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LETTERS

Homogeneous Chiral Autocatalysis: A Simple, Purely Stochastic Kinetic Model

Gábor Lente

University of Debrecen, Department of Inorganic and Analytical Chemistry, Debrecen 10, P.O.B. 21, Hungary, H-4010

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A continuous-time, discrete-state stochastic approach was used to study a simple, chiral autocatalytic model that was composed of the following three reactions: $A \rightarrow 0.5B_R + 0.5B_S$ ($v_1 = k_u[A]$), $A + B_R \rightarrow 2B_R$ ($v_2 = k_c[A][B_R]$), $A + B_S \rightarrow 2B_S$ ($v_3 = k_c[A][B_S]$). It is shown that the final distribution of enantiomers B_R and B_S is described by the one-parameter probability function $Cx^\delta(1 - x)^\delta$, where x is the molar fraction of B_R, $\delta = 0.5/\alpha - 1$ (where $\alpha = k_c/(k_u N_A V)$, N_A is Avogadro's constant, and V is the volume of the sample), and $C = \Gamma(1/\alpha)/\{\Gamma(0.5/\alpha)\}^2$ (where Γ is the gamma function). Comparison with two published examples shows that the probability function introduced here gives a reasonable interpretation of the experimental results.

Introduction

Chiral autocatalysis is usually defined as an enantioselective chemical reaction in which the chiral product acts as an asymmetric catalyst for its own production. It is known that chiral autocatalysis can lead to the random formation of measurable enantiomeric excesses in certain reactions without asymmetric reagents.[1−3] Although chiral autocatalysis is most often associated with crystallization, homogeneous examples are also known and are probably among the most interesting.[1] The implications of spontaneous generation of optically active material have considerable importance for the ongoing research aimed at understanding the origins of biological homochirality.

This paper presents a detailed and mathematically rigorous stochastic kinetic description of a very simple chiral autocatalytic system. Only the results will be given in the text of the paper; the mathematical proofs are deposited in the Supporting Information.

* Author to whom correspondence should be addressed. E-mail address: lenteg@delfin.unideb.hu.

Results and Discussion

The Model. One of the simplest possible kinetic models for chiral autocatalysis involves three steps. In the first, a chiral product B is generated from a nonchiral reactant A in a kinetically first-order process:

$$A \rightarrow B\ (0.5B_R + 0.5B_S) \qquad \text{(for this reaction, } v_1 = k_u[A]) \tag{1}$$

The enantiomers of B are B_R and B_S. Each enantiomer opens a new, overall second-order, autocatalytic pathway for its own formation:

$$A + B_R \rightarrow 2B_R \qquad \text{(for this reaction, } v_2 = k_c[A][B_R]) \tag{2}$$

$$A + B_S \rightarrow 2B_S \qquad \text{(for this reaction, } v_3 = k_c[A][B_S]) \tag{3}$$

Simple considerations about symmetry suggest that the second-order rate constants in eqs 2 and 3 are equal. The usual

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deterministic approach in chemical kinetics is based on solving the differential rate equation(s). The model given in eqs 1−3 is so simple that an analytical solution can be found without much difficulty, using the deterministic approach. The time-dependent concentrations of A, B_R, and B_S are given as (initial concentrations $[A] = [A]_0$, $[B_R] = [B_S] = 0$) follows:

$$[A] = [A]_0 \exp\{-(k_u+k_c[A]_0)t\} \times \frac{k_u + k_c[A]_0}{k_u + k_c[A]_0 \exp\{-(k_u+k_c[A]_0)t\}} \quad (4)$$

$$[B_R] = [B_S] = \frac{1}{2}[A]_0\left(1 - \exp\{-(k_u+k_c[A]_0)t\} \times \frac{k_u + k_c[A]_0}{k_u + k_c[A]_0 \exp\{-(k_u+k_c[A]_0)t\}}\right) \quad (5)$$

Because $[B_R] = [B_S]$ at any time (assuming that the initial concentrations $[B_R]_0 = [B_S]_0 = 0$), this deterministic approach predicts no formation of enantiomeric excess. Even if there is a small difference between the initial concentrations of B_R and B_S that is due to external fluctuations, this does not get amplified under the deterministic dynamics.[3] However, it is easy to envision an extreme case in which the autocatalysis is so efficient that the very first molecule of B formed will result in a rate v_2 or v_3 (depending on whether the first molecule of B is B_R or B_S) that is much higher than v_1. In this extreme case, only one of the two possible enantiomers will be formed by the end of the process, and not a mixture of the two. Since the usual deterministic approach of chemical kinetics assumes that matter is infinitely divisible, it cannot handle this case. At this point, it should be noted that the chemical model considered here is similar to that first proposed by Frank[4] in 1953 to interpret chiral autocatalysis and spontaneous asymmetric synthesis. Mathematical analyses of fluctuations in simple autocatalytic processes[5] and irreproducibility in chain reactions[6] using stochastic approaches were also published in earlier literature. These early theoretical contributions[5,6] clearly showed that it is possible to interpret seemingly irreproducible kinetic phenomena by rigorous statistical analysis. However, no successful attempts have been made to predict the statistical distribution of enantiomeric products in a chiral autocatalytic system.

The Stochastic Approach. Because of the problems outlined in the previous paragraph, a stochastic approach to chemical kinetics seems to be advantageous when the autocatalysis is highly efficient in the model given in eqs 1−3. The mathematics of stochastic approaches has already been developed in detail.[7] In this work, the continuous-time, discrete-state stochastic approach will be used.[7a]

In this approach, one state is identified by counting the different molecules present. Initially (at time $t = 0$), the number of A molecules present is n and the number of B_R and B_S molecules present is zero. Note that the conservation of mass ensures that giving only the number of B_R and B_S sufficient to identify any possible state of the system unambiguously, (r,s) will denote a state where the number of B_R molecules is exactly r, the number of B_S molecules is exactly s, and, consequently, the number of A molecules is exactly $n - r - s$. Let $P(r,s,t)$ denote the probability that state (r,s) occurs at a certain time instant t. In the full stochastic description of the system, an ordinary differential equation (ODE) can be written for each state.[7b] The equations have the following forms in the model used here:

$$\frac{dP(r,s,t)}{dt} = -(\kappa_u + \kappa_c r + \kappa_c s)(n - r - s)P(r,s,t) + \{0.5\kappa_u + \kappa_c(r-1)\}(n - r - s + 1)P(r-1,s,t) + \{0.5\kappa_u + \kappa_c(s-1)\}(n - r - s + 1)P(r,s-1,t) \quad (\text{for } r > 0 \text{ and } s > 0) \quad (6)$$

$$\frac{dP(r,0,t)}{dt} = -(\kappa_u + \kappa_c r)(n - r)P(r,0,t) + \{0.5\kappa_u + \kappa_c(r-1)\}(n - r + 1)P(r-1,0,t) \quad (\text{for } s = 0) \quad (7)$$

$$\frac{dP(0,s,t)}{dt} = -(\kappa_u + \kappa_c s)(n - s)P(0,s,t) + \{0.5\kappa_u + \kappa_c(s-1)\}(n - s + 1)P(0,s-1,t) \quad (\text{for } r = 0) \quad (8)$$

$$\frac{dP(0,0,t)}{dt} = -\kappa_u n P(0,0,t) \quad (\text{for } r = s = 0) \quad (9)$$

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. Equations 6−9 constitute a system of homogeneous linear first-order ODEs with constant coefficients, which can be solved analytically for any values of the parameters. Furthermore, the relationship between the deterministic parameters k_u, k_c and stochastic parameters κ_c, κ_u is given as[7b]

$$\kappa_u = k_u$$
$$\kappa_c = \frac{k_c}{N_A V} \quad (10)$$

where N_A is Avogadro's constant and V is the total volume of the sample.

The Final Distribution. Although it is possible to solve eqs 6−9 analytically, the procedure is computationally very demanding for large values of n. In addition, the actual time dependence of the entire process is only of marginal interest as the distribution of B_R and B_S molecules in the final state is much more important. A state is final if $r + s = n$, because no more A molecules remain. It will be shown that the distribution of the final state can be calculated without making efforts to handle the time dependence numerically.

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:

$$Q(r,s) = \lim_{t\to\infty} P(r,s,t) + \int_0^\infty (\kappa_u + \kappa_c r + \kappa_c s)(n - r - s)P(r,s,t)\,dt \quad (11)$$

It can also be shown that the values of Q are dependent only on the ratio of κ_c and κ_u, which will be referenced as α in the following discussion:

$$\alpha = \frac{\kappa_c}{\kappa_u} = \frac{k_c}{k_u N_A V} \quad (12)$$

The following equations can be shown to hold for $Q(r,s)$:

$$Q(r,s) = Q(r-1,s)\frac{0.5+\alpha(r-1)}{1+\alpha(r+s-1)} + Q(r,s-1)\frac{0.5+\alpha(s-1)}{1+\alpha(r+s-1)} \quad (\text{for } r>0 \text{ and } s>0) \quad (13)$$

$$Q(r,0) = Q(r-1,0)\frac{0.5+\alpha(r-1)}{1+\alpha(r-1)} \quad (\text{for } s=0) \quad (14)$$

$$Q(0,s) = Q(0,s-1)\frac{0.5+\alpha(s-1)}{1+\alpha(s-1)} \quad (\text{for } r=0) \quad (15)$$

Based on the recursive definition in eqs 13−15, for $r > 0$ and $s > 0$, it can be proved that

$$Q(r,s) = \binom{r+s}{r}\frac{\prod_{j=0}^{r-1}(0.5+\alpha j)\prod_{j=0}^{s-1}(0.5+\alpha j)}{\prod_{j=0}^{r+s-1}(1+\alpha j)} \quad (16)$$

and, for $r = 0$ or $s = 0$,

$$Q(k,0) = Q(0,k) = \frac{\prod_{j=0}^{k-1}(0.5+\alpha j)}{\prod_{j=0}^{k-1}(1+\alpha j)} \quad (17)$$

The final distribution of B_R and B_S molecules can be obtained by calculating $Q(r,s)$ for states $(r,n-r)$, where $r = 0, 1, ..., n$. The final distribution reduces to a simple binomial distribution if $\alpha = 0$. Where n is large enough to be chemically meaningful ($\sim 10^{20}$), calculation of the Q values using eq 16 is not feasible. However, it can be proved that the distribution converges to a continuous probability function (f) as the value of n increases. It is convenient to introduce f as a function of the molar fraction of B_R in the final mixture ($x = r/n$). First, f is defined for finite values of n:

$$f\left(\frac{r}{n},n\right) = nQ(r,n-r) \quad (18)$$

Assuming $\alpha > 0$, it can be shown that

$$f(x) = \lim_{k\to\infty} f(x,k) = \frac{\Gamma(1/\alpha)}{\Gamma[1/(2\alpha)]\Gamma[1/(2\alpha)]}x^{1/(2\alpha)-1}(1-x)^{1/(2\alpha)-1} \quad (19)$$

where Γ is the gamma function.[8] The probability function given in eq 19 is normalized. Figure 1 shows the probability distribution for five different values of α. For $\alpha = 0.5$, the distribution is flat, i.e., every final state is equally probable. For $\alpha < 0.5$, the distribution has a maximum at $x = 0.5$ (racemic mixture). For $\alpha > 0.5$, the distribution has a minimum at $x = 0.5$.

Comparison with Experimental Data. To compare the predictions of eq 19 with experimental results, two published examples[9,10] will be used where spontaneous generation of optically active material was observed and the stochastic nature of the process was also demonstrated by several repetitions. The first example (E1) 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 (20 individual runs).[9] The second example (E2) is the generation of a pyrimidyl alkanol in the reaction between pyrimidine-5-carbaldehyde and diisopropylzinc (37 individual runs).[10]

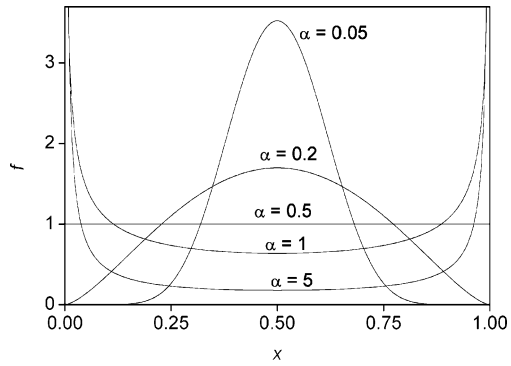

Figure 1. Probability function of the distribution of enantiomers, according to eq 19, shown for five values of α.

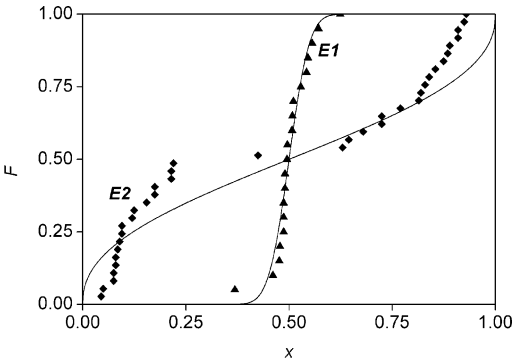

Figure 2. Cumulative distribution function of the distribution of enantiomers in two experimental examples. Markers: measured points, solid lines: curves fitted based on eq 19. Triangles: example E1, $\alpha = 0.0060$; diamonds: example E2, $\alpha = 1.16$. (See text for the identification of examples.)

There is no advantageous way to compare experimental data with the probability function f. Although histograms are often used for this purpose, they are dependent on the selection of base intervals and are very arbitrary when the number of experiments is relatively small. A better way to compare results and theoretical predictions is possible using the cumulative distribution function $F(\tau)$ (Figure 2). In this case, $F(\tau)$ is the probability that the molar fraction x is smaller than τ. The cumulative distribution function is associated with the probability function as follows:

$$F(\tau) = \int_0^\tau f(x)\,dx \quad (20)$$

In Figure 2, the experimental results are shown as markers. The solid lines were numerically calculated based on eqs 19 and 20 with α values that gave the best fit to the experimental points ($\alpha = 0.0060$ for example E1, and $\alpha = 1.16$ for example E2).

Concluding Remarks. Based on the results, it is possible to find the limiting conditions at which the stochastic effects become important and the deterministic approach is not applicable anymore. At $\alpha = 2 \times 10^{-4}$, the probability of obtaining an enantiomeric excess of >1% is very close to 50%; this gives a somewhat arbitrary lower limiting value. It should also be considered that the highest possible value for a second-order rate constant is the diffusion-controlled limit ($\sim 10^{10}$ M^{-1} s^{-1} at 25 °C in water).[11] Using $\alpha = 2 \times 10^{-4}$ and 100 μL as the smallest workable volume, eq 12 shows that the largest possible

value of k_u is 8×10^{-7} s^{-1}. This corresponds to an "uncatalytic" half-life of at least 10 days; however, the autocatalytic reaction itself reaches practical completion within 1 μs under these conditions.

Interestingly, the final distribution is dependent on the volume of the sample but not on the initial concentration of A. This might only reflect the simplicity of the model used and is probably not valid for more-complex systems. Another important point is that a purely stochastic model that contains only first-order autocatalysis predicts the random formation of considerable enantiomeric excess under certain conditions. This may be unexpected as mathematical analysis of possible perturbations using the deterministic approach showed that amplification of initial enantiomeric excess cannot occur if the autocatalysis is first-order kinetically.[3]

Although the mechanisms of the reactions that are used as examples[9,10] are very likely to be more complex than the simple scheme given in eqs 1−3 in this paper, the agreement between the measured and fitted probability curves in Figure 2 is remarkable. This may indicate that the distribution given in eq 19 could be applicable more widely for chiral autocatalytic systems.

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Supporting Information Available: Mathematical proofs for equations appearing in the paper (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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