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ORIGINAL PAPER

Stochastic and empirical models of the absolute asymmetric synthesis by the Soai-autocatalysis

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Abstract Absolute asymmetric synthesis (AAS) is the preparation of pure (or excess of one) enantiomer of a chiral compound from achiral precursor(s) by a chemical reaction, without enantiopure chiral additive and/or without applied asymmetric physical field. Only one well-characterized example of AAS is known today: the Soai-autocatalysis. In an attempt at clarification of the mechanism of this particular reaction we have undertaken *empirical* and *stochastic analysis* of several parallel AAS experiments. Our results show that the *initial steps* of the reaction might be controlled by simple *normal distribution* ("coin tossing") formalism. Advanced stages of the reaction, however, appear to be of a more complicated nature. *Symmetric beta distribution* formalism could not be brought into correspondence with the experimental observations. A *bimodal beta distribution* algorithm provided suitable agreement with the experimental data. The parameters of this bimodal beta function were determined by a Pólya-urn experiment (simulated by computer). Interestingly, parameters of the resulting bimodal beta function give a *golden section ratio*. These results show, that in this highly interesting autocatalysis two or even perhaps three catalytic cycles are cooperating. An attempt at constructing a "designed" Soai-type reaction system has also been made.

Keywords Absolute asymmetric synthesis · Asymmetric autocatalysis · Empirical models · Soai reaction · Stochastic models

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Introduction

Chirality [1–5] on the molecular level has two particular features: (a) enantiomers of chiral molecules represent an ideal example of materially realized binary code [6, 7], which however, (b) are of the same energy [8], leading to equal formation probability [9–12]. An important practical aspect of these features is rooted in the fact that living organisms are using chiral molecules as *only one* of the enantiomers. This phenomenon, called *biological chirality* [13–18], is a very important condition enabling the unparalleled selectivity of *in vivo* biochemical reactions and contributes decisively to the high information content of living organisms [6, 7, 19, 20].

The circumstance of *equal formation probability* of enantiomers in achiral to chiral chemical reactions (*in vitro*) however makes it very difficult to obtain enantiomerically pure (or at least enriched) chiral compounds by usual laboratory techniques, from achiral precursors and without the influence of asymmetric physical fields [21–23]. Such reaction, called *absolute asymmetric synthesis* (AAS), would be the dream of all preparative organic chemists or of chemical industry managers [24]. At present, only *one* sufficiently documented example of AAS is known: the Soai reaction [25–33].

The reaction discovered by Kenso Soai and his coworkers in 1995, is an alkylation reaction of N-heterocyclic aldehydes, by di(isopropyl)zinc, as alkylating agent (Fig. 1).

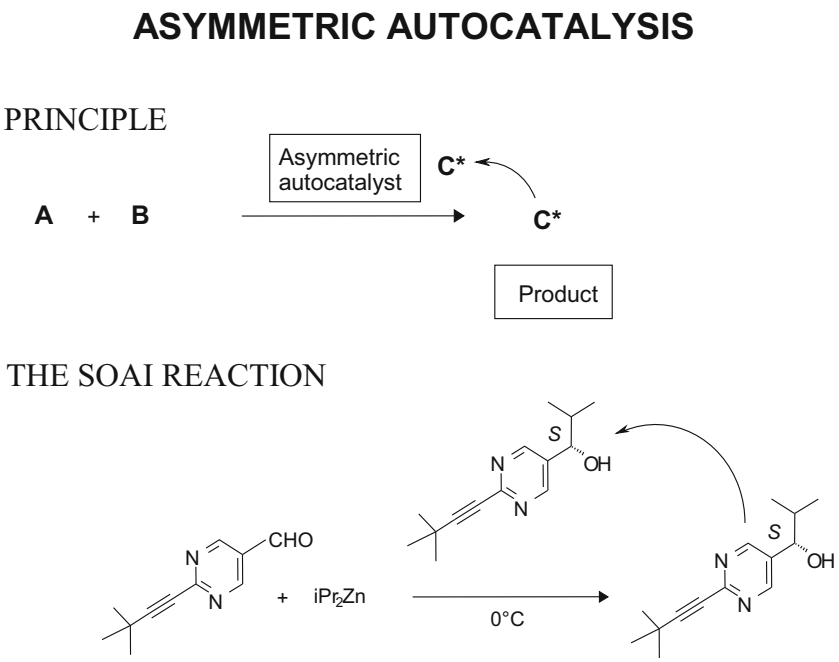

Fig. 1 Schematic representation of the asymmetric autocatalysis and the Soai-reaction

Soai and his team recognized soon, that this reaction might be suitable for the realization of AAS, which later became amply documented [34–37]. In this AAS reaction one could obtain high enantiomeric outcomes in the product, but it could not be said in advance which sense of chirality will be dominant. This behavior appeared to be a typical stochastic one and this prompted us to undertake an empirical and then a stochastic analysis of several parallel experiments. The results of this study will be summarized here. Some preliminary summaries of this research were published elsewhere [38–40].

Empirical approach

The analysis of the shape of enantiomeric excess (*ee*, Eq. 1) vs. time curves in the Soai reaction, realized with added more or less initial quantities of (enantiopure) product [41–43] or in consecutive catalytic cycles [44, 45], provided a very simple algebraic formula (Eq. 2) describing the evolution of chirality [46] in asymmetric autocatalysis. A simple transformation of this expression led to a closed formula (Eq. 3), describing the evolution of enantiomeric excess in terms of the number of consecutive catalytic cycles, applied in a one-pot manner [47]. These calculations underlined the exceptional efficiency of this one-pot more-cycles method, which enabled up to 630,000 times chiral amplification in a three-cycle experiment [45].

$$ee = 100\frac{R-S}{S+R} \text{ or } \quad ee = 100\frac{S-R}{S+R}\,[\text{in}\%]\,, \tag{1}$$

where R and S are molar quantities of the R and S enantiomers of the chiral compound in question; *ee* should be always positive.

$$ee_{prod} = ee_{max}\frac{ee_{start}}{B + ee_{start}}, \tag{2}$$

where ee_{prod} is the enantiomeric excess of the product, ee_{start} is the initial enantiomeric excess of the product at the moment of the start of the reaction, ee_{max} is the maximum enantiomeric excess reached with the given system.

$$ee_{prod(i)} = \frac{ee^{i}_{\max}}{ee^{-1}_{start(i)}B^{i} + \frac{B^{i}-ee^{i}_{\max}}{B-ee_{\max}}}, \tag{3}$$

where i refers to the ith catalytic cycle, others as above.

The formulae in Eqs. 2 and 3 are useful for the calculation of the limits of the Soai reaction (Figs. 2, 3, and 4) [48]. The analysis of multiple cycles in a one-pot experimental setup has shown that at the very beginning the reaction proceeds in a

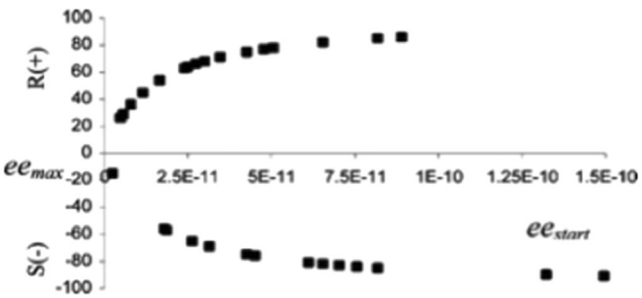

Fig. 2 Correlation of ee_{max} and ee_{start}

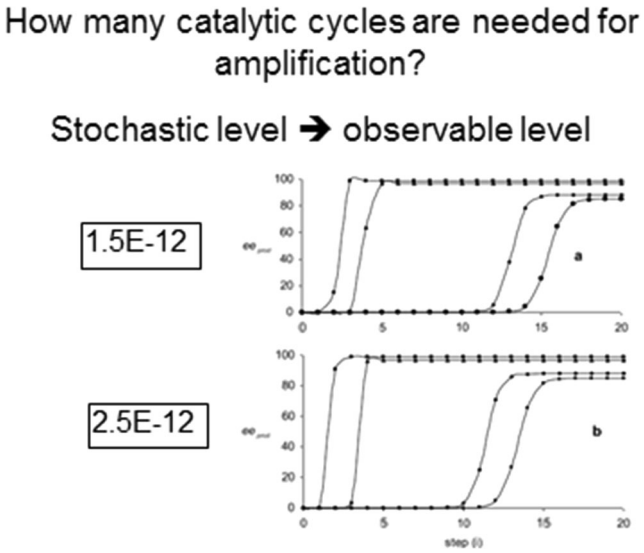

Fig. 3 Amplification of initial chirality by AAS

non-catalytic stochastic manner [47]. This observation called our attention to the stochastic features of this particular autocatalysis. Results of these studies will be reported later in this paper.

Several efforts at the kinetic description of the Soai reaction have been published. One of these, suggested by Buhse [49], led us to the discovery of chemical *oscillations* in asymmetric autocatalysis (Fig. 5a) [50]. In the course of these studies we also calculated by Eq. 2 the evolution of the enantiomeric excess, with initial *one molecule excess* from one of the enantiomeric products. It turned out, that after a very limited number (6–10) of oscillations (Fig. 5b) an "enantiomeric takeover" occurs. This result represents a *model* of one of the possibilities of the chemical evolution leading to the start of the biological chirality in very early stages of terrestrial life.

Following the indication obtained under conditions of chemical oscillations, we calculated the possible numbers of

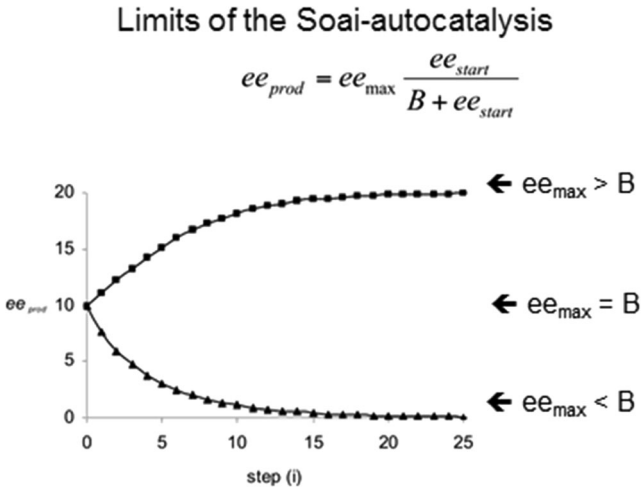

Fig. 4 Limits of the Soai reaction in terms of integration constant *B* in consecutive catalytic cycles

non-oscillating one-pot consecutive catalytic cycles by Eq. 3 (Fig. 3) [51]. It has been found that reasonable number of catalytic cycles (20–30, depending on *B*) are sufficient for obtaining from very low initial to "macroscopically significant" (product) enantiomeric excesses. We shall come back to the particular role of the very first chiral molecule in an achiral-to-chiral reaction, later in this paper.

Stochastic approach

As mentioned earlier, there are very strong indications, that *stochastic* phenomena play a decisive role in the Soai asymmetric autocatalysis. We performed a systematic study in this direction.

For statistical analysis two data sets (of parallel experiments) were available: Set A (S_A) with 37 observations [35] and set B (S_B) with 84 measurements [36]. The configuration of the enantiomers of the product will be defined, as usual, by R and S molar quantities of these enantiomers will be indicated by *R* and *S*.

We started our analysis [52] under the supposition of the case, which is the most obvious one at the "first sight": Hypothesis of *symmetric normal distribution*, which is the case usually called "coin tossing" experiment [53–55]. This hypothesis, however, raises some important conditions, which can also be controlled numerically. Such conditions are:

(a) The mean values (M) of the enantiomeric excesses (*ee*) in subsets M_R and M_S should be equal or very close.
(b) The number of experiments (n), producing excess from enantiomers R or S (n_R or n_S) should be equal or very close.
(c) The $(S\text{-}R)/(S+R)$ ratios sould be distributed *symmetrically* with respect to zero, defined as $S=R$.
(d) Standard deviations in subsets S_R and S_S (σ_R and σ_S) should be equal or very close. The relation $|M_R - M_S| < 3\sigma_R$ or $< 3\sigma_S$ should be satisfied.
(e) The distribution of the *ee* values could (should?) be described by a *binomial distribution*, which could be satisfactorily approximated by a *normal* (Gaussian) *distribution*.

The numerical analysis of these conditions showed the following highly interesting results.

Means (M) showed *S*-preference in both groups, in S_A: $M_S > M_R$ by 9.8 %, while in S_B: $M_S > M_R$ by 14.1 %. Since this difference in S_A 9.8 % $< 3\sigma$, only the difference in S_B (14.1 % $> 3\sigma$) can be regarded as significant. This result is in agreement with the *screwness* values, for S_A -0.0693, and for S_B -0.1379, which again shows a clear *S*-preference for (the more numerous group of) S_B. A similar tendency has been

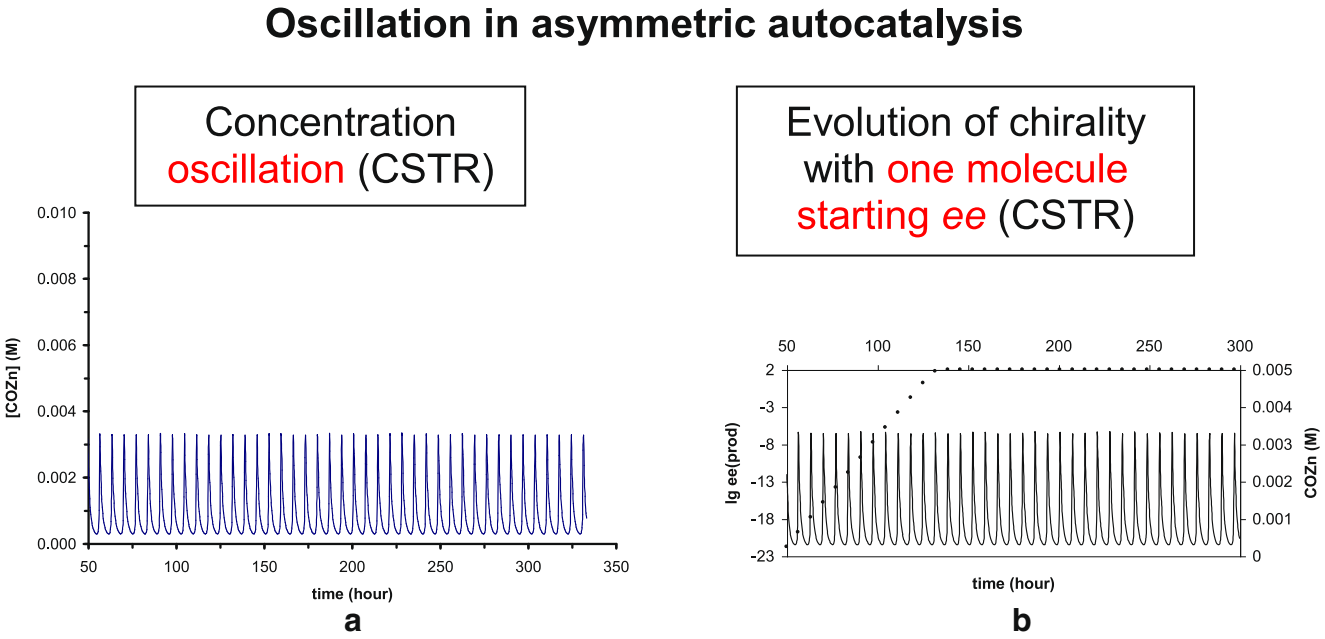

Fig. 5 Chemical oscillations in the Soai reaction in continuous-flow stirred tank (CSTR) reactor. (**a**) Without chiral "additive". (**b**) One molecule starting enantiomeric excess, $ee_{start}=1.66\times10^{-22}$ %)

observed by data analysis in the sets S_A and S_B: Here the *S*-preference is 5.3 % and 13.3 % respectively.

If the result for the *S*-preference holds true, it has a far-going significance. According to one of the theories about the origin of biological chirality, this origin would be controlled *not* by stochastic, *but* by deterministic factors. One of the most evident deterministic factors could (would?) be the *asymmetry of weak nuclear forces* [56]. It was hypothetically assumed that these forces could give some prevalence to the formation of one of the enantiomers in an achiral-to-chiral chemical reaction. This effect, however, is very small (femtoJ mol^{-1} to picoJ mol^{-1} range [57–59]). Several theoretical studies have been made for detecting the effect of weak nuclear forces in the thermodynamic and kinetic balance of such reactions and their products. These studies initially have shown some preference for the naturally occurring enantiomers of chiral biomolecules [60–71], but later, with more refined calculations this preference appeared to be either too small, or — at least — within the limits of the experimental (or calculation) error [72–77]. Neither preference for chiral conformations, e.g., double helix of DNA could be detected [73]. In this "undecided" situation of the relevant theories, it is of dramatic importance that the *experimental* observations, at least in the case of S_B (with 84 parallel experiments), indicate a clear preference of one of the possible enantiomers. This aspect is one of the most important theoretical consequences of the Soai reaction.

Results of the calculations aimed at testing the hypothesis of possible Gaussian distribution of the *ee* values obtained experimentally are in accordance with the above argumentation. It has been found [52] that a one-sample Kolmogorov-Smirnov test rejected the probabilistic independence (a basic property of binomial and Gaussian distributions) and required a two-sample approach. This result is a clear indication of the *violation of distribution symmetry.*

Calculations [52] of the Student t-test and the Welch two-sample test showed only a very low probability (~0.008) for the hypothesis of $M_R=M_S$. This again is in agreement with an asymmetric distribution of the experimental results.

Another attempt at finding a suitable mathematical description of the experimental observations S_A and S_B was made on the basis of literature suggestions using a purely stochastic kinetic model [78–80], based on the hypothesis of *symmetric β distribution*. According to our calculations [52], both data sets, S_A and S_B show a clear deviation from linearity in a quantile vs. quantile diagram (Fig. 6).

A one-sample Kolmogorov-Smirnov test resulted no significant outcome for S_A, but *clearly rejected* a symmetric β distribution for S_B.

The above outlined negative results raised the question, *whether at all* it would be possible to find a continuous law, with finite mean, which describes the experimental observations of *ee* values, under the conditions of absolute asymmetric synthesis? We calculated the expected number of parallel experiments [53–55] using the formalism of the central limit theorem (CLT) and the calculations according to Chebysev, both at p=9.1 % level. CLT requires 128 experiments with 95 % confidence interval of σ^2, while 287 parallels for 99 % confidence. The corresponding, more rigorous, Chebyshev results were 964 and 5320, respectively. From practical point of view, the 100 to 300 parallel experiments would still be realizable (c.f. [35, 36]), but the requirement of 1000 to

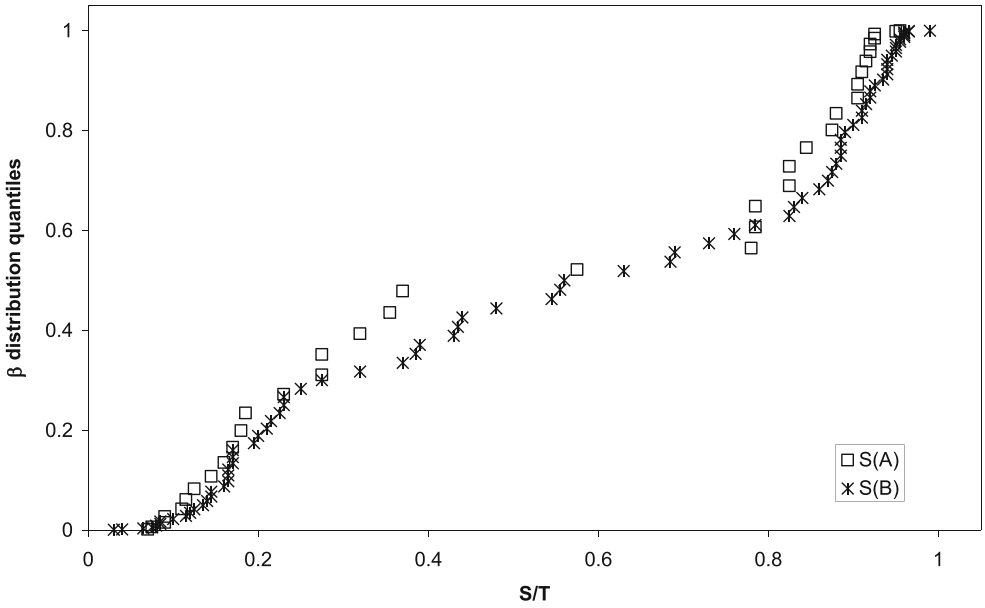

Fig. 6 Quantiles of beta-distribution vs. quantiles of *S/T* in S(A) and S(B)

6000 parallel experiments is going beyond even the legendary diligence of Japanese doctoral/postdoctoral research associates.

Instead of making a great number of experimental efforts, we started from another viewpoint. We supposed, the fact of exclusion of simple stochastic formalisms for the description of the absolute AAS variant of the Soai reaction might indicate a more complicated mechanism, which might be described by a more complex stochastic law. Interestingly, while we were working on the statistical approach from this point of view, Ercolani and Schiaffino [81–85], in a couple of excellent papers arrived qualitatively at the same conclusion, on a very different basis, by theoretical calculations, in an attempt at identifying possible intermediates of the Soai autocatalysis.

In an attempt at finding that "more complex stochastic law" which could correctly describe the experimental observations which were obtained by the absolute asymmetric synthesis variant of the Soai reaction, we tried to use a *bimodal β distribution* function, *h(x)*, constructed [86] from the combination of a convex, *f(x)*, and a concave, *g(x)*, component (Eq. 4), taking into regard the:

$$h(x) = f(x) + g(x), \tag{4}$$

shape of the histogram (Fig. 7) constructed from the experimental data. The shape of the *h(x)* function is shown in Fig. 8.

In this formalism we used $x=N_S/N_T$, where $N_T=N_S+N_R$ and N corresponds to the number of molecules. A more detailed form of Eq. 4 [53] is shown in Eqs. 5 and 6.

$$h(x) = \frac{l}{l+m}\beta(a,b)x^{a-1}(1-x)^{b-1} + \frac{m}{l+m}\beta(c,d)x^{c-1}(1-x)^{d-1} \tag{5}$$

In Eq. 5 $\beta(\ldots)$ is the weight factor of the combination of components *f(x)* and *g(x)* in *h(x)*, for example:

$$\beta(a,b) = \frac{1}{\int_0^1 x^{a-1}(1-x)^{b-1}dx}. \tag{6}$$

Constants *a,b* and *c,d* are shape parameters of the functions *f(x)* and *g(x)* respectively, as well as the *l* and *m* parameters give the *mixing ratio* of the component functions.

In an attempt at finding suitable values of these parameters (if our algorithm was correct) we applied the so-called Pólya urn model [87–89], which is (surprisingly) rarely used in chemistry [90]. According to the idea of György Pólya one makes thought experiment(s) designed for following the evolution of the changes of numbers of natural species (atoms, molecules, microorganisms, etc.). The "thought experiment" can be done also materially, or by computer too. In this

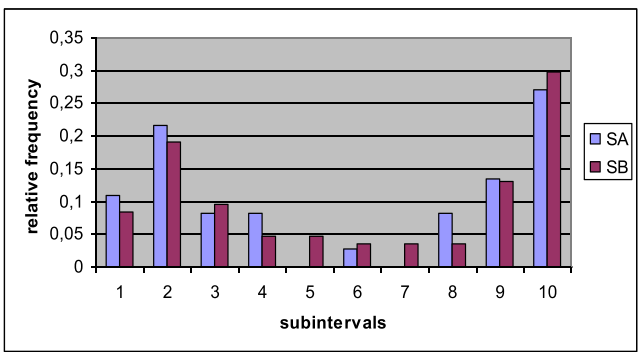

Fig. 7 Histogram of the enantiomer S of data populations in systems S_A and S_B

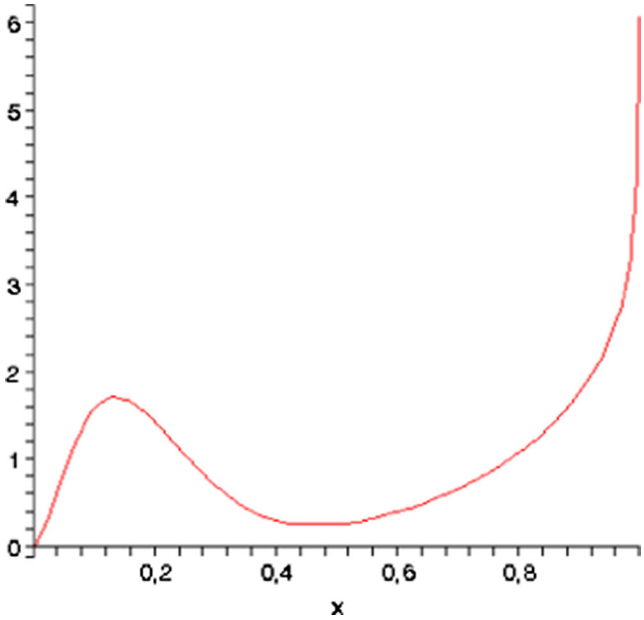

Fig. 8 Graphical representation of the combined bimodal beta distribution, *h(x)*, according to Eqs. 4, 5, and 6, with the computed *a, b, c*, and *d* parameters (see text)

experiment one takes a (one or more) container, called "urn", puts in it material objects, called "spheres" or "marbles" with different external features, "colors", and defines an algorithm for proceeding with these. According to this algorithm one takes one (or more) from these marbles from one (or more) of the urns, notes its color and according to rules of the algorithm adds marbles to this (these) urn(s) and observes after several such operations the changes in the composition(s) of colored marbles in the urn(s). Obviously it is easy to follow this process by computer, as we have done it too [40, 86, 91].

We studied a Pólya urn variant with *one urn* and *two populations of marbles:*

(a) The first population consisted of large numbers of two "achiral" species, A and Z_0, (these numbers were chosen as 1 mol=6×10^{23} marbles each) and a few pieces of "chemical", Z", and "chiral inductor" S and R marbles. Considering the chemical background (Fig. 1) the following two "reactions" could display (Eqs. 7 and 8):

$$A + Z_0 + Z" + S \rightarrow 2S + Z" + Z \quad (7)$$

$$A + Z_0 + Z" + R \rightarrow 2R + Z" + Z \quad (8)$$

The constants *a* and *b* of Eq. 5 were related to the staring numbers of species S and R, consequently the sum *a*+*b* will define the value of Z (chemical catalyst) and Z" will be "imported" from the second cycle.

(b) *Mutatis mutandis*, the second population was chosen according to similar rules and resulted Eq. 9 and 10:

$$A + Z_0 + Z + S" \rightarrow 2S + Z + Z" \quad (9)$$

$$A + Z_0 + Z + R" \rightarrow 2R + Z + Z". \quad (10)$$

Similarly as above the values of constants *c* and *d* are related to the starting numbers of species S" and R".

The following algorithms were defined. For the *first population*: three marbles are drawn casually and if A is drawn together with S and Z", then this A gets exchanged for (or more "chemically": transformed to) an S marble and one Z_0 gets exchanged for (transformed to) a Z marble. The rule is analogous if A and Z" are drawn together with an R marble. For the *second population*: Again three marbles are drawn casually and if A is drawn together with S" and Z, then the A marble gets exchanged for (transformed to) an S" marble and one Z_0 gets exchanged for a Z" unit. The rule works similarly with starting R" (Eq. 10).

Several combinations of the constants *a, b, c*, and *d* were screened by χ^2-test [92]. The closest fit was obtained by the combination *a*=2, *b*=10, *c*=5, *d*=1, yielding *df*=9 (where *df* is for degree of freedom) in the χ^2 –test, on a 95 % level (ε=0.05), $\chi^2_{crit.}$ = 16.9, while the statistics for Eq. 4 with respect to S_A resulted χ^2_A=6.64, for S_B gave χ^2_B=10.18. Both χ^2 values are *much lower than the critical value*, indicating an excellent fit to the experimental data. Small changes in these "optimum" parameters resulted very large changes in the goodness of fit. Sets of these parameters with *a*=2, *b*=**12**, *c*=**6**, *d*=1; or *a*=2, *b*=**6**, *c*=**3**, *d*=1 gave χ^2 values of 20.3 and 24.9, respectively, both of which are significantly higher than the critical value.

The values of the coupling parameters *l* and *m* were generated inherently in this model from the ratios *l*/(*l*+*m*) and *m*/(*l*+*m*). Since the ratio of the numbers of Z and Z" follows the evolution of a Fibonacci series [93–95] in these two populations, it will lead to a *golden section* ratio [96, 97]. The appearance of the golden section ratio in the quantitative description of the Soai reaction, might give an indication toward the not yet fully understood particular character of this very important autocatalysis. In other words, one could suspect, that the extreme high selectivity and efficiency of the Soai reaction could be due to the *cooperation of more than one catalytic cycle* which are the most efficient if acting in the golden section ratio.

Considering all of these results and considerations the numerical form of the *h*(*x*) function is as follows:

$$h(x) = 0.382 \cdot 110x(1–x)^9 + 0.618 \cdot 5x^4. \quad (11)$$

The bimodal β distribution diagram is shown in Fig. 8 drawn on the basis of the numerical values in Eq. 11. The shape of this curve shows an excellent agreement with the shape of the the *ee* histogram in Fig. 7.

It appears, thus, that the stochastic analysis of the Soai reaction presented above gives a satisfactory description in the form of a bimodal β distribution function. One of the most interesting features of this result is, that it indicates *two cooperating catalytic cycles* as the main molecular events in the Soai asymmetric autocatalysis, but the *cooperation* of these cycles materializes in a *third catalytic cycle* as shown in Fig. 9.

These "superficial" observations provide, however, *no mechanistic picture*, give only a starting point for mechanistic considerations.

A few points regarding the above stochastic picture should still be shortly summarized.

(a) The analysis of the *ee* data in the AAS variant of the Soai reaction is (obviously) of *thermodynamic* nature, not allowing *kinetic* considerations. Kinetic studies on the Soai reaction did not yet reach such a conclusion, which could be regarded as the final solution of the problem [49, 78–80, 98–104].

(b) The experimental data sets S_A and S_B obey the *same* distribution laws, consequently: Even if the experimental conditions are somewhat different [35, 36], the decisive molecular events should be the same in these two groups of parallel experiments.

(c) The fact, that in the "elevated" stage the Soai reaction (without additive) obeys a bimodal β distribution law, opens the possibility, that in the *very beginning stage* the reaction starts with molecular events obeying *normal distribution*, as pointed out elsewhere [47, 51].

(d) The recent theoretical results about the possibility of "intermediates in equilibrium" [81–85] (according to our interpretation this means more than one intermediate) appears to be in agreement with the above outlined result concerning the *more than one catalytic cycle* cooperating in the Soai autocatalysis.

(e) *Cooperating catalytic cycles* represent the core hypothesis on the origin of terrestrial life, according to the theories of Gánti [105–109] and Eigen [110–112].

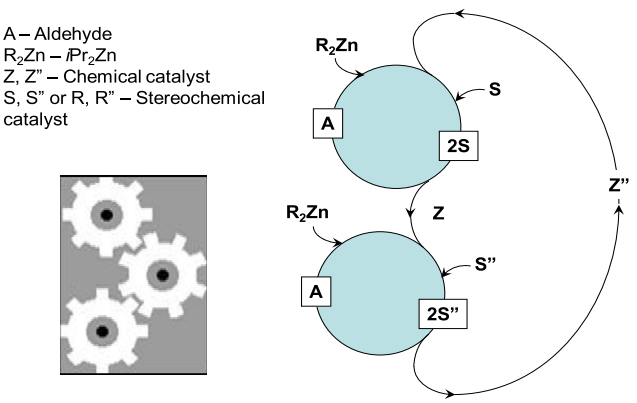

Fig. 9 Schematic representations of the cooperating catalytic cycles in the Soai reaction on the basis of the bimodal β distribution hypothesis

Single molecule chirality. The Caglioti principle

Empirical mathematical analysis of the Soai autocatalysis provided an indication of the *normal distribution* ("coin tossing") character in the very early stage of the reaction [47]. This result prompted us to investigate somewhat nearer the conditions in systems with only a few molecules of both enantiomers of a chiral substance [22].

If an achiral-to-chiral reaction takes place, a 1:1 mixture of the two enantiomers is formed according to all laboratory experience of preparative chemistry (*except* the Soai reaction [34–37]). This mixture is called "racemate", which, however is *not* a chemical category, being only a mixture of two substances. It has been recognized very early (1898), that in such mixtures the number of such enantiomers is controlled by laws of probability [9–11]. Elementary combinatorial calculations [22] show very interesting results in this respect. In a system containing only *ten molecules* from the two enantiomers, the probability of having a 5:5 mixture (which is the only combination being a "true racemate"!) has a probability of only 24.6 %, while various mixtures with enantiomeric excesses from one or the other enantiomer are formed with 75.4 % probability. Even more, the probability of the formation of a "pure" enantiomer, that is 10:0 or 0:10, is 0.2 %. At *100 molecules* these numbers are 7.7 %, 92.3 % for the first two situations, respectively, while the probability of a pure enantiomer is only 1.58×10^{-28} %, which is negligible. At *1000 molecules* these values are 2.5 %, 97.5 %, and 1.87×10^{-299} %, while in a system consisting of 10^8 *molecules* (cca. femtomol level) the probability of the 1:1 mixture practically vanishes too, with its 0.008 % probability. The numbers of molecules considered above, are *even* numbers, in the case of any *odd* number (50 % of all cases!!!), the formation of a "true racemate" is impossible, at least one molecule excess should be present from one of the enantiomers. These considerations have some important consequences:

(i) In all "racemates" of practical size (>femtomol) the mixture is *not* a true racemate, in overhelming majority of the cases the sample contains more-less excess from one of the enantiomers. In the case reactions with such extreme sensitivity as the Soai reaction [34–37, 41–43, 45], this should be seriously considered.

(ii) In systems of low molecule number very high enantiomeric excesses are "usual", with consequences of their

chiral induction power, as found in the early stage of the Soai reaction [47].

These considerations brought Luciano Caglioti (University "La Sapienza, Rome) to the idea, that if only one chiral molecule is present in a very diluted system, this will possess, *per definitionem*, 100 % enantiomeric excess. This is what we call Caglioti principle. The basic idea of a single chiral molecule was then tested from various aspects [51, 113–116]. Here we mention only one: the calculations by Eq. 3 for finding the possibility of consecutive "one-pot" multi-cycle Soai reaction experiments for amplifying *one molecule* initial excess from one of the enantiomeric autocatalysts. These calculations (Fig. 10) enabled to determine the number of catalytic cycles necessary for amplifying this one molecule excess to macroscopically significant *ee*s, by such Soai reaction types, which have medium to high *B* constant [48]. It is clearly visible from Fig. 10, that the number of cycles necessary to realize this enormous "jump" of chirality is reasonable under common laboratory conditions. These results too, demonstrate the exceptional efficiency of the Soai asymmetric autocatalysis. The idea of the Caglioti principle was also later discussed by others [117–119].

Toward designed Soai-type systems?

Both intellectual intuition and several pieces of experimental evidence suggest, that chemistry in terrestrial living organisms is working in many aspects according to principles of the Soai reaction. However, in spite of world-wide efforts of the scientific community — no comparable reaction has been found yet. The only hope is coming from the University Erlangen-Nürnberg [120–124] and some others [125, 126], through reports on Mannich and aldol reactions, which are in several aspects similar to the Soai autocatalysis. These reactions, however, were discovered a few years ago accidentally, identified as autocatalysis and worked out by this excellent reasearch team in Germany and some other authors.

A few years ago the catalysis team at the University of Modena started cooperation with the University of Debrecen, with the bold goal, to *construct* a Soai type reaction system.

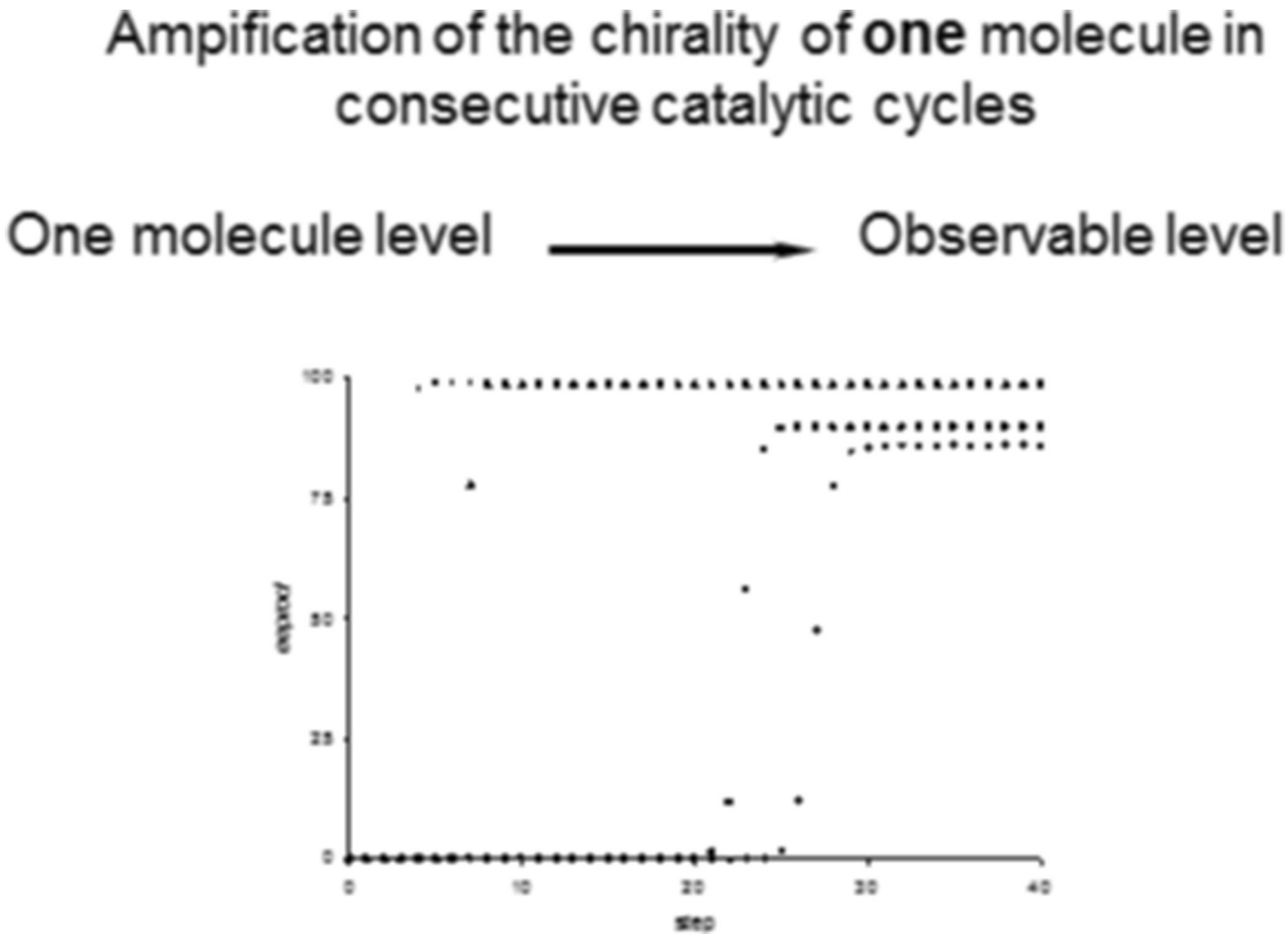

Fig. 10 Amplification of one molecule enantiomeric excess in consecutive one-pot Soai reaction cycles to macroscopically significant *ee*s

As the starting point the experience of the Debrecen group with the use of Cr(II) complexes in reduction of organic functional groups [127–129] was utilized, with the modification, that for N,O-donor ligands we chose pure enantiomers of amino acids. This reducing system was first tested in the reduction of various ketonic substrates [130–132], then with ketoximes [133]. In both cases medium to high enantiomeric excesses were found in the products. On the basis of this experience we tested the reduction of α-oximino carboxylic acids, which are direct precursors of the (natural) α-amino acids (Fig. 11) [134, 135].

In fact, these reactions resulted such amino acid products, which were substantially enriched in one of the enantiomers. The results are now (still?) far from being autocatalytic, but we are working on this aspect. Some relevant analytical problems were already successfully resolved [136–138].

Conclusions

The discovery of the first *asymmetric autocatalysis* by **Kenso Soai** and coworkers, in 1995, which had since then an enormous impact on theoretical and preparative chemistry (the number of independent citations to the papers of the Tokyo University of Science group is over 10,000). Numerous preparative, theoretical and biochemical studies have been induced by this discovery. In the present paper we summarized only a small part of this research, performed mostly in Modena, Rome, Budapest, and Debrecen, dealing principally with the *absolute enantioselective synthesis* variant of the Soai reaction. The results, mathematical and preparative *models*, obviously, do not resolve all problems regarding the Soai autocatalysis, but in certain aspects contribute to the clarification of some points relevant to this important reaction:

(a) Simple empirical formulae enable the quantitative description of the evolution of the *ee* in the course of the reaction, without mechanistic speculations.
(b) These empirical formulae allow to calculate the number of cycles in consecutive reaction chains realized in a one-pot manner, which are necessary for obtaining practically significant (>50 % *ee*) optical yields.
(c) Statistical studies have shown that the Soai autocatalysis starts with (most probably non-catalytic) reaction steps which can be described by *normal* (Gaussian) *distribution*. This phase is operating in that stage, where the first few chiral molecules are formed. Special importance can be attributed to the formation of the very first chiral molecule from achiral precursors (Caglioti principle).
(d) The statistical studies, however, indicated that after the very initial stage, the reaction becomes catalytic, which

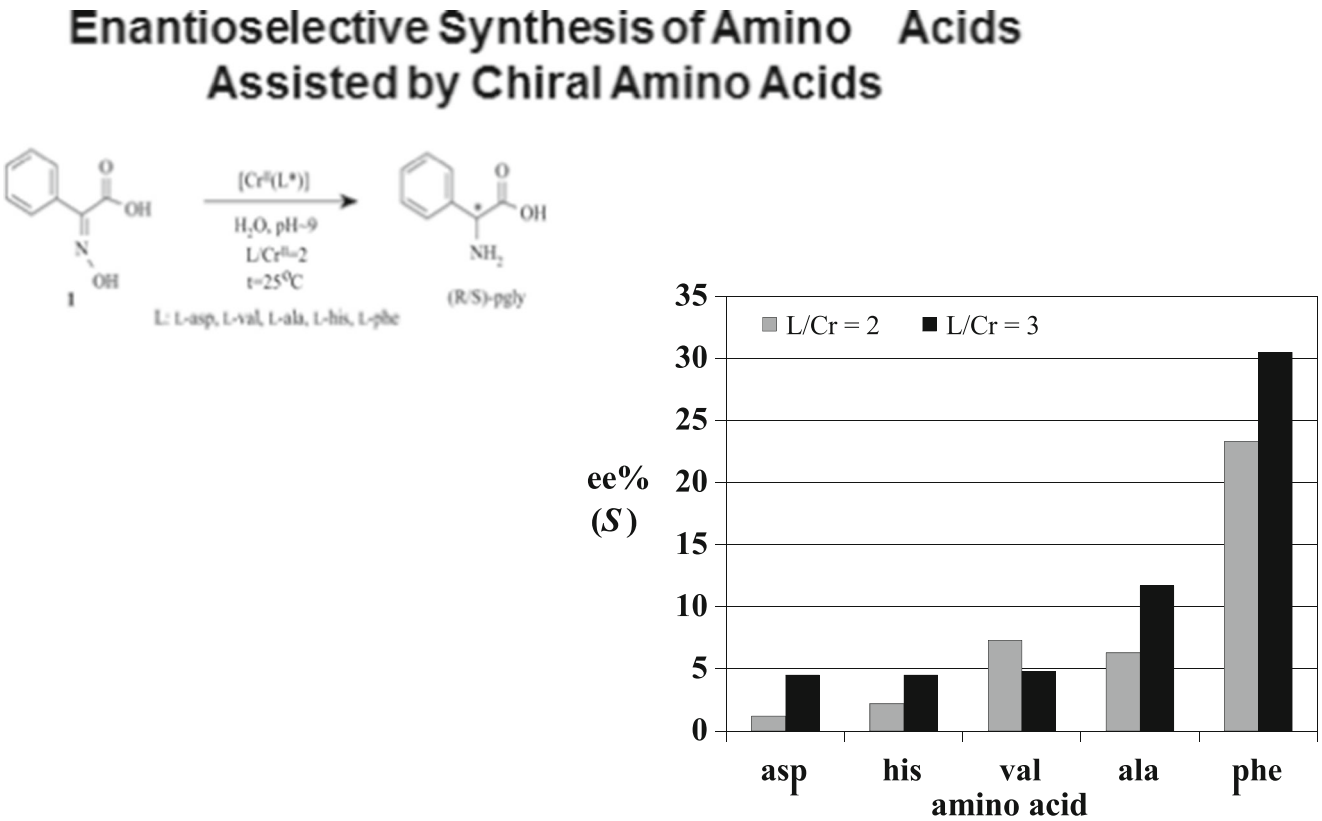

Fig. 11 Enantioselective synthesis of α-amino acid by Cr(II) complexes of (natural) α-amino acids

appears to be the result of the cooperation of more than one (most probably three) catalytic cycles.

(e) The empirical and statistical *models* of the Soai reaction allowed an attempt at the construction of a Soai-type reaction system on the basis of chiral natural amino acid complexes of chromium(II). This reaction system allows to transfer chirality of the ligand amino acids to product amino acids, which were obtained by reduction with Cr(II) ions from an achiral precursor, but its efficiency is (yet?) far from the efficiency of the Soai autocatalysis.

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