Grants-in-Aid for Scientific Research and the Exploration of Asymmetric Autocatalysis

Kenso Soai

Professor, Faculty of Science, Tokyo University of Science

Research Theme Implemented in FY2015:

Research on the origins of chirality in asymmetric compounds by using asymmetric autocatalysis (Grant-in-Aid for Scientific Research (B))

The program of Grants–in-Aid for Scientific Research (Kakenhi) comprises a diversity of research categories for projects with budgets ranging from comparatively small to large in scale. This allows researchers to file applications under categories suited to the current funding needs of their individual projects and in keeping with the principles of free and independent thought. I consider this to be one of the defining strengths of the Kakenhi program itself. After beginning my career as a professional researcher, as a rule, I made it a point to apply for Kakenhi every year except in those cases that involved projects extending over the next fiscal year. Given that Kakenhi have provided an immense measure of support for my research, I would like to detail my experiences with the program together with the highlights of my research career.

If you look at your left hand in a mirror, the mirror image appears to be shaped exactly like your right hand. However, you cannot superimpose your left and right hands over one another as they are in fact different shapes. A left-handed baseball glove does not fit your right hand, and in daily life, of course, we also make this distinction between left and right with our shoes. Amino acids and many other crucial compounds that form the structures of living things are similar in that they have isomers that are mirror images of one another and cannot be superimposed (that is, they cannot be superimposed without breaking and rearranging chemical bonds). This condition is termed asymmetry and these stereoisomers are referred to as enantiomers. Interestingly, all life forms comprise compounds that are weighted almost exclusively in one enantiomer. Natural amino acids, for example, are overwhelmingly of the left-handed (L-) variety whereas sugars are almost exclusively of the right-handed (D-) type. In fact, all life forms are composed of asymmetric compounds that incorporate the same L-type enantiomers of amino acids. This homochirality is one of the principal defining characteristics of life. Whereas it is easy for two individuals to shake hands with their right hands, it is awkward if one uses his right hand while the other attempts to shake with his left. In the same fashion, proteins or genes formed with irregular bonds between the left-handed and right-handed enantiomers of biomolecules undergo changes in their chemical structure and are

rendered incapable of sustaining biological activity because they do not facilitate enzymatic action or the accurate transmission of genetic information. Also, in the same way that a glove for the left hand interacts differently with the right hand, medical drugs with asymmetric chemical structures bearing both enantiomers will have different biological activities because living organisms are made up of asymmetric compounds. This is why asymmetric synthesis that allows for the selective synthesis of only the useful enantiomer has become an important research theme in the field of chemistry.

However, how was the first asymmetric organic compound emerged, and through what process did such compounds, once formed, become heavily enriched in only one type of enantiomer? These are questions surrounding the origin of chirality, an unsolved riddle for over 160 years that has continued to interest the research community to this day. Inorganic quartz crystals and circularly polarized light are among the candidates cited by theories proposed to explain the origin of chirality in organic compounds. However, these factors account for an extremely marginal share of the asymmetry induced in organic compounds, and the process that leads to one type of enantiomer observed in life forms remains unknown.

I have been engaged for many long years in research on asymmetric synthesis at the Tokyo University of Science. The products of ordinary chemical reactions are mixtures containing equimolar amounts of left- and right-hand enantiomers. By contrast, in asymmetric synthesis, an asymmetric catalyst is utilized with the goal of inducing a product with an excess in one of its two enantiomers. The key here lies in the design of an effective asymmetric catalyst for that purpose. With Kakenhi funding in the categories of Encouragement For Young Scientists (now Young Scientists), General Scientific Research (now Scientific Research) (C), and Scientific Research for Priority Areas, and Scientific Research on Priority Areas, I was able to pursue research on asymmetric reduction of ketones, catalytic asymmetric addition reactions of aldehyde with organo-zinc reagents, asymmetric addition reactions of imine, and catalytic asymmetric conjugate addition reactions of unsaturated ketones.

In the process of pursuing these lines of research, I came up with a number of ideas. First of all, if an asymmetric catalyst could be utilized to asymmetrically synthesize asymmetric products bearing the same chiral structure, it might be possible to achieve asymmetric autocatalysis based on principles entirely different from traditional approaches. If this were achievable, it was certain to be perceived as a highly intriguing phenomenon because it would facilitate the processes of asymmetric compound self-replication and automultiplication as observed in living organisms. Compared to conventional methods of asymmetric synthesis, the

products of asymmetric autocatalysis function as new catalysts themselves and increase the quantity of catalyst in reaction; the decrease in catalyst quantity and deterioration in catalytic activity observed with conventional methods do not occur. Another conceivable advantage of this approach is that it does not require separation of the catalyst from the reaction product because they share the same chemical structure. However, at the time, examples of asymmetric compounds functioning as catalysts and facilitating asymmetric automultiplication were entirely unknown, and the question of whether such reactions could actually take place remained unexplored.

To address that question, I performed an experiment involving the reaction of a zinc reagent containing an isopropyl substituent with a nitrogen-containing aldehyde that incorporated a pyridine ring, utilizing a pyridyl alkanol as the asymmetric autocatalyst. With this experiment, I discovered a reaction that preferentially synthesizes products bearing the same structure as the asymmetric autocatalyst (1990). That was the first finding on the automultiplication of asymmetric compounds. Around that time, I was also involved as a participant in Kakenhi-funded research in the category of Scientific Research for Priority Areas (currently the category of Scientific Research on Innovative Areas), yearned to pioneer the development of asymmetric autocatalysis, and engaged in an investigation of the structure of various types of substrates.

After numerous investigative trials, in 1995 I finally succeeded in discovering an extremely efficient protocol for asymmetric autocatalysis. Utilizing a pyrimidyl alkanol as the asymmetric autocatalyst, I initiated a reaction of an aldehyde containing a pyrimidine ring with two nitrogen atoms and a zinc reagent containing an isopropyl substituent and discovered that this efficiently synthesizes a product with only the enantiomer bearing the same structure as the asymmetric autocatalyst. Additionally, I found that this reaction significantly amplifies the enantiomeric excess (the difference of percentage between dominating enantiomer and the other) in the product sample even if it utilizes an asymmetric autocatalyst with an extremely low level of enantiomeric excess. In other words, I had demonstrated the existence of reactions that, even if started with an asymmetric autocatalyst marked by extremely low enantiomeric excess, continue with repeated reactions utilizing the product (with the same structure as the catalyst) itself as an asymmetric autocatalyst and ultimately result in the synthesis of an asymmetric compound with an extremely high level of enantiomeric excess. These findings led to the approval of Kakenhi applications for projects in the categories of Scientific Research (B and A) and Scientific Research on Priority Areas, and enabled me to achieve major research strides.

Next, I began utilizing asymmetric autocatalysis to unveil the mystery surrounding the origin of chirality. Given that quartz is a chiral mineral, I utilized it as a chiral trigger in a reaction involving a zinc reagent and an aldehyde containing a pyrimidine ring, and discovered a method for the highly reproducible synthesis of products with levels of chirality that correlate closely with the asymmetry of the crystal trigger. This was the first success in establishing a correlation between quartz asymmetry and one of the enantiomers of organic compounds. I also succeeded in formulating reactions that harness circularly polarized light as the chiral trigger as well as methods of absolute asymmetric synthesis that utilize statistical fluctuations as their origin of chirality. For these research undertakings, I was aided by large-scale Kakenhi in the categories of Specially Promoted Research and Scientific Research (S). I was highly encouraged by this national government mandate to pursue large-scale research, and accordingly forged ahead with my work.

To summarize, I discovered an asymmetric autocatalytic reaction that can amplify asymmetry from infinitesimal to almost enantiomerically pure. I also pursued research on asymmetric autocatalysis utilizing crystals, circularly polarizing light, and absolute asymmetric synthesis as the origin of chirality. As a researcher, I am extremely honored that this reaction is now frequently cited as the Soai reaction by literature in many scholarly fields ranging from chemistry, physics, and biology to space science. My accomplishments in this research field would not have been possible without the cooperation and assistance I received from the many colleagues that have been involved in the work of my laboratory. I am deeply grateful for the support I have received to date through the Grants-in-Aid for Scientific Research. The program provides broad coverage for academic research driven by the free and independent thought of researchers themselves. As a national foundation for the pursuit of scientific research, it is an extremely valuable program, and I am hopeful it will continue to expand and be an effective source of support for future generations of researchers in the years ahead.