Chirality of the Very First Molecule in Absolute Enantioselective Synthesis

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Abstract

In the present paper the role of the very first chiral molecule formed in achiral-to-chiral reactions, is discussed. This molecule represents obligatorily 100 % *ee*, with important consequences for absolute enantioselective synthesis. Calculations show that Soai-type autocatalytic reactions could amplify even one molecule initial enantiomeric excess to high *ee* under reasonable conditions, which enables also an experimental control.

Introduction

Chirality, a feature of molecular geometry, in general, as well as enantioselective autocatalysis, in particular, are frontier issues of chemistry.[1-6] The origin of (molecular) chirality in living organisms (biological chirality) is also a first grade challenge since a long time.[7] It is generally accepted, that asymmetry can be generated only by (physical or molecular) asymmetry. Several hypotheses were proposed, how enantiopure chiral substances could be formed without asymmetric influence. These include stochastic fluctuations,[8-13] amplified by autocatalytic mechanisms[14] to high enantiomeric purity. Such chiral autocatalytic reactions[14] were experimentally demonstrated recently.[15,16] Our groups found an empirical approach[13] fairly useful in understanding some features of these reactions.

We would like to point out here an obvious, but rarely (if ever?) mentioned aspect of chirality: the role of the very first chiral molecule formed from achiral precursors, which is now highly actual also in the light of recent important developments in single molecule chemistry.[17]

If a chiral molecule is prepared from achiral precursor(s), the very first molecule formed in this transformation will necessarily represent 100% enantiomeric excess, until this species is alone. This fact can be regarded as an **axiom** ("primary" statement, which needs no proof) of preparative stereochemistry.

The quantitative "enantioselectivity" of the first chiral molecule is not exceptional, but it is a general feature of all achiral-to-chiral transitions. Even more, if the first chiral molecule disappears from the system by a (fast) secondary reaction, then all molecules could become "first", with obvious effects for preparative consequences. Some of these are as follows:

- First, in the absence of chiral additives and/or asymmetric physical fields, the synthesis of the first chiral molecule (from achiral precursor(s)), in any such reaction, corresponds to the most rigorous criteria of absolute asymmetric synthesis;[12]
- Second, under these conditions, however, the sense of chirality (R or S, L or D) of this first molecule can not be predicted;
- Third, the above statement is limited to the case where (and until) the first molecule alone "dominates" the system with its 100 % *ee*;
- Fourth, in the absence of chiral additive and/or asymmetric fields, the sense of chirality of a second molecule (in the same system) can not be predicted too, if its formation is independent of the first molecule. Consequently, at this point the system bifurcates. If the 2nd, 3rd, 4th, etc. molecules are formed independently from the first one (and from each other), statistics "awakes" and the system can be described in terms of probability.[8-11, 18] If, on the other hand, the chirality of the first molecule predisposes the preferential formation of one of the two enantiomers (especially if it does so by a reaction rate exceeding the rate of its own formation) a true chiral autocatalysis can develop. Asymmetric autocatalysis has been the goal of several research efforts, however, only one well-documented example has been reported yet: the alkylation of N-heterocyclic aldehydes by zink dialkyls.[15, 16, 19]

The fate of the very first chiral molecule could take an additional, important turn: it could react with another chiral (or prochiral) molecule, e.g. the first molecule of an amino acid ($RCH(NH_2)COOH$) could react with a carbohydrate (already chiral) or with a glycerol-2-monoester or -2-monoether (prochiral). This reaction would necessarily lead to (potential) diastereomeric products, which are no more subjected to the law of equal probabilities. Both the autocatalytic amplification of the very first molecule or its transformation to diastereomeric products could

have been those early event(s) which was(were) operative at the origin of biological chirality.

The formation of chiral crystals from achiral molecules is similar to chiral (chemical) autocatalysis. In fact, in these experiments[20] the influence of the first chiral (crystal) nuclei can lead to a similar chiral takeover in the whole sample, as the first chiral molecule can do in autocatalysis. Similarly, the observed high enantioselectivity of chain propagation in polymerization or polycondensation reactions[21] can also be related to the influence of the first molecule in the chain.

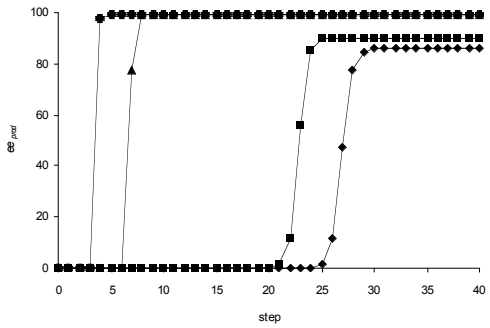

Figure 1. Step-by-step evolution of enantiomeric excess in consecutive autocatalytic cycles with *one molecule* as starting enantiomeric excess (ee_{start} = 1.66 10^{-22} %) in Soai-systems of different sensitivity (ee_{max},%-*B* respectively: 99-3.7 10^{-5} –•–; 97-3.3 10^{-2} –▲–; 97-9 –■–; 98-13 –◆–).

Model Calculations

We tested the compatibility of the above argumentation with chemical reality using a recently deduced empirical formula for the description of chiral autocatalysis[13]:

$$ee_{prod} = ee_{max} \frac{ee_{start}}{B + ee_{start}} \qquad (1)$$

where

ee_{prod} – is the enantiomeric excess of the product in the individual reaction cycle (%);

ee_{max} – is the maximum enantiomeric excess achieved in the given system (%);

ee_{start} – is the starting enantiomeric excess of the product at the beginning of an individual cycle, which is defined for the first reaction cycle as added quantity of the product prior to the start of the reaction with respect to the substrate (mole-%);

ee – (as usual) = *(R-S)*/(*R*+*S*) 100 or *(S-R)*/(*R*+*S*) 100, where *R* and *S* are the molar quantities of the *R* and *S* enantiomers formed in the reaction (%);

B – constant.

In consecutive autocatalytic cycles, this formula allows to calculate the evolution of *ee* during the whole operation as a function of the number of autocatalytic "steps". Figure 1 shows the results for different Soai-systems, with one molecule initial *ee*.

The "absolute" variant of the most sensitive Soai-reaction reaches after three cycles near-quantitative enantioselectivity.[15,16] The diagrams in Figure 1 indicate, that similar *ee*-s can be obtained by more reaction cycles even with the less sensitive variants, with **one molecule initial excess**. For the second best system six and for the least sensitive reaction cca 25-27 cycles would be necessary to achieve high enantiomeric excess. These results have two important messages: First, the initial influence of the very first molecule at a realized chiral autocatalysis seems to provide plausible cycle numbers. Second, it can be expected, that there might be several chemical systems, which could be of chiral autocatalytic nature, only nobody has ever looked for these, while several (more than 3-5) repetitions of the catalytic cycle seemed to be senseless.

Formula (1) enables the definition of a hypothetical Soai-type system, where only **one molecule initial excess** leads to near-quantitative enantioselectivity in *one step*. The results are shown in Figure 2: such Soai-system should have a *B* constant of cca. 10^{-24}. This is orders of magnitude lower than the *B* value of the most sensitive Soai-system, but it does not seem impossible to reach it.

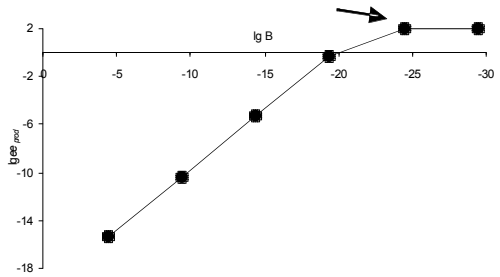

Figure 2. Dependence of ee_{prod} on *B* of the first cycle, with one molecule as starting enantiomeric excess for Soai-reactions of different sensitivity (arrow shows the hypothetic system which reaches 100% ee_{prod} in one step).

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