

# Evolution of chirality in consecutive asymmetric autocatalytic reaction cycles\*\*

Marco Maioli

*Department of Mathematics, University of Modena and Reggio Emilia, Via Campi 213,  
I-41100 Modena, Italy*

Károly Micskei

*Department of Inorganic and Analytical Chemistry, University of Debrecen, Egyetem tér 1,  
H-4010 Debrecen, Hungary*

Luciano Caglioti

*Department of Chemistry and Technology of Biologically Active Compounds,  
University "La Sapienza" – Roma, P.le A.Moro, 5, I-00185 Roma, Italy*

Claudia Zucchi and Gyula Pályi\*

*Department of Chemistry, University of Modena and Reggio Emilia, Via Campi 183,  
I-41100 Modena, Italy  
E-mail: palyi@unimo.it*

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Closed algebraic formulae were deduced for the description of the quantitative evolution of chirality in consecutive asymmetric autocatalytic reaction cycles. These formulae enable the estimation of the initial enantiometric excesses in the very first cycles of absolute enantioselective syntheses performed by Soai-autocatalysis. The initial (statistical) excesses in the homogeneous variant of the Soai-autocatalysis show normal (Gaussian) distribution, corresponding to the "coin-tossing" model of an achiral-to-chiral transformation.

**KEY WORDS:** asymmetric autocatalysis, absolute enantioselective synthesis, Soai-reaction, chirality

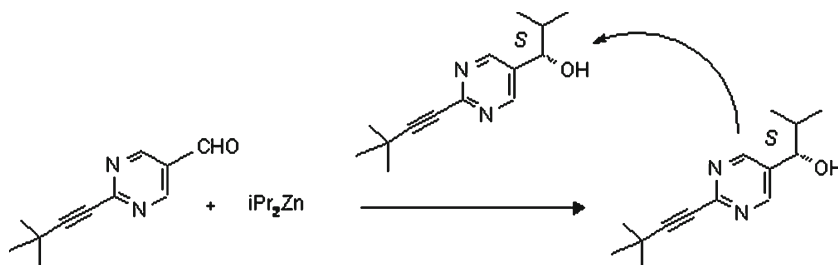
## 1. Introduction

Asymmetric (enantioselective) autocatalysis is believed to be one of the most important chemical phenomena which are responsible for the origin and

\* Corresponding author.

\*\* This paper is dedicated to the 60th birthday of Prof. P.G. Mezey, a pioneer of modern theoretical chemistry.

actual operation of life [1]. Even if this link is known (theoretically) since more than a half of a century [2], it was only a decade ago when the first experimentally well-documented chemical system of this kind was reported [3] by Soai et al.



Scheme 1. (with the R isomer the reaction proceeds analogously).

This reaction (now generally called Soai-reaction, *Scheme 1*) was found to be extremely sensitive, capable to the amplification of even very small enantiomeric excess<sup>1</sup> of its product (added at the beginning of the reaction) in a few repeated (consecutive) reaction batches [4]. This sensitivity prompted the Tokyo group to attempt the realization of asymmetric synthesis from achiral substances without any chiral additive, in the absence of asymmetric physical fields [5]. These conditions correspond to the most rigorous definition of absolute asymmetric enantioselective synthesis (AES) [6], a problem which emerged more than 100 years ago [7]. It can be reasonably believed, that in this “absolute” variant of the Soai-reaction the statistical fluctuation of the numbers of molecules of the two enantiomers is amplified to measurable (even very high) levels [2, 7]. These results represent a strong argument, that the Soai-autocatalysis is the closest model of the origin of the biological chirality [1, 6c, 8] ever found and consequently it is of fundamental importance both for biology and for chemistry. Well understandable, that these weighty circumstances induced feverish research activity in several Laboratories, aimed at better understanding and (eventual) generalization of this reaction. These studies utilized chemical kinetics [9], probability [10], spectroscopy [11] and other theoretical approaches [12] to achieve these goals, however, a real “breakthrough” has not yet been achieved. Our groups joined these efforts by deducing a simple, but efficient empirical formula for the quantitative description of the asymmetric autocatalysis [13], which manifested itself to be fairly useful in the analysis of some important aspects of

<sup>1</sup>Enantiomeric excess,  $ee = [S] - [R] / ([S] + [R])$ , or  $[R] - [S] / ([S] + [R])$  where [S] and [R] are the molar (mol/L) concentrations of the S and R isomers of a chiral product, these ratios are usually multiplied by 100 and expressed as *ee* %.

the Soai-reaction [14]. In this report, we present the mathematical background of this formula, together with some model calculations to demonstrate its utility.

## 2. Results and discussion

The empirical formula for the (time-independent) quantitative description of enantioselective autocatalysis relates the enantiomeric excess in the product ( $ee_{\text{prod}},\%$ ) to the maximum  $ee$  achieved in the given system ( $ee_{\text{max}},\%$ ) and the initial excess of the product ( $ee_{\text{start}},\%$ ) which last parameter is defined as added quantity of the product in the first catalytic cycle (expressed as mol % with respect to the substrate aldehyde). A dimensionless constant is coming from integration (B). This equation is as follows:

$$ee_{\text{prod}} = ee_{\text{max}} \frac{ee_{\text{start}}}{B + ee_{\text{start}}}. \quad (1)$$

In the case of consecutive autocatalytic steps  $ee_{\text{prod}}$  of the  $i$ th reaction becomes  $ee_{\text{start}}$  of the next  $(i + 1)$ th step:

$$ee_{\text{prod},i+1} = ee_{\text{max}} \frac{ee_{\text{start},i+1}}{B + ee_{\text{start},i+1}} = ee_{\text{max}} \frac{ee_{\text{prod},i}}{B + ee_{\text{prod},i}}. \quad (2)$$

These equations can be used for comparison of different autocatalytic systems as well as for step-by-step analysis of consecutive catalytic cycles. The step-by-step calculations could be performed by computer. Here we demonstrate that the problem can be handled also by an algebraic approach.

Let us define (for clarity) the following

$$\begin{aligned} ee_{\text{prod}(i)} &\equiv x(i), \quad \text{where } i = 0, 1, 2, \dots, \\ ee_{\text{max}} &\equiv a, \\ B &\equiv b. \end{aligned}$$

Then for  $i = 0, 1, 2, \dots$  we obtain  $x(i) = a \frac{x(i-1)}{b+x(i-1)}$ , with  $a, b > 0$  and  $x(0) \equiv x > 0$ . Setting

$$g(x) = \frac{ax}{b+x} \quad (4)$$

we consider the composition of functions defined by:

$$g^2(x) := g \circ g(x) \equiv g[g(x)], \quad g^{i+1}(x) := g \circ g^i(x) \equiv g[g^i(x)]. \quad (5)$$

All such compositions exist since the range of  $g$  is contained in the domain of  $g$  : indeed  $g(x) > 0$  for any  $x > 0$ . Then  $x(i + 1)$  is obtained by iteration of the composition of functions:

$$x(i + 1) = g[x(i)] = g^2[x(i - 1)] = \dots = g^{i+1}[x(0)]. \tag{6}$$

We want to prove that

$$g^i(x) = \frac{a^i}{x^{-1}b^i + b^{i-1} + ab^{i-2} + \dots + a^{i-2}b + a^{i-1}} \quad \text{for any } i \in N, \tag{7}$$

where  $N$  is the set of natural numbers. Indeed the formula holds for  $i = 1$ :

$$g(x) = \frac{a}{x^{-1}b + 1}. \tag{8}$$

Now let us suppose that (7) holds for an index  $i$  (inductive hypothesis). Then

$$\begin{aligned} g^{i+1}(x) &= a \frac{g^i(x)}{b + g^i(x)} = a \frac{\frac{a^i}{x^{-1}b^i + b^{i-1} + ab^{i-2} + \dots + a^{i-2}b + a^{i-1}}}{b + \frac{a^i}{x^{-1}b^i + b^{i-1} + ab^{i-2} + \dots + a^{i-2}b + a^{i-1}}} \\ &= \frac{a^{i+1}}{x^{-1}b^{i+1} + b^i + ab^{i-1} + \dots + a^{i-1}b + a^i}. \end{aligned} \tag{9}$$

Therefore, by the induction principle, the formula (7) is proved for all  $i \in N$ . In particular, if  $a = b$  formula (7) reads:

$$g^i(x) = \frac{a^i}{x^{-1}a^i + ia^{i-1}} \quad \text{for } a = b, \quad i \in N. \tag{10}$$

In all other cases, by algebraic factorization the final formula is:

$$g^i(x) = \frac{a^i}{x^{-1}b^i + \frac{(b^i - a^i)}{b - a}} \quad \text{for } b \neq a, \quad i \in N. \tag{11}$$

With the original notation we have:

$$ee_{\text{prod}(i)} = \frac{ee_{\text{max}}^i}{ee_{\text{start}(0)}^{-1} B^i + \frac{(B^i - ee_{\text{max}}^i)}{B - ee_{\text{max}}}}, \quad B \neq ee_{\text{max}}. \tag{12}$$

It appears that the inflexion point of the  $ee_{\text{prod},i}$  versus  $i$  diagrams could be a very useful parameter characterizing the sensitivity of the given autocatalytic system.

For the deduction of the inflexion point let us consider the right-hand side of formula (11), or (10) as a continuous function  $f(i)$ , for  $i > 0$ , having fixed  $x, a, b$ . We have:

$$\lim_{i \rightarrow 0} f(i) = x, \quad \lim_{i \rightarrow +\infty} f(i) = \begin{cases} a - b, & b < a, \\ x, & b = a, \\ 0, & b > a. \end{cases} \tag{13}$$

Therefore an increasing inflexion is expected when  $b < a$  and  $x < a - b$ . In such a case we set

$$f(i) = \frac{a^i}{cb^i - \frac{a^i}{b-a}}, \quad \text{where} \quad c = x^{-1} + \frac{1}{b-a}. \tag{14}$$

Since  $\frac{d}{di} a^{2i} = 2(\log a)a^{2i}$ ,  $\frac{d(ab)^i}{di} = (\log ab)(ab)^i$ , the first and the second derivatives are:

$$\begin{aligned} \frac{df(i)}{di} &= \left( cb^i - \frac{a^i}{b-a} \right)^{-2} \cdot \left\{ a^i (\log a) \left( cb^i - \frac{a^i}{b-a} \right) - a^i \left[ cb^i (\log b) \right. \right. \\ &\quad \left. \left. - \frac{a^i}{b-a} \log a \right] \right\} = \left( cb^i - \frac{a^i}{b-a} \right)^{-2} \cdot c \left( \log \frac{a}{b} \right) (ab)^i, \end{aligned} \tag{15}$$

$$\begin{aligned} \frac{d^2 f(i)}{di^2} &= \left( cb^i - \frac{a^i}{b-a} \right)^{-4} \cdot \left\{ \left[ c \left( \log \frac{a}{b} \right) (\log(ab)(ab)^i) \cdot \left( cb^i - \frac{a^i}{b-a} \right)^2 \right. \right. \\ &\quad \left. \left. - 2 \left( cb^i - \frac{a^i}{b-a} \right) \left[ cb^i \log b - \frac{a^i}{b-a} \log a \right] \cdot c \left( \log \frac{a}{b} \right) (ab)^i \right\}. \end{aligned} \tag{16}$$

Dividing by  $c(ab)^i \log \frac{a}{b} \left( cb^i - \frac{a^i}{b-a} \right)$ , and setting  $f''(i) = 0$  we obtain:

$$(\log ab)b^i c - \frac{a^i}{b-a} (\log ab) - 2b^i c (\log b) + 2 \frac{a^i}{b-a} (\log a) = 0. \tag{17}$$

This gives

$$cb^i (\log ab - 2 \log b) + \frac{a^i}{b-a} (-\log ab + 2 \log a) = 0 \tag{18}$$

or

$$cb^i + \frac{a^i}{b-a} = 0. \tag{19}$$

Thus,

$$f''(i) = 0 \quad \Leftrightarrow \quad \left( \frac{b}{a} \right)^i = \frac{1}{c(a-b)}, \tag{20}$$

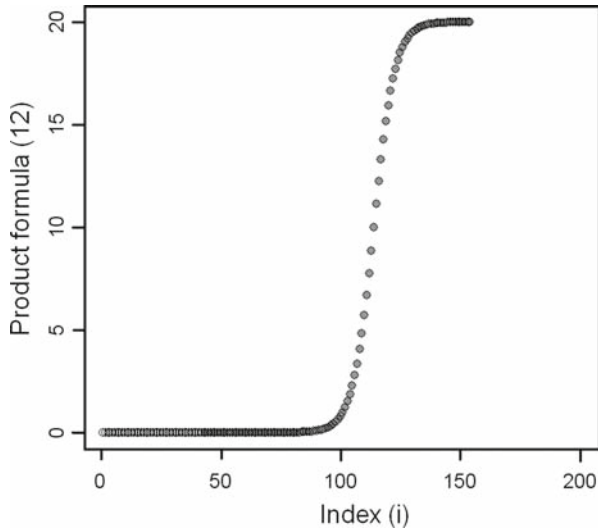


Fig 1. Evolution of product *e.e.* with  $a = 98, b = 78, x = 10^{-10}$ .

when

$$i_o = \frac{\log[c(a - b)]}{\log \frac{a}{b}}, \tag{21}$$

In the following part of the present paper we show two examples of the application of the results (Examples 1 and 2).

**Example (1).** We show here the sensitivity of the  $f(i)$  function (Figures 1–3) to the integration constant  $b$  with respect to the  $ee_{\max}$ . For  $a = 98, b = 78, x = 10^{-10}$  we have  $c = x^{-1} + (b - a)^{-1} = 10^{10} - \frac{1}{20} \cong 10^{10}$  so that  $i_o \cong \log(10^{10}20)(\log \frac{98}{78})^{-1} = 114.0004$ . The value of  $f$  at the inflexion point:

$$f(i_o) \cong f(114) = \frac{98^{114}}{10^{10} \cdot 78^{114} + \frac{(78^{114} - 98^{114})}{98 - 78}} \cong 10,$$

which is about a half of the difference between the limiting values of  $f$ :

$$\lim_{i \rightarrow \infty} f(i) - f(0+) = \frac{1}{2}(a - b - x) = \frac{1}{2}(98 - 78 - 10^{-10}) \cong 10.$$

For  $a = 98, b = 0.1, x = 10^{-10}$  we have  $c \cong x^{-1} = 10^{10}$  so that  $i_o \cong \log(10^{10} \cdot 97.9)(\log \frac{98}{0.1})^{-1} = 4.008651$ . The value of  $f$  at this inflexion point is  $f(i_o) = f(4.008651) = 48.95$ , which is about a half of the total increment of  $f$ :  $\frac{1}{2}(98 - 0.1) = \frac{97.9}{2} = 48.95$

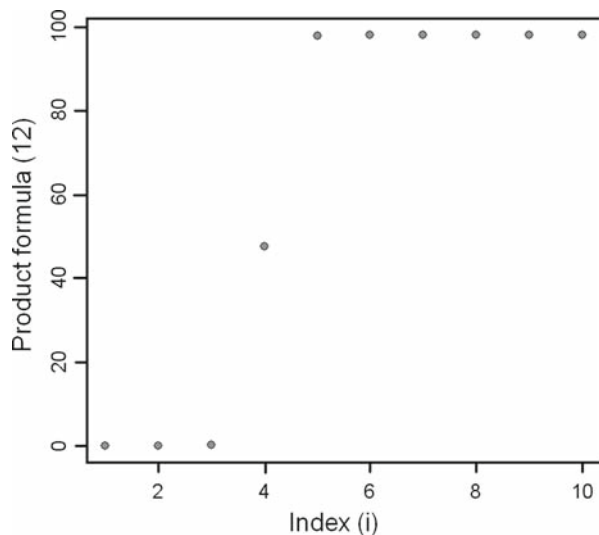


Fig 2. Evolution of product *e.e.* with  $a = 98, b = 0.1, x = 10^{-10}$ .

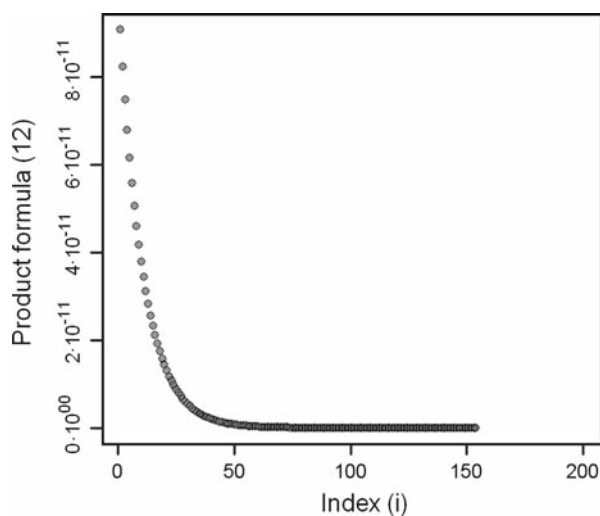


Fig 3. Evolution of product *e.e.* with  $a = 98, b = 108, x = 10^{-10}$ .

For a case, where  $a < b$ , as  $a = 98, b = 108$  (figure 3) no chiral enrichment, even just the contrary, “racemization”, occurs. This behaviour is general:  $f$  vanishes if  $i$  increases for all  $a < b$  cases.

**Example (2).** In this example, we show the usefulness of formulae (11) or (12) for the calculation of initial (non-measurable) enantiomeric excesses ( $ee$ ) from final (measurable)  $ee$ -values, knowing the number of catalytic cycles  $i$  used for this amplification of chirality.

While the formula (11) gives the enantiometric excess product at the  $i$ th step as a function  $g^i(x)$  of the initial value  $x = ee_{\text{start}}(0)$ , it may be useful to write explicitly the inverse formula, too. Setting  $y = g^i(x)$  we find

$$y \cdot x^{-1} b^i + y \cdot \frac{b^i - a^i}{b - a} = a^i, \quad (22)$$

that is

$$\frac{1}{x} = \frac{a^i(b - a) - y(b^i - a^i)}{b^i y(b - a)}. \quad (23)$$

Therefore the inverse function of  $g^i$  has the following expression:

$$x = g^{-i}(y) = \frac{b^i y(b - a)}{a^i(b - a) - y(b^i - a^i)}, \quad i \in N, b \neq a. \quad (24)$$

In the original notation this means that

$$ee_{\text{start}}(0) = \frac{B^i \cdot ee_{\text{product}}(i) \cdot (B - ee_{\text{max}})}{ee_{\text{max}}^i (B - ee_{\text{max}}) - ee_{\text{product}} \cdot (B^i - ee_{\text{max}}^i)}, \quad i \in N. \quad (25)$$

Formulae (24) or (25) can be used conveniently for the determination of the initial  $ee$ -s in absolute enantioselective catalytic experiments. From the data set S(A) and S(B) we obtain the  $ee_{\text{start}}$  values by the formula (25) applied with  $i = 3$ ,  $ee_{\text{max}} = 99$ ,  $B = (3.7) \cdot 10^{-5}$ . The plots of the  $ee_{\text{prod}}$  values (%), with sign, versus the corresponding  $|ee_{\text{start}}|$  (absolute) values of the third backward step are shown in figure 4 (for S(A)) and figure 5 (for S(B)).

A statistical evaluation of the “initial”  $ee$ -values (with sign) has been performed by a Kolmogorov-Smirnov test [15]. In case S(A) the  $ee_{\text{start}}$  data (third step backward) are compatible with normality of the distribution:  $D = 0.1024$ , with  $p$ -value = 0.8325. As a consequence, this is compatible with a binomial initial distribution of the enantiomers. On the contrary, the  $ee_{\text{start}}$  values corresponding to S(B), at the third step backward turn out to be non-normally distributed, with the Kolmogorov-Smirnov statistics  $D = 0.2035$  and  $p$ -value 0.001909. The graphical comparison supports these interesting results (figures 6 and 7).

### 3. Conclusions

(A) The equation deduced in the present work can be successfully utilised for the calculations:

- (i) determination of the “statistical” initial  $ee$ -s in absolute enantioselective catalytic experiments. The values obtained are in good agreement with the values expected on the basis of probability theory;



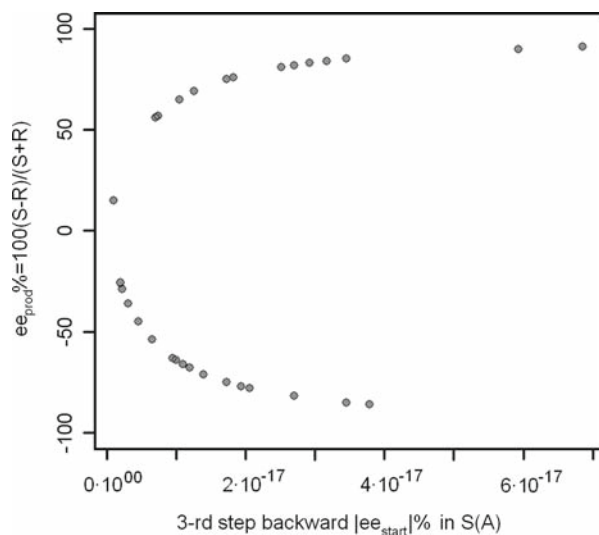


Fig 4. The  $ee_{\text{prod}}$  data from S(A) versus the  $|ee_{\text{start}}|$  values as calculated by the inverse formula (25).

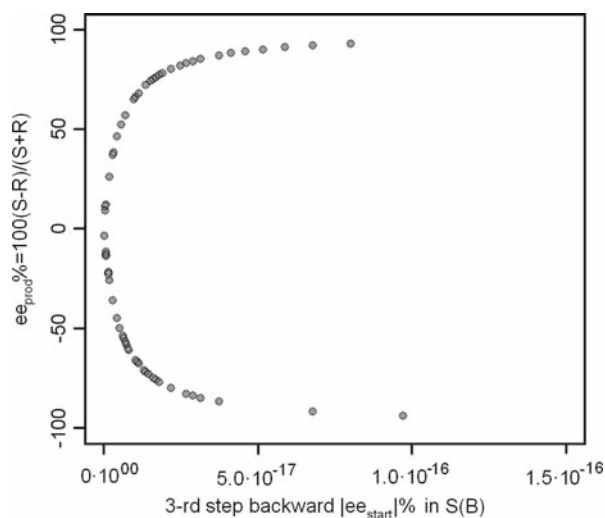


Fig 5. The  $ee_{\text{prod}}$  data from S(B) versus the  $|ee_{\text{start}}|$  values as calculated by the inverse formula (25).

- (ii) determination of the number of catalytic cycles needed in a system of a certain sensitivity (given  $ee_{\text{max}}$  and B) for achieving high  $ee_{\text{prod}}$  values;
- (iii) determination of the limits of the Soai-type systems: catalytic amplification of chirality can be expected only if  $B < ee_{\text{max}}$ , while for  $B = ee_{\text{max}}$  no change and for  $B > ee_{\text{max}}$  inhibition (“racemization”) occurs.

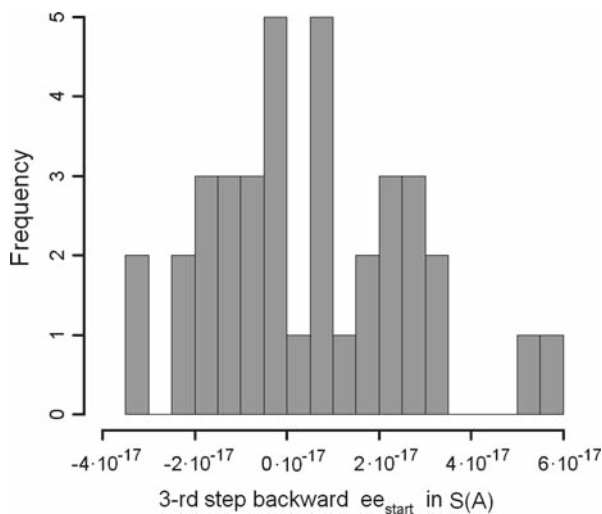


Fig 6. The histogram of the  $ee_{\text{start}}$  data from S(A).

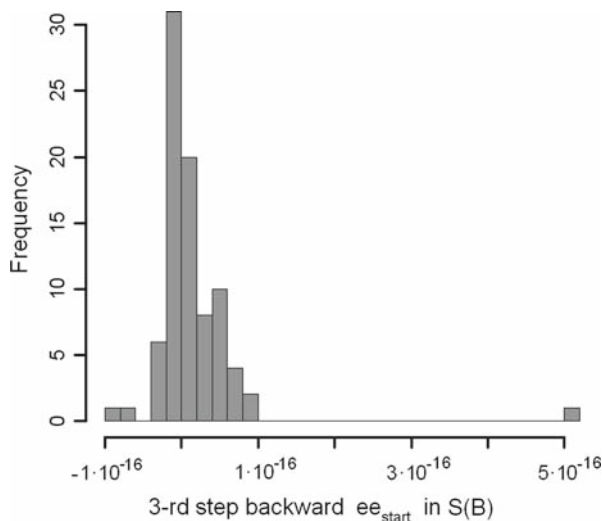


Fig 7. The histogram of the  $ee_{\text{start}}$  data from S(B).

It is expected that the use of the mathematically based formulae for the quantitative description of the Soai-autocatalysis will contribute to efforts at generalization of this exceptionally important reaction.

(B) System S(A) is essentially homogeneous, while S(B) heterogeneous. The fact that S(A) at the very beginning of the molecular events shows a behaviour close to normal distribution is (a) unexpected in the light of our recent analysis of the data obtained after the third catalytic cycle [16], but (b) it is of high

diagnostic value regarding the nature of the earliest phase [9, 12] of the Soai-autocatalysis. The deviation of also the initial phase of S(B) from normality might be due to its heterogeneous character.

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