

Data-Based Stochastic Approach to Absolute Asymmetric Synthesis by Autocatalysis[#]

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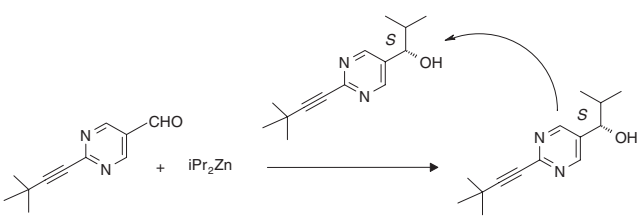
Statistical distribution of enantiomeric excesses obtained by two sets of parallel experiments of absolute asymmetric synthesis by asymmetric autocatalysis was analyzed. It has been found that experimental data give an excellent fit to a bimodal β distribution formula, where the components are in a golden section ratio. The parameters of this higher order β distribution were found by computer-simulated Pólya urn model experiments. The urn model experiments indicate that the Soai-autocatalysis might operate by three concerted cooperating catalytic cycles. These results may provide also a general model of asymmetric autocatalysis.

The origin(s) of biological chirality is(are) still a focus of debate.[1–5] It appears however that consensus has been reached about the key role of asymmetric (enantioselective) autocatalysis[6–11] in the events leading to a high or quantitative enantiomeric excess (ee)[12] levels of chiral molecules in living organisms. Beyond this fundamental theoretical significance, suitably controlled asymmetric autocatalysis offers also a highly valuable tool for synthetic organic chemistry.

The main problem with asymmetric autocatalysis is that its well-documented experimental realization is confined, for the moment, to only one reaction type: the alkylation of N-heterocyclic aldehydes with zinc dialkyls, known as the Soai-reaction[6–8] (Scheme 1). This reaction, with some substrates, shows outstanding power for amplification of chirality, even more: it enables the first documented realization of absolute asymmetric (enantioselective) synthesis (AAS)[13,14] in the strictest sense of its definition.[11b,15] Consequently, Soai's asymmetric autocatalysis can be regarded today as the closest model of the origin of biological chirality.

These aspects show dramatically the importance of finding tools for the generalization[11d] of the Soai reaction. This ambitious goal requires, first of all, understanding the mechanism of the asymmetric autocatalysis, especially in its AAS form. Numerous kinetic[16] and spectroscopic[10,17] attempts have been made to resolve this problem. Even if important experimental results and conclusions have been reached in these studies, the problem cannot be regarded as fully resolved yet.



Scheme 1.

Our groups have chosen another approach, by deducing empirical formula for the evolution of the ee during the Soai reaction[11c,11d,18] as well as by the statistical evaluation[19] of the final ee values obtained in the AAS variant.[11g] The statistical analysis indicated that the distributions of ee-s cannot be interpreted in terms of simple statistical models, but probably by a higher order combination of distributions. We present here results of a study aimed at finding a suitable stochastic description of two sets of ee values obtained by AAS asymmetric autocatalysis.

Earlier mechanistic studies were conducted by supposing a certain mechanism for the asymmetric autocatalysis, deducing the corresponding kinetic equations and after suitable mathematical treatment the calculated and experimental results were confronted. We proceeded differently, after a preliminary study of the published ee data sets a suitably flexible mathematical algorithm was chosen and the parameters of this description were iterated until an excellent goodness-of-fit was reached. The "iteration" procedure was performed by Pólya-urn models, a kind of first-principles approximation, which is rarely used in chemistry, but which was found to be suitable for our purpose. In a chemical context, the "marbles" of the Pólya-urn models and the changes in the numbers of these marbles, could be regarded as representing elementary molecular events. Taking into consideration that the continuous model is a combination

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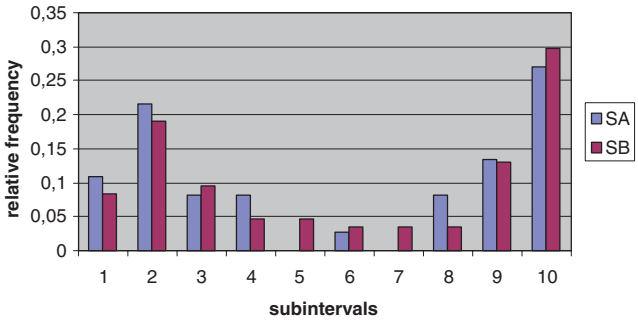

Figure 1. Histogram of the enantiomer S of data populations in systems S_A and S_B.

of two β distributions, it is natural to relate it to the Pólya-urn model, since it is a well known mathematical result that the limit distribution of the ratio of black and white "marbles" in the Pólya-urn experiment is a β distribution.

Results and Discussion

Data Sets. The numerical bases of our calculations were two data sets (S), ee values obtained in several parallel experiments[13b,13c] (S_A 37, S_B 84 parallels). The elements of those data sets show the enantiomeric excess, that is for example 60 means that there are 20% "R" and 80% "S" enantiomers in the total amount of material. We were interested in the percentage of "S" enantiomer in the material, hence a mapping was made by transforming the data from both sets (S_A and S_B) to the (0,1) interval in the following way. The ee values of the experiments where the R enantiomer was in excess were multiplied by -1 and the union of the sets S (S enantiomer in excess) and R was mapped by using the $x \rightarrow (x + 100)/200$ function. Thus x variable means from now the percentage of the "S" enantiomer expressed in decimal number. After partitioning the (0,1) interval into 10 equal parts, we counted how many elements of the data set lie in each subset. This operation gives the histogram shown in Figure 1.

Combined β Distribution. The histogram shown in Figure 1 has a two-humped morphology. This morphology cannot be related to any of the usual elementary distributions, as it has been discussed in our previous publication on this topic.[11g] The experimental data however indicate that a higher-order β distribution might control the statistics. According to general experience in probability theory[20] a combination of a convex ($f(x)$) and a concave ($g(x)$) β distribution function (see Additional Supporting Information) appeared to be the most practicable formalism. We constructed then the convex combination ($h(x)$, eq 1), of these two functions, $f(x)$ and $g(x)$.

$$h(x) = \frac{l}{l+m}\beta(a,b)x^{a-1}(1-x)^{b-1} + \frac{m}{l+m}\beta(c,d)x^{c-1}(1-x)^{d-1} \quad (1)$$

In eq 1 $\beta(a,b)$ and $\beta(c,d)$ are the weight factor in the density function of the (component) β distributions, that is

$$\beta(a,b) = \frac{1}{\int_0^1 x^{a-1}(1-x)^{b-1}\mathrm{d}x}$$

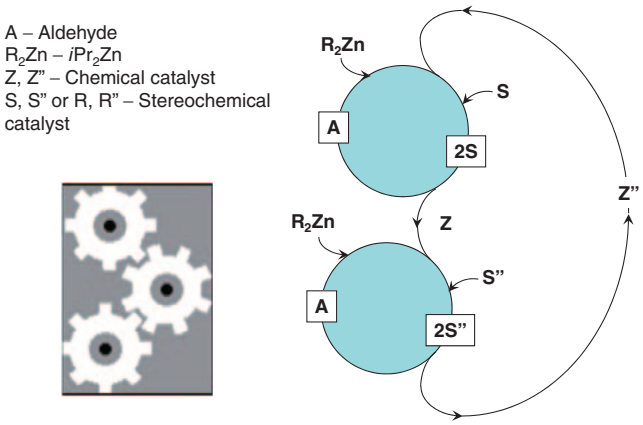

Figure 2. Schematic view of the catalytic cycles.

Here a and b as well as c and d are shape parameters of the functions $f(x)$ and $g(x)$, respectively, while l and m parameters defining the mixing ratio of the two components.

A tentative chemical interpretation of these formula would include the following features.

(i) The bimodal structure of eq 1 could reflect the presence of two cooperating catalytic cycles in the asymmetric autocatalysis.

(ii) The parameters l and m are a kind of coupling parameter and therefore these could reflect the degree of concertedness of the cooperating cycles.

(iii) The fact, that functions $f(x)$ and $g(x)$ contain two shape-determining parameters each, could indicate, that chemical and stereo chemical catalyses are due to different species in each component cycles.

(iv) The cooperation of these two cycles materializes in a third cycle connecting the former two like connected cogwheels, as shown in Figure 2.

These, at the first sight fairly bold suppositions, however find some support in published theoretical and experimental studies which however were interpreted differently. Suppositions (i) and (ii) appear to be in excellent agreement with the recently found possibility that under certain conditions oscillatory dynamics could develop in the Soai reaction.[21] Hypothesis (iii), on the other hand gains support from the experimentally well documented fact, that addition of very different enantiopure chiral auxiliary materials[22,23] to the reaction mixture of the Soai autocatalysis results a very sensitive chiral induction which follows the chiral information obtained from the auxiliary material, but this succeeds without any appreciable change of the chemical catalytic activity of the system. It is practically impossible, that each additive could have the same (moreover very elevated) chemical catalytic activity.

It should be emphasized however, that our interpretation is only one possible model, which appears to us reasonable, but certainly other models could also be worked out. The validity of the present model could be best controlled by finding another example of asymmetric autocatalysis (a "non-Soai-type" system) and analyzing the quantitative outcomes of such a system. We are currently working on this aspect.[24a–24e] Another promising system was published recently.[24f]

Accepting these mathematical and chemical arguments as a reasonable starting hypothesis we determined the parameters of

the $h(x)$ function by constructing a suitable Pólya's urn model, utilizing the inherent connection between these urn experiments and β distribution.[25]

Pólya's urn Model Experiments. Pólya's urn model experiments consist of the following steps: (i) put a given number of two or more kinds of "marbles" into one or more box(es) ("urn(s)"), (ii) draw "blind" (by chance) one or more of these marbles, (iii) add, depending on the outcome of (ii), according to an algorithm additional marbles to the urn(s), (iv) observe the evolution of the distribution of marbles when these operations are repeated, and (v) determine the final distribution after infinite repetitions.

Pólya's urn experiments are going back to simple elementary events and therefore represent a kind of first principles approach to the problems. It is just this simplicity, why we have chosen the Pólya method. The elementary character of events giving the backbone of the urn experiments provides an easy possibility to translate these stochastic events to molecular ones, but it must not be forgotten, that this translation is tentative and lacks the time element. This latter limitation means that kinetic conclusions cannot be reached by this approach.

According to these general rules and to the above outlined chemical considerations we constructed the following urn model experiment. The experiment was conducted in one urn by two populations of marbles.

The first population consisted of very large number (1 mol, 6×10^{23} pieces each) of the two achiral species **A** and $\mathbf{Z_0}$, and a few pieces from chemical ($\mathbf{Z''}$) and chiral (**S** or **R**) catalyst species. The sum of the numbers of marbles scarlet colored (**S**) and red colored (**R**) was equal to the number of the $\mathbf{Z''}$ species.

According to these conditions the following elementary transformations can be deduced schematically:

$$\mathbf{A} + \mathbf{Z_0} + \mathbf{Z''} + \mathbf{S} \rightarrow 2\mathbf{S} + \mathbf{Z''} + \mathbf{Z} \tag{2a}$$

Correspondingly for the other enantiomer:

$$\mathbf{A} + \mathbf{Z_0} + \mathbf{Z''} + \mathbf{R} \rightarrow 2\mathbf{R} + \mathbf{Z''} + \mathbf{Z} \tag{2b}$$

Where the starting numbers of **S** and **R** can be related to the constants a and b in eq 1, the starting number of the **Z** species becomes therefore $a + b$ and where product **Z** is the chemical catalyst in the second population and the starting number of the $\mathbf{Z''}$ species gets imported from the second cycle.

The second population was defined mutatis mutandis similarly: This consisted of very large number (1 mol, 6×10^{23} pieces each) of the two achiral species **A** and $\mathbf{Z_0}$, and a few pieces from chemical (**Z**) and chiral ($\mathbf{S''}$ or $\mathbf{R''}$) catalyst species. The sum of the numbers of marbles $\mathbf{S''}$ and $\mathbf{R''}$ equals the number of the **Z** species:

$$\mathbf{A} + \mathbf{Z_0} + \mathbf{Z} + \mathbf{S''} \rightarrow 2\mathbf{S''} + \mathbf{Z} + \mathbf{Z''} \tag{3a}$$

and for the other enantiomer:

$$\mathbf{A} + \mathbf{Z_0} + \mathbf{Z} + \mathbf{R''} \rightarrow 2\mathbf{R''} + \mathbf{Z} + \mathbf{Z''} \tag{3b}$$

Where the starting numbers of species $\mathbf{S''}$ and $\mathbf{R''}$ are related to constants c and d in eq 1, chemical catalyst **Z** is the product of the first cycle (eqs 2a and 2b), as well as the product ($\mathbf{Z''}$) of this second cycle becomes chemical catalyst in the first cycle.

The algorithm for the modified Pólya's experiments was defined as follows.

First cycle: If an **A** is drawn together with **S** and $\mathbf{Z''}$ then this **A** will be exchanged for (transformed to) an **S** species and one $\mathbf{Z_0}$ gets exchanged for (transformed to) a **Z** marble. Mutatis mutandis with **A** and **R**.

Second cycle: if an **A** is drawn together with $\mathbf{S''}$ and **Z** then this **A** is exchanged for (transformed to) an $\mathbf{S''}$ species and one $\mathbf{Z_0}$ gets exchanged for (transformed to) a $\mathbf{Z''}$ species. Analogously it will happen with **A** and $\mathbf{R''}$.

It is a particular feature of this model, that it gives inherently the values of m and l parameters in form of the ratio of the $l/(l+m)$ and $m/(l+m)$ expressions. This ratio is equal to the golden section ratio, which is generated by the fact, that the ratio of the **Z** and $\mathbf{Z''}$ values is evolving according to the Fibonacci series[27] in the two cycles. Under these conditions eq 1 goes over into eq 4 (Details of evolution of the numbers of the various species are given in the Supporting Information (SI-4)).

$$h(x) = 0.382 \cdot 110x(1-x)^9 + 0.618 \cdot 5x^4 \tag{4}$$

Several combinations of constants a, b, c, and d were tested. A good fit was obtained with $a = 2$, $b = 10$, $c = 5$, and $d = 1$ combination. The resulting distribution diagram is shown in Figure 3. The goodness of fit was controlled by a chi^2-test.[26] The critical value of this test for $df = 9$ (df: degree of freedom) on a 95% level ($\varepsilon = 0.05$) is $\chi_{\text{crit.}}{}^2 = 16.9$, while the statistics for the function in eq 1 with respect to S_A is $\chi^2 = 6.64$, and to S_B is $\chi^2 = 10.18$. Both are much below the critical value, indicating an excellent fit of the experimental data to the results of the above statistical analysis (Some additional remarks are given in the Supporting Information (SI-5)).

Relation to the Soai Autocatalysis. The fact that the enantiomeric excesses (ee) obtained in several parallel experiments[13b,13c] are perfectly obeying the bimodal β distribution described by eq 4 gives a very strong argument for the possibility to describe Soai-type autocatalytic reactions by double cooperating catalytic cycles. The (enantiomeric) yields are thermodynamic parameters; therefore one could not allow

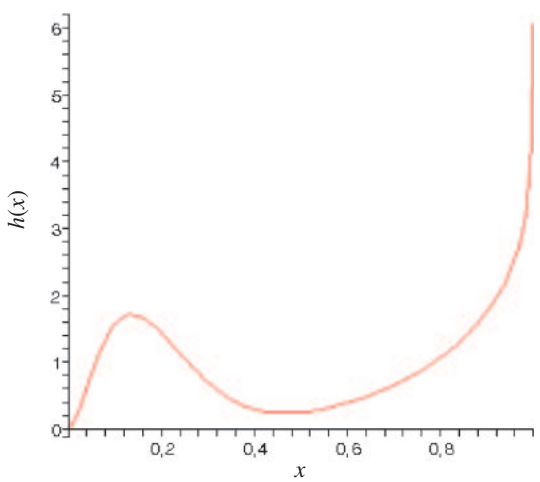

Figure 3. Graphical representation of the combined β distribution, $h(x)$, according to eq 4 with the computed a, b, c, and d parameters (see text).

further speculations regarding the possible kinetic picture of these processes. This will be the goal of a forthcoming study.

Beyond this fundamental statement there are some other important points to be considered.

(i) The fact that S_A and S_B can be described by the same distribution is an interesting new fact, which could not be detected by our previous statistical study[11g] on sets A and B. In these experiments the final ee-s were obtained with 3 consecutive catalytic cycles in each experiment. Calculations[18b] on the distribution of the initial situation in these experiments indicated, however, that the "zeroth" (starting) distribution in S_A can be described by a normal distribution ("coin tossing") model.

(ii) Kinetic studies on the mechanism of the Soai autocatalysis[16] provided deep insights into the molecular events but did not yet reach a final consensus, which can be due to the major number of kinetic parameters than that of the measurable data.

(iii) Our recent study[21] on the possibility of oscillatory dynamics in Soai-type systems, and its role of evolution of chirality in asymmetric autocatalysis are in good agreement with the final conclusions of the present study.

(iv) Spectroscopic studies on reaction mixtures of the Soai-autocatalysis indicated the presence of some additional materials, which could not be brought in perfect correspondence with the actually accepted mechanistic picture. Some of these were indicated as possible side products of the reaction. Our picture with two chemical and two chiral catalysts (one from each kind for the catalytic cycles) could be in agreement with the presence of more than one intermediate.

(v) A very recent, highly interesting theoretical study[28] concluded that the Soai reaction may be the result of a fairly complicated reaction cycle running through di-, tetra- and hexamolecular intermediates. Two couples of these intermediates were in equilibrium. This latter supposition means implicitly that the reaction is composed of more than one (maximum 4) cooperating catalytic cycles. This conclusion gives an interesting additional new dimension to our results.

(vi) Theories of Gánti[29] and Eigen[30] on the origin(s) of terrestrial life are based on cooperating catalytic cycles, even if these were deduced for achiral biochemical processes. Our picture fits thus very well into these theories and confirms the connection between the Soai reaction and the origin of biological chirality.[31]

(vii) The initial odds given to one of the enantiomers in our model might be of statistical nature at the initial very few molecules[11b] (in the above calculations we gave these odds to enantiomer S, to conform with the experimental facts), but there exists the possibility that the parity violating energy difference caused in the two enantiomers by the weak nuclear forces[32] is responsible for the observed asymmetry of the ee data. It should be noted, however, that this possibility has been questioned recently on the basis of theoretical considerations.[11f,33]

(viii) Parameters a, b, c, and d in eq 1 are required by the experimental data of the AAS variant of the Soai reaction. Several sets of these parameters could give qualitatively the same chemical end result. Therefore eq 1 can be regarded as a general tool for finding new Soai-type reaction systems. It appears to us, that this could be a high-priority goal of future preparative research.

(ix) The golden section ratio of the component functions $f(x)$ and $g(x)$ in $h(x)$ may be an accidental fact, generated by the attempts to fit to the experimental data, but it could be carrier of a deeper underlying message. We are working now on this point.

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Supporting Information

SI-1: Graphical presentation of the density functions, SI-2: Pearson's chi-square text, SI-3: Pólya's urn model, and SI-4: Detailed explanation of the modified Pólya's urn experiment used to model the Soai's reaction. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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