RICON−The Computer Program for the Quantitative Investigations of Cyclic Organic Molecule Conformations

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The methods of quantitative conformational analysis of cyclic fragments in molecules and the computer program RICON (RIng CONformations) developed by us for this purpose are considered. Program RICON uses atomic coordinates obtained from X-ray studies or force field/quantum chemical computations and allows one to analyze geometric parameters of a molecule, to compute the puckering parameters of rings in the molecule using various methods, and to obtain a verbal description of a ring conformation. The abilities of the program are described, and the examples of its application are given.

INTRODUCTION

The conformational analysis of cyclic molecules is an important field of stereochemistry. Such terms as "chair" and "boat" are widely used for the qualitative description of conformations for many years. However, very often it is necessary to analyze the deviation of a distorted conformation from an ideal one or to consider the whole spectrum of conformations of cyclic molecules on the basis of some unified description, *etc.* Sometimes it is difficult to find, whether a conformation of the molecule under study is named unambiguously or the name assigned to it is based only on the opinion of a particular researcher. Thus, the necessity in some quantitative parameters for the unique description of the ring spatial forms is evident.

The quantitative conformational analysis of cyclic molecules has a rather long history. For many years the main problem was the absence of the universal routine for the transfer from the Cartesian atomic coordinates to a small number of parameters sufficient for the adequate description of the ring shape. For the majority of small- and medium-size rings in real molecules the spatial shape of a ring is determined mainly by the out-of-plane displacements of atoms from some mean plane. The special cases of small in-plane distortions in such planar rings as benzene cycles are not discussed in this paper.[1]

The first theory of ring puckering was developed by Kilpatrick, Pitzer, and Spitzer[2] in 1947. It was shown that atomic displacements z_j from the mean squares plane in cyclopentane can be resolved by the following formula

$$z_j = \sqrt{2/5}\, q \cos(2\psi + 4\pi(j-1)/5)$$

where q is the puckering amplitude and ψ is the phase angle describing the shape of a molecule. However, this equation can be applied only to the rings with equal bond lengths and equal valent angles. Another description of ring puckering was suggested by Geise, Altona, and Romers.[3] Their method is based on the usage of torsional angle values

$$\phi_j = a \sin(P + 4\pi j/5)$$

where a is an amplitude and P is a phase angle. But the

puckering amplitude calculated by this method slightly depends on the atomic numbering. A number of later studies[4−6] also concerned with the conformations of five- and six-membered rings, but all of them were oriented to the rings of a particular size.

A significant contribution to the systematization of the conformational analysis of cyclic molecules was made by Hendrickson.[7−9] The conformations were classified on the basis of the signs of torsional angles taking into account the presence of the plane or axis of symmetry. Owing to the strict rules of naming conformations Hendrickson's nomenclature was widely used in further theoretical studies.

The first nonempirical quantitative approach to ring puckering based on the group theory was suggested by Pickett and Strauss,[10] who described puckering as out-of-plane vibrational displacements of atoms of a regular planar N-membered ring. The symmetry of vibrational displacements can be specified in terms of the properties of a symmetry group of the planar ring, D_{Nh}:

$$\Gamma(\text{even}) = B_{2(g,u)} + E_{2u} + ... + E_{(N/2-1)(g,u)}$$

$$\Gamma(\text{odd}) = E''_2 + ... + E''_{(N-1)/2}$$

The E_m vibration in both even and odd rings corresponds to the z_j displacements computed as follows

$$z_j = \rho_m \cos(\phi_m + 2\pi m j/N)$$

where $m = 2, 3, ..., N/2\text{-}1$ for even N, $m = 2, 3, ..., (N-1)/2$ for odd N. $B_{2(g,u)}$ vibration corresponds to the displacement

$$z_j = (-1)^j Q$$

However without a routine of finding "mean" plane for rings with the nonequal bond lengths or valent angles Pickett−Strauss symmetry-adopted parameters can not be used for the majority of real molecules.

A general method for the description of a ring with any shape and size was suggested by Cremer and Pole.[11] As a measure of ring nonplanarity the atomic displacements from the special mean plane were used. The ring shape in Cremer−Pole (CP) method is described by $N - 3$ puckering parameters obtained from $3N$ Cartesian coordinates. The

description of the CP method is given in the next section of this paper. The equations of the CP method are very similar to those in the Pickett−Strauss one. It was shown that the parameters in these methods are symmetry equivalent.[12] The CP method gives the unique description of ring puckering, the puckering amplitudes do not depend on the atomic numbering, and displacements of ring atoms from the mean plane can be exactly restored from the puckering parameters.

The CP method not only is a powerful and useful tool for the conformational analysis but also has some shortcomings. For the rings with significantly unequal bond lengths the CP method often gives the conclusions contradicting with the commonly used stereochemical notions based on torsional angle values.[12] The method proposed by us uses sines of halves of endocyclic torsional angles instead of atomic displacements in the CP method.[13] Our method will be also discussed in detail in the next section.

In the subsequent years further theoretical studies were carried out[12,14−16] and numerous investigations of rings with the size from five to nine atoms were performed.[16−24] In recent publications Haasnoot[25,26] discussed the use of torsional angles and NMR coupling constants for the description of ring shapes on the basis of puckering parameters.

Thus, the methods of quantitative conformational analysis of rings based on puckering parameters are widely used in stereochemical studies. However the calculations in these methods are rather complicated, and the computer programs for this purpose should be useful. Such software can serve as a convenient tool for the description and comparison of ring conformations (e.g., for the search for the rings with similar shape in 3D databases) when the atomic coordinates are available from some experimental or computational data.

MATHEMATICAL DESCRIPTION OF METHODS APPLIED IN THE RICON PROGRAM

Computer program RICON (RIng CONformations) is designed for the quantitative conformational analysis of cyclic molecules on the basis of puckering parameters. For this purpose both Cremer−Pople[11] (CP) and our[13,16] (ZP) methods are included into the program.

CP AND ZP METHODS

The CP method[11] uses the Cartesian coordinates (x_j, y_j, z_j) of atoms of N-membered ring as the input parameters. The out-of-plane displacements of atoms from the special mean plane serve as a measure of ring puckering. To obtain these displacements a ring is to be shifted and rotated in space to satisfy the following requirements[11]

$$\sum_{j=1}^{N} R_j = 0 \qquad (1)$$

$$\sum_{j=1}^{N} z_j \cos(2\pi(j-1)/N) = 0 \qquad (2)$$

$$\sum_{j=1}^{N} z_j \sin(2\pi(j-1)/N) = 0 \qquad (3)$$

where R_j is the vector corresponding to the jth atom. After the fulfillment of these requirements z-coordinates of atoms in the new coordinate system are equal to the displacements

from the mean plane. This plane is defined uniquely and does not depend upon the atomic numbering.

Then the set of puckering parameters $\{q_m, \varphi_m\}$ is computed using the following formulas

$$q_m \cos \varphi_m = \sqrt{\frac{2}{N}} \sum_{j=1}^{N} z_j \cos[2\pi m(j-1)/N] \qquad (4)$$

$$q_m \sin \varphi_m = -\sqrt{\frac{2}{N}} \sum_{j=1}^{N} z_j \sin[2\pi m(j-1)/N] \qquad (5)$$

where $q_m \geq 0$, $0 \leq \varphi_m \leq 2\pi$, and $m = 2, ..., N/2 - 1$ for even N, $m = 2, ..., (N-1)/2$ for odd N. For even rings there exists an additional puckering parameter $q_{N/2}$

$$q_{N/2} = \sqrt{\frac{1}{N}} \sum_{j=1}^{N} \sin(z_j/2) \cos[\pi(j-1)] \qquad (6)$$

Equations 4−6 uniquely define a set of $N - 3$ puckering parameters (puckering amplitudes q_m and phase angles φ_m).

All z-coordinates can be exactly restored from puckering parameters using equations 7 and 8:

$$z_j = \sqrt{\frac{2}{N}} \sum_{m=2}^{(N-1)/2} q_m \cos(\varphi_m + 2\pi m(j-1)/N) \qquad (7)$$

for odd N

$$z_j = \sqrt{\frac{2}{N}} \sum_{m=2}^{N/2-1} q_m \cos(\varphi_m + 2\pi m(j-1)/N) + \sqrt{\frac{1}{N}} q_{N/2}(-1)^{j-1} \qquad (8)$$

for even N.

Normalization coefficients in eqs 4−6 provide the following relation

$$\sum_{j=1}^{N} z_j^2 = \sum_{m} q_m = Q^2 \qquad (9)$$

where Q may be referred to as the total ring puckering.

The ZP method[13,16] uses the same mathematical basis as the CP method. But instead of displacements z_j the ZP method applies $\sin(\phi_j/2)$ values, where ϕ_j is the endocyclic torsional angle between the atoms with numbers j, $j + 1$, $j + 2$, and $j + 3$. The eqs 4−6 of the CP method correspond to the following ones in the ZP method

$$s_m \cos \psi_m = -\sqrt{\frac{2}{N}} \sum_{j=1}^{N} \sin(\phi_j/2) \sin[\pi m(2j+1)/N] \qquad (10)$$

$$s_m \sin \psi_m = -\sqrt{\frac{2}{N}} \sum_{j=1}^{N} \sin(\phi_j/2) \cos[\pi m(2j+1)/N] \qquad (11)$$

$$s_{N/2} = \sqrt{\frac{1}{N} \sum_{j=1}^{N} \sin(\phi_j/2) \cos[\pi(j-1)]} \quad (12)$$

where s_m and ψ_m are the puckering parameters of the ZP method. Values of the parameters calculated by the CP and ZP methods for real molecules are often close to each other but not equal due to the different interpretation of puckering itself.

The values of torsional angles ϕ_j can be approximately regenerated from the values of ZP puckering parameters using the following equation

$$\phi_{j(\text{reg})} =$$
$$2 \arcsin \left\{ -\sqrt{\frac{2}{N}} \sum_{m=2}^{(N-1)/2} [s_m \sin(\psi_m + \pi m(2j+1)/N)] \right\}$$
$$(13)$$

for odd N

$$\phi_{j(\text{reg})} =$$
$$2 \arcsin \left\{ -\sqrt{\frac{2}{N}} \sum_{m=2}^{N/2-1} [s_m \sin(\psi_m + \pi m(2j+1)/N)] + \right.$$
$$\left. \sqrt{\frac{1}{N}} s_{N/2}(-1)^{j-1} \right\} \quad (14)$$

for even N. The sum of $\sin(\phi_j/2)$ is not equal to zero for an arbitrary ring as the sum of z_j in the CP method. Thus, $\phi_{j(\text{reg})}$ is not exactly equal to $\phi_{j(\text{ini})}$ for the majority of the rings. The deviation of the calculated values of torsional angles $\phi_{j(\text{reg})}$ from the initial ones $\phi_{j(\text{ini})}$ can be estimated with the parameter σ:

$$\sigma = \sqrt{\sum_{j=1}^{N} (\phi_{j(\text{ini})} - \phi_{j(\text{reg})})^2/(N-1)} \quad (15)$$

The usage of the ZP method has shown that σ values mostly do not exceed $3-5°$ for small and for the majority of medium-size rings and often are within the experimental errors. A great σ value also means the necessity of more than $N - 3$ parameters for the adequate description of the ring shape.

CONFORMATIONAL SPACE

The set of puckering parameters forms a multidimensional space which can be referred to as a conformational space. It can be represented as an $(N - 3)$-hypersphere with the radius equal to the total ring puckering. Each point on the surface of this hypersphere corresponds to some ring conformation. For further usage, we introduce the notion of an equator of a multidimensional hypersphere as a set of points, for which only one s_m or q_m puckering amplitude is nonequal to zero. Points with only $s_{N/2}$ (or $q_{N/2}$) amplitude being nonequal to zero are the poles of a hypersphere. The vectors ($s_m \sin\psi_m$, $s_m \cos\psi_m$) are used as the basis vectors of the conformational space, and the rings corresponding to them have sequences of out-of-plane displacements or endocyclic torsional angles, corresponding to the irreducible representations of the D_{Nh} point group. Each of these vector sets defines a conformation

called "basic" or "primitive".[12] The basic conformations are located on equators and poles of a hypersphere, while other points on the hypersphere correspond to the intermediate conformations. It should be noted that there exists a significant number of highly symmetric intermediate conformations, as well. There are two types of basic conformations at each equator, one with a plane and another one with an axis of symmetry. These two types of conformations are alternated on the equators with the interval depending upon the number of hypersphere dimensions and the equator number. Conformations belonging to one type are geometrically equivalent but have different atomic numbering. On the two poles of a hypersphere (if any) two crown conformations are located which can be transformed one into another by reversing the order of numbering. Thus for an N-membered ring $N - 3$ basic conformations exist in the conformational space.

For example, the conformational space of six-membered rings can be represented as a sphere in 3D-space (the part of this sphere is displayed on RICON screenshot on Figure 4). The boat and "twist-boat" basic conformations are located on the equator of the sphere while the chair forms are located on its poles.

Basic conformations correspond to the basis vectors of a conformational space; therefore, a ring conformation can be represented as a linear combination of basic conformations (*i.e.*, z-displacement of each atom in a ring is the sum of z-displacements of this atom in basic conformations in CP approach). Evans and Boeyens[15] showed that puckering amplitudes of basic conformations computed with the CP method composing the conformation of a ring under study can be found from the following equations

$$c_m = \frac{q_m(-\cos \varphi_m \sin b_m + \sin \varphi_m \cos b_m)}{\sin a_m \cos b_m - \cos a_m \sin b_m} \quad (16)$$

$$d_m = \frac{q_m(\cos \varphi_m \sin a_m - \sin \varphi_m \cos a_m)}{\sin a_m \cos b_m - \cos a_m \sin b_m} \quad (17)$$

where c_m and d_m are puckering amplitudes of "sin-type" and "cos-type" basic conformations (with plane and with axis of symmetry) from mth equator, a_m and b_m are phase angles of basic conformations closest to the conformation under study with φ_m phase angle. We have simplified these equations using trigonometric transformations

$$c_m = \frac{q_m \sin(\varphi_m - b_m)}{\sin(a_m - b_m)} \quad (18)$$

$$d_m = \frac{q_m \sin(a_m - \varphi_m)}{\sin(a_m - b_m)} \quad (19)$$

Thus, any conformation under study can be considered as a combination of basic conformations located on equators with c_m and d_m puckering amplitudes and the basic conformation located on the pole with $q_{N/2}$ amplitude (only for even rings). For the ZP method the equations are the same after replacement of q_m and φ_m for s_m and ψ_m.

The values of puckering parameters depend on the order of numbering of ring atoms. For five- and six-membered rings it is possible to reduce the puckering parameters into an interval using a permutation of initial atomic numbers.
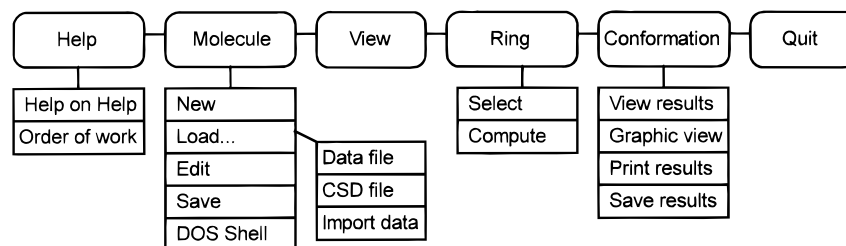
Figure 1. Scheme of main menu structure in RICON program.

This procedure suggested by us[16] allows one to use only a small part of the hypersphere instead of the whole sphere as well as to compare the conformations independently from their atomic numbering. For the N-membered rings, there are two types of possible permutations: the cyclic permutation P_c^j, i.e., the shift of atomic numbering by j, and the permutation P_s corresponding to a change in the direction of numbering $(1\text{-}2\text{-}3\text{-}...\text{-}N \rightarrow 1\text{-}N\text{-}(N-1)\text{-}...\text{-}2)$. The application of P_c^j permutation leads to the following new phase angles: $\psi_m^{(j)} = \psi_m^{(0)} + 2\pi mj/N$ and for even rings $s_{N/2}^{(j)} = (-1)^j s_{N/2}^{(0)}$. For the P_s permutation the new phase angles are related to the initial ones in the following way: $\psi'_m = -\psi_m + \pi$, for even rings $s'_{N/2} = -s_{N/2}$. So, $2N$ ways of numbering exist for N-membered ring, but they are not sufficient for the reduction into the unique interval for rings larger than six-membered ones, because the number of permutations is less than the total number of basic conformations. Evidently, the reduction of the puckering parameters into the interval for these rings is possible only for one equator. Additional possibility of 2-fold reduction of the field of variation of the puckering parameters arises if the inversion operation can be applied to the atomic coordinates (i.e., the change of the sign of all coordinates).[16]

RICON ABILITIES AND INTERFACE

For quantitative and qualitative description of ring conformations in organic and inorganic molecules on the basis of puckering parameters we have developed for IBM PC compatible computers the program RICON (Ring Conformations).[27] RICON uses atomic coordinates as the initial data and gives the name to the conformation of the cyclic molecule under study. RICON also provides some useful functions for studying geometrical parameters of a molecule and working with databases. Steps of work with a molecule resulting in the name of a molecule conformation are performed using the highly developed menu system. The detailed hypertext help system is available at any step of work with RICON.

RICON has a convenient menu system (Figure 1) which can be navigated through with the help of a keyboard or a mouse. The initial geometrical data (cell parameters and fractional atomic coordinates or Cartesian coordinates) can be either input from a keyboard or loaded from a file. RICON uses either its own format of files or MMX format. The data for a new molecule can be also loaded from Cambridge Structure Database files. For other formats the program has the option "import data" which allows one to load the data from the files in arbitrary text format by marking with the RICON file viewer the positions of atomic coordinates, names of atoms, and cell parameters on the screen.

RICON allows one to view and rotate the molecule, to obtain the values of bond lengths, bond angles, and torsional angles clicking the appropriate atoms on the screen.

The bond matrix is generated from interatomic distances and atom types using the method suggested by Baber and Hodgkin.[28] After automatic generation of bonds in the mode "edit bonds" it is possible to create new bonds between atoms or to delete the generated ones.

The next step of the work with RICON is the selection of a ring in a molecule for further analyzing its conformation with the help of the puckering parameters.

RICON automatically searches for all rings in a molecule after entering Select dialog screen. The molecule is represented as a graph consisting of vertices (atoms) and edges (bonds), and the perception of rings in this graph is performed using the variation of a standard "walking" technique.[29] The search algorithm is the following.

At the beginning of each iteration all "trees" in a graph are deleted. It is performed by the iterative erasure of all vertices with the connectivity equal to one. If all vertices in the graph are deleted during this process, then all rings in the graph are found. Otherwise some vertex is selected (further, the "first" vertex) and another vertex (the "second" vertex) connected with the first one. Then the algorithm walks about the graph (beginning from the first vertex through the second one) while noting the path traced and the branch points met. If the second vertex is a branch point it is noted too. Finally the path closes on the first vertex (then this path is a ring that is stored) or on another vertex (then the whole path is not a ring). Then the path is shortened to the last branch points with the untraced edges. After all paths have been traced from every noted branch point, all rings containing the edge between the first and second vertices are found. This edge is deleted and the next iteration starts.

The ring for the computations of puckering parameters can be selected either from the "rings list" window with automatically found rings or entered by selecting atoms in the molecule window one by one.

RICON can compute both the CP puckering parameters[11] and ZP puckering parameters;[13,16] the parameters for six-membered rings can be automatically reduced into minimal interval[16] using the procedure of renumbering atoms.

NAMES OF CONFORMATIONS

The method of verbal naming of conformations on the basis of puckering parameters is the following. A name is given for a ring with the size from 5 to 10 excluding 6 using the contributions of basic conformations into a conformation under study using eqs 18 and 19 (four-membered rings can be only "puckered" or "flat", and six-membered ones are analyzed with the advanced method discussed below).

Table 1. Names of Basic Conformations for Ring with Sizes from 5−10

size of a ring	second equator	third equator	fourth equator[a]	pole
5	envelope, twist			
6	boat, twist−boat			chair
7	boat, twist−boat	chair, twist−chair		
8	boat−boat, boat	long chair, chair		crown
9	boat−boat, twist−boat−boat	C_{3v}, D_3	chair−chair′, twist−chair−chair′	
10	boat−boat, twist−boat−boat	chair−chair, twist−chair−chair	boat−chair−boat′, long chair′	crown

[a] The basic forms located on this equator are equivalent in symmetry for 9-membered rings to a chair−chair and a twist−chair−chair and for 10-membered rings to a boat−chair−boat and a long chair but not exactly correspond to such conformations adopted by cyclic fragments in real molecules (see ref 24). We use prime in the names of these basic forms.

Names of basic conformations [Note that some basic forms (e.g., located on the fourth equator) do not correspond exactly to the conformations adopted by the cycles in real molecules but serve as the contributions into other conformations.] are listed in Table 1. If a contribution of a basic conformation *X* is greater than 95%, then a conformation under study receives the name "X". If a contribution of a conformation *X* is greater than 80‰, then the target name will be "distorted X". If a sum of contributions of conformations *X* and *Y* is greater than 80% and a contribution of *X* is greater than that of *Y*, then the target name will be "intermediate between X and Y" if *X* and *Y* are located on the same equator and "combination of X and Y" otherwise. If a sum of contributions of conformations *X* and *Y* is greater than 80% and a contribution of *Y* is greater than that of *X*, then the target name will be "intermediate between Y and X" or "combination of Y and X", respectively. If a sum of contributions of conformations *X*, *Y*, and *Z* is greater than 80%, then the target name will be "combination of X, Y, and Z" (the order of basic conformations names in the target name is from the maximal contribution to the minimal one as for the previous case). If a combination of contributions of basic conformations does not match any case listed above, then the target name will be "combination of more than three basic conformations".

For six-membered rings there are three basic conformations and three other highly symmetric conformations which may be represented as a combination of basic ones. To include all six standard conformations into naming process we have developed the following procedure. Three contributions of basic conformations P_1, P_2, and P_3 each varying from 0 to 1 form a three-component triangle diagram which can be considered as an alternative presentation of the conformational map. This map is divided into the areas with the unique name of a conformation in each area (Figures 2, and 3). If a sum

$$S = \sum_{i=1}^{3} |P_i(\text{conf under study}) - P_i(\text{standard conf})|$$

for one of six standard conformations named *X* is less than 0.1, then the target name will be X; if this sum is less than 0.2, then the target name will be distorted X. Otherwise a conformation under study is intermediate between two standard conformations. The pair of standard conformations *X* and *Y* is chosen in such a way that a distance between a point under study and a line between *X* and *Y* is minimal among all possible pairs and a projection of a point on this line is between *X* and *Y*. The target name will be intermediate between X and Y if the conformation *X* is closer to a conformation under study than *Y*, otherwise the name will
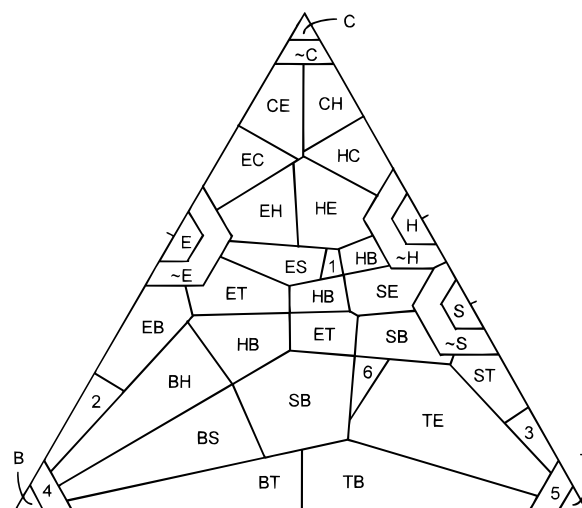

Figure 2. Partition of the conformational space of six-membered rings computed by ZP method into the fields with different names (1 − SE, 2 − BE, 3 − TS, 4 − ∼B, 5 − ∼T, and 6 − ET).
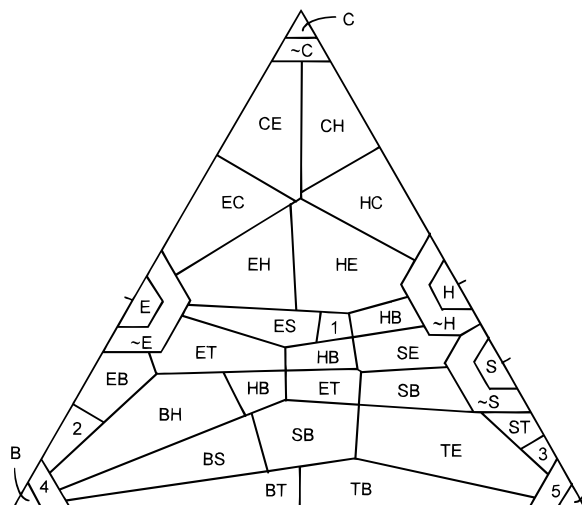

Figure 3. Partition of the conformational space of six-membered rings computed by CP method into the fields with different names (1 − SE, 2 − BE, 3 − TS, 4 − ∼B, and 5 − ∼T).

be intermediate between Y and X. In Figures 2 and 3 C means chair, B − boat, T − "twist boat", E − "envelope", H − "half chair", S − "screw", ∼ means "distorted", and XY means intermediate between X and Y.

The verbal description of conformations obtained with the help of RICON can be used for several purposes, e.g., for the unambiguous description of ring shape, for the search for similar conformations in 3D databases, and for clustering molecules on the basis of their shape.

After computing parameters for the ring conformation one can browse them in the text mode and view graphic images
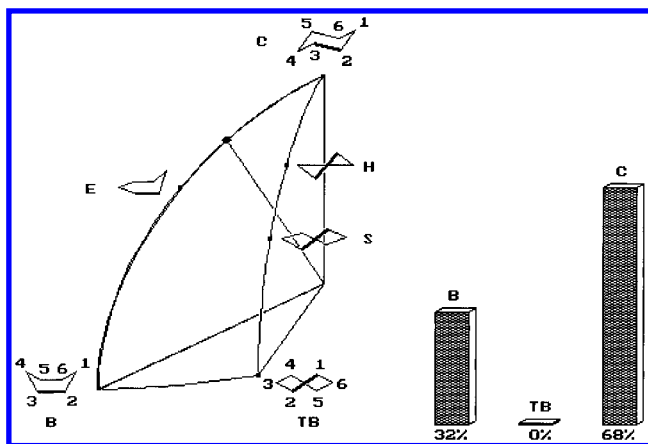
Figure 4. Hard copy of the graphic image created by the program RICON of all basic ring conformations of six-membered rings and the position of the conformation of an example ring in the molecule **1** with respect to them.
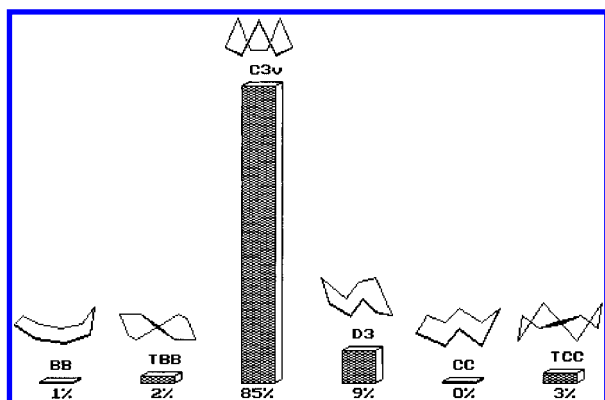

Figure 5. Hard copy of the graphic image created by the program RICON of contributions of all basic ring conformations of nine-membered rings into the conformation of an example ring in the molecule **3**.

of all basic ring conformations, the position of a conformation under study with respect to them, and the name of the conformation. The style of displaying the information depends on the dimension of the surface of the conformational hypersphere for a ring under study:

•Four-membered ring: The hypersphere surface is zero-dimensional (point). Nothing to display.

•Five-membered ring: The hypersphere surface is one-dimensional (circle). The arc between envelope and twist basic conformations is displayed. The flashing dot shows the position of the conformation under study.

•Six-membered ring: The hypersphere surface is two-dimensional (3D-sphere). The part of a sphere obtained from the whole sphere by using the procedure of reduction of puckering parameters into the minimal interval is displayed. Three basic conformations (a chair, a boat, and a twist-boat) and three highly symmetric intermediate conformations (an envelope, a half-chair, and a screw-boat) are located on the sphere, the position of three latter conformations depends on the method used (CP or ZP). The flashing dot shows the position of the conformation under study (Figure 4).

•Seven-, eight-, nine- and, ten-membered rings: The hypersphere surface is three−six-dimensional and cannot be represented on the screen. The contributions of basic forms into the conformation under study are shown as 3D-bars (Figure 5).

•Eleven-membered and greater rings: Neither hypersphere surface is displayed; no contributions are computed.

The results of computations and the graphic images can be dumped on the printer.

EXAMPLES OF RICON USAGE

The RICON program was successfully used for the conformational analysis of hundreds of various cyclic molecules. As an illustration consider the analysis of X-ray structural data for several organic molecules containing cyclic fragments.[30−32]

In the bicyclic structure **1** (Figure 6a) both six-membered rings have the conformation close to the envelope. However,
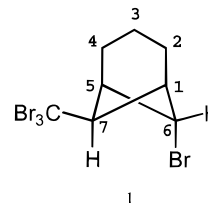
with the help of RICON one can find out that the position of the conformation of the ring 7-1-2-3-4-5 with CBr_3 substituent on the hypersphere is shifted to the pole of the sphere ($\psi_2 = 0.3°$, $\theta = 25.5°$) (Figure 4), and this conformation is named by RICON as "intermediate between envelope and chair", while the conformation of the ring 6-5-4-3-2-1 with Br substituent is shifted to the equator of the sphere ($\psi_2 = 0.0°$, $\theta = 50.2°$) and is named "distorted envelope" (puckering parameters of an ideal envelope according to the ZP method are the following: $\psi_2 = 0.0°$, $\theta = 39.2°$).

With the help of RICON one can also compare a computed and experimental (e.g., obtained from single crystal diffraction analysis) molecular geometry. For example, RICON analysis of results of MM2 force field optimization of the structure **1** shows that the envelope conformations of both six-membered rings are somewhat more distorted for the computed geometry than for the experimental one ($\theta = 22.6°$ for 7-1-2-3-4-5 ring and $\theta = 53.0°$ for 6-5-4-3-2-1 ring); however, the difference is not very significant.

The tricyclotridecene **2** (Figure 6b) contains one five-membered ring 6-2-3-4-5 (which adopts the "intermediate

$$X = OCH_2OCH_3 , Y = CH_2OCH_2C_6H_5 ,$$
$$E = COOCH_3$$
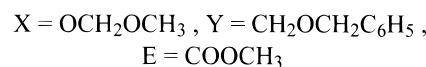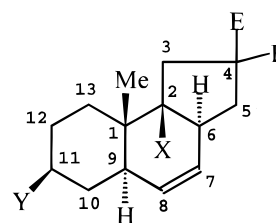
2

between envelope and twist" conformation, $s_2 = 0.643$, $\psi_2 = 8.3°$) and two six-membered rings. The six-membered ring 6-2-1-9-8-7 adjacent to the five-membered ring has a conformation named by RICON the "distorted boat" ($S = 0.862$, $\psi_2 = 1.6°$, $\theta = 88.7°$); the conformation of 1-9-10-11-12-13 ring is the "distorted chair" ($S = 1.119$, $\psi_2 = 12.5°$,
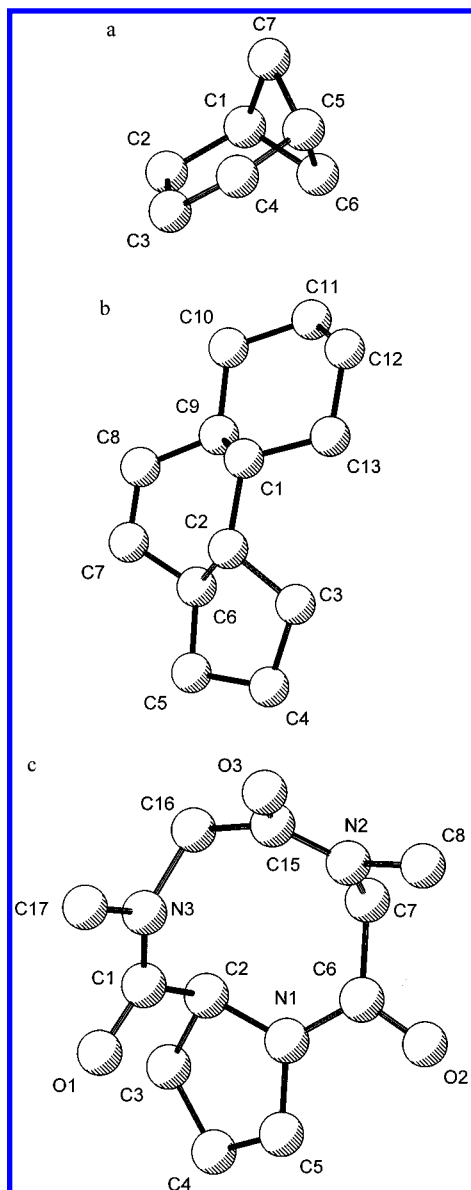
Figure 6. ORTEP drawings of structures **1** (a), **2** (b), and **3** (c) (for compounds **1** and **2** only ring atoms are shown, for compound **3** phenyl rings are deleted).

$\theta = 5.1°$). For this compound RICON can be used as a tool for quantitative analysis of the substituent influence on the ring shape (if the X-ray data for similar compounds are available).

RICON is also useful for the correct description of the shape of medium-size rings. For example, RICON allows one to analyze the conformation of a nine-membered ring in the dibenzyl substituted tripeptide (structure **3**, Figure 6c)
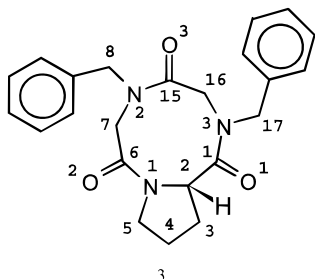
on the basis of the puckering parameters ($s_2 = 0.047$, $\psi_2 = 152.2°$, $s_3 = 1.833$, $\psi_3 = 122.8°$, $s_4 = 0.064$, $\psi_4 = 271.3°$)

and unambiguously characterize it as a "distorted C_{3v}". The computed parameters can be used for the comparison of the conformation of structure **3** with the conformations of other tripeptides. It should be mentioned that the analysis of this conformation by "ordinary" methods is rather difficult.

Recently RICON have been used for the analysis of ring conformations for a large number of nine-membered rings[33] and for the analysis of the shape of pseudocycles formed by six heteroatoms in 450 18-crown-6 molecules.[34]

CONCLUSION

A new computational tool RICON for the conformational studies of cyclic molecules on the basis of puckering parameters has been developed. RICON allows one not only to compute and analyze geometric and puckering parameters of cyclic fragments (using as the input data experimental or computed 3D atomic coordinates) but also to obtain the verbal description of the ring conformation.

ACKNOWLEDGMENT

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CI960115F