

## Kinetic Aspects of Soai's Asymmetric Autocatalysis

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**Abstract.** Recent kinetic studies are discussed that shed light on the reaction mechanism of the autocatalytic addition of diisopropylzinc to pyrimidine carbaldehydes (Soai reaction). Soai's reaction stands for the exclusive example of chirally autocatalytic reaction system in organic chemistry and has attracted close attention from several viewpoints: as possible account for the origin of biomolecular homochirality, as potential innovation in enantioselective synthesis or as a further remarkable manifestation of nonlinear dynamics in chemical systems. It is indicated that the reaction is driven by enantioselective autocatalysis and mutual inhibition as the essential components. A numerical approach reveals that experimentally observed chiral amplification and mirror-symmetry breaking can be readily reproduced by a comparatively simple kinetic model that considers monomers as the catalytic species.

**Keywords:** Soai reaction, asymmetric autocatalysis enantioselection.

**Resumen.** Se discuten estudios cinéticos recientes que dan luz sobre el mecanismo de reacción de la adición autocatalítica de diisopropilzinc en pirimidilcarbaldehídos (reacción de Soai). La reacción de Soai se mantiene como un ejemplo exclusivo de un sistema de reacción quiralmente autocatalítico en química orgánica y que ha atraído la atención desde diversos puntos de vista: como una explicación para el origen de la homoquiralidad biomolecular, como innovación potencial en la síntesis enantioselectiva o como una notable manifestación de la dinámica no lineal en sistemas químicos. Se ha mostrado que la reacción es dirigida por autocatalisis enantioselectiva e inhibición mutua como procesos esenciales. Una aproximación numérica revela que la amplificación quiral observada experimentalmente y el rompimiento de la simetría especular pueden ser reproducidas a partir de un modelo cinético comparativamente simple y que considera monómeros como las especies catalíticas.

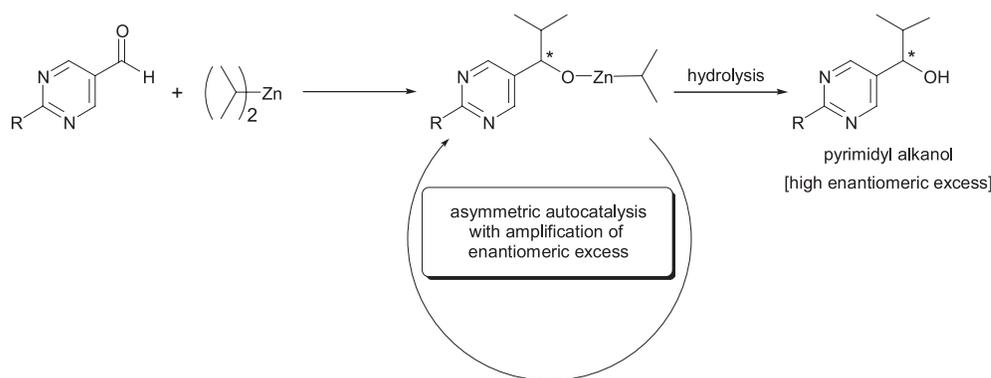
**Palabras clave:** Reacción de Soai, autocatalisis asimétrica enantioselección

### Introduction

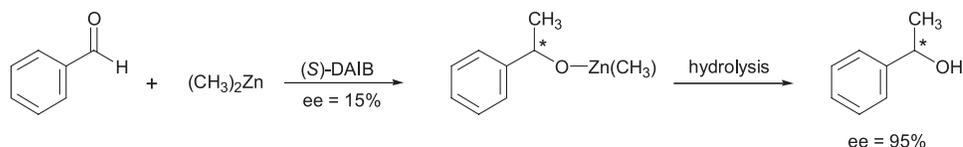
Hardly ever a newly discovered chemical reaction has turned established organic chemistry textbook knowledge upside down as happened in 1995 when Kenso Soai and co-workers revealed the first example of chiroselective autocatalysis in an organic reaction system (Scheme 1) [1]. This reaction was shown to amplify spontaneously trace amounts of initial enantiomeric excess (ee) to the highest degree [2] and – even more – it made it possible to generate extensive ee from “nothing”

in repeated experiments, i.e. by starting from entirely achiral initial conditions and without the influence of any chiral field [3-5]. Obviously, the later phenomenon stood in deep contrast to long-standing chemists' acquaintance about asymmetric synthesis where the presence of a chirally asymmetric factor was considered as vital for creating chiral imbalances during the course of a chemical reaction [6].

Soai's discovery opened a new and challenging perspective in asymmetric synthesis although amplification of initial ee has been observed in various asymmetric reactions before



**Scheme 1.** The addition of diisopropylzinc to pyrimidine carbaldehyde yielding isopropylzinc alkoxide that, after hydrolysis, is converted into a stable chiral pyrimidyl alkanol (Soai reaction). The arrow indicates the autocatalytic feedback resulting in an amplification of enantiomeric excess. R = H, CH<sub>3</sub>, *t*-Bu-C≡C-, (CH<sub>3</sub>)<sub>3</sub>Si C≡C-.



**Scheme 2.** The alkylation of benzaldehyde with dimethylzinc catalyzed by (2*S*)-3-*exo*-(dimethylamino)-isoborneol, (*S*)-DAIB, (Noyori reaction) yielding a higher enantiomeric excess of the resulting phenyl alcohol than that of the initially added (*S*)-DAIB. The observed chiral amplification is due to a positive nonlinear effect in asymmetric synthesis.

[7]. Among those one can find the amino alcohol-catalyzed alky zinc addition to benzaldehydes that has been pioneered by Noyori in 1989 (Scheme 2) [8].

Noyori's reaction falls in into the category of so-called nonlinear effects (NLE) in asymmetric synthesis [7, 9] in which the relation between the ee of the chiral auxiliary and the ee of the chiral reaction product deviates from linearity. Recall that the ee of a substance obtained by chiral resolution or classical asymmetric synthesis is usually less than, or at most, equal to that of the chiral initiator while in the case of NLE the product ee exceeds the ee of the catalyst or auxiliary [10]. NLE in asymmetric synthesis reflect the complexity of the reaction mechanism involved and are usually caused by the self-association of chiral species such as chiral intermediates or metal-organic complexes during the course of the reaction. In the case of dimerization, diastereomeric homochiral (*RR* or *SS*) and heterochiral (*RS* or *SR*) dimers can be formed in different relative amounts due to possible differences in their thermodynamic stabilities or rates of formation or dissociation. Supposed that heterochiral dimers would display higher thermodynamic stability as their homochiral counterparts, the overall ee of the remaining R and S monomers would increase by the formation of a heterochiral reservoir containing an optically inactive *RS meso* compound (reservoir model). Moreover, homochiral and heterochiral dimers may display different reactivity if they take part for example as catalytic species in the further reaction processing. Such a processing refers to the so-called "ML<sub>2</sub> system" introduced by Kagan [11] in which dimers or oligomers play the role of catalytic species in contrast to the reservoir model where monomers are considered as catalytically active.

Soai's reaction tops the above mentioned NLE by the fact that the asymmetric catalyst is not externally added such as the DAIB in the case of Noyori and co-workers but the catalyst is the reaction product itself. Reactions in which the reaction product catalyses its own formation are called autocatalytic. Hence the Soai reaction is *chirally* autocatalytic, i.e. the chiral product and chiral catalyst are identical and the reaction is simultaneously accelerated and stereoselectively directed by the same species that is generated *in-situ*.

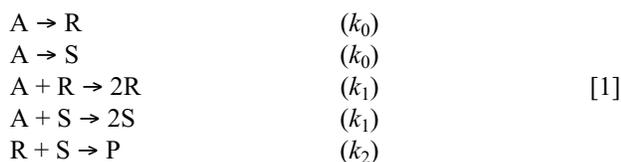
## The emergence of Nonlinearity and Stochastic Behavior

While organic chemists talk about "nonlinear effects" if the ee of the chiral catalyst is not linearly correlated with the ee of the chiral product, physical chemists call "nonlinear" the chemical feedback as displayed by autocatalytic kinetics. Nonlinearity of that sense is at the origin of many phenomena for instance the dreadful dynamics of thermal explosions or the remarkable breaking of temporal or spatial symmetry in oscillating reactions [12]. In asymmetric reactions, autocatalytic kinetics can result in so-called 'mirror-symmetry breaking' [13]. This phenomenon is related to the coexistence and to instabilities of stationary or pseudo-stationary states and can only occur if the reaction system is situated far enough from thermodynamic equilibrium [14] which applies to almost every chemical reaction in its earlier stages.

Basically, a chiral reaction system is characterized by two dominant states: an optically active state and a racemic one. Under certain conditions, nonlinear kinetics can cause the instability of the racemic state where the optically active state becomes stable and *vice versa*. The transition between the two states is called bifurcation and has dramatic consequences: for example, a system in an unstable racemic regime becomes highly susceptible to smallest fluctuations like a marble placed on the tip of a needle so that it will be driven inevitably from the racemic state into the optically active one. This means, as long as the constraints are not altered and the system is further kept from equilibrium there is no other option as to remain optically active. Fluctuations – for instance thermal ones – are inherent to any real chemical system. Even if these fluctuations are infinitesimal small, they will push the system away from an unstable state but they are undirected. Hence it remains unpredictable for each individual experiment in which optically active state the system will be driven, i.e. if the *R* or the *S* species will dominate like it is impossible to predict exactly the trajectory of the marble falling from the needle tip. Of course, for a larger number of experiments an equal distribution between *R* and *S* dominance is expected if the initial conditions do not involve any preferences. Such phenomenon is called mirror-symmetry breaking and intro-

duces an element into chemical sciences that has been ignored for long time – namely, the manifestation of stochastic behavior that questions the dogma of always achievable reproducibility [15].

A further characteristic of autocatalysis is auto-amplification such as the vicious feedback of a microphone connected to an amplifier and directed to its own loudspeaker. Chiral amplification can occur in a similar way: the *R* enantiomer amplifies its own formation and the *S* enantiomer does the same for its individual growth. However, as it can be readily deduced, the auto-amplification of *R* and *S* is necessary but not sufficient to amplify an initial ee. In fact, none of the both *R* and *S* products would finally make the race since at best their initial distance would remain the same throughout the reaction. Obviously, this is not the case in Soai's reaction where very small initial ee is amplified to a great extent. Hence a further aspect has to be considered that is so-called mutual inhibition. Mutual inhibition is the reaction between the two enantiomers to form a (kinetically) inactive product. With the two considerations, autocatalysis and mutual inhibition, we have the ingredients to construct the simplest kinetic model that reproduces chiral amplification as it has been already done by Frank [16] more than 50 years ago,



where A stands for the achiral substrate, *R* and *S* for the enantiomeric products, and P for an inactive and not further specified species. Note that by the given rate constants  $k_0$  and  $k_1$  the model remains entirely symmetric, nevertheless, it can lead to an amplification of *any* initial ee - no matter how small - up to nearly 100%.

Despite of its short and elegant notion, Frank's model remained completely general from the chemical point of view. In fact, it could merely refer to any existing system because the first laboratory case of chiral autocatalysis - occurring in the stirred crystallization of NaClO<sub>3</sub> [17] - has been reported about 40 years after Frank's landmark paper. Until today, the Soai reaction remains the exclusive example of such kind in organic chemistry, i.e. the only chirally autocatalytic system in which a chiral carbon is formed. The emergence of chiral carbon-based chemistry developing complex molecules and the creation of chiral imbalances in terms of L-amino acids and D-sugars is typically associated to the early conditions for the emergence of life. Hence Soai's successful experimental realization has attracted close interest to those searching for the origin of biomolecular homochirality [18] – one of the still unsolved key questions related to universal symmetry principles on one hand and to the origin of life on Earth and perhaps elsewhere in the universe on the other. Since homochirality is

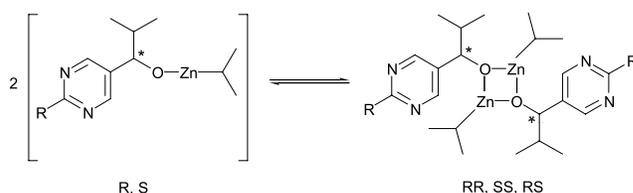
overwhelmingly considered as a prerequisite and not as a consequence of life, one was hoping to find a laboratory case for a chemical scenario of spontaneous chiral amplification since the early times of Frank that perhaps now has been uncovered – at least technically. The Soai reaction remains hardly realistic from a prebiotic point of view because of its comparatively complex reactants and reaction conditions that require a dry and air-free environment. However, it gives insight into a possible reaction network that can display chiral amplification and create chiral imbalances “from nothing” not only by theory but in experiment.

Many information about the Soai reaction can be obtained such as the experimental observation of tremendous chiral amplification where in a one-pot approach an ee  $\approx$  50% is obtained from a tiny initial imbalance of initially ee =  $5 \times 10^{-5}$  % [2], the control of the enantiomeric direction of the reaction using only few thousand chiral molecules as initiator [4], or the systematic generation of ee without adding any chiral substances resulting in a probabilistic predominance of either *R*- or *S*-product species in each experiment [3-5]. However, attempts to understand better the mechanism and dynamics of the Soai reaction are still at the beginning. Dynamic considerations and kinetic modeling as developed by our group [19] could help to obtain a better insight.

## Kinetic strategies: Two Viewpoints

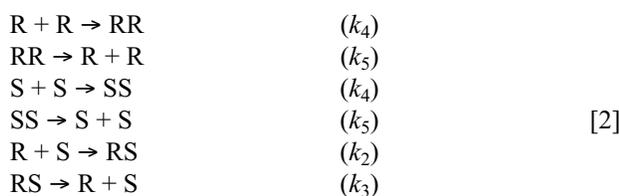
Up to now, two different main kinetic strategies for gathering mechanistic information of Soai's reaction have been employed: 1. An analytical approach [20-22] derived from Kagan's instructive description of the ML<sub>2</sub> system that requires a number of simplifications in order to remain mathematically tractable and 2. A numerical approach [23, 24] avoiding *ad hoc* assumptions or approximations but loaded with a larger number of variables and parameters. Both strategies were based on available experimental information.

As an analogue to Noyori's system and recently verified by NMR studies [25], the Soai reaction exhibits the formation of isopropylzinc alkoxide dimers (Scheme 3) that presumably play an essential role in the amplification dynamics. Hence as a fundamental requirement for any kinetic modeling the formation of dimers or oligomers has to be considered.



**Scheme 3.** Dimerization equilibria of the type  $R + R \rightleftharpoons RR$ ,  $S + S \rightleftharpoons SS$ , and  $R + S \rightleftharpoons RS$  giving rise to the formation of diastereomeric homochiral and heterochiral dimer species in the Soai reaction (note that  $RS = SR$ ). The  $[Zn-O]_2$  ring structure has been predicted as the most stable configuration (ref. 24).

Accordingly, dimers are taken into account in the analytical approach but no explicit mention of the role of the monomers is made. This is because only dimers but not monomers are considered as catalytically active species. As a consequence, this simplification suggests that dimer formation occurs instantly and that an expected uncatalyzed product formation *via* involvement of the monomers remains kinetically insignificant throughout the reaction. Considering the dimerization equilibria:



the following parameters are used in the ML<sub>2</sub> model:

$$\begin{array}{ll} \beta = \text{RS}/(\text{RR} + \text{SS}) & [3] \\ g = k_{\text{RS}}/k_{\text{RR}} & [4] \end{array}$$

where  $\beta$  represents the relative amounts of the dimers and  $k_{\text{RS}}$  and  $k_{\text{RR}}$  the rate constants of the catalyzed formation of the R and S products according to:

$$\begin{array}{ll} d\text{R}/dt = k_{\text{RR}} \text{RR} + 0.5 k_{\text{RS}} \text{RS} & [5a] \\ d\text{S}/dt = k_{\text{RR}} \text{SS} + 0.5 k_{\text{RS}} \text{RS} & [5b] \end{array}$$

The ee is calculated from the above rates of formation as follows:

$$ee = [\text{RR} - \text{SS}]/[\text{RR} + \text{SS} + (k_{\text{RS}}/k_{\text{RR}}) \text{RS}] \quad [6]$$

Introducing  $\beta$  and  $g$  results in:

$$ee = \{[\text{RR} - \text{SS}]/[\text{RR} + \text{SS} + \text{RS}]\} [(1+\beta)/(1+g\beta)] \quad [7]$$

where the first factor  $\{[\text{RR} - \text{SS}]/[\text{RR} + \text{SS} + \text{RS}]\}$  is associated to the ee(aux), i.e. to the ee of the initial catalyst so that

$$ee(\text{product}) = ee_0 \times ee(\text{aux}) \times [(1+\beta)/(1+g\beta)] \quad [8]$$

where  $ee_0$  is the maximum value reached when using an enantiopure catalyst. By considering only dimers, i.e. neglecting the presence of monomers, the following equilibrium constants appear:

$$\text{RR}/\text{R} \times \text{R} = \text{SS}/\text{S} \times \text{S} = k_4/k_5 = K_{\text{HOMO}} \quad [9a]$$

$$\text{RS}/\text{R} \times \text{S} = k_2/k_3 = K_{\text{HETERO}} \quad [9b]$$

where we arrive at:

$$K = \text{RS}^2/\text{RR} \times \text{SS} = (K_{\text{HETERO}}/K_{\text{HOMO}})^2 \quad [10]$$

A relationship between  $\beta$  and  $ee_{\text{aux}}$  is related to the  $\text{RR} + \text{SS} \rightleftharpoons 2\text{RS}$  equilibrium:

$$\beta = \{-m + \text{SQRT}[-4m + K(4+m)]\}/(4+m) \quad [11]$$

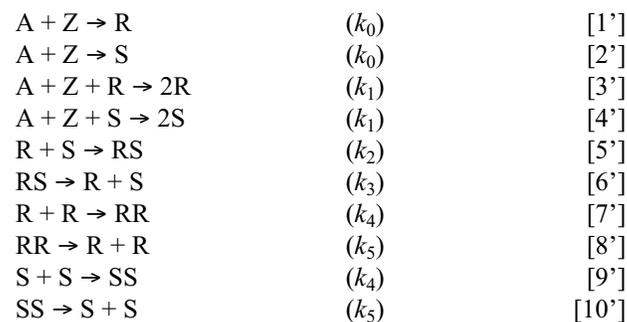
with  $m = K \times ee_{\text{aux}}^2$ . A comparison of the  $\beta$  values calculated by numerical integration of the  $k_4/k_5$  and  $k_2/k_3$  equilibria *versus* those obtained by eq. 11 is given in Table I.

**Table 1.** Comparison of the dimer ratio  $\beta$  calculated by numerical integration and obtained by eq. [11] (in brackets).

| $ee_{\text{aux}} \downarrow K \rightarrow$ | 0.25          | 1             | 4             |
|--|---------------|---------------|---------------|
| 0.99                                       | 0.009 (0.007) | 0.10 (0.09)   | 0.1 (0.1)     |
| 0.50                                       | 0.200 (0.193) | 0.365 (0.355) | 0.600 (0.600) |
| 0.01                                       | 0.250 (0.250) | 0.500 (0.500) | 1.000 (1.000) |

It is indicated that differences between the analytical and the numerical approach are apparent and can become substantial if the  $ee_{\text{aux}}$  is large and the value of  $K$  is small. Note that these differences already appear only by considering the set of equilibria as given by eq. 2, i.e. still not including the chemical conversion of reactants to products.

The numerical approach is based on a set of differential equations coming from a series of elementary reactions that represent the best guess of a possible reaction mechanism. One possible "best guess" for Soai's system could be the kinetic model as follows:



where A = pyrimidine carbaldehyde, Z = diisopropylzinc, R or S = enantiomeric zinc alkoxide, RR or SS = homochiral zinc alkoxide dimers, and RS = heterochiral zinc alkoxide dimer.

Considering available experimental information, such as the presence of two reactants, the observation of autocatalytic kinetics, and the formation of dimers, the above model can be considered as a minimal scheme consisting of foremost chemically realistic steps. Model steps [1'] and [2'] describe the uncatalyzed direct formation of the S and R products. Such consideration is necessary because some experiments were started only with A and Z and – nevertheless – generated significant ee [3-5]. The autocatalytic steps [3'] and [4'] are

given as termolecular reactions. Obviously, a termolecular notation remains unlikely from the chemical viewpoint but it reflects the lack of knowledge and experimental information of this key process. Steps [5'] to [10'] denote the dimerization equilibria where the mutual inhibition is expressed by step [5'] in the form of a reversible reaction. Hence in contrast to the Frank model [16] mutual inhibition is part of a dynamic process that depends on the concentrations of R, S and RS as well on the rate constants  $k_2$  and  $k_3$ .

In contrast to the analytical approach, many more parameters and variables are involved in the above model but – in turn – no *a priori* approximations have been imposed, i.e. all possible species are considered, the equilibria can be slow or fast, and the uncatalyzed direct formation of the products is taken into account. The strategy of kinetic modeling is less focused on the extraction of rate parameter values and instead on the exploration of the dynamics of the system. Usually a qualitative reproduction of experimental data followed by a quantitative one gives support for the model chosen or – in the case of divergence – it undermines the choice and requires a different model. Once quantitative agreement with the experiment is established, the model system can be examined for the sensitive processes and parameters that govern the dynamics and predictions for future experiments can be established.

### The numerical approach: How does it perform for the Soai reaction?

Model system [1'] to [10'] translates into the following set of differential equations:

$$dA/dt = -2k_0 AZ - k_1 AZ(R+S) \quad [12]$$

$$dZ/dt = -2k_0 AZ - k_1 AZ(R+S)$$

[13]

$$dR/dt = k_0 AZ + k_1 AZR - k_2 RS + k_3 (RS) + 2k_5 (RR) - 2k_4 RR \quad [14]$$

$$dS/dt = k_0 AZ + k_1 AZR - k_2 RS + k_3 (RS) + 2k_5 (SS) - 2k_4 SS \quad [15]$$

$$d(RS)/dt = k_2 RS - k_3 (RS) \quad [16]$$

$$d(RR)/dt = -k_5 (RR) + k_4 RR \quad [17]$$

$$d(SS)/dt = -k_5 (SS) + k_4 SS \quad [18]$$

where two mass-balance relations can be identified:

$$dA + dR + dS + d(RR) + d(SS) + d(RS) = 0 \text{ and} \quad [19]$$

$$dA = dZ \quad [20]$$

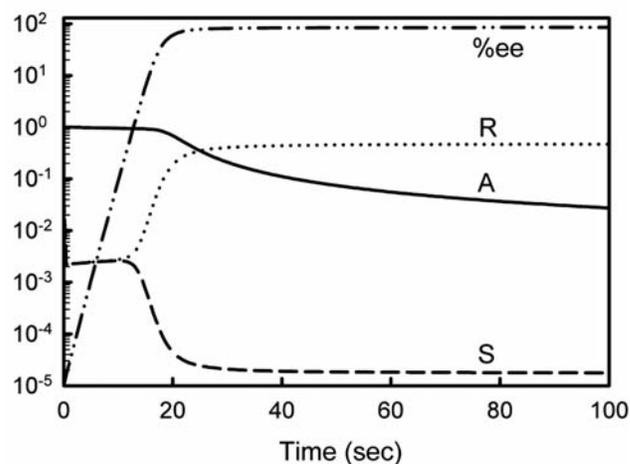
rendering the model into a 5-variable system.

As shown in Fig. 1, with the above set of rate equations the experimentally observed chiral amplification from extremely low initial values to very high final ee can be readily reproduced. However, in order to observe such amplification, two important restrictions apply for the choice of the rate parameter values that also gives closer insight into the mechanistic properties of Soai's reaction:

- The rate constant  $k_0$  has to be adequately small. For instance, chiral amplification as shown in Fig. 1 does not occur if  $k_0 \geq 0.2 \text{ M}^{-1}\text{s}^{-1}$ . It is obvious that if the chirally unspecific process  $A + Z \rightarrow R$  or  $S$  proceeds too fast it generates a high amount of racemic matter that 'inundates' the amplification process displayed by the autocatalytic steps and the mutual inhibition.
- More important, the mutual inhibition rate constant  $k_2$  ( $R + S \rightarrow RS$ ) must be higher than  $k_4$  ( $R + R \rightarrow RR$  or  $S + S \rightarrow SS$ ), i.e. the heterodimerization has to occur faster as the homodimerization. Moreover, taking into account the equilibrium constants  $K_{\text{HETERO}} = k_2/k_3$  and  $K_{\text{HOMO}} = k_4/k_5$ , it is essential that  $K_{\text{HETERO}} > K_{\text{HOMO}}$ , i.e. the heterochiral dimer has to be thermodynamically more stable than its homochiral counterpart. This is in agreement with semi-empirical energy calculations of the RS and RR or SS dimers [24].

Still more intriguing as the capability of huge chiral amplification in Soai's reaction is the experimental observation of spontaneous generation of ee from entirely achiral starting conditions. In fact, this discovery is fundamental since it incorporates all studies of amplification into one experiment. It appears that Soai's reaction displays highest sensitivity so that even no starting catalyst is needed to yield considerable ee. The systems already responds to statistical imbalances of racemates.

The first chiral material generated under such achiral starting conditions can only originate from the unspecific process  $A + Z \rightarrow R$  or  $S$ , i.e. has to be considered as racemic. However, a closer look reveals that no racemate can be ideally racemic, i.e. there is always a slight statistical deviation from the racemic state that is inversely proportional to the square root of the number of chiral molecules involved [26]. This is

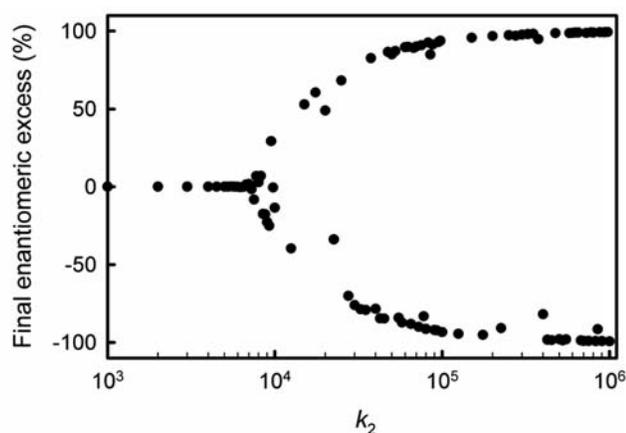


**Fig. 1.** Time evolution of A, R, S and the corresponding ee (log scale) by kinetic model [1'] to [10'] where an ee(initial) of  $10^{-5}$  % is amplified to about 85%. Note the branching of R and S after about 10 sec reaction time. Initial conditions (arbitrarily chosen):  $[A]_0 = [Z]_0 = 1\text{M}$ ,  $[R]_0 + [S]_0 = 0.1\text{M}$ ;  $k_0 = 10^{-6} \text{ M}^{-1}\text{s}^{-1}$ ,  $k_1 = 1 \text{ M}^{-2}\text{s}^{-1}$ ,  $k_2 = 10^5 \text{ M}^{-1}\text{s}^{-1}$ ,  $k_3 = 10 \text{ s}^{-1}$ ,  $k_4 = 10 \text{ M}^{-1}\text{s}^{-1}$ , and  $k_5 = 10 \text{ s}^{-1}$ .

the starting point where two possible scenarios arise: 1. We run a “classical” chemical reaction or consider a system at equilibrium in which the deviation remains at a minute level representing nothing more than an undirected chiral noise around a stable racemic state. In this case there is no measurable impact on the outcome of the process or 2. The system is nonlinear, equipped with an appropriate feedback mechanism and sufficiently far from equilibrium so that randomly generated tiny ee – no matter how small – can be amplified to a macroscopic level. In this case, the system is driven from an unstable racemic state to an optically active one.

Obviously, the second case applies for Soai's reaction. Consequently, mirror-symmetry breaking includes chiral amplification as already described further above but also requires an additional dynamic condition rendering the racemic state unstable. Hence amplification and mirror-symmetry breaking are strongly related phenomena but amplification of ee can take place in a different parameter range as mirror-symmetry breaking in such way that amplification always occurs where there is also symmetry breaking but not necessarily the other way round.

Fig. 2 shows that with the rate equations [12] to [18] mirror-symmetry breaking is observed even in our simulations. At the first glance, this result is surprising because numerical simulations are deterministic and if started under symmetric (achiral) initial conditions a symmetric (racemic) result should be expected. However, fluctuations do not occur only in the laboratory case but also in the form of inevitable rounding errors in numerical computations. Normally, these errors remain insignificant and level out readily. This again can be greatly different in a nonlinear system where fluctuations are amplified like it is the case in the real Soai reaction as well as in our computer simulations. Surpassing a critical value of  $k_2$  of around  $6 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$ , each computer simulation – started



**Fig. 2.** Mirror-symmetry breaking reproduced by kinetic model [1'] to [10'] in which  $k_2$  acts as a bifurcation parameter (same conditions as in Fig. 1 except  $[R]_0 + [S]_0 = 0$ ). Each mark represents the result of one computer simulation. Note that for  $k_2 > 6 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$  the system becomes optically active and that the positive and negative values of the resulting ee are equally distributed.

under completely achiral conditions – afforded an optically active result. Analogous to the laboratory experiments, the chirality sign (positive or negative ee) remained unpredictable for each individual simulation but resulted equally distributed over the total of experiments. Despite this unpredictability each computational run with the same initial conditions and internal calculation parameters was perfectly reproducible.

As indicated by the reproduction of selected experimental key observations of Soai's reaction, the proposed model and the numerical method on which it is based demonstrate their reliability. This becomes apparent for the case of mirror-symmetry breaking that has not been described by any variation of the  $\text{ML}_2$  model.

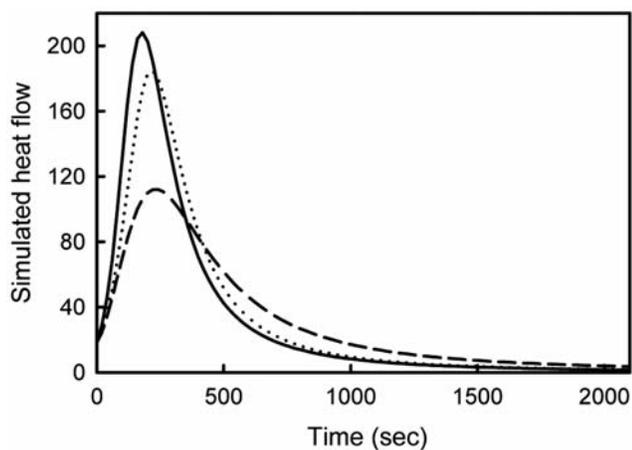
### Monomers vs. Oligomers: Some Controversy

In the framework of the analytical approach, Blackmond and co-workers [20] proposed the following autocatalytic rate law for the Soai reaction:

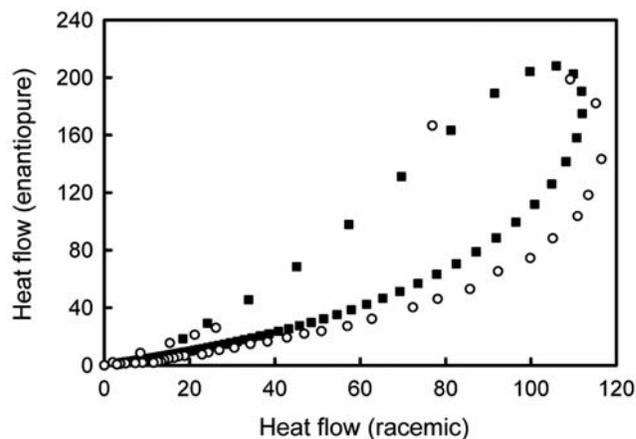
$$\text{rate} = k[1][Z][2](1 + g\beta)/(1 + \beta) \quad [21]$$

where 1 stands for the aldehyde and 2 for the total reaction product. Expression [21] refers to a dimer catalyzed reaction network that has been deduced from experimental observations. Microcalorimetric studies [20] revealed that the reaction rate depends on the enantiomeric purity of the initially added catalyst where the rate becomes roughly half when a racemic instead of an enantiomerically pure catalyst was used while both normalized rates as a function of the fraction conversion matched. It was reasoned that if the catalyst would be monomeric, asymmetric amplification required higher stability of the heterodimer against the homodimer  $K_{\text{HETERO}} > 2K_{\text{HOMO}}$ . On the other hand, it is argued that the rate catalyzed by the enantiopure catalyst can be only twice of the rate catalyzed by the racemic catalyst if  $K_{\text{HETERO}} = 2K_{\text{HOMO}}$ , i.e. if both dimers exhibit the same stability. In turn, same stabilities of homo- and heterochiral dimers exclude the occurrence of chiral amplification because of too weak mutual inhibition as already mentioned above. According to the authors, this paradox could be only explained if the catalyst was dimeric or higher oligomeric [20, 21].

Nevertheless, it appears that a straightforward discrimination between monomer and dimer catalysis requires further investigation. As shown in Fig. 3a, our model [1'] - [10'] can qualitative reproduce the effect of the catalyst enantiomeric purity on the reaction rate without the need to consider dimers as the catalytic species, i.e. the above stated paradox simply vanishes by considering a kinetic model that is – compared to the modified  $\text{ML}_2$  expression [21] – less loaded with *ad-hoc* assumptions. Fig. 3a shows a reproduction of the experimental heat flows by assuming that the consumption of A is the only exothermic process, i.e. the simulated heat flows have been taken proportional to eq. [12]. Good agreement with experimental data is achieved by considering initially 1 mol % of



**Fig. 3a.** Simulation of reaction heat flows vs. time by kinetic model [1'] to [10'] similar to experimental observations by micro-calorimetry (ref. 20); ee(initial): 100% (solid line), 43% (dotted line), 0% (dashed line). Initial conditions:  $[A]_0 = [Z]_0 = 0.2\text{M}$ ,  $[R]_0 + [S]_0 = 0.002\text{M}$ ;  $k_0 = 6.8 \times 10^{-8} \text{M}^{-1}\text{s}^{-1}$ ,  $k_1 = 6.3 \times 10^{-1} \text{M}^{-2}\text{s}^{-1}$ ,  $k_2 = 2.2 \times 10^3 \text{M}^{-1}\text{s}^{-1}$ ,  $k_3 = 18 \text{s}^{-1}$ ,  $k_4 = 3.0 \times 10^2 \text{M}^{-1}\text{s}^{-1}$ , and  $k_5 = 77 \text{s}^{-1}$ .



**Figure 3b.** Heat flows in the presence of enantiopure vs. racemic initial catalyst showing roughly a 2:1 relation. Filled squares: simulation (same conditions as in Fig. 3a); open circles: experiment as taken from ref. 20.

total catalyst although experiments have been performed with 10 mol %. This discrepancy may originate from the conversion of reaction heat flows to concentration based data as used in our modeling that requires further verification.

In contrast to the authors' report about a "constant rate ratio of 0.5 for racemic versus enantiopure catalysts" [20], the experimental points in Fig. 3b disclose that this correlation remains rather approximate but, nonetheless, can be reproduced by model [1'] - [10'], i.e. the model responds even fairly well to this deviation from the 0.5 ratio giving rise to the experimentally observed curvature.

Concerning the proposed equal stabilities of heterochiral and homochiral dimers, our modeling showed [24] that neither monomer catalysis nor dimer catalysis can give rise to mirror-symmetry breaking under such condition. Hence arguments supporting the dimer hypothesis have to be viewed more cautiously. In resume, and for the time being, dimer catalysis can not be excluded but neither can a monomeric catalytic network.

## Conclusion

Kinetic modeling confirms that chiral amplification and mirror-symmetry breaking in the Soai reaction are driven by a reaction network that contains enantioselective autocatalysis and mutual inhibition as the essential ingredients. In this sense, Soai's reaction forwards the early concepts of Frank [16] into the reality of today's laboratory [27]. Taking into account the formation of isopropylzinc alkoxide dimers, an evaluation of the parameter space in which amplification and symmetry-breaking are observed indicates that the heterochiral dimers display a higher thermodynamic stability and have

to formed faster than the homochiral ones, i.e. thermodynamics and kinetics play a symbiotic and essential role in these phenomena. The necessity of such delicate interplay may explain why reactions like Soai's type are so scarce.

Although our kinetic modeling reproduces well amplification effects when the reaction is started with an ee of the reaction product itself (the chiral isopropylzinc alkoxide or pyrimidyl alkanol), it is still completely undecided how to explain a number of astonishing effects when various chiral initiators other than the reaction product were used. In particular, amino acids, epoxides, helicenes, circularly polarized light, even enantiomorphous crystals such as quartz or solid  $\text{NaClO}_3$  and many more chiral factors have been shown [28] to induce high selectivity although used in catalytic amounts with small ee.

In fact, the combined studies of kinetic and structural aspects become more and more important in order to shed light on the catalytic processing of Soai's reaction, i.e. on processes [3'] and [4'] that have been tentatively designated as termolecular processes in our model. Regardless of the surprising variety of possible chiral initiators, a first hint is given: it has been observed that there was no chiral amplification observed with ferrocenyl or 3-pyridyl carbaldehydes [29], while the amplification effects increased from 3-quinolyl to 5-pyrimidinyl and 2-methylpyrimidinyl to 2-alkynyl-5-pyrimidinyl carbaldehydes [30]. Mirror-symmetry breaking has been reported so far with the largest alkynyl aldehydes. Also the influence of solvent effects and product precipitation has been discussed [31].

Allowing first insight into the structural aspects, recent NMR studies indicate that additional equilibria between the dimer species and a further diisopropylzinc molecule have to be considered yielding *RR-Z*, *SS-Z*, and *RS-Z* association complexes [25]. These studies combined with further kinetic

experiments will have to decide about the closer reaction network in Soai's reaction as well as about the catalytic action of monomer or dimer species. Furthermore, obtaining better knowledge about the catalytic mechanism of Soai's reaction could efficiently nourish the discussion about the origin of biomolecular homochirality by focusing the search on prebiotically more plausible systems with clearer defined properties.

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