Clean and practical oxidation using hydrogen peroxide

— Development of catalysis and application to fine chemicals —

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Oxidation is an important component in over 30 % of chemical processes. However, oxidation typically creates environmentally damaging waste products. Hydrogen peroxide (H_2O_2) is a good candidate for environmentally benign oxidation because the only by-product is water. By integrating key technologies for halogen-free, organic solvent-free processes, and designing suitable metal catalysts, we succeeded in the development of H_2O_2 oxidation. This achievement is the first concrete example of Green Sustainable Chemistry (GSC). Based on this new technology, we further attempted to establish H_2O_2 oxidation as a practical method for the formation of fine chemicals of high performance. Novel catalysts optimized for practical usage were developed by resolving key issues such as cost reduction and scalability through joint research between AIST and various chemical companies.

Keywords : Green sustainable chemistry, oxidation, hydrogen peroxide, catalysis, fine chemicals

1 Introduction

Chemical products are contained in various products around us including automobiles, home appliances, office appliances, clothes, and drugs. Our lives will be set back without chemical products. The chemical industry is an important key industry for Japan, and Japan is one of the primary chemical product producers in the world.[1] Although oxidation reaction is the most important reaction that dominates over 30 % of all chemical processes, it is also known as a process that severely contaminates the environment, as large amounts of waste derived from oxidants are produced as by-products of the reaction.[2] Table 1 summarizes the major oxidants, waste products after the reaction, percentage of active oxygen, and appropriateness as clean oxidants. Nitric acid (HNO_3) is an oxidant used in the production of adipic acid that is used as the raw material of chemical fibers, and water (H_2O) and nitrous oxide (N_2O) are produced after the reaction. Nitrous oxide is known as a greenhouse gas, and it is calculated that 2.2 million ton/year of adipic acid is produced worldwide, and 400 thousand ton/year of nitrous oxide is produced as waste. Sodium hypochlorite (NaClO) and paracetic acid (CH_3COOOH) are used in the production of electronic materials and drugs, and compounds containing chlorides (NaCl) and acetic acid (CH_3COOH) are produced in amounts greater than the target product after reaction.[3] These waste products severely contaminate the environment and cannot be released directly into the air, river, or ground, and therefore, the manufacturers must design a process where the waste derived from the oxidants are collected, recycled, and reused. However, considering the construction of facilities that do not leak waste products, energy needed for processing, and efforts to reduce exposure during work and safety maintenance, the load on the environment is extremely high. For a fundamental solution, it is necessary to use an environmentally benign oxidant from the beginning. Oxygen (O_2) is ideal as an oxidant with low environmental load, but using both of the oxygen atoms in O_2 in the oxidation reaction is an unknown reaction in actual science although it may be discussed in theory. Even if a reaction system is designed where one of the oxygen atoms is used in oxidation while the other atom is emitted as water, it is difficult to have only the target reaction to progress or to control it, and there is the disadvantage that the oxidation may progress all the way to carbon dioxide (CO_2) past the target chemical product.

We looked at hydrogen peroxide (H_2O_2) as a clean oxidant. Hydrogen peroxide is a colorless, transparent liquid discovered by a French chemist, Thénard in 1818. Currently, the solution with concentration of 60 % or less is available as an industrial product. The domestic shipment of hydrogen peroxide has been stable at about 180~200 thousand ton/year for the past few years,[4] and it is used widely in our daily lives. For example, it is known at home as liquid bleach detergent or disinfectant oxydol. In industrial use, it is used for bleaching paper and pulp, wastewater treatment, soil improvement, or semiconductor cleansing. The structure is a combination of two each of hydrogen (H) and oxygen (O) in the form of H-O-O-H, and it has equivalent percentage of active oxygen as oxygen (47 %) and the waste is water only. Until now, hydrazine, catechol, oxime, and propylene oxide manufacturing have been industrialized, and it is expected that chemical product synthesis using hydrogen peroxide will increase in the future (Fig. 1). However, the oxidative

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Table 1. Comparison of various manufacturing methods

Oxidant or manufacturing method	Waste product	Percentage of active oxygen (%)	Appropriateness as clean oxidant and remarks
Oxygen (O_2)	None	100	◎(Difficult to control, catalyst required)
Oxygen (O_2)	Water (H_2O)	50	○(Difficult to control, catalyst required)
Hydrogen peroxide (H_2O_2)	Water (H_2O)	47	○(Catalyst required)
Nitric acid ($2HNO_3$)	Water + nitrous oxide (N_2O)	51	△(Emit greenhouse gas)
Sodium hypochlorite (NaClO)	Sodium chloride (NaCl) etc.	22	×(Emit chlorine compounds)
Peracetic acid (CH_3COOOH)	Acetic acid (CH_3COOH)	18	×(Produce acetic acid)

◎: Optimal, ○: Appropriate, △: Treatment necessary, ×: Inapplicable

capacity of hydrogen peroxide itself is low, and activation by optimized catalysts is necessary for its application to various chemical reactions. For hydrogen peroxide to be used widely and generally as a clean oxidant, it is necessary to develop not only the basic chemical products, but also the core technology for new catalysts that allow application to fine chemicals, electronic materials, and drug manufacturing.

2 Background of the development of environmentally benign hydrogen peroxide oxidation technology

Here, we describe the steps that lead to the start of the development of our hydrogen peroxide oxidation technology against a background of green sustainable chemistry. The social trends in industry and environment are shown on the left side of Fig. 2 while the technological trends of hydrogen peroxide oxidation are shown on the right side. As shown on the left side of Fig. 2, environmental pollution was recognized from the latter half of the 19th century. From the 1950s to 1980s, the issue of environmental pollution such as air, water, and soil became serious due to the development of various chemical product manufacturing processes, and the industries were obliged to reduce and process the waste before release. In the 1990s, the movement to conserve the environment became active internationally. In 1991, Paul Anastas stated the 12 principles of green chemistry,[5] and in 1997, Kyoto Protocol that stated the reduction target for carbon dioxide

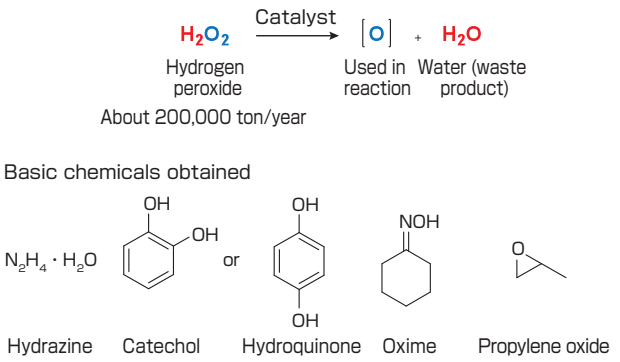

Fig. 1 Hydrogen peroxide oxidation technology in the manufacturing of basic chemical products

for each country was adopted. Active discussions were engaged internationally on the environmentally friendly manufacturing method for chemical products, and the direction of constructing environmentally benign chemical processes was indicated as part of the solution. On the other hand, a specific guideline for what kind of technology should be developed to realize an environmentally benign chemical process had not been discerned at this point. Next, looking at the right side of Fig. 2, the oxidation technology for hydrogen peroxide was developed at about the same time when the environmental conservation movement became active. The publications on activating hydrogen peroxide using catalysts were seen from around 1950, and in the 1980s, catalyst technologies with high selectivity or high applicability for actively synthesizing target compounds were published abundantly. For example, in 1983, Venturello *et al.* reported the hydrogen peroxide oxidation reaction using a catalyst containing tungsten acid, and in 1988, Ishii *et al.* reported the hydrogen peroxide oxidation reaction consisting of two components, tungstophosphoric acid and quaternary ammonium salt.[6]-[8] However, although such catalytic reaction implied clean reaction using hydrogen peroxide, it did not actively promote a practical, environmentally benign method, and used halogen compounds and organic solvents to enhance the catalytic activity. It is insufficient

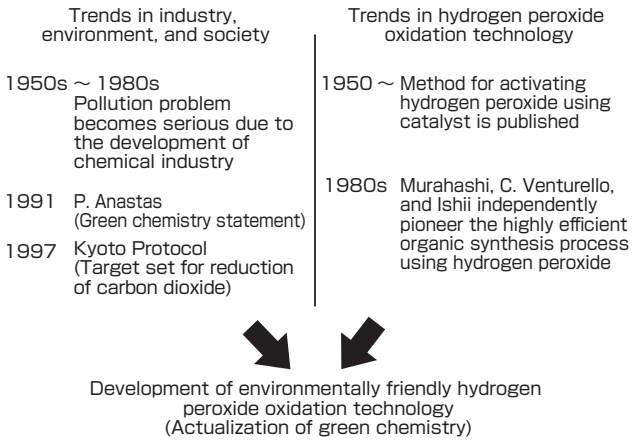

Fig. 2 History of the development of environmentally friendly hydrogen peroxide oxidation technology

to simply use hydrogen peroxide to achieve a sustainable chemical reaction, and it must be clean for the entire process from the raw material stage, manufacturing, refining, through to cleansing. With this way of thinking, we set the objective to conducting the hydrogen peroxide oxidation in an environmentally benign manner. We thought we could achieve an effective environmentally benign process if we could manufacture specific catalysts that can synthesize target products with high yield and high selectively under the conditions of halogen free and organic solvent free, and started the development of the basic technology for oxidation process including the catalyst development.

3 Development of a new catalyst that enables environmentally benign hydrogen peroxide oxidation technology

Under Professor Ryoji Noyori, who is world renowned for reduction reaction, we engaged in the development of oxidation reaction, and after a five-year period of trial-and-error during which we were unable to publish papers or make presentations at academic societies, we developed a new catalyst. The specific flow of research was: set a working hypothesis → verify the hypothesis through experiment → extract problems through examination → set a working hypothesis again. This was repeated until we discovered a catalyst that allowed us to obtain the target substance at high yield. By repeating the trials-and-errors and reviews over several hundred experiments, the key point of the oxidation by hydrogen peroxide became clear, and we extracted the following elemental technologies: (1) halogen-free technology, (2) organic-solvent-free technology, and (3) metal catalyst design technology. By conducting the catalyst design repeatedly to avoid the decrease of reactivity that may occur due to the combination of various elemental technologies, we were able to discover the true active species of the reaction, and succeeded in developing a sustainable hydrogen peroxide oxidation technology.[9] For catalyst development, the technological development up to this point is reconsidered from the perspective of the integration of elemental technologies, and we propose it as one of the guidelines for a highly efficient way of developing a new catalyst.

3.1 Design of a tungsten catalyst based on conventional knowledge

On the hydrogen peroxide oxidation technology as described in chapter 2, the basic research for the activation of hydrogen peroxide by catalysts became active from the 1950s. From the findings so far, it is known that the efficiency of hydrogen peroxide increases when tungsten is used as a catalyst, since it does not decompose hydrogen peroxide. For the structure of the active species, according to the prior research by Venturello *et al.*, the binuclear or tetranuclear complexes were proposed, with a triangle composed of tungsten and two oxygen atoms as the basic unit (Fig. 3, Catalyst A).[10] Moreover, since the hydrogen peroxide oxidation reaction is a two-phase reaction between the organic phase (raw material) and the liquid phase (hydrogen peroxide), simple mixing does not bind them, and it is known that the use of quaternary ammonium salt, which is a type of a phase transfer catalyst, is necessary to efficiently promote the reaction. Utilizing the findings from the prior research, we decided to develop the catalyst based on the combination of the tungsten metal catalyst and the phase transfer catalyst.

3.2 Reaction mechanism of the tungsten catalyst and the effect of a halogen solvent in the conventional method

There were two problems in the conventional method: the use of organic solvents such as a halogen solvent and the use of halogenated quaternary ammonium salt. However, at the time, it was common knowledge that the halogen solvent was necessary to increase the efficiency and selectivity of the reaction in hydrogen peroxide oxidation technology.[11] The reason will be explained alongside the description of the reaction mechanism. Quaternary ammonium salt becomes stable as it is in neutral condition by becoming cation and anion species. The tungsten catalyst also forms salt with the sodium cation, after forming active anion species by directly bonding with hydrogen peroxide (Fig. 3, Catalyst A). Then through the cation species exchange from sodium cation to quaternary ammonium cation, the active anion species is transferred to the organic phase using the power of quaternary ammonium salt that readily dissolves in the organic phase (Catalyst B). After the reaction in the organic phase, the salt of tungsten anion species with one less oxygen atom and the quaternary ammonium cation (Catalyst C) return to the liquid phase along with the sodium cation that readily dissolves in water, through the exchange from the quaternary ammonium cation to sodium cation (Catalyst D). Then, it comes in contact with hydrogen peroxide to recreate the active anion species (Catalyst A). The cycle of Catalyst A → B → C → D is repeated as the reaction progresses. To promote the reaction efficiently, smooth transfer from

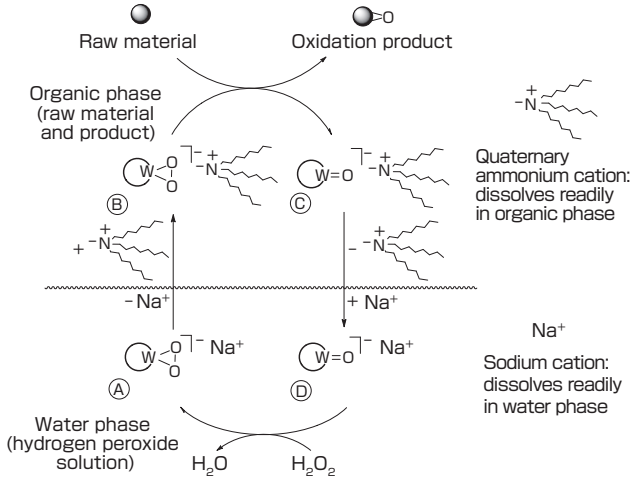

Fig. 3 Reaction mechanism of the hydrogen peroxide oxidation technology using tungsten catalyst

water to the organic phase (transfer from Catalyst A to B) is considered most important. Since the halogen solvent has particularly high affinity with quaternary ammonium salt among the organic solvents, it is said to be the optimal solvent for the transfer from water to the organic phase. Also, since the halogen solvent does not readily mix with water, the reaction phase (organic phase) and the catalyst-activating phase (water phase) do not undergo mutual mixing, and the individual routes from Catalyst B to C and Catalyst D to A progress highly efficiently.[12] However, since the top priority objective of this research was the development of an environmentally benign process, we could not use any of the organic solvents including the halogen solvent. It was necessary to develop a highly efficient, new catalyst that greatly surpassed the disadvantage of using no organic solvents including halogen.

3.3 Development of the halogen-free and organic solvent-free tungsten catalyst technology

In the oxidation reaction from 2-octanol to 2-octanone, when only the organic solvents were removed using the conventional tungsten catalyst, the yield dropped from 90 % to 11 % and the reaction almost ceased to progress. While it involved simply removing the organic solvents, for organic synthesis in which the core technology was the optimal selection of the organic solvents, the reaction system where organic solvent could not be used was a system where the conventional knowledge was totally useless, and new concepts had to be pioneered. As a solution, we made a main assumption that the reaction will not occur unless the raw material and the active species came into contact, and investigated the improvement of the phase transfer catalyst that greatly affected the contact. Quaternary ammonium salt used for the phase transfer catalyst is composed of an ion pair of quaternary ammonium cation and chloride ion (anion species), and as shown in the reaction mechanism (Fig. 3), the quaternary ammonium cation pairs with the tungsten active species to become actively involved in the reaction, while chloride ion is not directly involved in the reaction mechanism. We first considered the improvement of the quaternary ammonium cation, but were unable to see hardly any increase in reactivity when the affinity to the organic solvent was enhanced by lengthening the alkyl chain two or three times longer. Next, we looked at chloride ions. As it did not appear in the reaction mechanism, it was thought that the change in chloride ion seemed to have no effect on reactivity, we decided to actively search for halogen-free anion species to replace the chloride ion to achieve environmental benignity for this technological development.

As we engaged in the experiments and reexaminations on the effects of the anion species, we learned that there was a possibility that the anion species actively affected the structure of the active species. That is, we found that the tungsten active species took on three structure types according to the strength of acidity (pH) of the water phase. Among the three, Type A2 had the highest reactivity, and this structure was present in pH 0.4-3.0 (Fig. 4). Based on the assumption that the reaction will progress extremely efficiently if the pH during the reaction could be maintained between 0.4 to 3, we investigated the effect of the anion species in the oxidation reaction of 2-octanol. We obtained the result that while the yield was 11 % in the case of chloride ion, the yield increased to 97 % when hydrogen sulfate ion was used, and the change of anion species clearly improved the reactivity. When the pH during the reaction were measured for chloride ion and hydrogen sulfate ion, the pH changed to 4 or more immediately after the start of the reaction for chloride ion while the pH stayed at an ideal condition of 2 to 3 in the case of hydrogen sulfate ion.

The examination of the anion species of quaternary ammonium salt that was started to establish the halogen-free, organic solvent-free technology led to the detailed clarification of the true active species of the tungsten catalyst, as a result. When conducting catalyst design, without changing the goals and conditions that were set initially, one can find a solution by accurately evaluating the experimental results, seeking the essential principle that lies deep down, and thoroughly understanding the reaction in accordance to the basic principle, even if the experimental results are not good. In this case, we set the elemental technologies for organic solvent-free and halogen-free processes, did not change them during the course of research, continued the search for the catalyst, and then, we became aware of the change of the structure of tungsten active species according to pH. Therefore, we reached a deep understanding of the tungsten active species and were able to develop a highly active catalyst unseen before.

3.4 Review of the working hypothesis to apply the developed catalyst to epoxidation reaction

The activity of the developed catalyst was extremely high, and it enabled the oxidation of various alcohols and the highly efficient synthesis from cyclohexene to adipic acid.[13]-[15] When the turnover number of the catalyst (how many raw materials

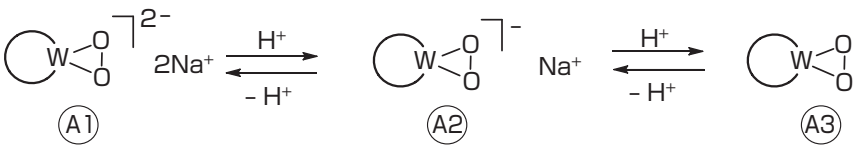

Fig. 4 Three forms of tungsten catalyst active species A according to pH

are oxidized by one catalyst) that is the index of catalytic activity was investigated, the number surpassed 70 thousand times, and this indicated that the catalytic activity was two digits higher than the conventional method using the halogen solvent. However, when epoxidation was attempted using this catalyst, unlike alcohol, extremely low reactivity of 5 % yield was seen in the reaction of 1-octene. Therefore, we improved the developed catalyst to be applicable to epoxidation. Since the route from active species A to B shown in Fig. 3 was optimized, we thought the reason for the slow reaction progress was in some other steps. As a result of investigation by various experiments, it was found that the oxygen of active species B was not readily attacked by the olefin moiety of the raw material. We redesigned the catalyst that combined phosphorus and nitrogen to the binuclear complex structure of tungsten so the oxygen of active species B would readily come in contact with the raw material (Fig. 5). That is, by adding the aminomethylphosphonic acid as a "reaction site activating catalyst," one of the catalyst component, a hydrogen bond formed between N-H and O-W, oxygen in W-O of the reaction side decreased the electric charge, and it would be readily attacked by the olefin. When the reaction was actually conducted by adding the aminomethylphosphonic acid in the oxidation of 1-octene, the reactivity dramatically increased even though only one component of the catalyst was added, and epoxides were given in 94 % yield.

3.5 Point of catalyst development

We succeeded in developing an environmentally benign oxidation technology that was halogen-free and organic solvent-free, through the combination of quaternary ammonium salt of hydrogen sulfate and aminomethylphosphonic acid, using a tungsten catalyst as the base. Without being bound by conventional way of thinking that halogen solvents were absolutely necessary or quaternary ammonium salt anion species were not involved in the reaction, we reached the true core of the reaction. We were able to develop a highly efficient catalyst through a strategy of thoroughly removing the uncertain factors by making minimal changes to the catalyst design to solve the problem and then to continue improving the catalyst. The developed technology led to the first paper in the world to specifically present which organic synthesis was effective for reducing the environmental load, in the green sustainable chemistry field that merely stated theories, and created a new trend in the research of green sustainable chemistry.

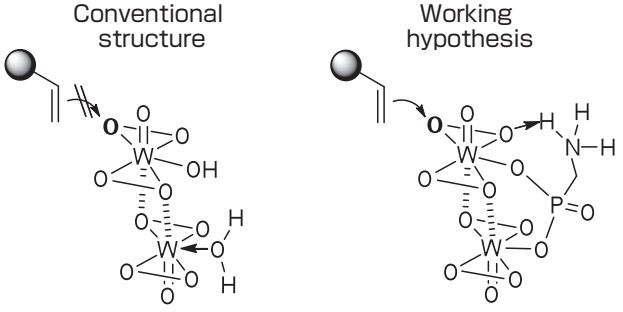

Fig. 5 Working hypothesis for the tungsten catalyst active species for epoxidation

4 Practical application of the adipic acid synthesis method for use in core technology

Although there are many kinds of chemical products, we looked at the adipic acid that is known as the raw material for 6,6-nylon that is necessary for chemical fibers, interior decorations, and automotive parts. Most of the industrial manufacturing method that are currently in operation are conducted by the nitric acid oxidation of cyclohexanol and cyclohexanone derived from benzene (Fig. 6). In nitric acid oxidation, nitrous oxide is produced as a co-product, and we thought that the merit of replacing it with hydrogen peroxide was great. Using the 30 % hydrogen peroxide solution as an oxidant and the tungsten catalyst system developed in subchapter 3.4,[13][14] we started joint research with companies for commercial industrialization. In industrial use, the points of not using organic solvents and reusing the catalysts were major advantages. However, cost was a problem. For the use of raw materials and catalysts, the raw materials were the same and the amount of catalyst used was small, and this did not greatly affect the cost. On the other hand, in the existing manufacturing method, the oxidant used was nitric acid that is less expensive than hydrogen peroxide. Since it became apparent that the newly considered process will incur higher cost compared to the conventional method due to the cost of oxidants, and there was additional expenditure to build a new plant, commercialization was not realized.

5 Elemental technologies that must be considered in realization research and setting of the integration system

The failure with adipic acid indicated that it is necessary to consider various factors such as cost and scaleup as well as the catalyst technology to achieve realization. Reflecting on

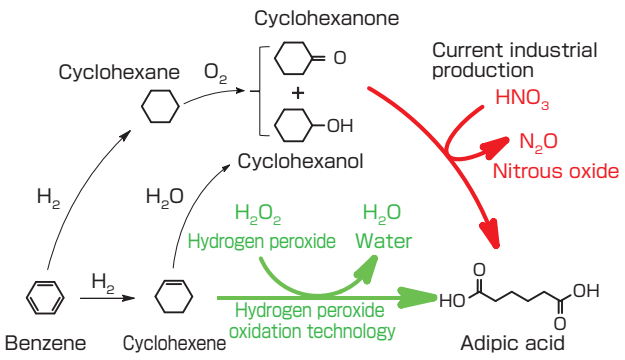

Fig. 6 Comparison of the conventional method and the manufacturing of adipic acid using hydrogen peroxide oxidation technology

these points, we set the milestones or elemental technologies that must be considered in the realization research (Fig. 7). Solving these elemental technologies individually means that the realization research will progress as the issues are cleared one by one while integrating the elemental technologies.

Although the core of our research is the creation of a new catalyst that may use hydrogen peroxide as an oxidant, simply creating a catalyst does not lead to practical use, and the selection of the target compound, scaleup, and investigation and research on cost estimates are essential. To promote such investigation and research, joint research with companies is mandatory, and the road to practical use will open through close collaboration with the parties involved. In the following sections, the importance of individual elemental technologies is considered taking the example of adipic acid, and the guideline for promoting realization research is presented.

5.1 Selection of the target compound

The product manufactured must not be the result of a mere replacement of a manufacturing method. It will not have market competitiveness unless it has strength or performance that far surpasses the conventional product. The replacement of the manufacturing process for which the method has matured and has a long history of operation is difficult unless the newly developed technology shows improvement and merit that further surpass the conventional technology. For example, adipic acid has been produced stably for several decades using the nitric acid oxidation method. The system to completely recover the emitted nitrous oxide and to convert it to nitric acid without much loss has been well established. Since the conventional method is mature, the possibility of employment of any new method is extremely low.

Moreover, in selecting the target compound as part of the environmental-load-reducing technology, it is necessary to consider the E-factor. Figure 8 shows the correlation of the manufactured amount of chemical products and the E-factor. The E-factor is the amount of waste produced when manufacturing one kilogram of a target product, and ideally, this value should be 0. As shown in Fig. 8, the E-factor becomes large in the manufacture of products with high added value because the manufacturing process becomes complex and multi-stepped.[16][17] Drugs and electronic materials have

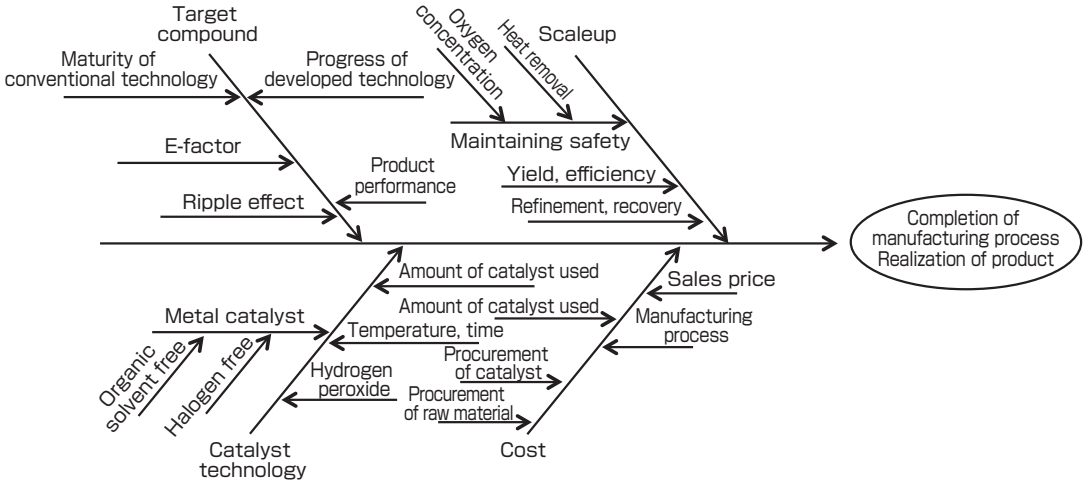

Fig. 7 Milestones that must be considered in realization research

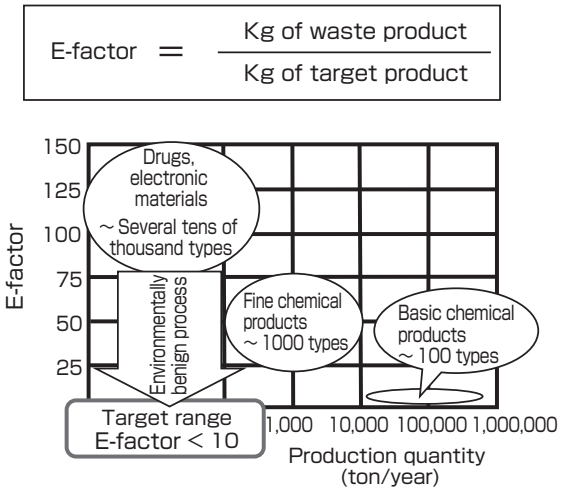

Fig. 8 E-factor in chemical industry

higher market prices compared to basic chemical products, and the size of their E-factors have been overlooked since profit can be made even though the cost of processing the waste is high. As a result, as there are many types of drug and electronic materials, even though the production volume per type is small, the total amount of waste generated amounts to more than half of the entire petrochemical industry.[2] Therefore, to convert the manufacturing method of the so-called functional chemicals including the intermediate and raw materials of the drugs and electronic materials that have large E-factors or large waste volumes to a method that is environmentally friendly will dramatically reduce the E-factor, and also reduce the total amount (or absolute amount) of waste. Since the adipic acid is a basic chemical product and the process is matured, the E-factor is basically low. If the target compound is selected according to the E-factor, the significance will be great if the manufacturing method of the so-called functional chemicals, such as the intermediate and raw materials of drugs and electronic materials that has E-factors that reach 100 to 150 and produce high volume of waste, can be changed to a method with E-factors of 10 or less.

In selecting the target compound, it is extremely important to consider the ripple effect and additional value. Since much labor and time is necessary for the development and realization of a new technology, it is essential during the R&D process to select a target compound assuming that the obtained new technology can be used for the manufacture of similar products or the produced materials can capture high percentage of share among materials due to its high performance. In the future, the demand will be high for a manufacturing method that is environmentally benign and also has high performance, not simply replacing the conventional technology with one that is environmentally benign. As it will be described later, the halogen-free technology has the potential to dramatically increase the performance of the electronic materials and therefore to create new values, and it can be a powerful elemental technology.

5.2 Catalyst technology

For catalyst technology, only the outline will be presented as the details are explained in chapter 3. We possess highly efficient, highly selective oxidation technology through the design of new catalysts based on metal catalysts under the condition of not using organic solvents and halogen and using hydrogen peroxide as the oxidant. The technology developed surpasses the existing catalysts in turnover number and has low environmental load. Specifically, it uses two component catalysts composed of tungsten and ammonium salt for the manufacture of alcohol and adipic acid, and also uses three component catalysts combining a single reaction site activating catalyst for epoxidation. To complete the catalyst technology as a process, it is also necessary to optimize the reaction time and temperature, adjust the adding method of raw materials or catalysts, and minimize the amount of catalysts used. Moreover, our technology is the basic technology of hydrogen peroxide oxidation and can be applied to various raw materials, but highly efficient reaction cannot be achieved even if the publicized technology is used directly for target reaction. Depending on the target reaction or structure of the raw material, the optimal catalysts are different. Therefore, it is necessary to pinpoint the metal catalyst, the phase transfer catalyst, or the reaction site activating catalyst that are specific to the manufacture of the desired target product, although the basic technological concept of the three-component catalyst system composed of tungsten acid, quaternary ammonium salt, and phosphorus compound is used. In doing so, a quick discovery of the optimal catalyst for the manufacture of a target product is only possible in the presence of the ability to select and discard the factors with maximum effect for promoting the reaction, through clarifying the reaction mechanism from the basic principle, backed by the knowledge and experiences that were obtained through the development of the basic technology for hydrogen peroxide oxidation. That is, in shortening the development period or gaining the economic competitive edge, it is necessary to maintain and deepen the platform of findings on the reaction mechanism and basic principles that were obtained through the development of the basic technology for catalysts, and to utilize them for the invention and discovery of the optimal catalyst system to synthesize the target product.

5.3 Cost

In considering the cost, joint research with companies is mandatory. To develop the technology by which one can claim that the environmentally benign method has clear cost advantage, through objective comparison of the conventional and new methods of manufacturing process, is essential for realizing environmentally benign oxidation technology using hydrogen peroxide. As a specific example, the cost comparison of the manufacture of adipic acid and epoxides, the raw material of the insulating film (explained later), is presented (Fig. 9). In the case of the adipic acid, the price difference of the oxidant is directly reflected in the cost because it does not have high added value as a product, although it can be produced in vast amounts. It is difficult to apply the hydrogen peroxide oxidation technology to the manufacture of chemicals with low price due to the cost of the oxidants. On the other hand, in the manufacture of epoxides for functional chemicals with relatively high price, although the difficulty of the manufacturing technology may increase, the merit of manufacturing using the hydrogen peroxide oxidation technology is obtained by developing the catalyst technology and scale-up technology (new methods are described in chapter 6). In reality, the calculation results shown here do not necessarily reflect the actual situation at the manufacturing plant, and the figures may be wrong in many cases. However, in conducting the realization research and engaging in joint research with the companies, it is necessary to exclude subjects that clearly do not match the price, and to recognize to some

degree the difference between the actual cost of the subjects that one wishes to pursue and the target values at a level that can be realized, at the start of the realization research.

5.4 Scaleup

In terms of extracting the problems in manufacturing, the consideration of scaleup is necessary. It is known that in the hydrogen peroxide oxidation technology, oxygen is produced through the decomposition of hydrogen peroxide. To check the safety during manufacturing, it is necessary to monitor the oxygen concentration during reaction, check the heat generation of the reaction vessel, and to take measures to keep it under the specified value. The hydrogen peroxide oxidation technology we developed is done in a batch reaction vessel where the raw materials, catalysts, and hydrogen peroxide solutions are all placed in one vessel and then mixed, and in scaleup, the issues of the removal of the reaction heat produced and the reduction of the reaction site due to decreased interface between the organic and water phases cannot be avoided. It is necessary to investigate the effects of such negative factors on the yield and the reaction speed, and it may become necessary to redesign the catalyst in some cases. Also, to stably manufacture a product in designated amounts, it is also necessary to consider the refining process and the recovery and reuse of catalysts.

6 Manufacture of the ultra-long life insulation film using the hydrogen peroxide epoxidation technology

6.1 Setting of the target compound

The development of alicyclic epoxide manufacturing process using hydrogen peroxide oxidation useful for insulation materials was conducted jointly with Showa Denko K.K.[18]-[20] The insulation materials are used in all sorts of electronic parts from large liquid crystal displays to cell phones. In the liquid crystal panel, the control board is made by directly installing the chip on the film substrate used for wiring, and the epoxy resin that can be readily painted on and hardened is used as the insulating material to cover the fine wires (Fig. 10). The pursuit of high functions and weight reduction of the electronic parts will continue further in the future, and the achievement of flexibility of the printed substrate and fine wiring (further narrowing of the pitch) are necessary technologies. Moreover, higher insulation performance and flexibility compared to the conventional materials are demanded for the materials that cover and protect the circuits. In the conventional manufacturing technology, the use of chloride compounds is necessary, and there are problems of not only producing large amounts of chloride waste, but the minute amount of organic chloride compounds remaining in the product may short-

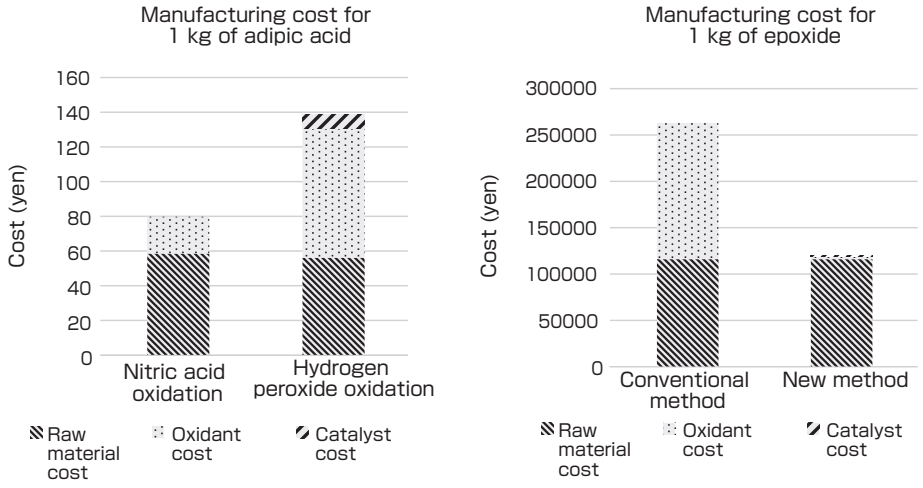

Fig. 9 Comparison of the manufacturing cost

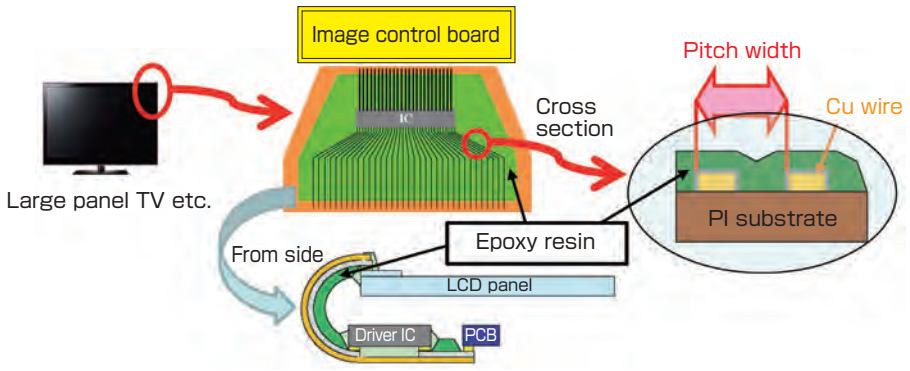

Fig. 10 Development of the epoxy resin for electronic material

circuit the fine wires and damage the long-term insulation property. We developed technology for hydrogen peroxide oxidation using new catalysts to manufacture epoxides while satisfying the above performances.

6.2 Catalyst development, cost reduction, and scaleup

We developed the catalyst considering the properties of epoxides based on our basic technology for hydrogen peroxide catalysts. We investigated the scaleup and cost. Ultimately, to meet the demands of the user companies, we achieved 10 times catalyst use efficiency by optimizing the catalyst reuse technology and the method of adding hydrogen peroxide, and reduced the cost of catalysts to one-tenth of the initial target value (Fig. 9). By devising the reaction vessel and mixing method as well as strict control of reaction temperature, we succeeded in developing a chloride-free selective epoxidation technology at 20 kg scale (71 % yield, 90 % selectivity). Since this step is an optimization of the process specific to the target chemical product and manufacturing equipment, although much time and labor are spent, the obtained findings cannot be written up as papers or patents. However, we felt that by achieving the target values of manufacturing process through working with the companies, we actually saw the possibility of realization of our developed technology.[21]

6.3 Fabrication and evaluation of the insulation film

By oligomerizing the obtained epoxide and combining with a hardener, we completed the ultra-long life insulation film (Fig. 11). To evaluate the performance as an insulation film, we conducted the test of insulating durability at high temperature and high humidity (85 ºC, 85 % Rh). As shown in Fig. 12, the conventional product short-circuited and the

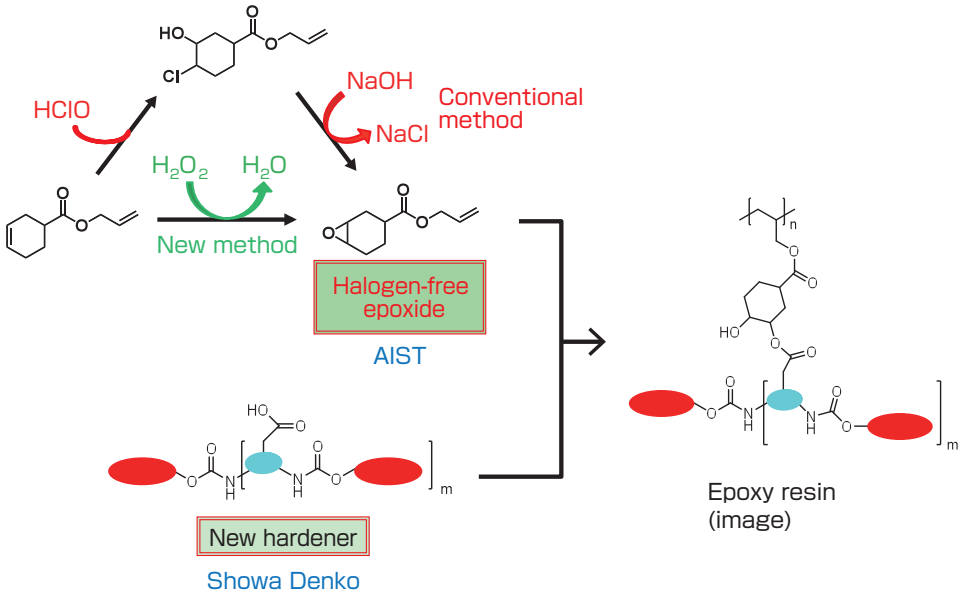

Fig. 11 Development of the oxidation technology using hydrogen peroxide and the manufacture of fabricated epoxy resin

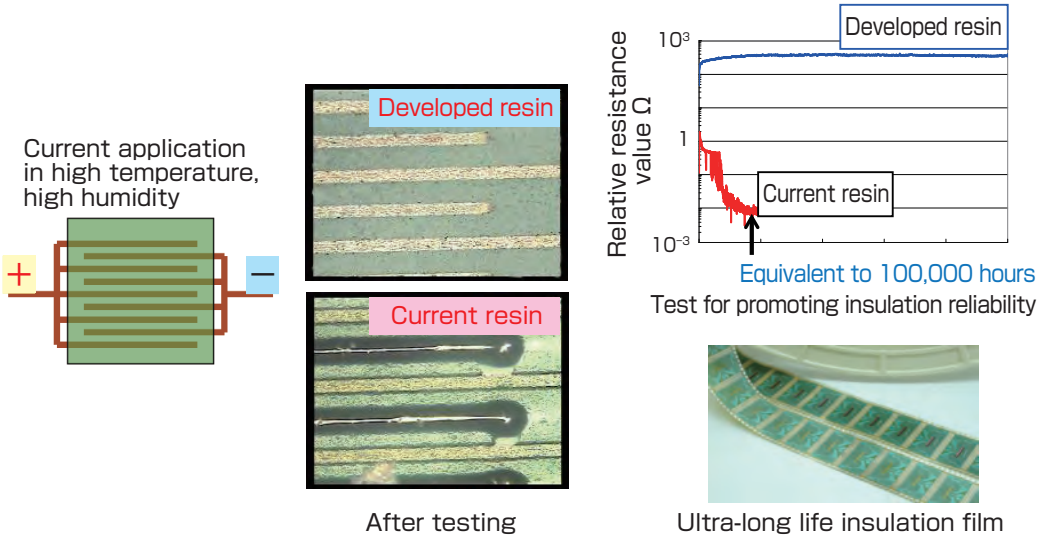

Fig. 12 Performance evaluation of the fabricated insulation material

insulation was not maintained. On the other hand, the film to which the newly developed resin was applied showed no deterioration after 100 thousand hours equivalent, showed more than two-digit higher insulating performance than the conventional products, and maintained the insulation property for a long time. This product enabled the size and weight reduction of electronic appliances, such as thinner LC displays. The newly adopted world share reaches 70 %.

7 Future development

The hydrogen peroxide oxidation technology developed this time is not limited to the manufacture of insulation film, but has the potential of contributing to all manners of functional chemical manufacturing using the oxidation technology. As a basic technology, we have the catalyst technology that allows environmentally benign oxidation using hydrogen peroxide. When realizing various products utilizing the hydrogen peroxide oxidation technology, we can achieve the goal at a short time because we have accumulated the knowledge and experiences of science and technology and therefore we are able to seek the essence of the reaction faster than the groups that are starting from zero. We are currently continuing to develop the basic technology.[22]-[24] For example, we are developing the technology to create many epoxies within one molecule, technology to directly epoxidize the polymer, and technology to synthesize epoxy only among several reaction sites[3]. The research continues spirally from basic research to product realization and then from application research looking at product realization to new basic research. The catalyst reaction developed several years ago is progressing to the step of realization now, and some has gone on to successful product realization. Currently, not only ultra-long life insulation films, but also the manufacture of diverse products including semiconductor sealants, next-generation adhesives, high-function surfactants, and radical polymers for battery materials are progressing to the stage of practical use or product realization.[25][26]

8 Summary

The chemical industry is a major industry in Japan with shipment of about 40 trillion yen, additional value of about 15 trillion yen, and about 880,000 employees. Particularly, the world share of functional chemical products is high, playing an essential role mainly in the material supply for advanced assembly industry such as automobile and information/communication fields. On the other hand, the chemical industry dominates about 16 % of all domestic industries in carbon dioxide emissions, and 13 % in the production of industrial waste in the Japanese manufacturing industries. There is increasing recognition that the manufacturing technology with low environmental load is mandatory for the future chemical industry. For example, starting with the establishment of the Green Chemistry Workshop in the Chemical Society of Japan in 1999, the Green Sustainable Chemistry Network (GSCN) was established in 2000 through industry-academia-government collaboration. Recently, the consciousness for clean chemical manufacturing methods has risen, and the “essential reduction of the amount of waste” was designated in the Johannesburg Plan of Implementation (WSSD 2020) at the 2002 World Summit on Sustainable Development (WSSD).

The strength of the Japanese chemical industry is that the individual companies engage in the manufacture of functional chemical products with their original know-how. Therefore, unless one has sufficient understanding of the sciences and possesses the highest level of basic technology, joint research is not possible and contribution cannot be made to realize the basic technology. Since we have the world’s highest level of elemental technology and scientific base for the highly selective activation of hydrogen peroxide, we were able to set clear chemical products and engaged in product realization through joint research with companies, and this led to product realization. Also, such ability to develop practical catalysts is not limited to hydrogen peroxide oxidation, but is an ability common to development and realization of any new catalysts. Currently, as new issues, we are taking on the direct manufacture from silicon raw materials using catalysts (using sand as a resource), manufacture of chemical products from carbon dioxide using catalysts, and direct manufacture of chemicals from oxygen and nitrogen in air (using air as a resource).

Acknowledgement

The development to realize the ultra-long life insulation material using the hydrogen peroxide epoxidation technology was conducted as a joint research with Showa Denko K.K., and we thank Mr. Hiroshi Uchida. The author Sato found the potential of hydrogen peroxide oxidation technology described in this paper while he was studying at the Nagoya University, and developed it as basic technology and realization technology with co-authors Kon and Tanaka at AIST. We are grateful to Professor Ryoji Noyori and the students of the Nagoya University, as well as Hiromichi Shimada, Masato Tanaka, Yoko Usui, and Masanori Okoshi of AIST. Part of this research was supported by the New Energy and Industrial Technology Development Organization (NEDO), and we express our thanks to all those involved.

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Discussions with Reviewers

Overall

Comment (Toshimi Shimizu, AIST; Akira Kageyama, Research and Innovation Promotion Headquarters, AIST)

This paper describes the research scenario for the synthesis and integration of elemental technologies, from the development of new catalysts as a basic research program to the manufacture and product realization at bench plant scale toward the final product realization, for the hydrogen peroxide oxidation technology that was presented by the authors for the first time in the world as a specific example of green sustainable chemistry. It is a paper on integrated chemical technology, and it addresses the importance of catalyst technology in chemical industry as well as the importance of different viewpoints and technologies that are necessary in practical application of new catalyst technology in the industry. It is appropriate for publication in *Synthesiology*.

1 Structure of the scenario and elemental technology

Comment (Toshimi Shimizu, Akira Kageyama)

In the first draft, the authors list five elemental technologies for the scenario to achieve the goal: 1) setting of the target compound, 2) development of new catalysts, 3) establishment of oxidation process, 4) cost reduction, and 5) manufacture at bench plant scale and evaluation of the product. While these are important technological factors to raise the hydrogen peroxide oxidation technology to a practical and industrial level, the core of this paper is the R&D of new catalysts. If 1) ~ 5) are presented on the same line, they give the reader an impression that the five factors are equivalent in importance. I think there needs to be a structure in explaining the scenarios and elemental technologies, for example: "The root of this research is the development of new catalysts that enables the industrial use of hydrogen peroxide as an oxidant, but for its realization, investigations and research for 1), 3), 4), 5) are necessary, as industrialization is not possible simply by creating a catalyst. In this paper, the integrating R&D for such elemental technologies will be explained." Also, I think you should consider the structure for what kind of working hypothesis was set up for the development of innovative catalysts, what kind of facts were found as a result, and how the problems were solved by presenting the sequential stories from the perspective of halogen-free technology, organic-solvent-less technology, catalyst recovery/reuse technology, metal catalyst design technology, phase transfer catalyst design technology, and others. Moreover, I think you should make some revisions because the explanations about the application to adipic acid synthesis that you first started and the subsequent conversion to epoxy resin synthesis are rather unclear.

Answer (Yoshihiro Kon)

We reconsidered the five items of elemental technologies in the first draft and removed them. Instead, we positioned the organic-solvent-less technology, halogen-free technology, and metal catalyst design technology as the elemental technologies of the basic catalyst technology that enables oxidation by hydrogen peroxide, and newly added chapter 3. There, we described the process of setting a working hypothesis, verification by experiment, examination, and repeating the process, in line with the basic R&D style for catalyst development in chronological order, taking care that there will be no misunderstanding. Also, we added chapter 5 to set up the elemental technologies that must be considered for realization research and the integration system. In that chapter, we argued that the catalyst technology using hydrogen peroxide was the basic technology, and there were three milestones - target setting, cost, and scaleup – needed to realize the technology. Also, we reconsidered the structure of the overall argument, and described the basic catalyst technology in the newly set chapter 3, the example of adipic acid in chapter 4, and the setting of milestones based on failure with adipic acid in chapter 5, in chronological order to help the readers' understanding.

2 Cost comparison

Question and Comment (Toshimi Shimizu)

The selection of desirable compounds that are the target of oxidation reaction, the design of the reaction plant for manufacturing, and the calculation of various costs are essential for industrialization. In the case in which the basic and functional chemicals are manufactured using the newly developed catalysts, the calculations of the costs of raw materials, catalysts, oxidants, facility investment, waste processing, and the value of final products are necessary. It is interesting to see what were the details (actual cost or the relative ratio) of the adipic acid manufacturing where the new method was withdrawn in comparison to the conventional method, as well as the details of the manufacture of ultra-long life insulation film (or epoxide) that was greatly successful. For example, if you present the particulars as a bar graph, I think the readers' understanding will deepen about the solution of the cost problem in manufacture realization described by the authors.

Answer (Yoshihiro Kon)

As you indicated, we added Fig. 9 as a cost comparison of the most possible clarity. In Fig. 9, it is clearly shown that the failure of adipic acid was due to the fact that nitric acid was overwhelming cheaper than hydrogen peroxide, and the key was the cost difference of oxidants. On the other hand, the factors of the success of epoxy resin were that the functional chemical products themselves are high added value products including the raw materials, the oxidation by nitric acid was impossible since

the oxidation reaction technology became increasingly complex, and therefore, the oxidation became extremely higher in cost using the conventional oxidants (described as the conventional method in Fig. 11). In chapter 5, we discussed how the development of the innovative catalyst technology that enabled the manufacture of epoxy resin using hydrogen peroxide provided the cost advantage, since the cost of hydrogen peroxide was overwhelmingly less than that of the conventional method, and that led to practical realization.

Question and Comment (Akira Kageyama)

It is important from the perspective of green sustainable chemistry to show the amount of nitrous oxide emission that occurs due to the production of 2.2 million ton of adipic acid. Also, can you show the cost of hydrogen peroxide as an index against the cost of nitric acid used as an oxidant, as well as the treatment cost of emitted nitrous oxide? I think you should have a description of a rough cost comparison.

Answer (Shinji Tanaka)

The emission of nitrous oxide that occurred due to adipic acid production was 400 thousand ton in 1999 (described in chapter 1). The cost was calculated from the perspective of compound cost related mainly to the manufacturing process, and this was added to subchapter 5.3.

3 Relationship of the two types of catalysts

Question (Akira Kageyama)

Is the way of thinking that the first type of catalysts (metal catalysts) and the second type of catalysts (phase transfer catalysts) can be developed independently a general way of thinking in the field of catalyst technology? If so, this may show that only the authors were aware that an interaction of two catalysts with different functions might occur. Can you say that it is necessary to design the chemical and conformational (three-dimensional) structures of the catalyst taking into consideration such interaction when investigating the metal catalyst and phase transfer catalyst? Also, will this interaction have some effect on scale-up?

Answer (Yoshihiro Kon)

As you indicated, we became aware that there might be interaction between the two catalysts with different functions that we developed, and utilized the interaction of the catalysts actively to improve their activity. In the revised draft, we added the section on catalyst technology development in chapter 3, and described the facts in chronological order. The relationship between the interaction and catalyst structure was added to chapter 3. Although there are effects of interaction of the catalyst components in scale-up, since the explanation of the two types of catalysts was not correct in the first place, we added the explanation in subchapters 5.2 and 5.4 from the perspective of the necessity of reviewing the catalyst when conducting scale-up.

4 Selection of target chemical product

Comment (Akira Kageyama)

In the first draft, you write, "Appropriate functional chemical products were selected as targets…," but can you describe the standard for "appropriateness"? I think the E-factor shown in Fig. 8 is one of them, but can you tell us the approximate value of the E-factor that is the standard? I think this is an extremely important point when judging the application range of this technology, and it is an original point that only the authors can claim. Also, I think this standard includes the added value factor of being able to prevent or control the negative functions of the products that accompany the use of chloride oxidants described later, not just the E-factor.

Answer (Yoshihiro Kon)

We think the "appropriate" standard is that the product has added value, has potential to sell, and possesses the potential for greatly reducing the E-factor theoretically. As an index, it must reduce the E-factor of the conventional method by one digit, and a ripple effect must be expected for the developed technology. We explained these in subchapter 5.1.

5 Epoxidation catalyst

Comment (Akira Kageyama)

I think the description of the epoxidation catalyst is the highlight of this paper, so please present the chemical structure of the catalyst and the reaction equation to obtain epoxide from olefin. Also, please show the detailed contents of the elemental technologies that were investigated and optimized to construct the integration system for this case. The first draft only describes the general theory, and what you did specifically is unknown. Since there are multiple elemental technologies, I think it is effective to present them using a fishbone diagram. Also, you write "the other type of catalyst," but can you use an expression that designates the function for this third type of catalyst, just as you did for the metal catalyst or the phase transfer catalyst?

Answer (Yoshihiro Kon)

The reaction equation of epoxidation was shown in Fig. 11 along with the description of adipic acid. To organize the milestones and elemental technologies in the progress toward realization, we created the fishbone diagram in Fig. 7 and offered an explanation in chapter 5.

I think the two types of catalysts for alcohol oxidation and adipic acid manufacture and the addition of the other type of catalyst for epoxidation are rather confusing. Therefore, we summarized the catalyst basic technology that enables oxidation by hydrogen peroxide in chapter 3. The third catalyst was called the "reaction site activating catalyst" to describe its function.

6 Future development

Comment (Akira Kageyama)

In future development, I think the authors have the knowledge and methodology to narrow down the candidate catalyst to some extent, compared to those who start from zero. Therefore, please describe the "methodology" for efficiently finding the optimal catalyst group. That is, how about stating that you have higher potential for achieving the objectives compared to those who start from zero, because the authors can use the accumulated knowledge and experience of science and technology?

Answer (Yoshihiro Kon)

As the methodology to efficiently find the optimal catalyst, as you indicated, I think we have the world's best understanding of the catalyst technology using hydrogen peroxide, all the way to the principle. We can quickly develop "specific" catalysts for target reaction by making minimum improvement to the basic technology based on this understanding, because we possess abundant knowledge and experience of the basic technology. I added this way of thinking to chapters 3~5 and 7. The knowledge of and experience with catalysts that we have accumulated do not stop at the hydrogen peroxide oxidation technology, but are common to the development of all practical catalysts.