

Simple one-electron invariants of molecular chirality

A.V. Luzanov*

STS "Institute for Single Crystals", National Academy of Sciences, Kharkov 61001, Ukraine
E-mail: luzanov@bestnet.kharkov.ua

Dmitry Nerukh

*Unilever Centre for Molecular Informatics, Department of Chemistry, Cambridge University,
Cambridge CB2 1EW, UK*

Received 21 November 2005; revised 8 February 2006

Pseudoscalar measures of electronic chirality for molecular systems are derived using the spectral moment theory applied to the frequency-dependent rotational susceptibility. In this scheme a one-electron chirality operator $\hat{\kappa}$ naturally emerges as a quantum counterpart of the triple scalar product, involving velocity, acceleration and second acceleration. Averaging $\hat{\kappa}$ over an electronic state vector gives rise to an additive chirality invariant (κ -index), considered as a quantitative measure of chirality. A simple computational technique for quick calculation of the κ -index is developed and various structural classes (cyclic hydrocarbons, cage-shaped systems, etc.) are studied. Reasonable behaviour of the chirality index is demonstrated. The chirality changes during the β -turn formation in Leu-Enkephalin is presented as a useful example of the chirality analysis for conformational transitions.

KEY WORDS: chirality measures, differential geometry, joint invariants, topological matrix, high-symmetry chiral systems

AMS subject classification: 81Q70 differential-geometric methods, including holonomy, Berry and Hannay phases, etc. or 92E10 molecular structure (graph-theoretic methods, methods of differential topology, etc.)

1. Introduction

Molecular chirality (dissymmetry) is a somewhat elusive notion from many viewpoints. Indeed, chirality as such is difficult to define in quantitative terms and many various approaches and methodologies are known for the chirality analysis. A very brief overview provided in this introduction illustrates the current state of the chirality problem.

*Corresponding author.

Most theoreticians concentrate on geometrical and topological aspects of molecular dissymmetry (for reviews see [1–9]) and the fundamental results given in [2,7,9] are especially worth mentioning. In particular, an intrinsic chirality for molecular graphs is proved in the form of exact theorems of the so-called topological chirality theory. Here, it is also appropriate to mention the combined geometrical-topological chirality measure originally proposed in [10]. Currently, the major focus is on elaborating the techniques for “chirality measurement” and the recent comprehensive overview [11] sums up the developments of this attractive field of theoretical chemistry.

Despite this progress, ignoring physical and especially quantum-mechanical (electronic) properties of the subject is, in our view, a certain drawback of most existing approaches. The work in [12,13] is interesting as the first attempt to define a physical chirality measure. Furthermore, the evaluation of the degree of symmetry deficiency given in [10,14] should also be viewed as a physical chirality theory when using the one-electron density distributions determined directly or indirectly by the molecular wavefunctions (for more details see [6,14,15]). Recent calculations and developments [16–18] clearly demonstrate this point. Likewise, the geometric continuous chirality measure approach [6,19] can be extended to the custom *ab initio* methods [20,21].

Another attempt to systematically construct a chirality theory at the quantum-chemical level was given by the authors in [22,23]. The main idea is to explore the differential geometrical properties of the spatial curves associated with the electron paths in molecules. The curve torsion is treated as a correct geometrical pseudo-scalar quantity and replaced with a quantum mechanical operator that determines a relevant average quantity referred to as the chirality index (κ -index). In this first version of the theory too crude an approximation was used for calculating the κ -index. This restricted the application of the scheme [22] to realistic chemical systems.

In the present study, the quantification of the molecular chirality by the κ -index is refined in two directions. First, a rather general scheme for constructing the quantum dynamical invariants for molecules by using a simple generalization of the spectral moments theory [24,25] is developed. In this scheme, the κ -index is now naturally derived as an electronic characteristic indirectly related to the optical activity. Second, an improved (but still simple) computational scheme for calculating the κ -index is proposed. Using it we obtained the numerical values of the chirality index for various complex molecules such as twistanes, helicenes and some high-symmetry chiral fullerenes. Along with considering these ‘static’ molecular structures special attention was given to describing the chirality changes during a conformational transition. As an example, important for biophysics a β -turn transition in Leu-Enkephalin in explicit water is analysed. Finally we discuss some principal difficulties in building a chirality measure theory.

2. Joint invariants from spectral moments theory

The key problem in the chirality measurement theory at the electronic level is to construct appropriate invariants that depend explicitly on the molecular many-electron wavefunction. The quantities chosen should be justified by certain physical considerations. We will restrict ourselves to the case of two physical quantities A and B and assume that the quantum-mechanical operators associated with A and B are well behaved. As usual, the same notation, A and B , will be used for the associated operators. This convention will also be applied to vector quantities such as the position vector \mathbf{r} or the angular momentum \mathbf{l} . In the case of such vector operators a scalar product AB will be implied as well.

It may appear that the problem of finding appropriate invariants is trivial if the wavefunction of the state in question, Ψ , is available. Indeed, the straightforward calculation of the conventional quantum averages

$$\langle \Psi | AB | \Psi \rangle, \quad \langle \Psi | A^2 B | \Psi \rangle, \dots \quad (1)$$

yields the joint invariants. However, in reality these quantities can vanish (as $\langle \Psi | \mathbf{l} \cdot \mathbf{r} | \Psi \rangle$ does in our problems) or can lack clear physical meaning. In any case, there is no unique way to produce the invariants and it seems sensible to consider different approaches, in particular, taking into account the dynamics related to the quantities A and B . A possible way to do this is to use the spectral moments theory [24,25].

Let us consider a frequency-dependent quantity $\chi_{A,B}(\omega)$, which allows the spectral representation

$$\chi_{A,B}(\omega) = \omega \sum_{n \neq 0} (\omega - \lambda_n)^{-1} A_{0n} B_{n0}, \quad (2)$$

where $A_{0n} = \langle \Psi_0 | A | \Psi_n \rangle$ stands for the usual transition matrix element between an initial (ground) state vector Ψ_0 and an excited state vector Ψ_n with λ_n being the corresponding excitation energy. By definition these states are the eigenstates of the respective Hamiltonian H . Expanding (2) with respect to $1/\omega$ we obtain the series

$$\chi_{A,B}(\omega) = m_{A,B}^{(0)} + m_{A,B}^{(1)} \omega^{-1} + m_{A,B}^{(2)} \omega^{-2} + \dots, \quad (3)$$

where the numbers

$$m_{A,B}^{(\alpha)} = \sum_{n \neq 0} \lambda_n^\alpha A_{0n} B_{n0} \quad (4)$$

are the generalized spectral moments associated with A and B . It is suggested that the moments (4) do exist as they appear in the quantum chemistry context that usually deals with finite-dimensional electronic models.

The fact that the spectral moments are connected with the quantum dynamics follows from the known relationship for the nondiagonal matrix elements

$$\lambda_n A_{0n} = -([H, A])_{0n} = i(\dot{A})_{0n} \quad (5)$$

often referred to as ‘off-diagonal hypervirial theorem’ [26,27]. Here the atomic units are used ($\hbar = 1$, etc.) and A is assumed to be not explicitly time dependent. To simplify the notations the following convention will be adopted. All operators will be considered real. Therefore, in the case of real-valued Hermitian operators such as the position operator \mathbf{r} , instead of Hermitian operators and associated matrices we will work with the real symmetric ones ($A = A^T$). In the case of pure imaginary Hermitian operators such as the momentum \mathbf{p} , we will work with the real skew-symmetric $A = -A^T$ matrices. In accordance with this convention relation (5) is replaced by

$$\lambda_n A_{0n} = (\dot{A})_{0n}, \quad (6)$$

$$\dot{A} = -[H, A] \quad (7)$$

thereby giving only real quantities.

Returning to the moments (4) we can represent them in terms of dynamical quantities. For instance,

$$m_{A,B}^{(0)} = \langle \Psi_0 | AB | \Psi_0 \rangle - \langle \Psi_0 | A | \Psi_0 \rangle \langle \Psi_0 | B | \Psi_0 \rangle, \quad (8)$$

$$m_{A,B}^{(1)} = \langle \Psi_0 | \dot{A} B | \Psi_0 \rangle = -\langle \Psi_0 | A \dot{B} | \Psi_0 \rangle, \quad (9)$$

$$m_{A,B}^{(2)} = \langle \Psi_0 | \ddot{A} B | \Psi_0 \rangle = -\langle \Psi_0 | \dot{A} \dot{B} | \Psi_0 \rangle = \langle \Psi_0 | A \ddot{B} | \Psi_0 \rangle \quad (10)$$

and so on. In deriving (9),(10) the fact that $|\Psi_0\rangle$ belongs to the eigenstate of the Hamiltonian is used.

We now proceed to imposing a supplementary condition on the dynamical quantities or their combinations, which can appear in the representations (8)–(11). We suggest the requirement of each moment being nonvanishing in the quasiclassical limit. Evidently, the operator quantities corresponding to such moments reflect the essential dynamical features inherent to the system at the classical level of description as well. In practice we impose even a stronger restriction. The corresponding dynamical quantity must give a nonzero value after the integration over the whole phase space. The condition imposed is equivalent to the additional requirement for any trace, such as $\text{Tr} AB, \text{Tr} A \dot{B}$, etc., to be nonzero since the following fundamental relationship is valid (in the atomic units):

$$\int A(\mathbf{P}, \mathbf{R}) d\mathbf{P} d\mathbf{R} = \text{Tr} A \quad (11)$$

with $A(\mathbf{P}, \mathbf{R})$ being the dynamical quantity associated with A [28]. Evidently, the full operator traces correspond to the equal-weight averages over all state vectors (see also [22]). We will call such traces the overall operator invariants. Thus, only the spectral moments related to the operators that have nonzero overall invariants will be used in our scheme.

To be more specific, let us introduce the operator traces of the special type:

$$\text{Tr } A^{(\alpha)} B^{(\beta)} \quad (12)$$

with $A^{(\alpha)}$ being the α -order time derivative determined by the recurrence relation

$$A^{(\alpha)} = -[H, A^{(\alpha-1)}], \quad A^{(0)} = A. \quad (13)$$

Simple identities can be easily derived from this definition. For example,

$$\text{Tr } A^{(\alpha)} B^{(\beta)} = -\text{Tr } A^{(\alpha-1)} B^{(\beta+1)}. \quad (14)$$

With this in mind consider the case, most important for our study, when

$$A = -A^T, \quad B = B^T. \quad (15)$$

Then $A^{(\alpha)}$ is skew-symmetric for even α and symmetric for odd α while the properties of $B^{(\alpha)}$ are opposite. Hence, for A and B obeying (15) a nonzero trace in (12) is realised if $\alpha + \beta + 1$ is an odd number, for example

$$\text{Tr } A^{(\alpha)} B^{(\alpha+1)} \neq 0. \quad (16)$$

Clearly, if condition (15) is assumed, the only set of operators $\{A^{(\alpha)} B^{(\alpha+1)}\}$ must be used in the proposed scheme.

3. Chirality invariants

In this section, we obtain physically acceptable invariants of molecular chirality at the electronic level of the problem. ‘Physically acceptable’ meaning that these invariants must satisfy the natural requirement to be extensive (in the thermodynamical terms). In other words, they should be the quantities that have an additive separability as most of the molecular characteristics have. Possible ‘intensive’ characteristics are not as convenient for the chirality quantification and are not discussed here. In contrast to the usual properties the majority of the molecular chirality properties manifest themselves in non-standard observable quantities. These quantities change their sign when the right-handed molecular form is replaced with the left-handed one. Using the invariant theory notations these quantities are referred to as the geometrical pseudoinvariants (pseudoscalars) and change the sign under the improper symmetry operations. Also, in a quantum mechanical treatment, they must be customary algebraic invariants

with respect to the linear transformations of the vector space associated with the corresponding quantum system. Therefore, the quantum-mechanical scheme described in the previous section can be used for our purposes.

To use the scheme we should choose a pseudoscalar spectral quantity of type (2). The simplest frequency-dependent function is the dynamical susceptibility $\beta(\omega)$. This describes the optical rotation as well as the Van der Waals interactions between chiral systems [29]. We define it by the expression

$$\beta(\omega) = \chi_{\mathbf{l}, \mathbf{r}}(\omega), \quad (17)$$

where \mathbf{r} and \mathbf{l} refer to one electron. A many-electron formulation is essentially the same but more cumbersome. Since the condition (15) is satisfied by the operators \mathbf{r} and \mathbf{l} , we first calculate the traces (16) for some initial integer numbers α starting with $\alpha = 0$. Taking into account that for the electronic systems $\mathbf{p} = \dot{\mathbf{r}}$ (in the atomic units), let us define the overall operator invariants (16) as the geometrical pseudoscalars

$$K^{[\alpha]} = -\text{Tr} \mathbf{l}^{(\alpha)} \cdot \mathbf{r}^{(\alpha+1)} = \text{Tr} \mathbf{l}^{(\alpha)} \cdot \mathbf{p}^{(\alpha)}. \quad (18)$$

Recall the relations $\mathbf{l} = \mathbf{r} \times \mathbf{p}$, $\dot{\mathbf{l}} = \mathbf{r} \times \dot{\mathbf{p}}$ and neglect the possible noncommutativity of the appearing operators. Hence, after simple algebra we get

$$K^{[0]} = \text{Tr} \mathbf{l} \cdot \mathbf{p} = 0, \quad (19)$$

$$K^{[1]} = \text{Tr} \dot{\mathbf{l}} \cdot \dot{\mathbf{p}} = 0, \quad (20)$$

$$K^{[2]} = \text{Tr} \ddot{\mathbf{l}} \cdot \ddot{\mathbf{p}} = \text{Tr} (\mathbf{p} \times \dot{\mathbf{p}}) \cdot \ddot{\mathbf{p}}, \quad (21)$$

$$K^{[3]} = 2\text{Tr} (\mathbf{p} \times \ddot{\mathbf{p}}) \cdot \ddot{\mathbf{p}}, \quad (22)$$

$$K^{[4]} = \text{Tr} (2 \dot{\mathbf{p}} \times \ddot{\mathbf{p}} + 3 \mathbf{p} \times \ddot{\mathbf{p}}) \cdot \mathbf{p}^{(4)} \quad (23)$$

and so forth.

It is striking that the first nonvanishing trace (18) is realised by the pseudoscalar (21)

$$K^{[2]} = \text{Tr} (\mathbf{p} \times \dot{\mathbf{p}}) \cdot \ddot{\mathbf{p}} = \text{Tr} \hat{\kappa} \quad (24)$$

involving the same chirality operator

$$\hat{\kappa} = \{(\mathbf{p} \times \dot{\mathbf{p}} - \dot{\mathbf{p}} \times \mathbf{p}) \cdot \ddot{\mathbf{p}} - \ddot{\mathbf{p}} \cdot (\mathbf{p} \times \dot{\mathbf{p}} - \dot{\mathbf{p}} \times \mathbf{p})\}/4, \quad (25)$$

which appeared in [22,23] from a formal differential geometrical consideration. Additionally, the operators occurring in (22), (23) can also be examined. However, they turn out to be more complex because they involve higher order time derivatives. We recommend using (22), (23) for those rather exceptional cases when the chirality operator (25) may give zero value for the key invariant (24), or in more sophisticated schemes discussed in the last section of the paper. Normally the chirality measure for a given electronic state Ψ will be determined by the ordinary one-electron average quantity named κ -index and computed as

$$\langle \kappa \rangle_{\Psi} = \text{Tr } \hat{\kappa} D_1. \quad (26)$$

Here, D_1 is the one-electron charge density matrix defined in [30] for the many-electron state vector Ψ (for some special properties see also [31]). It is interesting that the quantities (26) reflect the high level of molecular complexity as it is assumed in [23].

4. Simple computational scheme

Our goal is to develop a computationally feasible method for quantifying the molecular chirality in realistic polyatomic systems containing hundreds of atoms. Therefore, we are forced to make very crude approximations in (26). In fact, we try to avoid rigorous quantum chemical calculations for such complex matrices as the chirality operator matrix (25) and related matrices. Some of the essential features of the scheme are the same as in [22,23], however, important changes are introduced.

For the method described above, the only information needed is the molecular geometry, given by a set of the atomic coordinates

$$\{\mathbf{R}_{\mu} = (X_{\mu}, Y_{\mu}, Z_{\mu})\}_{1 \leq \mu \leq M}, \quad (27)$$

where M is the number of atoms in the molecular system in question. We replace the whole electronic shell by an effective one comprising the valence s-AOs only. The latter are treated in a semi-empirical fashion by introducing the typical approximations for the one-electron Hamiltonian matrix h and the coordinate operator matrix \mathbf{r} . In the previous version of the theory [22,23], the Hamiltonian matrix was taken as in the Hückel method, that is, in the form of the topological bond matrix B^{top} (adjacency matrix of a spatial graph):

$$h = \beta_0 B^{\text{top}}, \quad (28)$$

$$B_{\mu\nu}^{\text{top}} = \begin{cases} 1, & \text{if } \mu \text{ and } \nu \text{ are connected,} \\ 0, & \text{otherwise} \end{cases} \quad (29)$$

and β_0 is a scaling energy factor. However, this approximation neglects the long-distance effects and often leads to a poor description of the chirality as previously observed in some model calculations [23]. Thus, a refined Hamiltonian is needed such that its simplicity and conformity to the approach in the whole is retained. For this we construct an ‘adjusted’ Hamiltonian h that have B^{top} (29) as the leading term. This can be made in many ways. We chose an effective special method [32] from the π -electron theory. The proposed expression is

$$h = \beta_0 B \quad (30)$$

with the new bond matrix B having all $B_{\mu\mu} = 0$ and off-diagonal elements

$$\begin{aligned} B_{\mu\nu} &= (\zeta_{\mu\nu}/R_{\mu\nu})^4, \\ \zeta_{\mu\nu} &= (\zeta_\mu + \zeta_\nu)/2, \end{aligned} \quad (31)$$

where $R_{\mu\nu} = |\mathbf{R}_\mu - \mathbf{R}_\nu|$ and ζ_μ is the atomic parameter that determines an effective action radius of the atom μ . The numerical values of these parameters are chosen such as to make h as close as possible to the topological matrix (29). For pure hydrocarbon systems it is realised by using the values

$$\zeta_{\text{C}} = 1.50\text{\AA}, \quad \zeta_{\text{H}} = 0.68\text{\AA}, \quad (32)$$

if the equilibrium geometry (27) is obtained by the AM1 method (this choice is adopted in all our calculations). The specific example of the ethane molecule in the chiral conformation with the D_3 symmetry demonstrates how the long-distance interactions appear

$$B = \begin{pmatrix} 0 & B_{\text{CC}} & B_{\text{CH}} & B_{\text{CH}} & B_{\text{CH}} & b_1 & b_1 & b_1 \\ & 0 & b_1 & b_1 & b_1 & B_{\text{CH}} & B_{\text{CH}} & B_{\text{CH}} \\ & & 0 & b_2 & b_2 & b_3 & b_4 & b_5 \\ & & & 0 & b_2 & b_4 & b_5 & b_3 \\ & & & & 0 & b_5 & b_3 & b_4 \\ & & & & & 0 & b_1 & b_1 \\ & & & & & & 0 & b_1 \\ & & & & & & & 0 \end{pmatrix}, \quad (33)$$

$$\begin{aligned} B_{\text{CC}} &= 0.900, \quad B_{\text{CH}} = 1.000, \quad b_1 = 0.064, \quad b_2 = 0.021, \quad b_3 = 0.003, \\ b_4 &= 0.007, \quad b_5 = 0.004. \end{aligned}$$

The approximation (30), (31) will be termed the quasi-topological scheme. This scheme gives reasonable results for saturated and unsaturated hydrocarbons,

as well as for usual heteroatomic systems with the parameters (AM1 molecular geometry)

$$\zeta_N = 1.40\text{\AA}, \quad \zeta_O = 1.35\text{\AA}. \tag{34}$$

Unfortunately, the quasi-topological scheme in the current form works poorly for the heavy heteroatoms that make longer bonds than the carbon atoms. However, this limitation can be removed by the following modification of the working formula (31). For every pair (μ, ν) containing a heavy heteroatom a damping factor is introduced in (31):

$$B_{\mu\nu} = (\text{Min}[\zeta_\mu, \zeta_\nu] / \text{Max}[\zeta_\mu, \zeta_\nu])^2 (\zeta_{\mu\nu} / R_{\mu\nu})^4. \tag{35}$$

Moreover, setting for convenience $\beta_0 = 1$ we obtain a formally dimensionless matrix (30). Thus, the Hamiltonian matrix is fully determined.

The coordinate matrix \mathbf{r} in the AO set is approximated by the usual diagonal matrix of the atomic coordinates (27), such that

$$\mathbf{r} = \parallel \mathbf{r}_{\mu\nu} \parallel, \quad \mathbf{r}_{\mu\nu} = (x_{\mu\nu}, y_{\mu\nu}, z_{\mu\nu}) \tag{36}$$

with $x_{\mu\nu} = X_\mu \delta_{\mu\nu}$, etc. What only remains is to give a rough estimation for the charge density matrix D_1 . For nonzero bond orders we propose the same bond matrix B as for the Hamiltonian.

Furthermore, we neglect the difference in the orbital occupation of the valence s -AOs by putting 1 for all occupation numbers. As a result the approximation

$$D_1 = I + B \tag{37}$$

is suggested. Hence, no new adjustable parameters appear and the only atomic parameters incorporating the specifics of the individual atoms are the action radii ζ_μ .

As a result, the computational scheme is as follows. First, compute the momentum matrices p^x, p^y, p^z via (7), for example:

$$p^x = -[h, x] = \parallel (X_\mu - X_\nu) B_{\mu\nu} \parallel. \tag{38}$$

From (38) the time derivatives are obtained as

$$\dot{p}^x = -[h, p^x], \quad \ddot{p}^x = -[h, \dot{p}^x]. \tag{39}$$

Then the chirality operator matrix is simply calculated:

$$\hat{\kappa} = \kappa_{(x)} + \kappa_{(y)} + \kappa_{(z)} \tag{40}$$

with

$$\kappa_{(z)} = ([p^x, \dot{p}^y] \ddot{p}^z - \ddot{p}^z [p^x, \dot{p}^y]) / 4 \tag{41}$$

and the rest of the components are obtained from (41) by the cyclic permutation of (x, y, z) . The calculation of the κ -index completes by taking the matrix trace (26). Evidently, by putting $\beta_0=1$ the chirality index becomes a quantity that has the dimension of volume.

5. Applications

5.1. High-symmetry chiral systems

Before discussing specific examples simple estimations can be made. Indeed, the κ -index, being the quantity measured as volume, depends on the molecular geometry and the action radii ζ_μ . We can assume that for small-sized hydrocarbons $\kappa \approx \zeta_C^3$ (specifically, 3.375 \AA^3 with the parameters (32)), which produces the expected order of magnitude of the κ -index for these systems. It is confirmed by the calculation for the fully substituted methane $\text{CH}_3\text{C}_2\text{H}_5\text{C}_3\text{H}_7\text{C}_4\text{H}_9\text{C}$ (MEPBM), where $\kappa = 3.78 \text{ \AA}^3$. This example suggests that the value

$$\kappa_C = \zeta_C^3 \quad (42)$$

can be taken as a natural scaling unit for the chirality measure in the carbon containing and related systems. Most of our results will be given in these units. Notice also that MEPBM, synthesized in [33], can be viewed as a system that has, in some sense, an average asymmetrical carbon atom. This makes MEPBM suitable for scaling the chirality within any theoretical description where the chirality measure is not dimensionless. Thus, using (42) as the unit of chirality measurement we in fact describe the electron-shell dissymmetry in terms of the number of the average asymmetric carbon atoms.

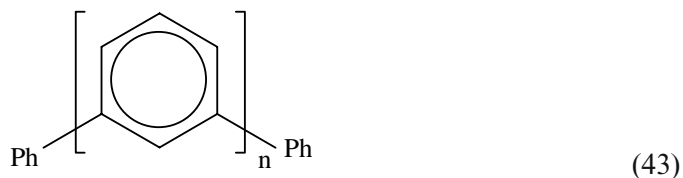
Our main interest in this section is in studying chiral organic molecules with high symmetry. The excellent review [34] remains important as a valuable source of information about typical dissymmetrical systems, in our study most of them are taken from this work. The first simple class of such systems is the cyclic hydrocarbons. The results obtained (table 1) demonstrate the expected behaviour

Table 1
Relative chirality index κ/κ_C for pure cyclic hydrocarbons.

Molecule	Symmetry group	κ/κ_C
Cyclohexane(twist)	D_2	4.3
Trans-1,2-dimethylcyclohexane	C_2	3.6
Cyclononane	D_3	15.6
Cyclododecane	D_2	34.2
1,2-cyclooctadiene	D_2	27.7
1,5,9-cyclododecatriene	C_2	32.4

of the chirality measure with growing the cycle size or lowering the chiral group symmetry (e.g., $D_2 \rightarrow C_2$). Especially interesting are the cage-shaped molecules such as twistane and related systems discussed in chapter 9 of Ref. [34]. As it can be seen from table 2, the chirality measure sharply increases for these structures with increasing the cage size and its number. These results demonstrate that the proposed κ -index conforms the expectations from the viewpoint of organic chemists. However, there are many complicated cases where the visual examination of the geometrical model cannot give a clear answer even for the mere presence of chirality.

Before going to another interesting class, twisted π -conjugated hydrocarbons, the important point concerning the κ -index additivity is worth discussing again. This is readily illustrated by a special series of chiral conjugated systems with the C_2 symmetry:



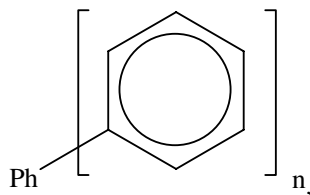
The κ/κ_c values for the first four members are

$$\kappa/\kappa_c = \{19.05, 19.88, 19.82, 19.76\}.$$

The values approach a limit because in these molecular systems the extension is due to increasing the flat part (achiral structural element) of the molecules. The limiting value is twice the value of the limit $\kappa/\kappa_c = 9.9$ for the following series:

Table 2
Relative chirality index κ/κ_c for some cage-shaped hydrocarbons.

Molecule	Symmetry group	κ/κ_c
Twistane	D_2	8.9
Ditwistane	C_2	21.1
Tritwistane	D_3	37.3
Bis-homocubane	C_2	4.0
Tris-homocubane	D_3	21.4
$C_{60}H_4$	C_2	0.2
$C_{60}H_6$	D_3	0.5
C_{28}	D_2	62.7
C_{76}	D_2	7.2
C_{78}	D_3	10.7
C_{80}	D_2	7.8
C_{84}	D_2	1.1



with $\kappa/\kappa_c = 9.6$ for the first member of the series (biphenyl with the D_2 symmetry). We do not expect this result to be straightforwardly reproduced by other known chirality models. As an example, for the same structural series (43) we did not observe any definite limiting value in the pseudoscalar quantity suggested in [35].

Among several analysed (some not included here) extended conjugated systems, a remarkable class of chiral π -systems, termed $[n]$ helicenes (C_2 symmetry), demonstrates the peculiarities of the dissymmetry analysis. The helicene series begins with [4]helicene or, in the trivial nomenclature, 3,4-benzophenanthrene for which optical isomers were reported more than 50 years ago [36]. For this molecule we obtained $\kappa/\kappa_c = 36.5$. For illustrative purposes the values for other molecules are presented in the form of the cubic regression ($v = n - 4, n = 413$):

$$\kappa/\kappa_c = a + bv + cv^2 + dv^3, \quad a = 35.84, \quad b = 3.31, \quad c = 2.34, \quad d = -0.125 \quad (44)$$

with the correlation coefficient 0.999. Evidently, the chirality changes nonlinearly but not as sharp as it could be expected from examining these structures visually. It is interesting to compare these results with the ones for propellicenes ([34], p. 224). For the simplest propellicene ([34], structure 110) $\kappa/\kappa_c = 46.8$, while for the closely related [6]helicene $\kappa/\kappa_c = 48.1$.

Notice that our results for the helicenes are different from those given in [20,37], where a nonmonotonic behaviour of the chirality measure with increasing n was presented. As shown in [37], such the nonmonotonicity (with the first maximum of the chirality index for [9]helicene) agrees rather well with the observed chirality properties. Possibly, the somewhat crude approximation of the quasi-topological model (31) does not allow us to reproduce these fine effects. On the other hand, the almost monotonic behaviour of the electronic chirality (44) would be more understandable if a natural tendency to increase the π -electron contribution to the molecular chirality of twisted conjugated systems is taken into account (in our scheme the π -system is treated implicitly via the large values of the hamiltonian elements (21) and the corresponding bond orders (37)). Notice, that a lack of size-consistency in the approach [37] can give too low chirality with increasing molecular size of such revealing spiral systems as helicenes. At any rate, more study is needed to elucidate the dissymmetry of the higher helicenes.

Finally, some high-symmetry chiral fullerenes taken from Thilgen et al. [38] will be briefly discussed. For $C_{60}H_4$ (C_2 symmetry) and $C_{60}H_6$ (C_3 symmetry) we

obtained the κ -index values 0.2 and 0.5, respectively. This is reasonable in comparison with $\kappa/\kappa_c = 0.03$ for the D_3 configuration of ethane, an elementary system having no chiral carbon backbone. The weak interatomic interactions involving the hydrogen atoms with a small action radius produce a very low chirality even for extremely large quasi-conjugated systems such as C_{60} . As for the pure carbon fullerenes (the last five entries in table 2), the chirality change in this structural class is not clear from the visual inspection. We obtained the following series:

$$C_{28} > C_{78} > C_{80} > C_{76} > C_{84}.$$

Another series,

$$C_{28} > C_{78} > C_{84} > C_{76} > C_{80}$$

follows from the results of Ref. [39] where an interesting topological chirality index was designed, though not taking into account the real molecular geometry.

5.2. Chirality of conformational transition in Leu-Enkephalin

The changes of the chirality during conformational transitions is a very interesting problem. As an example we analyse a β -turn formation in Leu-Enkephalin previously examined by us in [40]. It is important to emphasize that studying the β -turn formation is fundamental for understanding protein folding. A great number of publications are devoted to the geometrical aspects of protein folding. The majority of them, however, consider somewhat straightforward descriptors. Such as, various distances in the polypeptide chain, radii of gyration, etc. Some of them are very important, for example, the i and $i+3$ C_α atoms distance is empirically proved to be effective in defining the β -turn. Nevertheless, the majority of works concentrates on different parts of the molecule, and the complexity of the whole system is not properly taken into account. In this section, we use the κ -index as an overall characteristic of the polypeptide chirality. We expect that it can also be employed to detect and analyse elementary folding events. To the best of our knowledge, the chirality measure was not used and realistic models of the dynamics of folding in water are still to be proposed.

To begin with let us consider the chirality for the individual aminoacids comprising the Leu-Enkephalin molecule (NH_3^+ -TYR-GLY-GLY-PHE-LEU-COO $^-$). It can be seen from table 3 that, excluding tyrosine, the zwitterion forms are substantially more chiral. This reflects a significant conformational rearrangement during the proton transfer from the oxy-group to the amino-group.

The details of the simulation are given in [40]. Briefly, we carried out all-atom classical molecular dynamics simulation of the Leu-Enkephalin molecule in explicit water. The zwitterionic form of the molecule was solvated in a rectangular box of 5826 SPC [41] water molecules. The GROMOS96 [41] forcefield was used. Four 3 ns long (of 0.002 ps time steps) simulations were performed

Table 3
Relative chirality index κ/κ_c for some aminoacids.

Molecule	Acid form	Zwitterion
Alanine	1.0	4.1
Phenyl-alanine	5.6	7.3
Leucine	4.1	9.6
Tyrosine	13.8	7.7

with weak coupling to heat and pressure baths at 300 K and 1 bar, respectively [42]. All bond-lengths were constrained using the SHAKE [43] and SETTLE [44] algorithms. The simulations were performed using GROMACS [45] package. The system was allowed to equilibrate for the first 100 ps before collecting data for the analysis.

A β -turn was defined for four consecutive residues if the distance between the C_α atom of residue i and the C_α atom of residue $i + 3$ is less than 7 \AA . Also, the two central residues should not be helical [46]. There are two possible β -turns in Leu-Enkephalin: 1–4 and 2–5. As it has been reported in the literature [47] and observed in this study, the β -turn in this molecule is not stable. However, it survives for long-periods of time and is created very quickly. This classifies it as an elementary event similar to that of protein folding. To smooth out the short-time fluctuations of the molecule, the coordinates of Leu-Enkephalin were averaged for 0.2 ps before calculating the chirality index at the given time. The calculated κ -index and its evolution in time is presented in figure 1 for two β -turn events. A similar pattern in the time change of the chirality is observed for both events. It has a relatively high value before the turn formation, then exhibits a quick drop that leads to a minimum on the studied interval. After the turn is formed the chirality rises to a somewhat higher than the average level. As a result the chirality index of Leu-Enkephalin undergoes a rapid change spanning almost the whole allowed interval of the values, exactly at the moment of the β -turn formation.

We would like to stress that this behaviour is not accidental; at least it has a strong correlation with other, completely different descriptions of the system (figure 2). Structural (the averaged dipole orientation with respect to the protein molecule) and dynamical (the averaged survival time of water molecules in the first solvation shell) characteristics are shown in figure 2(c) and (d). Based on these and other data, the conclusion that ‘freezing’ of the water network before the transition and its increased mobility during the β -turn formation was made [40]. The dynamic complexity reflecting the chaoticity of the system dynamics (the details of the methodology are given in [48,49]) is plotted in figure 2(e) and (f) for the peptide and water atoms, respectively. The wider span of the minima is caused by the necessary 4 ps intervals used to calculate each value of the

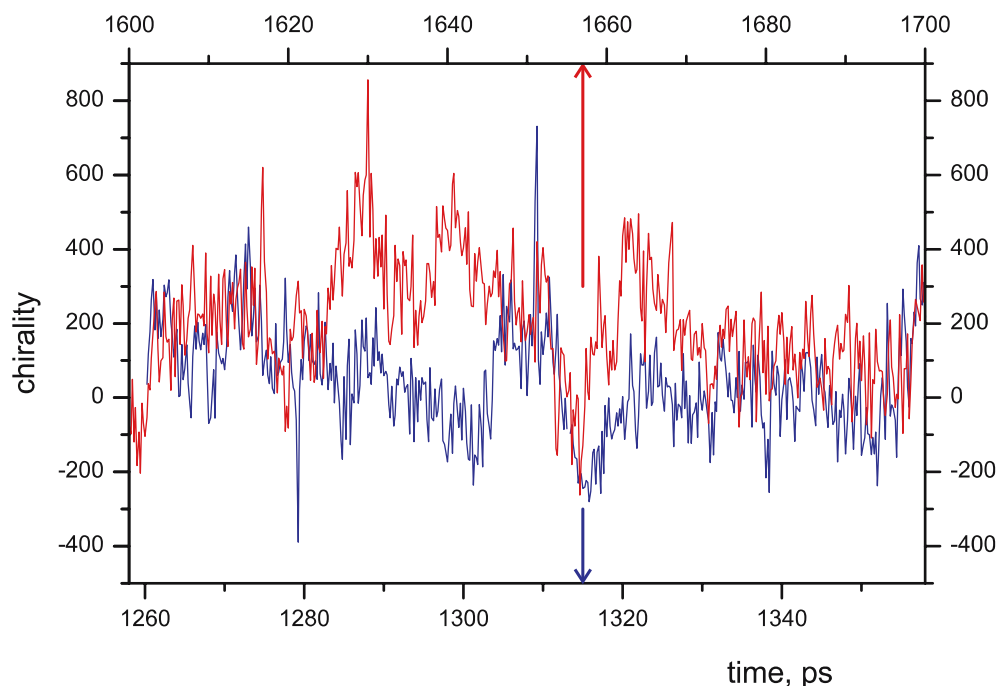


Figure 1. Chirality index for two β -turn transitions. Blue (red) graph corresponds to the bottom (top) time axes. The arrows indicate the transition time.

complexity. These results will be published shortly. The obvious similarity in the behaviour of all these characteristics indicates specific dynamic processes manifested in the system parameters of a very diverse nature. Possible reasons of this behaviour is the subject of our consecutive investigations.

6. Concluding remarks

The method for quantifying molecular chirality at the electronic level by the κ -index (27) provides a useful tool for studying 'static' chemical structures as well as dynamics of molecular systems under their transformation. Using the proposed computational scheme we examined, in particular, high-symmetry chiral hydrocarbons with C_n and D_n symmetry. We also observed an interesting effect of the chirality changes during a β -turn formation in a model polypeptide chain. It is essential that, given a molecular geometry, little computational efforts are required for evaluating the κ -index properly since it uses elementary matrix operations only. Hence, this chirality analysis for static and dynamic descriptions of very large molecular and polymer systems can be recommended. Other chirality quantification schemes are usually more computationally demanding. For

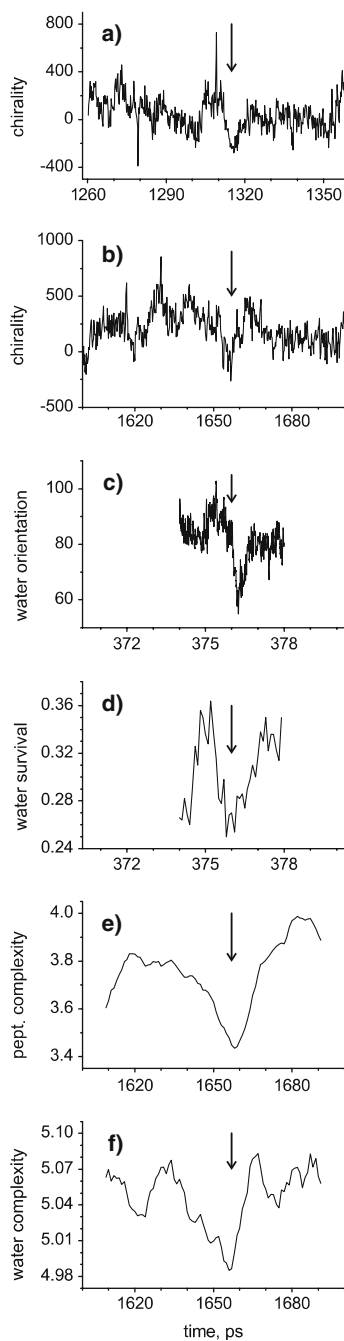


Figure 2. Similarity in the time change of (a,b) chirality indices (c) averaged orientation, and (d) survival time of the first solvation shell water molecules around 2GLY, topological complexity of (e) the peptide and (f) the first solvation shell water atoms. The arrow indicates the transition time.

example, the one described in [35] requires too high-performance computers as described in the recent paper [50].

Before discussing further developments in this field one principal issue should be considered. It is connected with the general properties of possible chirality measures. As we have already mentioned in section 3, for any chirality measure to have a physical meaning it should be defined as an extensive (additive) quantity or an intensive one. The majority of the observed properties are additive and the same would be naturally desired for chirality measures. At the same time, certainly non-negative or, simply, positive chirality indices (chirality functions) would seem to be preferable. ‘Chiral’ theoreticians provided various approaches for treating the molecular chirality by the positive indices derived from purely geometrical or topological considerations [11]. A typical viewpoint is that since a chirality pseudoscalar function takes opposite signs when passing from an optical isomer to its antipode. Therefore, this function must vanish somewhere on the potential surface of the system in question, even with a chiral configuration (‘chiral zeros’) [51]. However, in reality such molecular configuration can be uninteresting (with many bonds broken). Of course, unpleasant cases with a difficult interpretation are also possible and it also shows that a fully universal additive chirality measure is unachievable. On the other hand, the use of positive chirality indices only has the following drawback: any positive chirality measure cannot be additive. Indeed, let $\chi(A)$ be an additive chirality measure for a species A . This means that for a composite system AB comprising of the isolated A and B , the additive separability, i.e. the additive relationship, should be true:

$$\chi(AB) = \chi(A) + \chi(B).$$

With $B = A^\#$, where $A^\#$ is a mirror image of A we have $\chi(AA^\#) = 0$, thus:

$$\chi(A^\#) = -\chi(A).$$

This defines $\chi(A)$ as a pseudoscalar quantity. Therefore, any positive chirality measure is not compatible with the additivity property. This is why we prefer to deal with the additive pseudoinvariants exploring the electron shells explicitly. We would like to emphasize that the critique [51] on using the pseudoscalar quantities for the chirality measures does not take into account this nonphysical behaviour of positive chirality functions. Yet, by using a set of independent pseudoscalars (‘chirality vector’) as discussed in [51], we may somehow improve our approach and propose a new ‘conditionally additive’ measure having only the homogeneity in the sense that

$$\chi(AA) = 2\chi(A),$$

$$\chi(AAA) = 3\chi(A),$$

$$\chi(AAA^\#) = \chi(A),$$

etc. This possibility is not realised in [51]. Taking the sum of the absolute values of the invariants (21)–(23) or the corresponding averages of the type (26) leads to the conditionally additive measure possessing no chiral zeros. However, more research is necessary before definite recommendations can be made.

In this work we realised only a crude scheme accounting for the molecular electronic shell. In doing so we derived one-electron invariants from spectral moments of the susceptibility related to the optical rotation and dispersion interaction theory. In the same manner other susceptibilities can produce new invariants reflecting specific features of the chiral electronic shells. The many-electron aspects of this problem deserve to be examined as well. The κ -index measure itself, as a simple matrix invariant generated by the chirality operator $\hat{\kappa}$ (26), seems to be the most natural from the physical viewpoint. Indeed, the chirality operator early introduced in [23] is a quantum counterpart of the triple scalar product involving velocity, acceleration and second acceleration. In our opinion, such internal connection of the latter with the electron kinematics makes this operator one of the fundamental entities of the electronic chirality theory.

Acknowledgments

The work is supported by the Isaac Newton Trust and Unilever. AVL wishes to thank Cambridge Hospitality Scheme and Darwin College, and especially Robert Glen and W. Brown for the invitation to Cambridge that made possible the preparation of the final version of the paper. The authors are grateful to Robert Glen and Herman J.C. Berendsen for fruitful discussions and valuable comments.

References

- [1] E. Ruch, *Acc. Chem. Res.* 5 (1972) 49.
- [2] D. Walba, *Tetrahedron* 41 (1985) 3161.
- [3] A.B. Buda, T.A.D. Heyde and K. Mislow, *Angew. Chem. Intern. Engl.* 31 (1992) 989.
- [4] P.G. Mezey, *Shape in Chemistry: An Introduction to Molecular Shape and Topology* (VCH Publishers, New York, 1993).
- [5] H. Zabrodsky and D. Avnir, *Adv. Mol. Struct. Res.* 1 (1995) 1.
- [6] D. Avnir, H. Zabrodsky and P.G. Mezey, in: *Encyclopedia of Computational Chemistry*, ed. P.v.R. Schleyer (Wiley, Chichester, 1998), vol. 4, p. 2890.
- [7] K. Mislow, *Top. Stereochem.* 22 (1999) 1.
- [8] R. Todeschini and V. Consonni, *Handbook of Molecular Descriptors* (Wiley*-VCH, New York, 2000).
- [9] E. Flapan, *When Topology Meets Chemistry* (Cambridge University Press, Cambridge, 2000).
- [10] P.G. Mezey, *Compu. Math. Appl.* 34 (1997) 105.
- [11] M. Petitjean, *Entropy*, 5 (2003) 271.
- [12] G. Gilat and L. S. Shulman, *Chem. Phys. Lett.* 121 (1985) 13.
- [13] G. Gilat *J. Phys. A, Math. Gen.* 22 (1989) L545.
- [14] P.G. Mezey, *Int. J. Quant. Chem.* 63 (1997) 105.

- [15] P.G. Mezey, *J. Math. Chem.* 23 (1998) 65.
- [16] P.G. Mezey, R. Ponec, L. Amat and R. Carbo-Dorca, *Enantiomer*. 4 (1999) 371.
- [17] G. Boon, C. Van Alsenoy, F. De Proft, P. Bultinck and P. Geerlings, *J. Phys. Chem. A* 107 (2003) 11120.
- [18] G. Boon, C. Van Alsenoy, F. De Proft, P. Bultinck and P. Geerlings, *J. Mol. Struct. (Theochem)*, 727 (2005) 49.
- [19] H. Zabrodsky and D. Avnir, *J. Am. Chem. Soc.* 117 (1995) 462.
- [20] S. Grimme, *Chem. Phys. Lett.* 297 (1998) 17
- [21] L. Bellarosa and F. Zerbetto, *J. Am. Chem. Soc.* 125 (2003) 1975.
- [22] A.V. Luzanov and E.N. Babich, *Stuct. Chem.* 3 (1992) 175.
- [23] A.V. Luzanov and E.N. Babich, *J. Mol. Stuct (Theochem)*. 333 (1995) 279.
- [24] U. Fano and J.W. Cooper, *Rev. Mod. Phys.* 40 (1968) 441.
- [25] V. Chernyak and S. Mukamel, *J. Chem. Phys.* 103 (1995) 7640.
- [26] C.J. Bradley and D.E. Hughes, *Int. J. Quant. Chem.* 3 (1969) 699.
- [27] C.A. Coulson and J.C. Nash, *J. Phys. B.* 7 (1974) 757.
- [28] S.R. de Groot and L.G. Suttorp, *Foundations of Electrodynamics* (North-Holland Publishers, Amsterdam, 1972).
- [29] D.P. Craig, E.A. Power and T. Thitunamachandran, *Proc. R. Soc. Ser. A.* 322 (1971) 165.
- [30] R. McWeeny, *Rev. Mod. Phys.* 32 (1960) 335.
- [31] A.V. Luzanov and G.E. Whyman, *Int. J. Quant. Chem.* 20 (1981) 1179.
- [32] H. Kon, *Bull. Chem. Soc Jpn.* 28 (1955) 275.
- [33] W.T. Hoeve, H. G. Wynberg, *J. Org. Chem.* 45 (1980) 2754.
- [34] K. Nakazaki, *Top. Stereochem.* 15 (1984) 199.
- [35] M.P. Neal, M. Solymosy, M.R. Wilson and D.J. Earl, *J. Chem. Phys.* 119 (2003) 3567.
- [36] G.M. Badger and I.S. Walker, *J. Chem. Soc.* (1954) 3238.
- [37] O. Katznelson, J. Edelstein and D. Avnir, *Tetrahedron: Asymmetry*. 11 (2000) 2659.
- [38] C. Thilgen, I. Gosse and F. Diederich, *Top. Stereochem.* 23 (2003) 1.
- [39] A. Rassat, I. Laszlo and P.W. Fowler, *Chem. Eur. J.* 9 (2003) 644.
- [40] G. Karvounis, D. Nerukh and R.C. Glen, *J. Chem. Phys.* 121 (2004) 4925.
- [41] W.R.P. Scott, P.H. Hunenberger, I.G. Tironi, A.E. Mark, S.R. Billeter, J. Fennen, A.E. Torda, T. Huber, P. Kruger and W.F. van Gunsteren, *J. Phys. Chem. A* 103 (1999) 3596.
- [42] W.F. van Gunsteren and H.J.C. Berendsen, *Angew. Chem. Int. Ed. Engl.* 29 (1990) 992.
- [43] J.P. Ryckaert, G. Ciccotti and H.J.C. Berendsen, *J. Comput. Phys.* 23 (1977) 327.
- [44] S. Miyamoto and P.A. Kollman, *J. Comp. Chem.* 13 (1992) 952.
- [45] H.J.C. Berendsen, J.P.M. Postma, W.F. van Gunsteren and J. Hermans, in: *Intermolecular Forces*, ed. B. Pullman (D. Reidel Publishing Company, Dordrecht, 1981), pp. 331–342.
- [46] E.G. Hutchinson and J.M. Thornton, *Prot. Sci.* 5 (1996) 212.
- [47] D. van der Spoel and H. J. C. Berendsen, *Biophys. J.* 72 (1997) 2032.
- [48] D. Nerukh, G. Karvounis and R.C. Glen, *J. Chem. Phys.* 117 (2002) 9611; *ibid*, 9618.
- [49] D. Nerukh, G. Karvounis and R.C. Glen, *Complexity* 10 (2004) 40.
- [50] A.G. Noto and K.L. Marshall, *Proc. SPIE.* 5936 (2005) 157.
- [51] N. Weinberg and K. Mislow, *Can. J. Chem.* 78 (2000) 41.