What kind of researcher is Karl Freudenberg?

* This manuscript is an English translation of the original manuscript written in Japanese.

1. Introduction

When you leaf through the pages of a book entitled "Lignins; occurrence, formation, structure and reactions"1), published in 1971, the first thing that catches your eye is an impressive photograph of Karl Freudenberg (hereafter 'Freudenberg'), accompanied by the following text:

> Professor Freudenberg and his school in Heidelberg, Germany have made an unparalleled series of contributions to the understanding of the biogenesis and the structure of lignins.

What kind of researcher was Karl Freudenberg? He was the great chemist who made significant contributions not only to the chemistry of lignin but also to that of other wood components and to stereochemistry.

First, I will describe his career history below. The descriptions mainly follow the collection of his lectures in Japan.2)

1886	Born on January 29th in Weinheim, Baden
1905-1910	Studied at the University of Bonn and the University of Berlin
1910	Received doctorate under Professor Emil Fischer at the University of Berlin
1910-1914	Assistant to Professor Emil Fischer at the same university
1914	Became a lecturer (privatdozent) at the University of Kiel
1914-1918	Served in the First World War
1920-1921	Lecturer under Professor Richard Willstätter at the University of Munich
1921-1922	Extraordinary professor under Professor Heinrich Wieland at the University of Freiburg
1922-1926	Full professor and head of the chemistry department at the Karlsruhe Institute of Technology
1926-1956	Head of the chemistry department at the University of Heidelberg
1931	Visiting professor at the University of Wisconsin, Madison and Dohme Lecturer at Johns Hopkins University, Baltimore.
1938-1969	Head of the Research Institute for the Chemistry of Wood and Polysaccharides at the University of Heidelberg (from its establishment on April 1, 1938 until its dissolution on August 31, 1969)

1983 Died at age 97 on April 3

Next, I will describe the life of Freudenberg and the work he did[2)-9)]. I must point out that some of the articles[4), 5), 8)] cited in this manuscript are written in German, and those were only machine translated, so they may contain some errors.

2. Life

This chapter mainly summarizes the information from the cited articles[3), 4), 8)]. Freudenberg's own words are included in double quotation. The headings of his career follow the description used in the collection of his lectures in Japan [2)].

More detailed descriptions and many other anecdotes that are not included here can be found in the cited articles. [3), 4), 8)] If you are interested in these, I encourage you to read those articles as well.

From birth to university age

Karl Freudenberg was born on January 29, 1886 in Weinheim, Baden (near Mannheim), the third of ten children. His father, Hermann E. Freudenberg, had run a large tannery in Weinheim since 1886 (1887?) and was president of the Mannheim Chamber of Commerce. The company*, now a multinational corporation, was run by the founder's grandson and great-grandson until 1997. [4)] Karl's mother, Helene Siegert, was the daughter of August Siegert, a professor at the Düsseldorf Academy of Fine Arts. Three of Karl's siblings later became famous in the leather industry, and three of his cousins were distinguished academically.

* For the company, see also "The development of the Freudenberg group (since 1849)" (Hermann E. Freudenberg: p5, 1997 as cited above: p20).
https://www.freudenberg.com/fileadmin/downloads/english/History-Brochure_EN.pdf

As a child, he enjoyed the countryside around Weinheim with his brothers, sisters and cousins. It was around this time that Freudenberg developed a strong love of botany, and his affection for botany lasted his whole life.

After studying humanities at high school, he moved to natural sciences at university. "The step from a humanistic high school to the natural sciences is not an easy one, but it is worthwhile, and it is good for scientists to have some knowledge of antiquity and history."

1905-1910 Studied at the University of Bonn and the University of Berlin
1910 Received doctorate under Professor Emil Fischer at the University of Berlin

Freudenberg entered the University of Bonn to study natural sciences and botany, but soon devoted himself to chemistry. He did not begin his chemistry studies until his second semester at Bonn, and this was said to be his first exposure to chemistry.8) In the summer of 1905, he decided to serve a year in the military, because he expected that interrupting his studies later would have a major negative impact on him, and because he thought military service would be easier to endure at a young age.

His decisive step was to move to Berlin in 1907 to become a doctoral student under the great Emil Fischer. Emil Fischer10) (Hermann Emil Fischer, October 9, 1852 - July 15, 1919) was a German chemist known for discovering the ester synthesis method (Fischer esterification) and developing the Fischer projection. He received the Nobel Prize in Chemistry in 1902. Freudenberg was greatly influenced by Emil Fischer throughout his life.

Fischer invited Freudenberg to his apartment to discuss the topic of his doctoral thesis, and Fischer suggested he would like to study tanning agents, to which Freudenberg replied, "That's great, my father runs a tannery." Tannins are still used as part of tanning agents today, but when Fischer talked about his research on tannins, he was interested in their composition, not the tanning process.

Freudenberg completed eight weeks of military training before beginning his doctoral studies. He then worked on *p*-hydroxybenzoic acid, which belongs to the same family as gallic acid. Around Christmas 1909, his experimental doctoral thesis was completed with a statement from Fischer that I could now finish. The first publication involving Freudenberg was received on January 10, 1910.

1910-1914 Assistant to Professor Emil Fischer at the same university

After receiving his doctorate in 1910, Emil Fischer offered Freudenberg the opportunity to continue working in his laboratory. "I was very pleased and also asked him for a week's vacation, telling him that I wanted to get married at the start of the vacation. "

Freudenberg was 24 years old at the time. Two years earlier, he had met his cousin's friend Doris Nieden in Bonn, and the wedding took place in Bonn on July 30, 1910. "I was privileged to live with her for 57 years and I don't know a day that has gone by when I haven't enjoyed this community." Three daughters and two sons were born from this happy marriage.

Between 1910 and 1914, six papers were written on the work supervised by Fischer and performed by Freudenberg. In 1913 Freudenberg began an independent study of stereochemical problems somewhat related to Fischer's work.

When Freudenberg completed his research on the configurational relationships of α-hydroxycarboxylic acids (he wrote that it was probably in February 1914), the following striking event occurred for Freudenberg4), 8). Fischer asked Freudenberg to report on this at the colloquium. And when Freudenberg finished presenting the above results at the colloquium, “As I left the lecture hall, Walter Madelung approached me and said appreciatively that it was a genuine Fischer work. If he had hit me on the head with a club, the same effect would have been achieved. What he said was true, frighteningly true, and it suddenly dawned on me to what extent I was trapped in my teacher's circle of thought. It became clear to me that if I continued to stay in Emil Fischer's presence, I would not be able to achieve my independence, and I only needed to open my eyes to find suitable opportunities.”

1914 Became a lecturer (privatdozent) at the University of Kiel

Freudenberg concluded that he should leave Berlin for his own independent development and went to Kiel where he became Privatdozent (private lecturer) in the laboratory of C. Harries (famous for the early work on rubber).

The First World War (1914–1918) broke out during this period. He served in the army in France from August 1914 to the end of 1917. He served as a battalion adjutant with the Baden Regiment at the Somme in France for two years, then went to Saint-Quentin as a chemist in the Gas Service (field gas defense), and finally became a teacher at the Army Gas School in Berlin in 1918. After transferring to the Army Gas School in Berlin on 1 January 1918, Emil Fischer gave Freudenberg a job in a nearby laboratory. The Army Gas School was dissolved on Saturday 9 November 1918. Freudenberg returned to Kiel in October 1918, where he was appointed professor adjunct.

Before the summer semester of 1919 had even ended, Freudenberg received the news of the death of Emil Fischer. Emil Fischer lived for 66 years and 10 months. He served as head of the chemistry department at the University of Berlin until his death. He developed cancer caused by exposure to phenylhydrazine, as well as depression, and he committed suicide in Berlin in 1919.10)

After the war, Freudenberg ascended the steps of the academic ladder in a rapid series of migrations. In October 1918 he returned to Kiel, where he was appointed extraordinary Professor. In 1920 he moved to Willstätter’s laboratory in Munich as Privatdozent, and the next year, as extraordinary Professor, to Freiburg-im-Breisgau. Then in October 1922 he obtained an independent appointment as ordinary Professor and Director of the Chemical Institute at the Technische Hochschule, Karlsruhe. Finally, he moved to the University of Heidelberg in 1926. The details of these are described below.

1920-1921 Lecturer under Professor Richard Willstätter at the University of Munich

During this time, Freudenberg began his groundbreaking research on cellulose and he published the correct structure for the first natural polymer in 1921. The outline of his research on cellulose is as follows6) (See also the Research work chapter)

- In 1921, he published the concept that cellulose is made up of glucose molecules connected by the same manner as cellobiose.
- Later, combining his own experimental results with those of the British School, he presented the structural formula for cellulose for the first time in 1928.

"The year in Munich was the most productive of my life and influenced my work for decades." His experience with cellulose provided a strong motivation for his later research on other natural polymers, including lignin.

The work on the constitution of cellulose had so consolidated Freudenberg's scientific reputation that he received offers from Hamburg, Dresden, and Vienna.

1921-1922 Extraordinary professor under Professor Heinrich Wieland at the University of Freiburg
1922-1926 Full professor and head of the chemistry department at the Karlsruhe Institute of Technology

He secured a permanent position in 1922, and determined to tackle the problem of lignin at this time. “This offered the opportunity to undertake long-term work, even at the risk of slow or even no results. Lignin fulfilled the first of these expectations all too thoroughly: it is a substance that cannot be separated from accompanying substances without alteration. It was not until 1952[11] that we achieved the breakthrough to a genuine chemistry of lignins, and this was compiled in a book[6] in 1968.”[4]

In 1923, Freudenberg and Wohl completed the family tree of the D- and L-series monosaccharides using the projection notation of monosaccharides introduced by Fischer[4]. The systematic family tree of the monosaccharides itself was originally proposed by Emil Fischer.

1926-1956 Head of the chemistry department at the University of Heidelberg
1938-1969 Head of the Research Institute for the Chemistry of Wood and Polysaccharides at the University of Heidelberg (from its establishment on April 1, 1938 until its dissolution on August 31, 1969)

In April 1926, Freudenberg was appointed Professor Ordinarius and Director of the Chemical Institute at Heidelberg in succession to T. Curtius, and he retained this position for 30 years, until he became a professor emeritus.

The institute did not have sufficient material resources at the time. “The Badische Anilin- und Sodafabrik (Baden Aniline and Soda Factory) very gratefully helped us with compressed gases, solvents, and chemicals of all kinds, which were picked up weekly with a trailer that my car had to pull. The German Research Foundation also proved generous, and finally, I have to thank my father's factory in Weinheim for contributions. The lignin problem, in particular, incurred costs that the current budget would never have been sufficient to cover.” 4)

In 1931, he taught as a visiting professor at the University of Wisconsin in Madison and as a lecturer at Johns Hopkins University in Baltimore.

While continuing his research on cellulose and lignin, Freudenberg also began to place emphasis on the study of stereochemistry. In 1933, a 1,509-page book on stereochemistry, "Stereochemie - Eine Zusammenfassung der Ergebnisse, Grundlagen und Probleme" (Stereochemistry - Summary of Results, Fundamentals and Problems), was published, of which Freudenberg was the editor and an important contributor. This book distinguished Freudenberg as a pioneer in stereochemistry, and the theory of configuration (stereochemistry) developed into another his lifelong theme. He also published a general textbook on organic chemistry (13 editions, 1938-1977, later co-authored with his son-in-law Hans Plieninger), which was translated into Spanish, English, and Japanese.

In papers published between 1935 and 1938, Freudenberg demonstrated that Schardinger dextrins were cycloamyloses (cyclic saccharides). This marked the discovery of the first inclusion compound.4)

In 1938 Freudenberg was appointed head of the Research Institute for the Chemistry of Wood and Polysaccharides at the University of Heidelberg, a position that he held for over 30 years until his retirement.

In 1939, Freudenberg postulated that amylose, a component of starch, has a helical structure. This is said to be the first experimentally demonstrated helical structure of a biopolymer 4).

The Second World War took place (1939-1945) during this period. Some related matters are described below.

“Heidelberg's first encounters with the spread of National Socialism are linked to the physicist Philipp Lenard (1905 Nobel Prize winner for the discovery of cathode rays8)). That was in 1926. Over time, the meetings and processions increased, but no one cared about them. We didn't take the 'movement' seriously. But after 1933, things became more serious. 4)

Meanwhile, the university leadership had been filled with overzealous partisans. They had placed their greatest hope in my supposedly Jewish name that they would get rid of me.” 4), 8)

The Third Reich placed Freudenberg in a very disturbing situation. He had a deep and permanent detestation of National Socialism, but he had to concede that the régime was in essence the lawful government of Germany. As a patriotic citizen he had to support the war. He and his wife, Doris, lost two sons during this war. On the other hand, he did a great deal to help threatened Jews, some of whom, including the Lembergs, he sheltered in his own household, at considerable risk to himself.3) Despite the many difficulties, his research work continued at roughly the same pace. Of the two sons mentioned above, meteorologist Herrmann was shot down over France during a meteorological reconnaissance flight in 1940, and the youngest son Klaus was died in action in Russia3) (Poland4)) a year later in 1941.

After the war, Freudenberg played a prominent part in the reconstruction not only of the university but also of the City of Heidelberg. He served as Rektor (president) of Heidelberg university in 1949-50, and was a member of the Heidelberg Stadtrat from 1951 to 1956. He was very active in city planning, and in education as president of the board of trustees for the Volkshochschule (adult education center) from 1953 to 1957. He played a prominent part in dealing with an industrial project that threatened the release of methyl mercaptan in the neighbourhood of the city. 3)

In November 1956 (at the age of 70), he became a professor emeritus and handed over his position as professor of chemistry to Georg Wittig.8) However, he continued to maintain his laboratory and conduct research.8)

Since 1950, lignin became his main research topic, and in 1952 (at the age of 66), he published a paper11) on DHP (Dehydrogenation product), which was the first real breakthrough in his lignin work.6) In 1968, at the age of 82, he published a summary of these lignin work in the book entitled "Constitution and Biosynthesis of Lignin"6), co-authored with A. C. Neish, with two-thirds of the content contributed by Freudenberg.

In 1967, his wife Doris died at the age of 80. Her energetic and faithful support was indispensable to Karl throughout his life.

In 1969, at age 83, Freudenberg retired from active research.3)

After the death of his wife, Freudenberg was well looked after by his relatives and maintained good health for a long time, remaining intellectually active until shortly before his death. He died peacefully in his sleep on Easter, April 3, 1983. He was 97 years old. Freudenberg's obituary in the Holzforschung5) describes him as "the last surviving disciple of Emil Fischer".

3. Research work

First, I would like to introduce an excerpt from Horst Nimz's obituary for Freudenberg in Holzforschung5), which gives an overview of Freudenberg's achievements.

Readers of Holzforschung primarily know Karl Freudenberg for his fundamental work on the chemical structure of lignin, cellulose, and tannins. Furthermore, during his sixty years as an active researcher, he played a key role in the structural elucidation of numerous other natural organic substances, including starch, cyclodextrins, sugars and sugar derivatives in general, catechins, flavans, and lignans, insulin, enzymes, and other proteins, including blood group substances. It is also well known his fundamental work on the optical activity and stereochemistry of organic compounds. The book on stereochemistry he published in 1933 was long considered the comprehensive standard work in this field worldwide. Also worth mentioning are the numerous preparative and analytical methods in organic chemistry that he developed, which are described in more than 600 publications in domestic and foreign journals.

This chapter introduces Freudenberg's research works, focusing mainly on the points that impressed me. Therefore, the content is somewhat largely about lignin. Note that the contents provided here are mainly a summary of the information in the references.2)-4), 6) If you are interested in the exact content, please refer to his original works. All information on Freudenberg's papers, books, patents, and collaborators is provided in the reference4).

3.1. Cellulose

As mentioned above, Freudenberg was the first to provide the correct structural formula for cellulose.

The experience gained from his cellulose work gave a great influence on his subsequent research on other natural polymers, including lignin. Therefore, I will begin the "Research Work" chapter with the work on cellulose.
What was the situation under which his work on cellulose was conducted at that time? The following descriptions from the collection of his lectures in Japan provide a good overview of the situation.2)

“When I think about the structure of cellulose, I remember the controversial period of my youth. At that time, in the early 1920s, there was a fierce debate as to whether cellulose consisted of small molecules held together by lattice forces or of a polymer with a normal type of linkages. However, it is no longer necessary to discuss such matters and it is not necessary to make it a problem, since the work of E. Fischer, Böeseken and others has made it clear that the linkage of cellulose is of the normal type (main valence). The cellulose polymer is known to be composed exclusively of glucose units and that they are linked together in the normal way. The question to be resolved is whether the glucose units are linked together in one and the same type of linkage or whether the glucose units are linked together in different types of linkage. Studies on the yield of cellobiose since 1921 and on the kinetics of the decomposition of cellulose (by Freudenberg et al.) have shown that there is only one type of linkage in cellulose and that it follows the type of cellobiose. Therefore, in the question of whether to employ low molecular weight or main valence chains, the latter position was naturally accepted. At that time, W.N. Haworth, H. Staudinger, Kurt H. Meyer and others held this unified theory of cellulose bonding, and this is still the case today.”

The following descriptions3) supplement the above question of "Is cellulose formed by low molecular weight molecules linked together by lattice forces?": Emil Fischer's view that cellulose consists of long chains of glucose linked together by normal valences was widely accepted in the early 1900s, and Freudenberg also strongly supported this view. However, various influences, including misinterpretation of X-ray data, later led to the view that cellulose consists of simple mononose or biose molecules linked together by OH groups with secondary valences.

In this context, in 1921, two years after the death of Emil Fischer (1919), Freudenberg published a paper in which he concluded that cellulose is a completely uniform chain molecule, with each glucose unit linked to the next glucose unit in the form of cellobiose. This was the first correct structure of a polymeric natural substance.4)

After the structure of cellobiose was proven to be 4-β-D-glucopyranosyl-D-glucopyranose in 1926, Freudenberg published an extract of the final formula for cellulose in Fischer's carbohydrate notation in 1928. In the same year, Haworth came to the same conclusion.

The above-mentioned work on the structure of cellulose is based on the results of the following studies 1) and 2). An overview of these studies is given below.

1) Consideration of the cellulose decomposition reaction from the perspective of cellobiose yield.
2) Comparison of optical rotation and reaction rate using oligosaccharides and polysaccharides.

3.1.1. Consideration of the cellulose decomposition reaction from the perspective of cellobiose yield 2), 3)

Freudenberg was interested in "how many cellobiose linkages exist in cellulose" at that time.2) Cellobiose acetate was obtained in a yield of 30-40% in the acetolysis of cellulose. Freudenberg also investigated how much cellobiose was decomposed during the acetolysis reaction, and it was found that at least about 20% cellobiose (acetate) was degraded in this reaction. In other words, assuming that further cleavage of the generated cellobiose occurs during the reaction, he calculated that about 60% cellobiose acetate should be generated in this reaction. According to Werner Kuhn's kinetic analysis, acetolysis of a homogeneous polymer in a homogeneous solution yields a maximum of 30-35% cellobiose acetate. However, a large amount of cellobiose acetate is removed from the mixture by crystallization. Kuhn's analysis predicted a yield of 67% of cellobiose under these circumstances.

Freudenberg considered the results of this experiment and concluded that the yield relationship of cellobiose could be reasonably explained if the glucose molecules in cellulose were linked to each other in the cellobiose type, and therefore there were no different linkage patterns in cellulose, but rather a single linkage pattern throughout the entire chain.

3.1.2. Comparison of optical rotation and reaction rate using oligosaccharides and polysaccharides [2), 3)]

In addition to the above-mentioned study on cellobiose, he compared the optical rotation and reaction rate of the cellulose-type oligosaccharides and polysaccharides. First, the study on optical rotation is introduced in the following.

For example, linear *n*-saccharides, such as cellotriose, are composed of the following three different units of glucose:

1) A terminal unit with an aldehyde group (a)
2) A middle unit (m)
3) A terminal unit located at the other end (e)

These three components show different optical rotatory, and the optical rotation of cellotriose is considered to be the sum of the different optical rotatory of these three, i.e., the tip unit (a), the middle unit (m), and the end unit (e). In case of cellulose, almost all of its constituent units are in fact middle units (m). If the above ideas are correct, the average molecular rotation per glucose unit of a saccharide consisting of a certain number (n) of glucose units can be expressed by the following formula.

$$\frac{[M]_n}{n} = \frac{a + e + m\,(n\text{-}2)}{n} = a + e - m + \frac{n - 1}{n}(2m - a - e)$$

Freudenberg plotted the ([M]n/n) values of various cellulosic sugars, from cellobiose to polysaccharides, against (n-1)/n and confirmed that they all fell on a straight line. Therefore, the optical rotatory of the intermediate unit is always constant, whether in a triose, a tetraose, or a polysaccharide. In other words, the linkage pattern between each glucose unit must always be the same since the optical rotatory of one glucose unit is exactly the same as that of the glucose unit immediately adjacent to it.

As another method to prove the uniformity of the linkages in the cellulose chains, Freudenberg used a similar approach to study the rate of degradation. He performed a homogeneous hydrolysis of cellulose with 50% H_2SO_4, which does not give damage (i.e. degrade) the glucose, and then measured the amount of -CHO liberated by iodometric titration after the reaction.

In this reaction, glucose generated is not degraded at all. On the other hand, cellobiose shows a decomposition rate that can be measured. If the initial reaction rate is examined, the initial reaction rate of cellotriose is smaller than that of cellobiose, and is even smaller for cellotetraose, and is only about one-third that of cellobiose for cellulose. If the decomposition rate constants of the linkages between (a)-(m), (m)-(e), and (m)-(m)* in tetrasaccharides or more are expressed as A, E, and M, respectively, the initial reaction rate constant V of the decomposition reaction of a sugar with N linkages can be expressed by the following equation, which is exactly the same type as the case of the additivity of optical rotatory.

* (a): The end unit with the aldehyde group, (m): The middle unit, and (e): The end unit located at the other end.

$$V = \frac{A + E + M\,(N-2)}{N}$$

The V of cellotetraose calculated from the V of cellulose and cellotriose is 0.53×10^{-4}, which is in good agreement with the actually measured value of 0.51×10^{-4}. This result can also be explained only if there is only one type of linkage between glucose units in both the cellulose chain and the cellulosic oligosaccharides.

3.1.3. Other matters concerning cellulose

Freudenberg published the above results on cellulose. However, there was strong opposition and difficulty at the time, as shown in the description below, because the concept of polymers was not yet well understood. 2)

"I hope it is now clear that the study on the structure of polysaccharides such as cellulose and starch (see 3.5.) requires different methods from those generally used for low molecular weight compounds. When these studies were carried out more than 30 years ago (from 1958), the concepts of macromolecules, chain molecules and polymerization had not yet been clarified. Therefore, it was even more difficult to make progress in research in such a situation. In the first half of the 1920s, many people disagreed with my views on the main valence linkages and chain structure of cellulose. Therefore, I had to fundamentally resolve this ambiguous problem."

There is also a description regarding the study of cellulose that "I could only report this with extreme caution, because the foundation was still too weak."4) One example of this is the following statement3).

Freudenberg emphasized his findings on the uniformity of linkages in cellulose, while recognizing that the fact that Haworth had decomposed methylated cellulose to 2,3,6-trimethylglucose (which he confirmed using fully methylated cellulose) did not logically exclude the presence of 1,5'-linked glucofuranose units.

Many years later Mark observed that “the cellulose problem might have been resolved sooner if Freudenberg had been more combative in the early 1920s”. 3)

3.2. From cellulose to other natural polymers including lignin

Freudenberg stated the following things in response to the above cellulose findings. "Impressed by the orderliness and simplicity that I had encountered in the molecular structure of cellulose, I set myself to enquire if the same sort of situation might prevail in other polymeric natural materials as well."6) He wrote on lignin in particular, "I was convinced from cellulose that lignin must also have a regular principle of organization."2) He also wrote, "Had it not been for the confidence in an orderly constitution of polymers that I had received from my early work on cellulose, I should never have risked attacking the problem of lignin, for not even the haziest notions about the nature of polymeric molecules were developed at that time."6) Although it took many years for his lignin research to achieve a breakthrough, these descriptions give us a glimpse of the confidence he had gained from his cellulose work and his conviction in tackling lignin research.

3.3. Lignin

Freudenberg stated about lignin as follows; "Lignin is composed of C_6C_3 building units that are irreversibly linked in a wide variety of ways. This makes the lignin problem extremely complicated, but it is a rewarding task to unraveling it."2) Freudenberg obtained a stable position in 1922. At that time, he decided to take on the work on lignin, but he stated that it took 30 years to make a breakthrough discovery (he described the progress of lignin research as "depressingly slow"6)) and another 17 years to evaluate it.4)

3.3.1. His first work on lignin

In the opening chapter “A. The Beginning” of his book6) published in 1968 at the age of 82, Freudenberg wrote the following, looking back on the history of his own lignin research. "In response to repeated requests I decided to retrace the diverse and devious pathways followed in the last five decades." In this chapter, there is the description about his encounter with lignin.6)

“My first encounter with lignin came as a matter of chance. In February, 1916, during my military service in World War I, I received an order to report to Berlin. My former mentor, Emil Fischer, had reclaimed me for the following reason: Chromium salts and vegetable tannins had become scarce in Germany and substitutes for them were being sought. In order to determine whether spent sulfite liquors could be used either as an expander for other tanning agents or to accelerate their effect, an improvised research program on sulfite liquors was started."

From his work on lignosulfonates, which is included in sulfite spent liquor, and his earlier work on tannins, etc., he realized that lignin and tannins did not seem very remote in their properties, and that he was convinced that lignin belongs to the phenols at this time (probably between 1916 and 1922).6) His research on lignosulfonates was completed in 1922.

3.3.2. Background on the aromatic nature of lignin and the C9 unit notation

After the clear order of cellulose was demonstrated, Freudenberg had the opinion as early as 1929 that lignin is also an aromatic polymer formed according to an order that can be understood4). However, he had to defend and justify his opinion against fierce attacks for more than 20 years4). This section will describe the situation at that time regarding the aromaticity of lignin6). Although it will deviate somewhat from Freudenberg's achievements, it is related to Freudenberg's later works on DHP and other topics.

Despite the fact that research had confirmed the aromatic nature of lignin, attacks on this property continued even after 1943. The theory that lignin was not an aromatic substance had enthusiastic supporters, and it took more than 25 years (probably between 1923 and 1948) for this opinion to disappear. One of the reasons for this was that it was originally believed that lignin was produced as follows:

1) Lignin existed in the wood as a carbohydrate-type compound.
2) This product was transformed into an aromatic artifact during its isolation.

The progress by which the aromaticity of lignin was confirmed is outlined below6). In 1927, Herzog and Hillmer observed the similarity between the ultraviolet absorption spectra of spent sulfite liquors and those of coniferin and isoeugenol. They also found similarities between lignin itself and derivatives of coniferyl alcohol by the comparison of these ultraviolet spectra. In 1929, Freudenberg et al. found that the refractive index of spruce lignin, either as it exists in wood or even when isolated, is closely similar to that of iodobenzene, vanillin, guaiacol, or eugenol. Spruce lignin is therefore an aromatic substance while still in the wood. The same conclusion was reached by Lange (1944,1945) when he measured the ultraviolet absorption of lignin directly in wood. From about 1930 onwards, arguments regarding the aromaticity of lignin strengthened year by year due to the research on vanillin yield and the studies by many researchers, including H. Erdtman (1933), B. Holmberg (1934-42), and E. Adler (1943).

The C9 unit for lignin was proposed by B. Holmberg in 1942, and became definitive around 1960. 6) An argument in favor of this concept was presented from Hibbert's laboratory (1939, 1943). Ketones which all had a C_6-C_3 skeleton were isolated by heating conifer woods with ethanol and hydrogen chloride. These ketones were the first degradation products of lignin in which the guaiacylpropane skeleton had remained intact. 6)

Here, I would also like to mention another achievement of Holmberg, who proposed the C9 unit for lignin.6) Holmberg began to use model compounds in research on the sulfite cooking of wood around 1935, and these researches led to the confirmation of the presence of benzyl alcohol (benzyl ether). In relation to this work, there is a description by Freudenberg12) which suggests that Holmberg was one of the earliest lignin chemists who used model compounds in experiments: "Since Holmberg established the reactivity of phenylcarbinol and its aliphatic ethers with bisulfite and compared it with the formation of lignosulfonate, detailed studies using model compounds have been increased on various reactions of lignin." He also conducted research work on thioglycolic acid lignin. In "Constitution and Biosynthesis of Lignin," co-authored by Freudenberg and A. C. Neish in 1968,6) the first page of the chapter contributed by Freudenberg contains the following sentence: "Dedicated to the Memory of Bror Holmberg (1881-1966)."

3.3.3. Situation before he started the DHP works

In the following subsections, Freudenberg's works on DHP and related topics will be described. The DHP is referred to as "Dehydrierungs-Polymerisat" in German in the collection of his lectures in Japan 2), and as "dehydrogenation product" in Freudenberg's book.6)

First, the situation before his DHP work began is explained by citing the following description from the collection of his lectures in Japan 2).

Although much has been clarified about lignin synthesis in the last few years (as of 1958), these findings are based on earlier observations. For example, the sap-rich layer between the bark and wood of spruce, known as the cambium, produces a large amount of the coniferin, the glycoside of coniferyl alcohol, during the growth period. This fact was revealed by Ferdinand Tiemann in Berlin in 1870-1880, who already expressed the opinion that there may be some biosynthetic relationship between lignin and coniferin. Peter Klason of Sweden further developed on this idea. He proposed a structural formula for a dimer consisting of coniferyl alcohol and coniferyl aldehyde, which has a phenylcoumaran structure. Herzog and Bror Holmberg also considered lignin to be related to coniferin. I had already proposed a structural formula for the phenylcoumaran structure in the early stages of my research based on the presence of etherified phenyl groups in lignin, but mine was differed from Klason’s one in that it was part of the polymer structure. Shortly thereafter, H. Erdtman discovered that the product obtained by Cousin and Hérissey in 1908 from isoeugenol using mushroom dehydrogenase had a phenylcoumaran structure, recognized its similarity to lignin, and proposed the theory that lignin is formed by dehydrogenation of guaiacylpropane building blocks with an oxidized side chain. After 15 years, we began to study the enzymatic dehydrogenation of coniferyl alcohol based on our previous research. We produced coniferyl alcohol from its glycoside coniferin and its benzoate which is found in "Siamese benzoin" at the time, but later we were able to produce it synthetically.

There are also the following descriptions in another reference. 6) As stated above, Klason believed that lignin was derived from oxidized coniferyl alcohol. As for Cousin and Hérissey, they discovered in 1908 that two molecules of isoeugenol were condensed with iron (III) chloride to form dehydrodiisoeugenol, and that dehydrogenase had the same effect as iron salts. Around 1933, Erdtman interpreted the results of isoeugenol as the dehydrogenation of phenol. Erdtman applied the results of isoeugenol to lignin, and suggesting that lignin is also produced by dehydrogenative polymerization. Thus, Klason's theory that lignin is an oxidized form of coniferyl alcohol was characterized as being the product formed by dehydrogenative polymerization.

The enzyme used by Cousin and Hérissey (1908, 1909) for the dehydrogenation of phenol, i.e., crude phenol oxidase obtained from mushroom juice, was not regularly available. A clear decision is also hampered by the nature of the mushroom extract, for heavy metal ions, which also catalyze the phenol dehydrogenation even when present only in traces, are difficult to remove or exclude from the system. As for the enzymes, Higuchi et al. discovered that the phenol dehydrogenase in mushrooms was laccase in 1958, and proposed that peroxidase was involved in the lignification of plant tissues in 1959. 13)

3.3.4. Research work on DHP

There are following descriptions that give a glimpse into his motivation why he began to study on DHP.

- Since degradation (of lignin) would not work, the course of the growth of the molecule had to be examined6).
- Freudenberg realized that there was not much to be learned from the analysis and degradation of these persistent polymers (lignins), so he turned to model synthesis methods. Coniferyl alcohol and its analogues were converted by dehydrogenases into products that were resembled lignins, and these products did not involve the difficulties of isolation and purification that are encountered with plant lignins.3)

The following descriptions, those are summarized from the collection of his lectures in Japan 2), show what Freudenberg did in his DHP and its related work. Only the main points are described here in order to understand the whole picture.

- The background of DHP (see 3.3.3.).
- Softwood lignin is demonstrated to be produced by the dehydrogenation reaction of coniferyl alcohol by comparing DHP and MWL.
- The mode of linkages in lignin was examined by terminating the DHP reaction at an early stage.
- DHP has no optical activity.
- Quinone methides can react with hydroxy groups, other than water.
- Confirmed the presence of coniferin and laccase in the cambium region.
- Indirectly confirmed the presence of β-glucosidase using indican.
- Administration of ^{14}C-labeled coniferin and phenylalanine to trees.
- The γ-position of the side chain in lignin is the source of formaldehyde generated by acid treatment of lignin.
- *l*-coniferin, which has *l*-glucose as a glycoside instead of *d*-glucose, is not incorporated into lignin.
- Sinapyl alcohol alone did not produce DHP. However, DHP was produced by using coniferyl alcohol together with sinapyl alcohol.

These matters will be explained in more detail below.

As already mentioned above, Freudenberg decided to take on a task on lignin in 1922, and it took him 30 years to make the first real breakthrough4). The first real breakthrough was the results of the study on DHP11) published in 1952. 6) It was also in a situation where another researcher published a paper in 1948 stating that lignin was a pure aliphatic compound4).

Freudenberg first performed the enzymatic dehydrogenative polymerization of coniferyl alcohol in 1943.14) When coniferyl alcohol is reacted with laccase, a phenol dehydrogenase, and atmospheric oxygen (or with peroxidase and hydrogen peroxide), an amorphous dehydrogenation product (DHP) is obtained as precipitate. Chemical and physical comparison of the resulting DHP with milled wood lignin (MWL) demonstrated that both products were identical except for minor quantitative differences (1956, 1960). 2), 4) Freudenberg stated from these results that "It has become clear that softwood lignin is produced by the dehydrogenation of coniferyl alcohol, and that at least 95% of softwood lignin is composed of coniferyl alcohol."2) As to the MWL, Björkman published papers on MWL including: "Isolation of Lignin from Finely Divided Wood with Neutral Solvents" in Nature in 1954 and "Studies on finely divided wood. Part I" in Svensk Papperstidn in 1956. Freudenberg compared the DHP with MWL, and the MWL became available at a time when his work on DHP was progressing. These facts show that the availability of MWL also contributed to the progress of his DHP work.

If the dehydrogenation reaction was terminated early, it is possible to capture the moment when the coniferyl alcohol has already disappeared, but a small amount of high molecular weight lignin is beginning to precipitate. At this moment, the reaction mixture contains products consisting of two coniferyl alcohols. Freudenberg states that "These circumstances enable us to clarify the structure of lignin, and thus find the long-awaited key to unlock the door of lignin chemistry."2) The intermediate products (lignols) that formed by the premature termination of the dehydrogenation reaction were separated by column chromatography and their compositions were elucidated. In 1952, this investigation led to the isolation of the product with a β-5 linkage (dehydrodiconiferyl alcohol)11). Freudenberg stated that "the detection of dehydrodiconiferyl alcohol encouraged us to investigate on a broad basis the intermediates of dehydrogenation of the *p*-hydroxycinnamyl alcohols."6)

After the linkage types of lignin became clear, Freudenberg's student Horst Nimz (who wrote an obituary for Freudenberg in Holzforschung5)) degraded spruce and beech lignins into dimeric, trimeric and tetrameric phenols using very mild hydrolysis conditions and thus provide a constitutional scheme for beech lignin. These investigations confirm Freudenberg's work and provide further evidence of the correctness of the oxidative coupling reaction of *p*-coumaryl, coniferyl, and sinapyl alcohols to the various lignins, whereby only the ratio of these alcohols varies. 4)

Freudenberg also investigated the dehydrogenative polymerization of sinapyl alcohol, and the main points of the results are summarized below6).

- No lignin-like polymer is produced when sinapyl alcohol alone was used in dehydrogenative polymerization (1951, 1952, 1958).
- However, a lignin-like DHP is produced when the ratio of coniferyl alcohol to sinapyl alcohol (1:1) was used (1952).
- When sinapyl alcohol is present in excess relative to coniferyl alcohol, the excess sinapyl alcohol is not incorporated into the polymer (1960, 1962).
- The above findings are consistent with the fact that no lignins have been found with a methoxy content in which the ratio of sinapyl alcohol to coniferyl alcohol is greater than 1:1 (approximately 23.3% OCH_3).
- When a molecular mixture of 5-deuteroconiferyl alcohol and sinapyl alcohol is dehydrogenated, the relative loss of deuterium is about the same as in the experiment with coniferyl alcohol alone, i.e., about 45% (1961, 1963). Coniferyl alcohol, therefore, seems to act in similar manner in the presence or absence of sinapyl alcohol.

The reaction mechanism of coniferyl alcohol by dehydrogenative polymerization, i.e. how coniferyl alcohol is dehydrogenated and then produces various dilignols (dimers) and oligomers, is described in the cited book6).

Another important point is that the enzyme used in the dehydrogenative polymerization only acts on the dehydrogenation of phenolic hydroxy groups, so the DHP, native lignin, and its degradation products are all optically inactive6), 14).

Freudenberg also investigated the linkage between lignin and carbohydrate6). He obtained a product in which sucrose was added to the α-position of the quinone methide by the dehydrogenation of coniferyl alcohol in a concentrated cane sugar solution. This compound was separated from many other products, mainly lignols (1959, 1960). He suggested that this is probably the main way in which lignin is grafted onto the carbohydrates of the cell wall.6), 14)

3.3.5. About the 1952 paper that Freudenberg called the "first real breakthrough" in lignin

Freudenberg first performed the enzymatic dehydrogenative polymerization of coniferyl alcohol in 1943 14), but the paper that he described as the first real breakthrough was published in 1952 11). What was described in this paper?

For reference, the abstract of the paper is given below. Note that at that time, it was not yet known that the enzymes that catalyze dehydrogenative polymerization were laccase or peroxidase (see the description of Higuchi et al. in 3.3.3). As already mentioned, this paper reported that it was the first to obtain a product with a β-5 linkage (dehydrodiconiferyl alcohol). The abstract below contains the strong statement that "Therefore, there is no doubt that this substance is an essential component of natural lignin."

Improved procedures are given for the preparation of coniferyl and sinapine alcohols. The dehydrogenative polymerization of coniferyl alcohol can be confined to a crystalline dimeric stage, dehydrodiconiferyl alcohol. Its constitution has been determined. Upon further dehydrogenation, it is transformed into lignin-like products. In addition to fungal redoxase, the redoxase system of lignified tissue can also be used for the preparation of dehydrodiconiferyl alcohol. Therefore, there is no doubt that this substance is an essential component of natural lignin.

3.3.6. Administration of ^{14}C-labeled coniferin and phenylalanine to trees 2), 6), 12), 14)

Freudenberg also investigated the administration of ^{14}C-labeled phenylalanine (1963) and ^{14}C-labeled coniferin (1953, 1957) to trees. He administered DL-phenylalanine labeled with ^{14}C at the middle carbon of the side chain to spruce and confirmed that phenylalanine was converted to coniferin. It was reported here that when the administration of labeled phenylalanine to the plant was terminated midway, the glycosides of labeled *p*- hydroxycinnamyl alcohols were obtained with a radioactive yield of about 0.03% (1965, 1967, 1969). They also confirmed that the administered phenylalanine is fixed in the xylem as lignification progresses.

Similar results were obtained when coniferin labeled with ^{14}C at the middle carbon of the side chain was administered to tree. The three types of wood, namely, wood obtained by administering radioactive phenylalanine, that obtained by administering radioactive coniferin, and DHP prepared from radioactive coniferyl alcohol, were compared by the several degradation reactions used in lignin analysis. The result showed that the obtained degradation products were radioactive and had similar yields as expected. Freudenberg concluded from these results that softwood lignin is produced from coniferin, and that softwood lignin and *in vitro* DHP are produced in the same manner.2)

They also confirmed that when *l*-coniferin containing *l*-glucose was administered to trees instead of the *d*-coniferin, it was not incorporated into lignin (1954, 1955, 1956). 2), 6), 12), 14)

3.3.7. Indirect confirmation of the presence of β-glucosidase using indican2), 6), 12)

In spruce and other conifers, a high concentration of coniferin is found in the tissues in the region around the cambium during the vegetative period. Traces of free coniferyl alcohol can also be detected in the sap from cambial tissues of freshly felled trees, but the low stationary concentration present is hardly sufficient to account for the profuse lignification going on. As mentioned above, aglycone-labeled coniferin administered to a plant was irreversibly incorporated into lignin, and the resulting lignin also gives the same degradation products as normal lignin by degradation analysis. On the other hand, laccase and peroxidase have no effect on coniferin even in the presence of a large quantities, which means that it is only the free phenolic alcohols and not their glucosides that can be transformed by the dehydrogenases into lignin. It was therefore suspected that a β-glucosidase must be present in the cambium tissues. However, attempts to detect a glucosidase in the cell sap were fruitless. It was therefore concluded that the enzyme must be firmly attached to the tissue. 6), 12)

Freudenberg then conducted experiments with indican, a type of glycoside, to demonstrate the presence of glucosidase (1952). Indican is a nearly colorless, water-soluble glycoside of indoxyl that is cleaved into indoxyl and glucose in the presence of β-glucosidase. The liberated indoxyl is then oxidized within a few minutes by O_2 in the air to indigo, which produces a color. In order to detect the β-glucosidase histologically, thin sections of the growing shoots were moistened with a solution of the glucoside indican, and it was confirmed that the indigo color was most pronounced in areas where lignification was currently in progress, although the color did not appear in areas where lignification was complete. This indirectly confirms that the glucosides, including coniferin, encounter β-glucosidase between the cambium and the wood.

He also left the interesting description about β-glucosidase as follows⁶⁾:

There may be a simple connection between lignification and the timberline. The timberline on mountainsides or in the far north is a limit beyond which woody plants cannot grow in clusters to a height of more than 5 to 6 feet. G. Sandberg (1960) has shown that in Lapland the limit of the birch forests is a function of the temperature. Above this limit the temperature is not high enough for regular lignification. The temperature coefficients of the various enzymes involved in lignification are not generally known. One or the other of these enzymes may be the limiting factor. It is known, however, that one of the β-glucosidases has a characteristically high temperature coefficient (Duerksen and Halvorson, 1958).

3.3.8. Methods for Lignin Analysis

This section describes the Freudenberg's contributions to analytical methods for lignin.

Freudenberg was contributed to produce samples of lignin suitable for elementary and other analysis, and spent considerable period to develop appropriate analytical methods, devising or improving procedures for the determination of alcoholic hydroxy groups, phenolic hydroxy groups, and aryl benzyl ethers.3) The mode of action of hydroiodic acid on lignin confirmed that the methoxy groups were of aromatic origin (1929).6)

He also made the following contributions to alkaline nitrobenzene oxidation6), which is the important analytical method for lignin chemistry.

In 1904, Grafe obtained a minute amount of vanillin by heating spent sulfite liquor with alkali. In 1939, Freudenberg reported that the yield of vanillin was augmented if carefully controlled amounts of air were present during the alkaline pressure reaction. This method was applied industrially after modifications, on a large scale in Canada and the USA. He also reported that much higher yield of vanillin was obtained when spent sulfite liquors, lignin or even wood were oxidized with aqueous alkali and nitrobenzene at 160 °C (1939, 1940).

3.3.9. Generation of formaldehyde from lignin. 2), 6), 12)

When lignin is treated with acid, especially sulfuric acid, formaldehyde is generated from part of the γ-position of the side chain in lignin. Freudenberg contributed to the clarification of this reaction.

It was known in the early days of lignin chemistry that distillation of hydrochloric lignin with strong acid gave a distillate that yielded a precipitate with phloroglucinol. This was originally assumed to be due to pentosans. Freudenberg (1927, 1928) identified the source of this precipitate as formaldehyde, not furfural, and estimated that approximately 2-3% formaldehyde was formed based on the lignin content (1928). He stated that this amount was remarkably large considering its low molecular weight⁶⁾. It was found by Freudenberg that cinnamyl alcohol liberates formaldehyde under the same conditions as lignin (1938), therefore the three-carbon side chain was taken into consideration as the potential source of the aldehyde.

It was not until 1943 that it became clear from work on lignin models, e.g. 1-guaiacyl-1-oxopropan-3-ol, that the formaldehyde is produced from the terminal primary alcoholic group of the side chain (1943). The question was finally resolved when it was shown that numerous model substances such as benzyl alcohol, dibenzyl ether and phenylpropanones of the above type all release formaldehyde under the same conditions as lignin (1947). Experiments carried out much later with a biosynthetic lignin made from coniferyl alcohol with a radioactive label in the terminal position of the side chain gave rise to radioactive formaldehyde under the same conditions (1953).⁶⁾

3.3.10. Other things about lignin: Mistletoe lignin⁶⁾, ¹⁴⁾

Freudenberg left the following interesting description on lignin in mistletoe ⁶⁾.

The lignin of *Viscum album*, the central European mistletoe, deserves interest. The plant is actually a dicotyledon which occurs in three varieties that are morphologically indistinguishable. One sort grows on numerous deciduous trees and can be transplanted within this group, e.g. from poplar onto apple trees or vice versa. The second variety grows on pines and cannot be transferred to hardwoods or other conifers. The third variety grows on silver fir (*Abies alba*) and can sometimes be grown with difficulty upon spruce and larch, but not on pine. It has been found that the mistletoe from deciduous trees contains a hardwood lignin while that from the two conifers contains a softwood lignin (1965). It seems that the mistletoe withdraws the nutrients for its lignin synthesis from the host plant. In accordance with this postulate, mistletoe does not give an indigo staining with indican (see 3.3.7) and therefore does not contain a detectable β-glucosidase. Consequently, lignification in mistletoe is not preceded as in other plants by a glycosidic cleavage of glucosides of the three *p*-hydroxycinnamyl alcohols. Mistletoe seems to receive the preformed *p*-hydroxycinnamyl alcohols directly from the host tree. It is not known if the host tree delivers the alcohols (*p*-hydroxycinnamyl alcohols) to the mistletoe before glucosidation or after releasing them from their glucosides.

3.3.11. Closing of the lignin section

Freudenberg presented a representative model formula for softwood lignin composed of 18 C_6-C_3, which takes into account the wide range of published results for coniferyl alcohol, its analogues, and important combinations of lignols[3), 6), 14)].

Freudenberg left the following impressive words about lignin. I introduce these words as the conclusion of the lignin section:

“The initial question, whether lignin has an understandable architecture, is answered: its constitution is clearly understood; but the classical concept of chemical architecture and methods must be extended and modified regarding this peculiar natural product.” 6)

"I was convinced based on cellulose that lignin must also have a regular principle of construction. This conviction did not change, although there seemed to be no regularity in the formation of lignin at first. In the end, however, it was found that there was a definite order, or principle of construction, although it was quite different from what I had first thought."2)

3.4. Stereochemistry 2), 4)

Freudenberg's research on stereochemistry can be summarized as follows: he elucidated the absolute configurations of important natural substances such as α-hydroxy acids, α-amino acids, terpenes, and steroids by determining the correlative configuration and applying his shift theorem of optical rotation, and resolved some contradictions that had arisen due to the optical rules. The highlights of his stereochemical work were the discovery of the shift theorem of optical rotation and correlative configuration determinations, such as the connection of the simplest optically active hydrocarbons to the absolute configuration of glucose4).

The following three of Freudenberg's achievements in stereochemistry are introduced here:

1) Completion of the family tree of D- and L-series monosaccharides (Zukker-Stammbaum) and related matters.
2) Discovery of the "Shift theorem of optical rotation" (Verschiebungssatz der optischen Drehung).
3) Development of a method to relate configurations.

3.4.1. Completion of the family tree of D- and L-series monosaccharides (Zukker-Stammbaum) and related matters.4)

The designation D and L of sugars refers to the position of the hydroxy group at the chiral center furthest from the carbonyl group, i.e., next to the primary hydroxy group. It is on the right in all D-sugars, and on the left in all L-sugars. The series designation D or L has been used for carbohydrates, α-hydroxy- and α-aminocarboxylic acids, and the *R*, *S* nomenclature of Cahn, Ingold and Prelog is used for all other optically active compounds.

Wohl and Freudenberg were able to complete the "family tree of monosaccharides " of the D- and L-series in 1923 using the projected notation of monosaccharides introduced by Emil Fischer, by experimentally demonstrating the configurational transitions from glucose via tartaric, malic, and glyceric acids to glyceraldehyde. 4)

Regarding this, Freudenberg himself wrote in his book6) that "Emil Fischer had established the systematic family tree of the monosaccharides." However, Freudenberg also describes the situation when Emil Fischer proposed the family tree of monosaccharides in another paper entitled “Emil Fischer and his Contribution to Carbohydrate Chemistry”15), as follows: “Emil Fischer suggested the now well-known family tree of the D-series of the aldoses, based upon their relationship to D-glyceraldehyde, despite the fact that this aldehyde and a number of other sugars were not known in his time. Figure 1 (the family tree of the D-series shown in this article) deviates in another point from the original nomenclature of E. Fischer. He had originally assigned the prefix *l* to the gulose, idose, xylose, threose series, to which we now assign the prefix D.”

The configuration of α-hydroxycarboxylic acids was determined by Wohl and Freudenberg according to the position of the hydroxy group next to the carboxy group.

Initially, "d" and "l" were used for the direction of rotation. Wohl and Freudenberg introduced the designation (+) and (-) for the direction of rotation and "d" and "l" for the steric series.

3.4.2. Discovery of the "Shift theorem of optical rotation" (Verschiebungssatz der optischen Drehung)2)

Freudenberg wrote that his 1921 observations on mandelic acid were contributed greatly to the discovery of the "Shift theorem of optical rotation" (Verschiebungssatz der optischen Drehung). Mandelic acid is strongly levorotatory, and its amides are also levorotatory. Therefore, according to Hudson's rule, the hydroxy group of mandelic acid must be written on the left side. Levene and Hudson formulated the amide and hydrazide rule in 1915 and 1917, which states that all α-hydroxycarboxylic acids that yield dextrorotatory amides or hydrazides belong to the D series. However, when levorotatory mandelic acid was hydrogenated to levorotatory hexahydromandelic acid and its amide was prepared, the resulting product showed dextrorotatory properties. Thus, Hudson's amide rule fails in this case, although this rule is applicable in many cases. However, the rule becomes more accurate if we define it as follows: "α-Hydroxy acids that exhibit a rightward shift in optical rotation when converted to amides belong to the D-series." According to this definition, the relationship between mandelic acid and hexahydromandelic acid is not contradictory.

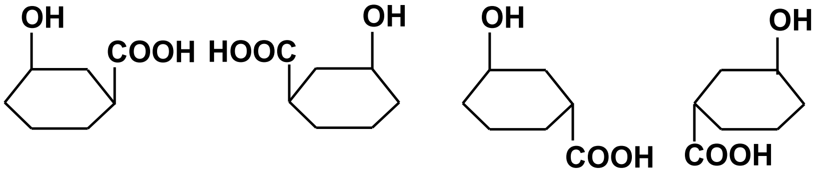
This rule, which Freudenberg named as the "Shift theorem of optical rotation" (Verschiebungssatz der optischen Drehung)," has proven to be extremely useful. In general terms, it states that an analogous change in an equivalently configured chiral center leads to a change in the optical rotation in the same direction.

The absolute configuration of numerous natural substances has been determined by the use of the shift theorem of optical rotation, such as those of α-amino acid, atrolactic acid, and catechins[4)]. In addition, the configuration of catechins was elucidated for the first time by combining the shift theorem of optical rotation and cis/trans stereoisomers.[2)]

3.4.3. Development of a method to relate configurations

Freudenberg stated that "The method of relating configurations was first established for sugars by my unforgettable teacher, Emil Fischer. He used two important methods in this work."[2)] The first method involves directly modifying a compound chemically while protecting the asymmetric carbons present in the molecule. The second method is described as follows. When a molecule is altered, it may become a substance in which both halves of the molecule have an identical symmetrical structure. In this case, if the lower half of the molecule is rotated 180 degrees on the paper, the optical rotation of both halves of the molecule cancels each other out. By altering the molecule in this way and observing whether it retains or loses optical activity, we can conclude the mutual configurational relationship of the two halves of the molecule.

Freudenberg also discovered the third method in addition to the two proposed by Emil Fischer, a method that combines cis-trans configuration with chemical alternation. This method is explained using cyclohexanol-3-carboxylic acid-1 as follows.



It is possible to determine whether a hydroxy acid has a cis or trans configuration by confirming whether a lactone is formed or not. Once this has been determined, one of the racemates is optically resolved into its enantiomers and the configuration of the carbinol group is confirmed by an appropriate method. Thus, the configuration of the tertiary carbon atom to which the carboxy group is attached can be determined. In this way, the configuration of the tertiary carbon atom can be determined from the secondary carbinol. This method makes it possible to relate the entire system of terpenes and sterols to the configuration system of glucose and glyceraldehyde using synthetic chemistry alone.

3.4.4. Other issues related to stereochemistry

The following statement remains regarding Freudenberg's interest in stereochemistry:

Freudenberg was aware of the importance of stereochemistry for chemistry and physiology, because optically active natural products occur with a consistently very high degree of optical purity. So he continued to follow the stereochemical literature even in his old age. 4)

3.5. Starch 2), 4)

The following three things from Freudenberg's starch work are introduced in this section:

1) Elucidation of the branching positions of amylopectin.
2) Discovery of cycloamylose (cyclodextrin).
3) First assumption that amylose has a helical structure.

3.5.1. Elucidation of the branching positions of amylopectin 2), 4)

Starch is composed of unbranched amylose and branched amylopectin. The concept that starch chains are branched was first proposed by Horst Elsner in 1935, and Staudinger came to a similar conclusion shortly thereafter based on viscosity measurements. However, the mode of branching was unknown at that time.

Freudenberg's laboratory established a method to produce a completely methylate starch without degrading it. In 1940, he reported that methanolysis using methanol/hydrochloric acid with fully methylated amylopectin, which was prepared with methyl iodide and lithium in ammonia at low temperature, yielded about 5% 2,3-dimethylglucose along with 2,3,6-trimethylglucose. Thus, the branching position was confirmed to be the 6-position of amylopectin.

3.5.2. Discovery of cycloamylose (cyclodextrin)2), 4)

One important problem in starch chemistry remained unsolved at the time of Freudenberg's investigations. In 1904, the Vienna bacteriologist Schardinger discovered a rod-shaped bacterium (named *Bazillus macerans*) that decomposed starch in a new way. Schardinger had isolated two crystalline products which he called α- and β-dextrin, and in 1935 Freudenberg discovered a third, γ-dextrin. Freudenberg contributed to the elucidation of the structures of these oligosaccharides.

In 1936-1938, Freudenberg reported that complete methylation and hydrolysis of these dextrins yielded only 2,3,6-trimethylglucose. And by using the kinetics of acetolysis and cryoscopic molecular mass determination of the crystalline methyl ethers, he confirmed that these dextrins were cyclic and contained only maltose linkages, thus demonstrating that they were cycloamyloses. This fact also explained their lack of reducing ability.

This result is considered to be the discovery of the first inclusion compound, which will be explained in the next subsection (3.5.3). 4)

3.5.3. First assumption that amylose has a helical structure2), 4)

In 1939, Freudenberg hypothesized that amylose has a helical structure4). The following Freudenberg's description from reference2) explains why amylose should have a helical structure, using the cycloamylose mentioned above.

The three cycloamyloses, namely α-, β-, and γ-cycloamyloses, are thought to be composed of six, seven, and eight glucose units, respectively, linked together in a maltose manner to form a ring configuration. When the molecular models are constructed, these cyclic oligosaccharides become hollow cylinders with diameters of the hollow parts of 6, 8, and 10 Å, respectively. Small molecules can enter the large hollow spaces and be held together by van der Waals forces. Therefore, Schardinger-amyloses are very easy to form an inclusion compound.

The α-cycloamylose reacts with iodine and turns a deep black-blue color like starch. β-cycloamylose produces brown iodine compounds, and γ-cycloamylose produces yellow ones. This suggests that the iodine compounds of α-cycloamylose and starch are very closely related. Now that the structure of cyclohexaamylose has been elucidated, the old iodine-starch reaction can be understood from a new perspective.

When a molecular model of α-cycloamylose is combined with a model of iodine, the iodine fits very well into the cavity at the right distance to form van der Waals bonds. Cramer and Borchert have found that cycloamylose is arranged to form long tubes in its crystalline state. In these tubes, the iodine is not in the form of I_2 molecules, but is arranged in chains with an average of 15 atoms evenly spaced. This structure of iodine results in an intense blue color.

The formation of tubes may also be postulated for starch. In fact, it is possible to form model of the tubular helical structures in starch that closely resemble the Schardinger amylose. It is therefore postulated that some parts of the starch chains have such a helical structure. Later, Rundle confirmed the helical structure of starch by X-ray diffraction. Therefore, for cycloamylose to be formed from starch chains by the action of the rod-shaped bacteria discovered by Schardinger, the positions of the chains that link to each other must be located in close proximity, i.e. the starch chains must have a circular, helical structure.

Amylose is unbranched and forms helical structures. Amylopectin, on the other hand, is highly branched and therefore has little ability to form helical structures, so the iodine-starch reaction is actually weakened.

3.6. catechin (2), (4)

Freudenberg wrote in the reference(2) that "In 1920, I decided to re-examine the chemical structure of catechin, which was then considered correct. This is because I became interested in it from a biochemical point of view."

His most notable achievements in this field were the elucidation of the constitution and configuration of catechins, the elucidation of the mechanism of acid-catalyzed polymerization of catechins, and finally the isolation of dicatechin, which made it possible to establish a constitutional scheme for catechin tannins. (4)

The following three things are explained here. In addition, the collection of his lectures in Japan (2) includes a figure summarizing the reaction pathways with a focus on cyanidin and explaining which reaction pathways Freudenberg's laboratory contributed to elucidating.

1) Method for the determination of the absolute configuration of catechin
2) Elucidation of the mechanism of acid-catalyzed polymerization of catechins
3) Discovery of novel hydroxyflavans

3.6.1. Method for the determination of the absolute configuration of catechin (2)

The absolute configuration of catechin was elucidated by the following three methods. Freudenberg contributed to the development of one of these methods.

1) Comparison of optical rotation taking into account the cis-trans conformation.
   (Freudenberg, see 3.4.2.)
2) Method of isolating the central part of *d*-catechin as deoxyadonite (Desoxyadonit) (Hardegger).
3) Method of asymmetrically synthesizing atrolactic acid according to Prelog's method.
   (Birch)

3.6.2. Elucidation of the mechanism of acid-catalyzed polymerization of catechins (2)

Catechins undergo changes when they are treated with acid, even at low temperatures. First, they form a water-soluble low molecular weight condensation product, and then a colored precipitate (phlobaphen) is formed when acid is applied for a longer period of time. The simplest hydroxyflavan that undergoes polymerization is 7,4'-dihydroxyflavan and he used it to study for the acid polymerization. As a result, Freudenberg concluded that catechin undergoes a bifunctional reaction, reacting electrophilically at C-2 and nucleophilically at C-6 or C-8⁴⁾. It was also confirmed that the reaction of the synthesized hydroxyflavans containing chlorine or methyl groups at the 6- and 8-positions did not show any change under acidic conditions or even when heated. 2) This result confirmed the correctness of the above-mentioned reaction mechanism of hydroxyflavans under the acidic conditions.

3.6.3. Discovery of novel hydroxyflavans 2)

Two types of hydroxyflavan with a hydroxy group at the 4-position were known in nature then. In addition to these, Leuco-robinetinidin-hydrate and Leuco-cyanidin-hydrate were synthesized in Freudenberg's laboratory and obtained as beautiful crystals.

3.7. Cyclic cations4)

While working with catechin, Freudenberg discovered the first phenyl migration, which proceeded with preservation of optical activity. This was published in 1927, and Freudenberg postulated a cyclic cation (two-electron three-center bond) as the intermediate for this rearrangement, which was first postulated at that time. This was then termed the "phenonium ion" by Cram in 1952. It was not until 40 years later that Olah, whose life's work was the extremely successful investigations on the structures, properties, and reactions of carbocations, highlighted Freudenberg's work in a report. He re-illustrated Freudenberg's original formulas from 1927 in his report, with the words, "Clearly, the concept of bridged phenonium ion was born."4)

3.8. Other matters related to research work

Freudenberg's achievements in carbohydrate chemistry have been introduced so far, including studies on cellulose, starch, and the establishment of the "family tree of monosaccharides " of the D- and L-series. Freudenberg made further contributions to carbohydrate chemistry, such as the hydrolysis of disaccharides, glucosides and acetone sugars, the establishment of the "system of methylpentoses", the preparation of cyclic acetates (orthoacetates) and the synthesis of crystallized methylated cellotriose4).

Freudenberg also conducted research on insulin, but he had to discontinue this research because the war made it impossible to obtain materials3).

4. Freudenberg's research style

Freudenberg's research style and its related things are introduced in this chapter using descriptions from the reference articles. 3)-5)

Freudenberg received his doctorate in 1910 in Berlin under the supervision of Emil Fischer at the institute, which was then the world's leading center for organic chemistry. Freudenberg worked as an unpaid assistant at the Chemical Institute in Berlin until 1914 and he inherited from Emil Fischer the essential characteristic of a researcher who always placed the experiment at the center, and remained faithful to this throughout his life.5) His revered teacher, Emil Fischer, was the subject of several eulogies, sometimes in connection with development of carbohydrate chemistry. Freudenberg also credited Fischer with the return of organic chemists to the study of organic Nature.3)

Freudenberg was described as active incessantly, *ohne Hast* (without haste), *ohne Rast* (without rest). 3) He was also described as working slowly, carefully, and tirelessly, with scrupulous attention to detail, and with the development of special analytical and other methods. He liked to leave a task properly finished and gave great attention to the composition of papers. He was opposed to presenting firm announcements of provisional conclusions. 3)

It was not until 1926 that he published his first work, with H. Urban, on spruce lignin, which he probably encountered through cellulose. From this point on, he became more and more intensive on research about lignin, which, unlike other natural substances, stubbornly resisted all conventional methods of structural elucidation. It was probably the difficulty of the object that may have prompted Freudenberg to do this, but it was also his characteristic tenacity in pursuing his goals and, last but not least, his love of natural materials and plants. 5)

Freudenberg provided a striking example of the correlation between chemical eminence and longevity.3) Freudenberg worked tirelessly and productively throughout his long career, and it was to his advantage that he always multitasked; whenever one project seemed to stall, he would turn to another until the first one cleared.3)

Finally, I will introduce his description "Freudenberg's Remarks on His Research Findings4)" written at the age of 89, in which we can find Freudenberg's ideas on how to conduct research.

In 1975, at the age of 89, Freudenberg wrote a final, short summary as a contribution to his catalogue of publications, which exists only in manuscript form. The first sentence reads:

"I have often been asked about the principles on which I have based my work and which results I like the most."

His answer:

"I have enjoyed every well-rounded and well-confirmed result; most of all, perhaps, the formulation of cellulose. In 1920, I was aware that I had taken the step towards high-molecular compounds with cellulose, but I could only report this with extreme caution, because the foundation was still too weak. Only when clean methylation was achieved and quantitative cellulose chemistry became possible was I able to combine the results of the British school with my own and consider the constitutional picture of the cellulose chain established. This gave me great satisfaction, and I was sure of my cause (1928). In stereochemistry, there were various bright spots: the correction of the optical rules by Hudson and van't Hoff through the discovery of the shift theorem of optical rotation and its extension to systems with more than one chiral center. Then, the physical foundation of the shift theorem by Werner Kuhn and the collaboration with him. And today, many decades later, I am delighted to have solved most of the tasks I set myself to such an extent that others can build on them.

According to what criteria did I base my work? Initially, none at all. A passion is at play here, driving one to answer questions that arise and uncover connections. Of course, the hiker must set a goal so that you don’t wander around in circles in the forest; you must have a sense of the attainability of the goal so that you don’t waste your energy on the impossible.

An example may clarify this: When I first gained insight into cellulose around 1920, I was preoccupied with the question of further arguments for my view. Extensive use of dimethyl sulfate in the processing of catechin taught me to use the reagent in cold conditions. I obtained crystal-clear, highly methylated fibers from ramie and was able to use them to test the yield of those products that the British authors had achieved in small quantities. Thus, a small achievement in another area can be useful for the first. It was an advantage for me over the years to have several problems in mind. If I couldn't make progress in one area, I could work on another until a new challenge arose for the first one. In this way, one can make progress here and there and avoid unexpected obstacles. When I had achieved what I called a permanent position in 1922, I decided to take on a task on lignin that would initially take decades and be thankless. It took 30 years for the breakthrough to occur, and another 17 years to evaluate it. I saw from Emil Fischer and Richard Willstätter that even such men have to endure times of low tide. I remembered this when I felt the same way. The weekly colloquium of the staff, for which I had to gather my thoughts and in which I received many useful suggestions from the students, often helped me. I think back on it with gratitude."

5. Activities other than research work [3)]

As mentioned in the biography section, Freudenberg served as president of Heidelberg University, a member of the Heidelberg city council, and president of the board of trustees for the

Volkshochschule (Adult Education Center).[3)] There are also records of his involvement in the construction of a new building for the Institute of Chemistry at Heidelberg University.[4), 8)]

Another notable side activity of Freudenberg is his historical research.[3)] Freudenberg took up historical and biographical research with serious commitment. He researched his own ancestry spanning more than three centuries and wrote extensively on the local history of Baden and the city of Heidelberg. He devoted considerable attention to the career and record of R. W. Bunsen, a distinguished practitioner of organic chemistry and spectroscopy in the early heroic period, and a predecessor in the chair at Heidelberg. He also published several short essays on the development of schools of chemistry, notably at Heidelberg, and also an illuminating analysis of the BASF's contributions to chemistry and science. He also wrote a biography of his father, Hermann E. Freudenberg, a ‘second founder’ of the family leather business. He appears as a man tirelessly devoted to his business in its widest as well as its most detailed aspects, scrupulously just in his dealings, and humanly capable of occasional relaxation. Only weeks before Freudenberg’s death he was collecting information relating to the builders of the house in Weinheim in which he was born.

The life and activities of the aforementioned R. W. Bunsen were repeatedly and enthusiastically recounted by Freudenberg. In particular, he published the extensive series of Bunsen's letters, (1) to his parents from his early "Grand Tour" to Berlin, Paris, and Vienna, and (2) to his then widowed mother from his expedition to Iceland. These were provided with introductions and notes which must have required some research.[3)]

6. Freudenberg's personality

The descriptions related to the personality of Freudenberg are introduced in this chapter.[3), 4)]

Freudenberg was an extraordinary man in terms of his education, openness to all new things, and tenacity in achieving his goals. He loved sociability, which was especially cultivated by his wife Doris[4)]. Another source states that he was relaxed, friendly, humorous, and well-educated[3)]. Freudenberg enjoyed traveling during his occasional holidays, especially in his beloved Alps. He had a deep interest in alpine plants and had a very professional knowledge of systematic botany. He also liked fine furniture and pictures, and even in his youth he bought works of young artists who later made their names[3)].

He was known for his frank personal interest in individual students and his general friendliness; he made a point of enabling his junior associates to have social contact with distinguished researchers.[3)]

The story of Professor Hou-min Chang, who actually met Freudenberg, is described in the section 7.1. Please also refer to this section as well, since it contains a description related to Freudenberg's personality.

Finally, a few lines from the eulogy pronounced at his graveside by Dr Reinhart Freudenberg is quoted here.3)

"This superior, distinguished, and dignified man could not only be admired and revered, but loved. For he never used his intellectual power, his ... universal education, to impress or overwhelm. He was a deeply humble man ... certainly due to his reverence for nature and its order."

7. Activities overseas, including in Japan 3), 4)

Freudenberg gained international recognition and undertook numerous lecture tours. Initially, he visited mainly England and the United States. During his visit to the United States in 1931, he spent a semester as the Carl Schwartz Professor at the University of Wisconsin-Madison. In the same year, he was the Dohme Lecturer at Johns Hopkins University in Baltimore. This visit and the numerous lectures he gave throughout the United States made a deep impression on Freudenberg. He went on to lecture frequently abroad, including Austria, Belgium, Czechoslovakia, Finland, France, England, Hungary, India, Ireland, Japan, the Netherlands, Pakistan, South Africa, Spain, Sweden, Switzerland, and Turkey.

He was a Corresponding Member of the Bavarian Academy of Sciences, and was elected to membership of the Finnish Academy of Sciences; the Royal Academy of Sciences, Stockholm; the Royal Spanish Society for Physics and Chemistry; the Chemical Society of Japan; and the Chemical Society of London. He took special pleasure in his Foreign Membership of the Royal Society.

7.1. Freudenberg's lecture at the University of Washington in 1964

In 1965, Freudenberg published a paper in Science14) summarizing his DHP and related work. The footnote of the paper states, "This article is based on a lecture given at the University of Washington, Seattle, 25 May 1964." The information stated here, such as the location and time, aligns with what I heard from Professor Hou-min Chang of NC State University when he met with Freudenberg.

Professor Hou-min Chang taught me about the situation at that time, which I will describe below.

Dr. Freudenberg was invited as a keynote speaker for the inauguration of a new forest product research building at the University of Washington on May 25, 1964. He presented the very first lignin structure in that lecture to more than 200 academic and industrial attendees. At the conclusion of his lecture, he received a standing ovation from the attendees, myself included. In my more than 60 years of research with lignin, I never saw such a spontaneous respect paid to an individual.

The next day Dr. Freudenberg, at the age of 78, spent a whole day listening to us young graduate students of Professor K.V. Sarkanen, giving comments and suggestions. I was extremely impressed with his energy level, his willingness to help young researchers and his wide knowledge. This was the reason I told you that he is a very kind person.

7.2. Freudenberg and English

He spoke excellent English and good French, and had a considerable knowledge of Spanish, Italian, Swedish, and Russian.3) Although it was mentioned above that he spoke excellent English, there is an impressive account4) of him practicing English.

"My poor knowledge of English worried me. While I had mastered French at a young age, I lacked any school knowledge of English. The first invitation to give a lecture in English reached me in the summer of 1929 on the ship to Cape Town. I had received an invitation from the Society for the Advancement of Science, and I accepted it despite my limited knowledge of English. The close group I traveled with was George Barger and his wife, as well as the writer E.M. Forster. I wrote down my lecture, scheduled for 20 minutes, in German and asked the helpful Barger to translate the text into English with me. We then practiced intonation and pronunciation, and the text was read aloud to my friend Barger. The whole thing was possible because we were at sea for 17 days between Tilbury on the Thames and Cape Town. During the lecture, I felt like a schoolboy reciting a poem, and they were polite enough to praise my first attempt."

I wondered if Freudenberg was really not good at English. I asked about this Professor Hou-min Chang, who met Freudenberg in Seattle in 1964 as stated above. His answer was that Freudenberg spoke English very well, it was not true at all that he was not good at English.

7.3. Freudenberg and Japan

Freudenberg visited Japan from April to May 1958 and gave the following lectures.2)

Lectures by Professor Freudenberg in Japan

- April 6th, Tokyo, The Chemical Society of Japan: The formation of wood and the constitution of lignin
- April 7th, Nagoya, The Pharmaceutical Society of Japan: Contributions to the chemical constitution of cellulose and starch
- April 17th, Kagoshima University: Contributions to the chemical constitution of cellulose and starch
- April 21st, Kyushu University: The formation of wood and the constitution of lignin

- April 23rd, Tokyo, Lignin Symposium: The formation of wood and the constitution of lignin
- April 25th, The University of Tokyo: Catechins and precursors of flower pigments
- April 30th, Tohoku University: The formation of wood and the constitution of lignin
- May 4th, Kyoto, Japan Society for Bioscience, Biotechnology, and Agrochemistry: Contributions to the chemical constitution of cellulose and starch
- May 6th, Osaka, Mengyo Kaikan Hall: The formation of wood and the constitution of lignin
- May 8th, Kyoto University: Contributions to stereochemistry

There is the following description16) that Freudenberg met Michiyo Tsujimura during his visit to Japan.

"Dr. Freudenberg came to Japan in April 1958 and gave lectures at the University of Tokyo and other institutions. Around this time, the University of Tokyo contacted Tsujimura, saying that Dr. Freudenberg would like to meet her, so Tsujimura visited the university accompanied by Yamanishi. Dr. Freudenberg highly valued and praised Tsujimura's works."

As for Michiyo Tsujimura (1888-1969), she discovered *l*-epigallocatechin and the 3-galloyl ester of epicatechin in tea leaves.2) She was Japan's first female doctor of agriculture, a professor at Ochanomizu University and later a professor emeritus at Jissen Women's University, and is known for her research on the chemical components of green tea, including being the first to isolate tea catechin.16), 17)

Sankichi Takei studied stereochemistry under Freudenberg at the University of Heidelberg from 1926 to 1928.18), 19) Freudenberg gave a lecture on stereochemistry only at Kyoto University during his visit to Japan. This is thought to be related to Takei, who was a professor at Kyoto University. A photograph taken in May 1958 showing the Freudenbergs and the Takeis together can be confirmed in the reference.19)

The collection of his lectures in Japan2) was compiled in German and Japanese translation and edited by the Japan Society for Bioscience, Biotechnology, and Agrochemistry. It is a valuable resource to learn about the details of Freudenberg's work in Japanese (however, there is no information on references).

There is an article and a conference abstract as other Japanese translated materials.12), 20) The abstract of Freudenberg's presentation20) was translated into Japanese by Akira Sakakibara*, who was a professor at Hokkaido University and studied in Freudenberg's laboratory. 21) Sakakibara wrote the following thing in his 1974 paper22): "Lignin is not only insufficient in terms of utilization, but also has many unclear aspects in its chemical structure. I recall that Freudenberg once described lignin as 'Lignin ist eine Puppe mit Lehmfüssen' (Lignin is a doll with clay feet)." Toshio Fukuzumi* also studied in Freudenberg's laboratory and published a paper23) on DHP with Freudenberg.

* The names "Sakakibara, A." and "Fukuzumi, T." can be confirmed in "Tab. 1. Coautoren und

Doktoranden (co-authors and doctoral students)" in the reference[4)]. In addition, "Nagai, W.", whose name can be confirmed in the same table, is thought to be Willy Nagai, the second son of Nagayoshi Nagai. Nagayoshi Nagai (Wilhelm Nagayoshi Nagai) is said to be the founder of pharmacology in Japan.

8. Final chapter: Word from Weinges and Plieninger

As the last part of this manuscript, I would like to introduce the words of Klaus Weinges and Peter Plieninger in their article “Erinnerungen an Karl Johann Freudenberg (1886-1983) [4)]”.

Freudenberg's findings have long been common knowledge and are all too often presented in textbooks and lectures without any thought given to the author. Those who were involved in the results, usually for only a relatively short period of time under his leadership, know the genius they were based on and the effort required to achieve them. May this report help ensure that Freudenberg's strong personality as a person and researcher remains vividly remembered by future generations of chemists.

9. Acknowledgements

First of all, I would like to express my sincere gratitude to Professor Hou-min Chang for sharing the valuable information about his experience when he met Freudenberg, and for giving me a permission to publish that information.

I would also like to thank Professor Noritsugu Terashima (who also met with Freudenberg at the Division of Cellulose, Wood, and Fiber Chemistry of American Chemical Society held in Atlantic City, USA in September 1965), Professor Toshiaki Umezawa, and Professor Shinya Kajita, for providing me with the information about Japanese researchers who studied at Freudenberg’s laboratory.

Finally, I would like to express my sincere gratitude to Professor Kazuhiko Fukushima, who advised me to write this manuscript and recommended publishing it on the Lignin Society's website, as well as the members of the Lignin Society who worked to make it possible to publish it.

10. Afterword

One day, I suddenly wanted to know about Karl Freudenberg. I knew that Karl Freudenberg was called as the "father of lignin chemistry" and he also seem to have made great achievements in research on other wood components. However, what I wanted to know at that time was rather "what kind of researcher was Karl Freudenberg?" who had conducted such extraordinary research works.

Driven by this motivation, I began to search for related materials on Freudenberg, and soon realized that several factors were now in place to make such a search possible. First of all, the German articles, which I had previously given up on because I do not read them, had become readable as long as I could extract the texts in digital form, thanks to the remarkable improvement in the accuracy of machine translation in recent years. This was one of the most important factors that made it possible to search for information about Freudenberg, including articles in German. It is also fortunate that the articles, including his obituaries and the collection of his lectures in Japan (with Japanese translations) are available to know what kind of researcher Freudenberg was, although some of the materials are only available in printed form and are very old and even turning brown. As I read these materials, I am truly humbled by the great authors who have left behind such valuable, and even passionate in a sense, materials including those translated into Japanese.

This article summarizes the descriptions from the cited literature. However, there are many descriptions that cannot be included here, especially about his research results. I must point out that some important research results may have been overlooked, because some of his research is outside my area of expertise.

What about my first question: "What kind of researcher was Karl Freudenberg?" My impression was that Freudenberg was never an eccentric researcher who did something particularly outlandish in order to achieve great accomplishments, but rather someone who carried out his research “step by step with great conviction”. Freudenberg's longevity in research is also a major factor in his success. In addition, the strength of his conviction is also an extremely important factor. Especially when it comes to lignin, his conviction that there must be some regularity in lignin runs through his research. I have always thought that research that is run through with conviction looks beautiful. This exploration for search on Karl Freudenberg made me think so again.

(May 2025, Hikaru Aimi)

References

1 "Lignins; occurrence, formation, structure and reactions", edited by Sarkanen KV, Ludwig CH, Wiley-Interscience, New York (1971)

2. Vorträge von Professor Dr. K. Freudenberg in Japan. Vorbereitet von der Japanishen agrikulturchemischen gesellschaft, April 1958

Lectures by Professor Dr. K. Freudenberg in Japan. Edited by the Japan Society for Bioscience, Biotechnology, and Agrochemistry, April 1958（Dr. K. Freudenberg 教授の日本における講演集、日本農芸化学会編、1958 年 4 月）

3. Stevens T.S. (1984) Karl Johann Freudenberg, 29 January 1886 - 3 April 1983. Biographical Memoirs of Fellows of the Royal Society. 30, 168–189

https://royalsocietypublishing.org/doi/10.1098/rsbm.1984.0006

4. Weinges K., Plieninger P. (1999) Erinnerungen an Karl Johann Freudenberg (1886–1983). European Journal of Organic Chemistry. 1999 (3), 707-736
https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/(SICI)1099-0690(199903)1999:3%3C707::AID-EJOC707%3E3.0.CO;2-R

5. Horst Nimz (1983) Personalia. *Karl Freudenberg* in memoriam. Holzforschung. 37(6), 278
https://www.degruyter.com/document/doi/10.1515/hfsg.1983.37.6.278/html

6. K. Freudenberg, A. C. Neish (1968) In: Constitution and Biosynthesis of Lignin. Springer-Verlag New York Inc., 47-122

7. Karl Freudenberg, Wikipedia
https://en.wikipedia.org/wiki/Karl_Freudenberg

8. Cramer F. (1984) Leben und Werk von Karl Freudenberg. In: Heidelberger Jahrbücher. 28, 57–72. Universitäts-Gesellschaft Heidelberg, Springer-Verlag, Berlin, Heidelberg.
https://link.springer.com/chapter/10.1007/978-3-642-82326-8_5

9. Freudenberg, Karl Johann, encyclopedia
https://www.encyclopedia.com/science/dictionaries-thesauruses-pictures-and-press-releases/freudenberg-karl-johann

10. エミール・フィッシャー（Emil Fischer）, Wikipedia（In Japanese）
https://ja.wikipedia.org/wiki/%E3%82%A8%E3%83%9F%E3%83%BC%E3%83%AB%E3%83%BB%E3%83%95%E3%82%A3%E3%83%83%E3%82%B7%E3%83%A3%E3%83%BC

11. Karl Freudenberg, Hans Hugo Hübner (1952) Oxyzimtalkohole und ihre Dehydrierungs-polymerisate. Chemische Berichte. 85 (12), 1181-1191
https://doi.org/10.1002/cber.19520851213
https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cber.19520851213

12. フロイデンベルグ特集、「リグニン及び木化の領域に於ける最新の知見」、「合成せるリグニン, 天然のリグニン並びにリグニンのモデル化合物の紫外吸収スペクトル」、1956年10月　(In Japanese)
＊ 本文中では「リグニン及び木化の領域に於ける最新の知見」を参照
Special issue on Freudenberg, "Latest knowledge in the field of lignin and lignification", "Ultraviolet absorption spectra of synthetic lignins, natural lignins, and model compounds of lignin", October 1956 (In Japanese).
* This manuscript refers to "Latest knowledge in the field of lignin and lignification".

13. 樋口 隆昌（1990）リグニンの生化学：生合成と微生物分解、木材研究・資料、26、p. 1-37
Higuchi T. (1990) Lignin Biochemistry: Biosynthesis and Biodegradation. Wood research and technical notes. 26, 1-37（In Japanese）
https://repository.kulib.kyoto-u.ac.jp/dspace/bitstream/2433/51465/1/KJ00000152943.pdf

14. K. Freudenberg (1965) Lignin: its constitution and formation from p-hydroxycinnamyl alcohols. Science. 148, 595-600
https://www.jstor.org/stable/1716792

15. Karl Freudenberg (1967) Emil Fischer and his Contribution to Carbohydrate Chemistry. Advances in Carbohydrate Chemistry. 21, 1-38
https://www.sciencedirect.com/science/article/abs/pii/S0096533208603148

16. 「辻村みちよをめぐる人々」、「序」 (2003) "辻村みちよ資料目録"、お茶の水女子大学ジェンダー研究センター、2003年3月、p.10-11、p.1（In Japanese）
"People Surrounding Michiyo Tsujimura", "Preface" (2003) Michiyo Tsujimura Materials Catalog. Gender Studies Center, Ochanomizu University, March 2003, p.10-11, p.1 (In Japanese), “Michiyo Tsujimura” p7-9 (In English)
http://www.igs.ocha.ac.jp/igs/IGS_publication/pdf/tsujimura_archive.pdf

17. Michiyo Tsujimura、Wikipedia（In Japanese）
https://ja.wikipedia.org/wiki/%E8%BE%BB%E6%9D%91%E3%81%BF%E3%81%A1%E3%82%88

18. 松本和男ら（2021）「20世紀末までの医薬・農薬に関わる日本の有機化学研究史、その1：1800年代から1900年までに誕生した有機化学の建設者」、薬史学雑誌. 56(1), 22（In Japanese）
Matsumoto K. (2021) History of Organic Chemistry in the Field of Medicinal Agrochemicals until the End of the 20th Century in Japan ―Part 1：Prominent Pioneers Born Before 1900―. Yakushigaku Zasshi (The Japanese Journal for the History of Pharmacy), 56(1), 22
https://www.jstage.jst.go.jp/article/jjhp/56/1/56_13/_article/-char/ja/

19. 松本和男（2010）「武居三吉」、和光純薬時報. 78(3), 28-31（In Japanese）
Matsumoto K. (2010) ‘Sankichi Takei’. 和光純薬時報. 78(3), 28-31
https://labchem-wako.fujifilm.com/jp/journal/docs/jiho783.pdf

20. K. Freudenberg (1961) 「リグニンの生合成と構造論」（榊原 彰訳）、木材化学、木材化学シンポジューム、p. 1-13（In Japanese）
※This is thought to be the following conference abstract, which was translated into Japanese by Akira Sakakibara: Freudenberg K. (1961) Biogenesis and Constitution of Lignin. Wood Chemistry Symposium, Abstract, Montreal.

21. Karl Freudenberg, Akira Sakakibara (1959) Weitere Zwischenprodukte der Bildung des Lignins. Justus Liebigs Annalen der Chemie, 623(1), 129-137
https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/jlac.19596230115

22. 榊原 彰（1974）リグニン形成とその構造，化学と生物，12(8)，508-518 (In Japanese)
https://www.jstage.jst.go.jp/article/kagakutoseibutsu1962/12/8/12_8_508/_pdf/-char/ja

23. Karl Freudenberg, John M. Harkin, Martin Reichert, Toshio Fukuzumi (1958) Die an der Verholzung beteiligten Enzyme. Die Dehydrierung des Sinapinalkohols. Chemische Berichte. 91(3), 581-590
https://chemistry-europe.onlinelibrary.wiley.com/doi/abs/10.1002/cber.19580910317