the variable in reaching the point A_{i+1} from A_i (Fig 1). It is convenient to use the following relations to provide a relative adaptation of the step:

$$\begin{aligned} k \cdot h_{j-1} & \text{ if } \Delta x_i^{(j-1)}/h_{j-1} > 2.0 \\ h_j &= h_{j-1}/k & \text{ if } \Delta x_i^{(j-1)}/h_{j-1} < 0.7 \\ h_{j-1}/2 & \text{ if } \Delta x_i^{(j-1)}/h_{j-1} > 2.5 \end{aligned} \quad (3)$$

where j is the number of iteration steps; $k = 0.8 + 0.95$ is a positive factor close to unity.

Several schemes can be proposed for the organization of the search.

(1) After the first iteration the step is done from point A_1 ($x_1^{(1)}, x_2^{(1)}, \dots, x_n^{(1)}$) along the line A_0A_1 (Fig 1), then the value of the essential variable (in which the function undergoes least change) is fixed and the function is subjected to minimization. In this case the starting points for local minimization would not be far from the bottom of the valley. At such search organization one may essentially save time because of the lesser number of iteration steps at each local minimization.

(2) Employing an experience of the earlier steps one may guess the coordinates of the next points. For example assuming that the function is monotonic one may write

$$\Delta x_i^{(j)} = m \cdot \Delta x_i^{(j-1)} \quad (4)$$

where m is a proportionality coefficient known from the previous test.

Assuming, e.g., $m = \Delta x_i^{(j-1)}/\Delta x_i^{(j-2)}$, Eq. (4) takes the form

$$\Delta x_i^{(j)} = [\Delta x_i^{(j-1)}]^2/\Delta x_i^{(j-2)}. \quad (5)$$

In spite of the fact that the time for each iteration step is shorter when one of the parameters is fixed, an increase in the accuracy would be due to a longer search time. Thus a choice of appropriate accuracy is an important criterion in organizing the search.

Computation of isomerization paths of α -D-glucose

The conformations of particular intermediate forms of the cyclic molecules and their energies have been discussed.^{3,4} However nowadays this problem has not yet been studied in sufficient detail. The method described above enables us to automatically search the isomerization paths and their respective transition barriers by optimizing the geometry at each step.

As a first attempt to employ this method we computed the isomerization paths and the barriers to the ring interconversion for the molecule of α -D-glucose.

The atom-atom potentials' method^{3,5} with an account of both the torsional and electrostatic interaction energies was used in the conformational calculations. In such an approximation the strain energy of the α -D-glucose molecule may be written in the following way

$$U_{\text{str}} = \sum_{i>j} f(r_{ij}) + 332q_iq_j/(kr_{ij}) + \frac{1}{2} \sum_i U_0^{(i)}(1 + \cos 3\varphi_i) + \frac{1}{2} \sum_i C_i(\Delta\alpha_i)^2 \quad (6)$$

In this equation the first sum presents the energies of nonbonded and electrostatic interactions; r_{ij} a distance between nonbonded atoms, entering the potentials of interatomic interactions which have the form of 6-exp

$$f(r) = -M r^{-6} + N \exp(-qr), \quad (7)$$

M , N , q being the empirical parameters universal for a particular pair of atoms.

The electrostatic energy is calculated in the monopole approximation, q being atomic charges (in electron units) and k being usually classified as the dielectric constant of the medium. The torsional potentials (second sum in (7)) have, as usual, a threefold symmetry, φ_i being rotation angles around the bonds of a ring, $U_0^{(i)}$ empirical constants dependent on the type of a bond. The last term of (7) presents the energy of bond angles' deformation, $\Delta\alpha_i$ being deviations of bond angles from their ideal values and C_i elastic constants.

Parameters M , N , q necessary for conformation calculations have been elucidated by Dashevsky^{5,6} from geometries of overcrowded molecules and thermochemical data. Their values are given in Table 1. Elastic constants for bond angles' deformations, C_C and C_O , assumed to be equal to 30 and 65 kcal. mole⁻¹. rad⁻², correspondingly, 109.5° and 90° being "ideal" angles for tetrahedral carbon and oxygen atoms.⁷ The atomic charge distribution was taken from.⁸ Torsional constants U_{C-C} and U_{C-O} assumed to be equal to 3 and 1 kcal. mole⁻¹, correspondingly.

The vaguest point of parametrization is use of a monopole approximation for electrostatic energy. One can hardly estimate the degree of confidence for atomic charges obtained by semi-empirical

methods of quantum chemistry, at the same time the experimental data on charge distribution being almost fully absent. In this paper we introduce a constant k defining it as a correction factor and not the dielectric permeability of a medium. In the conformational calculations, a correction factor k which provides better agreement with experiment usually exceeds unity.^{9,10}

The numeration of the atoms of α -D-glucose and the internal parameters are shown in Fig 2. The

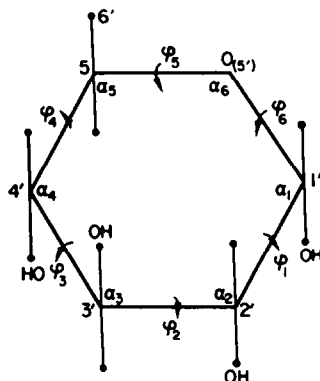


Fig 2. Molecular geometry of α -D-glucose with internal parameters.

method of calculation, the atoms' coordinates through the values of the independent geometric parameters and the problem of taking into account the ring-closure conditions are discussed in our paper.⁷ In these calculations the following slight simplifications were used:

(a) interaction between the hydroxylic hydrogens and the atoms bonded with C (6) is neglected.

(b) the valence bonds are rigid, $r(C-C) = 1.53$, $r(C-O) = 1.42$, $r(C-H) = 1.10$ Å, the glucoside bond $C-C$ being equal to 1.39 Å.

(c) the bond angles HCO and HCC are respectively 106.8 and 107.8°, as taken from the calculation of the optimal conformation of α -D-glucose (C 1).

For estimating a degree of approaching the experiment due to electrostatic contribution to the potential function as well as to make a choice of the correction factor, an equilibrium conformation of α -D-glucose was computed for k equal to 1.0, 3.5, 7.0, 10.0, 20.0 and ∞ (Table 2) (choice of independent parameters is described below).

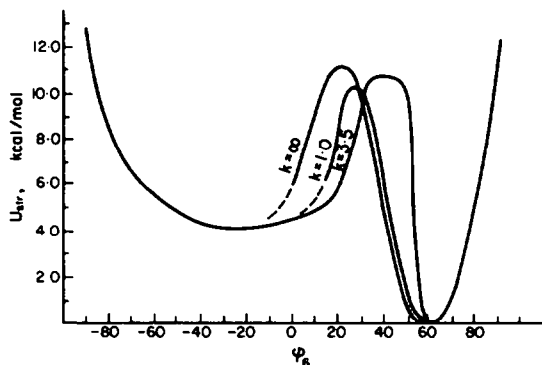
A comparison with experiment 11 shows that the torsional angles φ_i are most sensitive whereas the bond angles α_i are less sensitive to the electrostatic interactions. A satisfactory coincidence with the experimental data can be observed for all equilibrium structures of Table 2. Moreover effects of electrostatic interactions on the value and shape of the potential barriers were investigated (Fig 3), the shape of the barrier being more sensitive than its

Table 1. Parameters of atom-atom potentials used in present calculations

| Interaction | M, kcal/mole · Å ⁶ | N, kcal/mole | q, Å ⁻¹ |
|-------------|-------------------------------|------------------------|--------------------|
| H...H | 40.1 | 2.86 · 10 ⁴ | 5.200 |
| H...C | 155 | 3.28 · 10 ⁴ | 4.130 |
| H...O | 122 | 5.75 · 10 ⁴ | 4.727 |
| C...C | 476 | 3.77 · 10 ⁴ | 3.513 |
| C...O | 441 | 6.37 · 10 ⁴ | 3.881 |
| O...O | 346 | 9.65 · 10 ⁴ | 4.333 |

Table 2. The equilibrium conformation of chair C1 of α -D-glucose at different values of k

| No. | k | α_1 | α_2 | α_3 | α_4 | α_5 | α_6 | φ_1 | φ_2 | φ_3 | φ_4 | φ_5 | φ_6 | Ref. |
|-----|----------|------------|------------|------------|------------|------------|------------|-------------|-------------|-------------|-------------|-------------|-------------|------|
| 1 | 1.0 | 109.4 | 112.0 | 109.8 | 114.4 | 111.7 | 111.9 | 57.2 | -50.0 | 47.5 | -53.7 | 62.0 | -63.0 | |
| 2 | 3.5 | 110.9 | 110.9 | 109.5 | 110.3 | 111.7 | 113.3 | 55.8 | -52.9 | 52.3 | -55.3 | 59.4 | -59.2 | |
| 3 | 7.0 | 111.2 | 110.6 | 109.4 | 110.1 | 111.7 | 113.6 | 55.4 | -53.4 | 53.2 | -55.6 | 58.7 | -58.3 | |
| 4 | 10.0 | 111.3 | 110.6 | 109.4 | 110.0 | 111.7 | 113.7 | 55.3 | -53.6 | 53.3 | -55.6 | 58.5 | -58.0 | |
| 5 | 20.0 | 111.4 | 110.5 | 109.4 | 109.9 | 111.7 | 113.8 | 55.1 | -53.7 | 53.8 | -55.7 | 58.3 | -57.7 | |
| 6 | ∞ | 111.6 | 110.4 | 109.3 | 109.9 | 111.7 | 113.9 | 55.0 | -53.9 | 54.1 | -55.8 | 58.0 | -57.4 | |
| 7 | | 110.1 | 111.1 | 109.8 | 111.2 | 108.7 | 113.8 | 54.1 | -51.3 | 53.3 | -57.5 | 62.2 | -60.9 | 11 |

Fig. 3. Inversion barrier of the heterocycle of α -D-glucose at k equal to 1, 3.5 and ∞ .

value. In further calculations a "best" value of k equal to 3.5 was adopted. Nevertheless we present in Fig 3 the results of calculations (U_{str} as a function of φ_6) obtained for three values of k (see Table 6 for discussion)

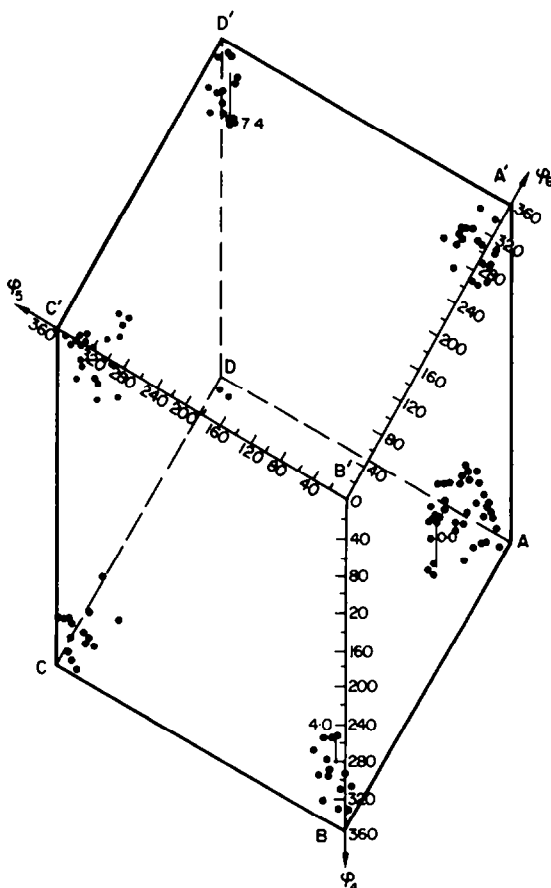
The conformational transitions were computed using six independent parameters $\varphi_4, \varphi_5, \varphi_6, \alpha_4, \alpha_5$ and α_6 , responsible for the inversion of the heterocycle (Fig 2). The parameters $\varphi_1, \varphi_2, \varphi_3, \alpha_1, \alpha_2$ and α_3 are dependent and could be estimated from Eqs (19-24).⁷ Angles φ_i were counted from the cis-position; φ_i 's were taken positive at the clockwise rotation of the remote ($i+1$)th bond about the nearest ($i-1$)th bond in looking along the i -th bond while the negative values were obtained by counter-clockwise rotation.

It should be noted that at the conformational transitions of α -D-glucose the torsional angles undergo the most variation in respect to the bond angles. Thus at the sufficient accuracy one may assume that the supersurfaces satisfying the condition $U_{str}(\varphi_4, \varphi_5, \varphi_6, \alpha_4, \alpha_5, \alpha_6) = \text{const}$ are three-dimensional ($\varphi_4, \varphi_5, \varphi_6$). Apparently the search along the valleys would be successful only if the suggestions (i) and (ii) given above are valid.

Therefore in the study of the conformations of α -D-glucose it is logical to start with a check of these suggestions. We investigated the region of internal parameters ($\varphi_4, \varphi_5, \varphi_6, \alpha_4, \alpha_5, \alpha_6$) by making a random choice with subsequent local minimization (until the difference $f_{n-1} - f_n$ where n is the

number of iterations in local search, would be less than 0.5 kcal/mole). A region was regarded as allowable if all given internal parameters provided the closure of the heterocycles. 127 random starting points were chosen within the allowed region, optimization in all the variables distributed them in the local minima at the desired accuracy.

Fig 4 shows distribution of points within the space of essential parameters ($\varphi_4, \varphi_5, \varphi_6$). It can be seen that only small regions near the vertices of

Fig. 4. Distribution of phase points in the space of essential parameters ($\varphi_4, \varphi_5, \varphi_6$) after random choice and subsequent minimization in the six internal parameters ($\alpha_4, \alpha_5, \alpha_6, \varphi_4, \varphi_5, \varphi_6$) at an accuracy of 0.5 kcal/mole.

cube with $\varphi_i = -70 \div 70^\circ$ are the allowed regions. In the case where φ_4 , φ_5 , and φ_6 have the same signs the allowed region would be essentially contracted (vertex *D*) or completely forbidden (vertex *B'*).

Phase points are most concentrated at the vertex *A* of the cube (Table 3), that is in the region of *C* 1 conformation. This can be explained by the greater number of valleys converging to a local minimum of *C* 1 conformation in respect to any other minimum. On the other hand *C* 1 conformation is known to be most stable. Hence in this case our suggestion (ii) is reasonable.

Table 3. Distribution of phase points of α -D-glucose in the space of internal parameters

| Distribution region | The number of points in phase region |
|---------------------|--------------------------------------|
| <i>A</i> | 39 |
| <i>B</i> | 13 |
| <i>C</i> | 15 |
| <i>D</i> | 1 |
| <i>A'</i> | 21 |
| <i>B'</i> | — |
| <i>C'</i> | 22 |
| <i>D'</i> | 16 |
| Total | 127 |

Next step in the study of α -D-glucose included the calculation of its isomerization paths. The search for local minima and the valley bottom was performed to an accuracy of 0.25 kcal/mole (this was completed when $f_{n-1} - f_n$ was less than 0.25).

The isomerization paths in the space (φ_4 , φ_5 , φ_6) with an indication of the intermediate strain energies are given in Fig 5. The values φ_4 , φ_5 and φ_6 could be readily found for any intermediate form from a position of phase point in the space and its projection on the plane (φ_5 , φ_6).

Positions of the respective forms of Reeve's boats¹² for a symmetrical molecule are denoted by circles *B*1, 2*B*, *B*3, 1*B* and 3*B*. The plane passing through all forms of the boat (Hendrickson's pseudorotation³) makes a dihedral angle equal to 55.7° with (φ_5 , φ_6) plane. For α -D-glucose the pseudorotation follows a curve close to the ideal (dash line). The conformations *C*1 and 1*C* locate at the opposite sides from the pseudorotation plane, thus *C*1 is above *B*3 while 1*C*—under 3*B*, transitions *C*1 \rightleftharpoons 1*C* being possible only through the intermediate boat forms.

Five possible transitions to the pseudorotation space from *C*1 (and three from 1*C*) were detected at the search for the isomerization paths.

Fig 6 shows the strain energies and positions of the atoms with respect to the plane passing through O(5'), C(1'), C(2') or C(3), C(4'), C(5') for some intermediate forms being in the isomerization path.

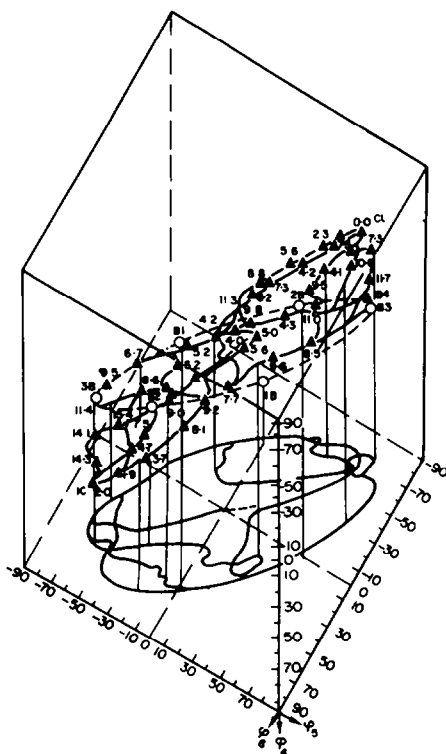


Fig 5. Isomerization path of α -D-glucose. Strain energy of the molecule is given in the intermediate points.

As seen from Fig 6 at the chair-boat transition the largest strain energy (saddle point) corresponds to such a conformation in which five atoms of the heterocycle locate approximately in the same plane while the sixth atom gets out of it over $0.7 \div 0.9 \text{ \AA}$, each isomerization path being specified by the exit of a certain atom. Thus the chair conformations *C*1 and 1*C* should provide at least six isomerization paths, considerably less being found by us (only three in the case of the 1*C* conformation). This can be explained by asymmetry of the α -D-glucose molecule; therefore an exit of each atom of the heterocycle from the plane of the other five atoms corresponds to the different values of strain energy. This difference may be so large that the exit of a certain atom becomes less probable. It is also not excluded that some of the paths have simply not been detected.

All isomerization paths from the chair conformations *C*1 and 1*C* pass the region of pseudorotation and are specified by the height of the potential barrier and the length of the phase transition. As seen from Table 4, transitions through saddle points corresponding to the exit of C(1'), C(2') or C(5') atoms from the plane of other five atoms are most favourable in terms of strain energy (in the isomerization from 1*C* conformation an exit of C(5') carbon is of low-probability).

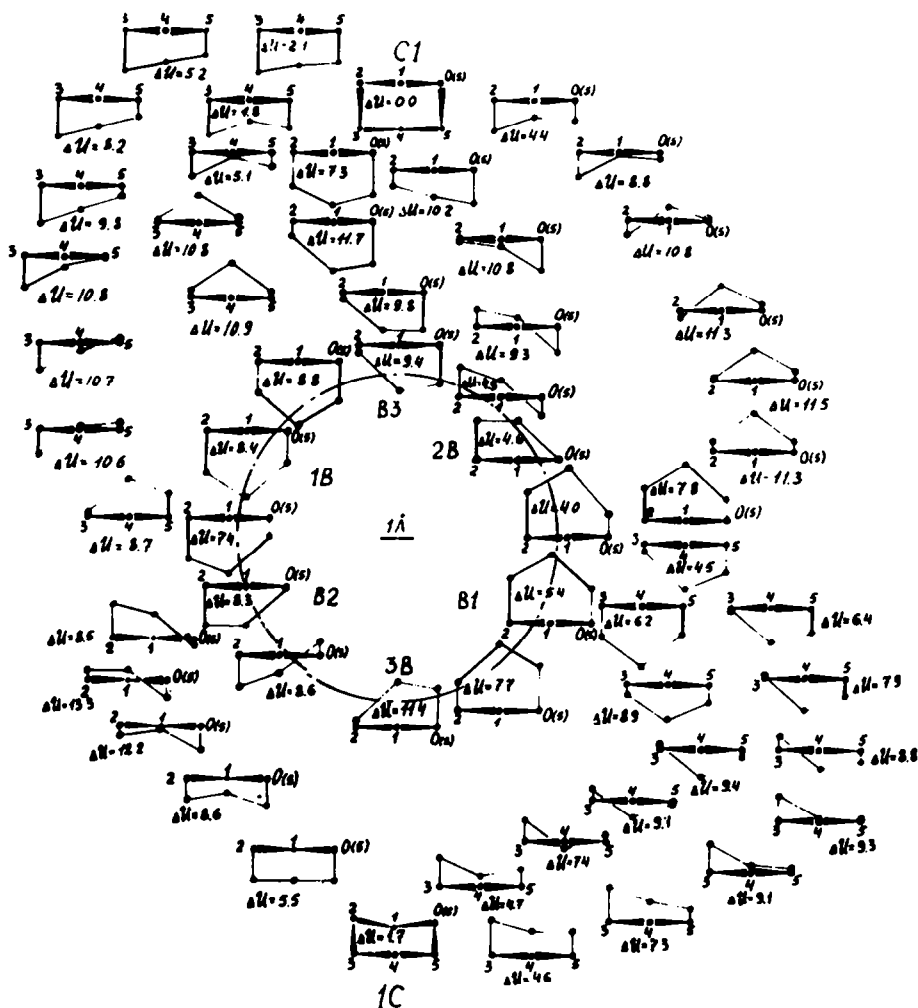


Fig. 6. The intermediate forms in the isomerization paths. The displacements of atoms from the plane $C(5')$, $C(1')$, $C(2')$ or $C(3')$, $C(4')$ are scaled. The respective strain energy is given for each intermediate form. The region of pseudorotation is shown by a dotted line.

Table 4. Potential barriers and get in regions in the isomerization from C1 and 1C conformations

| Nos. | Exit of atoms in the saddle points of phase space | Isomerization from C1 | | | Isomerization from 1C | | |
|------|---|--|---------------------------------|--|--|---------------------------------|--|
| | | U_{str} in the saddle points kcal/mole | Get in region at the transition | U_{str} in the get in region kcal/mole | U_{str} in the saddle points kcal/mole | Get in region at the transition | U_{str} in the get in region kcal/mole |
| 1 | C(1') | 10.9 | B3 ÷ 1B | 8.8 | 9.4 | B1 | 5.4 |
| 2 | C(2') | 10.8 | B2 ÷ 1B | 7.4 | 9.3 | B1 ÷ 2B | 4.0 |
| 3 | C(3') | — | — | — | — | — | — |
| 4 | C(4') | 11.5 | B1 ÷ 2B | 4.0 | — | — | — |
| 5 | C(5') | 10.8 | B3 ÷ 2B | 4.9 | 13.3 | B2 | 8.3 |
| 6 | C(6') | 11.7 | B3 | 9.4 | — | — | — |

¹Strain energy of the chair conformation C1 is taken as a reference point.

Table 5. The calculated bond and torsional angles and contribution to the potential energy for some conformations of α -D-glucose (from which the conformations C1, 1C and "twist" are equilibrium ones)

| No. | Conf. | α_1 | α_2 | α_3 | α_4 | α_5 | α_6 | φ_1 | φ_2 | φ_3 | φ_4 | φ_5 | φ_6 | U_{anz} | U_{low} | U_{hb} | U_{el} | U_{itr} | ΔU_{tr} | |
|-----|-------------------------|------------|------------|------------|------------|------------|------------|-------------|-------------|-------------|-------------|-------------|-------------|------------------|------------------|-----------------|-----------------|------------------|------------------------|--|
| 1 | C1 | 110.6 | 110.7 | 109.7 | 110.4 | 111.5 | 113.2 | 56.2 | -52.8 | +52.0 | -55.2 | -59.8 | -60.0 | 5.7 | 0.3 | 89.4 | 5.8 | 101.2 | 0.0 | |
| 2 | 1C | 111.7 | 109.2 | 111.8 | 112.6 | 113.4 | 114.4 | -57.6 | 51.3 | -46.2 | 46.0 | -53.2 | 59.7 | 6.3 | 0.9 | 89.1 | 6.7 | 102.9 | 1.7 | |
| 3 | 1B | 110.5 | 113.2 | 113.1 | 112.9 | 117.4 | 116.6 | 57.6 | -16.0 | -30.9 | 42.5 | -1.0 | -48.6 | 7.6 | 5.6 | 89.5 | 6.9 | 109.7 | 8.4 | |
| 4 | B1 | 109.4 | 110.9 | 112.1 | 113.0 | 116.8 | 114.8 | -64.0 | 18.2 | 32.6 | -45.0 | -0.3 | 54.3 | 6.7 | 5.2 | 90.0 | 4.7 | 106.6 | 5.5 | |
| 5 | 2B | 115.6 | 109.7 | 112.1 | 112.2 | 111.8 | 115.0 | -50.0 | 47.0 | +1.0 | -52.2 | 52.3 | 0.0 | 6.8 | 4.7 | 90.1 | 4.2 | 105.8 | 4.6 | |
| 6 | B2 | 115.7 | 110.2 | 111.7 | 114.1 | 113.6 | 116.8 | 49.1 | -50.0 | 5.1 | 43.9 | -47.2 | 0.0 | 7.8 | 5.0 | 89.8 | 6.9 | 109.5 | 8.3 | |
| 7 | 3B | 113.3 | 109.9 | 116.1 | 111.9 | 111.1 | 113.7 | -8.2 | -40.7 | 41.0 | 8.5 | -60.7 | 61.3 | 6.2 | 7.1 | 92.0 | 7.3 | 112.6 | 11.4 | |
| 8 | B3 | 112.4 | 111.9 | 112.7 | 111.2 | 113.2 | 113.5 | 9.2 | 42.8 | -47.5 | 0.0 | 55.6 | -60.6 | 5.9 | 6.8 | 90.9 | 7.2 | 110.6 | 9.4 | |
| 9 | "Twist" | | | | | | | | | | | | | | | | | | | |
| | B1 \leftrightarrow 2B | 112.3 | 109.6 | 111.6 | 110.9 | 113.6 | 114.9 | -64.1 | 28.3 | 27.6 | -59.1 | 25.6 | 35.0 | 6.6 | 4.3 | 90.0 | 4.3 | 105.2 | 4.0 | |
| 10 | "Twist" | | | | | | | | | | | | | | | | | | | |
| | B2 \leftrightarrow 1B | 113.8 | 111.5 | 111.8 | 112.9 | 114.6 | 116.4 | 58.5 | -33.7 | -17.8 | -53.8 | -13.2 | -24.0 | 7.5 | 4.8 | 89.3 | 7.0 | 108.6 | 7.4 | |

Table 6. Experimental and calculated barriers to inversion for some hexacyclic molecules

| No. | Molecule | Experimental data kcal/mole | Calculated data | Ref. |
|-----|-------------------------------------|--------------------------------|--------------------|-----------------|
| 1 | Cyclohexane- <i>d</i> ₁₁ | 10.6 | | 15 |
| | | 10.5 | | 16 |
| | | | 11.0 | 17 ^a |
| | | | 14.3 | 3 ^b |
| 2 | Tetrahydropyran | 10.5 ± 1.2 | | 14 |
| 3 | Tetracetate of β-D-rybopyranose | 10.5 | | 17 |
| 4 | α-D-glucose | | 10.8 | this work |

^aExtended Hückel method.

^bThe conformational calculation with inclusion of non-bonded interaction, bond angles deformations and torsional energies.

Table 5 lists the bond (α_i) and torsional angles (φ) and the energies computed for the chair and boat conformations of α -D-glucose. The conformations 3B and B3 have the highest strain energies due to an overlap of three bonds at the torsional angles C(2') \rightarrow C(1') and C(5') \rightarrow C(4') with bulky substituents.

It should be noted that our results somewhat disagree with published data.¹³ These authors have employed the method of atom-atom potentials in the study of 8 possible forms of the pyran cycle and arrived at the conclusion that the conformations C1, B1 and 3B are the most stable whereas the forms 1B and B2 and 3B are most unstable ($U_{str} = 40$ kcal/mole). In these calculations all pyran cycles were taken as rigid (the geometric parameters have been cited only for the C1 form) although no experimental data is available for the choice of geometric parameters of all boat and 1C-chair conformations.

We revealed two local maxima in the region of pseudorotation: one with an energy of 4.0 kcal/mole in the region between the boats 2B and B1, another with energy of 7.4 kcal/mole between the forms 1B and B2. Table 4 shows the geometric parameters and strain energies for the equilibrium conformations of α -D-glucose.

Thus pseudorotation is hindered and has the transition barriers of 5.4 and 7.4 kcal/mole (from the first minimum, $U_{str} = 4.0$ kcal/mole) and 2.0 and 4.0 kcal/mole (from the second minimum, $U_{str} = 7.4$ kcal/mole). It should be noted that in view of the hindered pseudorotation, chair-chair transitions *via* the twisted boats are more favourable energetically (Fig 6).

In 1967 Gatti *et al.*¹⁴ determined the free activation energy of the tetrahydropyran cycle from NMR data and equilibrium constants. Its conformational mobility has been found to be insensitive to the effect of oxygen. The predicted inversion barriers of α -D-glucose almost match the experimental data and calculated data for cyclohexane

and some oxygen-containing heterocycles (Table 6).

It can be noted that according to the conceptions of classical physics, all the particles whose kinetic energy (atomic vibrations) exceeds the potential energy pass through the barrier. As for transition paths of the particular molecules their prediction is rather difficult (they depend upon the initial pulse and a kinetic energy excess). It is evident that the transition pattern in the phase space closely approaches the saddle point. Experimental energies are measured namely for the saddle points.

In conclusion it should be pointed out that probably our isomerization paths are typical for all hexacyclic molecules with saturated carbon-carbon bonds and torsional potentials having a three-fold symmetry axis.

Acknowledgement—The authors thank Dr. M. M. Voronovitsky for assistance in discussing some mathematical features of the problem.

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