Stochastic Kinetic Models of Chiral Autocatalysis: A General Tool for the Quantitative Interpretation of Total Asymmetric Synthesis

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Received: August 16, 2005; In Final Form: October 7, 2005

A continuous time discrete state stochastic kinetic approach is used to study various chiral autocatalytic models in which the possibility of total asymmetric synthesis arises. It is shown that this approach is superior to the deterministic approaches used earlier and is able to interpret many aspects of chiral autocatalysis. First-order autocatalysis, independently of further kinetic details of the system, leads to a unique final statistical distribution of enantiomers. Higher order autocatalysis, on the other hand, leads to a final state where one of the enantiomers is in overwhelming excess over the other. Criteria are postulated to differentiate between inherently stochastic phenomena in chiral autocatalytic reactions and irreproducibility because of insufficient control of external factors.

Introduction

Asymmetric autocatalysis is often implicated in theoretical interpretations of the emergence of homochirality in the originally racemic environment of Earth and is assumed to have played an important role in the chemical evolution that preceded the biological evolution.[1−7] This interpretation is certainly very attractive because, unlike all the alternatives suggested thus far, asymmetric autocatalysis can be modeled without assuming any unknown external factors. In 1953, Frank proposed a simple model of chiral autocatalysis and showed that it leads to amplification of very small initial enantiomeric excesses.[8] This model proved that random formation of a nonracemic mixture of enantiomers is possible in the absence of any initial asymmetric external effects because very small fluctuations are naturally present in any reaction system. Experimental examples of this phenomenon, often called absolute asymmetric synthesis, have been reported during the past decade.[9−16] It should be noted that separation of different enantiomers through crystallization, which has been known since the discovery of chirality,[17] can be considered as some sort of heterogeneous version of chiral autocatalysis to form solids,[18−20] although this process does not involve chemical reactions. The parity-violating electroweak interaction has also been considered as a possible origin of homochirality.[21] However, the energy differences between enantiomers are so small that they alone cannot interpret any observable symmetry breaking.

There are two conceptually different ways of interpreting absolute asymmetric synthesis. In the first type, spontaneous generation of chirality occurs in an open system with continuous inflow and outflow of substances, the chiral state is a sort of steady state and the phenomenon itself is the manifestation of dissipative structure.[2,8] In models assuming isolated systems, however, the spontaneously generated enantiomeric excess is a transient state and can only occur before the final thermodynamic equilibrium is reached.[12−16] The model used in this work assumes isolated systems and therefore falls into the second type.

The mathematics of the Frank model, which was originally introduced for an open system but is also useful in an isolated one, contained an assumption that is kinetically rather dubious: the formation of one enantiomer should slow the formation of the other one in a manner that is inversely proportional to the concentration of the first enantiomer.[8] In addition to being mathematically meaningless for initial conditions where no chiral product is present, this −1-order inhibition kinetics can only arise in a limited concentration range and through a complicated mechanism; therefore the model would probably be deemed unreasonable if not practically impossible by many experimental kineticists. Later theoretical work[5−7,22−28] on chiral autocatalysis showed that this step is not necessary for chiral amplification: when the order of reaction is higher than 1 for the autocatalytic species, the resulting system will amplify small initial enantiomeric excesses even without any inhibition steps.[6−7,22] These improved attempts still used a deterministic approach to chemical kinetics and relied on fluctuations at an initial stage of reaction to interpret total asymmetric synthesis. Although this is a perfectly justifiable assumption and a sound qualitative interpretation, the method is unable to give quantitative predictions for the statistical distribution of enantiomers in the final mixture because of the difficulties associated with describing the initial fluctuations. A recent attempt tried to introduce a stochastic element to the models by assuming random fluctuations in the values of rate constants.[24] However, the kinetic description of the system used the deterministic equations and was unsuitable to give predictions for the final distribution.

In a previous recent work of the present author, the continuous time discrete state stochastic kinetic approach was used to study a particular very simple chiral autocatalytic model with first-order autocatalysis.[29] It was clearly shown that the method can be used to calculate theoretical final distributions, and an example was given where efficient first-order autocatalysis led to total asymmetric synthesis.

In the present paper, a detailed stochastic kinetic analysis of several different classes of chiral autocatalytic models are carried out and the theoretical distributions obtained are compared with

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10.1021/jp054613f CCC: $30.25
Published on Web 11/10/2005

experimental observations. Emphasis is also given to finding methods to decide whether a set of experimental results indeed shows the inherently stochastic nature of chiral autocatalysis or simply exhibits irreproducibility because of an uncontrolled external factor. Only the results are given in the text of the paper, the mathematical proofs are deposited in the Supporting Information.

Results and Discussion

Stochastic Approach to Chemical Kinetics. The usual deterministic approach to chemical kinetics is based on using continuous concentration−time functions. Despite being in obvious contrast with the particle-based, noncontinuous view of matter, this approach is satisfactory for the overwhelming majority of problems because the number particles is large. Under certain conditions, especially when the number of particles is low, the deterministic approach to kinetics is insufficient. Several different mathematical approaches have been developed under the name of stochastic kinetics.[30] The continuous time discrete state (CDS) stochastic approach is probably closest to the accepted particle-based view of matter. The mathematics of this approach has been developed in detail[30] and only a very brief summary is given here.

In the CDS approach, a state of the system at a given time instance is identified by giving the numbers of each particle present. A differential equation for the probability distribution function of every state is set based on the kinetic scheme. These differential equations are linear and can in principle be solved analytically, but this is often extremely difficult to handle because the number of possible states and differential equations is too large. It should be noted that the CDS approach is superior to the usual deterministic approach in a sense that it incorporates the particulate nature of matter without making any assumptions not present in the deterministic approach.[30] In theory, every conclusion drawn with the deterministic approach can be reached as a limiting case of the CDS approach for very high particle numbers. It is in fact surprising that the CDS approach has not been used extensively to interpret chiral autocatalysis, especially because the use of an early, but mathematically sound, version of this approach for autocatalytic reactions was reported by Delbrück as early as 1940.[31] Other applications of stochastic kinetics have been developed;[32−39] e.g., it was used to interpret single-enzyme catalysis.[34,38]

General Model of Homogeneous Chiral Autocatalysis. In this paper, a general chemical model is studied in which the nonchiral precursor molecule A is transformed to a chiral product B, usually using some sort of reagent(s) and/or catalyst(s). The enantiomers of B are B_R and B_S. Homogeneous chiral autocatalysis is represented by two parallel reactions and rate expressions:

$A \rightarrow B_R$

$$v_1 = 0.5g(a) + h(a,r) \tag{1}$$

$A \rightarrow B_S$

$$v_2 = 0.5g(a) + h(a,s) \tag{2}$$

In these equations, a denotes the number of A molecules, r the number of B_R molecules, and s the number of B_S molecules present. The two mathematical equations are rate expressions that give the "stochastic rate of reaction" for a given set of initial concentrations, or molecule numbers. In the rate expressions, function $g(a)$ represents the uncatalytic pathway and it is only dependent on a. It should be noted that eqs 1 and 2 are also valid if the rate actually depends on additional reagents and catalysts because functions g and h only give the rate in a single kinetic run and may be different for different initial conditions, especially for different initial concentration(s) of reagent(s) and/or catalyst(s).[30] In this sense, eqs 1 and 2 are rather different from the usual deterministic rate equations of chemical kinetics. It should be noted that the model used in the only previous work using CDS approach to chiral autocatalysis was the simplest special case of this model with $g(a) = \kappa_u a$ and $h(a,r) = \kappa_c ar$.[29]

Initially ($t = 0$), the number of A molecules present is n, the number of B_R and B_S molecules present is 0. Conservation of mass ensures that giving only the number of B_R and B_S molecules is sufficient to identify any possible state of the system unambiguously: (r,s) will denote a state where the number B_R molecules is exactly r, the number of B_S molecules is exactly s, and consequently, the number of A molecules is exactly $a = n - r - s$. Later, the total number of B molecules, $b = r + s = n - a$, will also be used. Let $P(r,s,t)$ denote the probability that state (r,s) occurs at a certain time instant t. From the rate expressions given in eqs 1−2 the (Kolmogorov-like) differential equations for the time dependence of $P(r,s,t)$ can be written

$$\frac{dP(r,s,t)}{dt} = -\{g(a) + h(a,r) + h(a,s)\}P(r,s,t) + \{0.5g(a+1) + h(a+1,r-1)\}\,P(r-1,s,t) + \{0.5g(a+1) + h(a+1,s-1)\}\,P(r,s-1,t) \tag{3}$$

For $r = 0$ or $s = 0$, the second or third additive term on the right should be deleted, respectively. The initial state (0,0) is certain at $t = 0$; therefore, $P(0,0,0) = 1$, and $P(r,s,0) = 0$ holds for every other state. In agreement with the general remarks about the CDS approach, eq 3 describes a set of $0.5 \times (n + 1) \times (n + 2)$ linear differential equations.

Final Distribution. The distribution of B_R and B_S molecules in the final state (i.e., where $r + s = n$) is probably the most important feature of a chiral autocatalytic system and can be calculated without determining every $P(r,s,t)$ function. Let $Q(r,s)$ denote the probability that the system goes through state (r,s) at any time during the process. $Q(0,0) = 1$ holds because (0,0) is the certain initial state. It can be shown that Q is related to P through the following equation:

$$Q(r,s) = \lim_{t\to\infty} P(r,s,t) + \int_0^\infty \{g(a) + h(a,r) + h(a,s)\}\,P(r,s,t)\,dt \tag{4}$$

After defining $\zeta(i,j) = h(i,j)/g(i)$, a recursive equation can be given for $Q(r,s)$:

$$Q(r,s) = Q(r-1,s)\frac{0.5 + \zeta(a+1,r-1)}{1 + \zeta(a+1,r-1) + \zeta(a+1,s)} + Q(r,s-1)\frac{0.5 + \zeta(a+1,s-1)}{1 + \zeta(a+1,r) + \zeta(a+1,s-1)} \tag{5}$$

This recursive definition shows that the final distribution only depends on the function $\zeta(i,j)$ and makes it possible to compute the values of Q for relatively low values of r and s. $Q(r,s) = Q(s,r)$ also follows from eq 5; therefore the final distribution must be symmetric. In the next sections, considerations will be presented for a few particular forms of $\zeta(i,j)$.

First-Order Autocatalysis. The term first-order chiral autocatalysis is used here in a rather general sense, meaning that the ratio of the catalytic and noncatalytic rates is directly proportional to the number of product molecules, i.e., $\zeta(i,j) =$

$h(i,j)/g(i) = \alpha j$ irrespective of the value of i. In this case, the recursive definition given in eq 8 reduces to a simple form

$$Q(r,s) = Q(r-1,s)\frac{0.5 + \alpha(r-1)}{1 + \alpha(b-1)} + Q(r,s-1)\frac{0.5 + \alpha(s-1)}{1 + \alpha(b-1)} \quad (6)$$

This is the same recursive definition as derived from the very simple CDS model where the specific functions $g(a) = \kappa_u a$ and $h(a,r) = \kappa_c ar$ were used.[29] Mathematical induction can be used to prove that the explicit form for the values of Q is

$$Q(r,s) = \binom{b}{r}\frac{\prod_{j=0}^{r-1}(0.5 + \alpha j)\prod_{j=0}^{s-1}(0.5 + \alpha j)}{\prod_{j=0}^{r+s-1}(1 + \alpha j)} \quad (7)$$

A continuous probability function (f) can also be obtained for very large values of n using the molar fraction of B_R in the final mixture ($x_r = r/n$).

$$f(x_r) = \lim_{n\to\infty, x_r = r/n} nQ(r,s) = \frac{\Gamma\left(\frac{1}{\alpha}\right)}{\Gamma\left(\frac{1}{2\alpha}\right)\Gamma\left(\frac{1}{2\alpha}\right)} x_r^{(1/2\alpha)-1}(1 - x_r)^{(1/2\alpha)-1} \quad (8)$$

where Γ is the gamma function. The derivation presented here clearly shows that this final distribution is valid for every case involving first-order autocatalysis irrespective of the actual kinetic scheme. In other words, the statistical distribution shown in eq 8 is general for first-order autocatalysis. The convergence to the continuous distribution is quite fast and eq 8 can be used for $n > 1000$ unless α is so low that no experimentally detectable enantiomeric excess forms.

Higher-Order Autocatalysis. Higher-order autocatalysis can be represented generally by $\zeta(i,j) = h(i,j)/g(i) = \beta j^{\xi}$. Obviously, $\xi = 1$ is the special case of first-order autocatalysis already dealt with, $\xi > 1$ is higher-order autocatalysis, and $\xi = 2$ is second-order autocatalysis. The recursive definition is not easily transformed to an explicit form for higher-order autocatalysis, but the probability of getting one enantiomer only is easily given:

$$Q(r,0) = \frac{\prod_{j=0}^{r-1}(0.5 + \beta j^{\xi})}{\prod_{j=0}^{r-1}(1 + \beta j^{\xi})} \quad (9)$$

For $\xi > 1$, it can be shown that

$$f(0) = f(1) = \lim_{k\to\infty} kQ(k,0) = \lim_{k\to\infty} kQ(0,k) = \infty \quad (10)$$

It follows that the final distribution for higher order autocatalysis and very large initial numbers of A is one where one of the enantiomers is in overwhelming excess over the other. This is in agreement with the prediction of the deterministic approach that higher-order autocatalysis amplifies a small initial enantiomeric excess.[6-7,22] However, it would be premature to conclude that higher-order autocatalysis necessarily leads to the formation enantiomeric excesses close to 100% because the convergence to the unique final distribution, unlike for first-order autocatalysis, may not be very fast. Practically meaningful values of β and n could lead to cases when the distribution does not approach this final limit and numerical calculations are necessary. This is not easy because no explicit formula could be given for $Q(r,s)$. A method for the numerical calculation of the cumulative distribution function will be given here. First, the appropriate values of $Q(r,s)$ are calculated for a relatively small value of b_0, e.g., 1000 or 10 000 using eq 5. The cumulative distribution function is calculated for this small b_0:

$$F\left(\frac{r}{b_0}\right) = \sum_{i=0}^{r} Q(i,b_0 - i) \quad (11)$$

Using the molar fraction at this point, $x_{r,i} = i/b_0$, the expectation for the final molar fraction is calculated using the following differential equation:

$$\frac{dx_r}{db} = \frac{0.5 + \zeta(n-b,r)}{[1 + \zeta(n-b,r) + \zeta(n-b,b-r)](b+1)} - \frac{x_r}{b+1} \quad (12)$$

For every initial value of $x_{r,i}$, numerical integration of eq 12 between the limits b_0 and n gives a final value for the molar fraction, $xx_{r,i}$. The final distribution is given by $F(xx_{r,i})$. It should be noted that this method of calculation is essentially equivalent to a mixed stochastic-deterministic approach,[30] where stochastic equations are used for low numbers of product molecules smaller than b_0, whereas the deterministic approach is used for product numbers higher than b_0.

Time Dependence and Transient Probabilities. In addition to the random distribution of enantiomers, chiral autocatalytic systems should show a number of further stochastic phenomena because of the autocatalytic nature of the reaction. As shown by the mathematical analysis of nonchiral autocatalysis,[31,32] these stochastic phenomena include random fluctuations in the reaction time and depend on the overall volume. To study these effects, the calculation of the $P(r,s,t)$ transient probabilities is necessary. Mathematical treatment is only given here for the relatively simple case of first-order catalysis. First, it is assumed $P(r,s,t)$ is related to $Q(r,s)$ by $P(r,s,t) = Q(r,s)\,R(a,t)$. Because $Q(r,s)$ is independent of time, eq 3 takes the following form:

$$Q(r,s)\frac{dR(a,t)}{dt} = -\{g(a) + h(a,r) + h(a,s)\}Q(r,s)\,R(a,t) + \{0.5g(a+1) + h(a+1,r-1)\}Q(r-1,s)\,R(a+1,t) + \{0.5g(a+1) + h(a+1,s-1)\}Q(r,s-1)\,R(a+1,t) \quad (13)$$

For first-order autocatalysis, $h(a,r) = \alpha r g(a)$ and similarly, $h(a,s) = \alpha s g(a)$. Combining this with eqs 6 and 13 gives

$$\frac{dR(a,t)}{dt} = -g(a)\{1 + \alpha(n-a)\}R(a,t) + g(a+1)\{1 + \alpha(n-a-1)\}\,R(a+1,t) \quad (14)$$

Equation 14 is exactly the CDS stochastic description of the autocatalytic reaction A → B without considering the enantiomers of B. This shows that the "chiral" and the "autocatalytic" part of the model can be separated for first-order chiral autocatalysis. The same is not generally true for higher-order autocatalysis.

Comparison with Experimental Data. As experimental examples are known for absolute asymmetric synthesis,[10,12-13] it is quite natural to ask how well the models considered in this paper interpret the actual findings. A major question arises before any comparison can be made: the CDS models show

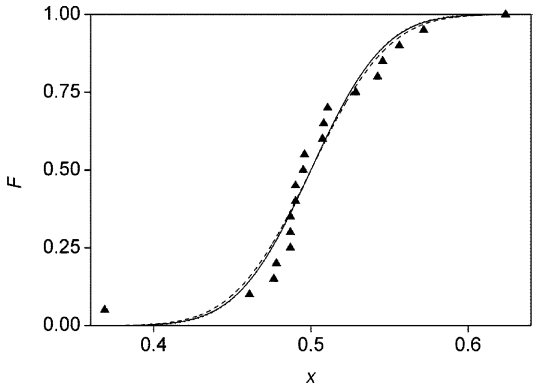

Figure 1. Experimental and fitted cumulative distribution functions for the random generation of enantiomers in the reaction producing $[CoBr(NH_3)(en)_2]^{2+}$. Solid line: normal distribution. Dashed line: first-order autocatalysis. Dotted line: second-order autocatalysis. As explained in the text, the three lines are very close to each other.

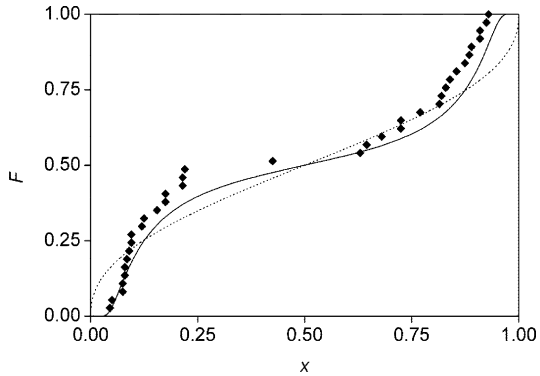

Figure 2. Experimental and fitted cumulative distribution functions for the random generation of enantiomers in the reaction producing the chiral pyrimidyl alkanol. Solid line: second-order autocatalysis. Dotted line: first-order autocatalysis.

that some variables in chiral autocatalytic reactions should show rather substantial random variations because of the inherent stochastic nature of the process. However, such random variations in the results of experiments are routinely attributed to irreproducibility caused by important but uncontrolled external factors. Therefore, a method should be developed to differentiate between random fluctuations arising from the inherent stochastic nature of a process and irreproducibility. Specifically, for chiral autocatalysis, there are at least four criteria the experimental results can be tested against:

1. The chiral autocatalytic nature of the reaction should be demonstrated by experiments where one of the pure enantiomers of the product is deliberately added before the reaction. These experiments should show shorter reaction times and increased excess of the enantiomer used for induction.

2. The experiment without any chiral inductor should be repeated several (preferably >50) times to show that the enantiomeric excesses are formed in a random fashion. The distribution obtained in these measurements should be symmetric. It has been suggested that very low levels of uncontrolled chiral (e.g., bacterial) contaminants may cause the formation of seemingly random enantiomeric excesses.[12,27] However, when a symmetric final distribution is obtained experimentally, this explanation can be ruled out practically. Wilcoxon's rank sum test[40] can be used to decide whether the distribution is symmetric or not: the molar fractions x_r and x_s $(=1 - x_r)$ must have the same statistical distributions for a symmetric case.

3. Random fluctuations should be seen in the kinetics of the reaction.

4. The distribution of final molar fractions and reaction times should be dependent on the overall volume even if the very same initial concentrations are used. As pointed out earlier,[29] the value of α in first-order autocatalysis depends on the volume and so does β for higher-order autocatalysis.

In the remaining part of this paper, the assumed experimental examples will be tested on the basis of these criteria.

The first example[10] is the preparation of a chiral cobalt(III) complex, *cis*-$[CoBr(NH_3)(en)_2]^{2+}$ from the reaction of trinuclear mixed valence $[Co(H_2O)_2\{(OH)_2Co(en)_2\}_2]^{4+}$ with NH_4Br in aqueous solution ($n = 6.0 \times 10^{20}$, 20 experiments). The measurements gave the cumulative distribution shown by the markers in Figure 1. Wilcoxon's rank sum test[40] showed that the distribution is indeed symmetric (see Supporting Information). Both first-order ($\alpha = 0.0060$, dashed line) and second-order autocatalysis ($\beta = 5.5 \times 10^{-24}$, dotted line) gave an excellent fit to the experimental points. Actually, the experimental distribution and the two fitted theoretical curves are very close to a normal distribution ($\sigma = 0.052$, solid line in Figure 1). This can be rationalized by noting that the enantiomeric excesses measured in this reaction are rather small and the distribution is narrowly centered around the racemic mixture. Thus, it does not seem to be unreasonable to find that these small fluctuations adhere to normal distribution.

The second known example is more interesting because larger enantiomeric excesses were formed. The chemical reaction is the formation of a chiral pyrimidyl alkanol in the reaction between pyrimidine-5-carbaldehyde and diisopropylzinc.[12,13] Random generation of optical activity was reported in this reaction by two different publications[12,13] In the first work,[12] the final distribution was obviously not symmetric and the authors concluded that low levels of some uncontrolled chiral impurity (most probably from the solvent) interfered with the measurements. The second set of data[13] gave a symmetric distribution ($n = 3.0 \times 10^{20}$, 37 experiments) as evidenced in this work (see Supporting Information) by Wilcoxon's rank sum test.[40] The markers in Figure 2 show the measured cumulative distribution, the solid line shows the best fit to a distribution calculated assuming second-order autocatalysis ($\beta = 3.8 \times 10^{-22}$), the dotted line represents the best fit to first-order autocatalysis ($\alpha = 1.16$). Graphically, second-order autocatalysis gives a slightly better fit. The goodness of fit was further studied by statistical tests. The Kolmogorov−Smirnov test[40] showed that both fits are acceptable at the 95% confidence level (see Supporting Information). Using the χ^2 test[40] for the same purpose was probably more informative. In the present example, discrete experimental points and a continuous distribution are compared and it is necessary to form classes containing at least 10 experimental points. A maximum of 3 such classes can be formed from the 37 data points measured, but the formation of classes is rather arbitrary. To avoid this arbitrary classification, the test was performed with several different sets of classes. Only 2 classes were formed in each case, the first containing every point for which x_r is smaller than a predetermined x_{lim} value, the second containing all the rest of the points. The values of χ^2 are then calculated for a range of meaningful x_{lim} values. Test results are shown in Figure 3 for first-order and second-order autocatalysis. The critical χ^2 values for this problem are 2.71, 3.84, and 5.02 at 90, 95, and 97.5% confidence levels. It is seen that first-order autocatalysis is rejected at 90 and 95% confidence levels if x_{lim} is close 0.22. In contrast, second-order autocatalysis is never rejected. This again shows that second-order autocatalysis fits the experimental points slightly better.

Unfortunately, no direct kinetic data have been published for the two asymmetric reactions[10,12−13] that could be compared

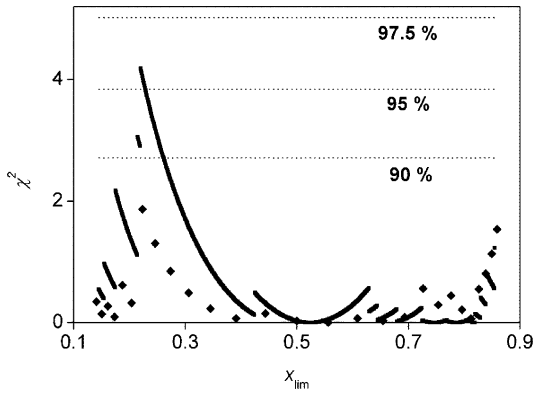

Figure 3. Results of the χ^2 test for the random generation of enantiomers in the reaction producing the chiral pyrimidyl alkanol. Large diamonds: second-order autocatalysis. Small squares: first-order autocatalysis.

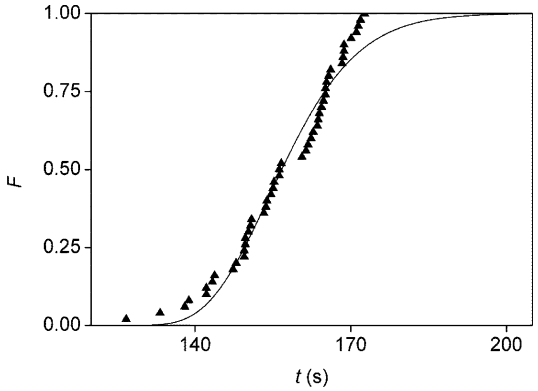

Figure 4. Experimental and fitted cumulative distribution functions for the reaction time in the crazy-clock (chlorite ion−iodide ion) reaction. Markers: measured points. Solid line: fitted distribution based on a first-order autocatalytic model.

with CDS predictions. However, the stochastic phenomena listed in criteria 3 and 4 arise from the autocatalytic nature of the process and for first-order autocatalysis they are independent of the chiral properties of the system. Stochastic phenomena in autocatalytic systems are known in nonchiral reactions, the most well studied example being the "crazy clock reaction" explored in detail by Nagypál and Epstein,[41] which is basically the redox reaction between chlorite ion and iodide ion. The process is characterized by the sudden appearance of the product iodine after a period referred to as the reaction time. The reaction times change in a random fashion within certain limits. The distribution of reaction times was influenced by the initial concentrations, overall volume, and stirring rate. The CDS models of autocatalysis mentioned here cannot interpret the dependence on stirring rate quantitatively without additional assumptions about spatial inhomogeneity. However, it should be noted that the same distribution was obtained at the two highest stirring rates suggesting that a region is reached where the distribution does not depend on the stirring rate any more. The distribution of reaction times obtained in a series of experiments at the highest stirring rate can be interpreted with CDS approach (Figure 4). The solid line is a theoretical distribution of reaction times calculated using eq 14 with $g(a) = \kappa_u a$. Although the actual mechanism of this clock reaction is much more complicated,[41] this simplistic model still gives some sort of basic interpretation of the stochastic phenomena observed in the system. The crazy clock reaction is important from a qualitative point as well: it clearly confirmed that the distribution of reaction times is influenced by the overall volume in agreement with criterion 4. Similar stochastic phenomena were also observed in the kinetics of the chlorite ion−thiosulfate ion system.[42]

Conclusion

This paper proves that the stochastic kinetic approach, and the CDS in particular, are suitable to interpret many aspects of chiral autocatalysis and also provide a method to differentiate between inherently stochastic phenomena and irreproducibility because of insufficient control of external factors. It is possible that researchers have actually encountered many more reactions with total asymmetric synthesis than the two reported in the literature, but the stochastic nature of the processes was mistaken for irreproducibility. These two known examples of total asymmetric synthesis seem to be far away from the biologically important chiral molecules. It would be rather interesting to find reactions in which amino acids or carbohydrates are prepared in a chiral autocatalytic fashion. In fact, an example is already known where amino acid complexes of a metal ion are asymmetric catalysts in the formation of amino acids,[43] although this falls short of chiral autocatalysis.

Acknowledgment. I thank an anonymous reviewer for calling my attention to the conceptual difference between the two types of interpretations mentioned in the Introduction.

Supporting Information Available: Proofs and derivations for equations and detailed results of statistic test appearing in the manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

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