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Empirical Description of Chiral Autocatalysis

Károly Micskei,*,[†] György Póta,[‡] Luciano Caglioti,[§] and Gyula Pályi[||]

Department of Inorganic and Analytical Chemistry, Faculty of Natural Sciences, University of Debrecen,
4010 Debrecen, Egyetem tér 1, P.O. Box 21, Hungary, Department of Physical Chemistry,
University of Debrecen, Egyetem tér 1, H-4010 Debrecen, P.O. Box 7, Hungary,
Department of Chemistry and Technology of Biologically Active Compounds,
University "La Sapienza" Roma, Ple. Moro 5, I-00185 Roma, Italy, and
Department of Chemistry, University of Modena and Reggio Emilia, Via Campi 183,
I-41100 Modena, Italy

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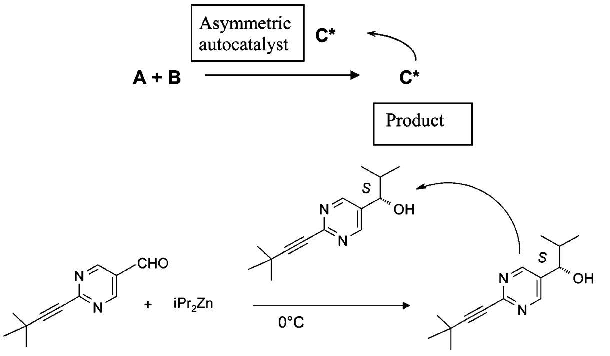
The only known example of chiral autocatalysis is the alkylation of N-heterocyclic aldehydes with $i\mathrm{Pr_2Zn}$ (Soai reaction). The mechanism and some details of this reaction are not yet clear. An empirical formula is proposed here for the description of this chiral autocatalytic reaction. This formula allows the calculation of some very informative parameters.

Chiral autocatalysis is a reaction where a chiral product formed from achiral precursors catalyzes its own formation, and at the same time, it also amplifies its own chirality (enantiomeric excess) in the product. Actually, the only well-documented reaction type known, which corresponds to these conditions, is the alkylation of N-heterocyclic aldehydes by diisopropyl zinc (the Soai reaction, Scheme 1)[1]. In the past decade, Soai's group succeeded in finding extremely sensitive variants of this reaction. These enable the autocatalytic amplification of a very low (down to 10^{-5}%) enantiomeric excess of the product.[2] Finally, they were able to produce the first clearly documented example[3] of absolute enantioselective synthesis (enantiopure chiral product from achiral precursors, without any chiral additive or asymmetric physical field[4]). These landmark results would naturally require the exact knowledge of the reaction mechanism, which could help in attempts at generalization of the principle of chiral autocatalysis.

Numerous efforts have beem published in the past few years aiming at the identification of the molecular events constituting the mechanism of this unusual and important reaction. These efforts used conventional kinetic methods (product analysis),[5] NMR spectroscopy,[6] microcalorimetry,[5b,f] and statistical formalism,[4,7] as well as a deduction on the basis of the single-molecule chirality principle,[8] supported by MO calculations.[9] Some important details were revealed, but it appears that there are too many equilibrium and kinetic parameters to follow.

In light of these difficulties, we tested another approach for the quantitative description of the Soai autocatalysis: This is to find a reasonable and possibly simple empirical formula for some quantitative purposes. We report here on our first results in this respect.

SCHEME 1



To find a very simple quantitative description of the Soai autocatalysis, we set up as a first approximation (neglecting the time dependence), the differential eq 1, where only the bimolecular dependence of the kinetics on the autocatalyst concentration was taken into consideration, since this is perhaps the best documented quantitative feature of the chiral autocatalysis[5]

$$\frac{\mathrm{d(ee_{prod})}}{\mathrm{d(ee_{start})}} = \left(\frac{B}{\mathrm{ee_{max}}}\right)\left(\frac{\mathrm{ee_{prod}}}{\mathrm{ee_{start}}}\right)^2 \qquad (1)$$

where $\mathrm{ee_{prod}}$ is the enantiomeric excess of the product in the individual reaction cycle (%); $\mathrm{ee_{max}}$ is the calculated maximum enantiomeric excess achieved in the given system (%); $\mathrm{ee_{start}}$ is the starting enantiomeric excess of the product at the beginning of the reaction (%); ee (as usual) = $R/(R + S) \times 100$ or $S/(R + S) \times 100$, where R and S are the molar quantities of the R and S enantiomers formed in the reaction; and B is a constant.

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* E-mail: kmicskei@delfin.unideb.hu (K.M.), palyi@unimo.it (G.P.).
[†] Department of Inorganic and Analytical Chemistry, Faculty of Natural Sciences, University of Debrecen.
[‡] Department of Physical Chemistry, University of Debrecen.
[§] University "La Sapienza" Roma.
[||] University of Modena and Reggio Emilia.

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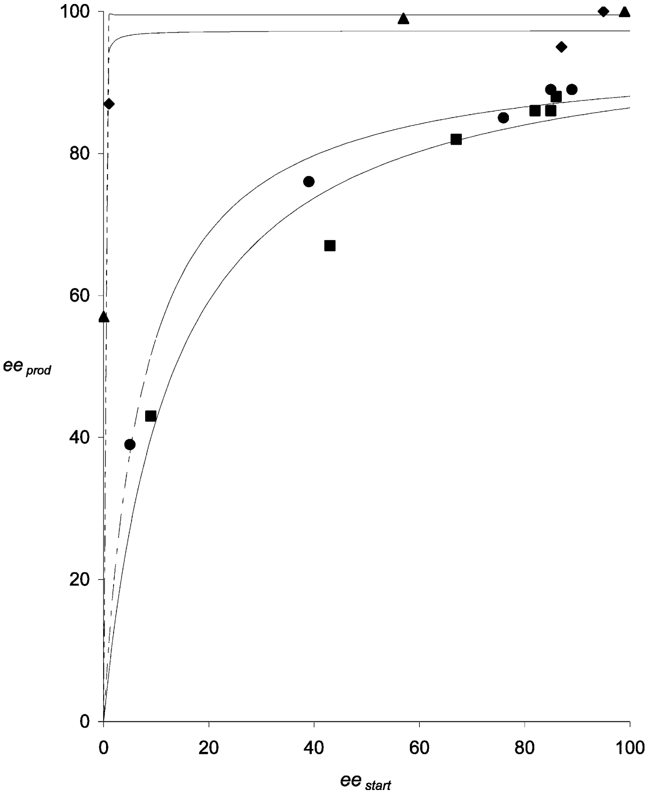


Figure 1. Evolution of the product enantiomeric excesses during chiral autocatalysis according to eq 1 and experimental data (—■—;[1b] -·-●-·—;[1a] -··-◆-··—;[1c] ··▲···[2]).

This equation can be solved through the steps in eqs 2−4

$$\frac{\mathrm{d}(\mathrm{ee}_{\mathrm{prod}})}{(\mathrm{ee}_{\mathrm{prod}})^2}\,\mathrm{ee}_{\mathrm{max}} = \frac{B}{(\mathrm{ee}_{\mathrm{start}})^2}\,\mathrm{d}(\mathrm{ee}_{\mathrm{start}}) \tag{2}$$

and after integration

$$\frac{\mathrm{ee}_{\mathrm{max}}}{\mathrm{ee}_{\mathrm{prod}}} = \frac{B}{\mathrm{ee}_{\mathrm{start}}} + C \tag{3}$$

where C is an integration constant.

Equation 3 can be rearranged as

$$\mathrm{ee}_{\mathrm{prod}} = \frac{1}{C}\,\mathrm{ee}_{\mathrm{max}}\,\frac{\mathrm{ee}_{\mathrm{start}}}{B/C + \mathrm{ee}_{\mathrm{start}}} \tag{4}$$

Equation 4 can be simplified by supposing $C = 1$, and thus

$$\mathrm{ee}_{\mathrm{prod}} = \mathrm{ee}_{\mathrm{max}}\,\frac{\mathrm{ee}_{\mathrm{start}}}{B + \mathrm{ee}_{\mathrm{start}}} \tag{5}$$

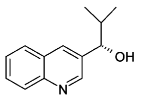
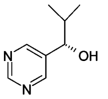
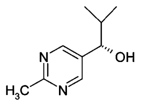
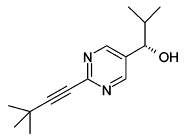
can be obtained.

This expression, eq 5, shows an (at least formal) analogy with the Michaelis−Menten equation[10] of enzyme catalysis. This challenging aspect merits some more detailed analysis, which is beyond the scope of the present paper.

Equation 5 reflects sensitively the experimental values of the enantiomeric excesses measured in the aldehyde plus $i\mathrm{Pr}_2\mathrm{Zn}$ chiral autocatalytic reaction. A few examples of $\mathrm{ee}_{\mathrm{prod}}$ vs $\mathrm{ee}_{\mathrm{start}}$ plots for less, moderately, and very sensitive systems are shown in Figure 1.

The parameter B in eq 5 appears to be indicative of the sensitivity of the actual system. We calculated B for some variants of the Soai reaction. The results are shown collectively in Table 1. The wide range of variation of this parameter supports that B not a kind of “substituent constant” (not even on a logarithmic scale), but it may reflect some important changes in the mechanism. Such changes could be due, for example, to the change in the coordination mode of the substrate to the metal (Zn) in that decisive phase where the “fate” of the newly generated stereocenter is decided. In this aspect, the analysis of B with more models can be helpful in the elucidation of the structures of intermediates and/or transition-state complexes of the reaction.

TABLE 1

Entry	Product	ee_{max}	B	Reference
1		98 (5)	13 (3)	1b
2		95 (2) 97 (5)*	8 (1) 9 (2)*	1a
3		97 (2)	3.3 (0.1) 10^{-2}	1c
4		99 (1) 97 (2)*	3.7 (0.1) 10^{-5} 5.8 (0.8) 10^{-5*}	2

In the simplified form (eq 5), our empirical formula indicates B as the inflection point of the course of the chiral autocatalysis, that is, the ee value when the reaction reaches one-half of $\mathrm{ee}_{\mathrm{max}}$. In this case, B can be regarded as indicative of the rate of the formation of the chiral autocatalyst and of its further transformation.

Another interesting application of eq 5 is the possibility that emerges if B has already been determined by “calibration” (known ee of the product); the $\mathrm{ee}_{\mathrm{start}}$ values can be calculated from the outcome of preparative experiments with unknown $\mathrm{ee}_{\mathrm{start}}$ values. This possibility is of particular importance in the analysis of the data set obtained under conditions of an “absolute enantioselective synthesis” (experiments without a chiral additive or asymmetric physical field(s))[3].

The results of these calculations (see Figure 2) have two important consequences: (i) The distribution of the points shows that the outcomes of the experiments are compatible with initial enantiomeric excesses derived from statistical fluctuations.[7] (ii) The range of the calculated $\mathrm{ee}_{\mathrm{start}}$ values ($\sim 10^{-10}-10^{-12}$%) is

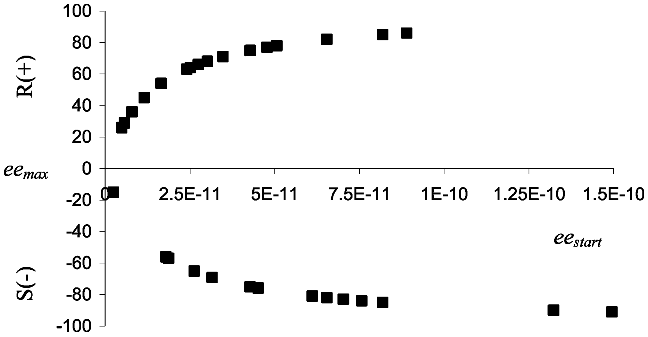


Figure 2. Correlation of the final and starting enantiomeric excesses in absolute enantioselective synthesis by the Soai reaction.[3b]

fairly reasonable from a statistical viewpoint; such fluctuations can be expected with high probability, while for the 10^{-4} molar quantity of the aldehyde used by the Soai group in the first run, the ee_{start} value which could be expected with a probability of $\geq 50\%$ is $8.70 \times 10^{-9}\%$ according to the Mills formula;[7a] consequently, the much lower ee_{start} values obtained by eq 5 seem to be fairly realistic.

It is worth noting that the "deterministic" enantiomeric excesses approximately expected on the basis of the systematic asymmetry of weak nuclear forces[11] are in the range which could have been detected by the most sensitive variant of the Soai reaction (Figure 2.). Whether this systematic influence is detectable in the presence of statistical fluctuations, which are a few orders of magnitude larger, could be decided only on the basis of much more experimental data than presently available.

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