STEREOCHEMICAL STUDIES. XXXIV.* QUANTITATIVE DESCRIPTION OF RING PUCKERING VIA TORSIONAL ANGLES. THE CASE OF SIX-MEMBERED RINGS

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The quantitative description of ring puckering suggested by the authors is compared with that of Cremer and Pople. The applicability of both methods is discussed for the case of six-membered rings with the use of model calculations simulating various ring distortions and with the analysis and comparison of puckering parameters computed on the basis of x-ray data for 40 six-membered rings in different cyclic structures. The $2N$ times reduction of the field of variation of puckering parameters for the N-membered ring is suggested and the algorithm for the renumbering of the ring atoms for this purpose is described for six-membered rings.

INTRODUCTION

The reliable experimental and computational methods accessible nowadays provide exhaustive and accurate information on the geometries of a great number of cyclic molecules. In this connection a problem arises: how to convert the long tables of atomic coordinates into a clear notion and brief quantitative description of the rings shape in molecules. The most usual description of the ring shapes is based on their intuitive comparison with some reference forms such as chair, boat or half-boat. This pictorial characterization is supported by some metric parameters, such as deviations of the torsional angles from the standard values or displacements of some atoms from a particular plane.

A number of quantitative methods are available for the description of the spatial forms of cyclic molecules, and each has its advantages and shortcomings. In this paper we describe the method suggested previously by the authors (for short communications see Refs 1 and 2) and compare it with the now commonly used Cremer and Pople (CP) method.[3]

The need for a general quantitative description of ring forms was realized long ago and a number of attempts have been made with the use of different levels of sophistication. Kilpatrick *et al.*,[4] in their pioneering work in 1947, considered the conformational interconversion in the cyclopentane ring in terms of 'pseudo-rotation of puckering.' According to this approach, any conformation of cyclopentane can be described by two parameters: the amplitude and phase angle of pseudo-rotation, both obtained from the out-of-plane displacements of five carbon atoms. Later the description of pseudo-rotation on the basis of endocyclic torsional angles was undertaken for certain types of cycles: five-membered,[5–8] six-membered[8–11] and seven-membered.[11–14] Attempts have also been made to use bond angles for the same purpose.[15,16] While all possible conformations of the five-membered ring can be described in terms of pseudo-rotation, in the case of larger rings there are conformations which are beyond the scope of this description, such as the most frequent 'chair' form of cyclohexane and all the intermediate forms between chair and boat, the twist–boat family. These forms were described by ring puckering coordinates with the use of the out-of-plane displacements of ring atoms, and such descriptions allowed them to be depicted schematically on a spherical surface with chair forms on the poles and pseudo-rotating boat and twist–boat forms on the equator.[17]

It should be noted that the above-mentioned studies did not contain accurate and general procedures for reducing the ring atomic Cartesian coordinates to a set of puckering parameters. Such a procedure was worked out for the first time in 1975 by Cremer and Pople,[3] who introduced 'the general definition of ring puckering coordinates' as a generalization of previous approaches. According to the CP method, for a ring of size N, the set of $N-3$ puckering coordinates (amplitudes and phase angles deduced from the deviations z_j of the ring

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atoms from the specially constructed 'mean' plane) leads to the description of the whole spectrum of possible conformations. In particular for the six-membered rings the CP method operates with three variable coordinates and provides a description of ring shape with the use of the polar coordinate system in terms of total puckering amplitude Q, polar angle θ^{CP} and phase angle ϕ_2. The essential advantage which distinguishes the CP method from the earlier treatments is the absence of approximations, although its applicability was questioned.[18,19] The CP method is currently widely used for the analysis of puckered ring forms[20-24] and for the unambiguous definition of ring substituent positions.[25] Another kind of puckering parameter, as suggested by Altona and Sundaralingam,[7] is based on the endocyclic torsional angles φ_j. The CP puckering parameters can be connected, as shown,[26,27] with the values of φ_j, where the approximate relationships between φ_j on the one hand, and the CP and Altona–Sundaralingam puckering parameters on the other, were derived. This approach was based on the Fourier transform of the geometrical parameters[28] and appeared to be fruitful in the analysis of conformations of seven-membered rings with torsional angles as such parameters.[29] For the same purpose the general relationship between the torsional angles in a seven-membered ring was applied.[30] The fact that the geometry of the five membered rings was described using the assumption of constant distances between the atoms and the mass centre of the ring[31] also should be mentioned.

As we pointed out previously,[1] the CP method leads to a re-definition of the notion of 'puckering' based on the angular parameters which seem to be generally accepted in stereochemistry.[32] To elucidate the essence of the problem, let us consider the chair conformation of 1,4-oxathiane[33] (shown in Figure 1) with the aim of determining which part of it is more flattened and which part is more puckered. The following criteria which are usually applied for the description of the ring forms can
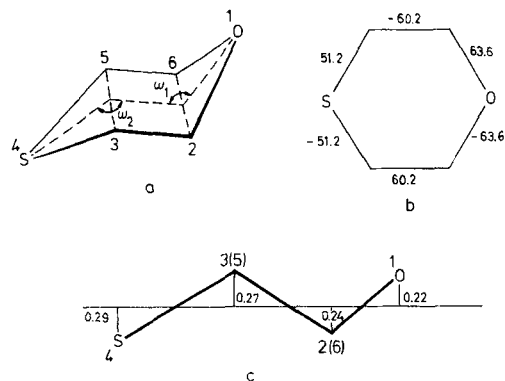
be used in this case. The first criterion is based on the comparison of the values of dihedral angles $\omega_1 = 124°$ and $\omega_2 = 133°$ (Figure 1a), and this clearly shows that the sulphur apex of the oxathiane ring is flattened in comparison with the oxygen apex. Evidently this criterion can be applied only to the six-membered rings with atoms 2, 3, 5 and 6 lying in one plane. The second and more general criterion is based on the comparative analysis of the pairs of the endocyclic torsional angles at each apex.[32] If the absolute value of the difference between the torsional angles (each taken with its sign[34]) at one apex is greater than another, the former fragment is considered to be more puckered than the latter. According to this criterion, in the case of 1,4-oxathiane (for torsional angles see Figure 1b), the sulphur-containing fragment is flattened noticeably compared with the C—O—C fragment. Thus, both criteria used in stereochemistry lead to the same conclusion.

In contrast, the CP method leads to the opposite conclusion, namely that the CP parameters ($Q = 0.62$, $\theta^{CP} = 5.5°$, $\phi_2 = 180°$) correspond to flattening of the oxygen apex compared with the sulphur apex (for normal deviations of atoms from the mean plane, see Figure 1c). A similar situation can take place in the metal-containing rings. In Figure 2b, ring A in the complex compound pictured in Figure 2a[35] is represented. The dihedral angles $\omega_1 = 119°$ and $\omega_2 = 137°$ show significant flattening of the Cu-containing apex. Consideration of the torsional angles which are shown in Figure 2c leads to the same conclusion. In spite of this, the CP method (for which the parameters are $Q = 0.63$, $\theta^{CP} = 1.5°$, $\phi_2 = 189°$) shows an almost ideal chair with a slightly flattened C—C—C apex.

Another problem arises when the puckerings of two equilateral rings are compared, such as the chair forms of cyclohexane (bond length 1.535 Å [36]) and cyclohexasilane (bond length 2.342 Å [37]). The dihedral angles $\omega_1 = \omega_2 = 130°$ and the endocyclic torsional angles of $\pm 55°$ for cyclohexane show that its puckering is close

Figure 1. Geometry of 1,4-oxathiane ring: (a) general view of the ring; (b) torsional angles; (c) z-coordinates in the CP method
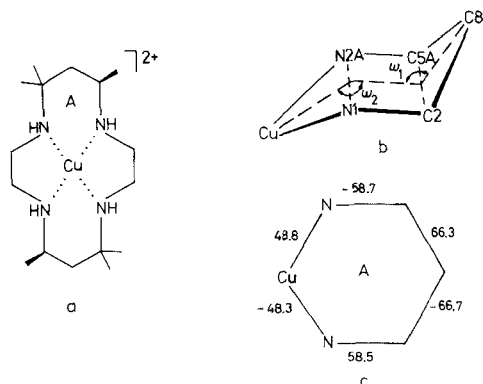

Figure 2. (a) Complex compound containing (b) the ring A (C-8—C-2—N-1—Cu—N-2A—C-5A); (c) torsional angles in ring A

to that of cyclohexasilane ($\omega_1 = \omega_2 = 127 \cdot 5°$; torsional angles of $\pm 58°$). However, the total puckering CP amplitudes Q which characterize the degree of puckering of the ring are $0 \cdot 565$ and $0 \cdot 916$ for cyclohexane and cyclohexasilane, respectively, indicating pronounced puckering for the latter ring in comparison with cyclohexane. It is also possible to envisage a situation where the less puckered, from the stereochemical viewpoint, equilateral ring has larger bond lengths than a more puckered ring. The CP method in this case will give a larger value for the total puckering amplitude for the ring which in fact is less puckered.

Thus the examples considered demonstrate that CP method can, in certain cases, give results in contradiction with the conventional definition of puckering and it introduces a new definition of this notion. The origin of the aforementioned discrepancies is rooted in the essence of the CP method. The CP description of puckering is based on the displacements of atoms from the 'mean' plane and hence any increase in z-coordinates caused both by a real angular distortion of the ring and by non-equality of bond lengths automatically leads to an increase in the resulting quantitative puckering characteristics. Thus, for the oxathiane cycle the difference in C—O and C—S bond lengths is large enough not only to disguise the angular distortions but even to overbalance them. The second example demonstrates that the total puckering amplitude Q takes into account not only the degree of puckering of the ring but also its space dimensions. Hence the comparison of the shapes of two cycles with different bond lengths is impossible by the direct application of the CP puckering analysis exclusively.

Attempts to supplement the CP method with some additional 'normalization' procedure to avoid the pronounced dependence of the CP parameters on bond lengths have failed and thus the necessity for another approach to the problem was recognized.

PUCKERING PARAMETERS BASED ON TORSIONAL ANGLES

In a previous paper[1] we suggested the use of the endocyclic torsional angles φ_j as a base for the CP calculational procedure. Thus, instead of the normal deviations z_j from the mean plane, the values of $\sin(\varphi_j/2)$ were used for calculations of the puckering amplitudes and phase angles which we denote s_m and ψ_m (to distinguish them from the corresponding CP denotions q_m and ϕ_m, respectively[3]). Equations (1)–(3), which correspond to equations (12)–(14) in Ref. 3 serve for the calculation of s_m and ψ_m for the N-membered ring, equation (3) being necessary only for even-numbered rings.

$$s_m \cos \psi_m = - (2/N)^{1/2} \sum_{j=1}^{N} \sin(\varphi_j/2)\sin[\pi m(2j + 1)/N] \quad (1)$$

$$s_m \sin \psi_m = - (2/N)^{1/2} \sum_{j=1}^{N} \sin(\varphi_j/2)\cos[\pi m(2j + 1)/N] \quad (2)$$

$$s_{N/2} = N^{-1/2} \sum_{j=1}^{N} \sin(\varphi_j/2)\cos[\pi(j - 1)] \quad (3)$$

where

$$m = 2, ..., M; \quad M = \mathrm{ENT}[(N - 1)/2] \quad (4)$$

As a torsional angle φ_1 the angle 1—2—3—4 is chosen, as φ_2 the angle 2—3—4—5, etc.

In the case of six-membered rings, $m = 2$ and any conformation is described by three parameters s_2, ψ_2, s_3 or, in terms of the polar coordinate system [equations (5) and (6)], by the polar and phase angles θ and ψ_2 and the total puckering amplitude S:

$$s_2 = S \sin \theta \quad (5)$$

$$s_3 = S \cos \theta \quad (6)$$

If only polar and phase angles θ and ψ_2 are considered, any conformation of the six-membered ring can be represented by a point on the surface of the sphere shown in Figure 3a, similar to the CP sphere.[3] Points on this sphere which correspond to the symmetrical conformations coincide exactly with those on the CP sphere, while other points are usually shifted. On the poles of both spheres ($\theta = 0$, $180°$) the chair conformations are located, and on the equators the boat forms with $\psi_2 = 60° \times n$ and the twist-boat forms with $\psi_2 = 60° \times n + 30°$ are located ($n = 0, 1, ..., 5$). For the equator of the sphere, see Figure 3b.

It should be noted that equations (1) and (2) are slightly different from those suggested in our previous work.[1] We have found it reasonable to modify the first version of our method (ZP) so that the points corresponding to the 'canonical' conformations (such as boat, or chair or twist—boat in six-membered rings) would be the same as on the CP sphere. The modified version based on equations (1)–(4) will be referred to here as ZPD. The phase angles ψ_m in the ZPD method are connected with ψ_m^{ZP} by

$$\psi_m = \psi_m^{ZP} - 3\pi m/N - \pi/2$$

The schematic representation of the ring forms on the surface of the sphere is of great use for the analysis of the ring distortions. Values of polar and phase angles for a given distorted ring reflect the distance between the point corresponding to this ring and the points of the canonical conformations (such as chair, boat or twist—boat) on the surface of the sphere. For example, some displacement of the point from the pole ($\theta = 0$) in the direction of the boat with $\psi_2 = 0°$ corresponds to flattening of the part of the cycle adjacent to fourth atom with respect to that adjacent to the first atom and vice versa for the displacement of the point in the direction of the boat with $\psi_2 = 180°$. For the points located

close to the equator, the distance from the adjacent boat form in the direction of the twist–boat describes the degree of twisting of the corresponding cycles.

For the ZPD method the values of $\sin(\varphi_j/2)$ involved in the computation of puckering parameters satisfy equations (5)–(7) for z-coordinates in Ref. 3 only approximately and the first amplitudes s_0 and s_1 [which can be calculated using equations (1) and (2) with $m = 0, 1$], although usually very small, may be different from zero. Thus the total puckering amplitude $S = (\Sigma_{m=2}^{M} s_m^2)^{1/2}$ can be slightly different from the value of $[\Sigma_{j=1}^{N} \sin^2(\varphi_j/2)]^{1/2}$ in some cases and torsional angles

a

b

Figure 3. (a) ZPD puckering parameters for the six-membered ring in a polar coordinate system; (b) the six-membered ring forms on the equator

φ_j can be generated from the values of $N - 3$ puckering parameters s_2, ψ_2, s_3, ..., also approximately using the following equation:

$$
\begin{aligned}
\varphi_{j\,\text{calc.}} = \\
2 \arcsin\Bigg\{ &- (2/N)^{1/2} \sum_{m=2}^{M} s_m \sin[\psi_m + \pi m(2j + 1)/N] \\
&+ N^{-1/2} s_{N/2} \cos^2(\pi N/2)\cos[\pi(j - 1)] \Bigg\} \quad (7)
\end{aligned}
$$

The deviation of the thus calculated values of torsional angles $\varphi_{j\,\text{calc.}}$ from the initial values φ_j can be estimated with the parameter σ:

$$
\sigma = \left[\sum_{j=1}^{N} (\varphi_j - \varphi_{j\,\text{calc.}})^2/(N - 1) \right]^{1/2} \quad (8)
$$

For five- and six-membered rings the σ values usually do not exceed 2–3° and in most cases are within experimental error, whereas for medium-sized rings such consistency is not always observed. The ZPD method describes well the conformation and distortions of cyclic molecules when σ does not exceed 3–5°. In the case of large σ values, ZPD puckering parameters should be analysed with caution, although even here the ZPD method in most cases describes the puckering of the ring correctly.

If one returns to the example of 1,4-oxathiane considered above, the ZPD puckering parameters ($S = 1\cdot20$, $\theta = 4\cdot6°$, $\psi_2 = 0°$) show that the oxygen apex is more puckered than the sulphur apex, which is in complete agreement with the stereochemical criteria. The ZPD parameters for ring A in the complex compound in Figure 2a ($S = 1\cdot19$, $\theta = 6\cdot6°$, $\psi_2 = 359\cdot4°$) indicate that the Cu apex is flattened, in agreement with conclusions obtained from consideration of dihedral and torsional angles.

In these cases, a significant difference between the two methods in the description of puckering is observed. How often can such contradictions be found? To answer this question and, in general, to evaluate the applicability of each method, comparisons of the ZPD and CP parameters (1) for the model cycles subjected to some geometrical distortions and (2) for a large number of the rings in cyclic molecules were made.

MODEL CALCULATIONS

Consideration of the model rings leads to the possibility of separating the geometrical factors which have an effect on the ring form and which are present in one combination or another in a real ring. For example, substitution of one of the carbon atoms in cyclohexane by a heteroatom X results in a change in the lengths of the two adjacent bonds and magnitudes of the bond angles, especially the CXC angle. The model calculations allow the effect of such geometrical distortions on
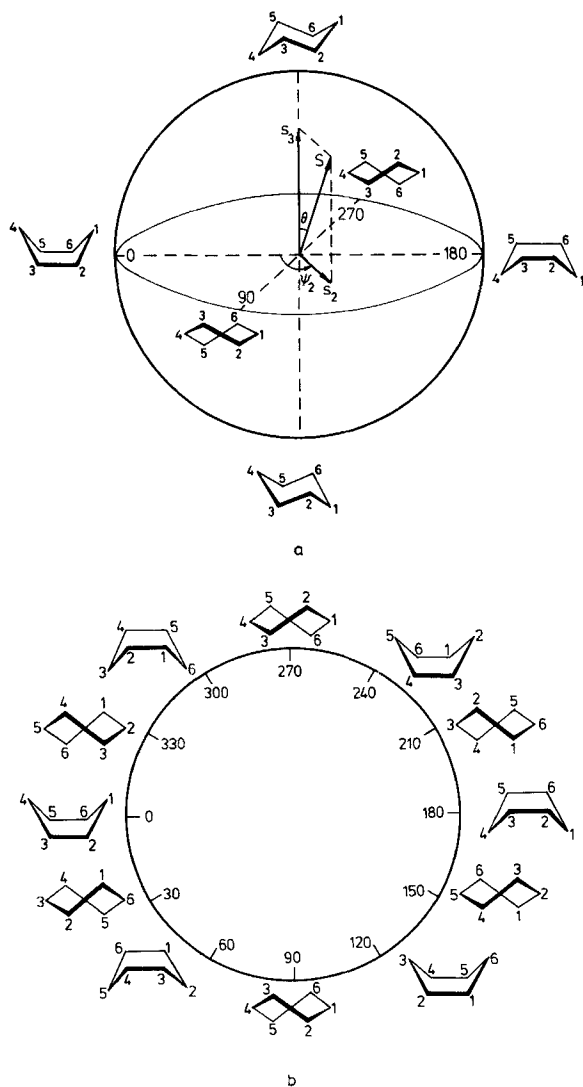
the CP and ZPD puckering parameters to be considered. Three canonical conformations of cyclohexane (chair, boat and twist–boat) were taken as the base for model calculations, bond lengths of $1 \cdot 535$ Å and bond angles of $111 \cdot 4°$ being used for the reference undistorted ring.[36] The results of two versions of the model calculations are considered in this section.

1. All the endocyclic torsional angles were kept constant ($\pm 55°$ for chair, 0, $+55$, $-55°$ for boat and 60, -30, $-30°$ for the twist–boat form). Two neighbouring bonds 'C—X' were lengthened or shortened simultaneously, with the constant values of $1 \cdot 535$ Å for the other ('C—C') bonds, and the values of the bond angles were obtained from the optimization procedure. Although this model is artificial (as the torsional angles are the most changeable among the inner geometrical parameters), it allows one to retain equal puckering of opposite apices according to the criterion based on torsional angles. The ZPD parameters are in agreement with that criterion while the CP parameters Q and θ^{CP} depicted in Figure 4 as a function of Δl ($\Delta l = l_{C-X} - 1 \cdot 535$ Å) are strongly dependent on Δl. The comparison of the dihedral angles 612/2356 and 345/2356 shows the slow increase in their difference with the lengthening of the 'C—X' bonds.

2. The model ring with the fixed dihedral angles 612/2356 (ω_1) and 345/2356 (ω_2), similar to ω_1 and ω_2 in Figure 1a, with $\omega_1 = \omega_2 = 130°$, was studied. The coordinates of five 'carbon' atoms 2, ..., 6 were fixed while l_{16} and l_{12} were changed simultaneously so that the 'heteroatom' X remained within the same plane 612 as in a regular chair
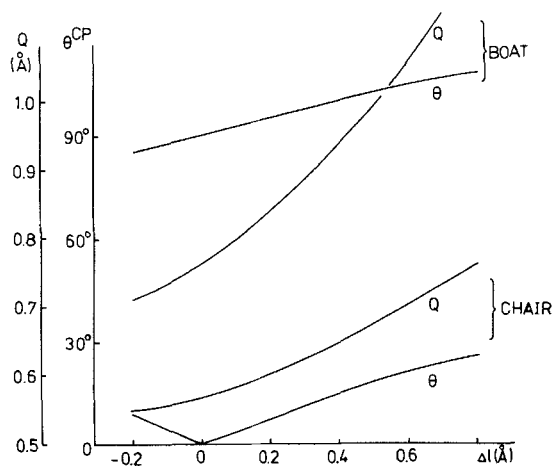

Figure 5. Dependence of the ZPD and CP polar angles θ and θ^{CP} on Δl for the model six-membered rings with fixed values of dihedral angles ω_1 and ω_2.

or boat form of cyclohexane. Figure 5 represents the dependence of the polar angles θ^{CP} and θ on Δl for the chair and boat conformations and shows that the CP puckering parameters are extremely sensitive to such types of distortions, in contradiction with the criterion based on dihedral angles ω_1 and ω_2. Analogous tendencies were found for total puckering amplitudes.

Other versions of the model calculations lead to similar conclusions.

REDUCTION OF THE PUCKERING PARAMETERS INTO MINIMAL SUFFICIENT INTERVALS

In practical applications of puckering parameters, a specific feature of all methods becomes evident. Let us consider again the oxathiane cycle (Figure 1a) and change the position of the first atom in it. In Table 1 the ZPD parameters for each numbering of the atoms in the ring are given. It can be seen that the total puckering amplitude S is the same, whereas the polar and phase angles θ and ψ_2 change their values from one numbering to another. The same dependence also exists for the CP

Figure 4. Dependence of Q and θ^{CP} for the chair and boat forms of model rings on Δl at constant values of all endocyclic torsional angles
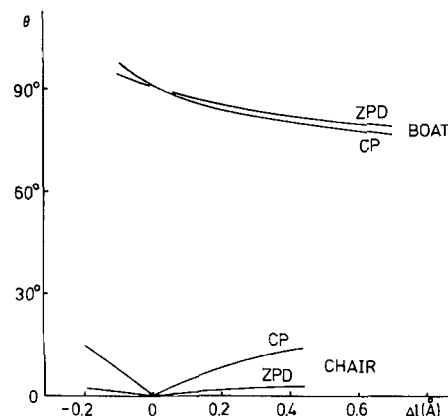
Table 1. Effect of choice of the first atom in the oxathiane ring (Fig. 1, see Ref. 33) on the puckering parameters θ, ψ_2

Atomic numbering	θ	ψ_2
1–2–3–4–5–6	4·6	0
2–3–4–5–6–1	175·4	120
3–4–5–6–1–2	4·6	240
4–5–6–1–2–3	175·4	0
5–6–1–2–3–4	4·6	120
6–1–2–3–4–5	175·4	240

method. Hence the puckering parameters in both methods depend on the atomic numbering, so for the single conformation there is a number ($4N$ for an N-membered ring, as will be shown in this section) of sets of parameters, which makes it difficult to compare the conformations of different rings.

Comparison of the puckering of numerous rings led to a problem of the reduction of the field of variation of the angular puckering parameters, i.e. phase angles and polar angle for even-membered rings. As will be shown below, such reduction can be achieved if the ring atoms are numbered in some special way unique to each cycle. Both the CP and ZPD methods lack a standard procedure for numbering of the ring atoms, and this ambiguity leads to the existence of $2N$ different sets of puckering parameters for a single N-membered ring, each set for a certain atomic numbering. The notion of atomic numbering used here includes both the choice of the first atom and the direction in which the numbers increase in the ring (either clockwise or counterclockwise). The numbering procedure proposed by Boeyens[38] is based on accepted nomenclature rules and, although it avoids ambiguity, it also leads to a sparseness of the points on the sphere. On the other hand, when a similar numbering procedure[39] was applied to a special type of ring (pyranoid rings), it resulted in a concentration of the points in a certain part of the sphere. The problem is to achieve a similar concentration of points for rings of general structure.

Here we describe a method for the evaluation of a unique atomic numbering for any N-membered ring which allows one to obtain the angular puckering parameters for both ZPD and CP methods, ψ_m, ϕ_m, and in the case of even rings, θ, θ^{CP}, in a minimal sufficient part V of their field of variation. For the case of six-membered rings, as will be shown below, area V in most cases occupies $1/24$th of the whole two-dimensional field of ϕ_2, θ^{CP} ($\phi_2 \in [0, 2\pi]$, $\theta^{CP} \in [0, \pi]$) for the CP method or ψ_2, θ($\psi_2 \in [0, 2\pi]$, $\theta \in [0, \pi]$) for the ZPD method. For the sake of convenience here we shall consider only ZPD puckering parameters and imply that the same conclusions can be drawn for the CP method.

Suppose that the atoms of the N-membered ring are numbered in some way, $1-2-3-\cdots-N$, and the puckering parameters $\psi_m^{(0)}$ and $\theta^{(0)}$ are obtained for this initial numbering. Another set of puckering parameters will be obtained for another atomic numbering. Each renumbering of ring atoms can be represented by permutation

$$P = \begin{pmatrix} 1 & 2 & \dots & N \\ k_1 & k_2 & \dots & k_N \end{pmatrix},$$

which means that number 1 goes to the atom initially numbered k_1, number 2 to k_2 etc. Obviously, only those permutations of the numbers of the ring atoms which do not change the succession of the atoms composing the ring are permissible in our case.

It will be shown below that the permissible permutations of the atomic numbers of the N-membered ring form the group which we denote P_N of the order $2N$. The generators of the group P_N are two permutations:

$$P_c^1 = \begin{pmatrix} 1 & 2 & 3 & \dots & N \\ 2 & 3 & 4 & \dots & 1 \end{pmatrix} \text{ and } P_s = \begin{pmatrix} 1 & 2 & 3 & \dots & N \\ 1 & N & N-1 & \dots & 2 \end{pmatrix}.$$

Now we consider in detail these two permutations and the resulting change in the puckering parameters.

1. The cyclic permutation P_c^1, i.e. shift of the atomic number by unity ($1-2-3-\cdots-N \rightarrow 2-3-4-\cdots-1$) leads to a rotation of the CP Cartesian coordinate system about the z-axis. With the use of equations (1)–(3) for the ZPD method [and equations (12)–(14) in Ref. 3 for the CP method], it can be shown that the phase angles $\psi_m^{(1)}$ corresponding to a new atomic numbering are connected with the initial phase angles $\psi_m^{(0)}$ by the relationships: $\psi_m^{(1)} = \psi_m^{(0)} + 2\pi m/N$ [for m see equation (4)]. Permutation P_c^1 has no effect on the puckering amplitudes s_m, the only exception being for the amplitude $s_{N/2}$ for even-membered rings: $s_{N/2}^{(1)} = -s_{N/2}^{(0)}$. A change in the sign of $s_{N/2}$ results in a change in the polar angle value: $\theta^{(1)} = \pi - \theta^{(0)}$. It is obvious that the recurring application of the permutation P_c^1 leads to the new set of puckering parameters, each set being connected with the previous one in the same way. Hence there are N permutations which are the degrees of P_c^1 and compose the cyclic group of order N:

$$\{P_c^j\} = P_c^1,\ P_c^2, \dots, P_c^j, \dots, P_c^N \equiv E.$$

The effect of P_c^j on the atomic numbering leads to new phase angles: $\psi_m^{(j)} = \psi_m^{(0)} + 2\pi mj/N$. For even-membered rings

$$s_{N/2}^{(j)} = (-1)^j s_{N/2};\ \theta^{(j)} = \begin{cases} \theta^{(0)} & \text{for } j \text{ even}, \\ \pi - \theta^{(0)} & \text{for } j \text{ odd} \end{cases}$$

In the case of a six-membered ring with $m = 2$, $\psi_2^{(j)} = \psi_2^{(0)} + 2\pi j/3$. Figure 6a illustrates the points corresponding to six possible atomic numberings of a six-membered ring which are obtained from the initial one (point 0) by application of P_c^j permutations ($j = 1, 2, \dots, 5$).

2. The second generator of the group P_N is permutation P_s corresponding to a change in the direction of numbering ($1-2-3-\cdots-N \rightarrow 1-N-(N-1)-\cdots-2$). It can be shown that the new phase angles ψ_m' are connected with the initial angles by the relationship $\psi_m' = -\psi_m + \pi$; further, for even rings $s_{N/2}' = -s_{N/2}$ and $\theta' = \pi - \theta$. The puckering amplitudes s_m ($m \neq N/2$) do not change. Figure 6b serves to visualize the effect of P_s on the position of the initial point (1) in the case of six-membered ring on the polar projection of the spherical surface. The resulting point (2) has
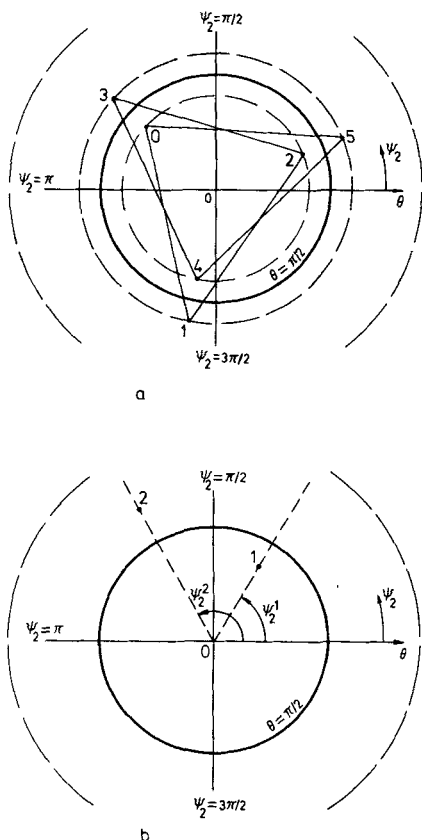
a

b

Figure 6. Effect of permutations (a) P_c^j and (b) P_s on the position of the point on the polar projection of the sphere

Figure 7. The minimal sufficient region V on the sphere

the coordinates $\psi_2^j = \pi - \psi_2$ and $\theta' = \pi - \theta$. If multiplication of permutations is defined as the successive application of P_s and P_c^j, then all the products $P_c^j P_s$ compose the right co-set of the cyclic subgroup $\{P_c^j\}$ with respect to permutation P_s. It can be proved easily that $\{P_c^j\}$ and its right co-set compose the group P_N of the order $2N$ of permissible permutations of the atomic numbers for the N-membered ring.

In the case of six-membered rings, P_6 contains 12 permutations which can be used for the dissection of the spherical surface into 12 equivalent regions, each of them being sufficient for the description of puckering of the whole variety of six-membered rings.

The additional possibility of reducing these two-dimensional sufficient regions arises if the substance exists in two enantiomeric forms. Usually the coordinates from the x-ray data on racemic crystal structures are given arbitrarily for one of two enantiomers contained in a unit cell. Taking into account that the Cartesian coordinates of two
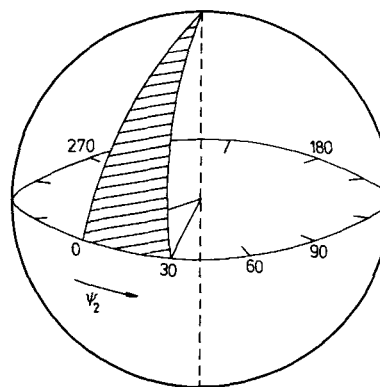
enantiomeric forms are connected by the inversion i operation, we may use it in addition to the permutations to obtain the extra two-fold reduction of the field of variation of the angular puckering parameters.

For the CP method, inversion i results in a change of the sign of all coordinates and for the ZPD one of the torsional angles and thus of the parameters $p_j = \sin(\varphi_j/2)$. Puckering parameters of a six-membered ring change in the following way:

$$\psi_2' = \psi_2 + \pi; \quad \theta' = \pi - \theta\,(\text{ZPD}); \quad \phi_2' = \phi_2 + \pi;$$

$$(\theta^{CP})' = \pi - \theta^{CP}(\text{CP}).$$

This means that inversion of the coordinates of the ring atoms leads to an inversion of the point on the sphere with respect to its origin.

Hence the minimal sufficient region V for six-membered rings (shown by hatching in Figure 7) makes 1/24th part of the whole field of variation of the angular puckering parameters if inversion is used. Figure 8 shows the whole two-dimensional area of θ, ψ_2 (ZPD) or θ^{CP}, ϕ_2 (CP) divided into 24 equivalent parts. In each region the operations are presented which serve to transform the polar and phase angles into the chosen 'canonical' intervals, which are: $\theta \in [0, \pi/2]$, $\psi_2 \in [0, \pi/6]$ (Figure 8).

It should be mentioned that the necessity for inversion i to reduce the puckering parameters in the canonical region can serve for the distinction of rings with coinciding and non-coinciding chirality.

To obtain the puckering parameters in a standard region, the procedure is as follows: (i) choice of an arbitrary atomic numbering; (ii) usual computation of puckering parameters according to the ZPD (CP) procedure; (iii) determination with the use of Figure 8 of the operations (permutations and/or inversion) leading to a required atomic numbering which provides the values of the phase and polar angles in a standard region; (iv) then there are two possibilities for obtaining the new values of puckering parameters which belong to
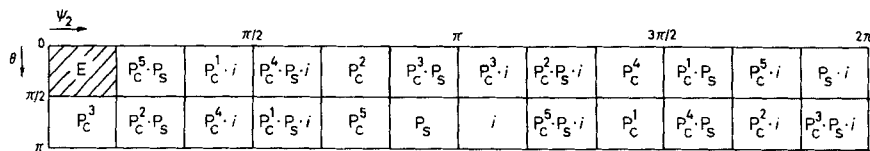
$\psi_2 \rightarrow$	0		$\pi/2$			π			$3\pi/2$			2π
$\theta\downarrow$ 0	E	$P_C^5 \cdot P_S$	$P_C^1 \cdot i$	$P_C^4 \cdot P_S \cdot i$	P_C^2	$P_C^3 \cdot P_S$	$P_C^3 \cdot i$	$P_C^2 \cdot P_S \cdot i$	P_C^4	$P_C^1 \cdot P_S$	$P_C^5 \cdot i$	$P_S \cdot i$
$\pi/2$ π	P_C^3	$P_C^2 \cdot P_S$	$P_C^4 \cdot i$	$P_C^1 \cdot P_S \cdot i$	P_C^5	P_S	i	$P_C^5 \cdot P_S \cdot i$	P_C^1	$P_C^4 \cdot P_S$	$P_C^2 \cdot i$	$P_C^3 \cdot P_S \cdot i$

Figure 8. The two-dimensional area of θ, ψ_2 for the ZPD method divided into equivalent parts. In each part the operation which transforms it into the 'canonical' area (E) is shown

a standard region: (a) with the use of the rules given above or (b) by the repeated ZPD (or CP accordingly) computation for the new atomic numbering (and/or for the opposite directions of the axes). This algorithm can be easily realized with a computer program.

Use of the puckering parameters in a canonical region opens wide possibilities for comparison of the conformations of various rings.

APPLICATION OF THE METHOD

The ZPD and CP puckering parameters calculated for 40 six-membered rings on the basis of x-ray data for arbitrary chosen compounds 1–20[20,40–56] shown in Figure 9 are summarized in Table 2. The atomic numbering for each ring was obtained according to the procedure described above to provide all points in the canonical region for ZPD parameters. Thus the numbering is such that the maximum flattening of the ring is always around the apex 4 and the maximum puckering around apex 1. As can be seen from Table 2, the

parameter σ has satisfactory values for the rings considered (except for 16A, which in fact consists of fused three- and five-membered rings).

Let us analyse the puckering of the rings in structures 1–20. Even a brief look at the puckering parameters in Table 2 allows one to evaluate the ring conformation in most cases. For example, the rings 10B, 11C, 17A, 17D and 19A are almost ideal chairs (θ from $0\cdot1$ to $0\cdot9°$). The rings 3, 4, 11A, 17B, 18A, 18D, 19B, 19D and 20A adopt a conformation close to a chair, although in these cases the fragment of the ring containing the fourth atom is slightly flattened and most of the rings are twisted to some extent (for a non-twisted ring $\psi_2 = 0°$, whereas for a ring twisted to a maximum extent for a given θ value $\psi_2 = 30°$). Such flattening is more significant for the rings 1, 9A, 11B, 16B, 18B and 19C (θ from $7\cdot7$ to $16\cdot7°$), and of these 9A is considerably twisted. The rings 2, 8 and 20B have nearly a half-chair conformation, ring 5 is close to a half-boat and rings 9B and 10A are intermediate between half-chair and half-boat. The rings 7, 12, 13, 14A, 14B, 15A–D, 17C and 18C are
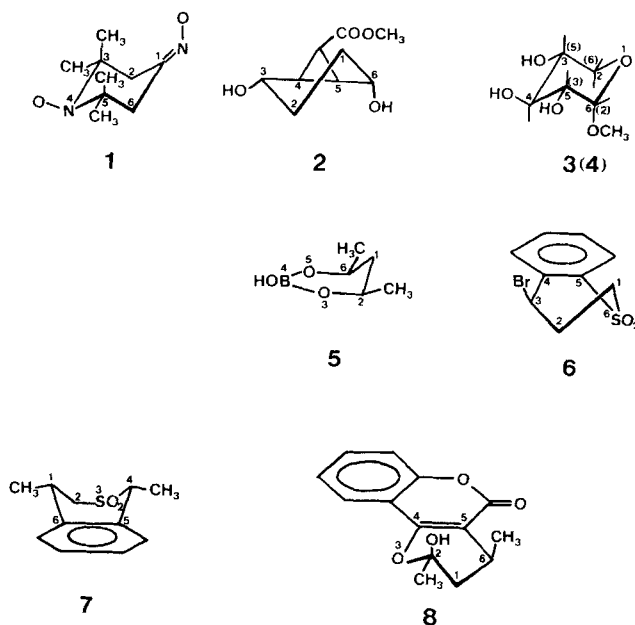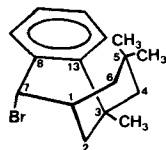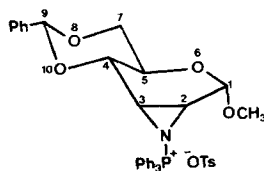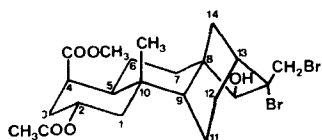

Figure 9. Structures 1–20 (for references see Table 2)
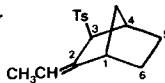
9   A 2-3-4-5-6-1
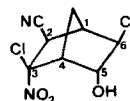   B 2-1-7-8-13-3

10 A 5-6-1-2-3-4
       B 8-9-10-4-5-7
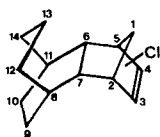
11 A 5-6-7-8-9-10
       B 14-13-12-11-9-8
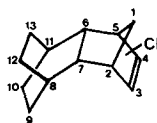   C 5-10-1-2-3-4
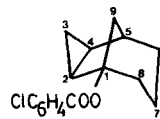
12

13

14 A 11-6-7-8-9-10
       B 5-4-3-2-7-6

15 A 2-7-6-5-4-3
       B 11-10-9-8-12-13
       C 11-6-7-8-12-13
       D 8-9-10-11-6-7

16 A 3-4-5-9-1-2
       B 9-1-8-7-6-5
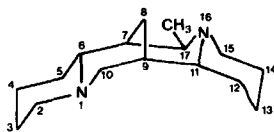
17 A 6-5-4-3-2-1   C 8-9-11-16-17-7
       B 8-7-6-1-10-9   D 13-12-11-16-15-14
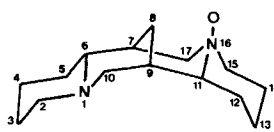
18 A 6-1-2-3-4-5   C 8-7-17-16-11-9
       B 8-7-6-1-10-9   D 15-16-11-12-13-14

19 A 2-1-6-5-4-3
       B 8-7-6-1-10-9
       C 8-7-17-16-11-9
       D 14-13-12-11-16-15
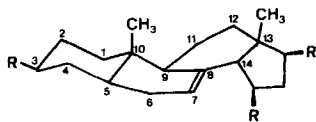
20 A 2-1-10-5-4-3
       B 10-5-6-7-8-9
       C 12-11-9-8-14-13

Table 2. ZPD and CP puckering parameters for six-membered rings in structures 1–20

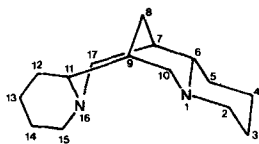| Ring	S	θ	ψ_2	σ^a	Q	θ^{CP}	ϕ_2	Ref.
1[b]	0·97	7·7	3·7	2·3	0·48	15·4	0·1	40
2	0·82	35·2	26·7	0·3	0·51	49·7	26·2	41
3[b]	1·13	3·7	4·4	0·5	0·55	3·0	6·8	20
4	1·17	3·7	26·9	0·1	0·57	4·4	50·2	20
5[b]	0·72	35·6	4·4	0·4	0·45	51·0	3·8	42
6	0·85	29·7	22·8	1·3	0·55	44·8	12·7	43
7	0·94	86·5	4·5	2·7	0·81	90·5	1·3	44
8[b]	0·68	35·2	22·6	0·3	0·42	50·3	20·8	45
9A[b]	1·09	9·5	12·0	0·6	0·56	17·9	13·6	46
9B[b]	0·83	34·7	13·3	0·3	0·52	50·2	13·1	46
10A	0·92	35·5	16·8	0·3	0·55	50·5	14·6	47
10B[b]	1·20	0·9[c]	9·1	0·8	0·58	2·4	248·5	47
11A[b]	1·09	5·7	29·7	2·6	0·55	10·0	18·7	48
11B	1·09	16·7	3·7	2·5	0·60	30·8	2·2	48
11C[b]	1·23	0·9[c]	5·0	0·8	0·63	1·2	147·4	48
12	1·13	89·7	0·5	1·5	0·98	90·2	359·8	49
13[b]	1·18	87·1	6·9	1·0	0·99	87·8	8·4	50
14A	0·75	89·5	0·7	1·3	0·62	89·9	0·7	51
14B	1·11	89·9	0·7	1·5	0·91	90·3	0·7	51
15A[b]	1·10	90·0	0·6	1·5	0·90	89·9	0·8	51
15B[b]	0·95	89·6	0·6	1·4	0·82	90·0	0·7	51
15C	1·04	89·6	0·0	0·3	0·91	89·9	0·1	51
15D[b]	0·90	89·6	0·4	1·4	0·73	89·9	0·3	51
16A	1·21	63·3	0·5	9·3	1·07	78·7	0·1	52
16B[b]	1·23	10·8	1·0	0·9	0·67	21·3	0·6	52
17A[b]	1·17	0·1[c]	4·1	0·6	0·58	3·7	3·6	53
17B[b]	1·18	5·4	11·2	0·4	0·60	10·6	14·8	53
17C[b]	0·96	86·6	0·7	0·6	0·79	87·6	0·9	53
17D[b]	1·23	0·5[c]	26·4	0·3	0·62	0·5[c]	241·8	53
18A	1·15	1·7	5·3	0·2	0·57	4·6	7·5	54
18B[b]	1·19	7·9	5·0	0·3	0·61	15·5	6·2	54
18C	0·92	85·2	0·5	0·7	0·76	86·8	1·2	54
18D	1·16	2·0	27·4	0·7	0·58	3·9	26·5	54
19A	1·19	0·4[c]	0·7	0·5	0·60	2·9	235·6	55
19B	1·19	4·5	19·0	0·1	0·60	10·4	17·4	55
19C[b]	1·12	8·2	0·8	0·9	0·58	15·7	3·6	55
19D[b]	1·16	5·4	16·0	1·2	0·59	11·1	19·7	55
20A	1·15	2·4	21·3	0·9	0·58	4·0	40·6	56
20B[b]	0·78	35·1	22·9	0·9	0·52	50·1	22·2	56
20C[b]	0·88	84·1	22·8	0·5	0·68	85·9	23·3	56

[a] The accuracy of the ZPD method was calculated according to equation (8).
[b] The inversion was used to obtain the ZPD puckering parameters in the canonical region.
[c] The small value of the polar angle θ leads to the great dispersion of the phase angle.
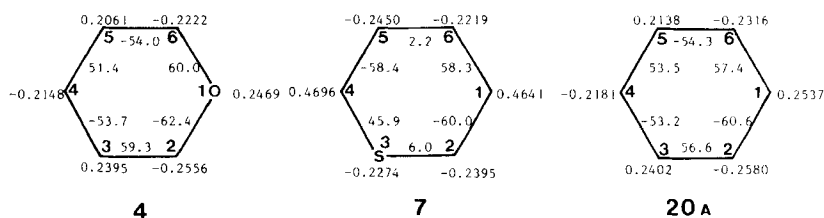
close to a boat form, some of them with the flattened apex 4, whereas ring 20C adopts nearly a twist-form. Hence even this straightforward kind of analysis allows one to evaluate the ring conformation.

Another application of puckering parameters relates to the comparison of ring conformations. For example rings 17C and 18C (differing in the presence of a methyl substituent in 17C) have approximately the same conformation with greater overall flattening in 18C. The comparison of boat conformations 12 and 13 shows that 13 is more twisted (which can be explained by the presence of five substituents in the ring). Hence the puckering parameters allow one to evaluate the effect of substituents on the ring form.

Among the cycles analysed we shall now consider those for which the ZPD and CP parameters lead to different conclusions. Let us compare the ZPD and CP description of conformations for these rings from the stereochemical point of view. For rings 4 and 20A the ZPD parameters show that the apex 4 is the most flattened part of the ring and the apex 1 is the most puckered ($\psi_2 = 26\cdot9$ and $21\cdot3°$, respectively). Such conclusions are in complete agreement with the results of torsional angle analysis given in Figure 10 with the use of the stereochemical criteria discussed above.[32] However, the CP parameters for the same atomic numbering are out of the canonical range ($\phi_2 = 50\cdot2°$ and $40\cdot6°$ for rings 4 and 20A, respectively) and lead to the conclusion that the greatest flattening is at apex 5 and puckering at apex 2 (for z-coordinates, see Figure 10), i.e. the CP description in these cases is in contradiction with the angular stereochemical criteria, despite the fact that the rings considered have approximately equal bond lengths (C_{sp^3}—C_{sp^3} in compound 20A).

One more contradiction between ZPD and CP descriptions is observed for the boat form 7. In terms of both ZPD parameters ($\theta = 86\cdot5°$) and stereochemical criteria, apex 4 is more flattened than apex 1, while the CP parameters ($\theta^{CP} = 90\cdot5°$) lead to the opposite conclusion (see Figure 10).

It should be mentioned that since for the chair conformation ($\theta = 0$) the value of the phase angle ψ_2 is indefinite, in the close vicinity of the pole the usual standard deviations of the initial x-ray data lead to meaningless values of ψ_2 (as with the rings 10B, 11C, 17A, 17D and 19A) and hence the atomic numbering for such rings can be chosen arbitrarily.

Figure 10. Torsional angles and z-coordinates for rings 4,[20] 7[44] and 20A[56]

Hence the examples considered demonstrate the utility of ZPD puckering parameters for the analysis and comparison of six-membered ring forms.

CONCLUSION

A careful analysis of the CP method shows that, although in many cases it leads to the correct stereochemical conclusions, it sometimes fails in the description of ring forms. This shortcoming can be explained by the dependence of the CP puckering parameters on the linear geometrical characteristics of the ring. On the other hand, the ZPD method based on the endocyclic torsional angles allows one to characterize quantitatively conformations and distortions of rings in fairly good agreement with criteria accepted in stereochemistry. Such conclusions are drawn from model calculations simulating the ring distortions and from the analysis of 40 six-membered ring forms in 20 structures. It has been shown here that the range of variation of the angular puckering parameters can be reduced significantly without any approximations or restrictions and thus for the case of six-membered rings only 1/24th of the puckering sphere surface needs to be used. Application of the narrowed region for the puckering parameters is of great use for the analysis and comparison of ring forms, its utility being evident for larger rings which are characterized by more than three puckering parameters.

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