N O T E

A note on the Noyori model for chiral amplification in the aminoalcohol-catalyzed reaction of aldehydes with dialkylzinc

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The Noyori model of chiral amplification in the alkylation of aldehydes by means of dialkylzinc, catalyzed by chiral aminoalcohols, is further elaborated. A direct, but approximate, relation is obtained between the enantiomeric excess of the catalyst added and the enantiomeric excess of the product.

Key words: chiral stereoselection, chiral amplification, chiral catalysis, asymmetric synthesis.

In a recent work Noyori and coworkers[1] proposed a mathematical model for the chiral amplification, earlier observed in the reaction of alkylation of aldehydes by means of dialkylzinc, in which a chiral aminoalcohol is used as a catalyst. Later, the Noyori model was slightly simplified by showing that the initial enantiomeric excess, ee_{ini}, of the added catalyst, and the enantiomeric excess, ee_{prod}, of the resulting chiral alcohol satisfy the relation[2]

$$ee_{prod} = ee_{ini} \left[1 + \frac{2(K_2 - K_1) [R] [S]/([R] + [S])}{1 + K_1 ([R] + [S])} \right] \tag{1}$$

In Eq. (1) $[R]$ and $[S]$ denote the concentrations of the two enantiomers of the active form of the catalyst, whereas K_1 and K_2 pertain to the equilibria between the species R and S and their (experimentally characterized[3]) dimers R_2, S_2 and RS:

$$\frac{[R]^2}{[R_2]} = \frac{[S]^2}{[S_2]} = K_{homo} = 2/K_1$$

$$\frac{[R] [S]}{[RS]} = K_{hetero} = 1/K_2$$

The enantiomeric excess ee_{ini} is defined as

$$ee_{ini} = \frac{R_0 - S_0}{R_0 + S_0} \tag{2}$$

with R_0 and S_0 standing for the amount of the two enantiomers of the added catalyst; as before,[2] it is assumed that $R_0 \geq S_0$. It has been shown[1,2] that for the other enantiomeric excess occurring in Eq. (1), the following simple relation applies:

$$ee_{prod} = \frac{[R] - [S]}{[R] + [S]} \tag{3}$$

Further details concerning the Noyori model and the notation used in the present note can be found elsewhere.[1,2]

<div align="center">A RELATION BETWEEN ee_{prod} AND ee_{ini}</div>

Within the Noyori model, the actual relation between the initial and final enantiomeric excesses has not been determined,[1,2] in spite of a seemingly simple connection between the quantities appearing on the right-hand sides of Eqs. (2) and (3):

$$R_0 = [R] + K_1 [R]^2 + K_2 [R] [S] \tag{4}$$

$$S_0 = [S] + K_1 [S]^2 + K_2 [R] [S] \tag{5}$$

In fact, solving Eqs. (4) and (5) in terms of $[R]$ and $[S]$ and finding the explicit functional dependence of $[R]$ and $[S]$ on the parameters R_0, S_0, K_1, K_2 seems to be practically impossible. In view of this, an approximate relation between ee_{prod} and ee_{ini} has been determined in this work.

Let $ee_{prod} = F(ee_{ini})$ be the required functional relation between the two enantiomeric excesses. Whatever is the form of the function $F(x)$, it must satisfy the following boundary conditions:[1,2]

$$F(0) = 0; F(1) = 1 \tag{6}$$

The simplest expression for $F(x)$ with the properties (6) is

$$F(x) = \lambda x + (1 - \lambda) x^2 \tag{7}$$

with λ being a pertinently chosen parameter (see below). Eq. (7) can be understood as the power-series expansion of $F(x)$, truncated at the quadratic term.

Because the chemically relevant values of the variable x lie in the interval $(0, +1)$ and because the main interest is for $x \approx 0$, the approximation

$$ee_{prod} = \lambda ee_{ini} + (1 - \lambda) (ee_{ini})^2 \tag{8}$$

may safely be accepted as a satisfactory one.

From Eq. (8) it follows:

$$\lambda = \frac{\partial ee_{prod}}{\partial ee_{ini}} \qquad\qquad \text{for } ee_{ini} \to 0 \tag{9}$$

By combining Eqs. (1) and (9), the following expression may be directly obtained

$$\lambda = 1 + \frac{2(K_2 - K_1)\,[R]\,[S]/([R] + [S])}{1 + K_1\,([R] + [S])} \qquad \text{for } ee_{\text{ini}} \to 0$$

$$= 1 + \frac{(K_2 - K_1)\,[R]}{1 + 2\,K_1\,[R]} \qquad \text{for } ee_{\text{ini}} \to 0$$

$$= \frac{1 + (K_1 + K_2)\,[R]_0}{1 + 2\,K_1\,[R]_0}$$

where $[R]_0$ is the value of $[R]$ in the limit case $ee_{\text{ini}} \to 0$. Recall that in this case, $[R]_0 = [S]_0$.

The value of $[R]_0$ is calculated from Eq. (4), *i.e.*, from

$$R_0 = [R]_0 + K_1\,[R]_0^2 + K_2\,[R]_0^2$$

resulting in

$$[R]_0 = \frac{\sqrt{1 + 4(K_1 + K_2)R_0} - 1}{2(K_1 + K_2)}$$

Here the quantity R_0 pertains to the limit $e_{\text{ini}} \to 0$, when it is equal to the total amount C of the added catalyst (*i.e.*, to the total amount of the added aminoalcohol). Therefore, the above formula is rewritten as

$$[R]_0 = \frac{\sqrt{1 + 4(K_1 + K_2)C} - 1}{2(K_1 + K_2)}$$

where $C = R_0 + S_0$.

In what follows, the term $\sqrt{1 + 4(K_1 + K_2)C}$ is abreviated by Q, so that

$$[R]_0 = \frac{Q - 1}{2(K_1 + K_2)}$$

and

$$\lambda = \frac{1}{2}\left[1 + \frac{K_1 + K_2 Q}{K_2 + K_1 Q} \right] \qquad (10)$$

By means of Eq. (10) the functional dependence between the initial and final enantiomeric excesses, Eq. (8), has been fully determined, at least in the quadratic approximation.

ON THE MAXIMAL CHIRAL AMPLIFICATION

From the form of the function $F(x)$, Eq. (7), it is clear that this function is concave if $1 - \lambda < 0$. Concavity means that in the interval $(0,+1)$ the inequality $F(x) > x$ is obeyed. In view of Eq. (8), the condition $1 - \lambda < 0$ implies $ee_{\text{prod}} > ee_{\text{ini}}$, that is, implies chiral amplification.

Using formula (10) it is easy to show that $1 - \lambda < 0$, and therefore chiral amplification, occurs if and only if $K_2 > K_1$. This is a previously known result.[1,2] Assume therefore that $1 - \lambda$ is negative.

By Eq. (8)

$$ee_{\text{prod}}/ee_{\text{ini}} = \lambda + (1 - \lambda)ee_{\text{ini}} \tag{11}$$

The second term of the right-hand side of Eq. (11) is necessarily negative-valued. Consequently, chiral amplification, as measured by the quotient $ee_{\text{prod}}/ee_{\text{ini}}$, is maximal in the limit case $e_{\text{ini}} \to 0$, and is then equal to λ. Hence, chiral amplification increases with increasing value of λ. On the other hand, the way in which λ depends on the basic parameters of the Noyori model has been established above and is given by Eq. (10).

At this point it may be of some interest to list the expressions for λ in some of the chemically most important limit cases.

If K_1 is very small, but not K_2, then

$$\lambda \approx \frac{1}{2}\left(1 + \sqrt{1 + 4K_2\,C}\right)$$

It both K_1 and K_2 are very small, $K_2 > K_1$, or if C is very small, then

$$\lambda \approx \frac{1 + (K_1 + K_2)\,C}{1 + 2\,K_1\,C} \approx 1 + (K_2 - K_1)C$$

If K_2 is very large, but not K_1, then

$$\lambda \approx \sqrt{K_2\,C}$$

И З В О Д

БЕЛЕШКА О НОЈОРИЈЕВОМ МОДЕЛУ ЗА ХИРАЛНУ АМПЛИФИКАЦИЈУ У РЕАК-
ЦИЈИ АЛДЕХИДА СА ДИАЛКИЛЦИНКОМ, КАТАЛИЗОВАНОЈ АМИНОАЛКОХОЛИМА

ИВАН ГУТМАН

Природно-математички факултет у Крагујевцу

Допуњен је Нојоријев модел хиралне амплификације у реакцији алкиловања алдехида помоћу диалкилцинка, катализованој хиралним аминоалкохолима. Изведена је директна, мада апроксимативна, релација између енантиомерног вишка доданог катализатора и енантиомерног вишка реакционог продукта.

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