

Retrosynthesis

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Abstract: This essay focuses on a very important part of organic chemistry, the retrosynthesis reactions. The essay goes from the shallow to the deep, starting with the most basic organic synthesis and transitioning to the retrosynthesis reactions. It is described in relatively simple and understandable terms, so that all readers can gain an understanding and insight after reading the paper.

1 INTRODUCTION

1.1 Why We Choose Retrosynthesis as Our Paper Topic?

At the very beginning we were all new to organic chemistry and had no previous in-depth knowledge of this area. It was with this enthusiasm and curiosity that we joined Prof. Brian's research project and spent almost a month and a half in lectures to learn more about organic chemistry. During one of the lectures, we heard the professor talk slowly about retrosynthesis reactions, which immediately caught our attention and curiosity. This was our first introduction to the subject, and as we studied and researched it, we became more and more curious about the retrosynthesis reaction and wanted to document it in writing.

1.2 Briefly Introduction

The full synthesis of complex molecules requires a thorough understanding of the reactions that form carbon-carbon bonds and the reactions that change one functional group into another. The largest number of chemical reactions used in synthesis involve the manipulation of functional groups. Furthermore, unless all aspects of chemical reactivity, functional group interactions, conformation and stereochemistry are fully understood, the synthesis of molecules is rarely successful.

Today, the term organic synthesis encompasses a large number of chemical reactions. The planning and use of organic transformations to piece together a

molecule is of course an important aspect of organic synthesis. In order to achieve this, a thorough understanding of the many organic reactions, reagents and chemical transformations that are now known is required. As mentioned earlier, the practice of organic synthesis requires an understanding of the chirality and stereochemistry of molecules, both to develop synthetic strategies and to select the reactions and reagents to be used in the various chemical transformations. (Corey, 1988) It is essential to understand the conformational analysis of each molecule, from the starting material to the final product, as chemical reactivity and stereochemistry are often influenced by conformation.

Perhaps the most important component of planning an organic synthesis is a thorough and in-depth knowledge of chemical reactions and reagents. If one knows only one reagent that converts an alcohol to a ketone, and if that reagent does not work for a particular system, then there is no alternative. On the other hand, if one knows of 30 different reagents for such conversions, there are many alternatives if one of them does not work. Perhaps more importantly, knowing these 30 reagents allows one to better plan the synthesis and use a certain reagent to maximise the chances that the synthetic sequence will go as planned. The same comments apply to making carbon-carbon bonds. (Corey, 1991) Presumably, a synthesis starts with a starting material of a few carbon atoms and the reaction will add carbon fragments to increase the complexity of the molecule as it is transformed into the final target in many steps. It is therefore essential to understand the different reactions and reagents used to form different

types of carbon-carbon bonds. (Corey, 1995)

2 BACKGROUND INFORMATION

Before I talk about retrosynthesis, I would like to start with an introduction to having synthesis. Synthesis is a subject that is usually introduced in organic chemistry and is introduced after you have studied the alkyne reaction. You will make use of it time and time again as the number of reactions you learn builds up.

2.1 What Is Retrosynthesis in Organic Chemistry?

The definition is in its name: organic synthesis simply means making organic compounds from scratch in the laboratory or in industry. (Leah4sci, 2016)

Well, organic synthesis is a field where the principles of organic chemistry are applied.

Most organic compounds come from living things. For example, ethanol comes from the fermentation of biomass. Ethanol is a simple and rich example of organic compounds, but there are some more complex organic compounds that are important but less common in nature.

One good example is the drug aspirin. Aspirin originated from willow bark. However, extracting aspirin from it is too time-consuming and wasteful because willow bark contains very little aspirin.

Some scientists have developed steps to synthesize aspirin from laboratory compounds such as salicylic acid. In this way, aspirin can be produced in a high-volume and low-cost manner (Dr. Pere Romea., 2014).

2.2 What Is Retrosynthesis in Organic Chemistry?

If you look at this word in its simplest form, retro means backwards, and synthetic means synthetic. Put them together, this is what we call a retrosynthetic reaction. Take an example from the results of the discoveries of E.J. Coe of Harvard University in the 20th century.

As shown in Figure 1, this simple example of a reverse synthetic analysis, the target molecule is envisaged to be produced by hydrolysis of 2-bromo-2-methylpropane. 2-Bromo-2-methylpropane is in turn envisaged to be produced from methyl propane via radical bromination. (<https://www.chem.ucla.edu/~harding/IGOC/R/retrosynthesis.html#:~:text=Inthissimpleexampleofretrosyntheticanalysis%2C,toariseviahydrolysisof2-bromo-2-methylpropane>).

2.3 Why Is It Important in Organic Chemistry

Retrosynthetic analysis can be used to get a clear idea about the structure of naturally available compounds. Also, it is a powerful tool to prepare compounds in order to analyze the mechanism of the reaction. There is a good example, which is the labeled compound. Furthermore, the novel problems present everyday requires advanced solutions that trigger developments of modern chemistry.

3 DISCONNECTION

As previously mentioned, retrosynthetic analysis is to disconnect target molecule into less complex structures. This procedure is repeated until form simple, easily available starting material. To accomplish this goal, it usually takes known or reasonable reactions as the account for the disconnections used in the analysis.

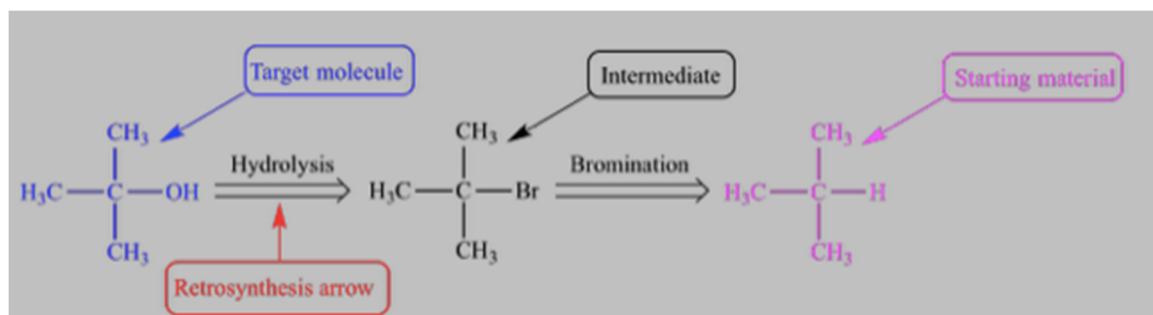


Figure 1: Simple example of retrosynthetic analysis.

The overall synthesis of any complex organic molecules requires a thorough knowledge of reactions. In the synthesis reactions, there are two main categories of reaction types. One is called carbon-carbon bond forming reaction. The other one changes one functional group into another, this is functional group exchange reaction.

Disconnection means breaking the bonds of the molecule to produce simpler fragments. Disconnection is actually a mental activity (we don't actually break bonds chemically), if we break a bond we must have a chemical process in mind to make that bond.

As a reverse reaction to synthesis, retrosynthesis disconnects the bonds and simplifies the target molecule.

3.1 Carbon-Carbon Bonds Disconnections

First and perhaps the most important retrosynthetic rule is related to the C–C bond, electronic structure and electronic charges of synthons that are designed by the disconnection of those C–C bond. This rule can be revealed in the products of disconnections which are ionic fragments or radicals. To be synthons, those particles should exist and be seen as reagents or synthetic equivalents.

Before considering the electronic structure and properties of synthons, there is a general scheme of retrosynthetic analysis.

In figure 2, the curving line and arrow on the C–C bond indicate the site of disconnection. The broader arrow indicates the disconnection from left (target molecule) to right (charged species). Then, disconnection process continues until simple, commercially available compounds are reached. (Vitimir Šunjić, 2016).

Now consider disconnections of the C–C bond in cyclic system in Figure 3. By disconnection of one bond in TM II, the ring is detached. Although there is only one synthon, it probably provides a new vision on how to separate the molecule in-depth. Of course, the complex open-chain structure requires further retrosynthetic consideration. This is just a possible path.

In the cyclic TM III, we disconnect two C–C bonds at the same time. Two synthons are obtained. The same, if one or both of this second generation still contains complex structures, retrosynthetic consideration continues.

To be more specific, the disconnection in TM III is a very well-known reaction called Diels–Alder reaction. With two simultaneously formed carbon-carbon bonds, Diels–Alder reaction becomes a reliable source to form plentiful required six-membered rings. Figure 4 reveals the most common Diels–Alder reactions.

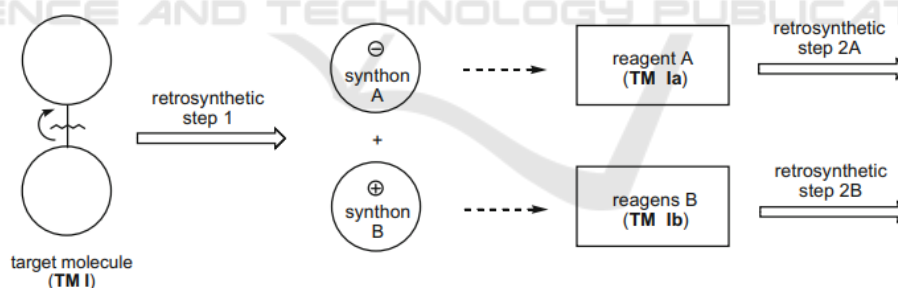


Figure 2: Disconnection steps.

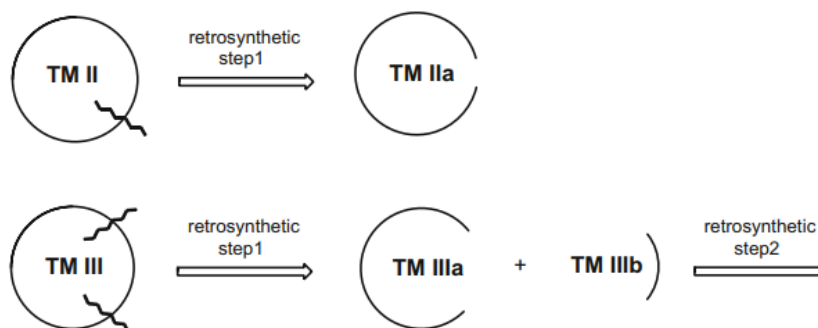


Figure 3: Common ways to break C–C bond in the cyclic system.

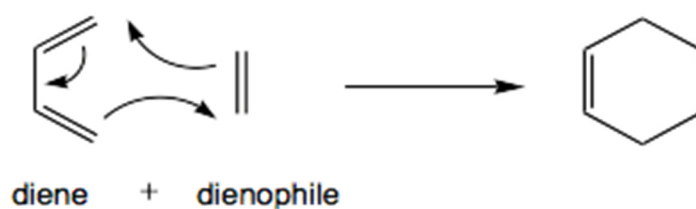


Figure 4: An usual Diels-Alder reaction model.

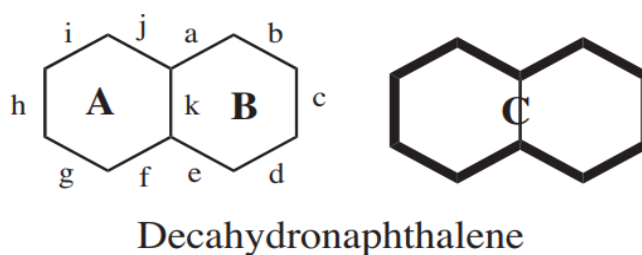


Figure 5: Strategic bonds.

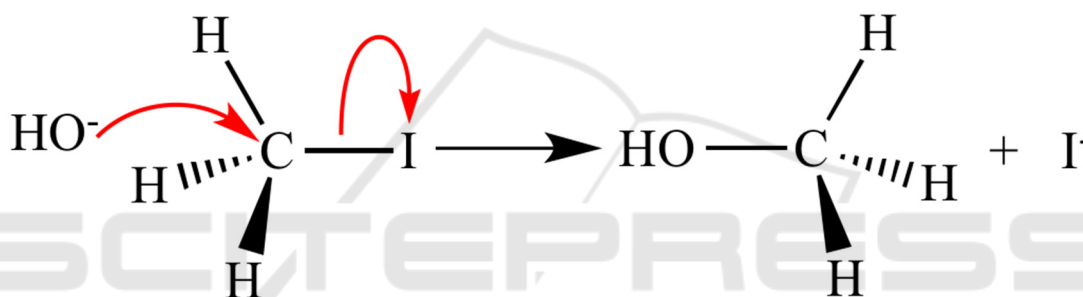


Figure 6: Electron transfer when breaking bond.

The reverse reaction of a Diels–Alder reaction becomes favorable at a high temperature, although this may not be significant to most of the Diels–Alder products. However, it makes abundant disconnection of carbon rings possible. This reverse reaction is known as the retro–Diels–Alder reaction.

Besides, there is another principle used to discern strategic bonds which is that the strategic bonds are in the primary rings, and they are not shared by two fused rings. Since Five-, Six-, Seven-membered rings are easy to form, whereas larger rings would be difficult to form using synthetic ways. As a result, any disconnections that generate rings containing more than 7 carbon atoms is not feasible. In figure 5, the bonds a-i are all strategic bonds except bond k. It can be seen more directly in molecule C. If the communal bond in the middle of the fused ring system is broken, a ten-membered ring will be built. (Michael, 2016).

3.2 Ionic Fragments or Radicals

In the process of retrosynthesis, there is movement of electrons that needs to be considered instead of just

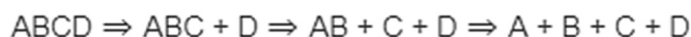
thinking about the framework of the target molecule. The arrow shown in the Figure 6 indicates the flow of electrons. Additionally, fragmented ions can be positively charged or negatively charged. Therefore, they can be replaced if required. First, the electron-withdrawing groups should be disconnected. Then, the group they used to attach will be positively charged and induce another group to form reaction. Nevertheless, it does not always obtain stable ions. In this circumstance, FGI can be used to get the desired ions.

There is another way to separate bonds called homolysis (Figure 7). It produces radicals. Comparing to polar reactions, although radical reactions is less frequently used, it is still regarded as a distinct genre and sometimes provides a lot of convenience (Abhik, 2014).



Figure 7: Homolysis - separate bond equally.

Linear synthesis:



Convergent synthesis:



Figure 8: Difference between two synthesis types.

4 GUIDELINES

4.1 Make the Pathway Short If Possible

In the laboratory, the ideal retrosynthesis pathway would include the highest safety and efficiency. Based on this principle, a short plan is favorable because it results in more yield from a given amount of reactant.

4.1.1 Convergence

Convergence is a strategy for multistep synthesis. Different from linear synthesis (also called consecutive synthesis), convergent synthesis apply much less steps. Since reactions cannot reach 100% yield, as steps increases, the percent yield of the target molecule decreases. Based on this belief, shortening the synthesis pathway leads to a higher efficiency using given amount of starting material. From Figure 8, we can see a clear difference between linear synthesis and convergent synthesis.

To summarize, the first step in the inverse synthesis of a complex target molecule is to analyse the oxidation level of each carbon atom. By analysing the oxidation levels, we can convert the binding to electronegative atoms into binding to oxygen. As a result, we can find possible dioxygen dioxide patterns, which indicate the type of disconnection carried out. The disconnection will result in simpler molecules that can be further disconnected. Furthermore, the dioxygen dioxide pattern guides the synthetic pathway of the target molecule, which is a purpose of retrosynthetic analysis as it provides known reactions that can produce the target molecule from the disconnected part.

4.1.2 Exploit Any Symmetrical Structure

Exploiting the symmetrical structure in the target molecule or its intermediate can dramatically simplify retrosynthesis. In addition, it provides significant chance to identify a convergent pathway.

4.2 Do the Retrosynthesis with Easily Accessible Synthons

On the practical aspect, a good retrosynthesis pathway should make its synthons easier to approach by buying or making in the process.

4.3 Transfer the Less Reactive Functional Groups into Reactive Ones

If any substructures interfere with a key process, it can be removed using transformation to other functional groups.

5 CONCLUSION

Our research continued for several months, and at the beginning, we studied abundant aspects of organic chemistry in detail. Then, we started to inquire about retrosynthesis in depth. In the process of research, we find it is effective to use retrosynthetic ways to analyze chemical substances. After the development, we group basic ideology and guidelines.

We find it with great significance that to produce more target from easier approached raw material. This demands a solid foundation on known chemical reactions. In organic chemistry, we may encounter problems that are too difficult for us to solve.

Learning reverse synthetic analysis allows us to think critically about problems from different perspectives, moving from forward to backward and then backwards again. Having such chemical intuition provides us a better understanding to more difficult chemical problems in the future. This way of thinking is not only applicable to our future chemistry studies but also to our school life.

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