

# Application Research of Organic Orientation Effect in Drug Synthesis

Hongxia Lv, Yuan Zhou

Medical College, Xi'an international University, Xi'an, 710077, China

**Keywords:** Drug synthesis, Organic orientation effect, Application

**Abstract.** In the process of drug synthesis when choosing synthetic route, it is necessary to fully consider the positioning effect factors and pay special attention to effects caused by the compound of different orientating groups so as to give full play to the role of the synthetic drug and achieve the desired application effect because the effects of synthesized products composed of different orientating groups in different aspects are different. This text elaborates the relationship between the orientation effect and drug synthesis on the basis of the analysis of the definition, generating factors and effects of orientation effect and finally research in the specific application of orientation effect in drug synthesis.

## Introduction

With the fast development of social economy, every industry is improving while the pharmaceutical industry is no exception. At this stage, more and more attention has been paid to drug synthesis in pharmaceutical industry, orientation effect has been introduced into drug synthesis, all these lead to very positive effect, for example, to a great extent, raised the qualification and productivity rate of drug synthesis. Facing the demand of rapid social development, the application prospect of organic orientation effect in drug synthesis is more and more extensive, this promotes the healthy and sustainable development of the pharmaceutical industry.

## Overview of Orientation Effect

### Definition of Orientation Effect

In organic chemistry, orientation effect refers to the directional effect of orientation from the original substituent to new substituent when benzene derivatives contain substituent are in aromatic electrophilic substitution reaction. In social psychology, people call the phenomenon a person's own selected role has no big changes under the condition of the interference of other factors as orientation effect. Once social psychologists tested for this phenomenon: during the meeting, they let everybody choose his/her location, and then rest for a while outside, after this again enter the conference room, they did this 5 to 6 times and found that most people would choose the position they first chose.

### The Generating Factors of Orientation Effect

#### *Preconceptions*

When in contacting with someone who is not familiar, the first impression is very important, generally this will affect the subsequent cognitive as well as leave a deep impression in people's heart, in the absence of special or major stimulus, this kind of first impression will weaken the effect of further stimulus unceasingly and make the first impression dominant status, this will not easily be changed. To some extent, the orientation effect is the action effect of preconceptions.

#### *Self-awareness Coordination*

In the absence of special requirements, people will generate a motivation of cognitive coordination, give a person an impression that he/she is the same before and after. Under the drive of this motivation, people will control their own behavior, attitude, etc. So it is easy to know through the test that people still tend to the first choice after several options, this is a kind of orientation effect generated under no intense stimulation to prevent behavior of not unified cognition.

### *Quality of the One Who Orients*

Under normal circumstances, the quality of the one who orients can be viewed as one of the main factors generates orientation effect. The one who orients orientation effect has the following qualities: (1) Constant force. A person would not be shifted under the influence of external factors but always focuses on object he/she chose. This kind of ability with focused and concentrated thought is constant force, not completely similar to the constant force of zen. Everybody has constant force while in varying degrees. People who has the quality of constant force is very easy to generate orientation effect, on the contrary is not easy to generate orientation effect and has the situation of easy to be changed when facing new condition or new circumstances, it is impossible for this kind of people to generate orientation thought. (2) Inertia Psychology. People have this kind of quality usually don't want to change the status quo, their temperament is not active: too lazy to talk, lazy to move, lazy to think and too lazy to change, that is to say, they will try their best to keep those can still remains the same, they are not so keen on innovation. Therefore, under the condition of no special or great pressure, people have this kind of quality are easy to generate orientation effect. (3) Excessive self-confidence. People have this kind of quality are very confident, always thinking they can not go wrong, especially their first choice. Therefore, people who have this kind of quality will not easily trust the opinions of others and are always going their own way, never going back on their word. People who have this kind of quality always think no small bear of oneself with excessive self-confidence, it is easy for them to generate orientation effect.

### **The Action of Orientation Effect**

A lot of the experimental results show that orientation effect can be divided into two types according to orientation effect of common groups: (1) Ortho-para directing group(the first kind of directing group). Introduce other groups in when there are already this kind of directing substituent group on benzene ring, these groups are mainly introduced in its ortho or para and the difficulty of the introducing of second substituent is obviously less than this substituent group, in other words, the substituent group activates the benzene ring to a certain extent. Atoms directly on the benzene ring in this kind of substituent group usually have no shared electron-pair and do not contain a double bond or triple bond. (2) Meta directing group(the second kind of directing group). Introduce other groups in when there are already this kind of directing substituent group on benzene ring, these groups are mainly introduced in meta, and the difficulty of the introducing of second substituent is obviously greater than this substituent group, in other words, this substituent group inactivates the benzene ring. Some atoms in the substituent group directly connected to benzene ring have positive charge, some contain a double bond or triple bond. Based on the analysis above, Ortho-para directing group belongs to electron donating group can increase the intensity of benzene ortho-para electron cloud, enhance the continuing work of electrophilic substitution reaction, give fully play to activating benzene ring; while the Meta directing group belongs to electron withdrawing group can increase the intensity of electron cloud on meta, create favorable condition for the continuing work of meta electrophilic substitution reaction, have the effects of inactivating benzene ring.

According to the orientation effect, it is possible to predict on the three substitution reaction generated by benzene ring. It has already had two substituent group on the Two substitution benzene ring, when the two substituents are in mutually reinforcing orientation effects position, it is possible to predict to three substituent position and be clear about product generated by substitution reaction. When these two substituent effects are in contradictory condition, it can be predicted according to the following rules: (1) The capability of position of deactivating group or weak activation group is significantly weaker than strong activation groups positioning ability, the order of group ability from weak to strong: meta directing group, methyl phenyl, NHCOR, - OR, - OH, NH<sub>2</sub>. (2) when two substituent groups are passivated, it mainly depends on the stronger passivated group. (3) when two groups are all in meta-position, because of the limitation of space position, it is very difficult to react substitution reaction.

To sum up, the orientation effect has two main functions: (1) to predict the main product substitution reaction; (2) to provide guidance for synthetic route, not only can obtain higher productivity, also can avoid the complex separation procedures.

### **The relationship between the orientation effect and drug synthesis**

To some extent, drug synthesis is a kind of organic synthesis. Related reaction in the process of drug synthesis, mainly include halogenated reaction, condensation reaction, diazotization reaction, nitration, sulfonation reaction, reduction reaction, oxidation reaction, rearrangement reaction, elimination reaction, acyl reaction, alkylation reaction, etc., while during halogenation, nitration, sulfonation reaction, rearrangement reaction, acyl reaction, alkylation reaction may involve orientation effect [3]

Thus it can be seen that in the drug synthesis route runs through orientation effect, the two are interdependent and complementary to each other. Set the benzene synthesis to chlorobenzoic acid as an example, because two substituents of the generated products on benzene ring are in state of para, and carboxyl is meta directing group, on the basis of analysis of substitution productivity and alkyl orientation effect, first through the alkylation reaction to make benzene toluene and then generate carboxylic acid through chlorination, oxidation reaction. Therefore, in the process of alkylation, chlorinated reaction of benzene, it is necessary to fully consider the orientation effect to ensure Chlorine can reach the corresponding position thus ensure the response to continue work. If the chlorine reached first, although it is possible to guarantee the accuracy of the chlorine in position, but because it belongs to deactivation group which greatly increased the difficulty of alkylation, blocked the continue work of reaction.

Again for instance, synthesized from methylbenzene to 2 - chloro - 4 - nitrotoluene. First use the methylbenzene to do sulfonation reaction, the phenomenon of temperature rise appears in most para product, and then chlorine replaces para product and does sulfonic acid group removing reaction under acidic conditions and finally get the corresponding products through nitration. Accordingly, sulfonic group is a temporary placeholder groups which can significantly improve productivity; at the same time, under the dual function of the orientation effect of benzene ring substitution group and nitro orientation effect, the product productivity can be significantly improved .

### **The application of organic orientation effect in drug synthesis**

#### **Synthesis of sodium amino acid**

During the process of synthesis of sodium amino acid, a lot of links involves orientation effect. The synthetic steps are as follows: (1) With toluene as the main synthetic raw materials, get nitrotoluene through total heat with sulfuric acid, nitric acid; (2) Get 2 - methyl - 5 - nitrobenzene sulfonic acid through the reaction of product and fuming sulphuric acid; (3) Get 2 - methyl - 5 - nitrobenzene sodium sulfonate through reaction of products and sodium hydroxide and then get 2 - methyl - 5 - nitrophenol sodium through further heating; (4) Generate 2 - methyl - 5 - nitrobenzene methyl ether through reaction of products and  $\text{CH}_3\text{I}$ ; (5) Generate 2 - methoxy - 4 - nitro benzoic acid through oxidation by potassium permanganate of products; (6) Further generate - methoxy - 4-2 amino acid through reactions of products and hydrochloric acid, iron; (7) Generate 2 - hydroxy - 4 - aminobenzoic acid through further reaction of products and hydrochloric acid; (8) Finally generate sodium aminosalicylate through the reaction of products and sodium bicarbonate.

Through the analysis of this drug synthesis route, specific application effect of orientation effect can be cleared. In the synthesis process, the product of the reaction of nitrotoluene and fuming sulfuric acid, at this time, there are methyl, nitrocellulose on benzene ring. Because methyl is Ortho-para directing group , while sulfonic group and nitrocellulose are meta directing groups, this make nitro replace methyl para-position, so sulfonic acid group can only enter ortho-position. However, nitro is meta directing group and can enter any position of both sides of methyl, so it is clear that sulfonic acid group is a replacement of methyl ortho.

## Synthesis of $\beta$ -receptor blocking pharmacological celiprolol

During the process of the synthesis of  $\beta$ -receptor blocking pharmacological celiprolol, it generates N - acyl chloride through the reaction on the amino benzene ether, N - diethylamine formyl chloride, this can reduce locating function of amino ortho para and extend amino ortho space to make subsequent reaction focus on phenolic hydroxyl ortho. [4] If in the actual response, friedel-crafts reactions were acted first, then N - acyl reaction would follow, so when during acetylation, at the same time it appears in the amine and phenolic hydroxyl ortho position, the products generated are more complicated.

## Synthesis of quinolones drug

In the process of quinolones drug synthesis, the link of synthesis of 3-chloro-4-fluoroaniline is very important, its nitration process is to selectively introduce nitration under the para of chlorine by using orientation effect of helium atom, if reaction condition control was not reasonable, the nitration would be introduced into other position and thus isomer generated and has a great deal of influence on the subsequent reaction and is difficult to be eliminated. This produces more drug impurity and thus seriously affects the effects of drug treatment, and even there will be some side effects. So, in the process of drug synthesis, this link must be strictly controlled to ensure the nitro be introduced into the correct position and avoid impurities and ensure pesticide effect.

## Mesalazine

Mesalazine is a kind of antiulcer drug, its main raw material is salicylic acid, during the process of the synthesis of mesalazine, nitro is needed to be introduced on benzene ring and after this restore nitro. The main content of the drug synthesis is introducing nitro salicylic acid on a particular location of salicylic acid benzene. The introduction of nitrocellulose is accomplished mainly through nitration, the reaction mechanism is in the range of electrophilic substitution reaction, the process is: electrophilic reagent generated by nitric acid will cause attack effect on benzene ring and thus generate carbonium ion intermediate and remove protons after this and realize reasonable introduction of nitro. At the time of introduction of nitrocellulose, its position mainly depends on carboxyl, hydroxyl of salicylic acid. Carboxyl belongs to meta directing group, hydroxy

Belongs to ortho-para directing group, both have the same orientation effect. For this purpose, it is possible to analyze synthetic process of mesalazine through the orientation angle.

## Synthesis of 2 - nitro - 1, 3 - benzodiazepines by 1, 3 - benzenediol

In the process of the synthesis, there is no direct nitration, instead sulfonation reaction is adopted. This link can be explained by orientation effect. The 4, 6 section of 1, 3 - benzenediol is very easy to be nitrified, during the synthesis process, to avoid the nitration of the 4, 6 section, they need to be protected, and for this sulfonation reaction is needed and also sulfonic acid group be introduced; after this is nitration to ensure orientation effect of hydroxyl and sulfonic group are the same and then do hydrolysis on this and remove protecting group and sulfonic acid group and at last generate 2 - nitro - 1, 3 - benzenediol.

## Conclusion

To sum up, the relationship between drug synthesis and orientation effect is very close, both interdependence, inseparable, and in the process of drug synthesis, orientation effect plays a very important role. In drug synthesis, if replace position of the orientating group was different, the drug effect was also different, may be beneficial, may also be harmful, and orientation effect just can avoid this kind of situation. Therefore, in the drug synthesis, one must be sure to pay attention to analysis and research of organic orientation effect, selecting rational synthesis route, fully considering various factors, effectively improving synthetic output and qualified rate, lay solid foundation for smooth completion of the drug synthesis.

## References

- [1] Hai-bo Sun. The application of organic orientation effect in drug synthesis. *Journal of Heilongjiang science and technology information*, 2014, (14) : 21-21.
- [2] Wang Jingwei. Discuss the application of organosilicon reagents in drug synthesis. *Journal of Heilongjiang science and technology information*, 2013, (02) : 8.
- [3] JiaoRun, Fan Shuli. Organic orientation effect in the application of drug synthesis. *Journal of information science and technology*, 2013, (15) : 100-101.
- [4] Kan Meiyun, Yang Hui, Jing Yun Rong, etc. The application of organosilicon reagents in drug synthesis. *Journal of synthetic chemistry*, 2011, 12 (6) : 689-693.
- [5] Ceng Chunjiao. The study of the synthesis and properties of amide bonding linked cytidine porphyrin compounds. Hunan university, 2011.