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QUANTITATIVE ASPECTS OF CHIRALITY. I. METHOD OF DISSYMMETRY FUNCTION

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To study molecular features connected with chirality, a procedure for the quantitative estimation of the chirality level of compounds of different classes is needed. A procedure for estimating the molecular asymmetry level relative to mirror-reflection axes of symmetry, S_1, S_2, S_4 and S_6, has been developed. The geometrical mean of these parameters is the disymmetry function (*DF*). To calculate the *DF*, the molecule must be fixed in the coordinate system, transferred to the main axes of inertia.

INTRODUCTION

At the present level of stereochemical knowledge, three fundamental concepts take a central position: chirality, configuration and conformation.[1] Chirality is the most common property of molecules, being involved in living matter.[2,3] For understanding and regulating stereospecific processes such as asymmetric synthesis and catalysis, substrate – enzyme and effector – receptor interactions, etc., and for interpreting and predicting the different properties of molecules due to chirality, the quantitative characteristics of this phenomenon need to be elucidated. Therefore, the elaboration of theoretical approaches for estimating the 'level of chirality' in chemical systems of various structures is necessary.

Numerous studies dealing with the quantitative aspects of chirality have been published (see, e.g., Refs 4–11). The papers by Ruch and co-workers[4,5] are important as the method of chirality function was proposed and applied. In terms of this model, one can quantitatively evalute the degree of chirality, although only for systems that can be represented as an achiral skeleton with different substituents (ligands), i.e. the chirality is determined by the difference in these substituents. In spite of these limitations, the method of chirality functions has been successfully applied in a number of cases (see, e.g., Refs 12 and 13) for solving practical problems. The possibilities with most of the other models for the quantitative evaluation of chirality were demonstrated only on various model examples. It is evident that the universal approaches to the quantitative analysis of chirality must be based on symmetry concepts. Symmetry, a universal property of matter, an organizing principle of its harmony,[14–16] is closely connected with chirality, since the latter is characterized by the absence (defect) of mirror-reflection axes of symmetry.

The main purpose of this work was to develop an approach[17,18] in which the degree of chirality could be defined by measuring the asymmetry of the objects under study concerning only mirror-reflection axes. It is important to note that elaboration of such an approach is also of great importance as a means of studying the influence of structural factors on properties of chiral compounds such as optical activity, stereoselectivity of reactions, efficency of induction of helical ordering in nematic liquid crystals under the influence of chiral dopants, enantiodifferentiating properties of macrocyclic complexes and many other properties conditioned by chirality.

The analysis of the influence of regularities of structural fragments on molecular dissymmetry may be useful for the design of novel compounds with a range of useful properties.

METHOD OF DISSYMMETRY FUNCTIONS

The quantitative aspects of chirality phenomena are one of the important and least studied field of stereochemistry, which is why we tried to elaborate an approach for measuring the degree of difference between enantiomers of a chiral object, i.e. to measure

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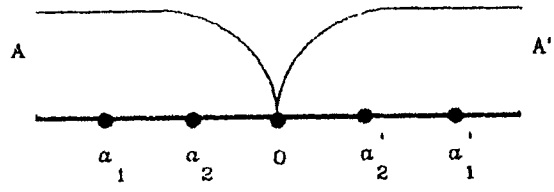
its 'chirality level,' defining the position of enantiomers with respect to the border between the homochiral subclasses. The following scheme illustrates the above:



where A and A' are homochiral subclasses,[19] a_i and a_i' are enantiomers and O is border between A and A', obviously including the achiral objects. It is clear that $|Oa_i| = |Oa_i'|$ is the wanted quantitative characteristic of an object a_i, chirality, which can be defined as half the length of the interval $|a_ia_i'|$. To put it another way, the greater the difference between an object and its antipode, the higher the 'chirality level' is. Thus, for example, if we try to put a left-hand glove on the right hand this will cause a certain discomfort, although it will be easier to do it with a mitten. It can be concluded that there is a greater difference between the antipodes of gloves than between the antipodes of mittens. Of course, such an intuitive analysis is not possible in all cases, and a formalized pattern of measuring the 'chirality level' is necessary which could be applied to chiral objects with various structures.

Any molecular object can be regarded as a system of points (atoms) in space. Let M be a set of marked points m of an object in a Cartesian system, consisting of k elements. Each point has its quantitative (weight) parameter p, characterizing some atom property, and they are also designated according to their 'kinds,' J:

$$M = \{m_i^j\} \qquad J = \overline{1,s} \qquad i = \overline{1,k}$$

where s is the number of the points 'kinds' ($s \leqslant k$). The indication of the 'kind' is important for differentiating points with the same p_i. Two elements of the set M are equivalent if in the case of their exchange the set M reflects into itself. In other words, two elements are equivalent only when their 'kinds' and weight parameters are the same. If we apply the symmetry S_n operation (corresponding to the mirror-reflection axis order n) to the figure M, the criterion of its chirality may be formulated as, if $\forall S_n\ S_nM \neq M$, then the figure is chiral. It is evident that if M is achiral then $\exists S_n$ $S_nM = M$. From the above, it can be concluded that the level of difference between the antipodes M and M' ($M' = S_nM$) may be a function of distance $r_{ii'}$ between each point m_i^j of the initial figure and equivalent point of enantiomer $(m_i^j)' \in M'$.

Thus, in order to define the extent of difference between the antipodes M and M', it is necessary to solve two problems: (1) to choose a common system of coordinates for M and M' that is invariant with respect to their structures and (2) to choose the function of $r_{ii'}$.

If we consider a molecular object as a physical body, its rotation can be described with the tensor of inertia $\mathbf{T}$:

$$\mathbf{T} = \begin{Vmatrix} \sum_i p_i(y_i^2 + z_i^2) & -\sum_i p_i x_i y_i & -\sum_i p_i x_i z_i \\ -\sum_i p_i y_i x_i & \sum_i p_i(x_i^2 + z_i^2) & -\sum_i p_i y_i z_i \\ -\sum_i p_i z_i x_i & -\sum_i p_i z_i y_i & \sum_i p_i(y_i^2 + x_i^2) \end{Vmatrix}$$

where p_i are the corresponding masses of the points and x_i, y_i and z_i are the coordinates of the ith point. The eigenvectors of the tensor $\mathbf{T}$ define the main axes of inertia corresponding to moments I_1, I_2, I_3. Hence the main axes of inertia may be used as the coordinate axes (the reduced coordinates system). The mentioned system has a characteristic feature: if an object has an axis or plane of symmetry, it will necessarily coincide with the corresponding element of the coordinate system.[20] It is evident that in such a system, closely connected with the object's symmetry, it is most convenient to compare the enantiomers only for such systems where any operation of the symmetry S_n applied to the achiral objects makes them reflect into themselves. Therefore, there appears to be a possibility of measuring the dissymmetry only for mirror-reflection axes which can serve as a quantitative measure of chirality.

The formalism of the method of measuring chiral objects can be illustrated by two two-dimensional examples (Figure 1).

Let $M = \{a, b, c\}$, a chiral triangle, orientated in a reduced system of coordinates, and $M' = \{a', b', c'\}$ is its image received resulting from the operation S_n (e.g. S_1) [Figure 1(A)]. In this case we observe a certain correspondence between M and M', $a \leftrightarrow a'$, $b \leftrightarrow b'$, $c \leftrightarrow c'$, and for each of these pairs we define the corresponding segments r_a, r_b, r_c, the centres of which form the achiral analogue M'' of enantiomers M and M'. Points a'', b'' and c'' are always on the coordinate axes (in the coordinate plane in three-dimensional space) if in the initial object there are no equivalent points. If M has such points b_1 and b_2 [Figure 1(B)], then from the possible pairs b_1–b_2 the least r_b should be taken (for b_1, $|b_1b_2'|$; for b_2, $|b_2b_1'|$). Only with such an approach for any achiral object [Figure 1(C)] do we have $r_a = 0$, $r_{b_1} = 0$, $r_{b_2} = 0$, i.e. $M \equiv M'$. It should be pointed out that for the systems with equivalent points the achiral analogue is a spatial figure (polyhedron).

Thus, bearing in mind the terms of moments of inertia, it is possible to define the quantitative characteristic of the difference between M and M' as the level of dissymmetry (LD):

$$LD = \Sigma\ p_i r_i^2$$

It can be readily shown that $LD^{1/2}$ possesses metric characteristics. In fact, the parameter LD reflects the weight distance of the enantiomer M (or M') relative the achiral analogue M''. Hence the value of LD can characterize the relative change of the object M's dissymmetry with different changes of the structure. It is evident that for each operation of symmetry S_n in a reduced system of coordinates a certain characteristic value which shows the degree of difference of an object and its reflection obtained as a result of the operation S_n can be obtained. We shall only consider the operations $S_1(\sigma)$, $S_2(i)$, S_4 and S_6, since chemical compounds with symmetry S_n where $n > 6$ are rather rare. Taking into account all possible ways of proceeding

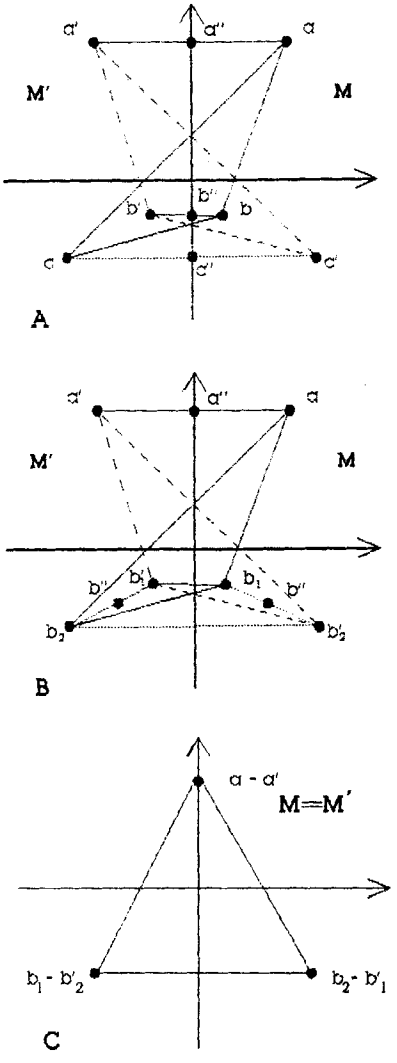


Figure 1. Dissymmetry function calculation scheme

with the operations S_1, S_2, S_4 and S_6 along the coordinate axes, a molecular dissymmetry (dissymmetry function, DF) is defined as a geometric average of the mentioned LDs:

$$DF = (LD^{S_1^x} LD^{S_1^y} LD^{S_1^z} LD^{S_2} LD^{S_4^z} \times LD^{S_4^y} LD^{S_4^z} LD^{S_6^z} LD^{S_6^y} LD^{S_6^z})^{1/10}$$

It is evident that $DF = 0$ if any $LD = 0$. This conclusion is valid if $I_1 \neq I_2 \neq I_3$. With the equality of the two principal moments of inertia the positions of two axes of the given scheme are not determined, in addition to the value of DF. In this case it is necessary to pick out the minimum value of DF with rotation of the object about the only defined axis. The choice of the minimum is stipulated by the fact that for an achiral object we must obtain $DF = 0$. At $I_1 = I_2 = I_3$ the value of DF is determined non-invariantly. However, such a situation can be realized only for chiral structures belonging to the axial groups of T, O, I symmetry, and molecules with this symmetry are rare. From the above, it is clear that the weight parameters of atoms are concerned both in defining the given system of coordinates and in calculating the DF. This is why the alternation of different characteristics of the atoms leads to the set of DF determining the dissymmetry of a molecule with respect to its different properties:

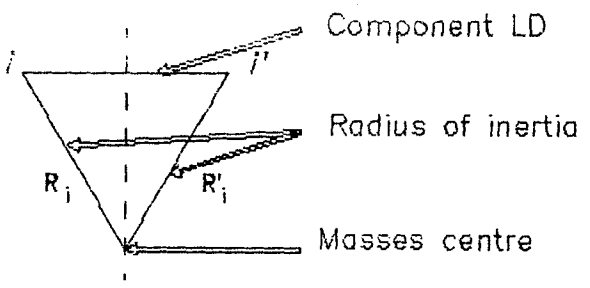
DF^M = dissymmetry function with respect to the atom masses ($p_i = m_i$);
DF^V = dissymmetry function with respect to Van der Waals volumes ($p_i = V_i$);
DF^R = dissymmetry function with respect to the atomic refractions ($p_i = R_i$);
DF^G = dissymmetry function characterizing only the spatial distribution of atoms for all p_i which are regarded as equal to unity.

It is probably possible to use other properties of the atoms for calculations of DF. For an adequate comparison of structures differing in number of atoms, size, etc., the characteristics of DF^J ($J = M, V, R, G$) should be normalized for the corresponding values. So, we define

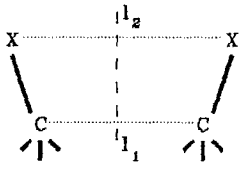
$$DF^J_N = DF^J/N$$
= Dissymmetry function, normalized for the number of atoms;

$$DF^J_P = DF^J \Big/ \sum_i p_i$$
= dissymmetry function, normalized for the sum of the weight parameters;

$$DF^J_R = DF^J \Big/ \sum_i R_i^2$$
= dissymmetry function, normalized for the sum of square radii of inertia (R_i).



In a number of cases a double normalization is used, e.g. DF_{PR}. For the analysis of the chiral environment of a group of atoms we calculate the dissymmetry function of the chiral environment. In this case the orientation of the structure in the given system of coordinates is defined taking into account all atoms of the molecule and calculation of DF is carried out only for a group of atoms:



$$DF^J(C-X) = f[LD^J(C-X)]$$
$$LD^J(C-X) = p_x l_2^2 + p_C l_1^2$$

It is evident that the types of DF offered have the same value for enantiomers.

The method of dissymmetry function is realized by means of the program DISMOL.

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