Recovering a simple pedagogical tool to determine the chirality of tetrahedral atoms: The bases and notation of an even number of exchanges

Aarón Pérez-Benítez* and Leopoldo Castro-Caballero

Facultad de Ciencias Químicas de la Benemérita Universidad Autónoma de Puebla.

14 Sur y avenida San Claudio. Col. San Manuel. C. P. 72570. Puebla, Pue. México.

E-mail: <aronper@siu.buap.mx>

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Abstract

To determine the chirality sense in tetrahedral atoms is necessary to put the minor priority substituent far from the viewer, but sometimes two-dimensional projections of stereogenic centers do not accomplish this requirement, being necessary to rotate mentally the molecule up to obtain the correct perspective. Instead of that mental procedure (that is quite difficult for many students) an even number of exchanges can be easily done. Bases and notation for this method are provided.

Introduction

The *chirality*, from the Greek word *chair* meaning *hand*, is the property of an object to be nonsuperimposable with its mirror image. In organic molecules, this property is sometimes due to the presence of a chiral carbon (also named as chiral or stereogenic center), a tetrahedral carbon atom that supports four different substituents (Wade, 2003).

The substituents linked to this atom can only be arranged in the space in two different ways (figure 1). In order to distinguish them, in 1956, Cahn, Ingold and Prelog proposed a system of nomenclature (named "absolute nomenclature"), in which the substituents are classified by priority order: *1>2>3>4* (or *a, b, c* and *d,* respectively) (Cahn, 1956), in such way that since a point of view opposed to the substituent of the minor priority (*4*), the orientation of *1-2-3* occurs in the clockwise or counter-clockwise sense. In the first case the *R* chiral descriptor is assigned and *S* in the second one (figure 1). These two letters comes from Latin words *rectus* and *sinester*, meaning *right* and *left*, respectively.
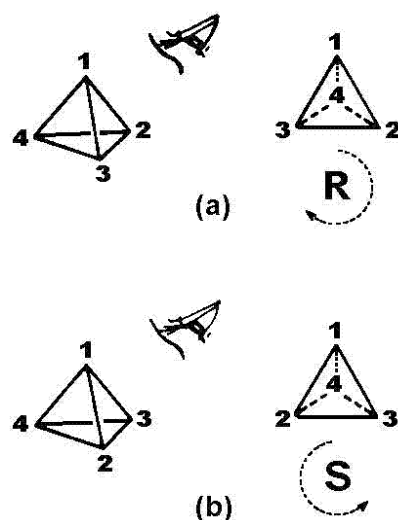
Figure 1. *R* and *S* chiral descriptors for a stereogenic tetrahedral center depending on the clockwise or counterclockwise rearrangement of *1-2-3* carbon's substituents (where the priority order is *1>2>3>4* and *4* is located far from the viewer).

However, it is very well known that many students experience difficulties in determining the chirality when the minor priority substituent is not projected far from the viewer. A proof of this fact is the different 2D and 3D attempts aimed to overcome this difficulty (Aalund, 1986; Ayorinde, 1983; Beauchamp, 1984; Bhushan, 1983; Brun, 1983; Bunting, 1987; Cahn, 1956; Dietzel, 1979; Epling, 1982; Garret, 1978; Idoux, 1982; Mattern, 1985; Reddy, 1989; Siloac, 1999; Thoman, 1976; Wang, 1992; Yongsheng, 1992).

Surprisingly, the same authors (C-I-P) discovered that an *Even Number of Exchanges*, *ENE*, between any pair of substituents of a chiral carbon drawn in Fischer's projection do not alter its absolute configuration and they published this fact in the same article (Cahn, 1956), but they did not give any theoretical nor factual support. That is probably the reason because the *ENE* method, which is

applicable whatever be the chiral carbon's projection, is not mentioned in the majority of the organic chemistry text books and in consequence many teachers do not know nor use it. So, the bases of the *ENE* method and three choices to indicate it are presented in this paper.

ENE method: bases and notation

When a chiral center (figure 2a) is reflected on a mirror, σ_1, the arrangement of its substituents is transposed (figure 2b) and it is not superimposable with the original. The initial molecule and the reflected one are named as *enantiomers*. Note that a new reflection on a σ_2 parallel to σ_1 does the substituents come back to the initial position (figure 2c), meaning that the original enantiomer is obtained.
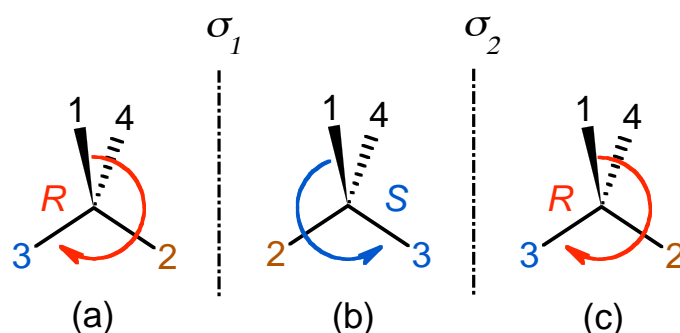

Figure 2. Reflecting a chiral tetrahedral center (a): The first reflection, σ_1, inverts its configuration in (b), while the second one, σ_2, restores it (c ≡ a).

By the other hand, the original configuration is also obtained if the second reflection is not applied in the same orientation that the first one, but in the mirror σ_3 or σ_4 perpendicular to σ_1 (figure 3b-c and 3b-d, respectively).
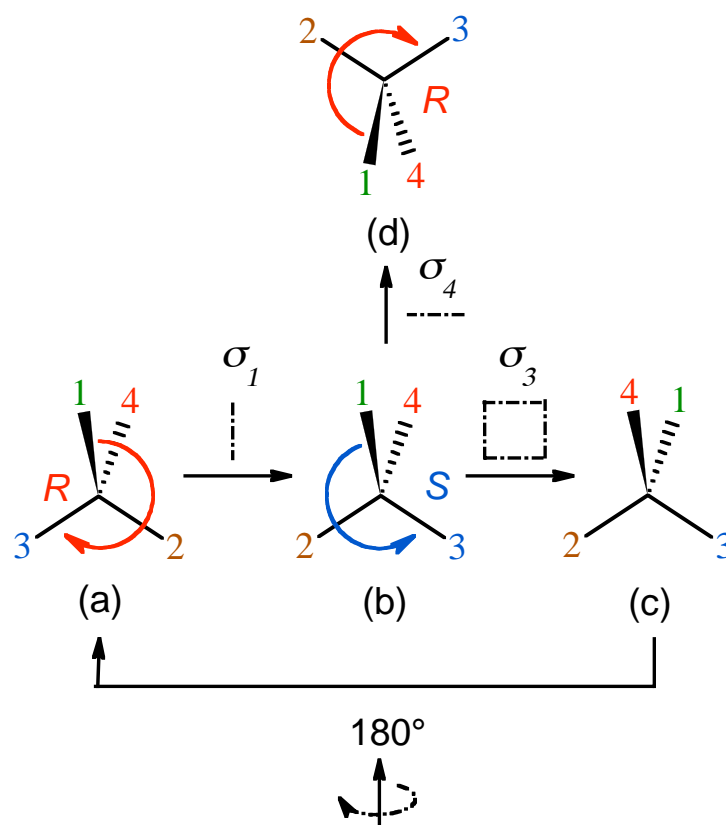
Figure 3. The application of a second reflection restores the original configuration of

the chiral carbon even if it is not done on a parallel mirror to the first one.

In this case the result of σ_1 followed by σ_4 can be seen directly (d ≡ a),

but to check the result of σ_1 followed by σ_3 is necessary to rotate by 180°

the molecule c (c = a).

Observe in figure 4 that the translation and application of σ_1 and σ_3 since the inner

of the molecule give the same result that their application since the outer. Moreover,

the order of the reflections was exchanged to illustrate that the process is

commutative ($\sigma_1 + \sigma_3 = \sigma_3 + \sigma_1$).

At this point is necessary to introduce a little change in the notation of σ_1, σ_2 and σ_3 because they are not symmetry but chirality planes. They are labeled in the following as $\sigma_n{}^*$.
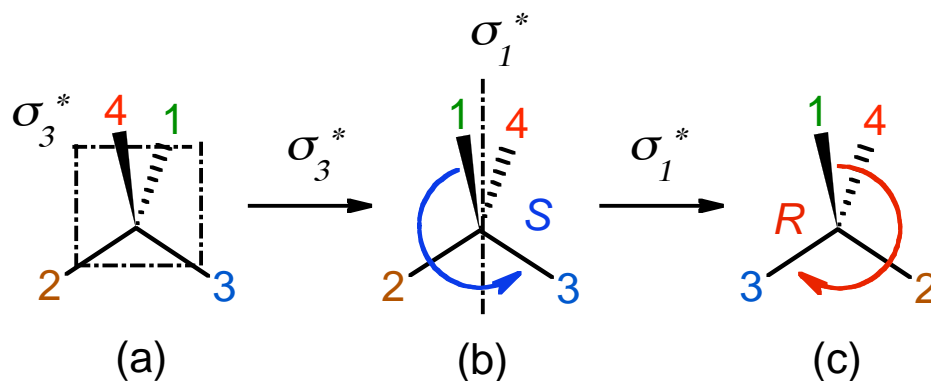
Figure 4. Reflecting a chiral center on the mirrors $\sigma_3{}^*$ and $\sigma_1{}^*$ translated to the inner of the molecule. The labels $\sigma_n{}^*$ are used to distinguish these chirality planes from symmetry planes. Contrast with figure 3a-b-c to check out the commutability of the process.

In accordance with figures 2-4 is possible to postulate:

> *"An even number of reflections carried out onto a chiral molecule*
>
> *does not alter its initial configuration independently of the position*
>
> *and the order of application of the mirrors".*

A simple demonstration of this fact can be performed reflecting a chiral object onto an arrangement of two mirrors having a common line. At a 0<α<90° angle is possible to appreciate at least one image identical to the real object (figure 5).
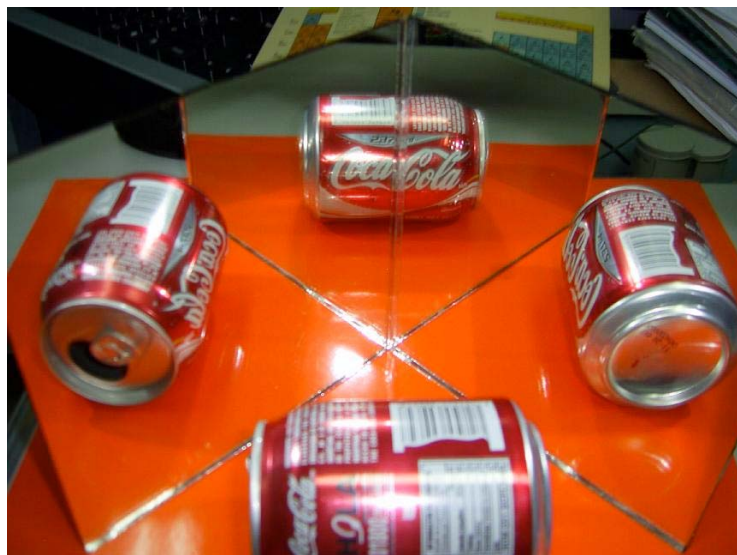
Figure 5. The reflection of a can onto two mirrors disposed at a 90° angle affords two enantiomorphic images (left and right) and one image identical (top) to the original object (down).

By the other hand, the application of $\sigma_n{}^*$ can be seen as a *permutation* that merely exchanges ("the place of") two substituents. In the figure 4 for example, the application of $\sigma_3{}^*$ moves substituent *4* to the position that substituent *1* was in and vice versa. These permutations (also called *transpositions*) are cycles of length two (two-element swaps) and they are written as a matrix of 2 x *n* elements, in which 2 is the number of rows and *n* is the number of columns (meaning the number of two-elements swaps). In this manner the application of $\sigma_3{}^*$ and $\sigma_1{}^*$ are equivalent to the permutation of substituents *4-1* and *2-3* and they are schematized in figures 6a-b and 6b-c as a 2 x *1* matrices; and $\sigma_3{}^* + \sigma_1{}^*$ as a 2 x *2* matrix in figure 6a-c. So, there is an analogy between both types of operations: *The application of an even number of them does not alter the initial configuration of a chiral carbon.*
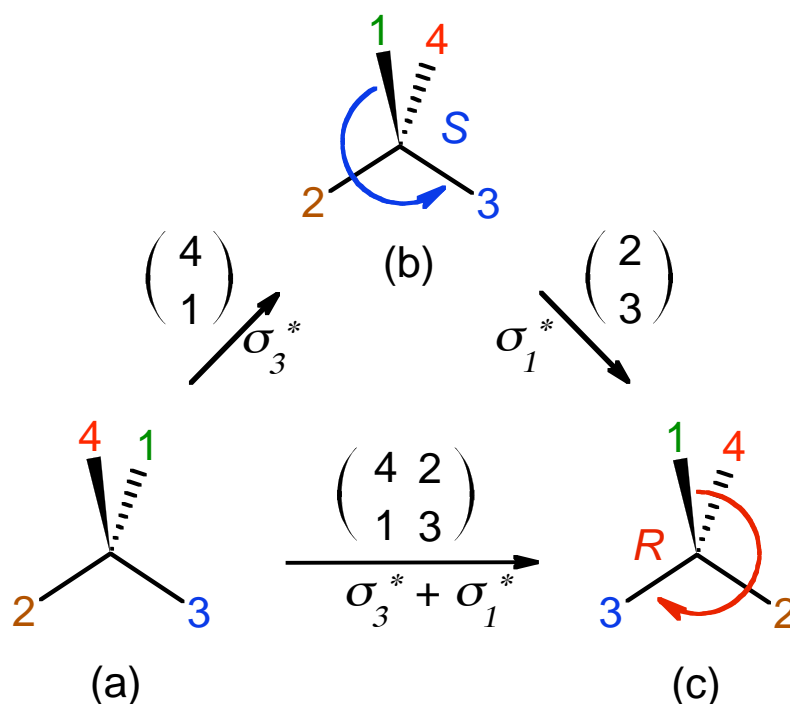
Figure 6. Viewing reflections as permutations whose 2 x *1* and 2 x *2* matrix notation are equivalent to the application of σ_n and $\sigma_n + \sigma_m$, respectively.

A second notation to describe a permutation is a two-line representation (figure 7c and 7d), in which the initial position of the substituents is in the first line (S_0) and the final position is in the second line (S_1), in such away that the swaps are symbolized by means of lines or arrows between them (Tumarello, 2006). Bearing in mind the objective of the *ENE* method (to translate the minor priority substituent to the back side), a little modification was introduced in the initial state with respect to that normally used in permutation theory: the numbers are written in reverse sense, it means, in the order 4, 3, 2, 1; in this manner the first swap will always include the minor priority substituent (*e.g. 4 - 1*).

With respect to the final state, one of two choices can be followed:

1). The new position of the substituents is written just below the old position independently of the order of the numbers (figure 7c);

2). The order of the numbers is retained (figure 7d).

Although the choice 1 is more direct than 2, probably this one is more appropriate for our objective because the number of intersections of the arrows indicates the parity order of the swaps.
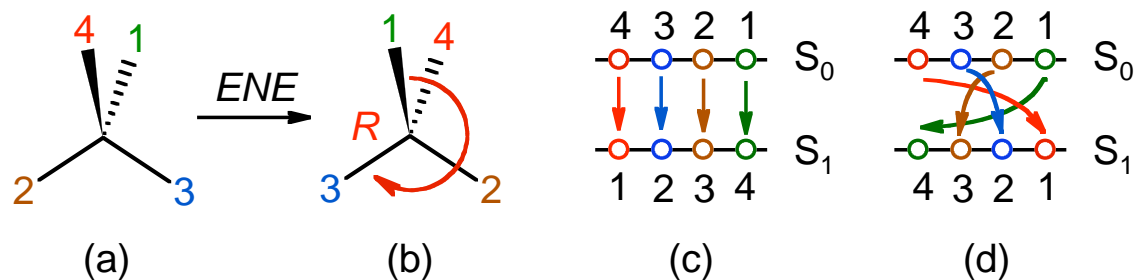

(a)　　　　　(b)　　　　　(c)　　　　　(d)

Figure 7. Representing the even number of exchanges as a two-line diagram, in which S_0 and S_1 are the initial and final positions of the substituents. In choice (c) the new substituent's position is just below the old one, while in (d) the order of the numbers is maintained and the parity order of the swaps is indicated by the number of intersections of the arrows.

May be the two-line representation is more simple than the matrix notation when one of the substituents remains unchanged because in this case is necessary to include a 3-cycle and 1-cycle matrices (figure 8). For example, if the substituent *2* is not moved in our model problem, the two notations will be as follows:
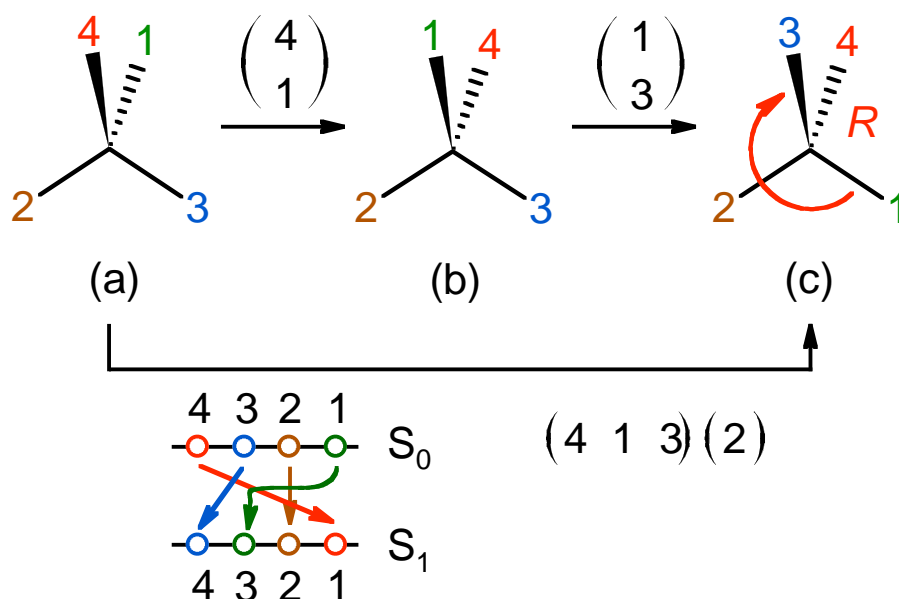
Figure 8. The application of an *ENE* that excludes the substituent of priority order *2*. The whole process of permutations is indicated at the bottom in the two-line diagram and as a combination of 1-cycle and 3-cycle matrices. 3-cycle matrix means the translation of 4 to 1, 1 to 3 and 3 to 4, and the even parity is got with the swap of 2 with itself.[1]

In a practical sense, a third more pictorial and simple notation can be introduced: Just indicate the transpositions by means of curved arrows (figure 9a).
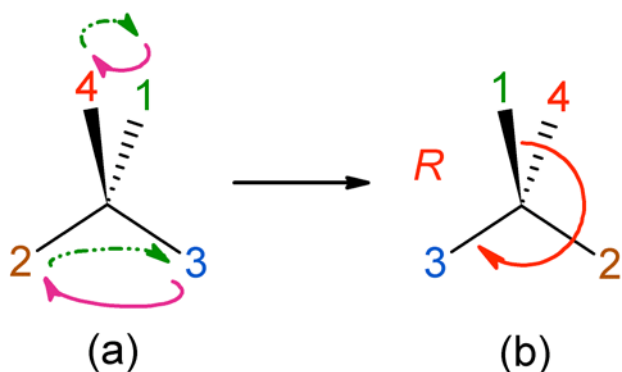

Figure 9. Indicating an even number of transpositions simply with curved arrows.

Procedure to determine in 2D, the chirality in a given tetrahedral stereogenic center by the *ENE* method.

Because the *ENE* method works in any projection in which the chiral center is given, the procedure is illustrated this time for an enantiomer of 2-hydroxipropanoic acid drawn in Fisher's projection as follows:

1. Interpret the projection in which the chiral center is given (figure 10a-b).[2]

2. Change chemical symbols by priority numbers and localize the minor priority substituent (figure 10b-c).[3]

3. Swap the minor priority substituent with any other localized at the back side (In our example there are two choices: *4-3* and *4-2* transpositions).

4. Swap the other pair of substituents to restore the initial configuration (In the first choice *2-1* transposition is done and *3-1* in the second one (figure 10c-d and 10c-e, respectively)).[4]

5. Once the minor priority is at the back side and an even number of exchange is done, check out the orientation of *1-2-3* and assign the corresponding chiral descriptor (figure 10d and 10e).
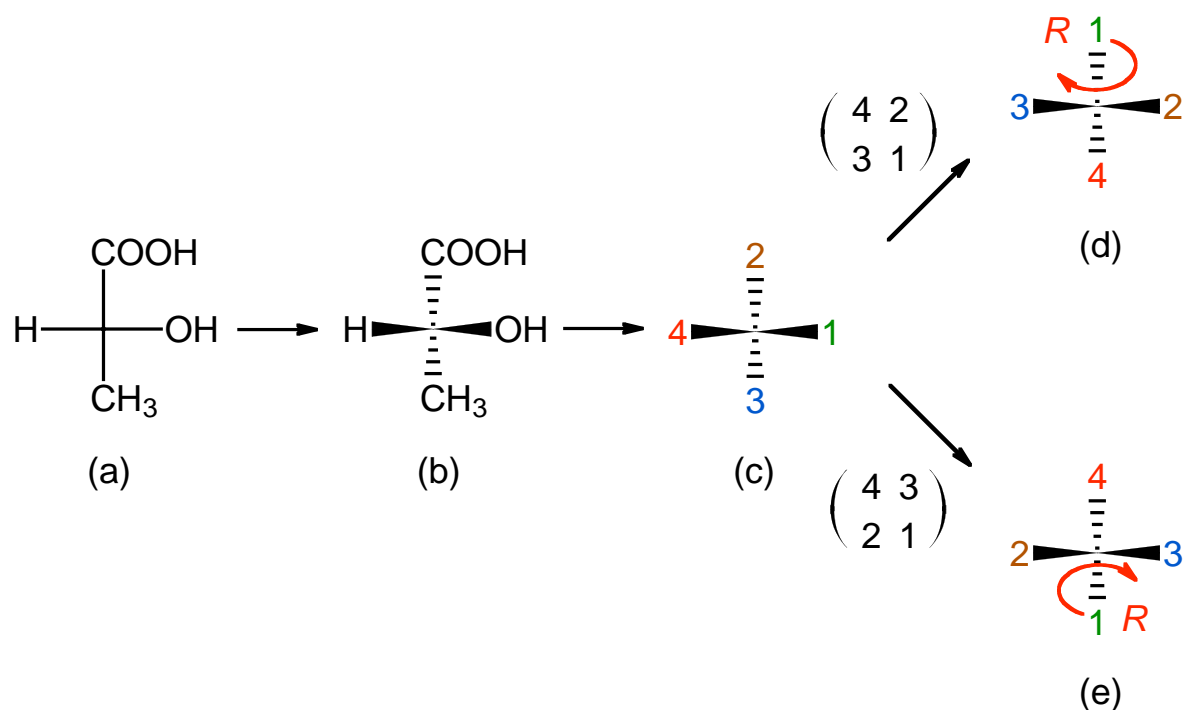
Figure 10. Illustrating the *ENE* method to determine the chirality of an enantiomer of 2-hydroxipropanoic acid, drawn in Fisher's projection: In (a-b) the projection is interpreted; in (c) the substituents are represented by their priority numbers; in (c-d) the *ENE* is done and in (d) the chiral descriptor is assigned. Observe that in (c-e) is followed another possibility to put the minor priority substituent at the back side.

It is necessary to mention that in a given projection is not always so easy to find and drawn the position of the mirrors that reproduce the exchanges. For example in the last problem the mirror that exchanges 4-3 contains to the substituents labeled 1 and 2 and bisects line 4-3, while the other mirror that exchanges 2-1 contains 3 and 4 and bisects line 1-3. It means that both mirrors are tilted with respect to the plane of the paper and are mutually orthogonal. Fortunately, the same method help us to put the chiral cabon's substituents in an adequate position to drawn those mirrors in an easily way (figure 11b)
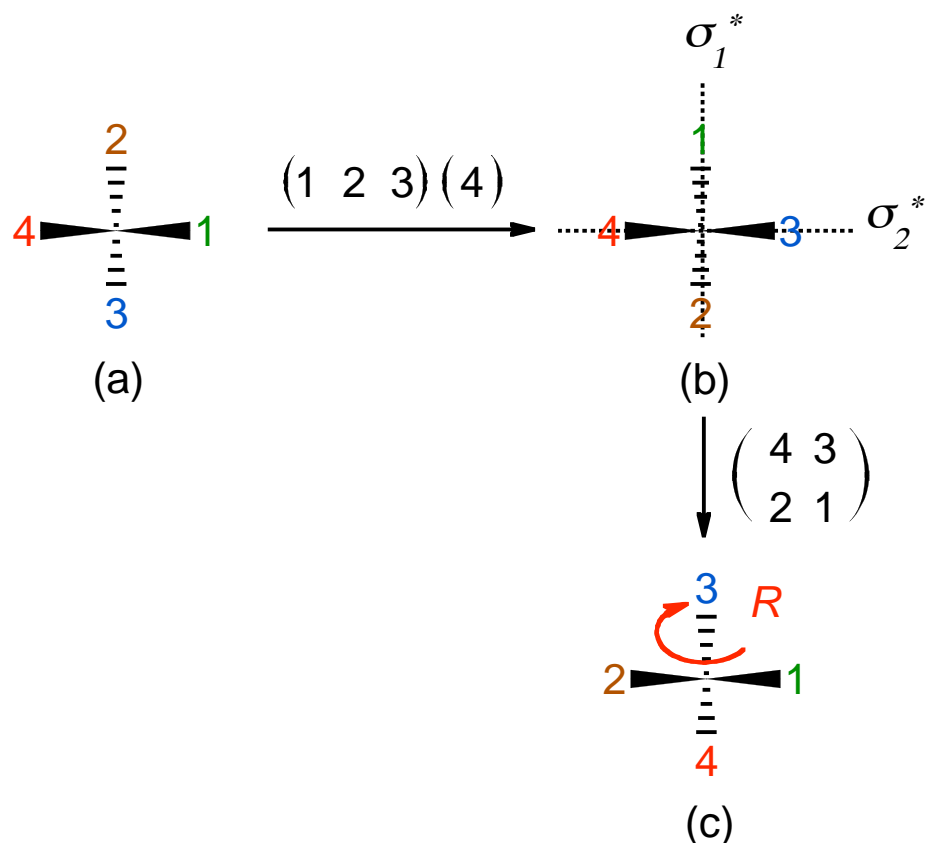
$$\sigma_1{}^*$$

(a)

$$(1\ 2\ 3)(4)$$

(b)

$$\sigma_2{}^*$$

$$\begin{pmatrix} 4 & 3 \\ 2 & 1 \end{pmatrix}$$

R

(c)

Figure 11. Using the *ENE* method to find the positions of the mirrors that exchange the substituents of the chiral carbon described in figure 10c-d. From this picture (b), the *ENE* method is applied to determine the chirality in (c).

Finally, in order to avoid misconceptions it is important to leave in clear that the exchanges between the chiral carbon's substituents is not a real process as it occurs in other atoms such as in some pentacoordinated phosphorous (Berry, 1960).

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Conclusion

The method of *Even Number of Exchanges* of chiral carbon's substituents is a very simple way for translating its minor priority substituent to the back side without a lost

of its original configuration. It works with any projection in which the tetrahedral stereogenic center was given and the method can be seen as the product of an even number of reflections, independently of the sequence and position of the mirrors.

Finally, the use of any of three notations (two of them coming from permutation theory) for representing the *ENE* were suggested.

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[1] Note in this case that the even number of two-element swaps is also equivalent to a 120° clockwise rotation around an axis parallel to the bond line *2*-C. This was treated by Eliel, for a chiral cabon drawn in Fischer's projection, as a single permutation of three-elements (Eliel, 1994, p. 61). Also in this case the parity is even:
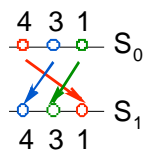
[2] In our experience, some errors in determining the chirality of a tetrahedral stereogenic center are due to an incorrect interpretation of the projections being the wedge projection the more understandable for our students.

[3] If the minor priority substituent is located far from the viewer determine directly the chiral descriptor as it is illustrated in figure 1.

[4] Although to restore the original configuration is valid to exchange any pair of substituents, the swap of the other pair is recommended for simplicity.