Description of the Condition for Asymmetric Amplification in Autocatalytic Reactions

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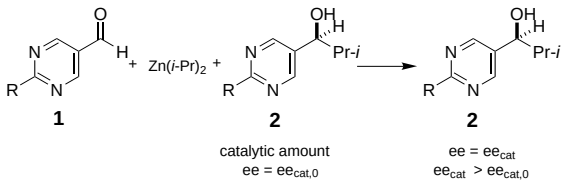
Abstract: Asymmetric amplification in autocatalytic reactions is only possible if a mechanism for suppression of production of the minor enantiomer is included in the kinetic model. Without inhibition, product (catalyst) ee will inexorably decrease over time. Reaction rate and enantioselectivity must be considered together in developing a kinetic model for rationalizing asymmetric amplification in autocatalytic reactions.

Keywords: asymmetric amplification; autocatalysis; kinetic modelling; reaction mechanisms.

Asymmetric autocatalysis accompanied by amplification of product enantioselectivity has been suggested as a mechanism for the evolution of homochirality of life on earth.[1] The remarkable discovery by Soai and coworkers that the alkylation of pyrimidyl aldehydes with *i*-Pr_2Zn using the corresponding alcohols as catalysts could lead to products of higher ee represented the first experimental demonstration of this concept (Scheme 1).[2]

We recently published a kinetic study of the Soai reaction of 2-methylpyrimidine-5-carbamaldehyde demonstrating that the reaction is catalyzed by dimer species which are formed without showing a disposition toward a more stable heterochiral dimer.[3] At about the same time, Soai's group published a kinetic analysis suggesting a different autocatalytic model and noting that they are continuing to investigate monomeric mechanisms for autocatalytic behaviour.[4]



Scheme 1.

While simple autocatalytic reactions are well known and kinetic rate laws for various mechanistic possibilities have been well-documented,[5] an asymmetric version offering an increase in catalyst ee over time requires a more sophisticated treatment. In order for amplification to be realized, an autocatalyst must not only be capable of reproducing itself, but it must also serve as an agent to effect suppression of production of its enantiomer. Inhibition in autocatalysis has been incorporated in models by Frank[1a] and by Bailey;[6] Kagan later presented a qualitative discussion of its importance to asymmetric amplification.[7] We provide here the first quantitative theoretical exposition that inhibition is indispensable to asymmetric amplification in autocatalysis. This derivation shows that the model invoked by Soai and coworkers cannot account for the amplification of ee observed in these reactions, and indeed that according to their model, enantioselectivity should decrease as the reaction proceeds.

Consider the case where a suppression mechanism is *absent* in an autocatalytic reaction, carried out in a batch reactor using a catalyst with initial concentration $[C_0]$ and an initial $ee = ee_{cat,0}$. For a given increment of conversion producing an increment of catalyst $\Delta[C]$, the total amount of new *R*-enantiomer formed is given by the sum of *R* formed by the *R*-catalyst and *R* formed by the *S*-catalyst. These fractions are dictated by the intrinsic enantioselectivity of the reaction, ee_{intr} [8] as shown in Equation (1). Analogous expressions may be written for the *S* fractions formed from each catalyst.

$$[R]_{new}\ (from\ R\text{-}catalyst) = \frac{[R]_{cat}}{([R]_{cat}+[S]_{cat})}\left(\frac{1+ee_{intr}}{2}\right)\Delta[C] \quad (1)$$

$$[R]_{new}\ (from\ S\text{-}catalyst) = \frac{[S]_{cat}}{([R]_{cat}+[S]_{cat})}\left(\frac{1-ee_{intr}}{2}\right)\Delta[C]$$

Therefore, the product formed in any conversion increment $\Delta[C]$ results in a catalyst ee is given by:

$$ee_{cat,new} = \frac{[R]_{\Delta[C]} - [S]_{\Delta[C]}}{[R]_{\Delta[C]} + [S]_{\Delta[C]}} = ee_{cat} ee_{intr} \quad (2)$$

Equation (2) reveals why a simple autocatalytic reaction cannot amplify initial catalyst enantiomeric excess over time. If the asymmetric catalyst performs with perfect selectivity ($ee_{intr} = 1$), the catalyst ee will be equal to $ee_{cat,0}$, maintaining but not amplifying ee. However, for any catalyst which does not effect a perfect asymmetric reaction ($ee_{intr} < 1$), the ee of the newly formed catalyst will be lower than the ee of the catalyst already present.

We may also calculate the ee of the catalyst mixture at any conversion during an autocatalytic reaction obeying Equation (2). This is determined by summing up the amount of catalyst present prior to, and that formed during, a conversion increment Δ[C]:

$$ee_{cat,total} = \frac{ee_{cat}([C] + ee_{intr}\Delta[C])}{[C] + \Delta[C]} \quad (3)$$

The change in ee_{cat} over a conversion interval from [C] to [C] + Δ[C] may be written as the difference between Equations (2) and (3). Taking the limit as Δ[C] approaches zero provides a differential equation for the change in ee_{cat} with [C]. Integrating this expression for a reaction which commences using a catalyst with $ee_{cat,0}$ at concentration $[C_0]$, forming a product with an intrinsic ee equal to ee_{intr}, allows us to describe the catalyst ee at the time when the catalyst concentration has risen to some value [C]:

$$ee_{cat}(t) = ee_{cat,0}\left(\frac{[C_0]}{[C(t)]}\right)^{(1-ee_{intr})} \quad (4)$$

For a reaction which goes to completion, the quantity ($[C_0]/[C]$) may be taken as the initial mole fraction of catalyst based on the catalyst and substrate concentrations employed at the outset of the reaction, x_{cat}, and the ee at the end of the reaction is given by Equation (5):

$$ee_{cat} = ee_{cat,end} = ee_{cat,0}(x_{cat})^{1-ee_{intr}} \quad (5)$$

These results are general and are dependent on neither the kinetic rate law for the particular system under study nor on the form that the active catalyst species takes.

Soai and coworkers offered no mechanism for suppression of formation of the minor enantiomer in their recent kinetic analysis.[4] Thus catalyst ee in their case will follow Equation (4) as the product (catalyst) concentration increases over the course of the reaction. Asymmetric amplification cannot occur, and initial catalyst ee will inexorably be eroded according to their model.[9]

Figure 1 illustrates the ee predicted as a function of time for one of the reactions reported by Soai,[4] the formation of 2-alkynyl-5-pyrimidyl alcohol in the alkylation of 2-alkynylpyrimidine-5-carbamaldehyde with Pr_2^iZn at 0 °C using 1 mol % of (*S*)-2-alkynyl-5-pyrimidyl alcohol (99.5% ee) as catalyst. The reaction profile simulated according to the Soai's rate equation[10] is also reproduced in Figure 1. The product (catalyst) ee decreases steadily over the course of the reaction, reaching 95.5% ee by the end of the reaction. Since it has been experimentally observed in Soai's work that asymmetric amplification does occur in this reaction, it is clear that the autocatalytic mechanism they proposed cannot account for their experimental observations.

A mechanism for suppression is also the key to achieving asymmetric amplification in reactions which are not autocatalytic. The most common rationalization of such phenomena, now routinely observed in catalytic systems, invokes the formation of dimers or higher order species which help to sequester a disproportionate fraction of the minor catalyst enantiomer into an inactive or less active catalytic species. The first such explanations proposed were the ML_n models developed by Kagan,[11] and Noyori and coworkers subsequently discussed models with single-ligand, monomeric species as the active catalysts.[12] Variations on these mechanisms have also been proposed.[13] One important difference between the Kagan and Noyori mechanisms

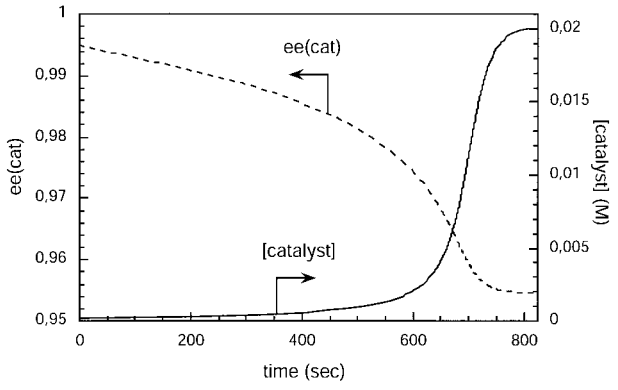


Figure 1. Theoretical plot of catalyst ee as a function of reaction time in the autocatalytic reaction shown in Scheme 1 employing a catalyst with 99.5% ee. Catalyst (product) ee is calculated according to Equation (4). The simulation for catalyst concentration is reproduced from the model proposed by Soai (Ref.[4]).

is that a bias towards preferential formation of the heterochiral species is required for catalysts following the monomeric model, while even a random, statistical distribution of ligands between homochiral and heterochiral species can effect asymmetric amplification when the ML_2 species itself acts as catalyst.[14] The implications of this difference, which were key to our rationalization of the observed autocatalysis with asymmetric amplification,[3] were not considered in Soai's kinetic analysis.[4] Our finding of a statistical distribution of ligands in the alkylation of 2-methylpyrimidine-5-carbamaldehyde with *i*-Pr_2Zn catalyzed by the corresponding alcohol precludes the monomeric catalyst model currently under consideration by Soai.

In summary, this theoretical treatment illustrates that a means to effect suppression of the minor enantiomer's role in an autocatalytic reaction is indispensable in order for asymmetric amplification to be realized. While models for simple autocatalytic reactions may be fit to simple rate expressions, rate and enantioselectivity must be considered together in developing a model for asymmetric amplification in autocatalytic reactions.

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[8] The intrinsic enantioselectivity ee_{intr} is defined as the product ee in a stoichiometric autocatalytic reaction employing an enantiopure catalyst. ee_{intr} is not a function of conversion.

[9] Soai and coworkers did not discuss enantioselectivity features of their model in Ref.[4] They justified the validity of their model by noting that fitted rate and equilibrium parameters were in agreement for reactions carried out under different conditions. However, this agreement rests on their employment of an arbitrary "fitting parameter" which is different for different conditions.

[10] Consideration of the kinetic model proposed by Soai in Ref.[4] reveals that the rate law they give does not correspond to the mechanism they propose. They describe the autocatalytic reaction of aldehyde **1** with *i*-Pr_2Zn. The active catalyst is a dimer of the product alcohol **2** formed in a monomer-dimer equilibrium reaction with equilibrium constant *K*. They give the rate law for this mechanism as:

$$r = kK[\mathbf{1}][\mathrm{Pr}_2^i Zn][\mathbf{2}]^2 \quad \text{(a)}$$

However, the concentration of **2** in solution at any given time during the reaction is dictated by its equilibrium monomer-dimer partitioning and is not equal simply to the total product [**2**] formed according to the reaction stoichiometry at that given extent of reaction. The correct rate equation corresponding to the mechanism described by Soai is:

$$r = kK[\mathbf{1}][\mathrm{Pr}_2^i Zn]\left(\frac{-1+\sqrt{1+8K[\mathbf{2}]}}{4K}\right)^2 \quad \text{(b)}$$

Simulations of the reaction using this equation cannot reproduce the behaviour observed by Soai [see Supporting Information for a derivation of Eq. b) and for plots of reaction simulations].

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