Violation of Distribution Symmetry in Statistical Evaluation of Absolute Enantioselective Synthesis

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Enantiomeric excesses obtained in absolute enantioselective synthesis by chiral autocatalysis (Soai-reaction) were statistically analyzed. Two sets of parallel experiments, which were performed under chemically different conditions, are available. One group contains 37, while the other contains 84 preparative results. The former group shows some interesting tendencies but does not give conclusive statistical results. The sample of 84 parallel experiments, providing 39 R- and 45 S-excesses have shown that these data represent two distinct, non-symmetric sets with different non-Gaussian distributions. Clear S preference was found.

Introduction

Biological chirality[1,2] is one of the most challenging problems of biochemistry. This phenomenon consists of the large or exclusive enantiomeric excess of one enantiomer over the other of biologically important molecules in all living organisms known today. The main problem connected with biological chirality is the origin of this selectivity. General experimental experience and thermodynamic theory shows that when a chiral compound is formed (prepared) from achiral precursors in the absence of enantiomerically pure chiral compound(s) or asymmetric physical field(s)[3] an exactly 1:1 mixture of the two isomers (racemate) is obtained.[4]

Several theories have been suggested as solutions for this problem,[2,5] which range from photochemistry,[6] through probability theory,[7] to nuclear physics (considering the asymmetry of weak nuclear forces).[8] Experimental verification of these hypotheses, however, is still in an initial stage or it could be achieved only in very particular cases.[9−11] Recently, the discovery of enantioselective autocatalysis (Soai-reaction),[12] and later its application for the first well-documented realization of an absolute enantioselective synthesis (AES),[13] could mean a dramatic break-through in this field. An empirical analysis[14] of the Soai reaction indicated stochastic origins of AES as a reasonable possibility. Independent theoretical work reached a similar conclusion.[7d,e,15]

The goal of the present study is to shed more light upon these problems through statistical analysis of the experimental data which have been published[13] to date.

Models. For the moment, two sets of parallel experiments on AES are available, which are sufficiently numerous to give hope for a reasonable statistical evaluation. Both are the results of the Tokyo Science University group but had been obtained under different experimental conditions. The chemistry is shown in Scheme 1 (the reaction with the S enantiomer was used as an example, autocatalysis with the R-isomer goes analogously, *mutatis mutandis*).

The first of these two systems, S(A), has been realized by three consecutive autocatalytic cycles (essentially) in the *homogeneous* phase, using an Et_2O/toluene solvent at 0 °C. Thirty-seven experiments were performed.[13a]

The second system, S(B), published recently[13b] is also comprised of three consecutive autocatalytic cycles, but under *heterogeneous* conditions, using toluene as the solvent for the liquid phase and a solid amorphous silica gel (probably as the O donor source, for the autocatalyst activation) at 0 °C. This series is composed of 84 parallel experiments.

In both systems, the chemical yield and enantiomeric excess ($ee = (R - S)/(R + S) \times 100$ or $= (S - R)/(R + S) \times 100$, %, where R and S are molar quantities of the R and S enantiomers of the product) were measured. Our analysis is concerned with the *ee* data sets.

The chemistry controlling these systems is chiral (enantioselective) autocatalysis, where the product increases the reaction rate of its own formation *and* an excess of one of its enantiomers enhances the formation of the *same* enantiomer. Systems A and B are sets of parallel experiments of this kind, however, without an added initial quantity of any chiral substance, including an enantiomer of the product, and without the influence of an asymmetric physical field (e.g., polarized light). Under these conditions, S(A) and S(B) correspond to the most rigorous conditions of AES.[3] Beyond these considerations, however, we avoid going into the mechanistic details of the reaction. In this manner, we expect to obtain a more general picture about the fundamental nature of the AES reaction by Soai autocatalysis.

Means as Preliminary Test. If the origins of AES were of symmetric stochastic nature (corresponding to the "tossing a

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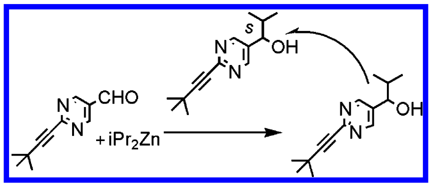
SCHEME 1



coin" experiment), the results should display the following characteristics:[7,16]

(a) The numbers (n) of experiments yielding an excess of the R or of the S enantiomer, $n(R)$ or $n(S)$, should be equal or very close.

(b) The values $(S - R)/(S + R)$, with sign, should be distributed symmetrically with respect to zero, defined as $R = S$.

(c) The mean *ee* values of these experiments, $M(R)$ or $M(S)$, should be equal or very close.

(d) The dispersion (standard deviation), σ (R) or σ (S), should be equal or very close and $|M(R) - M(S)| < 3\sigma$ (R) or 3σ (S) should hold.

(e) The distribution of the results could correspond to a binomial distribution, in a regime well approximated by a normal (Gaussian) distribution.

As a preliminary screening of the data samples, we analyzed the above conditions (a) to (d). The results were as follows.

ad(a) For S(A), $n(R) = 18$ and $n(S) = 19$ was reported, thus $n(R)$ is by ~5.3% lower than $n(S)$. At S(B), $n(R) = 39$ and $n(S) = 45$ was found, consequently $n(R)$ is by ~13.3% lower than $n(S)$. The difference in the excesses R and S at S(A) is not significant since the total number of experiments ($n(S) + n(R) = 37$) is odd, while at S(B), if the individual probability would be 0.5, then $P(n(S) \geq 45)$ is about 29%.

ad(b) The skewness, defined by

$$\frac{1}{n}\sum_{k=1}^{n}(x_k - m)^3/s^3$$

for a sample of length n (where m and s^2 are the mean and variance of the sample, respectively), turns out to be -0.1379 in S(B) (-0.0693 in S(A)). Such a negative skewness is favorable to an asymmetric distribution, with a prevalence of S.

ad(c) The mean *ee* values are (M) the following: At S(A), $M(R) = 62.9\%$ and $M(S) = 72.7\%$, consequently, $M(S) - M(R) = 9.8\%$. For S(B), $M(R) = 59.3\%$ and $M(S) = 73.4\%$, consequently, $M(S) - M(R) = 14.1\%$.

ad(d). The standard deviations of these data samples are as follows:

For the series S(A), σ (R) = ±4.6% and σ (S) = ±4.1%, thus, $M(S) - M(R) < 3\sigma$ (3σ (R) = 13.8%, 3σ (S) = 12.3%).

System S(B) gives σ (R) = ±3.9% and σ (S) = ±3.5%, therefore, $M(S) - M(R) > 3\sigma$ (3σ (R) = 11.7%, 3σ (S) = 10.5%).

Condition (e) will be discussed later.

The results of this preliminary screening show that S(B) can be regarded as composed of two sets of data, since $M(R)$ and $M(S)$ are confidentially *different average measurement values.* For S(A), however, the separation of the averages is too small, with respect to the standard deviation, to be regarded as two different data sets.

It is interesting, but not rigorously meaningful, that for *both* S(A) and S(B) $n(S) > n(R)$ holds true, even more interesting is that the percentual excess of the S-prelevant outcomes at S(B)

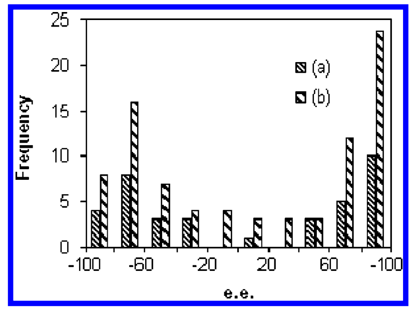


Figure 1. Histogram of 37 (a) and 84 (b) values of $ee = 100\,(S - R)/S + R)$ in S(A) and S(B).

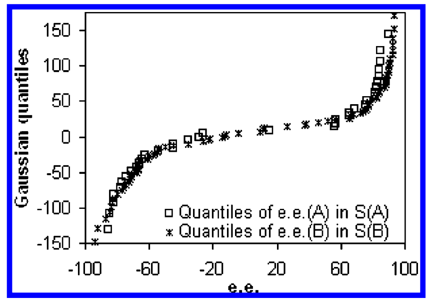


Figure 2. Gaussian quantiles vs sample quantiles of $ee(A) = 100(S - R)/(S + R)$ and $ee(B) = 100(S - R)/(S + R)$ in S(A) and S(B).

(13.3%) is fairly close to the $M(S) - M(R)$ difference (14.1%) in the same system.

Interesting, but again not strictly meaningful, is the fact that with both of these two chemically different systems a prevelance of (at least the number of) *ee* (S) outcomes was observed, similar to a related study[17] which cannot be evaluated statistically.

In the light of these results, we expose a more detailed statistical analysis.

Binomial Hypothesis. If we consider the $ee = 100(S - R)/(S + R)$ and set $S + R = T$ (total number of moles per liter), it can be regarded as follows

$$ee = 100\,\frac{S - R}{S + R} = 100\,\frac{S - (T - S)}{T} = 200\left(\frac{S}{T} - 0.5\right) \quad (1)$$

Thus, in the coin-tossing hypothesis, the variable S/T would be proportional to a binomial random variable, with a probability of 0.5.

This is not the case, as shown by the calculation of the expected value and the variance. The expected value (E) and the variance (V) of the binomial distribution with parameters N and p are $E = Np$ and $V = Np(1 - p)$, respectively. Because $1 - p$ is less than 1, the variance is always smaller than the expected value. In our data sets, just the opposite is true; the variance is much greater than the expected value: in S(A), $E = 6.72$ and $V = 5056$, while in S(B), values of $E = 11.79$ and $V = 4996$ were obtained. Moreover, both histograms do not look Gaussian at all (Figure 1).

The quantiles–quantiles plots[20] are very far from being linear (Figure 2). A one-sample Kolmogorov–Smirnov test[21] for the goodness of fit totally rejects normality, with $D = 0.242$ and p-value 0.025 in system A and with $D = 0.4931$ and p-value $= 2.2 \times 10^{-16}$ in system B. It can be concluded that there is a convincing evidence against a Gaussian (hence against binomial, symmetric) distribution of the variable.[2,16] This means two distinct facts: first, the *rejection of probabilistic independence*, that is, the basic property of binomial distribution and of Gaussian approximation and second, the *violation of symmetry*, but the analysis of this feature, needs a two-sample approach.

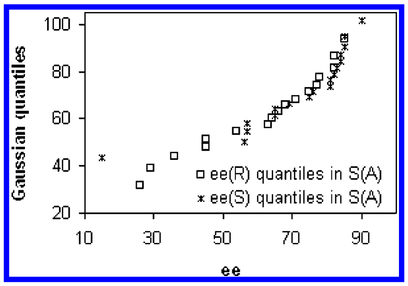


Figure 3. Gaussian quantiles vs $ee(R)$ and $ee(S)$ quantiles in S(A).

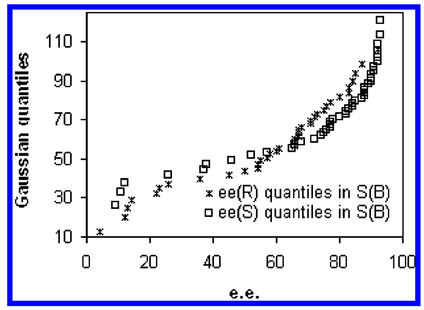


Figure 4. Gaussian quantiles vs $ee(R)$ and $ee(S)$ quantiles in S(B).

In other words, violation of symmetry, by these facts, has to be tested by separate consideration of the positive and the negative values of *ee*: $100(S - R)/(S + R)$, when $S > R$, and $100(R - S)/(S + R)$, when $R > S$. Tests on two independent samples, $ee(R)$ and $ee(S)$, are the most appropriate in this context.

Mean Values with Equal Variances. We supposed, as a working hypothesis, that the two data populations ($ee(R)$ and $ee(S)$) were of the same mean value (null hypothesis), and we also assumed that the two samples have equal unknown variance, so we performed **Student's t-test**.[18] The alternative hypothesis is that the mean values $M(R)$ and $M(S)$ are not equal. We intend to test this hypothesis at significance level of 95%. This calculation yielded the following values: $t = -1.5981$, df $= 35$, and p-value $= 0.119$ for case A; $t = 2.7113$; df $= 82$, and p-value $= 0.008163$ for case B.

Conclusion is as follows: In experiment B, if the expected $M(R)$ and $M(S)$ values are equal, then the probability of the observed $M(S) - M(R)$ difference (14.1%) would be ~0.008. This probability is very small, indicating that it is very unlikely such a big difference between $M(S)$ and $M(R)$ would be observed. Hence, the null hypothesis must be rejected.

A limitation to this statement is that the t-test could be applied confidentially only to normal (Gaussian) distribution with equal variance. In an attempt at clarifying this aspect, we studied also the nature of the distribution of the two data populations with the mean values of non-equal variances in S(A) and S(B).

Mean Values with Non-equal Variances. The working hypothesis is as follows: The two populations are normally distributed with variances supposed to be non-equal. In this case, the **Welch two-sample test** can be applied[19] with the alternative hypothesis:

$M(R) - M(S) \neq 0$ are supposed to be *non-equal* (tested at 95% significance level). For this situation, the Welch formula gives the suitable degrees of freedom to be inserted into the Student's t-test. This Welch two-sample test[19] gives the following values: for S(A), $t = -1.5946$, df $= 34.382$, and p-value $= 0.1199$; for S(B), $t = 2.7076$; df $= 79.859$, and p-value $= 0.008287$.

The conclusion is as follows: In S(B), both Student's and the Welch t-tests give almost the same results. The p-value, by which the null hypothesis $M(R) = M(S)$ is rejected by the experiment, is very small ~8/1000.

To be more rigorous, we have tested normality for the separate samples, $ee(R)$ and $ee(S)$, as a condition for the full validity of the t-tests. A control possibility is offered by the graphical comparison[20] and then by the **Kolmogorov−Smirnov test** of the $ee(R)$ and $ee(S)$ samples.[21]

The graphical inspection was performed by quantile−quantile diagrams (Figure 3 for S(A) and Figure 4 for S(B)). These are expected to be linear in the case of the normal (Gaussian) distribution.[20] In the present case, however, both samples, $S(A)$- and $S(B)$, show a rather clean deviation from linearity. It is important to note that these diagrams of data vector vs (supposed) normal quantiles, from the two data populations, show different tracks. This latter circumstance could indicate that the two non-normal distributions are governed by different physical laws.

The **Kolmogorov−Smirnov test of goodness of fit** allows us to determine[21] whether normal distributions are good fits for the $ee(R)$ and $ee(S)$ populations. This test can also give an indication whether the kind of distribution of the two samples is identical (or similar, meaning that they have the *same type of distribution* with a different parameter value) or not.

System A gives $D = 0.169$ ($p = 0.19$) for $ee(R)$ and $D = 0.205$ ($p = 0.40$) for $ee(S)$, thus S(A) can be classified as "it can be normal". If normality is rejected, then the probabilities of error are 68% and 40%, respectively.

System B gives $D = 0.173$ ($p = 0.19$) for the $ee(R)$ set, while $D = 0.221$ ($p = 0.02$) for the $ee(S)$ set. Consequently, the classification of the $ee(S)$ set is clearly "non-normal", while the $ee(R)$ set is "perhaps non-normal", with a probabilities of error of 2 and 19%, respectively.

Since the t-tests are not fully supported by normality of the data sets $ee(R)$ and $ee(S)$, we performed a nonparametric test,[22] to obtain a confirmation (or not) of the important question: Are the two distributions of the same kind? A suitable test for this purpose is a variant of the Kolmogorov−Smirnov test, which was suggested for two independent samples.[23]

In the case of S(B), this test yielded a very clear answer: the two data populations are certainly in *different distributions*, with $D = 0.4291$ and a very small p-value, $\sim 9 \times 10^{-4}$, giving a high level of credibility to this result.

The problem, whether the $ee(R)$ and $ee(S)$ data sets are of the same or of different kinds of distributions, is of fundamental importance for the present analysis. Therefore, we performed also an additional control, the **Wilcoxon-test**.[24] For S(B), this test gave $w = 510$ on the $ee(R)$ and the $ee(S)$ data sets. If $ee(R)$ and $ee(S)$ would have been of the same kind of distribution, then the w-value should have been in the range of $w = 543.01$ and 1211.98, with a p-value of 99%. Consequently, this test also *rejects* the hypothesis that the $ee(R)$ and $ee(S)$ samples are of the same kind of distribution.

Symmetric Beta Distribution Hypothesis. If the AES is of *symmetric stochastic nature*, taking into account the influence of chiral molecules on each other, a purely stochastic kinetic model must be considered.[7d] Under such a hypothesis, the ratio between the numbers of molecules $x = N_S/N_T$ is distributed according to a beta probability law[7d,25]

$$f(x) = \frac{\Gamma(1/\alpha)}{\Gamma(1/2\alpha)\Gamma(1/2\alpha)} x^{1/(2\alpha)-1}(1-x)^{1/(2\alpha)-1},\ 0 < x < 1 \tag{2}$$

with equal exponents $1/(2\alpha) - 1$, where $\alpha > 0$ and the gamma-function is denoted by Γ.

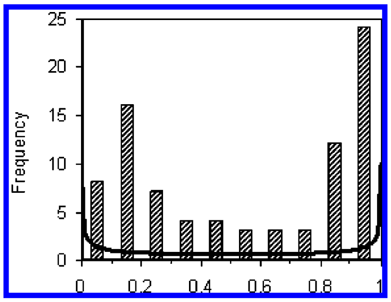


Figure 5. Histogram of *S/T* from the sample S(B), compared with the beta density fitting (full line) the distribution of *S/T* in the same system.

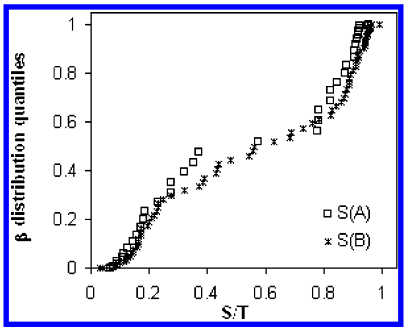


Figure 6. Quantiles of beta-distribution vs quantiles of *S/T* in S(A) and S(B).

We made an attempt at applying this "microscopic" (molecular) picture to the data sets of S(A) and S(B).

Since the beta distribution[25] has an expected value of $E = 0.5$ and variance

$$V = \frac{1/(4\alpha^2)}{(1/\alpha)^2(1/\alpha + 1)} \tag{3}$$

and since, by eq 1

$$\frac{S}{T} = 0.5 + \frac{ee}{200} \tag{4}$$

the goodness of fit has to be tested for α satisfying the equality of variances

$$\frac{1/(4\alpha^2)}{(1/\alpha)^2(1/\alpha + 1)} = V\left[\frac{S}{T}\right] = 40000^{-1}V[ee]$$

Therefore, we obtain for S(A) $1/(\alpha^{-1} + 1) = 5056.8 \times 10^{-4}$ and for S(B) $1/(\alpha^{-1} + 1) = 4997.0 \times 10^{-4}$, that is, $\alpha = 1.0229$ in S(A) and $\alpha = 0.9988$ in S(B). One can compare, for example, the beta-density with $\alpha = 0.9988$, with the histogram of the ratio S/T of system B (Figure 5).

The goodness of fit is first evaluated by a graph of the beta-distributed quantiles vs the sample quantiles (Figure 6).

In both systems, one can see a clean deviation from linearity. A **one-sample Kolmogorov−Smirnov test** on the goodness of fit gives $D = 0.174$, with p-value $= 0.212$, in S(A) and $D = 0.154$, with p-value $= 0.0373$ for S(B).

While the 37 repetitions of experiments in system A do not give a significant answer, the number (84) of data in sample B are sufficient to rule out the symmetric beta distribution.

Arbitrary Distribution Hypothesis. Let the variable *ee* be distributed according to any continuous law with finite mean μ and finite variance σ^2. Since the 84 experiments in S(B) are independent, we have 84 independent and identically distributed random variables. Now, on the basis of the central limit theorem,[21] let us assume that $Z = 1/84(y_1 + ... + y_{84})$ is an approximately normal random variable with mean μ and variance 1/84 σ^2. Now, a one-sided 95% confidence interval for the variance[21] is given by $\sigma^2 < 6582.8$. Thus, the variance of Z is, at most, $6582.8/84 = 78.36$. If the null hypothesis is $\mu = 0$ (perfect symmetry) against the alternative $\mu > 0$, then it turns out that the null hypothesis is rejected by the total sample mean $M = 11.80$ with a probability of error of the first kind $p = 9.1\%$. This is a fairly clear (even if non-rigorous) indication that the distribution underlying the whole S(B) data set has a mean greater than 0.

Under the same assumption (i.e., that the number n of data allows us to consider $Z_n = (1/n)(y_1 + ... + y_n)$ as an approximately normal random variable, according to the central limit theorem), and taking into account the 95% or 99% confidence intervals of σ^2, the number of experiments needed to obtain 5% or 1% significance levels on the basis of a sample mean $M = 11.80$ is $n = 128$ or $n = 287$, respectively.

Alternatively, on the basis of the Chebyshev inequality,[21] (more rigorous, without the need of the above assumption, but less powerful), the corresponding numbers of experiments are $n = 946$ (5% level) and $n = 5320$ (1% level). (The Chebyshev inequality, however, necessarily refers to a two-sided test).

Conclusions

The enantiomeric excess (*ee*) data sets of two documented examples of absolute enantioselective synthesis (by the Soai autocatalysis) were investigated using statistical methods.

These data sets, S(A) and S(B), are composed of 37[13a] and 84[13b] parallel experiments, respectively.

The main statistical features of the populations S(A) and S(B) were the following:

(i) Any hypothesis of binomial (hence Gaussian) distribution is totally rejected by the data sets $(S - R)/(S + R)$ (with sign) both in the smaller and in the larger sample. This could be ascribed to involvement of nonlinear stochastic phenomena in the mechanism.

(ii) Hypothesis of symmetric beta distribution, as predicted by a symmetry assumption in simplified kinetic stochastic models, is rejected by the larger set of data in S(B). This result, however,can be due to the relatively low number of experiments available (<100).

(iii) In the larger S(B) data set, there is a significant preference for the S-enantiomer, beyond the 5% level, on the basis of both parametric tests and rank methods.

(iv) In S(B), the *ee*(*R*) and *ee*(*S*) data populations appear to be ordered in different distributions.

These features can be rationalized, taking into consideration the extreme sensitivity[26] and the complexity of the mechanism[27] of the Soai reaction (at least with the substrate in ref 13) as follows: The reason for the observed S preference could be either (a) chemical or (b) physical. For a chemical reason (chiral contamination) presumably of biological origin (bacteria) could be inferred, as it has been done with a chemically related system.[17] The most likely candidate for a physical influence is the (catalytically amplified) parity violating energy difference (PVED) of the weak nuclear forces.[8,15] Choosing between these possibilities needs additional experimental and theoretical efforts.

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Supporting Information Available: Formulas and Programs used in calculations. This information is available free of charge via the Internet at http://pubs.acs.org.

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