

Cahn-In Gold-Prelog R/S System Revisited: Simplifying Assignment of Configuration in Chiral Compounds

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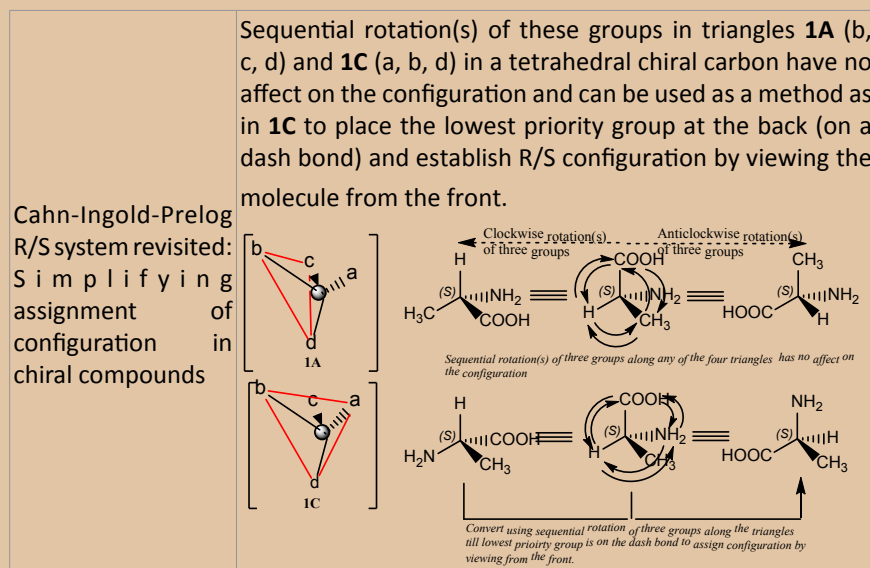
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Citation: Kundu B. Cahn-In Gold-Prelog R/S System Revisited: Simplifying Assignment of Configuration in Chiral Compounds. J Org Inorg Chem. 2016, 2:2.

Abstract

A practically useful method following Cahn-Ingold-Prelog R/S system is described for establishing R/S configuration in chiral compounds. The method is based on the fact that in a given tetrahedral chiral carbon sequential rotation of any three groups in any of the four triangular formats does not affect the configuration. This provides an opportunity to rotate the three groups particularly including the lowest priority group either in a clock- or anticlockwise manner till the lowest priority group is behind the plane of the paper and thus viewing the molecule from the front for establishing R/S configuration. The utility of the method has been demonstrated in chiral compounds involving both cyclic and acyclic structures bearing one/two carbon atom(s).



Keywords: Stereochemistry; R/S configuration; Chirality; Cahn-Ingold-Prelog R/S system

Received: July 26, 2016; **Accepted:** August 16, 2016; **Published:** August 25, 2016

Introduction

The unambiguous assignment of enantiomers of a chiral compound is generally carried out using Cahn-Ingold-Prelog R/S system. The method involves prioritization of substituents starting from highest atomic number to lowest followed by assignment of R and S configuration by placing the lowest priority substituents at the back [1]. There are two methods widely taught to graduate

students to assign R/S configurations: one that involves use of model kits and second that involves mental rotation of molecule. In both the cases entire molecule is rotated so that the lowest priority group is at the back and then remaining three groups in the order of priority is examined either in clock or anticlockwise directions. Yet another method that is also used and discussed in several text books involves mental viewing of the molecule from the reverse side of the lowest priority group (**Figure 1**). I

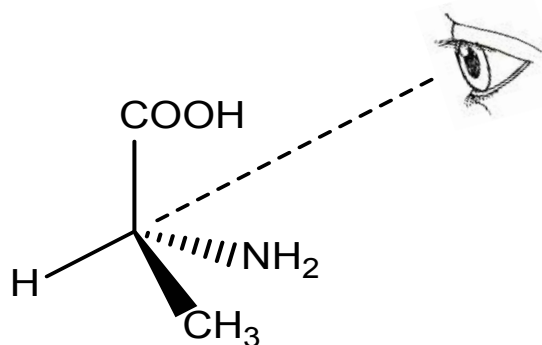


Figure 1 Conventionally used method to establish R/S configuration discussed in text books.

found that although all the three methods are taught to graduate students, a large percentage of students remain wary to these methods and often fail to either understand the basics or are unable to extrapolate the methodology to molecules with more than one chiral center. This can be mainly attributed to mental exercise involving visualization of chiral molecules to assign configuration. I opine that while introducing R/S configuration to graduate students, an alternative method of teaching by drawing structures instead mental visualization to address the issue of R/S assignment may be more beneficial.

In this communication I discuss a simple method that involves drawing of additional flying-wedge structures on a paper of the structure in question and then predict the R/S configuration without mental visualization. The idea stems from the presence of four set of triangles in any tetrahedral chiral carbon. The latter in the flying wedge projection comprises two bonds present on the plane of paper, one wedge bond above the paper and a dash bond going below the plane of the paper (**Figures 1 and 2**). A close examination of the tetrahedral structure **1** reveals that at any given time, four triangles can be formed by connecting the three groups attached to the chiral carbon (**Figure 2**). Out of the four triangles: **1A** comprises groups a, b, c; **1B** comprises groups a, c, d; **1C** comprises groups a, b, d and **1D** comprises groups a, c, d.

I argue that three substituents in the triangle **1B** with priority from $a \rightarrow c \rightarrow d$ (**Figures 2A and 3**) when placed in a circular format, can be sequentially rotated along the periphery either clockwise (**Figures 2B and 3**) or anticlockwise (**Figures 2C and 3**) without affecting its configuration. It is pertinent to mention that the presence of a single bond between the chiral carbon and the substituent b (**Figures 2A and 3**) allows one to rotate this bond. Indeed, the depiction of tetrahedral carbon **2A** with triangle **1B** also provides a bottom view of the compound which in turn will provide graduate students with a better understanding with regard to the orientation of four bonds in any tetrahedral carbon in 3D space.

We then examined the configuration in **2A/2B/2C** and as expected, the direction of priority from $a \rightarrow c \rightarrow d$ remained clockwise in all the three situations leading to the assignment of R configuration (**Figure 3**). In other words assignment of R or S

configuration with sequential rotation of substituents along the triangle is not affected. This also provides an option to assign configurations in **2B** and **2C** by simply transforming them to **2A** by sequential rotation of three groups along the triangle in either directions and then looking at the molecule from the front to examine the direction of priority from $a \rightarrow c \rightarrow d$.

The above alternative method for the assignment of configuration was demonstrated by using alanine as a model chiral compound by maintaining the direction of priority of functional groups $a(\text{NH}_2) \rightarrow c(\text{COOH}) \rightarrow d(\text{CH}_3)$ as in **2A** using triangular format **1B**. Accordingly, NH_2 functionality is placed on a, c is replaced with COOH and d is replaced with CH_3 . The resulting flying wedge structure **3A** (**Figure 4**) was examined using molecular model kit which exhibited R configuration. Now anticlockwise sequential rotation of the substituents NH_2 , COOH and CH_3 along the triangle **1B** by holding the H group will furnish flying wedge structure **3B** (**Figure 4**) whereas clockwise sequential rotation of NH_2 , COOH and CH_3 will furnish flying wedge structure **3C** (**Figure 4**). Gratifyingly, both **3B** and **3C** despite sequential rotations of functional groups in either direction along the triangle **1B** exhibited R configuration.

Next, the above alternative method for the assignment of configuration was further demonstrated by using (S)-alanine (**4A**)

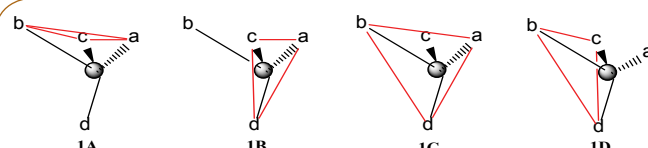


Figure 2 Four triangles **1A**, **1B**, **1C** and **1D** in a tetrahedral chiral carbon.

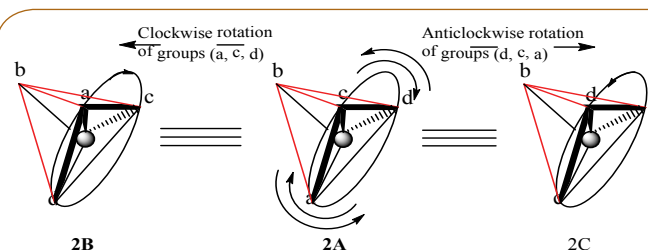


Figure 3 Sequential rotation of substituents $a \rightarrow c \rightarrow d$ along the triangle **1B** both in a clock and anticlockwise format in a tetrahedral carbon retained R-configuration.

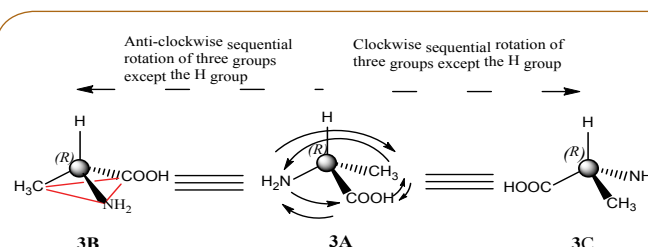


Figure 4 Sequential rotation of the three substituents NH_2 , CH_3 and H in Alanine (**3A**) along the triangle **1B** both in a clock and anticlockwise format retained the R-configuration.

as a model substrate. Using the flying wedge projection involving triangle **1B**, (*S*)-alanine **4A** was drawn by deliberately placing COOH functionality on b (alternatively one can replace b with H/CH₃/NH₂ to draw flying wedge projection of (*S*)-alanine (**Figure S1**), while c has been replaced with H, d has been replaced with CH₃ and a has been replaced with NH₂ functionality (**Figure 5**). Now anticlockwise sequential rotation of the substituents NH₂, H and CH₃ along the triangle **1B** by holding the COOH group will furnish flying wedge structure **4B** whereas clockwise sequential rotation of NH₂, H and CH₃ will furnish flying wedge structure **4C**.

We then examined the configuration of **4A**, **4B** and **4C** using molecular model kit and as expected gratifyingly all the three flying wedge structures despite sequential rotation of three substituents exhibited *S*-configuration. This implies that if one has to assign *R/S* configuration in a given flying wedge structure, the three groups can be sequentially rotated in a triangular format in either directions till the lowest priority group is on the dash bond. This then provides option to the viewer to examine the configuration as in **4C** by directly looking from the front without applying the conventionally used method of mental visualizations. Thus to establish configurations of **4A** and **4B**, one can transform them to **4C** by placing the lowest priority group hydrogen back and view the molecule from the front.

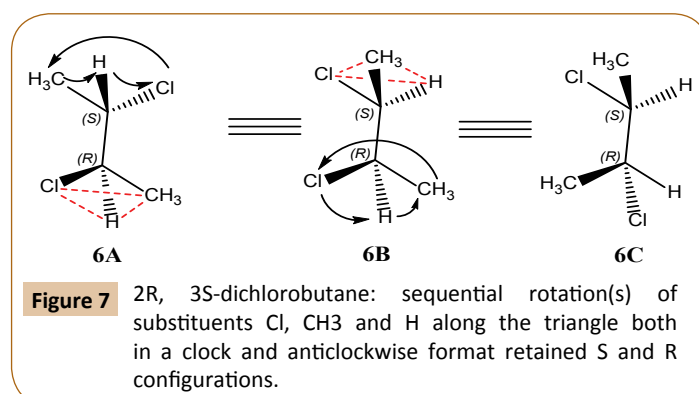
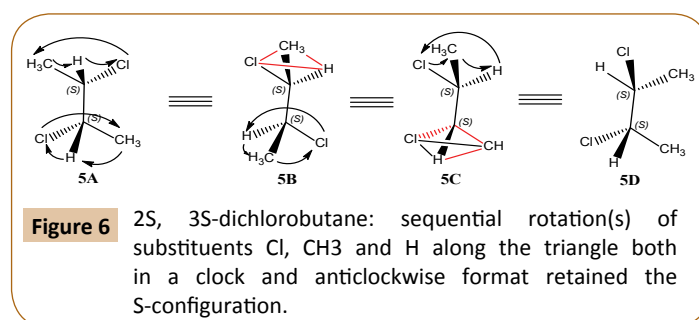
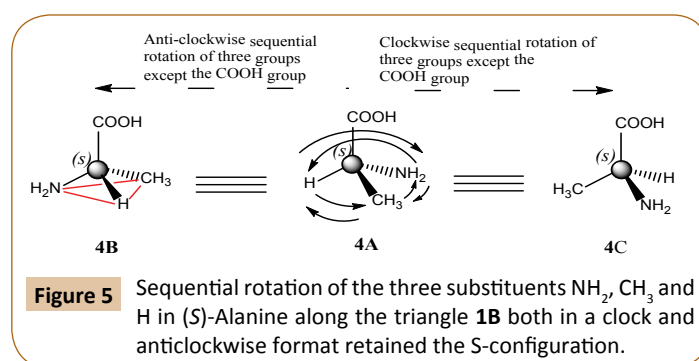
The exercise was then repeated one by one for the remaining three triangles **1A**, **1C** and **1D** (**Figure 2**) where one group was held stationary and remaining three substituents were rotated sequentially along respective triangles. (**Figure S2**) as envisaged no deviation was observed from *S*-configuration despite sequential rotation of substituents along the triangles. I further observed that even multiple sequential rotations of substituents along the triangles did not affect the configuration (**Figure S3**). It is noteworthy that for a given chiral tetrahedral carbon compound such as (*S*)-alanine, a maximum of 12 flying wedge structures based on triangles **1A**, **1B**, **1C** and **1D**. One can easily draw these flying wedge structures by sequential rotations of groups around the four triangles without bothering about checking the configurations (**Figures S4 and S5**). To the best of my knowledge, till date this information of drawing a maximum of 12 flying wedge structures with retention of configuration for a chiral compound with an asymmetric centre is not available in the literature. Out of 12 only 3 flying wedge structures have lowest priority group on the dash bond.

In order to further prove the general applicability of the method for establishing configuration, the method was extended to two carbon acyclic chiral compounds. For this 2*S*, 3*S*-dichlorobutane **5A** was initially selected as a model substrate (**Figure 6**). In the first instance, the three substituents were rotated sequentially on each of the chiral carbons till H on both the chiral carbons was on the dash line as in **5B**. The configuration of **5B** with lowest priority group on the dash bond for the both the carbons was then assigned by simply looking from the front which was also confirmed using molecular model kit and as expected **5B** to exhibited 2*S*, 3*S* configuration. I further sequentially rotated the three substituents on either of the chiral carbons both in clockwise and anticlockwise direction to generate structures

5C and **5D**. Molecular model kits for both **5C** and **5D** confirmed that sequential rotation of three substituents in a given flying wedge structure either in clockwise or anticlockwise directions did not had any bearing on its *R* or *S* configuration. Thus, in a given situation, *R/S* configuration in either of the three structures **5A/5C/5D** can be assigned by converting them to structure **5B** by sequential rotation of substituents along the triangle.

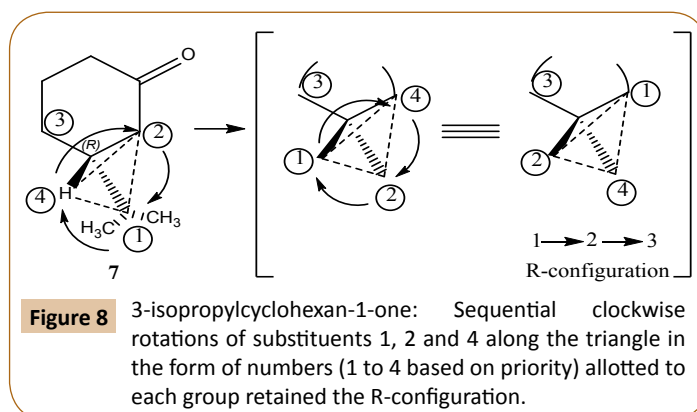
Similarly, the configuration of 2*R*, 3*S*-dichlorobutane in **6A** (**Figure 7**) was assigned following sequential rotation of substituents along the triangle for one of the carbons only till the H was placed on the dash bond as in **6B** (**Figure 7**). For the second carbon, the H was already placed on the dash bond. Next, looking at both the carbons in **6B** from front confirmed the presence of *R* and *S* configurations. In further studies the structure the substituents in the second carbon **6B** was sequentially rotated to study effect on configuration. The resulting structure **6C** (**Figure 7**) was examined using molecular model kit which confirmed the presence of *R* and *S* configurations.

Finally, the utility of the method demonstrated in a cyclic structure 3-isopropylcyclohexan-1-one **7** having a chiral carbon in a ring



(Figure 8). Since in the cyclic structure, the four substituents are placed in a manner that they cannot be moved in a triangle sequence as demonstrated above. In this situation, the four substituents can be numbered starting from number 1 for the highest priority group and number 4 to the lowest priority group. Next, instead substituents only the numbers can be rotated along the triangle in a sequential manner till the lowest number is on the dash line (Figure 8). Finally, one can view the molecule from the front and establish the R/S configuration by simply moving from priority number 1 to 3. Thus, using this method one can easily assign R configuration to the structure 7.

Indeed in some of the examples discussed above where the lowest priority group is on the wedge bond, one can assign R/S configuration by applying the conventional rule of reversing the observed direction of the priority based on atomic numbers. The method described here is more practical and remains applicable in all situations and involves sequential rotations of three groups along the triangle till the lowest priority group is on the dash bond (behind the plane of paper). The R/S configuration can then be assigned by looking at the resulting molecule from the front instead rotating the molecule mentally or using molecular model kits. The four triangles 1A, 1B, 1C and 1D on one hand can be used to demonstrate that sequential rotation of groups in the respective triangle have no affect on the configuration, on the other hand any one of the triangles 1A, 1B and 1C can be chosen to assign R/S configuration in a given chiral compound by pushing the lowest priority group on the dash bond following sequential rotations (s). The R/S configuration can then be assigned by simply looking from the front of the molecule for the direction of priority from highest to lowest atomic numbers.



Conclusions

In summary, a practical method involving sequential rotation of any of the three out of four groups in any of the four triangular formats in a tetrahedral chiral compound can be applied for establishing R/S configurations. In other words in addition to conventionally used method based on mental exercise, an alternative method involving sequential rotations of any three groups in a triangular format will provide additional option for assignment of R/S configuration.

Acknowledgements

I am thankful to Sengupta SK, Head of the Department, Department of Chemistry, DDU University, Gorakhpur, Uttar Pradesh, India for inviting me as visiting fellow to teach R/S configuration to graduate students.

Reference

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