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Beginner Guide to Retrosynthesis Analysis

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Abstract

Retrosynthesis Analysis is an important technique in Organic Chemistry. There can be many ways a molecule can be form. It can be difficult for new organic student to construct an efficient pathway for a target molecule. In this work, four useful guiding principles were introduced and explained which can help student to determine crucial steps when deconstructing a target molecule. The general goal for these principles is to simplify the target structure as much as possible by using molecules shape and structure. The "common ion" approach is emphasized for its effectiveness, and accuracy. By breaking bonds between two common ions, the target molecule can be separated into two much simplified molecules. Other retrosynthesis principles focus on mainly using molecule's symmetry to simplify a target molecule.

Keywords

Retrosynthesis Analysis Beginner Guide; Common Ion Approach; Simplify Complexity.

1. Introduction

Retrosynthetic analysis is a chemistry technique that one thinks back forward instead of forward for chemical reactions. In nature, there are many complex molecules where we can extract from plants, and animals that are beneficial to humans. It is not enough for us to know its functions; it is also essential for us to know how we can synthesis these complex molecules in the most efficient and Green way possible. When picturing a chemical reaction, it is common to think forward: A+B = C. This method is fine when dealing with simple molecules, and it may involve many trials and errors. Retrosynthetic analysis reversed this method where we first have our Terminal Molecule C, and by certain pattern and law, finding the simpler precursors A and B. "The concept of retrosynthetic analysis was developed in the first half of the 20th century, but some of the most significant advances came in the 1960s when Elias J. Corey (b. 1928) of Harvard University applied it to construct complex synthesis schemes. This changed the face of organic synthesis and helped earn Professor Corey the 1990 Nobel Prize in Chemistry"[1]. For a complex Terminal Molecule C, it may require steps of deconstructing, which may lead to multiple synthesis routes. Chemists need to figure out which routes are most friendly and easiest to achieve. Hence, I present a guide to Retrosynthetic analysis that can greatly increase the efficiency to figure out curial steps of deconstructing a Target molecule.

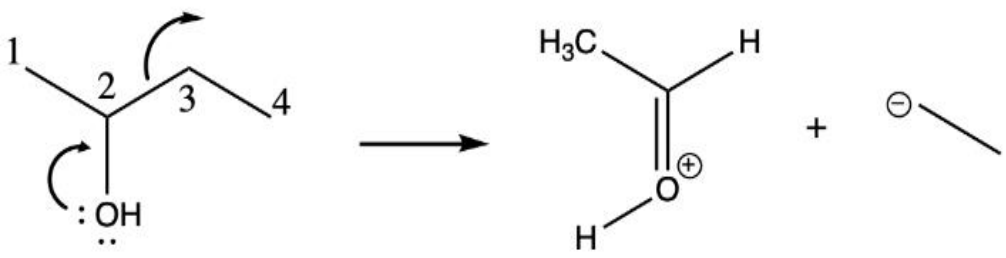

Figure 1. Example for one group disconnection

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2. Different Types of Disconnections

Before learning about retrosynthesis analysis, knowing some basic types of Disconnections is curial. First is One group Disconnection, where one functional group plays a central role. A simple example is shown in figure 1.

In this molecule, there is only an alcohol functional group. In this disconnection, one pair of electrons formed a double bond with the second Carbon atom. As a result, an existing bond of that Carbon needs to break, in this case, the bond between atom 2 and 3.

Second is a two-group disconnection. Like one group Disconnection, two group disconnection involves two functional groups. One example is the disconnection of a 1,3-*dioxygention* as shown in Figure 2.

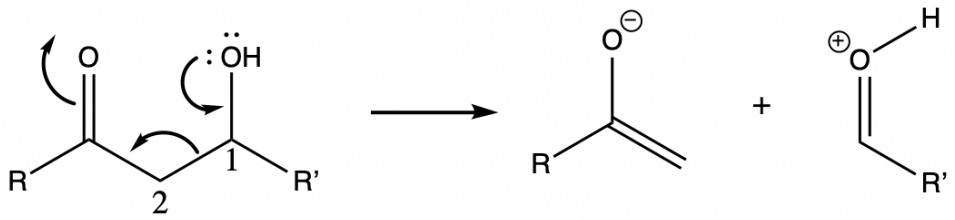

Figure 2. Example for two group disconnection

In this disconnection, one pair of electrons from the oxygen in the OH group would form a double bond with the first carbon atom. Now one existing bond of the first carbon needs to break, and since this molecule has two functional groups, the bond between the two functional groups, the bond between carbon 1 and 2, would break. Then after the 1-2 carbon bond break, the electron density moves with the red arrow to the other oxygen retro synthetically.

The third type is called an Electrocyclic Disconnection. One example is shown below in figure 3.

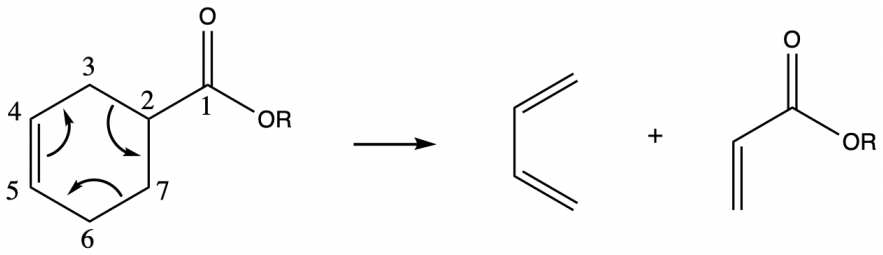

Figure 3. Example for Electrocyclic Disconnection

A compound like this can be retrosynthesis by pushing elections around in a ring. We break the bond between carbon 2 and 3, 7 and 6, and relocation the electron density follows the blue arrow.

The fourth type is called an Antithetical or Illogical Disconnection. One example is shown in Figure 4.

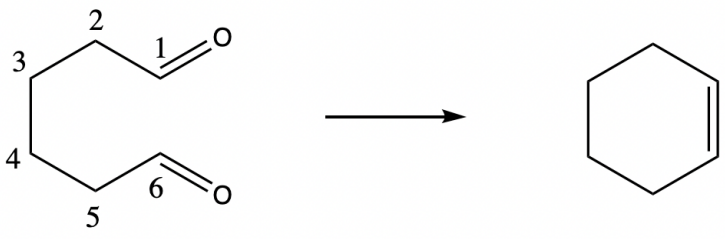

Figure 4. Example for Illogical Disconnection

ISSN: 2414-1895 DOI: 10.6919/ICJE.202107_7(7).0023

The retrosynthetic step for this molecule is to connect the first and sixth carbon atom in a double bond because the resulting molecule can be further broken down by Electrocyclic Disconnection.

Finally, there are three types of disconnection which can be combined. First is functional group addition, where a functional group is added to a molecule for strategic purposes and remove it later. Second is functional group removal, where a functional group is removed from the Target molecule for strategic purpose and add it back later. The third is functional group interconversion, where one functional group on the molecule is changed to another for an easier retrosynthesis process. "Manipulation of functional groups can lead to significant reductions in molecular complexity" [2]. The last third types are useful techniques when got stuck at a Target molecule. We must minimize the use of these techniques when another method is available.

3. Four Retrosynthesis guiding principles

The first retrosynthesis principle is to simplify the 3D- complexity of the Target molecule because the goal is to simplify the Target molecules with the greatest efficiency. The 3D complexity of molecules can be evaluated with the number of functional groups and the number of rings a molecule has. The less the molecule has, the simpler it becomes. One simple example is shown below in figure 5.

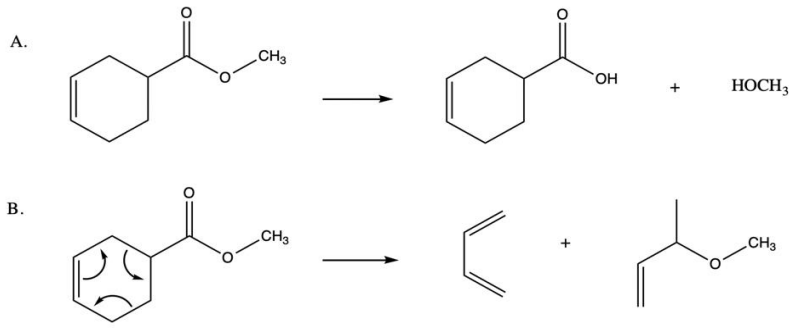

Figure 5. Example of two possible retrosynthesis routes for a target molecule

Route A and B are two retrosynthesis steps for the same target molecule. The target molecule has one ring and two functional groups. The precursors also have a ring and two functional groups. However, in route B, the ring has been broken down through an electrocyclic Disconnection, which is much smaller and simpler. So, in this case route B is the preferred retrosynthesis step.

There are many ways to determine which bond to disconnection to simplify the molecule structure. One technique is often used for Polycyclic compounds. Polycyclic compound is a specific kind of molecule which is made of two or more closed rings, usually carbon, joining together. One example of a Polycyclic compound is Longifolene. For this kind of Compound, one useful technique is called the "common ion" approach. We define common ion as atoms that are common in two or more rings. For example, the common ion in a naphthalene molecule is labeled 1,2 in the picture below in figure 6.

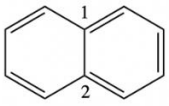

Figure 6. Naphthalene molecule

For compounds like the one above, the preferred retrosynthesis step is to break the bond between these common ions. By breaking the bond, we can greatly simplify the compound. More complex molecules, such as Longifolene can also simplify by this method. For molecule Longifolene, the common atom is labeled 3,4,11,10,9, in figure 7. These 5 atoms are the most strategically important

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atom. Breaking any bond between these atoms would greatly simplify the compound. Breaking two bonds is easier than three bonds, so our first retrosynthesis step can be breaking the bond between atom 9 and 3, 9, and 10, which give the compound in figure 8. Then the forward reaction becomes carbon 9 forming one bond to carbon 10 and carbon 3, which is a possible synthesis route.

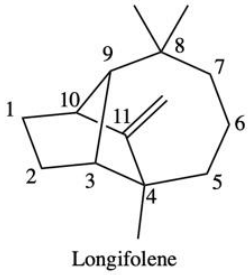

Figure 7. Longifolene before bond breaking

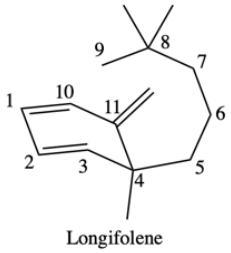

Figure 8. Longifolene after bond breaking

The purpose of this common atom approach is to decrease the 3-D complexity of the molecules. For the example above, after the first step of retrosynthesis, a complex 3d longifolene molecules became a ring and a chain. If we don't follow this common atom approach, by breaking the bond between atom 4 and 5, 5, and 6, the resulting molecules will still be quite complex, two rings and a chain.

The second guiding principle is to disconnection molecules into similar complexity pieces. What this means is that if there is a chain-like compound. It is preferred to disconnect it in the middle to give us two roughly equivalent compounds, and then disconnect these two again in the middle, and continue like this. This is called a convergence process. On the other hand, a linear process that disconnects one bond at a time from one end to another is not preferred. This is because each chemical step decreases the yield by a certain amount, and a convergence process undergoes less linear steps than a linear process, so the yield for a convergent synthesis is higher than a linear synthesis. One example is shown below in figure 9 [3].

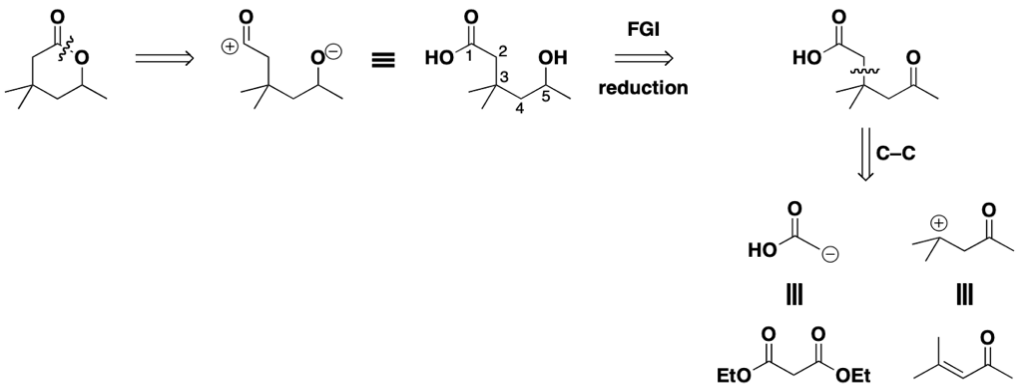

Figure 9. Example of retrosynthesis. Reproduced with permission. [3] Copyright, Gareth J. Rowlands.

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After the first disconnect of the C-O bond, the ring structure became a roughly symmetric carbon chain with oxygen on each side. The dicarbonyl are formed with a FGI (function group Interconversion). Then by following the second guiding principle, the reasonable disconnect is between carbon 2 and 3, which divides the compound into roughly equivalent prat.

The third guiding principle is multiple group Disconnection is better than one group disconnection. This is easy to understand. If there is a molecule fulfill the condition for a one group disconnection and also a two-group disconnection. Use two group disconnections because it will decrease the complexity of the molecule and it will likely be a convergence process. The Retrosynthesis step in figure 10. [4] is a great example of this principle.

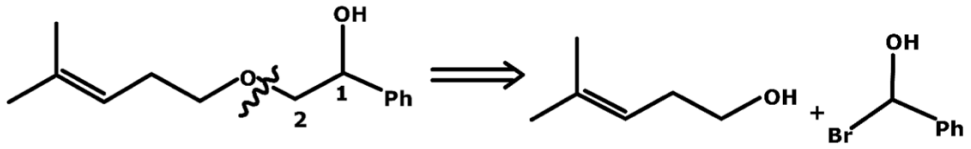

Figure 10. Hydroxylether retrosynthesis pathway. Reproduced with permission. [4] Copyright, University of Delhi

Instead of a one group disconnection at Carbon 1 and Ph group that still leaves the OH group and ether together, a 1,2 disconnection effectively separates the two functional groups.

The fourth guiding principle is to exploit symmetry if possible. Symmetry makes everything easier because multiple identical parts of the molecule can be disconnection together. One example is shown below in figure 11.

Figure 11. Example of disconnection using symmetry

Molecule in figure 11 has a nice symmetric structure. One retrosynthesis step is to break the two bonds in red in the same time. The disconnect of the two parts can be done in one step since they are identical. This property allows efficient retrosynthesis for symmetric molecules.

Figure 12. Example of disconnection using symmetry. Reproduced with permission.[5] Copyright, Oxford Univ. Press.

Figure 12. [5] above is another example of this principle. Disconnection are being made at both sides of the center carbon.

4. Conclusion

These four-guiding principles of retrosynthesis analysis give a general path for students to follow. When an obstacle has been encountered, student can look for the common ions and try to disconnect bonds between them. And in any time, use convergent synthesis, instead of linear synthesis since it can produce a higher yield. Remember to exploit symmetry if possible and disconnect multiple groups

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instead of single group disconnection. All the principles in this work have the goal to simplify the target molecule and help student find the most efficient retrosynthesis route possible. All the principles are not defined but often provides great insight when doing retrosynthesis analysis.

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