Chemical Systems Involving Two Competitive Self-Catalytic Reactions

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ABSTRACT: Self-catalytic reactions are chemical phenomena, in which a product catalyzes the reactions of substrates further to yield products. A significant amplification of product concentration occurs during the reactions in a dilute solution, which exhibit notable properties such as sigmoidal kinetics, seeding effects, and thermal hysteresis. Chemical systems involving two competitive self-catalytic reactions can be considered, in which the competitive formation of two products occurs, which is affected by environmental changes, subtle perturbations, and fluctuations, and notable chemical phenomena appear such as formation of different structures in response to slow/fast temperature changes, chiral symmetry breaking, shortcut in reaction time, homogeneous−heterogeneous transitions, and mechanical responses. Studies on such chemical systems provide understanding on biological systems and can also be extended to the development of novel functional materials.

1. CHEMICAL SYSTEMS INVOLVING TWO COMPETITIVE SELF-CATALYTIC REACTIONS

1.1. Self-Catalytic Reactions in Chemical Network systems. Biological processes employ chemical network systems composed of a set of molecules and a set of regulatory interactions, through which chemical information flows forward/backward and in multiple directions, as observed in gene expression, cell development, signal transduction, and cell differentiation.1−14 Cell responses in terms of timing, sensitivity, dynamic range, and persistence are controlled by chemical reactions involving both covalent and noncovalent bond formation and cleavage, and the regulated interactions involve positive and negative feedbacks. The chemical network systems provide various chemical outcomes, depending on the environmental conditions such as concentration, temperature, and substances added.

Positive and negative feedbacks, through which a reaction is, respectively, promoted and retarded by products and intermediates in a chemical network system, are an essential feature in biological processes. A positive feedback provides switchlike network responses, which generate bistability and multistability, amplifies signals, converts analog inputs into digital outputs, and generates persistent memory.5−8 A negative feedback provides robustness against noise, adaption to perturbations, tuning of range and transition rate, maintenance of homeostasis, and time delay. To understand and control biological systems, studies of synthetic chemical network systems are critical, in which chemical phenomena can be systematically examined, and such studies can be extended to the development of novel functional materials.

Self-catalysis (autocatalysis) is an important positive feedback mechanism in biological processes, through which a product catalyzes reactions to convert substrates into products.10−16 A set of chemical reactions involving self-catalysis plays pivotal roles, for example, by mutual catalysis, cross-catalysis, and collective autocatalysis.17−22 Therefore, it is interesting to study synthetic chemical systems involving self-catalysis, although such systems are rare.23,24 Self-replication reactions of nucleic acids and related compounds have been examined, which involve the catalysis phenomenon byproducts.25−30 The reactions, however, often suffer from product inhibition and become slow at an early stage. The Belousov−Zhabotinsky reaction is characterized by chemical oscillation, in which an inorganic species periodically changes its concentration in a stirred solution during the oxidation of malonate to carbon dioxide.31−33 Under unstirred conditions, homogeneous−heterogeneous transitions occur, giving the appearance of travelling waves. Complex reaction mechanisms involving self-catalysis were clarified in the formation of HBrO₂, the concentration of which oscillates. Self-catalysis is also involved

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in organometallic reactions. The Soai reaction is an interesting example of a self-catalytic reaction producing enantiomers, which exhibit chirality symmetry breaking caused by a subtle chiral perturbation.

Chemical kinetics of the competitive reactions provide the rate laws \(-d[A]/dt = (k_1 + k_2)[A]^2\), \(d[B]/dt = k_1[A]^2\), and \(d[C]/dt = k_2[A]^2\), where \([A]\), \([B]\), and \([C]\) are the concentrations of \(A\), \(B\), and \(C\), respectively. The rate constant to form \(B\) and \(C\) is then determined by the relative rate constant \(k_1/k_2\), which does not significantly change during the reaction. Thus, high selectivity requires large differences between the rate constants; for example, a 99:1 ratio is derived from \(k_1/k_2 = 10^5\).

In the transition-state theory, \([B]/[C]\) is determined at a later stage. The Boltzmann distribution is not applicable because the reaction is not at equilibrium. Another example is chiral symmetry breaking, in which both paths are energetically identical, but \([B]/[C]\) is not 1 (Figure 2c).

Another limitation is that deterministic kinetics are applicable to systems with huge numbers of molecules, for example, on the order of the Avogadro's number, and may not be applicable to a system with a small number of molecules. For example, consider a biological cell containing \(10^7\) molecules of a protein. Then, the standard deviation \((10^{30})^{1/2} = 10^{-7}\) indicates that a statistically exceptional chemical reaction occurs for every 100 molecules, which is not small when considering the huge number of chemical reactions in a cell.

Stochastic kinetics has been developed to depict such systems. This model is based on the concept that molecules undergo chemical reactions in a dissipative manner, not continuously, and is described by the chemical master equation with probability.
Figure 3. Chemical reaction network system, in which reactions occur from 2A to B and C, as described by the chemical master equation. \( P_i, P_j, \ldots \) are the probabilities for the system to be in the state \( i, \) and \( q_{12}, q_{13}, \ldots \) are the transition probabilities, which are functions of time \( t \).

\[
dP(t)/dt = \sum_j (q_{ij}(t)P_j(t)) - q_{ji}(t)P_i(t)
\]

where \( P_i(t) \) is the probability for the system to be in the state \( i \) at the time \( t \); \( q_{ij}(t) \) is the transition probability of molecule \( j \). \( P(t) \) is formally the concentrations of molecules, and \( q(t) \) is the rate constant, which are both time-dependent. Numerical analysis methods to solve the equation have been developed. Stochastic kinetics qualitatively depict chemical reaction phenomena, for example, oscillation and chiral symmetry breaking.\(^{65,66} \) It is, however, not easy experimentally to determine \( q(t) \) for each reaction, and qualitative analysis of chemical reactions based on stochastic kinetics awaits future development.

To depict the mechanism of the chemical systems involving two competitive reactions, microscopic multiple pathways, which is the subject of the quantum mechanics, and macroscopic multiple pathways, which is subject studied in statistical mechanics, must be considered.\(^{43-46,67-70} \)

1.3. Chemical Systems Involving Two Competitive Self-Catalytic Reactions. Consider a chemical system involving two competitive self-catalytic \( 2A + B \to 2B \) and \( 2A + C \to 2C \) reactions, where \( B \) catalyzes the \( 2A \to B \) reaction, and \( C \) catalyzes the \( 2A \to C \) reaction (Figure 1b). In such systems, the product distribution \( [B]/[C] \) can vary substantially even under fixed environmental conditions because of the amplification of subtle perturbations and fluctuations by the self-catalytic reactions, in which the concentration of product \( B \) or \( C \) significantly increases once a certain concentration of \( B \) or \( C \) is reached. In addition, changes in environmental conditions during the reactions significantly affect \( [B]/[C] \). Then, the macroscopic pathways become complex, that is, how many molecules visit microscopic pathways to form \( B \) and \( C \). Such experimental examples of chemical network systems are described in the following sections.

The thermodynamics allow a single equilibrium state under a single environmental condition. Then, when \( A \) is thermodynamically the most stable at equilibrium, \( B \) and \( C \) are metastable; when the relative thermodynamic stabilities inverted between \( A \) and \( B \) by a change in environmental conditions, \( B \) can be at equilibrium, and \( A \) and \( C \) can be metastable.

The macroscopic multiple pathways are complex in a chemical system of two competitive self-catalytic reactions. In the systems involving two competitive self-catalytic \( 2A + B \to 2B \) and \( 2A + C \to 2C \) reactions, three structures \( A, B, \) and \( C \) are available, and then the concentration changes are complex in terms of the concentrations \([A], [B],\) and \([C]\). The following macroscopic multiple pathways, for example, can occur (Figure 4): one-directional three-state systems, \( A \to B \to C \) to \( A \) and \( A \to C \to B \to A \); competitive systems, \( A \to B \to A \to C \) and \( A \to B \to A \to C \); four-state systems, \( A \to B \to C \to A \) and \( A \to B \to A \to C \); five-state systems, \( A \to B \to C \to A \to C \) and \( A \to B \to A \to C \to A \).

Figure 4. Macroscopic multiple pathways between three states \( A, B, \) and \( C \) involving a system of two competitive self-catalytic reactions (green arrows).

Figure 5. Energy diagrams of a chemical system involving two competitive self-catalytic \( 2A + B \to 2B \) and \( 2A + C \to 2C \) reactions over time. Red arrows indicate macroscopic pathways, and the blue bold lines indicate the number of molecules. The green arrow indicates self-catalytic reaction. Molecules do not visit dashed pathways because of the lack of \( B \) or \( C \).

B/A-to-ent-B, where ent-B is the enantiomer of \( B \); and selective A-to-B without A-to-C and A-to-C without A-to-B.

1.4. Kinetic Aspects of Chemical Systems Involving Two Competitive Self-Catalytic Reactions. On the basis of previous considerations, the mechanism underlying chemical systems involving two competitive self-catalytic reactions is discussed. The mechanism of a self-catalytic \( 2A + B \to 2B \) reaction is provided by a two-path model involving the bimolecular \( 2A \to B \) reaction, which is applied to the competitive system of two self-catalytic \( 2A + B \to 2B \) and \( 2A + C \to 2C \) reactions (Figure 5). Initially, the bimolecular \( 2A \to-

and \( 2A \to C \) reactions are slow because of the high barriers to the formation of either \( B \) or \( C \). Once \( B \) is formed in a certain amount, the low-barrier self-catalytic path is opened, which is amplified by the self-catalytic \( 2A + B \to 2B \) reaction to provide large amounts of \( B \). Thus, switching the pathway is a critical aspect in a competitive system.

Deterministic chemical kinetics provide the rate law

\[-d[A]/dt = k_3[A]^2[B] + k_4[A]^2[C]\]

where \( k_3 \) and \( k_4 \) are the self-catalytic rate constants for the formation of \( B \) and \( C \), respectively. With a small difference between \( k_3 \) and \( k_4 \), assuming the same initial concentrations \([B]_0\) and \([C]_0\) of \( B \) and \( C \), respectively, and the initial state of the reaction with \([A] = [A]_0\), the selectivity is expressed by

\([B]/[C] = \exp((k_3 - k_4)[A]_0^{-2}t)\]

\[d[A]/dt = k_3[A]^2[B] + k_4[A]^2[C]\]
A numerical analysis with $\left[A\right]_0 = 10^{-3}$ M, $\left[B\right]_0 = \left[C\right]_0 = 10^{-6}$ M, $k_3 = 1 \times 10^8$ M$^{-2}$ s$^{-1}$, and $k_4 = 0.9 \times 10^4$ M$^{-2}$ s$^{-1}$, and $\left[B\right]/\left[C\right]$ = 2.7 at $t = 10$ s yields $\left[B\right]/\left[C\right] = 150$ at $t = 50$ s. The analysis indicates significant selectivity enhancement by 10% difference between the rate constants. Note that the rate $d\left[B\right]/dt = k_1\left[A\right]^2\left[B\right]$ is dependent on the concentration of the product $\left[B\right]$, and accordingly $\left[B\right]/\left[C\right]$ can exhibit a complex nature.

The chemical system involving two competitive self-catalytic $2A + B$-to-$2B$ and $2A + C$-to-$2C$ reactions shows some similarity with a chemical system with a small number of molecules, despite the involvement of huge numbers of molecules. A chemical reaction of a molecule is considered to be completed on the order of picosecond. For example, consider a reaction involving $10^{20}$ molecules (0.15 mmol), that is completed in $10^8$ s (approximately 3 h). Then, $10^4$ molecules react every picosecond, which is not a large number. The standard deviation $(10^{-30})^{1/2} = (10^{-4})^{1/2} = 10^{-2}$ indicates that a statistically exceptional reaction can occur for every 100 $A$ molecules. In general, such fluctuations can be time-averaged in $10^{16}$ picoseconds (approximately 3 h), and deterministic kinetics are applicable, in which fluctuations become negligible. However, in the case that a statistically exceptional reaction to form $B$ or $C$ is amplified by self-catalysis, a large number of either $B$ or $C$ molecules can form. Then, chaotic phenomena appear, in which subtle differences in the concentration of $B$ or $C$ significantly change $\left[B\right]/\left[C\right]$. This can formally be regarded as a system with a small number of molecules, and stochastic kinetics may be applied.

1.5. Environment Changes, Subtle Perturbations, and Fluctuations. The origins of imbalance in the product distribution $\left[B\right]/\left[C\right]$, which is generated by a statistically exceptional reaction, may be classified as follows: (1) the initial imbalance in $\left[B\right]/\left[C\right]$ is generated by the initial reaction conditions (Figure 6a); (2) the imbalance is generated by subtle perturbations in conditions during the reaction (Figure 6b); and (3) the imbalance is generated by fluctuations during the reaction (Figure 6c).

As shown in the following sections, changes in environmental conditions can significantly affect $\left[B\right]/\left[C\right]$ in the systems involving two competitive self-catalytic reactions, which involve not only the temperature high/low but also temperature increases/decreases, fast/slow temperature changes, and concentration changes as well as history of temperature changes. Such changes can also be induced by contact with materials such as crystals, vessel surfaces, and seeds of exogenous substances, and alternatively by physical perturbations such as surface contact and mechanical stirring. The systems involving two competitive self-catalytic reactions are highly sensitive to subtle perturbations. This sensitivity is in contrast to usual competitive reaction systems, in which $\left[B\right]/\left[C\right]$ is relatively insensitive to the environmental changes, and subtle perturbations do not have a serious effect on $\left[B\right]/\left[C\right]$.

It may be appropriate to define perturbation and fluctuation in this article. Perturbation refers to small changes in the environment and is deterministic, for which repeated experiments provide the same product distribution. Fluctuation is defined here as a disturbance of motion, course, arrangement, or state, and is stochastic, for which repeated experiments provide different product distributions. The mechanistic difference between these two is that perturbation changes thermodynamic states, whereas fluctuation changes concentrations without changing thermodynamic states.

Subtle perturbations and fluctuations are often below the limit of detection, and generally negligible and eliminated by averaging, particularly when huge numbers of molecules are involved over a long reaction time. However, when the number of molecules is small, the reaction time is short, or amplification is involved, subtle perturbations or fluctuations become detectable. Amplification of such statistically exceptional events exhibits chemically interesting phenomena. Biological cells involving small numbers of molecules and amplification mechanisms appear to possess mechanisms to control such subtle perturbations and fluctuations.

1.6. Amplification of Subtle Perturbations and Fluctuations by a Chemical System of Two Competitive Self-Catalytic Reactions. Subtle perturbations and fluctuations play important roles in nature. The Brownian motion is the fluctuation of small particles in solution, which are driven by the collisions with water molecules. Crystallization from a supercooled solution and explosion close to critical points exhibit fluctuations in concentration. Chemical reactions are affected by the temperature perturbation, as well as photo-, mechanical, electronic, and information perturbations.

Temporal and spatial amplifications, respectively, indicate when and where the amplifications of subtle perturbations and fluctuations occur, which is discussed here with regard to the system involving two competitive $2A + B$-to-$2B$ and $2A + C$-to-$2C$ self-catalytic reactions. When the concentration of $B$ exceeds a threshold owing to subtle perturbations or fluctuations, the subsequent amplification results in the predominant formation of $B$. When the amplification is sufficiently effective, subtle perturbations and fluctuations become detectable. Experimentally, an induction period arises, during which $B$ is accumulated to a threshold concentration, and self-catalytic $2A + B$-to-$2B$ reaction amplifies $B$, which provide sigmoidal kinetics. The effect of seeding is also significant, and addition of $B$, which is the catalyst, during the induction period accelerates the self-catalytic $2A + B$-to-$2B$ reaction.

In a chemical system involving two competitive self-catalytic reactions, subtle perturbations and fluctuations can be experimentally discriminated by repeated experiments (Figure 7). The predominant formation of $B$ over $C$ by repeated experiments is referred to as product deterministic in this article, which is derived from subtle perturbations. The formation of $B$ or $C$ with comparable probability by repeated experiments is referred to as product stochastic, which is derived from fluctuations. When amplification occurs at a specific domain in space over a certain period of time, such a phenomenon is...
referred to as space/time deterministic. When amplification occurs at variable domains and times, such a phenomenon is referred to as space/time stochastic. As an example of a space/time deterministic phenomenon, amplification occurs at a certain domain in a solution, on the vessel surface, or even in a homogeneous solution, and examples are described in Section 6.

Amplifications of chemical reactions derived from subtle perturbations and fluctuations are described in the following sections. Thermal hysteresis in Section 2 involves the product deterministic and time/space deterministic phenomena. The stochastic chiral symmetry breaking described in Section 3 involves the product stochastic and space/time deterministic phenomena. The deterministic chiral symmetry breaking described in Section 3 and the shortcut in reaction in Section 4 involve the product deterministic and space/time deterministic phenomena. Homogeneous-heterogeneous transition described in the Section 6 involves the space/time stochastic phenomena.

In this article, chemical reactions are defined for both covalent and noncovalent bond cleavage and formation with structural changes of molecules. The approach is reasonable because both are described by the same principles of thermodynamics, chemical kinetics, and transition-state theory. In addition, biological systems employ a diversity of chemical reactions involving the cleavage and formation of noncovalent bonds, including those between proteins and those between proteins.
and small molecules. The reaction energies for both processes can be comparable, as previously described for the dissociation of the homo-double-helix of a sulfonamide helicene oligomer: \( \Delta H = +267 \text{ kJ/mol}, \Delta S = +0.75 \text{ kJ/mol} \), which are comparable to those of the dissociation of methyl iodide: \( \Delta H = +237 \text{ kJ/mol}, \Delta S = +0.12 \text{ kJ/mol} \). Therefore, it may not be unreasonable to treat the cleavage and formation of covalent and noncovalent bonds as chemical reactions.

2. CHEMICAL SYSTEMS INVOLVING TWO COMPETITIVE SELF-CATALYTIC REACTIONS WITH AMINOMETHYLENE HELICENE OLIGOMERS

2.1. Pseudoenantiomer Mixture of Aminomethylene-helicene Oligomers. In our studies on the synthesis and function of chiral helicene derivatives of 1,12-dimethylbenzo-[c]phenanthrene, their oligomers were developed, in which the helicene is connected by \( m \)-phenylene spacers and two-atom linking groups. Many such oligomers above a certain number of helicene unit formed dimeric aggregates, most likely double helices. In the series of oligomers, the number of helicenes, spacer, linking group, and side chain can be systematically varied, which provided a versatile method to develop synthetic double-helix forming compounds. A notable feature is that double helices can be formed in a dilute solution, in which molecular properties explicitly appear. In this article, we treat aminomethylenehelicene oligomers and oxymethylenehelicene oligomers, as two groups of two-atom-linked helicene oligomers (Figure 8a).

Figure 9. (a) One-direction three-state change of 2A-to-B-to-C-to-2A by \((P)-1/(M)-2\) mixture. (b) Relative thermodynamic stabilities of 2A, B, and C are shown with microscopic pathways. Red lines show self-catalytic pathways.

Figure 10. (a–c) CD spectra (5 mM) in fluorobenzene and structure change modes of the \((P)-1/(M)-2\) mixture in the 2A-to-B-to-C-to-2A reaction. (d) \( \Delta \varepsilon \) (315 nm)/temperature profiles and structural change modes of the \((P)-1/(M)-2\) mixture at a heating/cooling rate of 2 K/min. Temperature was increased from 5 to 70 °C and then decreased from 70 to 5 °C. The \( \Delta \varepsilon \) at equilibrium is indicated by the purple line. This is reproduced from ref 89 with permission from American Chemical Society.
oligomers themselves form homo-double-helices in dilute solution, and a mixture of pseudoenantiomers forms hetero-double-helices, which predominate homo-double-helix formation (Figure 8b). A pseudoenantiomer mixture of aminomethylene helicene oligomers exhibit thermal hysteresis, which provide a chemical system involving two competitive self-catalytic reactions. Double-helix formation by foldamers has attracted much interest,87 and the above dynamic properties appear to be a characteristic feature of helicene oligomers.

A 1:1 mixture of pseudoenantiomer aminomethylene helicene (P)-tetramer (P)-1 and (M)-pentamer (M)-2 formed three structures, namely, the random-coil 2A, the hetero-double-helix B, and the hetero-double-helix C (Figure 9a).38,39 B and C showed enantiomeric circular dichroism (CD) spectra, which indicated the pseudoenantiomeric three-dimensional structures of B and C ascribed to the hetero-double-helix structure with right- and left-handed helical senses, which are analogous to the structures of B-DNA and Z-DNA. B can be depicted as the (M*-)-(P*-1)/(M*-2) complex and C as the (P*-)-(P*-1)/(M*-2) complex, where the (P*) and (M*) configurations are derived from the helical senses, the absolute configurations of which are tentative. The pseudoenantiomers in random-coils are referred to as 2A in the following discussion, although they are not identical molecules, because the structures of the pseudoenantiomers are very similar and the use of such a term simplifies discussion.

At high temperatures, dissociated 2A is thermodynamically the most stable, and, at low temperatures, associated C is thermodynamically the most stable (Figure 9b). Then, B is metastable over the entire temperature range. The chemical system of two competitive self-catalytic 2A + B-to-2B and 2A + C-to-2C reactions is involved, where B and C catalyze the reactions to form B and C from A, respectively.

2.2. Three-State One-Directional Structural Changes in Chemical Systems Involving Two Competitive Self-Catalytic Reactions. The (P*-1)/(M*-2) mixture exhibits one-directional three-state structural changes in solution between 2A, B, and C, which is induced by a single cooling and heating procedure (Figure 9a). The structural changes exhibit the nonequilibrium nature of the reaction, which occurs in one direction. This behavior is in contrast to the chemical equilibrium between three structures, in which the interconversion occurs in both directions.

At 70 °C, a 1:1 mixture of (P)-1 and (M)-2 (5 mM) in fluorobenzene formed dissociated 2A (Figure 10a). When the solution was cooled to 25 °C at the rate of 2 K/min and allowed to stand for 20 min, associated B was formed, which showed a very strong negative Cotton effect at 315 nm. Slow inversion of the CD spectra occurred after allowing the B solution to stand at 25 °C for 70 h, and C was formed (Figure 10b). The B-to-C reaction involved the inversion of the helix sense, for which a kinetic study indicated the monomolecular nature of the reaction. Then, the C solution was converted to the 2A solution by heating at 70 °C (Figure 10c). The overall process provided a one-directional three-state change, 2A-to-B-to-C-to-2A, exerted by a single cooling/heating operation (Figure 9a), where essentially all the molecules changed structures between 2A, B, and C.

A constant-rate temperature change experiment was conducted by determining Δε at 315 nm, and the Δε/temperature profiles obtained are shown (Figure 10d). The C-to-2A-to-B reaction occurred when the temperature was increased from 5 to 70 °C and then decreased from 70 to 5 °C at a rate of 2 K/min. The heating curve was close to the equilibrium curve. On cooling from 70 to 5 °C, Δε decreased indicating the formation of B, which departed from the equilibrium curve. When the B solution was allowed to stand at 25 °C, the C solution was formed. The Δε/temperature profiles showed thermal hysteresis, which showed different curves during heating and cooling.

A mechanism of the thermal hysteresis in the systems involving two competitive self-catalytic 2A + B-to-2B and 2A + C-to-2C reactions is provided (Figure 11). At high temp-

![Figure 11. Mechanistic model of three-state one-directional structural changes of the (P*-1)/(M*-2) mixture involving two competitive self-catalytic 2A + B-to-2B and 2A + C-to-2C reactions, which shows microscopic and macroscopic pathways. Red arrows indicate the macroscopic mechanism, and green arrows indicate self-catalytic reactions. Solid arrows indicate major reactions and dotted arrows indicate minor reactions.](https://example.com/figure11.png)
hysteresis phenomenon supports the involvement of self-catalytic $2A + B \rightarrow 2B$ reaction.

The absence of C formation under the above conditions is due to fast cooling, and slow cooling provided the C solution. The $2A$ solution at 70 °C was cooled in a stepwise manner, that is, cooled to 50 °C over 630 min, 40 °C over 250 min, and 25 °C over 250 min, until $\Delta \varepsilon$ reached steady states at these temperatures (Figure 12a). The overall process was calculated to proceed at a low average cooling rate of 0.043 K/min. Then, the cooling curve was close to the equilibrium curve, where C was formed from $2A$ without forming the metastable B solution.

Comparison of the 2 and 0.043 K/min cooling experiments indicates that different cooling rates can provide different products in the chemical systems involving two competitive self-catalytic reactions: fast cooling provides the B solution and slow cooling provides the C solution, and essentially all the molecules in the solutions are converted into B or C. That is, the cooling rate, being a time-dependent phenomenon, is translated in terms of the molecular structure, which exerts a memory effect on the past event, being either fast or slow cooling.

A C solution was also formed during heating of the B solution at a low rate (Figure 12b). A B solution was obtained by cooling the $2A$ solution from 70 to 5 °C at 1 K/min, and heating the solution at 0.1 K/min provided an inclined upward curve, which indicated the formation of C; the heating curve approached the equilibrium curve. The phenomenon is derived from the self-catalytic $2A + C \rightarrow 2C$ reaction.

Another temperature-change experiment was conducted (Figure 12c). Cooling the $2A$ solution to 40 °C at 1 K/min provided a small amount of B. Then, the B solution was cooled to 5 °C at a rate of 0.067 K/min, resulting in the formation of equilibrium C solution at 5 °C. Then, the solution was heated at 1 K/min, and the $2A$ solution was formed via a curve close to the equilibrium curve. This slow cooling experiment showed minimal formation of B, and thermal hysteresis appeared as a result of the interconversion between $2A$ and C, which is consistent with the involvement of self-catalytic $2A + C \rightarrow 2C$ reaction. Information on environmental changes in rate and mode was translated to molecular structures.

As discussed in Section 1, stochastic and deterministic phenomena can appear in a nonequilibrium phenomenon in response to environmental changes. The experiments on the $(P)-1/(M)-2$ mixture are reproducible in terms of thermal hysteresis curves and illustrate a product deterministic and space/time deterministic phenomenon (Figure 7).

The chemical systems involving two competitive self-catalytic reactions exhibit high sensitivity to cooling and heating modes and cooling rates and provide different product distributions $[B] + [C]$ with high selectivity. The high sensitivity is in contrast to the responses of usual chemical reactions to high or low temperatures, in which relatively small changes in the product distribution occur. For example, consider the competitive reactions to form B and C from $2A$: the relative rate constant $k_B/k_C = \exp(-\Delta E_a/RT)$, assuming the same frequency factor is provided, where $\Delta E_a$ is the difference in the activation energy. In the case of $\Delta E_a = -2.5$ kJ/mol, the temperature change from 300 to 350 K in steps of 50 K changes $k_B/k_C$ only from 2.7 to 2.3. In the systems involving two competitive self-catalytic reactions, environmental changes in conditions or subtle perturbations are amplified in the product distribution in a highly sensitive manner (Figure 7).

The macroscopic multiple pathways are shown in the $(P)-1/(M)-2$ mixture by various curves of the temperature/concentration profiles beyond the equilibrium curve in a chemical reaction from $2A$ at a high temperature to the C at a low temperature, where the $2A$ and C solutions are in the equilibrium state at such temperatures. The system involves three structures $2A$, B, and C, and the complex nature of temperature dependence is derived from the relative concentration of the structures, and is enhanced by the reversible nature of the chemical systems involving two competitive self-catalytic $2A + B \rightarrow 2B$ and $2A + C \rightarrow 2C$ reactions (Figure 4).

Microscopic pathways (Figures 5 and 11) describe the relative thermodynamic stabilities of $2A$, B, and C. It is emphasized here that microscopic pathways (Figure 11), which is the numbers of molecules to visit the microscopic pathways, are significantly affected by perturbations, fluctuations, and thermal history (Figures 6 and 7).
3. CHIRAL SYMMETRY BREAKING

3.1. Chiral Symmetry Breaking in Chemical System Involving Two Competitive Self-Catalytic Reactions.

Chiral symmetry breaking is a phenomenon, in which the achiral symmetric state is transformed into a chiral asymmetric state.\(^{41,42}\) The phenomenon has been observed in the crystalization of a single enantiomer formed from achiral molecules: NaClO\(_3\) itself is achiral, but it crystallizes in the chiral form, in which either D- or L-crystals are predominantly produced. Chiral symmetry breaking appears also during the self-assembly of achiral molecules to form fibers, liquid crystals, and colloids. Racemic organic substances, which are 1:1 mixtures of enantiomers, can exhibit chiral symmetry breaking during crystallization under racemization conditions. In general, chiral symmetry breaking of molecules occurs during the formation of solid materials, in which strong intermolecular interactions can stabilize the chiral structures. Chiral symmetry breaking by racemic organic substances in solution, which do not racemize, is also possible, in which various mixing experiments can be employed to control the phenomenon. Such a system is described in this section using the pseudoenantiomer (\(P\)-1)/[(\(M\)-2)].

A chemical reaction of an achiral substrate to form a chiral product generally provides a 1:1 mixture of two enantiomeric molecules that form a racemic mixture in the absence of an external chiral source. This is because no difference in the energetic state is involved in the microscopic pathways to form the enantiomers because 2A-to-B and 2A-to-C (=ent-B) reactions are symmetric. Deterministic kinetics involve the formation of the enantiomers B and ent-B as follows: \(E_B(B^3) = E_B(\text{ent-B}^3)\), \(k_1 = k_0\), and then \([B]/[\text{ent-B}] = 1\), which forms racemic mixtures. Strictly speaking, a chemical reaction involving huge numbers of molecules, for example, \(10^{20}\) molecules, fluctuates and does not provide a mixture of exactly 0.50000000 \(\times 10^{20}:0.50000000 \times 10^{20}\). This is, however, generally not a serious issue, because the deviation is considered extremely small; the standard deviation (\(10^{-20})^{1/2} = 10^{-10}\) is far below the limit of detection.

The situation changes in chemical systems involving two competitive self-catalytic 2A + B-to-2B and 2A + (ent-B)-to-2(ent-B) reactions because of the strong tendency of amplification mixture. It is an interesting chemical system, in which two powerful amplification reactions compete. When subtle perturbations or fluctuations in terms of time and space are amplified by self-catalysis, chiral symmetry breaking occurs providing predominantly B or ent-B.

The origin of chiral symmetry breaking can be subtle asymmetric perturbations, which include very small amounts of external chiral substances, biological contamination, polarized light, the Coriolis force, and mechanical stirring, which are collectively termed the cryptochiral environment (Figure 6a,b). Stochastic fluctuations in this environment can also be considered (Figure 6c). Another origin is the asymmetric nature of our world, such as parity violations in quantum physics, which is generally thought to be too subtle to affect chemical reactions.

The nature of chiral symmetry breaking can be clarified by the repeated experiments based on product stochastic and deterministic phenomena (Figure 7). It is generally thought that repeated experiments provide B or ent-B in an equal probability because of the symmetric nature of the formation of B and ent-B, and such a product stochastic phenomenon involving the product ratio B/ent-B is referred to as stochastic chiral symmetry breaking in this article. For example, 100 experiments provide 50 and 50 experiments to form the enantiomers. Alternatively, repeated experiments can predominantly provide B, and such a product deterministic phenomenon of the product ratio B/ent-B is termed deterministic chiral symmetry breaking: for example, 100 experiments provide an enantiomer B in 90 experiments and ent-B in 10 experiments.

The chemical systems involving two competitive self-catalytic \(2A + B\)-to-2B and \(2A + (\text{ent-B})\)-to-2(ent-B) reactions can exhibit chiral symmetry breaking to form B or ent-B. Chiral symmetry breaking predominantly provides one enantiomer B, or ent-B, by subtle chiral perturbations or fluctuations, and the product distribution \([B]/[\text{ent-B}]\) is amplified. To depict chiral symmetry breaking phenomena by deterministic kinetics, a model with a small difference in the rate constant \(k_1 = 0.9k_2\) is considered in Section 1. Alternatively, stochastic kinetics is also considered on the basis of the chemical master equation.\(^{63,66}\)

Numerical analyses can provide enantiomers with comparable probability in the bimodal distribution, which is referred to as stochastic chiral symmetry breaking.

The system with a predominant enantiomer is in a metastable state, and in principle, the racemic mixture is considered thermodynamically the most stable by the entropic reasons. Then, after a sufficiently long time, the chemical system with a predominant enantiomer will be converted into the racemic mixture, but not the reverse.

3.2. Chemical Systems Involving Two Competitive Self-Catalytic Chemical Reactions Using Racemic Amino-methylene Helicene Oligomers. A 1:1 mixture of pseudoenantiomer aminomethylene helicene \((P)\)-tetramer \((P)-1\) and \((M)\)-pentamer \((M)-2\) was discussed in Section 2, in which the oligomers possess different numbers of enantiomeric helicene units, and the mixtures are close to racemic (Figures 8a and 13b). In this section, a 1:1 mixture of \((P)-\)pentamer \((P)-2\) and \((M)-\)pentamer \((M)-2\), which is racemic, is examined. The racemic mixture exhibited chiral symmetry breaking during the formation of hetero-double-helix B and ent-B from random coil \(2A\) (Figure 13a). Compared with the \((P)-1/(M)-2\) mixture, the only difference from the \((P)-2/(M)-2\) mixture is the number of helicene unit in the \((P)-\)isomer; accordingly, it is reasonable to...
Stochastic and deterministic chiral symmetry breaking. Procedure and structure change mode of homo-double-helix/random-coil mixing experiment using the \((P)-2/(M)-2\) mixture in toluene (1 mM) at 25 °C, which stochastically provided B and ent-B. Heating and cooling of the states X and Y deterministically provided B. This is reproduced from ref 90 with permission from John Wiley and Sons.

3.3. Deterministic Chiral Symmetry Breaking. Equal amounts of \((P)-2\) and \((M)-2\) were weighed using a microbalance and dissolved in toluene (1 mM). The solution was heated to 90 °C for 30 min to obtain a 2A solution, which was optically inactive (Figure 14a). Then, the solution was cooled to 70 °C, at which the negative Cotton effect appeared at 315 nm. VPO analysis and the Job plot experiment showed 1:1 hetero-aggregation. Chiral symmetry breaking appeared during the formation of enantiomeric structures of hetero-double-helices (heating/cooling experiment).

The solution was cooled from 70 to 25 °C, at which the Cotton effect became stronger. The mixture at 25 °C was viscous, and atomic force microscopy (AFM) analysis showed fibrils 80–150 nm width and 2–5 nm height, which were formed from particles 80–150 nm diameter.90 The heating/cooling experiment was repeated 4 times using different lots of samples, and the negative Cotton effect at 315 nm was observed in all samples. Thus, deterministic chiral symmetry breaking appeared during hetero-double-helix formation and self-assembly of molecules in a racemic mixture.

Cooling and heating between 90 and 25 °C at a rate of 1 K/min provided \(\Delta \varepsilon/\text{temperature profiles showing thermal hysteresis; different cooling and heating curves were obtained.}^{90}\)

The result indicates the involvement of self-catalysis: the hetero-double-helix B and ent-B catalyze the reaction of two random-coils 2A to become the hetero-double-helix B and ent-B,
respectively. The kinetics of constant-temperature experiments yielded sigmoidal curves, in which the formation of hetero-double-helix and self-assembly were initially slow and then accelerated, which can also be explained by self-catalysis. Thus, chiral symmetry breaking appeared during the formation of hetero-double-helix and self-assembly of the \((P)-2/(M)-2\) mixture, which involved self-catalysis.

Experiments at ambient temperatures and different mixing ratios (ambient-temperature-mixing experiments and different-ratio-mixing experiments) were conducted using the racemic \((P)-2/(M)-2\) mixture (Figure 14b). Equal amounts of the enantiomers were weighed and mixed in the solid state, to which toluene was added at 25 °C. Then, the mixture was dissolved by sonication. The B solution with the negative Cotton effect at 315 nm was obtained in 18 out of 20 experiments using the same and different lots of samples, which confirmed deterministic chiral symmetry breaking.

The mixing ratio (enantiomeric excess) of \((P)-2\) to \((M)-2\) was changed between 40:60 and 60:40, by taking advantage of the racemic nature of this system without racemization (different-ratio-mixing experiment). All 16 experiments at 40:60, 45:55, 55:45, and 60:40 ratios exhibited the negative Cotton effect at 315 nm, which is in contrast to general thought that mixtures of enantiomers exhibit symmetric nature with regard to the mixing ratio. The phenomenon was consistent with deterministic chiral symmetry breaking (Figure 14b). The driving force of chiral symmetry breaking should be strong enough to override the imbalances between the 40:60 and 45:55 ratios, and the chiral symmetry breaking is not due to the slight differences between the numbers of \((P)-2\) and \((M)-2\) molecules in the racemic mixture. These are product deterministic and space/time deterministic phenomena (Figure 7).

3.4. Stochastic Chiral Symmetry Breaking. Another experimental procedure, in which the homo-double-helices and random-coils of \((P)-2\) and \((M)-2\) in solutions were mixed to obtain a racemic \((P)-2/(M)-2\) mixture (homo-double-helix/random-coil mixing experiment), showed stochastic chiral symmetry breaking (Figure 15). A solution of \((P)-2\) in toluene (1 mM) at 70 °C, which contained random coils, was mixed with an equal amount of \((M)-2\) (1 mM) in toluene at 25 °C, which contained homo-double-helices. The mixture at 25 °C appeared to govern the reaction to form B or ent-B. It was also observed that the stochastic mode was switched to the deterministic mode by heating and cooling.

The chiral symmetry breaking phenomenon was governed by subtle chiral perturbations, the origin of which may be below the limit of detection, and their subsequent amplification to form an enantiomeric self-assembly occurred (Figure 6). The presence of either synthetic or biological chiral substances in our laboratory atmosphere could be the origin of the perturbation (cryptochiral environment). Such sensitivity may be used to sense subtle changes in the environment, and biological events of the cell fate such as gene expression, metabolism, and growth are considered to involve stochasticity, in which the events occur at a certain probability.

4. SHORTCUT IN REACTION TIME BY THE THERMAL HISTORY

4.1. Change of Macroscopic Pathways due to Thermal History: Memory Effect. Molecules dispersed in a solution are considered to possess no memory because the solution quickly reaches thermal equilibrium, which is thermodynamically the most stable state, and then loses memory of its past. In the solid or liquid state, molecules can retain their memory because molecules cannot readily reach thermal equilibrium because of strong intermolecular interactions. Thermal history can thus affect the formation of a metastable state, which is far from equilibrium. Molecular memory is derived from not the molecular structure but from the relative concentrations of certain structures of molecules in the metastable state, which is a non-Boltzmann distribution. A single molecule does not memorize, but ensembles of molecules do, which is the subject of statistical mechanics.

As described in Section 2, a product deterministic phenomenon appeared in the pseudoenantiomeric the \((P)-1/(M)-2\) mixture because the competitive self-catalytic reactions were not energetically symmetric (Figure 5). It is described in this section that the \((P)-1/(M)-2\) mixture responds to thermal history to provide B and C in an extremely sensitive manner, which is the memory effect in a product deterministic manner (Figures 6b and 7). It should be noted that the phenomenon is derived from molecules dispersed in solution.

4.2. Effect of Thermal History on Hetero-Double-Helix Formation of Pseudoenantiomer Oxyethylenehelicene Oligomers. In the chemical system involving two competitive self-catalytic reactions, the product distribution \([B]/[C]\) is significantly
affected by subtle perturbations derived from thermal history: snap cooling of the 2A solution of the (P)-1/(M)-2 mixture to −25 °C followed by heating to 25 °C provided C in 3 h (frozen−defrost experiment); cooling of the 2A solution to 25 °C provided C in 60 h (simple-cooling experiment). The only difference between the two procedures is the cooling to −25 °C before the initiation of the reaction to form C from 2A, which significantly changed the macroscopic pathways (Figure 16).

![Diagram](https://example.com/diagram.png)

**Figure 16.** Shortcut in reaction time of the (P)-1/(M)-2 mixture because of thermal history and the structural change mode: (a) 2A-to-C reaction at 25 °C completes in 3 h in the frozen−defrost (70 to −25 to 25 °C) experiment and in 60 h in the simple-cooling (70−25 °C) experiment; (b) experiments are shown by concentration/temperature profiles.

A frozen−defrost experiment was conducted. A 1:1 mixture of (P)-1 and (M)-2 in fluorobenzene (0.5 mM) was heated to 70 °C to prepare a 2A solution, which was snap cooled to −25 °C (frozen). The solution was transferred to a CD cell precooled to −25 °C and allowed to stand for 15 min, during which no change was observed in the spectra with a weak Cotton effect (Figure 17a). Then, the 2A solution was heated to 25 °C (defrost), and Δε at 315 nm slightly decreased and then significantly increased giving a C solution.

The structural change was monitored on the basis of Δε (Figure 17c). Δε 0 cm−1 M−1 was obtained immediately after allowing the solution to stand at 25 °C, which was precooled at −25 °C. Then, Δε decreased to −105 cm−1 M−1, increased, and reached +390 cm−1 M−1 after 240 min. The result indicated the initial formation of a small amount of B, which was then converted to C.

For comparison, a simple-cooling experiment was conducted. When a 2A solution at 70 °C was immediately cooled to 25 °C, Δε decreased to −420 cm−1 M−1 after 20 min, providing a B solution. The B solution was allowed to stand at 25 °C for 60 h, and a C solution with Δε +420 cm−1 M−1 was formed, which is in equilibrium (Figure 17b,c).

A notable difference in the reaction rate was shown between the two reactions from the A solution at 70 °C to C at 25 °C: snap cooling of the A solution from 70 to −25 °C and warming to 25 °C followed by standing at 25 °C for 3 h gave the C solution (frozen−defrost experiment); cooling of the A solution from 70 to 25 °C followed by settling at 25 °C for 60 h gave the C solution (simple-cooling experiment). This is a shortcut in reaction time induced by thermal history. The only difference between the two reactions is the frozen pretreatment to reach 25 °C from 70 °C. No heating was provided, no concentrations were changed, and no catalyst was added for the shortcut phenomenon, and then thermodynamic stability of 2A, B, and C did not change at 25 °C. This behavior does not appear in usual chemical reactions.

The metastable 2A solutions formed in the initial 25 °C state were compared in the frozen−defrost and simple-cooling experiments, which provided essentially the same CD, UV−vis, and 1H NMR spectra. Thus, spectroscopically, the same 2A

![Diagram](https://example.com/diagram.png)

**Figure 17.** CD spectra of (P)-1/(M)-2 mixture in fluorobenzene (0.5 mM) showing structural changes from 2A at 70 °C to C at 25 °C (a) in a frozen−defrost experiment and (b) simple-cooling experiment. (c) Δε (315 nm)/time profiles showing structural changes from 2A at 70 °C to C at 25 °C in a frozen−defrost experiment (green circles) and simple-cooling experiment (blue circles).
solutions were obtained at 25 °C in both experiments, which, however, exhibited quite different macroscopic pathways (Figure 16b). The initial imbalances were below the limit of detection, and the slight difference in the relative concentrations of B and C was significantly amplified at the later stage, which appears to be a memory effect in a chemical reaction. These are product deterministic and space/time deterministic phenomena (Figures 6c and 7).

4.3. Temperature Effect in the Frozen–Defrost and Simple-Cooling Experiments. The effect of reaction temperature to form a C solution from a 2A solution was compared between two experiments. The frozen–defrost experiment was conducted at different temperatures between −10 and 50 °C, and Δε was obtained after 20–30 min of heating to each target temperature and was plotted against temperature (Figure 18, red circles). Δε consistently appeared in the positive region, indicating the occurrence of the self-catalytic 2A + C-to-2C reaction. For comparison, the plots were obtained in equilibrium states between 10 and 50 °C attained by holding the reaction mixtures for a sufficiently long time (blue circles).

The simple cooling experiment was conducted between −20 and 50 °C, and Δε at 20–30 min on cooling to each target temperature was plotted against temperature (Figure 18, red diamonds). Between −20 and 40 °C, negative Δε indicated the predominant formation of B. A positive Δε was obtained at 50 °C, which indicated the predominant formation of C over B. The results showed high sensitivity of the chemical systems involving two competitive self-catalytic reactions to form B and C. The tendency to form the C solution in the frozen–defrost experiment and the B solution in the simple cooling experiment appears over a broad temperature range, in which the formation of the B and C solutions is determined by their thermal history. A substantial competition occurs at 40 °C, at which both reactions appear to be strongly amplified. It is shown that the chemical systems involving two competitive 2A + B-to-2B and 2A + C-to-2C self-catalytic reactions significantly affect the product distribution [B]/[C], which is derived from the amplification of subtle perturbations.

4.4. Mechanistic Aspects of Shortcut in Reaction Time. Small differences in thermal history provide shortcut pathways allowing shorter reaction times via the amplification involving two competitive self-catalytic 2A + B-to-2B and 2A + C-to-2C reactions in the (P)-1/(M)-2 mixture. The phenomenon is derived from the initial slightly predominant formation of B or C by subtle perturbation (Figures 5 and 6b). The frozen–defrost experiment provides a frozen 2A solution at −25 °C, which on warming to 25 °C slight predominantly forms C; C is amplified by self-catalysis reaching equilibrium within 3 h. The simple cooling experiment of a 2A solution from 70 to 25 °C provides slight predominantly B, which is amplified by self-catalysis; a slow reaction follows to form C in the equilibrium state, which takes 60 h. Subtle initial imbalances between two competitive self-catalytic reactions are significantly amplified and change the macroscopic pathways. The phenomenon is repeatable and is a product deterministic chaotic phenomenon, in which subtle perturbations in the initial conditions provide quite different results (Figure 7).

It should be emphasized again that the memory effect of the (P)-1/(M)-2 mixture is not derived from the molecular structure but from the relative concentration: the relative concentrations of 2A, B, and C, being in the non-Boltzmann distribution, were memorized. The memory effect in the (P)-1/(M)-2 mixtures originated from subtle differences in the concentrations of the products at a fixed temperature T, which provides different macroscopic pathways resulting in the different concentrations of the products B and C.

5. SPATIAL HETEROGENEITY IN THE SELF-CATALYTIC CHEMICAL REACTIONS

5.1. Fluctuation and Amplification in Space. A chemical reaction in a dispersed solution of molecules is thought to occur equally in all domains. Thermodynamically, the free energy is minimum and the entropy maximum in the homogeneous state. Kinetically, the reaction rate is identical in all domains. Homogeneous chemical reactions in dilute solutions generally do not spontaneously form spatially heterogeneous structures, and a chemical reaction from the metastable state to equilibrium homogeneously and monotonically occurs.

![Figure 19. Spatially homogeneous–heterogeneous transition in a self-catalytic chemical reaction in dilute solution. Light yellow and red circles are substrate molecules before and after the self-catalytic reactions, respectively. Light blue circles are solvent molecules. The structural change mode is also shown, in which the green arrow indicates self-catalysis. This is reproduced from ref 92 with permission from John Wiley and Sons.](image-url)
A chemical reaction in principle is a dissipative and stochastic phenomenon because molecules react one by one, and concentration fluctuates at different times and spaces. In general, such fluctuations are minimal because fluctuations are averaged by a huge number of molecules and in a large space compared with the very small volume of a single molecule.

As have been discussed in the previous sections, subtle perturbations or fluctuations in concentration are amplified by chemical systems involving two competitive self-catalytic reactions. It is noted in this section that spatial fluctuation can be amplified at a certain domain in a solution, and then a homogeneous solution can be converted to a heterogeneous solution, a process termed homogeneous–heterogeneous transition (Figure 19). The self-catalytic $2A + B$-to-$2B$ reaction of the pseudoenantiomer aminomethylenehelicene oligomer $(M)$-$1/(P)$-$2$ mixture exhibits such transition.92

When a $2A$ solution was heated and cooled, $2A$ was converted to $B$ by the self-catalytic $2A + B$-to-$2B$ reaction, in which the homogeneous–heterogeneous transition appeared (Figure 19). A metastable homogeneous $2A$ solution was converted to a metastable heterogeneous state by self-catalytic amplification, and eventually homogeneous $B$ solution at equilibrium was formed.

5.2. Heterogeneous Nature of Self-Catalytic Reaction.

The process of the self-catalytic $2A + B$-to-$2B$ reaction was monitored for the $(P)$-$1/(M)$-$2$ mixture by UV–vis/CD imaging at 320 nm in an area of 7.7 mm$^2$ and 1 mm thickness. A solution of a 1:1 mixture of $(P)$-$1$ and $(M)$-$2$ (0.5 mM) was heated to 70 °C to form $2A$. The UV–vis imaging analysis showed homogeneously bright areas (Figure 20a). Then, the solution was allowed to cool to 30 °C, which took approximately 15 min. Dark domains with 1 mm in size started to appear at 38 °C, which showed a weaker UV–vis absorption at 320 nm than the bright domains (Figure 20b). The emergence of the dark domains indicates the formation of $B$, which exhibits a weaker absorption at 320 nm than $2A$. The dark domains changed their shapes approximately at a rate of 1 mm/min, as they moved and rotated. A meteor-like shape of 1 mm diameter also appeared from the bottom to the top, which moved at a rate of 1 mm/min (Figure 20b). The homogeneous–heterogeneous transition appeared in different shapes and positions, showing a space/time-stochastic nature derived from spatial fluctuation (Figure 7).

CD imaging at 320 nm provided additional information on the homogeneous–heterogeneous transition. The tip of the meteor-like pattern (Figure 20c) is shown in blue, which has negative $\Delta \varepsilon$, indicating the formation of $B$. This is a space/time-deterministic phenomenon (Figure 7).

Regarding the energetic aspect, the homogeneous–heterogeneous transition is a downhill chemical reaction from the $2A$ solution to the $B$ solution, during which the metastable heterogeneous state emerges. The reaction occurs locally because of the strong amplification of the self-catalytic $2A + B$-to-$2B$ reaction, and $B$ domains expand. Eventually, $B$ predominates in the entire solution, which becomes homogeneous. Biological processes appear to utilize such spatially stochastic phenomena in homogeneous-to-heterogeneous transitions in cell differentiation and in the physiological patterns of animals and insects.84,85

The homogeneous–heterogeneous transition exhibits the space/time stochastic nature (Figure 7), that is, the transition occurs at the different domains by molecules dispersed in the solution.
When the dissociation of the B−B complex is slow, the B−B complex interacts with another A molecule to form the A−B−B complex, which react with still another A molecule to form the B−B−B complex. Subsequent reactions provide B−B−B−B and higher homologs, which self-assemble to form fibrils (Figure 21).\textsuperscript{93–96} Then, the self-assembly of hetero-double-helix B can also be considered to involve self-catalysis. The difference between the mechanisms of self-catalytic reaction and self-assembly is derived from the difference in the nature of interactions in the B−B complex: rapid dissociation provides 2B in solution, which induces self-catalytic reaction; slow dissociation and rapid A−B−B formation provide self-assemblies. The latter example is described in this section.

Chemical reactions, conformation changes, and aggregations of organic molecules at the liquid—solid interfaces are important phenomena in nature and exhibit different properties from those in solution. The differences can be ascribed to the interactions of molecules with a surface, higher concentrations of molecules on a surface, and confined formation of molecules on a surface. When self-assembly occurs at a liquid—solid interface, fibril films are formed, which extend along the interface. Important biological events are induced by such fibril film formation on membranes, cells, and solid surfaces as exemplified by amyloid fibrils.

The process of fibril film formation at the liquid—solid interface is another interesting subject. Heterogeneous nucleation-growth mechanisms may be involved in such a process, where the initially slow formation of cluster aggregates of a certain size (nucleation) is followed by rapid polymerization (growth).\textsuperscript{81–83,97} Experimentally, sigmoidal kinetics with an initial lag time are obtained. In seed experiments, in which the solution comes in contact with fibrils, the process is accelerated with the disappearance of lag time. The chemical properties of self-assembly are similar to those of self-catalytic reactions.

### 6.2. Chemical Reactions of Pseudoenantimer Oxy-methylene Helicene Oligomers on a Solid Surface

Oxymethylenehelicene oligomers are the oxygen analogs of aminomethylene helicene oligomers, described in previous sections (Figure 8a). A pseudoenantimer mixture of oxymethylenehelicene (P)-pentamer (P)-3 and (M)-hexamer (M)-4 formed hetero-double-helix, which self-assembled to form fibril films\textsuperscript{98} and aggregates.\textsuperscript{99} The (P)-3/(M)-4 mixture, analogous to the (P)-1/(M)-2 mixture, provided (P*)-[M]-4/(P)-3, hetero-double-helix B, and (M*)-[M]-4/(P)-3, hetero-double-helix C, in which the tentatively assigned (P*) and (M*) configurations are those of the helical senses. The (P)-3/(M)-4 mixture provides metastable random-coil 2A in solution by simple heating and cooling procedures. The resulted solution responds to subtle physical perturbations of vessel surface contact and mechanical stirring and forms B or C, which are pseudoenantimers as shown by CD: fibril films derived from B was formed at the liquid—solid interface; aggregates derived from C was formed in solution by mechanical stirring (Figure 22). Slight differences in the subtle physical perturbations induced by surface contact and mechanical stirring provided B and C, respectively (Figures 5 and 6b), which self-assembled to different forms. The (P)-3/(M)-4 mixture provides a chemical system involving two competitive self-catalytic reactions (Figure 22), which is described in this section.

### 6.3. Formation of Hetero-Double-Helix B and Fibril Films

A 1:1 mixture of (P)-3 and (M)-4 in trifluoromethylbenzene (0.5 mM) was heated in a quartz cell to 60 °C, at which point dissociated 2A solution was formed. The solution was cooled to 25 °C and allowed to stand for 9 h, when no change was observed by CD (Figure 23a). The 2A solution was then cooled to 5 °C and allowed to stand for 3 h, after which a strong negative Cotton effect appeared at 316 nm, which indicated the formation of hetero-double-helix B (Figure 23a). It was observed that thin films were formed on the surface of the quartz cell. The Job plot experiment on the films showed formation of the 1:1 complex, and AFM analysis indicated the formation of fibril films on the surface. Thus, on cooling the solution of the (P)-3/(M)-4 mixture, B was formed on the quartz cell surface, which self-assembled to form fibril films. In contrast, the (P)-3/(M)-4 mixture remained dissociated in the 2A in the solution phase.

The process of self-assembly on the solid surface was a discontinuous phenomenon. CD (316 nm)/time profiles showed a sigmoidal curve with a lag time of 30 min (Figure 23b). AFM images at 5 min showed a number of flat and round particles, which were uniformly 50 nm in diameter and 2–3 nm in height (Figure 23c). The particles are critical for the start of fibril formation, and short fibrils were formed from some particles. At 10 and 15 min, many longer fibrils of 50 nm width appeared. This is a space/time stochastic phenomenon (Figure 7).

Seed experiments revealed the disappearance of lag time in the fibril film formation.\textsuperscript{98} A 2A solution of (P)-3/(M)-4 at 60 °C was cooled to 25 °C, allowed to stand for 1 h, and then added to dry fibril films in a quartz cell. The CD of the mixture at 25 °C showed an immediate decrease in intensity. The 2A solution at 25 °C was metastable, and seeding by contact with the fibril films initiated self-assembly. These observations are consistent with the involvement of self-catalysis in fibril film formation.

Fibril film formation was affected by the surface materials used. Larger amounts of fibril films were formed on poly-(ethylene terephthalate), polypropylene, cellulose, and gold-coated plates, and smaller amounts were formed on Teflon, glass, quartz, poly(lactate), and aluminum.\textsuperscript{98} The amounts of fibril films differed 20-fold between poly(ethylene terephthalate) and aluminum. These results indicated the involvement of physical perturbation derived from the contact of molecules on the solid surface in the self-catalytic formation of B.

### 6.4. Mechanistic Aspects of Surface-Induced Hetero-Double-Helix B Formation and Self-Assembly

A probable
The mechanism of the fibril film formation is as follows (Figure 24). At 60 °C, the 2A solution in the (P)-3/(M)-4 mixture is at equilibrium, and cooling to 25 °C produces a metastable 2A solution, which does not change for at least several hours. On cooling to 5 °C, B forms on the solid surface, which self-assembles to form particles with 50 nm diameter. It is likely that the particles have a certain regular structure with higher thermodynamic stability than those with diameters smaller and larger than 50 nm. Then, the particles cease to grow, and fibrils with 50 nm width start to form. The initiation of the formation of B on the solid–liquid interface is catalyzed by the solid surface, and a process occurs at any domain on the surface.
in a spatially stochastic manner, which is a space/time stochastic phenomenon (Figure 7). The sigmoidal kinetic curves and seeding experiments are consistent with the self-catalytic nature of the hetero-double-helix formation and self-assembly. The discontinuous nucleation is programmed in the molecular structures of \((P)-3\) and \((M)-4\).

6.5. Formation of Hetero-Double-Helix C and Self-Assembly Induced by Mechanical Stirring. Biological cells sense and respond to mechanical stimulations, which control growth, motility, and differentiation. In materials science, mechanical stimulation responding materials are critical for applications requiring mechanical switching and mechanical endurance. Mechanical stimulations and responses of synthetic and biological macromolecules in solution are well documented. In contrast, small organic molecules dispersed in a solution are generally not responsive to mechanical stimulations because hydrodynamic flow usually does not dominate Brownian motion. The \((P)-3/(M)-4\) mixture responds to mechanical stirring of a solution (Figure 25a).99

A 1:1 mixture of \((P)-3\) and \((M)-4\) in trifluoromethylbenzene (0.5 mM) was heated to 80 °C for 3 min in a cylindrical glass vial (21 mm in diameter), and the resulting 2A solution was cooled to 25 °C, providing a metastable 2A solution, which was mechanically stirred in a clockwise direction with an oval-shaped Teflon magnetic stirring bar (0.4 g weight) at a rate of 2000 rpm. The solution became turbid after 9 h, and CD spectra with a positive Cotton effect at 298 nm were observed (Figure 25b). When mechanical stirring was continued, the positive Cotton effect shifted to 322 nm: the intensity increased considerably after 179 h, which was ascribed to the formation of hetero-double-helix C. It is noted that the CD spectra of C were enantiomeric to those of B, as shown in the experiment at 5 °C (cf. Figure 23a). The process was monitored on basis of \(\Delta \varepsilon\) at 322 nm, which provided a sigmoidal curve.

The structure of self-assembly materials was determined by AFM analysis. At 9 h, when \(\Delta \varepsilon\) started to decrease, bundles of 0.3 \(\mu\)m average width and 20 nm height appeared; they contained twisted fibers 50 nm diameter with a right-handed helical structure (Figure 25c). It is shown thereby that the \((P)-3/(M)-4\) mixture formed C, which self-assembled to form fibers and bundles.

The mechanical stirring rate affected the formation of C and self-assembly. Without mechanical stirring, no self-assembly occurred at 25 °C after 150 h.99 When the rate was reduced from 2000 to 1500 rpm, the process was retarded. Inversion of the stirring direction to counterclockwise provided the same CD spectra as those in the clockwise direction. The addition of glass beads considerably promoted the formation of C and self-assembly. The results indicated an important role of the surface area of contact between the vessel, the stirring bar, and beads. When the solution of \((P)-3/(M)-4\) was alternately mechanically stirred and not stirred (stop-stirring experiments), the formation of C occurred only during mechanical stirring.99

6.6. Mechanistic Aspects of Formation of Hetero-Double-Helix C and Self-Assembly by Mechanical Stirring. The experimental results are consistent with the generation of local and temporal high-temperature domains induced by friction derived from mechanical stirring (Figure 26). Friction induced by mechanical stimulation generates heat, electrons, and plasma, during which local and temporal temperatures can reach several thousand kelvins. The mechanical response observed herein originated from the generation of local and temporal high-temperature domains, which provided sufficient energy to overcome the barrier to form C from metastable 2A.

A question is then raised regarding why hetero-double-helix C formation was induced during heating, which is in contrast to the general phenomenon that molecular aggregates dissociate upon heating. The behavior may be ascribed to the balance between the kinetic promotion of C formation and its thermodynamically unfavorable formation. The barrier between 2A and C is relatively high, and mechanical stirring generates local and temporal high-temperature domains, which provide the energy to form C. Rapid relaxation of the high-temperature domains occurs, and C diffuses from the surface to the solution phase through self-assembly. This may be an interesting heterogeneous system generated in a homogeneous solution, and such phenomena can occur in nonequilibrium states. Mechanical stirring can provide an interesting reaction medium, in which local high-temperature domains are temporally generated, which is a space/time stochastic phenomenon (Figure 7).

The mixture of the pseudoenantiomer oxymethylenehelicene oligomers \((P)-3/(M)-4\) mixture provided a chemical system of two competitive self-catalytic reactions to form hetero-double-helix B and C, which are pseudoenantiomers with regard to the helical sense. Simple heating and cooling provided metastable 2A solution, and the responses to subtle physical perturbations such as surface contact and mechanical stirring provide different structures of hetero-double-helix which self-assembles to form fibril films (Figures 5 and 6). It may be noted that the dynamic phenomena have some similarity with crystallization.82,83 Crystallization in some cases is referred to involve self-catalytic nature, in which molecules change their structure on crystal surfaces.

7. CONCLUSIONS

7.1. Macroscopic Multiple Pathways in Chemical Reactions. Chemical reactions are complex phenomena.43 In this article, we have described the macroscopic multiple pathways of reversible nonequilibrium-to-equilibrium chemical reactions under fixed and variable temperature conditions. Pseudoenantiomer mixtures of aminomethylene and oxymethylenehelicene oligomers undergo reversible chemical reactions between hetero-double-helices and random coils, which are chemical systems involving two competitive self-catalytic reactions. As a result, various unusual chemical phenomena occur, which were derived from the amplification of subtle perturbations and fluctuations.

Microscopic pathways determine the structures of intermediates and transition states in a chemical reaction, which are
subject to quantum mechanics, and do not change at a fixed temperature. Macroscopic mechanisms determine how many molecules visit the microscopic pathways connecting the intermediates and transition states, which are the subject of statistical mechanics, and vary at a fixed temperature. A nonequilibrium-to-equilibrium chemical reaction, which occurs from a metastable state to a thermodynamically stable equilibrium state, proceeds via macroscopic multiple pathways depending on the number of molecules or concentration.43–46

Macroscopic pathways are affected by multiple factors such as the extent of progress of the reaction, temperature change, reversibility, deterministic/stochastic nature, subtle perturbations, fluctuations, and even thermal history.

The macroscopic pathways increase when a nonequilibrium-to-equilibrium chemical reaction involves reversibility. Reversibility in a chemical reaction is derived from small differences in the thermodynamic stability of substrates and products; that is, temperature changes can significantly affect relative thermodynamic stability. Various macroscopic multiple pathways can emerge, particularly when temperature changes during the reaction. For example, consider the 2A-to-B reaction from metastable state I, which is far from the equilibrium curve, to equilibrium II, during which the temperature changed from $T_1$ to $T_2$, as indicated by the concentration/temperature profiles (Figure 27). The relative thermodynamic stability at states I and II inverts between 2A and B, as shown by the equilibrium curve.

The reaction starts from metastable state I at $T_1$ and reaches equilibrium II at $T_2$. In the case of the irreversible nonequilibrium-to-equilibrium chemical reaction, $[B]$ changes in the domain between $[B]_{\text{start}}$ and $[B]_{\text{equil}}$ (Figure 27a). In contrast, in the case of the reversible nonequilibrium-to-equilibrium chemical reaction, $[B]$ can change in the domain between $[B] = 0$ and $1/2[A]_0$ (Figure 27b). Temperature changes largely enhance the macroscopic multiple pathways of the reversible nonequilibrium-to-equilibrium chemical reaction.

### 7.2. Macroscopic Multiple Pathways in Chemical Systems Involving Two Competitive Self-Catalytic Reactions

Catalysis is an important concept in chemical reactions, in which structural changes of molecules are affected by their interactions with other substances, by either the formation of covalent or noncovalent bonds. A catalyst can be externally added or incorporated in the chemical reaction system itself. Self-catalysis is a notable example of the latter, in which a product catalyzes the substrates to become products, exhibiting a substantial increase in the reaction rate. The involvement of the self-catalytic $2A + B$-to-$2B$ reaction increases the macroscopic multiple pathways of nonequilibrium-to-equilibrium chemical reactions, as described in this article.43–46

Biological systems employ such complex chemical reaction networks involving the positive feedback of self-catalysis.

When two self-catalytic reactions compete, the macroscopic multiple pathways still increase. At a fixed temperature, subtle perturbations and fluctuations are significantly amplified, and one of the self-catalytic reactions predominates. When the temperature is changed during the reactions, unusual chemical phenomena occur.

General features of chemical systems involving two competitive self-catalytic reactions are summarized in Section 1. Then, this section summarizes chiral symmetry breaking phenomena involving $2A + B$-to-$2B$ and $2A + \text{ent-B}$-to-$2(\text{ent-B})$ self-catalytic reactions, in which an enantiomer B or ent-B is predominantly formed. Because the microscopic pathways involved in the formation of the enantiomers B or ent-B are energetically identical, a reaction generally forms B and ent-B in equal amounts to provide a racemic mixture in a symmetric state.

![Figure 27. Macroscopic multiple pathways of nonequilibrium-to-equilibrium chemical reaction, during which temperature changed, as depicted by concentration/temperature profiles. Chemical reactions with the irreversible system (a) and reversible system (b) are shown.](image)

![Figure 28. Energy diagrams of chiral symmetry breaking in a chemical system involving two competitive self-catalytic reactions. Subtle perturbations or fluctuations (blue arrow) convert a symmetric state to an asymmetric state, which is amplified by self-catalysis (green arrow) to increase the number of molecules that visit a single pathway (red solid arrow). A model shows two cars with powerful engines pulling in opposite directions.](image)
In chiral symmetry breaking, the predominant formation of enantiomer B or ent-B occurs via different macroscopic pathways, which is asymmetric (Figures 5 and 6), and is derived from self-catalytic amplifications of subtle perturbations and fluctuations often below the limit of detection (Figure 28).

The phenomenon can be discussed in terms of energy. Note that the microscopic pathways are fixed at a fixed temperature, which does not change during the reaction. Via macroscopic pathways, a small perturbation of fluctuation (blue arrow) induces the predominant formation of B or ent-B, owing to the preference in the number of molecules that visit one of the macroscopic pathways. Self-catalysis (green arrow) opens a new microscopic pathway, and the number of molecules that visit the pathways significantly increases (red arrow), resulting in an asymmetric state. Such chemical kinetics of chiral symmetry breaking is discussed by stochastic kinetics (Figure 3). A model system is shown, in which two cars with powerful engines are pulling in opposite directions (Figure 28), and a small fluctuation can be amplified because of mutual tense, and a car starts to move rapidly on one side.

Stochastic and deterministic chiral symmetry breaking appears in repeated experiments (Figure 29). Stochastic chiral symmetry breaking implies that chemical reactions stochastically form B and ent-B at a comparable ratio in repeated experiments, which is also referred to as product stochastic (Figures 6c and 7). Deterministic chiral symmetry breaking implies that a chemical reaction deterministically forms a single enantiomer B in repeated experiments, which is also referred to as product deterministic (Figure 6a,b).

Chemical systems involving two competitive self-catalytic reactions exhibit extremely high sensitivity toward environmental changes and various notable phenomena. Subtle perturbations and fluctuations can trigger chemical reactions at various domains and times, thereby amplifying the chemical reactions. Triggers include the range and rate of temperature changes, surface contact, and mechanical stirring. Chemical reactions are extremely complex and interesting phenomena.

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