"Materials and Production" Field

Achievement : Leading contributions to precision synthesis of helical polymers and development of practical chiral materials for separating chiral drugs

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Summary

Even among two molecules of the same chemical composition, some have a three-dimensional structure with a mirror image that cannot be superimposed on to the other, as it is the case with our left and right hand. Such molecules are said to be in an enantiomeric relationship. Among enantiomers, physical properties such as the melting point and boiling point are the same, but their physiological effects on the human body can differ. This can cause major problems for the production of pharmaceuticals.

Despite the above being the case, ordinary chemical synthesis can only produce enantiomer mixtures. Along with the advancement of the technique for synthesizing only one hand of the molecule with a catalyst, the convenient method for separating the generated mixture has also come to be widely used. This was made possible by helical polymers. When one-handed helical polymer is coated onto silica gel, packed in a column and enantiomer mixture is injected through, the enantiomer that is more prone to being captured by the helical polymer remains in the column for a long period of time, and the other enantiomer that is less prone to being captured flows out first.

Prof. Yoshio Okamoto was the first in the world to achieve the synthesis of a one-handed helical polymer, and even demonstrated its utility in the separation of enantiomers. Today, products that have been derived from the application of these discoveries are being widely used throughout the world for the research & development and the manufacturing of pharmaceuticals, aroma chemicals and functional materials. Prof. Okamoto's achievements that span the advancement of basic polymer synthesis science to its practical application are highly regarded by the international community.

The different physiological effects among enantiomers

Enantiomers with different three-dimensional structures, like our left and right hand, often have different physiological effects on the body (Figure 1).

With menthol, for example, one of the enantiomers has the aroma of mint, but the other has very little aroma. With monosodium glutamate, the umami seasoning is derived only from one of the enantiomers, as red blood cells can only carry just one of the enantiomers when transporting glucose. The ability of organisms to distinguish enantiomers is related to the fact that the proteins that make up the living body are composed of amino acids from just one of the enantiomers.

One of the reasons that enantiomers have attracted public attention was the Thalidomide drug disaster that occurred during the early 1960s. Thalidomide has two types of enantiomers. Although one has the effect of a sleep-inducing drug, the other can sometimes cause malformation of the fetus when taken by a pregnant woman. At that time, the difference in the pharmacological effects of enantiomers was not well understood, which led to a series of serious drug poisoning incidents. It was much later that the technique to selectively synthesize different enantiomers (asymmetric synthesis) and the technique to separate different enantiomers (chiral resolution) were developed, hence enabling us to examine the various effects on body. Today, we also know that both enantiomers are partially inverted in the body.

Ordinary chemical synthesis can only produce mixtures of enantiomers with equal proportions. In the development and manufacturing of many chemical products, there was a major demand for the technique to selectively obtain just the useful enantiomers with a high degree of precision and efficiency. This was particularly an important aspect in the development of pharmaceutical drugs where efficacy and safety are crucial.

Column for high-precision separation of enantiomers

Amid these circumstances, there was a growing need for asymmetric synthesis, the technique to selectively obtain just one of the enantiomers, and chiral resolution, the technique to separate enantiomers.

From the 1980s onward, there was substantial progress in the research & development of asymmetric synthesis for selectively synthesizing the desired enantiomers using a catalyst. However, synthesis with high precision is not easy even with today's technology.

Meanwhile, the chiral resolution technique, which is highly convenient for separating target substances from synthesized mixtures, saw major advances and widespread adoption. Among them, chiral resolution by way of High-Performance Liquid Chromatography (HPLC) has especially seen high adoption in research & development and the production field for being a versatile technique capable of high precision separation. In HPLC, the mixture of enantiomers is injected into the column with the solvent, then separated by utilizing the time difference with which the substances flow out. By infusing the column's filler with a substance that captures one of the enantiomers, the other enantiomer can flow out faster, thereby enabling the separation of the two with high precision and efficiency.

The revolutionary substance that led to the realization of chiral resolution by HPLC was the helical polymer that Prof. Okamoto succeeded in synthesizing in 1979. The one-handed helical polymer can recognize and capture just one of the enantiomers. As it is easy for two right hands to be shaken, and is difficult for the left and right hand to be shaken, precision separation was achieved by the mechanism in which one of the enantiomers stays in the column (easy to handshake) and the other flows out faster (difficult to handshake) (Figure 2). Based on this breakthrough, Prof. Okamoto embarked on a joint research with a domestic chemical manufacturer, and in 1982, commercialized the world's first practical chiral resolution column for polymeric HPLC.

The chemical synthesis of one-handed helical polymers

Early during his polymer research, Prof. Okamoto worked on “asymmetric selective polymerization”, a chemical reaction to polymerize just one of the enantiomers in an enantiomer mixture. Although many researchers had worked on this matter, none were able to produce good results. However, Prof. Okamoto in 1977 realized the asymmetric selective polymerization with high selectivity by using a catalyst derived from natural substances. Following this breakthrough, he used the same catalyst to achieve the world's first "helix-selective polymerization" which is the selective polymerization of one-handed helical polymers.

A left-handed helix and a right-handed helix have a symmetrical three-dimensional structure when reflected onto a mirror, and are in an enantiomeric relationship with each other (Figure 1). Prof. Okamoto confirmed that if a molecule he had been experimenting with was polymerized, a bulky structure would generate on one side of the polymer chain which consequently generated a stable one-handed helix even in solutions. Until then, the conditions under which helical polymers could retain its stable structure in solutions had

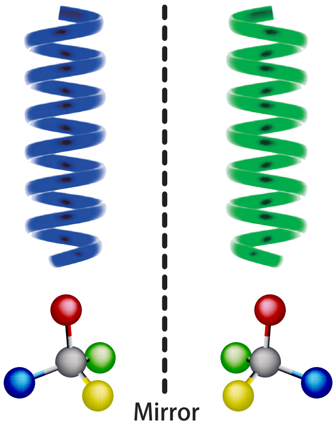

Figure1: Molecules in an enantiomeric relationship and left and right-handed helical polymers

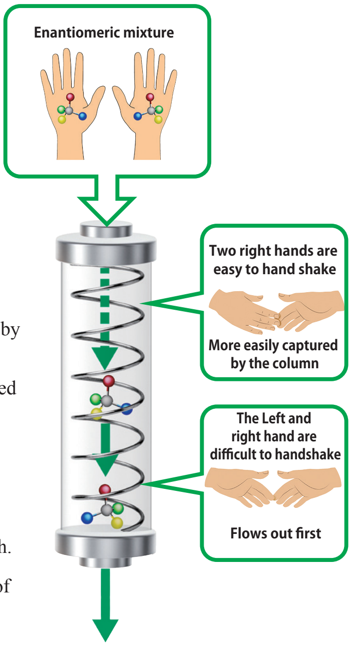

Figure2:
Separation of enantiomers by a helical polymer column

When the mixture is injected into the column of High-Performance Liquid Chromatography, the charged helical polymer captures one of the enantiomers. The other enantiomer flows out first because it is harder to catch. This mechanism enables high-precision separation of enantiomers.

been unknown. Furthermore, no one had predicted that a stable one-handed helical polymer could be formed by polymerizing such a molecule.

This breakthrough greatly stirred up the field of organic synthetic chemistry and the synthesis of helical polymers have since been actively pursued by researchers all over the world. Helix is the fundamental structure of biopolymers responsible for biological phenomena such as proteins, DNA and polysaccharides, and is the primary factor that gives rise to the advanced and diverse functions of life forms.

With so much potential, helical polymers are substances of great appeal. As research on the synthesis and dynamics of helical polymers move forward, a new field of helical polymer science has also been expanding.

Today, there is high anticipation surrounding its applications toward catalysts and nanomaterials.

Achievements that span from basic research all the way through to practical applications

Prof. Okamoto studied the functions of helical polymers he had synthesized and confirmed its ability to distinguish enantiomers. As a result, the aforementioned column filler was born. In search of filler material with better separation capacity, he next focused on cellulose and amylose, which are polymers of natural polysaccharides. To examine their functions, he made various chemical modifications to these macromolecules and succeeded in obtaining a filler with higher capacity.

Today, the HPLC column with filler material made of polysaccharide-infused silica gel is used by the overwhelming majority of research institutions and companies around the world. This column, which can separate enantiomers at a very high success rate, has not only contributed to the research & development of pharmaceuticals, aroma chemicals and functional materials but has also been widely adopted in the production field, thereby enabling the separation of enantiomers in tons.

Currently, many pharmaceutical drugs such as antidepressants, antiepileptics and hyperlipidemia drugs are manufactured using chiral resolution column with polysaccharide fillers.

It has also played an important role in the production and development of esomeprazole, a gastric acid secretion inhibitor, of which the global annual sales (up to June 2014) amounted to 894 billion Yen ($8.83 billion USD).

With the advancement of chiral resolution technology, it has been recommended in Japan since the mid-1980s that the manufacturing of pharmaceutical drugs take enantiomers into account and only use the more effective enantiomer.

In this manner, Prof. Okamoto's achievements, which include the development of asymmetric selective polymerization, helix selective polymerization, and chiral materials utilizing helical polymers, and span from basic research all the way through to practical applications, are highly regarded for its immense contributions to society.