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Principles for designing an achiral receptor promoting asymmetric autocatalysis with amplification of chirality

Gianfranco Ercolani *

Dipartimento di Scienze e Tecnologie Chimiche, Università di Roma Tor Vergata, Via della Ricerca Scientifica, 00133 Roma, Italy

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ABSTRACT

The idea that an achiral receptor can promote asymmetric autocatalysis with amplification of chirality is presented and discussed in the light of two models, dubbed ACM1 and ACM2, corresponding to the autocatalytic versions of the classical Kagan and Noyori models for non-linear effects in asymmetric catalysis. The chiral amplifications produced by the two models have been investigated. The results suggest that an achiral receptor working according to the ACM1 model presents distinct advantages over the ACM2 counterpart, both in terms of elegance of design and performance.

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1. Introduction

The origin of homochirality in biological molecules, such as L-amino acids and D-sugars, is one of the most intriguing questions still awaiting a satisfactory answer.[1] In principle, however, an efficient mechanism of asymmetric autocatalysis with amplification of chirality is all that is needed to generate homochirality even from achiral species or racemic mixtures.[2] This concept, proposed theoretically more than half a century ago,[3] has been unequivocally demonstrated by the experimental studies of Soai et al. on the addition of diisopropylzinc to pyrimidine carbaldehydes.[4] Although enantiomeric enrichment can also be induced by physical methods involving the partition of enantiomers between solution and solid phases,[5] the Soai reaction is the only known chemical transformation that starts from achiral reactants to give a product with a specific handedness in the presence of any imaginable chiral inductor (circularly polarized light, chiral compounds, chiral organic and inorganic crystals, chiral isotopomers, etc.)[4] or a product of unpredictable handedness in the absence of chiral inductors.[6] Unfortunately there is no agreeable mechanism which can explain all of the important experimental features displayed by the reaction,[7–9] but it is well understood that chiral amplification must require some level of self-association of the product-catalyst.

It is quite disconcerting that after more than 20 years from the discovery of the Soai reaction, the chemical community has not been able to master the principles that would allow the invention of other reactions matching its performance. No doubt, a major obstacle to such an endeavour is the difficulty in envisaging molecular structures capable of both autocatalysis and self-aggregation. We reasoned that a receptor with suitable binding sites could make the design of an autocatalyst capable of chiral amplification easier. Herein our aim was to explore the characteristics of such a receptor and its scope with the belief that the field of asymmetric catalysis could benefit from this new paradigm.

2. Results and discussion

2.1. Stating the problem

Amplification of chirality manifests itself as a positive deviation from the usual linear relationship observed between the enantiomeric excess of reaction products and the enantiomeric excess of the chiral catalyst used. Such non-linear effects in asymmetric catalysis are indicative that the catalyst is involved in a process of self-aggregation, no matter if the active catalyst is actually the monomer or one oligomeric species. In Scheme 1 the two archetypal models are shown for non-linear effects in asymmetric catalysis, namely the Kagan model[10] and the Noyori model.[11]

In both models, two molecules of a chiral catalyst, in the *R* or *S* enantiomeric forms, reversibly bind to each other to yield the homodimers *RR* and *SS* with an equilibrium constant K_{homo} and the heterodimer *RS* with an equilibrium constant K_{hetero}. The difference between the two models is that in the Kagan model, the actual catalyst is constituted by the dimers whereas in the Noyori model is constituted by the monomers. In order to discuss the behaviour of the two models, it is useful to introduce the metathesis equilibrium between the homodimers and the heterodimer, shown in Eq. 1, whose equilibrium constant *K* is given by Eq. 2.

* Tel.: +39 0672594383; fax: +39 0672594328.
E-mail address: ercolani@uniroma2.it

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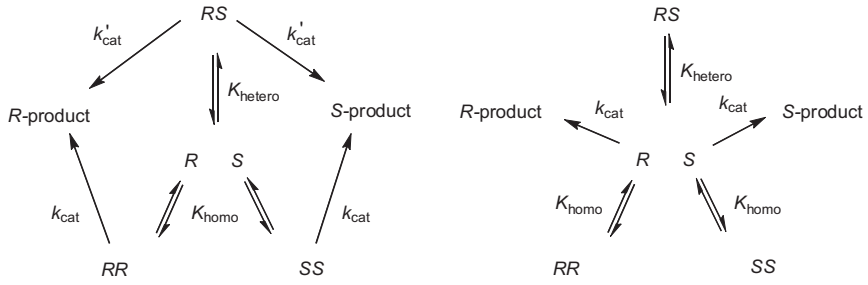


Scheme 1. Kagan model (on the left) and Noyori model (on the right) for non-linear effects in asymmetric catalysis.

$$RR + SS \overset{K}{\rightleftharpoons} 2RS \tag{1}$$

$$K = \left(\frac{K_{\text{hetero}}}{K_{\text{homo}}}\right)^2 \tag{2}$$

A value of $K = 4$ corresponds to a statistical distribution of homochiral and heterochiral dimers, whereas larger values of K indicate that the heterodimer is thermodynamically more stable than the homodimers. While in the Noyori model to observe chiral amplification, it is required that a significant amount of catalyst is in the dimeric form and that $K > 4$, in the Kagan model asymmetric amplification may be observed even with a statistical distribution of dimers provided that the heterochiral dimer as catalyst is inactive or less active than the homodimers ($k'_{\text{cat}} < k_{\text{cat}}$). In both cases the positive non-linear effect is due to the fact that a fraction of the minor enantiomer larger than that of the major enantiomer is trapped into the heterochiral dimer. This fact makes the enantiomeric excess of the active catalyst (monomers in the Noyori model, mainly homodimers in the Kagan model) larger than the overall enantiomeric excess. Effects on reaction rates for both models have been discussed by Blackmond.[12]

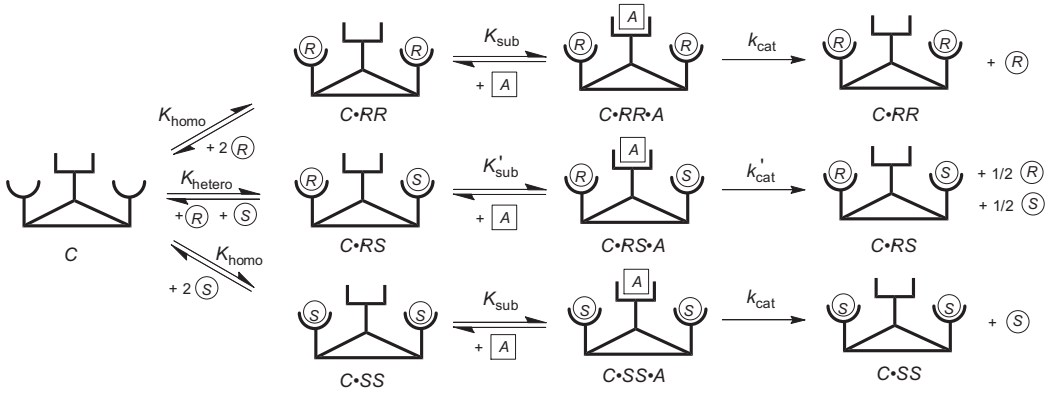
By allowing the product to be identical to the catalyst, the two models in Scheme 1 are modified for autocatalysis. For the sake of convenience, we have called the autocatalytic versions of the Kagan and Noyori models autocatalytic model 1 (ACM1) and autocatalytic model 2 (ACM2), respectively. In this respect, there are evidences that the Soai reaction with 2-methylpyrimidine-5-carbaldehyde at ambient temperature follows the ACM1.[8,12c]

The question that we want to address is the following: can a suitable achiral receptor (co-catalyst) promote autocatalysis with amplification of chirality according to either the ACM1 or the ACM2?

2.2. An achiral receptor designed for the ACM1

In the autocatalytic model 1, the active catalyst is a homodimer; thus a suitable receptor C designed to enforce such a model should provide two sites for the reversible binding of two molecules of the chiral product and a third site (the active site) to bind the achiral substrate A. The corresponding kinetic scheme is depicted in Scheme 2.

The achiral receptor C could either be a synthetic organic receptor or a metal; it behaves as a co-catalyst that upon binding two molecules of the chiral product transforms itself into the actual catalyst that can be present in the form of the homodimers, $C{\cdot}RR$ and $C{\cdot}SS$, and the heterodimer, $C{\cdot}RS$. These three complexes, once formed, ideally behave as enzymes which bind the substrate A, transform it into the corresponding chiral product, R, S, or a 1:1 mixture of the two, respectively, and then re-deploy for multiple turnovers. Of course by increasing the enantiomeric excess of the chiral product the distribution of the three complexes changes in favour of one of the two homodimeric complexes. In order to make the kinetic treatment of such an elaborate scheme manageable, a number of simplifying assumptions are required: (i) all binding steps are reversible and fast with respect to the rate of the first-order chemical process that is considered irreversible; (ii) the achiral receptor C as well as the monomeric complexes $C{\cdot}R$ and $C{\cdot}S$ (not shown in Scheme 2) are catalytically inactive; (iii) the reactivity of the heterochiral complex $C{\cdot}RS{\cdot}A$ is negligible with respect to that of the homochiral complexes $C{\cdot}RR{\cdot}A$ and $C{\cdot}SS{\cdot}A$ ($k_{\text{cat}} \gg k'_{\text{cat}}$); this condition is the most favourable for chiral amplification. With these simplifying assumptions, the two homochiral complexes $C{\cdot}RR$ and $C{\cdot}SS$ behave like enzymes obeying the classical Michaelis–Menten mechanism.[13] Therefore, the reaction rate, v, will depend on the concentration of receptor C and on the concen-



Scheme 2. Kinetic scheme for the autocatalytic model 1 directed by an ad-hoc receptor.

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