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Towards a theory of molecular recognition*

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Abstract Why do we have a continuous conception of the opening of doors? Actually because the rotations around the hinges act as conceptual tools that allow us to "think" of door arrangements as continuously interchangeable states. If our geometrical tooling were reduced to the identity, then our conception of door opening would reduce to the dichotomous alternative closed/non-closed. This example highlights the role of geometry in the conception of physical phenomena. Accordingly, the recently introduced "gauge" geometries result in an original approach to molecular recognition when applied to quantum molecular states. In particular, this theory features a graphical description of molecular recognition between biomolecules. The 2D theory is discussed. The application of 2D gauge geometry to the description of chirality is also briefly presented.

Key words: Molecular recognition – Ligand-protein binding – Gauge geometry – Chirality – Structure-based drug design

1 Introduction

The foundations of an original approach to molecular recognition will be presented in this article. One outcome of this theory is a graphic representation of the matching between two potentially associating molecules, to be constructed here in the case of electrostatic interactions. This theory can potentially be applied to any biological system, for example, protein complexes with ligands, proteins or nucleic acids. As a result, new screening tools, though not developed here, become available to structure-based drug design. Now, this theory results from the application of a geometry to a natural phenomenon, here molecular recognition. In this statement lies an intricacy faced by any presentation of the theory. How can a geometry be of interest to a physicochemical issue? We attempted to cope in the simplest way with this question (Sects. 2, 3) before dealing with gauge geometries (Sects. 4–6) and their application to molecular recognition (Sect. 8). Only the simpler 2D theory will be discussed. The application of 2D gauge geometry to the description of chirality will also be briefly presented (Sect. 7), so as to show the versatility of this approach.

2 What is a geometry?

As stated above, the proposed theory is but one application of a geometry, to be henceforth called a "gauge" geometry. We must stress that the word "geometry" is understood here in the mathematical context. For the sake of clarity, let us first briefly present this context. Geometry has long been concerned with the study of "geometrical figures." However, historically, mathematical interest has progressively shifted from the figures themselves to the transformations enabling them to be handled, and the properties invariant under these transformations. For example, lengths are "properties" invariant by translations, rotations and mirror reflections, but not by dilations. In the contemporary context then, as first stressed by Klein and Riemann [1, 2], geometry could be defined as the study of transformation groups and their invariants. Every transformation group can be considered to define a geometry. Unitary geometries, for example, are associated with unitary groups in Hilbert spaces. In Euclidean spaces – the real affine spaces where the notion of distance between points is defined – Euclidean geometry is associated with the group of distance-conserving transformations – the group of isometries. Rotations, reflections and translations are isometries. Now translations are somewhat trivial operations, and a classical result is that every isometry can be factorized as the product of a translation by an isometry that leaves invariant ("stabilizes") an arbitrary point O [1]. The subgroup Is_O of the

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isometries stabilizing O thus appears as the "core" of the isometry group. Subgroups attached to different points are isomorphous. Accordingly, Is_O can be considered to define Euclidean geometry "locally" at O. Our interest will henceforth be focused on local geometries.

3 Geometries are tool boxes

A geometry in this context is a group of tools that allows a definite level of "handling" of the objects considered, hence a definite level of "understanding" of their properties. This idea is central to the following. Let us illustrate it by a simple example. Imagine that on a remote planet there is a wall and, in that wall, a door framed so as to open on both sides of the wall. Let us assume that the planet folks know nothing of Euclidean geometry and only master the more primitive concept of identity. What could be their understanding of the door/wall system? They would indeed "see" that all possible door arrangements are different, but they lack conceptual tools to "think" about them – except when there is "identity" between the door and the wall planes. Therefore the closed arrangement is the only one that they can conceptually grasp. All other situations cannot be conceived, except through the negative fact that they differ from the thinkable one – they are nothing but "non-closed" arrangements. Now let our folks additionally know of the reflection σ through the wall plane. This assumption turns the set of available geometrical tools into the group containing identity and σ, to be denoted $O(1)$[1]. σ allows our folks to think of a definite relationship – enantiomerism – between a door arrangement and its σ image. Non-closed situations are still individually unthinkable, but the closed case is now defined by a symmetry property, as the single arrangement superposable on its σ image. A prominent scientist of theirs could express this conception according to the following $O(1)$ definition. However, this conception is radically altered in the framework provided by Euclidean geometry, because the larger conceptual tool box provided by the isometry group includes rotations, which are indeed fit to conceive the door pivoting movement around its hinges. Door arrangements can be "thought" of as a continuous manifold of individual states interchanged by rotation, and the door/wall system as featuring a single rotational degree of freedom (Fig. 1).

$O(1)$ definition of door opening: "I call any door non-closed (open), and say it has opening, if its σ image cannot be brought to coincide with itself."
Euclidean definition of door opening: Door opening is the continuous phenomenon of rotation of the door with respect to the wall.

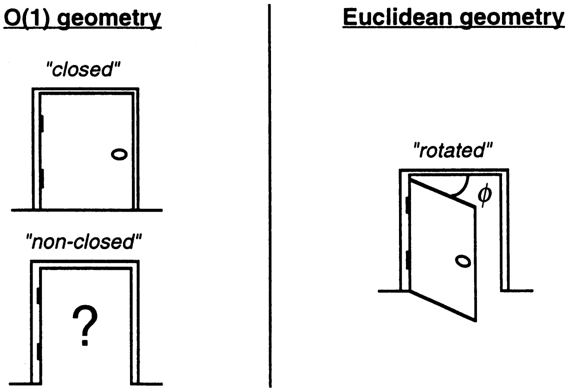

Fig. 1. The phenomenon of door opening as seen through two different geometrical tool boxes. *Left*, a tool box reduced to the group $O(1)$ (see text) can only allow us to "think" of the symmetry property associated with the closed arrangement. *Right*, the larger Euclidean tool box allows us to "think" of the rotational degree of freedom of the door/wall system. This results in a continuous conception of door opening describing the way the previous symmetry is breaking

The former conception is dichotomous while the latter is continuous, but both deal with one and the same phenomenon – door opening. The two conceptions are not conflicting but are hierarchically related, since they are associated with different levels of geometrical analysis. Therefore it is indeed possible that a single phenomenon appears under two widely different guises in two different geometries. In the $O(1)$ conception door opening is negatively defined. The actually defined concept, closing, reduces to a symmetry property. In the Euclidean conception door opening is a positively defined, continuous and extensive phenomenon. How is this breakthrough possible? Because Euclidean geometry correctly brings out the nature of the internal degree of freedom of the door/wall system. The key fact is that for every degree of freedom there is a set of operations canonically associated with it, enabling it to be "manipulated". Here, the rotations interchanging door arrangements are associated with the door degree of freedom. There is a duality between geometrical degrees of freedom and geometrical operations. Conversely, this set of operations is required if we are to "think" of this degree of freedom. Were the required set unavailable, the degree of freedom could not be thought of properly. This is why $O(1)$ geometry fails to provide a continuous conception of door opening. In this respect, the "larger" is the "richer" – shifting to larger groups cannot but enrich our conception of the phenomenon considered. The important practical result is that shifting from $O(1)$ to Euclidean geometry provides a continuous description of the way the dichotomous "closing" symmetry is breaking. It is the only possible description of symmetry breaking insofar as all degrees of freedom are comprehensively dealt with. Still richer geometries cannot improve this description since the single rotational degree of freedom has already been dealt with, so the previous description of symmetry breaking appears unique. This description reflects the particular nature of the degree of freedom involved, thus the fact that its formal expression looks so different from the previous symmetry criterion. Lastly, in no way are $O(1)$ and Euclidean geometries limited to tackling the question of

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[1] O (1) denotes the 1D orthogonal group, to which this group can be identified

door opening. Similarly, the gauge geometries to be constructed will be applied to two largely unrelated phenomena: chirality and molecular recognition.

4 Why bother with square-integrable fields?

The example of door opening illustrated a result that was argued [3] to be typically at stake in geometrical argumentations – describing the breaking of a discrete symmetry. Gauge geometries will be briefly discussed now. The first question relates to the type of object that these geometries enable to be "handled." In other words, what are the "geometrical figures" of the so-called gauge geometries? Their geometrical figures are fields. The proofs proposed up to now [3–5] apply to square-integrable (L^2) fields. "Fields" stand for the spatial distributions $\psi(\vec{r})$ of complex numbers, and "square-integrable" means that $|\psi(\vec{r})|^2$ is integrable (Eq. 1) with respect to the integration element (the Lebesgue measure dm) appropriate to the dimension considered (e.g. in 3D $\mathrm{d}m = \mathrm{d}x\ \mathrm{d}y\ \mathrm{d}z$). L^2 fields form vector spaces featuring a rich structure, called Hilbert spaces and denoted L^2 (R^d, dm) in dimension d [6]. This structure in a way plays the role of the hinges previously described, putting the door/wall relationship on firm grounds.

$$\int |\psi(x,y,z)|^2\ \mathrm{d}x\ \mathrm{d}y\ \mathrm{d}z \quad \text{is finite} \tag{1}$$

Why can these spaces be of interest in protein or nucleic acid studies? Simply because these are molecules, and because molecules are described by L^2 wave functions in non-relativistic (NR) quantum mechanics. Fields fulfilling Eq. (1) describe spinless particles. Non-zero spin particles such as electrons are described by adding a discrete spin coordinate σ to the spatial ones. Wave functions are still required to be L^2, albeit summation is also carried out on σ. Assuming spinless nuclei, molecules are described by wave functions of the form $\psi_{\sigma_1\ldots\sigma_N}(\vec{r}_1\ldots\vec{r}_N;\vec{R}_1\ldots\vec{R}_A)$ fulfilling Eq. (2), where $\vec{r}_1,\sigma_1,\ldots\vec{r}_N,\sigma_N$ $(\vec{R}_1\ldots\vec{R}_A)$ are electron (nuclei) coordinates.

$$\sum_{\sigma_1=\pm1}\cdots\sum_{\sigma_N=\pm1}\int \left|\psi_{\sigma_1\ldots\sigma_N}(\vec{r}_1\ldots\vec{r}_N;\vec{R}_1\ldots\vec{R}_A)\right|^2 \mathrm{d}^3r_1\ldots\mathrm{d}^3r_N\mathrm{d}^3R_1\ldots\mathrm{d}^3R_A \quad \text{is finite} \tag{2}$$

All these descriptions are variants of the same basic form (Eq. 1). In the NR quantum framework, the states of all forms of molecular matter can be described as L^2 fields. Since handling the wave function (Eq. 2) is practically cumbersome, it is fortunate that this conclusion also applies to simplified or partial levels of molecular description. Thus nuclear skeleton quantum states, one- or many-electron orbitals and densities[2], describing protein residues, enzyme active sites or DNA bases, are L^2 fields. Broadly speaking, proteins, nucleic acids, drugs and other molecules appear as geometrical figures from the viewpoint of gauge geometries. In this preliminary account, the discussion of gauge geometries and their applications will be limited to the case of 2D scalar L^2 fields, which physically describe 2D spinless particles. 3D gauge geometries are briefly tackled in Refs. [3, 4] and will be dealt with in greater detail elsewhere.

5 Gauge geometries

Gauge geometries can be defined as "gauge generalizations" of classical geometries – Euclidean geometry in this case. The origin of this designation will be explained below. The 2D local group at an arbitrary fixed origin O in the sense of Sect. 2 will be presented now. Our "geometrical figures" are thus the fields $\psi(x,y)$ square-integrable with respect to $\mathrm{d}m = \mathrm{d}x\,\mathrm{d}y$. Let us consider such a field just as the door/wall system was considered, and look into the way Euclidean geometry enables us to "think" of its degrees of freedom as seen from O. There are two kinds of local isometries: the rotations of centre O (determinant $+1$) and the indirect isometries (determinant -1) which in 2D are the reflection axes containing O. Rotations enable the field orientation to be changed without deforming it. In other words, rotations handle a specific type of degree of freedom, which could be said to be "external." Reflection axes do not add much to this, as they change the field as a whole into its symmetrical counterpart just as the door was moved by σ. Clearly, isometries provide us with a rather crude understanding of L^2 fields. Is it possible to achieve a breakthrough comparable to the one previously provided by Euclidean geometry in the door/wall case? Recalling the discussion in Sect. 3, this would require the identification of the field degrees of freedom escaping the reach of isometries – the internal degrees of freedom – and the construction of operations enabling them to be handled. Is this possible? Gauge geometries were designed as a positive answer to this question, albeit initially in a more specific context. This construction is detailed elsewhere [3–5] so it will only be briefly described here for the real case. Theory identifies the geometrical degrees of freedom of real L^2 fields as the *orientations* of a double series of *symmetry groups* called "*radial canonical groups*" (RCG). The guiding line of this theory is a structural decomposition of symmetry groups. The first step is simple. All isometries stabilizing O move field values along the circles of centre O. Thus field restrictions to circles are geometrically independent whatever their other relations. The symmetry group $G^{(r)}$ is associated with the field restriction $\psi^{(r)}$ of ψ to the circle of radius r. Now $\psi^{(r)}$ itself is a composite object, and theory shows that it should be projected along the irreducible representations of the local isometry group. The resulting projections $\psi_n^{(r)}$ are defined by Eq. (3) and $\psi^{(r)}$ satisfies $\psi^{(r)} = \psi_0^{(r)} + \sum_{n\geq1}\psi_n^{(r)}$. The RCGs are the symmetry groups $G_n^{(r)}$ of the $\psi_n^{(r)}$.

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[2] Continuous integrable fields vanishing at infinity are L^2. This result applies to molecular electron and nuclear densities, which are square moduli of wave-functions

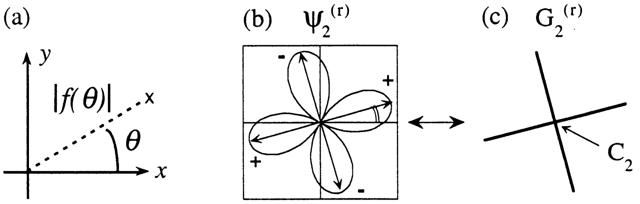

Fig. 2a–c. The origin of radial canonical groups. Field restrictions to circles are functions of only one angular variable θ measured with reference to an arbitrary reference frame at O. Such a real function, say $f(\theta)$, can be represented in polar form, that is in the 2D version of the usual representation of spherical harmonics, found in classical textbooks. For every θ value, a point is drawn at the angle θ and the distance $|f(\theta)|$ from the origin (**a**). The function then is represented by a closed curve. The sign of $f(\theta)$ is reported separately. In this form $\psi_n^{(r)}$ appears as a $2n$-leaf "clover," here pictured in the case $n = 2$ (**b**). The advantage of this representation is that symmetries become obvious. The symmetries of the $2n$-leaf clover with alternating signs are a C_n rotation centre and n (not $2n$) reflection axes forming a n-star (**c**)

$$\left\{\begin{array}{l}\psi_n^{(r)}(\theta) = \Delta_n(r)\frac{1}{\sqrt{2\pi}}\mathrm{e}^{\mathrm{i}n\theta} + \bar{\Delta}_n(r)\frac{1}{\sqrt{2\pi}}\mathrm{e}^{-\mathrm{i}n\theta} \\ \Delta_n(r) = \int_0^{2\pi}\psi(r,\theta)\cdot\frac{1}{\sqrt{2\pi}}\mathrm{e}^{-\mathrm{i}n\theta}\mathrm{d}\theta\end{array}\right. \qquad n \geq 1 \qquad (3)$$

In the polar representation, $\psi_n^{(r)}$ looks like a $2n$-leaf clover and it becomes evident that the structure of $G_n^{(r)}$ is well defined (Fig. 2). $G_n^{(r)}$ contains a C_n rotation centre, and n reflection axes crossing at O forming a so-called n-star [3–5]. It turns out that, up to the scale factor $|\Delta_n(r)|$, $\psi_n^{(r)}$ is entirely determined by its symmetry group $G_n^{(r)}$. This and the fact that RCGs have a well-defined structure are basic properties of this approach [3–5]. What happens when ψ is rotated? It turns out that this amounts to rotating all RCGs as a whole. In particular, it is clear that $|\Delta_n(r)|$ is invariant in such operations and thus plays no geometrical role in itself. $|\Delta_n(r)|$ simply measures the amplitude of the projection $\psi_n^{(r)}$. Consequently, the only geometrical degree of freedom of $\psi_n^{(r)}$ is the orientation of $G_n^{(r)}$, and this orientation completely defines $\psi_n^{(r)}$ up to a scale factor. Accordingly, as seen from O, L^2 fields appear to be made out of a double series of "clovers" ($\psi_n^{(r)}$) whose geometrical degrees of freedom (RCGs orientations) are well defined. The equivalent of a door arrangement here is a distribution of RCG orientations. Having identified the geometrical degrees of freedom of L^2 fields, we can now turn to the geometry enabling them to be handled. The rotations interchanging door arrangements were associated with the door degree of freedom. Here, distributions of RCG orientations must be interchanged. However, Euclidean rotations move RCGs as a whole. Therefore, rotations are not able to change their relative orientations, hence they are not versatile enough to settle our problem. The isometry group is not rich enough to enable us to think of L^2 field degrees of freedom, just as $O(1)$ geometry was not rich enough to enable us to think of the door degree of freedom. The required operations must be able to change the relative orientations of RCG, hence they must rotate them independently. Rotations must be applied individually to every $\psi_n^{(r)}$, rotating $G_n^{(r)}$ by the arbitrary angle $\alpha_n(r)$ (Eq. 4). The resulting operations, which we propose to call gauge rotations, generalize Euclidean rotations. A 2D gauge rotation is defined by the set of angular functions $\alpha_n(r)$ $(n \geq 1)$.

$$\left\{\begin{array}{ll}\psi_n^{(r)}(\theta) \mapsto \psi_n^{(r)}(\theta - \alpha) & \text{Euclidean rotation} \\ \psi_n^{(r)}(\theta) \mapsto \psi_n^{(r)}[\theta - \alpha_n(r)] & \text{Gauge rotation}\end{array}\right. \qquad (4)$$

Reflection axes can be similarly generalized. Together with gauge rotations, these operations form an infinite-dimensional Lie group that contains the local isometry group. This situation is strikingly similar to that of the door/wall system. The name "gauge geometry" was chosen with reference to the notion of gauge transformation that proved so important in relativistic quantum field theory [7]. In short, the present gauge operations are to Euclidean operations what second-order gauge transformations are to first-order ones. The present construction is a mechanism of gauge extension of the classical geometries, rather than an isolated new geometry.

6 Radial loops

A door arrangement can be characterized by an angle. A L^2 field is characterized by the distribution of an infinite number of RCGs. Is there a convenient representation of that distribution? The answer is "yes". Radial loops provide a simple graphical representation of the field degrees of freedom. Radial loops are briefly discussed here. Up to now the factors determining the orientation of $G_n^{(r)}$ were not precised. It turns out that this orientation only depends on the phase $\varphi_n(r)$ of the complex function $\Delta_n(r)$ defined by Eq. (3) [3]. Accordingly, at fixed $|\Delta_n(r)|$, the direction of $\Delta_n(r)$ in the complex plane and the orientation of $G_n^{(r)}$ are "mechanically" related just as cog wheels in a gear box (Fig. 3). This relation is the basis of radial loop theory. Firstly, because of this relation, the graph of $\Delta_n(r)$ as a function of r provides a faithful representation of the distribution of RCG orientations along r at the fixed order n. For theoretical reasons, this graph is to be called the nth order absolute radial loop (ARL) whilst $\Delta_n(r)$ is called the absolute radial function (ARF)[3]. An advantage of ARLs is that the amplitude information $|\Delta_n(r)|$ is merged with the phase information $\varphi_n(r)$, so that ARFs sum up all the information contained in $\psi_n^{(r)}$ at the order n. A narrow ARL is the signal of weakly radially misaligned RCGs and a wide ARL indicates largely misaligned RCGs. Secondly, the orientation of $G_n^{(r)}$ does not change with r alone, but also with n at fixed r. It turns out that a second type of radial loop, to be called a relative radial loop (RRL), is associated with this phenomenon. Theory shows that indices should be considered by pairs n, $m \geq 1$. Now clovers with different numbers of leaves should be compared at fixed r, and it

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[3] Gauge geometries were initially introduced during the analysis of chirality [5]. The fact that these geometries are completely independent from this particular application was not recognized initially. This resulted in "radial loops" being called "chiral loops" in [3–5]. A more correct denomination is introduced here

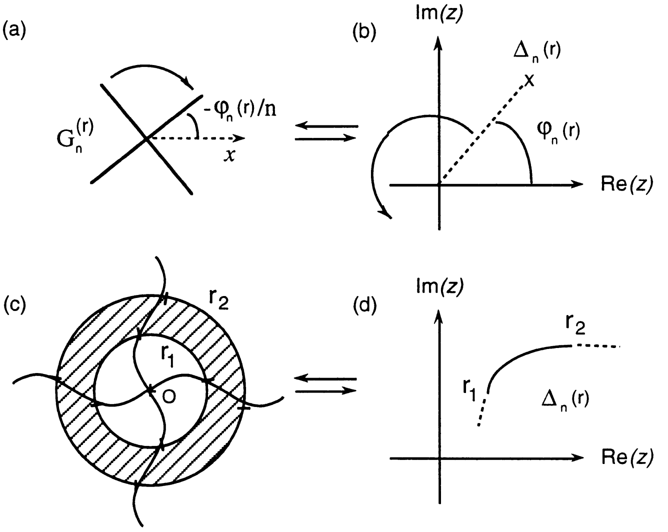

Fig. 3a–d. The origin of absolute radial loops. The orientation of a n-star is determined as soon as that of a single axis is known. Denoting $D_n[\alpha]$ the group containing a C_n rotation centre and the n-star featuring one axis at the angle α, theory shows [3] that $G_n^{(r)} = D_n[-\varphi_n(r)/n]$, where $\varphi_n(r)$ is the phase of $\Delta_n(r)$ (**a**). As a result, the orientation of $G_n^{(r)}$ and that of $\Delta_n(r)$ in the complex plane are connected just as those of cog wheels in a gear box (**b**). If $G_n^{(r)}$ is rotated by π/n then $\Delta_n(r)$ is changed into its opposite (*arrows* in **a**, **b**). Radially gathering RCGs between two radii r_1 and r_2 at fixed n ($n = 2$ in **c**), we get a curve portion in the complex plane (**d**). The completed curve forms a loop – the so-called absolute radial loop – as it is shown to begin and end at the origin [3–5]. ARLs are oriented in the direction of increasing r

turns out that the misorientation of $G_n^{(r)}$ and $G_m^{(r)}$ is related to the phase of the relative radial function (RRF) $\Delta_{n,m}(r) = [\bar{\Delta}_n(r)]^M[\Delta_m(r)]^N$ just as the orientation of $G_n^{(r)}$ was related to the phase of $\Delta_n(r)$. Here $N = n/p$ and $M = m/p$, p being the highest common factor of n, m [4]. $G_n^{(r)}$ and $G_m^{(r)}$ have at least one common axis if and only if $\Delta_{n,m}(r)$ is real. The RRL of order n, m is the graph of $\Delta_{n,m}(r)$ in the complex plane, and gathers this relative information for all possible r. Radial loops are practically invaluable because they can be directly obtained from the field through Eq. (3). Radial loops picture the field as seen “from the inside”.

7 First application: describing molecular chirality

The first application of these seemingly abstract results is the description of molecular chirality. Since the resulting theory of chirality is detailed elsewhere [3–5], only a brief account will be found here. Kelvin’s definition [8] states that a molecule is achiral if it is superposable on its image in a plane mirror, and chiral otherwise. Glycine is achiral, whilst L- and D-alanine are chiral. In other words, a molecule is achiral if its symmetry group G contains at least one indirect isometry, and chiral otherwise. The latter form provides the dimension-independent definition to be applied in 2D. Chirality appears as a dichotomous symmetry issue in this framework – the *Euclidean* framework. Now recall that in $O(1)$ geometry, door opening also appeared as a dichotomous symmetry issue. The $O(1)$ conception of door opening is indeed closely similar to Kelvin’s conception of chirality. Both door opening and chirality are negatively defined. The actually defined concepts – closing and achirality – reduce to symmetry properties. The closed situation is the case when the symmetry group of the system contains the indirect isometry σ – in all other situations the symmetry group contents reduce to the identity. The relationship between σ-image door arrangements parallels the mirror-image relationship between L- and D-alanine, and was indeed called enantiomerism in anticipation in Sect. 3. Shifting from $O(1)$ to Euclidean geometry provided a conceptual breakthrough in the understanding and the description of the door/wall system. Do gauge geometries provide a similar achievement in the case of chirality? Yes. It turns out that it is both chemically and theoretically fruitful to first reduce the problem to the notion of local chirality. Local chirality is chirality viewed from an arbitrary origin O. An object is said to be (locally) achiral at O if it is superposable on its image in a mirror containing O. Otherwise, it is said to be (locally) chiral at O. In other words, denoting $G(O) \subset G$ the subgroup of the field symmetries that stabilize O, a field is achiral at O if $G(O)$ contains at least one indirect isometry, and chiral at O otherwise. Now, in the case of L^2 fields, chirality is shown to be a *special case* of local chirality – simply because it is shown that L^2 field symmetry groups always stabilize at least one point A, typically the field inertia centre, so that chirality and local chirality at A are one and the same thing [3]. Thus the local definition of chirality practically brings about the freeing of the selection of the origin. For example, asymmetric carbons or protein active centres can be selected at will. Now, what is relevant to chiral recognition, the chirality of a protein as seen from its inertia centre, or rather from its active site? The notion of local chirality can thus be argued to be highly relevant to (bio)chemistry [3]. Let us then focus on the understanding of local chirality provided by gauge geometries. Recall that gauge geometries were ultimately based on a theory of symmetry groups (Sect. 5). A local symmetry group is accordingly “structured” as the intersection of well-defined elementary building blocks [3–5]. These building blocks are precisely the RCGs $G_n^{(r)}$. The explicit expression of $G(O)$ is Eq. (5):

$$G(O) = \bigcap_{n \geq 1} \bigcap_{r > 0} G_n^{(r)} \quad . \tag{5}$$

Any element of $G(O)$ must therefore be contained, with the same orientation, in every $G_n^{(r)}$. In particular, if the field is achiral at O then $G(O)$ contains a reflection axis. Since $G_n^{(r)}$ only contains reflection axes under the form of n-stars, the n-stars must be oriented so as to contain this axis, so that all RCGs n-stars must be aligned. The converse statement is trivial. Local achirality then appears as the phenomenon of alignment of the indirect elements of RCGs, just as closing appeared as the phenomenon of alignment of the door and the wall planes. Now, just as the “closing” symmetry is broken when the door is rotated, the achiral symmetry is broken – reflection axes are "torn away" – when RCGs are rotated with respect to one another. Just as Euclidean geometry provided the tools to think of door opening as the misalignment phenomenon introduced by the door rotation with respect to the wall, gauge geometries provide the tools to think of chirality as the misalignment phenomenon introduced by the relative rotation of the *n*-stars. Therefore the gauge conception of chirality is much richer than the Euclidean one, and the resulting definition of chirality is strikingly close to the Euclidean definition of door opening.

Euclidean definition of chirality at *O* (Kelvin's definition): "I call any geometrical figure ... chiral [at *O*], and say it has chirality [at *O*], if its image in a plane mirror [containing *O*] ... cannot be brought to coincide with itself." [8]
Gauge definition of chirality at *O*: Chirality [at *O*] is the continuous phenomenon of misalignment of the indirect elements of RCGs (*n*-stars in 2D).

Now again, both definitions deal with one and the same phenomenon – chirality. All the remarks of Sect. 3 also apply here. Note that only two special forms of chirality appear – misalignment over *r* at fixed *n*, and over *n* at fixed *r*. For theoretical reasons, the former was called absolute chirality and the latter relative chirality [3–5]. Chirality is the addition of absolute and relative chirality just as a vector is the addition of its projections on a basis. A major reward of this approach is that radial loops provide a graphical representation of chirality, simply because the "spreading out" of radial loops provides a faithful picture of the amount and the distribution ("how" and "where") of *n*-stars misalignment (Sect. 6). Absolute chirality is read off ARLs whilst relative chirality is read off RRLs. The more spread the *n*th order ARL is in the plane, the more absolutely chiral is the field at order *n*. The more distant from the real axis is the RRL, the more relatively chiral is the field. Radial loops show us "how" and "where" molecules are chiral. This description can be applied to the evolution of chirality during chemical reactions (Fig. 4). In the gauge framework, the solution of this century-old concern of chemists – how to describe molecular chirality – appeared quite straightforwardly.

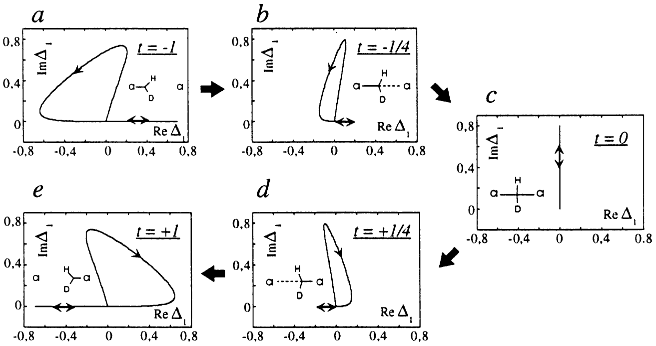

Fig. 4a–e. In the gauge framework, chirality is a continuous time-dependent phenomenon during chemical reactions. This is illustrated by a 2D model of the S_N2 nucleophilic substitution [3]. A nucleophile "*Cl*" impinges on a 2D chiral trivalent centre (**a**, **b**), induces Walden inversion (**c**) then symmetrically expels the opposite "*Cl*" (**d**, **e**). This figure shows the $n = 1$ order ARLs of the total system electron density at various times *t*. Enantiomers have symmetrical ARLs run in opposite directions (**a**, **e** or **b**, **d**). Diastereomers have ARLs of different shapes (**a**, **b**). In the course of this model mechanism, the electron density absolute chirality decreases steadily down to null (**c**), then increases symmetrically. Unit: Å^{-2}

8 Second application: towards a theory of molecular recognition (MR)

Broadly speaking, the matching of molecular shapes like those of puzzle pieces as a condition for the formation of protein/ligand, protein/protein or protein/DNA complexes, for example, is the core of MR, and the role of this geometrical condition is emphasized in biology because interactions are weak and delocalized over molecular surfaces. How could our understanding of MR benefit from the introduction of gauge geometries? This section is devoted to a preliminary answer to this question. For the sake of clarity, the nature of the understanding to be expected will be illustrated by the analysis of a simplified example problem rather than presented formally. The problem considered is that of the complex formation between a protein *P* and a ligand *S*. A 2D rigid model of the protein active site will be given, and two potential ligands will be compared. The active site will be assumed to feature a rotational C_6 symmetry at the centre *O*, to be henceforth selected as the origin. The chosen ligands are two enantiomers *L* and L^* – this condition is by no means imposed – and feature C_3 rotational symmetry at the centre O'[4]. The degrees of freedom of the rigid ligands are their orientation and the position of O'. For the sake of simplicity, the latter degrees of freedom will not be dealt with, and O' will be assumed to be equal to *O*. The only degree of freedom considered is the orientation α of the ligand in the active site cavity (Fig. 5). We shall now focus on the thermodynamic aspect of MR and, as regards this aspect, our viewpoint will be that MR between *P* and a ligand *S* is measured by the Gibbs energy ΔG of the complex formation reaction $P + S \leftrightarrows PS$, on which the equilibrium constant $K = [PS]/[P][S]$ depends. Furthermore, entropy effects will be dropped and our interest will be focused on the electrostatic energy contribution ΔE to ΔG:

$$\Delta E = \int \rho_1(\vec{r})\, V_2(\vec{r})\, \mathrm{d}x\, \mathrm{d}y \ , \tag{6}$$

where $\rho_1(\vec{r})$ is the ligand charge density and $V_2(\vec{r})$ the host potential. In this framework, the more negative ΔE, the stronger the association and the better the recognition between *P* and *S*. All these simplications can be dropped but the general theory is beyond the scope of this paper. Let us only note that the need for a natural origin like *O* disappears when the problem is studied in

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[4] α-Cyclodextrin, because of its planar ring-like structure, inspired the construction of this 2D active site model cavity.

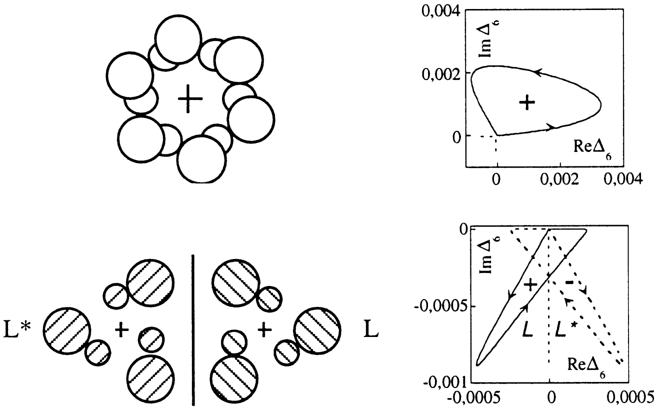

Fig. 5. *Top row*: 2D model of the protein active site potential $V_2(\vec{r})$. $V_2(\vec{r})$ is the sum of *s*-type Gaussians lying at the vertices of two hexagons. This is only a matter of convenience, ARFs being known analytically in the Gaussian case. First (second) hexagon vertices are distant by 1.54 Å (2 Å) from *O*. The Gaussian width σ is 1 Å (1.5 Å). The second hexagon is tilted by −20°. Gaussians are pictured by *circles* of radius $\sigma/2$. For C_6 symmetry, only $\Delta_0, \Delta_{\pm 6}, \Delta_{\pm 12} \ldots$ are non-zero. The sixth-order ARL is represented on the *right*. *Bottom row*: charge densities $\rho_1(\vec{r})$ of the two ligands L, L^*. L is the superposition of *s*-type gaussians lying at the vertices of two equilateral triangles. The first (second) triangle vertices are distant by 1.8 Å (1 Å) from O'. Gaussian widths are 1.5 Å (0.8 Å). The second triangle is tilted by −40°. L^* is the enantiomer of L. *Right*: sixth-order ARLs of L, L^*. Whilst third-order ARFs of L, L^* are non-zero, the sixth-order is the first order relevant to molecular recognition with P (Eq. 7). *Crosses* denote O, O'

Fourier space. The simplest way to investigate the understanding brought by gauge geometries in this typical problem in biochemistry is to introduce the geometrical description of the fields ρ_1 and V_2 in the expression of ΔE. Denoting $\Delta^1_n(r)$ $[\Delta^2_n(r)]$ the ARFs of $\rho_1(V_2)$, it is readily shown that ΔE can be developed as $\Delta E = \Delta E_0 + \Delta E_1 + \cdots$ where ΔE_n is given by Eq. (7) for $n \geq 1$, Re denoting a real part. ΔE_0 has no influence on α, so will not be discussed.

$$\begin{cases} \Delta E_n = \int_0^{+\infty} r\,\mathrm{d}r \{ \int_0^{2\pi} \rho^{(r)}_{1n}(\theta - \alpha) V^{(r)}_{2n}(\theta)\,\mathrm{d}\theta \} = 2\mathrm{Re}\left[I_n \mathrm{e}^{-\mathrm{i}n\alpha} \right] \\ I_n = \int_0^{+\infty} \Delta^{1,2}_{n,n}(r) r\,\mathrm{d}r \end{cases} \tag{7}$$

The complex number I_n is the integral of the radial function $\Delta^{1,2}_{n,n}(r) = \bar{\Delta}^1_n(r)\,\Delta^2_n(r)$ over the associated radial loop, to be called the mutual recognition loop (MRL). Analysis will now be focused on a single order $n \geq 1$. The first result is that the minimum of ΔE_n is Eq. (8). This minimum is attained when α takes a value – defined up to $2\pi/n$ – determined by the phase of I_n. In our framework, this minimum defines the ligand equilibrium orientation as far as the *n*th order is concerned. Hence, as far as the *n*th order is concerned, the phase of I_n determines the ligand equilibrium orientation. On the other hand, the modulus of I_n determines the minimum of ΔE_n. As far as the *n*th order is concerned, the larger $|I_n|$, the better MR. Therefore, a single complex number, I_n, concentrates all the information relevant to MR at every given order.

$$(\Delta E_n)_{\mathrm{minimum}} = -2\,|I_n| \tag{8}$$

Now, knowing that I_n is the key quantity as regards MR at the *n*th order, what factors control its value? I_n depends on the radial function $\Delta^{1,2}_{n,n}$, and the answer lies in the interpretation of this relation. Let us first discuss the structure of $\Delta^{1,2}_{n,n}$. Since the geometrical matching of the two fields ρ_1, V_2 is at stake, a posteriori it appears natural that one ARF from each field contributes to $\Delta^{1,2}_{n,n}$. Besides, $\Delta^{1,2}_{n,n}$ clearly has the structure of a RRF of order $n = m$, since $p = n$ and $N = M = 1$ in this case (Sect. 6). This is also quite intuitive: in the gauge framework, fields are pictured as gatherings of elementary "clovers" and Eq. (7) shows that ΔE_n results from a comparison between the clovers $\rho^{(r)}_{1n}$ and $V^{(r)}_{2n}$, materialized by the integration over θ. The θ integral is zero by symmetry when the numbers of "leaves" are different, so only clovers with the same number of leaves $(n = m)$ need to be compared. Besides, apart from amplitude factors, $\rho^{(r)}_{1n}$ and $V^{(r)}_{2n}$ are completely determined by the orientation of their RCGs so, given the interaction isotropy, this comparison cannot but depend only on the relative misalignment of RCGs. Accordingly, each elementary contribution depends only on the RRF that measures this misalignment $(\Delta^{1,2}_{n,n})$ and I_n results from gathering these RCG misalignment contributions radially. Each interval $]\,r, r + \Delta r\,[$ contributes the complex number $\Delta^{1,2}_{n,n}(r) r \Delta r$. Now the sum of two complex numbers has the largest modulus when they point in the same direction, and the smallest modulus when they point in opposite directions. They "interfere" constructively in the former case and destructively in the latter one, just as optical vibrations in Young's fringes experiment. Hence $|I_n|$ attains its maximum Eq. (9) when all elementary contributions are aligned along the same direction, i.e. when the MRL is contained in a half line starting from the origin. All other shapes contain destructive inter-

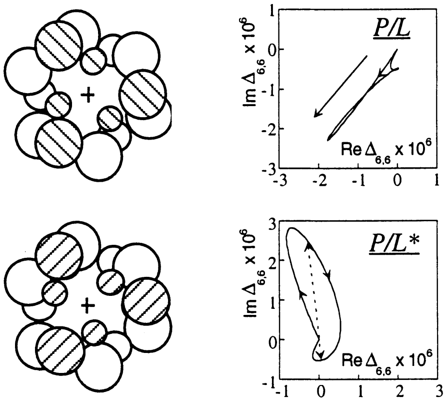

Fig. 6. Mutual recognition loops of the couples P/L (*top row*) and P/L^* (*bottom row*). In the first case, the MRL is close to a half-line segment apart from a small radial region near $z = 0$. Therefore radial interferences are constructive almost everywhere (just as bright fringes in Young's experiment) and $|I_6|$, hence the minimum association energy contribution ΔE_6, is graphically predicted to be much larger than in the P/L^* case (*bottom row*), where parts of the complex interfere destructively at short and long distances from *O*, as exemplified by *dotted arrows*. MRLs are oriented in the direction of increasing *r*

ferences, that is, some parts of the loop tend to cancel each other, thereby decreasing $|I_n|$ (Fig. 6).

$$0 \leq |I_n| \leq \int_0^{+\infty} |\Delta_{n,n}^{1,2}(r)| r \, \mathrm{d}r \qquad (9)$$

In the gauge framework MR thus appears as a phenomenon of *radial interference* of RCG misalignment contributions. Just as light interferences, this phenomenon features both amplitude and phase aspects. MRLs provide a graphical representation of MR because MRLs display the radial distribution of the interfering contributions. The more spread an MRL, the more destructive the interferences between various parts of the complex PS, the worse the MR. Thus examination of MRLs can show which of several ligands is best recognized by a given host at every order. For example, the MRLs in Fig. 6 show that L features a better electrostatic matching with P than L^* at the leading order, MR being almost perfect in the former case. In this framework, MR at the nth order is naturally measured by the dimensionless parameter κ_n Eq. (10).

$$0 \leq \kappa_n = \left| \int_0^{+\infty} \Delta_{n,n}^{1,2}(r) \, r \, \mathrm{d}r \right| \Big/ \int_0^{+\infty} \left| \Delta_{n,n}^{1,2}(r) \right| r \, \mathrm{d}r \leq 1 \qquad (10)$$

9 Conclusion

This paper was first devoted to a non-technical presentation of a recently introduced class of geometries called gauge geometries. The understanding brought by 2D gauge geometries was then briefly investigated, first in the case of chirality, then in that of molecular recognition, because of the importance of these questions in biology and chemistry. In both cases, an original description was found, featuring a graphical representation through specific tools of gauge geometries called radial loops. Molecular recognition was studied in a simplified 2D context in the hope of clarifying the ideas underlying this apparently unprecedented approach. Results nevertheless suggest promising prospects for the 3D theory. This approach indeed features graphic comparisons between ligands that may be applied to structure-based drug design. Protein/protein and protein/nucleic acid docking are also within the scope of this description.

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