Chiral Autocatalysis, Spontaneous Symmetry Breaking, and Stochastic Behavior

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ABSTRACT

During the past decade, chirally autocatalytic systems that exhibit unusual and interesting phenomena, such as spontaneous chiral symmetry breaking and stochastic behavior, have been identified. In this Account we outline the context in which chiral autocatalysis is of interest, summarize recent advances, and discuss our current understanding of the underlying kinetics and mechanisms. In addition, we note some fundamental aspects of amplification of enantiomeric excess and sensitivity of symmetry breaking transitions to asymmetric factors.

Introduction

Autocatalysis plays a special role in systems that are far from thermodynamic equilibrium. It can produce concentration oscillations, propagating chemical waves, and beautiful spatially symmetric patterns in which reacting compounds are neatly segregated through a complex interaction between diffusion and chemical reactions.[1] As the system evolves to equilibrium, these oscillations and patterns disappear.

Chiral autocatalysis adds another dimension to nonequilibrium phenomena. Due to symmetry, the autocatalyst comes in enantiomeric pairs. The autocatalytic growth

then becomes a competition between the enantiomers in which one enantiomer may become dominant. The result is a stochastic or unpredictable behavior in which a small random enantiomeric excess (ee) is greatly amplified. In a particular experiment, the ee generated by these systems cannot be predicted because it depends on random events that happen during the course of the reaction. In some chirally autocatalytic systems, the produced ee is greater than 90% in every run, the dominance of either enantiomer being random. This is an instance of *spontaneous chiral symmetry breaking* in which the probability distribution for the ee is bimodal, with peaks near ±100%. In this Account we will describe spontaneous chiral symmetry breaking, stochastic behavior, amplification of asymmetry, sensitivity to small asymmetric factors, and related phenomena in chirally autocatalytic systems.

Since its discovery by Louis Pasteur, the origin of biomolecular asymmetry—the dominance of L-amino acids in proteins and D-sugars in DNA and RNA—has been of much interest. To provide a simple chemical example of spontaneous generation of chiral asymmetry, Frank devised a kinetic model with chiral autocatalysis in 1953.[2] Subsequently, several model reactions have been proposed,[3] but the first experimental realizations of spontaneous chiral symmetry breaking[4] and chiral autocatalysis[5] were reported only 10 years ago. Since then, other chirally autocatalytic systems were found by Asakura et al.[6] and Soai et al.[7] Though the original motivation for investigating chirally autocatalytic systems has been the origin of biomolecular chiral asymmetry, these systems are interesting in their own right, for they exhibit many unusual and interesting properties.

In the next section, we provide a brief overview of the general theoretical framework for chiral symmetry breaking. This is followed by a summary of experimental examples and analysis of their kinetic and stochastic behavior. We conclude with remarks on open questions and future prospects of research in this field.

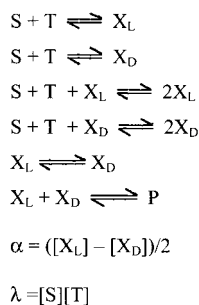## Spontaneous Chiral Symmetry Breaking in Nonequilibrium Systems

At thermodynamic equilibrium there can be no ee. However, in nonequilibrium systems a state of nonzero ee can spontaneously arise from an achiral or a racemic state through a chiral-symmetry-breaking transition. The general formalism of such transitions is best understood through a simple example based on an extension of Frank's model.[8] The extension gives us a clear picture of how, as the system is driven away from thermodynamic equilibrium, a symmetry-breaking transition occurs.

The model we consider is Scheme 1, in which the chirally autocatalytic species, X_L and X_D, are produced from achiral reactants S and T. Since enantiomer interconversion (racemization) and reverse reactions are included in this scheme,[8c] the system can evolve to the

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Scheme 1

$$S + T \rightleftharpoons X_L$$

$$S + T \rightleftharpoons X_D$$

$$S + T + X_L \rightleftharpoons 2X_L$$

$$S + T + X_D \rightleftharpoons 2X_D$$

$$X_L \rightleftharpoons X_D$$

$$X_L + X_D \rightleftharpoons P$$

$$\alpha = ([X_L] - [X_D])/2$$

$$\lambda = [S][T]$$

equilibrium symmetric state in which $[X_L] = [X_D]$. An inflow of S and T and an outflow of the product P can maintain this system away from equilibrium (Figure 1a). In this state, if the product of the concentrations of S and T, $[S][T]$, is above a critical value, the symmetric state becomes "unstable"—as a state does in a phase transition. The instability means that a small ee in X, that may arise spontaneously due to random fluctuations, may grow and drive the system to an *asymmetric state* in which $[X_L] \neq [X_D]$. The instability and transition to the asymmetric state is entirely a consequence of the reactions in Scheme 1.

In this context, one speaks of "broken symmetry" in the following sense. The chemical reactions which are symmetric in the two enantiomers X_L and X_D may yet produce an asymmetric state in which $[X_L] \neq [X_D]$. Such a state is said to have a "broken symmetry". In fact, there must be two such states: if a state in which $[X_L] > [X_D]$ is possible then, by symmetry, its mirror-image state, $[X_D] > [X_L]$, must also be possible.

The instability of the symmetric state and the consequent transition to an asymmetric state has a rather simple mathematical description in terms of the variables $\alpha = ([X_L] - [X_D])/2$ and $\lambda = [S][T]$; the value of λ above which the asymmetric states spontaneously arise is denoted by λ_C. For values of λ near λ_C, it is possible to derive an equation of the form[8a,b]

$$\frac{d\alpha}{dt} = -A\alpha^3 + B(\lambda - \lambda_C)\alpha \qquad (1)$$

in which the coefficients A and B are functions of the kinetic rate constants of the reactions in the scheme. For a scheme that can break chiral symmetry, such as Scheme 1, λ_C can be explicitly calculated.[8a,b]

At a fixed λ, α will evolve to its steady state, at which $d\alpha/dt = 0$. For positive A and B and $\lambda < \lambda_C$, it follows from (1) that the *symmetric state*, $\alpha = 0$, is the only stable steady state; any perturbation from $\alpha = 0$ will decay back to zero. For $\lambda > \lambda_C$, two new steady states, $\alpha = \pm[B(\lambda - \lambda_C)/A]^{1/2}$, emerge or "bifurcate" from $\alpha = 0$ at λ_C; these are the *asymmetric states*, each dominated by one of the enantiomers. At λ_C, precisely when the asymmetric states emerge, the symmetric state begins to become unstable; when $\lambda > \lambda_C$, a small random perturbation from $\alpha = 0$ will grow and produce an asymmetric state. The steady states of α as functions of λ and the resulting "bifurcation diagram" are shown in Figure 1b.

The evolution of α is not deterministic because we cannot predict, using eq 1, to which branch, $\alpha > 0$ or $\alpha <$

$$\alpha = ([X_L] - [X_D])/2 \quad \lambda = [S][T]$$


(a)

(b)

(c)
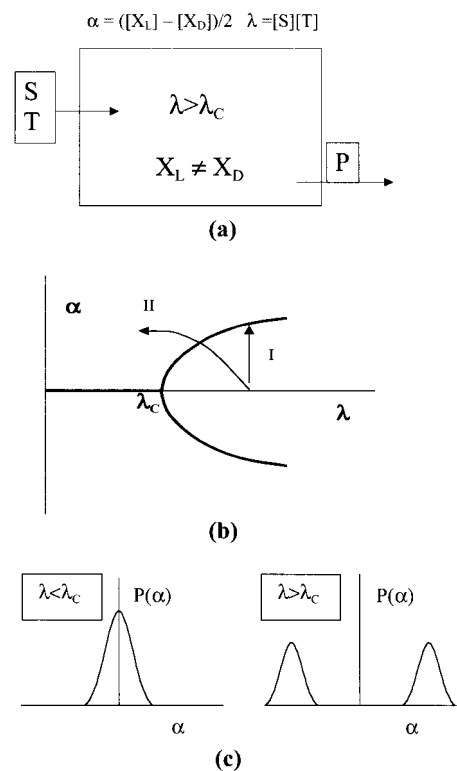
FIGURE 1. Spontaneous chiral symmetry breaking in nonequilibrium chemical systems. (a) Open flow systems. (b) Bifurcation of asymmetric states. I and II indicate the trajectories in open and closed systems, respectively. (c) Probability distributions associated with stochastic behavior.

0, the system will evolve. It is probabilistic with a probability distribution $P(\alpha)$. Below λ_C, due to small random fluctuations in α, the probability distribution will be monomodal centered around zero; above λ_C it will be bimodal (Figure 1c) because repeated runs will result randomly in both positive and negative values of α. A bimodal probability distribution is a clear signature of a symmetry-breaking transition.

Finally, we note that, though eq 1 was obtained for Scheme 1, it is in fact quite general: its form really derives form the two-fold symmetry of chirality. For any reaction scheme that leads to spontaneous chiral symmetry breaking, eq 1 is valid; only the numerical values of A and B and the physical meanings of α and λ will be different. In the case of stirred crystallization that we will discuss below, λ is the concentration of the achiral solution (λ_C, concentration at saturation) and α is the difference in the number of levo- and dextrorotatory crystals.

In open systems, the inflow of S and T and an outflow of P can maintain λ at a fixed value. When $\lambda > \lambda_C$, if $\alpha = 0$ initially, it may follow the trajectory I shown in Figure 1b. What happens in a closed system which initially has achiral reactants, S and T, at a concentration level that corresponds to $\lambda > \lambda_C$? In this case, as S and T are converted to the chiral product X, $\lambda = [S][T]$ will decrease, and the system will evolve to an asymmetric state following a trajectory such as II shown in Figure 1b; furthermore, if racemization rates are virtually zero, it will remain in this state.[9] In fact, the experimental examples of chiral
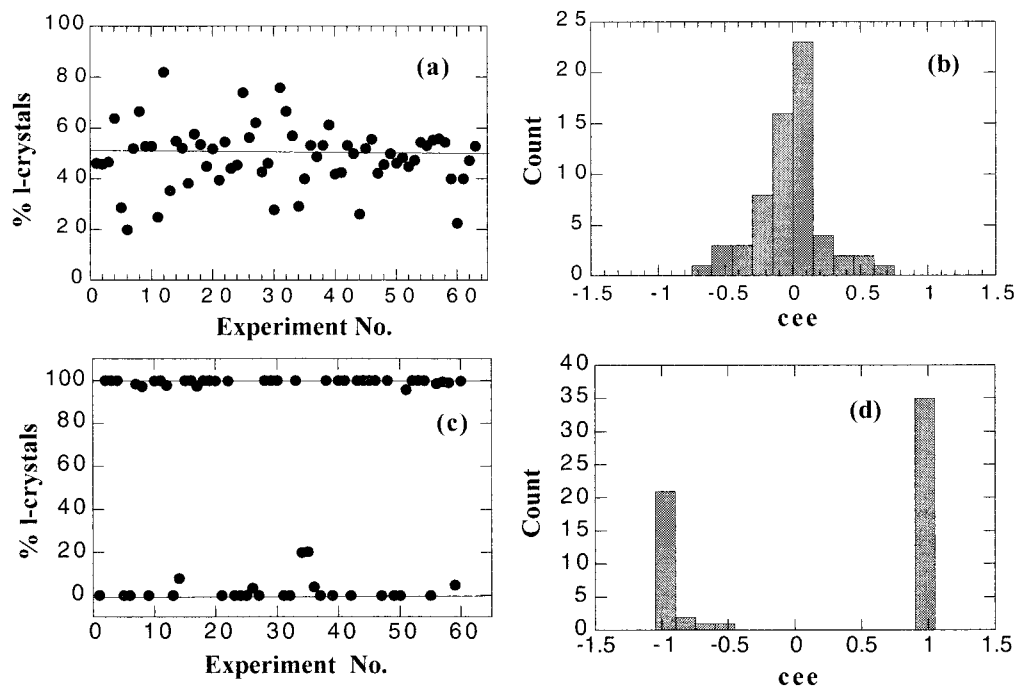
FIGURE 2. Spontaneous chiral symmetry breaking in $NaClO_3$ crystallization. (a) The percentage of l crystals obtained in 63 independent unstirred crystallizations and (b) the corresponding histogram of crystal enantiomeirc excess (cee) = $(N_l - N_d)/(N_l + N_d)$. (c) The percentage of l crystals obtained in 60 independent stirred crystallizations and (d) the corresponding histogram of cee.

symmetry breaking in stirred crystallization we present below are of this type.
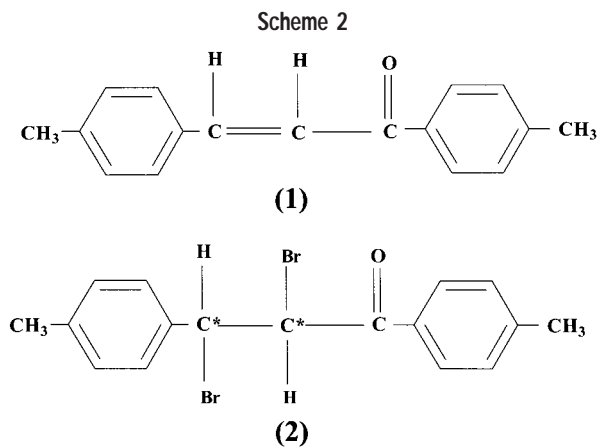
Spontaneous Symmetry Breaking in Crystallization from a Solution

Calvin suggested crystallization as a process through which asymmetric states can arise,[10] but he was not aware of the dramatic role stirring could play in generating them. In 1990, we found that stirred crystallization of $NaClO_3$ resulted in spontaneous chiral symmetry breaking.[4] The achiral compound $NaClO_3$ crystallizes in enantiomeric forms (cubic space group $P2_13$). The optical activity of $NaClO_3$ crystals (about a millimeter or larger) can easily be detected using a pair of polarizers. Static solvent evaporation produces the expected statistically equal number of levo- (l) and dextrorotatory (d) crystals, as was shown by Kipping and Pope over 100 years ago,[4,11] (Figure 2a). The corresponding probability distribution for the crystal enantiomeric excess (cee) is monomodal (Figure 2b) centered at zero (cee = $((N_l - N_d)/(N_l + N_d))$, in which N_l and N_d are the number of l and d crystals, respectively). However, if the solution is continuously stirred, the resulting crystals are almost all l or almost all d in every crystallization. As summarized in Figure 2c, the dominance of l and d crystals is often more than 98% and completely random in any particular crystallization. The resulting probability distribution for the cee is bimodal (Figure 2d)—the signature of spontaneous chiral symmetry breaking. The simple act of stirring makes $NaClO_3$ crystallization chirally autocatalytic, with kinetics that result in spontaneous chiral symmetry breaking.

When stirred, "secondary" crystal nuclei are generated from the surface (or the vicinity) of an existing crystal, and an overwhelming number of these secondary nuclei can have the same crystal structure, l or d, as the parent crystal. Symmetry breaking occurs because the "first crystal" rapidly clones itself through secondary nucleation and dominates the system. One must note that chirally autocatalytic generation of crystals alone is not sufficient for symmetry breaking. For the dominance of one enantiomeric form, the proliferation of crystals of one form must prevent the proliferation of crystals of the mirror-image form. In stirred crystallization this happens because the concentration drops rapidly due to secondary nucleation, and this drop virtually stops the formation of more nuclei, primary or secondary, during the rest of the process. Thus generated percentage of l crystals is close to 0 or 100 in each crystallization. (In Scheme 1, the autocatalytic growth of one enantiomer suppresses the growth of the other through the reaction $X_L + X_D \rightarrow P$.)

The above phenomenon also occurs in the crystallization of $NaBrO_3$. Since most, if not all, crystals can generate secondary nuclei, one might expect chiral symmetry breaking in crystallization of other achiral compounds that crystallize in enantiomeric forms. (A list of such compounds has been tabulated by Jacques et al.[12])

Identifying the two enantiomeric crystals in general, however, is not as easy as identifying those of $NaClO_3$ or $NaBrO_3$ which, because of their isotropy, exhibit optical rotation regardless of their orientation. Furthermore, crystals that are about 1 mm in size, needed to detect optical activity easily, are not always easy to obtain. Other methods must be used to identify the two enantiomeric forms confined to the solid state. For the achiral com-
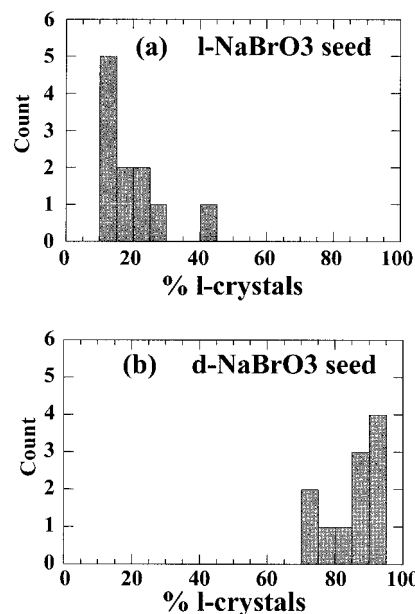
Scheme 2

(1)

(2)

FIGURE 3. Secondary nucleation due to fluid flow over seed crystals. Note that $NaBrO_3$ and $NaClO_3$ crystals with enantiomerically similar structure have opposite optical rotations. (a) The distribution of percent levorotatory crystals obtained by flow of $NaClO_3$ solution on l-$NaBrO_3$ crystals. (b) The distribution of percent levorotatory crystals obtained by flow of $NaClO_3$ solution on d-$NaBrO_3$ crystals.

pound 4,4′-dimethyl-chalcone (**1**, Scheme 2), which crystallizes in enantiomeric forms, this can be done by reacting the crystals with bromine vapor to generate chiral molecule **2**. Penzien and Schmidt established[13] that reacting crystals of **1** with bromine vapor generates **2** almost exclusively in the trans form. The two trans isomers are enantiomers. Reaction with a pure single crystal produces about 6% ee in the chiral product **2** (specific rotation = 10°). We performed stirred crystallization of 4,4′-dimethyl-chalcone and assessed the ee in the solid state through bromination.[14] The product's bimodal optical activity indicated that chiral symmetry breaking also occurs in stirred crystallization of 4,4′-dimethyl-chalcone. Such generation of chiral molecules from chiral crystals shows us how, in nature, chiral asymmetry in crystals may spread during the processes of chemical evolution.

The above results suggest that chiral symmetry breaking can be expected to occur in stirred solution crystallization of any achiral compound that crystallizes in enantiomeric forms.

The Nature of Chirally Autocatalytic Secondary Nucleation

Before we present other chirally autocatalytic systems, we take a closer look at secondary nucleation, the key step in the above experiments. Secondary nucleation, though easily observed and even noted in elementary books on crystallization,[15] is a rather complex process: even after decades of studies, empirical rate laws are widely used because details of its mechanism are not known. Solid−solid contact between a crystal and the stir bar, or the impeller in industrial crystallizers, can generate a large number of secondary nuclei.[16] Following our report,[4] McBride and Carter[17] have videotaped the collision of a $NaClO_3$ crystal and the stir bar and the subsequent rapid production of secondary nuclei. We have also observed this phenomenon. However, solid−solid contact is not essential for the generation of secondary nuclei. The most through study of secondary nucleation in $NaClO_3$ was done by Quian and Botsaris,[18] who showed that (a) secondary nuclei can be generated from a suspended crystal due to fluid convection alone; (b) secondary nucleation occurs at supersaturation levels at which the primary nucleation rate is negligible; (c) at low supersatu-

ration the secondary nucleation is highly enantioselective but at higher supersaturation it is less so.

Indeed, chirally selective nucleation of $NaClO_3$ occurs near the surface of a $NaBrO_3$ crystal. By making $NaClO_3$ solution drip over a $NaBrO_3$ crystal, we were able to generate a large number of crystals with the same enantiomeric form as the $NaBrO_3$ crystal;[19] no solid−solid collision or contact was involved (Figure 3). That fluid flow disperses the secondary crystals can be clearly seen from the fact that a statistically equal number of l- and d-$NaClO_3$ crystals are produced from an unstirred $NaClO_3$ solution when a $NaBrO_3$ seed crystal is placed in the solution. Such experiments show that secondary nuclei generated near the catalyzing chiral surface are easily displaced by gentle fluid flow.

Recently, Qian and Botsaris formulated a theory of secondary nucleation,[20] noting that forces between clusters and surfaces of crystals can lead to higher nucleation rates. The classical expression for the nucleation rate J is

$$J = J_0 \exp\left(-\frac{16\pi}{3kT}\frac{\gamma^3 V_m^2}{\Delta\mu^2}\right) \qquad (2)$$

in which γ is the interfacial energy, V_m is the molar volume of the solid phase, and $\Delta\mu$ is the chemical potential difference between the solution and the solid phases. In the simplest approximation, $\Delta\mu = RT \ln(C/C_S)$, where C is the concentration and C_S the saturation concentration. J increases with (C/C_S) almost like a step function as shown in Figure 4.

Qualitatively, high chiral selectivity at a low supersaturation and lower selectivity at higher supersaturation may be due to a shift in the nucleation rates in the vicinity of a chiral surface (Figure 4); chiral selectivity arises because
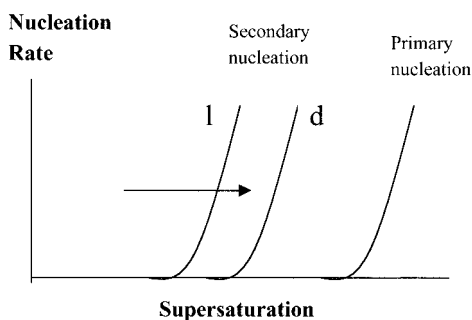
FIGURE 4. Nucleation rate as a function of supersaturation for l and d crystals near the surface of a l crystal.

l and d nucleation rates shift by different amounts. Thus, there is a supersaturation range in which only the l nuclei are produced in the vicinity of an l crystal surface, but both l and d nuclei are generated at higher supersaturation.

Symmetry Breaking in Crystallization from a Melt

At 158 °C, 1,1′-binaphthyl melt crystallizes as a conglomerate of *R* and *S* enantiomers. In its molten state, the enantiomers interconvert rapidly, the racemization half-life being less than a second. The ee in 1,1′-binaphthyl crystals can be easily measured because its racemization half-life in solution is about 9 h at room temperature. In their classic experiment, Pincock et al.[21] crystallized 200 mg samples of the melt, dissolved the resulting crystallite in benzene at room temperature, and measured specific rotations. A large data set thus collected resulted in a Gaussian-like probability distribution for the ee, with a maximum at zero. In this distribution, one out of 150 samples has an ee larger than 90%.

Our investigation of stirred crystallization of 1,1′-binaphthyl melt[22] showed that chiral symmetry breaking could also be realized in the crystallization of melts. When 2.0 g samples of 1,1′-binaphthyl melt were crystallized while the melt was being stirred by a Teflon stir bar, we found that ee generated in almost every crystallization is greater than 80%. The probability distribution of the ee in this case is bimodal (Figure 5), in contrast to the monomodal distribution obtained in the experiments of Pincock et al.[21]

Chiral Autocatalysis and Stochastic Behavior in the Synthesis of Octahedral Chiral Co-complex

In 1994, we[6] noticed random generation of ee in the synthesis of an octahedral chiral cobalt complex (Figure 6). The reaction proceeds through a racemic intermediate as shown in Scheme 3.

In this reaction, though probability distribution is not bimodal as in stirred crystallization, the spontaneous generation of ee is significant: in some runs the ee was as much as 30%. Furthermore, the average ee generated depends on the stirring rate.[23]

In this reaction, chiral autocatalysis seems to arise from the low solubility of the product which crystallizes as a

conglomerate. The autocatalytic rate increases with supersaturation. The rate of production of the chiral product **D** following Scheme 3 is

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

If **B** is in excess, and hence essentially constant,

$$\frac{1}{[\mathbf{B}]}\frac{d\ln[\mathbf{C}]}{dt} = -k \tag{3}$$

We observed that the production rate of **D** increased with an increase in its concentration. Using ln [**C**] vs time data, it is possible to obtain the effective rate constant *k* as a function of [**D**]. As shown in Figure 7, we found that *k* increased rapidly with supersaturation, $S = [\mathbf{D}]/[\mathbf{D}]_S$, in which $[D]_S$ is the concentration at saturation.[24]

We could explain the dependence of *k* on supersaturation using a "cluster model". In this model, clusters form as [**D**] increases, and clusters containing *M* or more molecules are enantioselective catalysts. Furthermore, since **D** crystallizes as a conglomerate of enantiopure crystals, the clusters are also assumed to be enantiopure. With these assumptions, an expression for *k* as a function of *M* can be obtained. Nonlinear curve-fitting to the data (Figure 7) gave the value of about 10 for the critical cluster size *M* ($M = 10$ at $T = 50$ °C and $M = 12$ at $T = 40$ °C).[24] This suggests that cluster formation may be involved in the observed chiral autocatalysis.

Stochastic Kinetic Model of Stirred Crystallization

A description of the chiral symmetry breaking in stirred crystallization is possible through kinetic models that are intrinsically stochastic.[25] In these models, primary and secondary nucleation are simulated using appropriate random number generators. The average primary nucleation rate is specified using the classical rate with parameters chosen to fit the experimentally observed rates. According to an empirical law[26] used in our model, the rate of production of secondary l nuclei, $R_{l,sec}$, is

$$R_{l,sec} = s\sigma_l K_S (C - C_S)^v \tag{4}$$

in which the parameter *s* depends on stirring RPM, s_l is the surface area of the l crystals, K_S is a constant, and *C* is the concentration which equals C_S at saturation. The exponent *v* is often given a noninteger value to fit the experimental data. For our data, $v = 2.75$. Such widely used ad hoc assumptions for the secondary nucleation rate only underscore the need for a basic theory.

Our kinetic model was able to reproduce the experimentally observed time evolution well.[25] Since the kinetic model is intrinsically stochastic, repeated computer runs give different numbers of l and d crystals, and thus the probability distribution of cee can be obtained. For example, the experimentally obtained change in the probability distribution of cee with change in the stirring RPM could be compared with the computer simulations.[27] As shown in Figure 8, present kinetic models can repro-
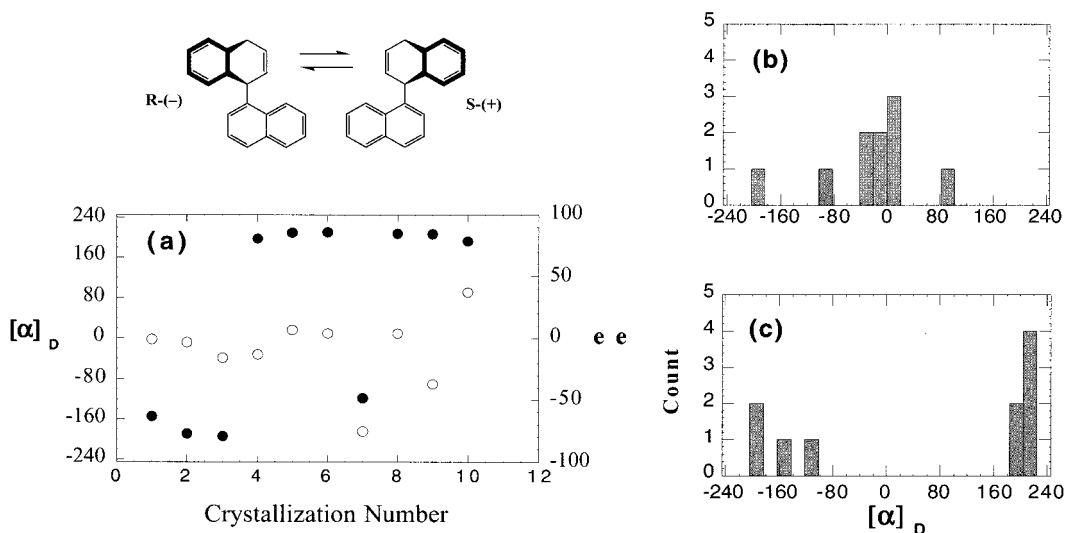
FIGURE 5. Spontaneous chiral symmetry breaking in crystallization of 1,1'-binaphthyl melt. (a) Specific rotations obtained in unstirred (○) and stirred (●) crystallization. Histograms of unstirred (b) and stirred crystallizations (c).
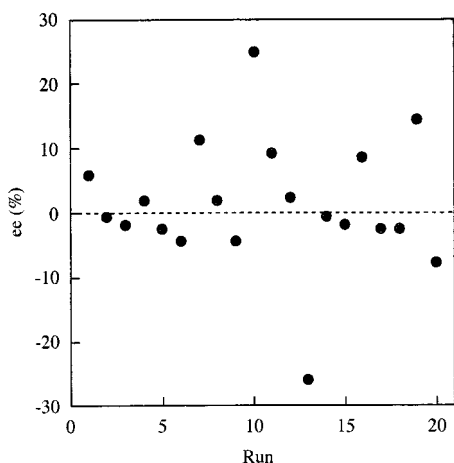

FIGURE 6. Random ee in the synthesis of chiral co-complex (Scheme 3).

duce the observed general trends. By comparing the average cee at each RPM, we could ascertain that the RPM-dependent parameter *s* expression (4) is approximately RPM/600. The stochastic model can also provides us with details about how the number of l and d crystals and crystal size distribution varies from run to run.

Amplification of Asymmetry by Chirally Autocatalytic Systems

Chiral autocatalysis in organic reactions was found by Soai et al. in the alkylation of certain aldehydes using dialkylzincs.[5] In these reactions, when a small amount of non-racemic product is added at the start, the enantiomer that is initially in excess is produced in a larger amount when the reaction is complete. It was also demonstrated that some of these reactions, though not all, are capable of amplifying a small initial ee and that they are also strongly influenced by the presence of chiral crystals[7d–f] such as quartz and NaClO$_3$. Indications of spontaneous symmetry breaking and stochastic behavior have been reported in a patent.[28]

In this context it must be noted that amplification of an initial ee depends on the order of autocatalysis. For example, the reaction scheme, S + T → X$_D$, S + T + X$_D$ → 2X$_D$ (with similar reactions for the other enantiomer) and rates k_1[S][T] and k_2[X$_D$][S][T], does not amplify an initial enantiomeric excess. For such a reaction scheme, it is easy to show that as the reaction proceeds

$$\ln\left[\frac{ee}{(2k_1/\beta) + k_2}\right] = \text{constant}$$

where $\beta = $ [X$_L$] + [X$_D$]. Hence, as the amount of X increases, ee must decrease if $k_1 \neq 0$; if $k_1 = 0$, then the ee remains constant during the reaction. (In Scheme 1, the amplification of random ee occurs because of the reaction X$_L$ + X$_D$ → P.)

If the autocatalytic rate is of higher order in X, then the ee can be amplified.[29] For second- and third-order autocatalytic reactions in which the rates are k_2[S][T][X$_D$]^2 and k_2[S][T][X$_D$]^3, respectively, the relationship between initial ee and the final ee along with some data reported by Soai et al.[7c,d] is shown in Figure 9. If the mechanism involves cluster formation, the autocatalysis will be of order higher than 1. Thus, one can deduce the order of the autocatalysis through a careful study of the ee amplification.

Symmetry-breaking transitions are also highly sensitive to small asymmetric factors. This sensitivity is particularly high in a dynamic process in which the critical parameter λ moves from a value below λ_C to a value above λ_C at some average rate γ, i.e., $\lambda = \lambda_0 + \gamma t$, where $\lambda_0 < \lambda_C$. Consider a small asymmetric factor which increases the rate constant of one of the enantiomers (presence of a chiral substance) or selectively destroys one of the enantiomers (circularly polarized light). When such a factor is introduced into the reaction scheme, eq 1 is modified to[8]

$$\frac{d\alpha}{dt} = -A\alpha^3 + B(\lambda - \lambda_C)\alpha + Cg + \sqrt{\epsilon}\xi(t) \quad \text{(5a)}$$

$$\lambda = \lambda_0 + \gamma t \quad \text{(5b)}$$

Scheme 3
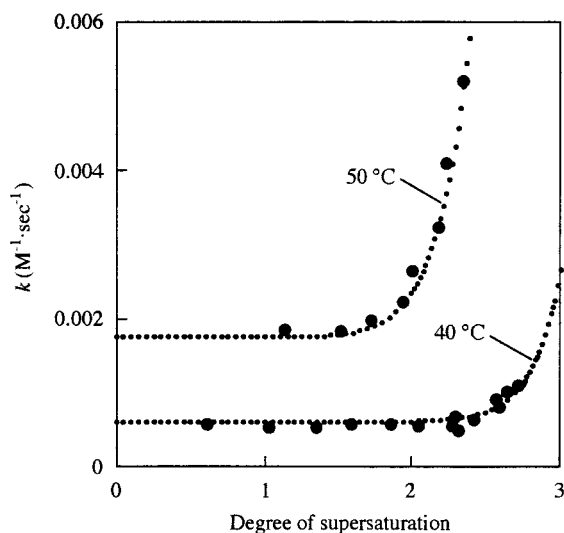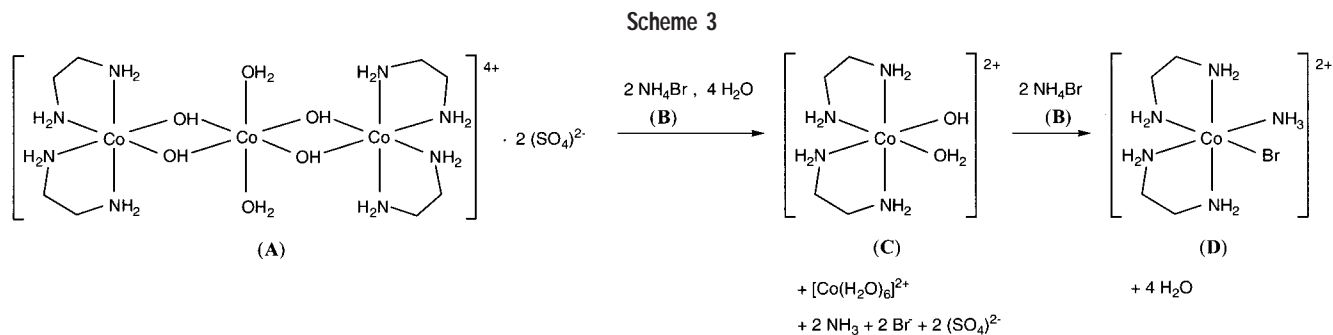
FIGURE 7. Co-complex rate constant as a function of degree of supersaturation, $S = [D]/[D]_S$. The dotted line shows the fit of the cluster model to the data.

in which C is a constant that depends on the rate constants and g is a measure of the asymmetric factor (which in some cases can be expressed as a dimensionless ratio ($\Delta E/kT$) in which ΔE is the asymmetric interaction energy). The last term in this equation represents random fluctuations in α with root-mean-square value $\sqrt{\epsilon}$. Our analysis of this situation[8b,c] resulted in a counterintuitive result: even when the magnitude, Cg, of the asymmetric factor is smaller than the root-mean-square value, $\sqrt{\epsilon}$, of the random fluctuations, the asymmetric factor can drive the system to a preferred asymmetric state with high probability. As the critical parameter λ traverses through the critical point, let us say the probabilities of transition to asymmetric states, $\alpha > 0$ and $\alpha < 0$, are P_+ and P_-, respectively. In the absence of the asymmetric factor, $P_+ = P_- = 1/2$; in its presence, we found that[8b,c]

$$P_+ = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{N} e^{-x^2/2}\,\mathrm{d}x \qquad N = \frac{Cg}{\sqrt{\epsilon/2}}\left(\frac{\pi}{B\gamma}\right)^{1/4} \quad (6)$$

This expression shows that P_+ depends on the rate, γ, at which λ traverses the critical point λ_C, the system being more sensitive when γ is small. For example, P_+ can nearly equal 1, even when $(Cg/\sqrt{\epsilon}) \ll 1$ if γ is sufficiently small. This prediction has been verified in noise-driven nonlinear electronic systems.[30] A recent report on the effect of the direction of stirring on chiral liquid crystals seems to be another example of such sensitivity.[31]
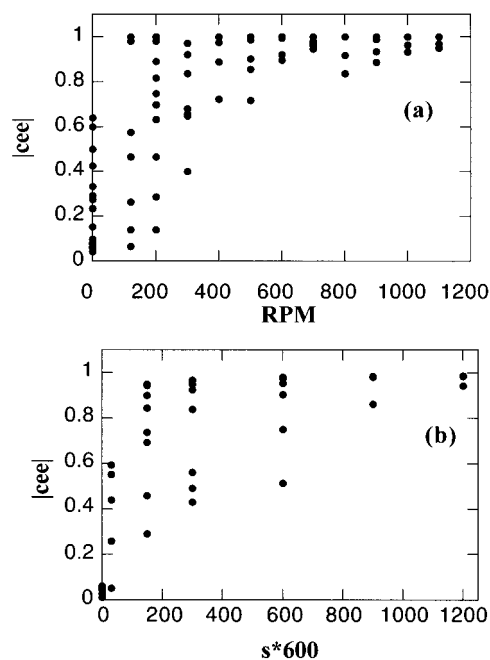
FIGURE 8. Stochastic behavior in stirred crystallization. (a) Experimentally observed random variation of cee in stirred crystallization of $NaClO_3$ with stirring RPM. (b) Results of stochastic computer simulation using rate law (4) for secondary nucleation.
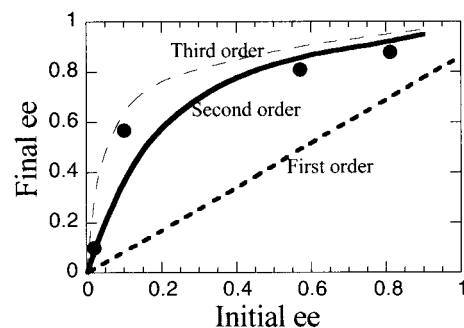
FIGURE 9. Relationships between initial and final ee in first-, second-, and third-order chirally autocatalytic reactions. ●, data from Soai et al.[7c,d]

Inhomogeneities and the Effects of Stirring

In nonlinear systems in general, and autocatalytic systems in particular, mixing through stirring or other means can have a significant effect on the outcome of a chemical reaction,[32] as is clear from the above experiments. Diffusion and stirring determine the spatial domains in which a fluctuation in ee can grow. A fluctuation of ee in a small volume δV can grow only when the autocatalytic growth

can overcome the diffusional loss. Autocatalytic growth of the ee is proportional to the volume, while diffusional loss is proportional to the surface area. Hence, when δV is very small, the diffusional loss of ee will exceed the autocatalytic growth and suppress it. Only when δV exceeds a critical size can a fluctuation grow (as in the case of nucleation). If diffusion is the only homogenizing process and the autocatalytic growth rate is $k[X_L]^2$, then it can be shown that a fluctuation in ee will grow only when the volume $\delta V > \delta V_C$, where

$$\delta V_C = \left(\frac{3\pi^2 D}{k\beta}\right)^{3/2}$$

in which D is the diffusion constant and $\beta = [X_L] + [X_D]$. In volumes $\delta V < \delta V_C$, fluctuations in ee cannot grow. All random fluctuation in ee in volumes δV_C or larger will grow; the overall ee will be the result of all such fluctuations and their growth.

When stirring is added, the size of δV_C will increase. This increase depends on the particular nature of the mixing process, but there is no simple way to quantify it. Nevertheless, qualitatively we can expect an increase in δV_C with increased mixing. If the entire system consists of only a few such volumes in which the growth of ee occurs, then we can expect a significant stochastic variation of the overall ee; if there are a large number of such volumes then, due to statistical averaging, the overall ee will be small. Thus, we may expect stirring to increase the random variation of ee. This is what we found in our studies of the chiral cobalt complex.[23] Our experiments, supported by computer simulations, also showed that thermal inhomogeneities together with autocatalysis can make the overall reaction rate significantly different from that of a homogeneous system, even with vigorous stirring.[24a]

Concluding Remarks

The identification of chirally autocatalytic systems in both inorganic and organic systems has given a new significance to theories formulated in the past 50 years. However, the mechanisms of the autocatalysis are not yet fully understood. In a recent review,[33] Oxtaby noted how recent studies of nucleation revealed many results that were not anticipated by classical nucleation theories. Perhaps future studies of secondary nucleation will reveal new and interesting aspects of nucleation in the vicinity of chiral surfaces. For processes that do not involve crystallization, there are indications that formation of clusters plays an important role, and this may provide new directions for asymmetric synthesis. Future studies will no doubt investigate these features. Finally, we would like to note that this is a field in which the novel kinetic and mechanistic aspects can be advanced though complementary research in inorganic, organic, and physical chemistry of nonequilibrium systems.

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