The Transformation of Organic Chemistry in Japan: From Majima Riko to the Third International Symposium on the Chemistry of Natural Products

Masanori Kaji

Tokyo Institute of Technology, Japan

Introduction: The Period from 1930 to 1960 as a Turning Point of Chemistry in Japan

Majima Riko (1874–1962), one of the first organic research chemists of Japan[1], is widely known especially for his study of urushiol, the main component of Japanese lacquer tree sap. His research strategy involved studying the structure of the components of Japan's local natural products using newly developed methods from Europe to catch up to and compete with chemists in more advanced countries in the West[2]. Majima's approach became the primary research method employed by research organic chemists in Japan until the 1950s.

After Fukui Ken-ichi received the Nobel Prize in chemistry in Japan in 1981, six Japanese chemists went on to receive the same award. Most of these scientists discovered and developed new methods or theories from the 1950s to the 1970s.

This paper considers the Third IUPAC Symposium on the Chemistry of Natural Products in Kyoto in 1964, two years after Majima's death, as indication of the transformation of organic chemistry in Japan. By analyzing the circumstances behind this symposium, the topics presented in the symposium, and its consequences in the 1960s, this paper will elucidate the major factors that influenced the transformation of organic chemistry research in Japan.

1. Majima's Research Strategy: Research on the Structure of Urushiol

Majima was born in Kyoto in 1874, the eldest son of an affluent medical doctor. His generation was the first to study within a completely modern educational system established after the Meiji Restoration in 1868. Majima entered the chemistry department of the Imperial University in Tokyo in 1896. Soon after his graduation in 1899, he remained in the department as a research assistant and a graduate student under the supervision of Professor Sakurai Joji (1858–1939), one of the first Japanese professors of the department. Sakurai gave him complete freedom to choose research topics, but provided no real advice as to what area he should focus on. Moreover, while Sakurai studied physical chemistry, Majima's interests focused on organic chemistry. Because of the lack of an advisor to guide his research in organic chemistry, Majima studied the works of well-known German organic chemists that had been published in German journals and were available in his department[3]. When he began

[1] In this paper, the author follows the Japanese custom with regard to personal names of historical figures: the family name is provided first, followed by the given name. Here, *Majima* is the family name and *Riko* is the given name. Japanese contemporary authors' names, including the author of this paper, follow the western custom, i.e., the given name is provided first. To learn more about Majima, see Masanori Kaji, "The Role of Riko Majima in the Formation of the Research Tradition of Organic Chemistry in Japan (in Japanese)," *Kagakushi-Kenkyu (The Journal of the Japanese Society for the History of Chemistry)* **38** (2011): 173-185.

[2] Majima Riko, "Waga Shogai no Kaiko (1)[Reminiscence of My Life (1)] (in Japanese)," *Kagaku no ryoiki*, **8** (1): 1-11 (1954), p.6.

[3] Monthly reading seminars of articles of western scholarly journals, called "Zasshikai," began in 1890 at the

to conduct research in organic chemistry, he decided to study local natural products to compete with chemists in the West and first studied the structure of urushiol, the main component of Japanese lacquer tree sap. The lacquer tree is an important indigenous commercial source of natural lacquer. Studies on lacquer tree components began in 1882 in Japan, with the main component being named urushiol by Miyama Kisaburo (1873–?) in 1906[4]. Majima asked Miyama to allow him to study the structure of urushiol; Miyama himself studies its application for lacquer.

In 1903, Majima was promoted to associate professor, and the Ministry of Education sent him to Europe for further study in 1907. During his Europe until 1911 he conducted research in Kiel under Carl Dietrich Harries (1866–1923) and in Zurich under Richard Willstätter (1872–1942). While in Europe, besides research on topics provided by his European supervisors, Majima continued to study urushiol using advanced methods available in the laboratory, including Harries' vacuum distillation and ozonolysis[5] and Willstätter's hydrogenation of alkenes by platinum catalysis[6].

Majima returned to Japan in January 1911 and became a professor of organic chemistry at Tohoku Imperial University, a newly established imperial university in Sendai, northern Japan, in March. After establishing his laboratory, he restarted his research on the structure of urushiol using newly introduced advanced instruments and methods from Europe. Within six years, he succeeded in elucidating the structure of urushiol as a catechol (*o*-dihydrobenzene) derivative.

Majima's approach to urushiol research and his study of local natural products using newly developed European methods was adopted as a major research method in Japan until the 1950s. Many of his students followed this line of research.

2. Research Tradition of Natural Products Chemistry in Japan after Majima and Its Consequences (I): Nozoe Tetsuo and Hinokitiol[7]

Nozoe Tetsuo was one of Majima's students at Tohoku Imperial University, and his research path showed how Majima's research line was developed by his students. Nozoe was born in Sendai in 1902. He entered the chemistry department of the science faculty at Tohoku Imperial University in 1923. During his tenure at the university, Majima became Nozoe's mentor and played a decisive role in his career.

After his graduation in March 1926, Nozoe stayed on as Majima's assistant but left Sendai for Formosa (now Taiwan) at the end of June 1926 to become a researcher at the Monopoly Bureau in Taipei, the capital of Formosa, a move he made under Majima's strong recommendation. Nozoe was a candidate professor at a newly planned imperial university in Formosa. In 1928, Taihoku Imperial University (Taihoku is the Japanese name for Taipei) was established, and young Nozoe was appointed as an associate professor the following year. Taihoku Imperial University was the second Japanese imperial university to be established

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chemistry department of the Imperial University. See *Tokyo Daigaku Rigakubu Kagaku-kyoshitsu no Ayumi* [in Japanese, The History of the Chemistry Department of the Science Faculty of the University of Tokyo], Tokyo: Kokusai Bunken Insatsu Sha, 2007, p.58 and the site: http://www.zasshikai.jp/html/2setsuritsu.html.

[4] Majima Riko, "Urushi seibun kenkyu no kaiko [in Japanese, Reminiscence on the studies of the Japanese lacquer components]" in *Majima Riko Sensei Iko to Tsuioku* [Majima Riko, his posthumous manuscripts and Reminiscence], Tokyo: Tokyo Kagaku Dojin, 1970, pp.63-102, p.64. This article was first published in 1945.

[5] Fischer, Emil und Carl Harries, "Ueber Vacuumdistillation," *Ber. Dtsch. Chem. Ges.* **35** (1902): 2158-2163; Harries, Carl, "Ueber die Einwirkung des Ozones auf organische Verbingungen," *Liebigs Ann. Chem.* **343** (2-3) (1905): 311-344.

[6] Willstätter, Richard, "Über Reduktion mit Platin und Wasserstoff beigewöhnlicher Temperatur. I," *Ber. Dtsch. Chem. Ges.* **41** (1) (1908): 1475-1480.

[7] Kaji, Masanori "Nozoe Tetsuo's Chemical Research at Taihoku Imperial University in Taiwan and Its Colonial Context," *Historia Scientiarum*, vol. 18-2 (2008): 132-139.

among its colonies after Keijo Imperial University in Keijo (now Seoul), which was founded in 1925. Nozoe's main research interests lay in the study of natural products, especially those found in Formosa, following his mentor's approach.

Nozoe's well-known work in Formosa concerned the chemical components of *taiwanhinoki*, a native conifer growing in high mountainous areas. Nozoe determined a new compound, hinokitiol, from the components of this species and reported it for the first time in 1936 in a special issue of *Bulletin of the Chemical Society of Japan* to celebrate Professor Majima's sixtieth birthday[8].

By studying hinokitiol's structure, Nozoe determined that the compound may be a new type of aromatics stabilized by resonance involving intramolecular hydrogen bonds after reading Linus Pauling's *The Nature of the Chemical Bond* (1939). While hinokitiol was later proven to exist not as a resonance hybrid but as a pair of tautomers that interconvert through intramolecular hydrogen bonds, Nozoe's idea was the first step in establishing new research on nonbenzenoid aromatics.

After World War II, Formosa was returned to the Republic of China and Taihoku Imperial University was renamed National Taiwan University. While most Japanese citizens left Taiwan for Japan, Nozoe stayed on in the country and worked as a chemistry professor at National Taiwan University under the orders of the Chinese government, who needed specialists to advance their academic agenda.

Since Nozoe regarded hinokitiol as a compound with a novel aromatic structure, he examined various substitution reactions, including halogenation, nitration, and azo coupling. He managed to return to Japan at the end of May 1948, with his alma mater, Tohoku University offering him a teaching position. The results of his group's research on hinokitiol at National Taiwan University were published in 1950–1952 in Japanese journals, especially in *Proceedings of the Japan Academy* in English.

When the symposium "Tropolone and Allied Compounds" was organized by the Chemical Society of London in November 1950, Nozoe's work on hinokitiol was mentioned as a pioneering contribution to tropolone chemistry, thereby helping Nozoe's research gain recognition in the West. Nozoe was able to publish his work on hinokitiol and its derivatives in *Nature* in 1951 thanks to J.W. Cook, the chairman of the symposium[9].

Nozoe's work, which began with research on natural products in Taiwan and became developed fully in Japan in the 1950s and the 60s, introduced a new field of organic chemistry, i.e., the chemistry of non-benzenoid aromatic comppounds. His work was well appreciated in Japan and Nozoe received the Order of Culture, the highest honor for contributing researchers and artists in 1958 at a relatively young age of 58. Nozoe's work is an excellent example of how Majima's students developed his line of research. Majima's research school demonstrated the level of organic chemistry research in Japan that had been reached by the 1950s.

3. Research Tradition of Natural Products Chemistry in Japan after Majima and Its Consequences (II): Shimomura Osamu and the Chemistry of Marine Natural Products

Shimomura Osamu, a Japanese biochemist who won the Nobel prize for chemistry in 2008, studied the chemistry of marine natural products by essentially following Majima's approach[10]. Shimomura's work is an example of how local approaches may transform into universal methods[11].

[8] Nozoe, Tetsuo, "Über die Farbstoffe in Holzteile des "Hinoki" Baumes. I. Hinokitin und Hinokitiol." *Bull. Chem. Soc. Japan*, 11 (1936): 295-298.

[9] Nozoe, Tetsuo, "Substitution Products of Tropolone and Allied Compounds," *Nature* 167 (1951): 1055-1057.

[10] To learn more about his biography and work, see (1) Osamu Shimomura - Biographical" <http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2008/shimomura-bio.html>; and (2) "Discovery of

Shimomura Osamu was born on August 27, 1928 in Kyoto prefecture. After graduating from the pharmaceutical special division, attached to Nagasaki School of Medicine, in 1951, he became an assistant in the analytical chemistry laboratory for students of Nagasaki University, into which Nagasaki School of Medicine was incorporated in 1949.

In 1955, he obtained a one-year leave of absence with pay to study in the organic chemistry laboratory of Hirata Yoshimasa (1915–2000) in Nagoya University, the last imperial university with prominence in research. During his stay at the university, he was asked by Prof. Hirata to purify and crystallize luciferin, an unstable light-emitting compound obtained from the sea-firefly; which no one had been able to do until then. After 10 months of hard work, Shimomura finally succeeded in crystallizing the compound and was invited to stay in the laboratory for another year to study its structure[12]. Shimomura's research attracted the attention of Dr. Frank Johnson of Princeton University, who later invited Shimomura to work in his laboratory.

At the end of August 1960, Shimomura left Japan for the United States with a Fulbright travel grant. Every summer beginning from 1961 until 1978, he and Dr. Johnson evaluated bioluminescent substances in luminous jellyfish found in Friday Harbor at San Juan Island, Washington State. As early as the fall of 1961, Shimomura had succeeded in extracting several few milligrams of purified protein aequorin, the first example of photoproteins ever discovered[13]. His work also uncovered trace amounts of another protein exhibiting bright green fluorescence; this protein was later named "green fluorescent protein (GFP)" by other researchers. Shimomura elucidated the structure of GFP in 1979 when he had obtained an adequate amount of GFP as a by-product of an 18-year study on aequorin[14]. GFP has become indispensable in molecular biological studies because it contains a fluorescent chromophore within its peptide chain and can be expressed in living bodies. Shimomura, along with other researchers, was awarded the Nobel prize for the discovery of GFP and development of its use as a tagging tool in bioscience.

4. The International Symposium on the Chemistry of Natural Products in Kyoto, 1964

The Third IUPAC Symposium on the Chemistry of Natural Products was held in Kyoto on April 12–18, 1964, two years after Majima's death[15]. This symposium was the first international conference on organic chemistry in Japan[16]. A total of 1,454 chemists consisting

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Green Fluorescent Protein, GFP," Nobel Lecture, December 8, 2008. <http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2008/shimomura_lecture.pdf>

[11] To learn more about problems of "places" in scientific activity, see David N. Livingstone, *Putting science in its place: geographies of scientific knowledge* (Science・Culture), University of Chicago Press, 2003.

[12] Shimomura, Osamu, Goto, Toshio and Hirata Yoshimasa, "Crystallin Cypridina luciferin," *Bull. Chem. Soc. Japan* 30 (1957): 929-933; Shimomura, Osamu, "Umi-Hotaru Luciferin no Kyozo [in Japanese, Structure of Cypridina luciferin] II," *Nihon kagaku zassi* (*J. Chem. Soc. Japan. Pure Chem. Section*) 81 (1960): 179-182.

[13] Shimomura, Osamu, Johnson, Frank H., Saiga, Y., "Extraction, purification and properties of aequorin, a bioluminescent protein from the luminous hydromedusan, Aequorea," *J. Cell Comp. Physiol.* 59 (1962): 223-239.

[14] Shimomura, Osamu, "Structure of the chromophore of Aequorea green fluorescent protein," *FEBS* [the Federation of European Biochemical Societies] *Lett.* 104 (1979): 220-222.

[15] To learn more about this symposium, see (1) Nihon Gakujutsu Kaigi [Science Council of Japan] Kokusai Tennenbutsu Kagaku Kaigi Soshiki Iinkai [the organizing committee of the International Symposium on the Chemistry of Natural Products], ed., *Kokusai Tennenbutsu Kagaku Kaigi* [in Japanese, the International Symposium on the Chemistry of Natural Products], Tokyo: Tokyo Kagaku Dojin, 1965; and (2) International Union of Pure and Applied Chemistry. Organic Chemistry Division and The Science Council of Japan, *Special lectures presented at the 3rd International Symposium on the Chemistry of Natural Products, held in Kyoto, Japan, 12-18 April, 1964*, London: Butterworths, 1964.

[16] Tsuda Kyosuke, "Interview: Yakugaku no ima to mukashi Tuda Kyosuke sensei ni kiku [in Japanese, Present and Past of Pharmacy: Interview with Professor Kyosuke Tsuda]," Faurmashia (Pharmaceutical Society of Japan) 29(12) (1993): 1351–1354, p.1353.

of 1,212 Japanese and 242 foreign scholars participated in the conference, and 223 presentations, including 11 special lectures, were given. Many Japanese participants considered this conference to be a success and a major turning point in the history of organic chemistry in the country[17].

In this symposium, presentations on the structure of tetrodotoxin, the poisonous compound of puffer fish, were given by four groups, two from Japan and two from the US. Tsuda Kyosuke (1907–1999) and associates at the University of Tokyo, Hirata Yoshimasa and associates at Nagoya University, and R. B. Woodward (1917–1979) of Harvard University presented recent independent results on the structure of tetrodotoxin; the findings of these groups were identical with one another. H. S. Mosher and associates at Stanford University proved that the structure of tarichatoxin, the poison extracted from the eggs of various species of Western American newts, is identical to that of tetrodotoxin. All of these groups employed instrumental analysis, including infrared, ultraviolet, nuclear magnetic resonance, and mass spectroscopy, as well as X-ray diffractometry.

While puffer fish and other species of its family are found in tropical and semi-tropical seas all over the world, they are prized as delicacies only in Japan and China because they are highly toxic when eaten. Tahara Yoshizumi (1855–1935), a Japanese pharmacologist, first isolated the poison from puffer fish and named it tetrodotoxin in 1907[18]. After a long pause in research on this component, Tsuda and his associates began to study tetrodotoxin in 1950. After two years, this group successfully crystallized the poison by following an improved crystallization method. Woodward did not discuss why he began to study the structure of tetrodotoxin; I suppose that he and his group only began work on it to show off their superb techniques after Woodward was invited in Japan as a keynote speaker in a special lecture on natural products chemistry. In the acknowledgement section at the end of his paper, Woodward gave special thanks to researchers in Loma Linda University in South California, who extracted pure tetrodotoxin from several tons of puffer fish entrails for Woodward's work[19].

These events in the International Symposium in Kyoto show the limitations of Majima's approach as a method to compete with those of top-level researchers overseas. One of Tsuda's co-workers later wrote about his group's work on tetrodotoxin and confessed that they first believed that one should only compete with colleagues in Japan because of the alleged unavailability of the poison and the difficulty of its crystallization. However, while only a limited number of people eat puffer fish, the fish itself lives in wide areas of tropical sea. Moreover, advances in instrumental analysis provided little "first-mover advantage" to scholars who had begun their research earlier; for top-level researchers, such as Woodward, these advances did not make any difference in their work.

5. Transformation of Organic Chemistry in Japan

Due to Instrumentation, Majima's approach was not valid anymore for competition with Western colleagues, like Woodward. However, the Japanese became well prepared to compete on an equal footing with their Western counterparts without taking advantage of local advantage by the end of the 1950s.

[17] See, for example, note 15 (1), p.iii; Ikegawa Nobuo et al., eds. *Yakugaku to tomoni Rokuju-go nen: Tsuda Kyosuke Sensei 85 sai kinen bunshu* [65 years with pharmacy: Collection of essays to commemorate the 85th birthday of Professor Tsuda Kyosuke], Tokyo: Hirokawa Shoten, 1992, pp.23, 30–31, 45, 230–233.

[18] Tahara Yoshizumi, "Fugu doku kenkyu hokoku [Studies on the poison of puffer fish]," *Tokyo Kagaku Kaishi* (1909): 121–173.

[19] R. B. Woodward, "The Structure of Tetrodotoxin," *Pure Appl. Chem.* 9 (1964): 49–74, p.74.

Majima's approach gave "first-mover advantage" to Japanese chemists during the period between 1906, when Majima thought out his research strategy and attempted to apply it to urushiol, and 1950, when Tsuda started to study tetrodotoxin.