Chirally Autocatalytic Reaction Performed in Highly Supersaturated Conditions

K. Asakura [†] *, K. Kurihara [†], A. Ikumo [†], A. Tanaka [†], T. Miura [†], T. Ozawa [†], Y. Kushibe [†], S. Osanai [†], D.K. Kondepudi [#]

[†] Department of Applied Chemistry, Faculty of Science & Technology, Keio University, 3-14-1, Kohoku, Yokohama 223-8522, Japan

[#] Department of Chemistry, Wake Forest University, Winston-Salem, North Carolina 27109, USA

SUMMARY: Spontaneous chiral asymmetry generation, which is the preferential production of one enantiomer in a non-chiral environment by chiral autocatalysis, could be observed in a preparation of a octahedral cobalt complex, cis-$[CoBr(NH_3)(en)_2]Br_2$. A concentration fluctuation in a far-from-equilibrium chemical system will grow if the rate of local autocatalytic production of a compound in a small volume overcomes its loss due to diffusion. In a chirally autocatalytic system, this phenomenon could produce a large variation in the enantiomeric excess. In a reaction that produces the cobalt complex, the reaction rate was found to increase in the highly supersaturated solution of the product. In supersaturated solutions, before crystals of the solute have nucleated, embryos, which are the clusters of the solute, are formed. Ternary water-solubility isotherm of each enantiomer of the cobalt complex suggests that each embryo consists of one exclusive enantiomer. Each chiral cluster, which could be regarded as polymeric material, thus formed in a highly supersaturated solution, may act as catalyst for the production of the same enantiomer. Life is a far-from-equilibrium self-organized polymeric system in which chiral symmetry is broken. This reaction system is thus a model for the generation and amplification of chiral asymmetry in polymeric materials; it provides some insight in to the mechanisms that might have produced the observed biomolecular homochirality.

Introduction

Origins of biomolecular homochirality have extensively attracted interests of scientists [1-5]. Wald's suggestion regarded the origin of the homochirality in nature as the autocatalytic chiral symmetry breaking that occurred during the evolution of life [6]. In his suggestion, the α-helical structure in proteins resulted from chance formation of a homochiral sequence of L-amino acids and such protein catalyzed the production of more L-amino acids. Our system shows similar behavior.

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A far-from-equilibrium transition to a dissipative structure arises if autocatalytic processes are involved in a chemical system, since the system become sensitive to fluctuation [7-9]. A transition to a state dominated by either L- or D-enantiomer may occur if there is chiral autocatalysis in a chemical system [10, 11]. As results of such reactions, a random enantiomeric excess (ee) that may arise due to a local fluctuation can rapidly grow and this process can result in stochastic behavior. In this article we review our study of such a system which involves the synthesis of a chiral cobalt complex [12-14].

The important feature of this reaction is that the autocatalysis occurs exclusively when the degree of supersaturation of the final product exceeds a certain threshold value. It indicates that each chiral molecule of the product does not have a catalytic activity. In supersaturated solutions, solutes form clusters called embryos. Each chiral cluster, which could be regarded as polymeric material, expected to be formed in highly supersaturated solution, may act as catalyst of the production of the same enantiomer as its component. This system is thus a model for origin of biomolecular homochirality in which chirally autocatalytic polymerization connected to chirally selective production of monomer unit by homochiral polymer.

Autocatalytic Chiral Asymmetry Generation on the Preparation of Chiral Octahedral Cobalt Complex

Tri-nuclear cobalt complex, $[Co(H_2O)_2\{(OH)_2Co(en)_2\}_2](SO_4)_2$ (**A**), reacts with NH_4Br (**B**) in aqueous media to produce the chiral octahedral cobalt complex, cis-$[CoBr(NH_3)(en)_2]Br_2$ (**D**). A typical reaction is performed as follows. A reaction mixture consisting of 0.80 g of **A**, 4.00 g of **B** and 4.0 ml of water are placed in a 50 ml reaction flask in 25 °C atmosphere and stirred using stir-bar (2.5 cm in length, 0.8 cm in diameter) at 500 rpm. After 1 min, the flask is placed in a 50 °C water bath and stirred for 5 min. The reaction was found to proceed through the intermediate complex $[Co(H_2O)(OH)(en)_2]^{2+}$ (**C**). It is then converted into the final stable chiral complex **D** by the ligand replacement of $(OH)^-$ and H_2O by NH_3 and Br^- as shown in Figure 1 [15].

Except for some specific cases, the absolute structure is not maintained in the ligand exchange reactions [16-19], which indicates that the reaction from **C** to **D** proceeds through an achiral transition state. Random preferential production of one enantiomer of the final product **D** was shown to spontaneously occur [12, 14]. Since the intermediate **C** is always produced as a racemic

compound and the absolute structure is generally not maintained in the ligand exchange reactions, the chiral asymmetry generation seems to occur in the reaction from the achiral transition state to the product **D**.

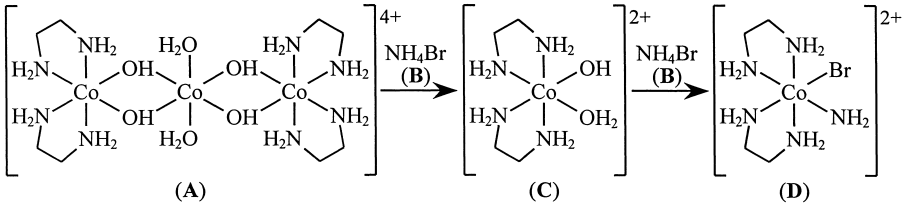

Fig. 1. Preparation of chiral octahedral cobalt complex in which autocatalytic chiral asymmetry generation occurs.

The reaction is chirally autocatalytic, since addition of crystals of one enantiomer to the reaction mixture results in the preferential production of that particular enantiomer as shown in Figure 2 [12-14]. In this case 1, 3, 10 or 40 crystals in the size-range 300 – 425 μm of $(-)_{589}$ or $(+)_{589}$- **D** were added to the reaction mixture in advance. We notice that an increase in the stirring rate and the use of a larger stir-bar increase not only the average ee but also the magnitude of its fluctuations.

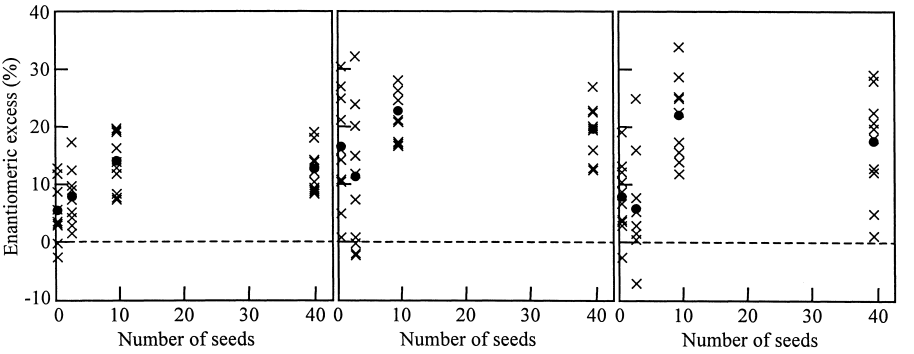

Fig. 2. Distribution of ee of **D** when synthesis is performed with crystal seeds. Positive and negative ee respectively indicates the preferential production of the same and the opposite enantiomer as the seed. a) Small stir-bar (1.2 cm in length, 0.5 cm in diameter), at 500 rpm; b) Small stir-bar, at 1500 rpm; c) Large stir-bar (2.5 cm in length, 0.8 cm in diameter), at 500 rpm. Solid circles show the average ee.

Kinetic Analysis of the Reaction System

In order to determine the mechanism of the observed large fluctuation in ee, kinetics of the reaction were investigated. The conversion of the intermediate, **C**, to the final product, **D**, was

monitored. The reaction was performed by adding 0.80 g of **A** into the mixture of 4.0 g of **B** and 4.0 ml of water (excess amount of **B** was added to keep the solution saturated with **B** throughout the reaction) in a 50 ml round bottomed flask. The temperature of the mixture was kept at 40 or 50 °C throughout the reaction. The conversion of **C** to **D**, the final step of the reaction, is expected to have a rate given by:

$$\frac{d[\mathbf{D}]}{dt} = -\frac{d[\mathbf{C}]}{dt} = k[\mathbf{B}][\mathbf{C}] \qquad (1)$$

Since [**B**] is in excess and does not change significantly during the reaction, the dependence of the rate constant k on product concentration [**D**] can be obtained by plotting $(1/[\mathbf{B}]) \cdot d\ln[\mathbf{C}]/dt = -k$ as a function of [**D**]. As can clearly be seen in Figure 3, the rate constant k increases with temperature, but more relevant to our discussion is the fact that it increases with increase of degree of supersaturation S (= [**D**] / $[\mathbf{D}]_S$ in which $[\mathbf{D}]_S$ is the saturation concentration of the product) as shown in Figure 3. Solubility of racemic and enantio-pure **D** and the X-ray conformational analysis of enantio-pure **D** crystal indicate that it crystallizes as a conglomerate, i.e. each crystal consists exclusively of one enantiomer [13, 20]. This suggests that each embryo consists of one exclusive enantiomer. Each chiral cluster, formed in a supersaturated solution, may act as a catalyst for the production of the same enantiomer as its component.

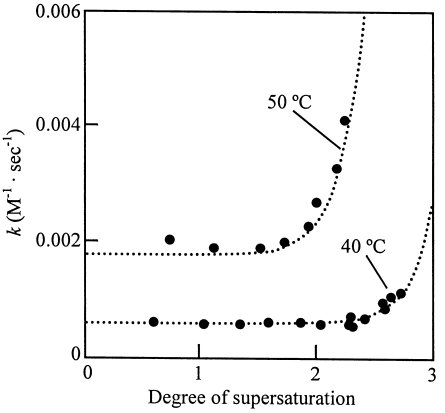

Fig. 3. The relationship between the rate constant (k) and degree of supersaturation (S). Dotted lines are the result of the simulations.

A "Cluster Model" was proposed to quantify this autocatalytic nature. We assume that as the supersaturating increases, the product **D** forms enantiomeric clusters, i.e., each cluster consists of exclusively $\mathit{\Lambda}-\mathbf{D}$ or $\mathit{\Delta}-\mathbf{D}$. When these clusters reach a critical size consisting of M molecules, they become chirally selective catalysts. For the formation of the clusters, we adopt the simple stepwise addition of monomers:

$$\mathit{\Lambda}-\mathbf{D}_n + \mathit{\Lambda}-\mathbf{D} \rightleftharpoons \mathit{\Lambda}-\mathbf{D}_{n+1} \qquad (2)$$

in which the subscript n indicates the size of the cluster. We assume that reaction (2) equilibrates rapidly and that the rate constant does not vary significantly with n so that:

$$\frac{[\Lambda - \mathbf{D}_{n+1}]}{[\Lambda - \mathbf{D}_n][\Lambda - \mathbf{D}]} = K \tag{3}$$

with a similar equation for the other enantiomer. It then follows that:

$$[\Lambda - \mathbf{D}_n] = [\Lambda - \mathbf{D}]^n K^{n-1} \tag{4}$$

The Λ-catalyst, $\mathbf{X}_\Lambda$, is the Λ-clusters of size M or larger, whose concentration equals:

$$[\mathbf{X}_\Lambda] = \sum_{i=M}^{\infty} [\Lambda - \mathbf{D}_i] = \sum_{i=M}^{\infty} [\Lambda - \mathbf{D}]^i K^{i-1} = \frac{[\Lambda - \mathbf{D}]^M K^M}{K} \sum_{i=0}^{\infty} [\Lambda - \mathbf{D}]^i K^i \tag{5}$$

The term $[\Lambda - \mathbf{D}]K$ will be less than one if $[\Lambda - \mathbf{D}_{n+1}] < [\Lambda - \mathbf{D}_n]$, which is generally true in normal supersaturated solution. Then (5) can be written as:

$$[\mathbf{X}_\Lambda] = \frac{1}{K} \frac{[\Lambda - \mathbf{D}]^M K^M}{(1 - [\Lambda - \mathbf{D}]K)} \tag{6}$$

The rate constant k in Eq. (1) can now be written as:

$$k = k_1 + k_2([\mathbf{X}_\Lambda] + [\mathbf{X}_\Delta]) \tag{7}$$

in which k_1 is the rate constant in the absence of the clusters. If $[\Lambda - \mathbf{D}] = [\Delta - \mathbf{D}] = [\mathbf{D}]/2$, then Eq. (7) can be written in terms of the degree of supersaturation $S = [\Lambda - \mathbf{D}]/[\Lambda - \mathbf{D}]_S$ ($= [\Delta - \mathbf{D}]/[\Delta - \mathbf{D}]_S$) (in which $[\Lambda - \mathbf{D}]_S$ and $[\Delta - \mathbf{D}]_S$ are the saturation concentration) as:

$$k = k_1 + \frac{2k_2}{K} \frac{S^M y^M}{(1 - Sy)} \qquad y = [\Lambda - \mathbf{D}]_S K \ (= [\Delta - \mathbf{D}]_S K) \tag{8}$$

Fitting the expression (8) to the experimentally obtained relationship between k and S can be done using the least-square "NonlinearFit" package of Mathematica. The result is shown in Figure 3 and the parameters values of the fit are shown in Table 1. The parameters shown in Table 1 indicate that clusters of size about 10 or larger have catalytic activity. In addition, k_2 and K respectively are represented as the function of temperature as:

$$k_2 = 3.89 \times 10^{93} \exp(-6.91 \times 10^4 / \mathrm{T}) \tag{9}$$

$$K = 3.85 \times 10^{-10} \exp(7.23 \times 10^3 / \mathrm{T}) \tag{10}$$

A comparison between the growth of the product **D** as a function of time given by the cluster model and the experimental data is shown in Figure 4. Though the theory qualitatively produces the shape of growth curve of **D**, the quantitative fit is poor [14].

Expression (8) indicates that the reaction is highly autocatalytic when Sy is closed to 1. This means that there is a critical degree of supersaturation at which the reaction suddenly takes off. The observed discrepancy between the theory and experiment and the stochastic variation

in **D** from run to run could be the result of local fluctuations in temperature and concentration that could grow rapidly.

Table 1. Parameters of rate constant as the function of degree of supersaturation obtained using least-square "NonlinearFit" package of Mathematica.

	50 °C	40 °C
M	9.86	11.99
k_2 / K	2.825	0.0015
y	0.188	0.278

Since the dissolution of **B** is endothermic, the temperature of the reaction mixture dropped to about 15 °C after 1 min stirring without heating. Then the system was immersed into 50 °C water bath. Temperature inhomogeneity is thus likely in the reaction system on a microscopic scale. The reaction proceeds faster in hotter parts. And, if the hotter part fragment is fractured and surrounded by cold bulk, the degree of supersaturation will suddenly increase to the critical value; the reaction then suddenly takes off. Results of the simulations indicated that the temperature of the hot cell dropped very rapidly while the concentration scarcely decreased to lead to the critical condition [14]. This local autocatalysis will increase the overall yield of **D**. Because the system is also chirally autocatalytic, small differences in ee will also be amplified and will result in a random distribution of ee.

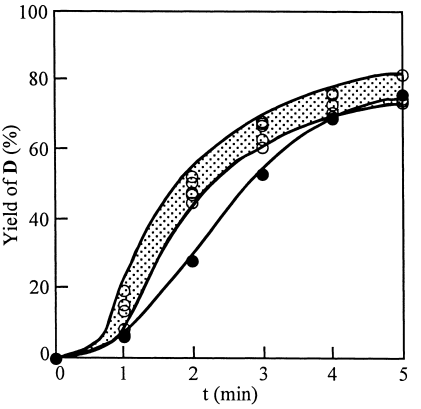

Fig. 4. Change of the yield of **D**. X-axis is the time after the flask was immersed into 50 °C water bath. The results of five times experiments (○) and simulation (●) are shown.

Chiral autocatalysis is of much interest in the context of the origin of biomolecular homochirality. Since the autocatalytic species, viz. enantiomeric clusters, are the homochiral polymeric materials which could catalyze the production of one enantiomer this system provides model for origin of homochiral biopolymers in nature.

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