

A simple model for chiral amplification in the aminoalcohol-catalyzed reaction of aldehydes with dialkylzinc

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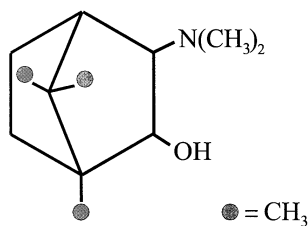
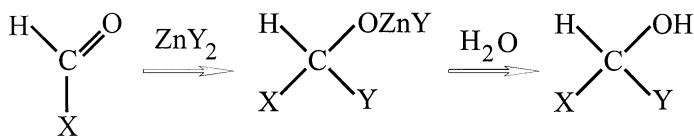
(Received 2 March 1999)

A simple explanation is offered for the recently discovered chiral amplification in the alkylation reaction of benzaldehyde by means of dialkylzinc, catalyzed by (dimethylamino)isoborneol. The model presented is similar to, yet somewhat simpler than, the model put forward by Noyori *et al.*

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

The alkylation of aldehydes by means of dialkylzinc is used for obtaining chiral alcohols, see Fig. 1.

The first step of this reaction proceeds only if some aminoalcohol is present as a catalyst. It was observed some time ago¹ that if a chiral aminoalcohol is used as the catalyst, then the enantiomeric excess² (*ee*) of the product can significantly



DAIB

Figure 1.

exceed the enantiomeric excess of the catalyst itself. (A characteristic result is the following³: If racemic, 3-*exo*-(dimethylamino)isoborneol (DAIB, see Fig. 1), is used as the catalyst in the reaction of benzaldehyde with diethylzinc, racemic 1-phenyl-1-propanol is obtained. If enantiomerically pure (2*S*)-DAIB is used in the same reaction, then the product is almost enantiomerically pure (*S*)-1-phenyl-1-propanol, *ee* = 98%. If, however, a mixture of (2*S*)- and (2*R*)-DAIB is employed, in which the *S*-form is only in slight excess, *ee* = 15%, the enantiomeric purity of the resulting alcohol is nevertheless very high, *ee* = 95%). Such phenomena, called chiral amplification, have been observed in quite a few reactions that proceed with the participation of chiral catalysts.⁴

In the case of the reaction of benzaldehyde with dimethylzinc, catalyzed by DAIB, it could be proven⁵ that dimethylzinc reacts with (2*R*)-DAIB and (2*S*)-DAIB, eliminating methane and forming a tricoordinated methylzinc (*R*)- or (*S*)-aminoalkoxide, which happen to be the active forms of the catalyst. In the following these enantiomeric methylzinc aminoalkoxides are denoted by *R* and *S* and their concentration by [*R*] and [*S*], respectively. It has been shown⁵ that under the conditions of the reaction, *R* and *S* partially dimerize, forming a pair of enantiomers *R*₂ and *S*₂, as well as a *meso*-diastereoisomer *RS*. The species *R*, *S*, *R*₂, *S*₂ and *RS* are in equilibrium:

$$\frac{[R]^2}{[R_2]} = \frac{[S]^2}{[S_2]} = K_{\text{homo}} \quad (1)$$

$$\frac{[R][S]}{[RS]} = K_{\text{hetero}} \quad (2)$$

The experimental values of K_{homo} and K_{hetero} are⁵ 3×10^{-2} and 1×10^{-5} , respectively. Thus, the heterochiral dimer (*RS*) is significantly more stable than the homochiral ones (*R*₂ and *S*₂).

It is reasonable to expect that the situation is also similar in other cases of aminoalcohol-catalyzed reactions of aldehydes with dialkylzinc.

A quantitative mathematical model explaining chiral amplification in the chemical reactions of the above described type has recently been elaborated by Noyori and coworkers.³ Here a somewhat simpler approach to the same problem is put forward.

ASSUMPTIONS OF THE MODEL

The reaction mechanism and the reaction conditions described below are the same as those adopted in the work by Noyori *at al.*³

The amounts of the two enantiomers of the catalyst added to the system (*e.g.* (2*R*)- and (2*S*)-DAIB) are denoted by *R*₀ and *S*₀. Thus, the respective initial enantiomeric excess is²

$$ee_{\text{ini}} = \frac{R_0 - S_0}{R_0 + S_0} \quad (3)$$

Without loss of generality, it will be assumed that $R_0 \geq S_0$.

Following the notation of Noyori *et al.*³ the substrate (*e.g.*, benzaldehyde) and the reactant (*e.g.*, dimethylzinc) are denoted by *Sub* and *Rea* and their concentrations by $[Sub]$ and $[Rea]$, respectively. Both $[Sub]$ and $[Rea]$ are supposed to be much greater than R_0 and S_0 and, as usual in chemical kinetics, their changes in time are neglected. The entire amount of the catalyst reacts with *Rea*, yielding the active forms *R* and *S*, as well as their inactive dimers R_2 , S_2 and RS . Therefore,

$$R_0 = [R] + 2 [R_2] + [RS] \quad (4)$$

$$S_0 = [S] + 2 [S_2] + [RS] \quad (5)$$

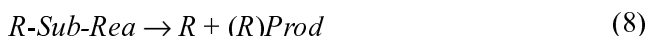
The enantiomeric excess of the active form of the catalyst is

$$ee_{\text{act.cat}} = \frac{[R] - [S]}{[R] + [S]} \quad (6)$$

The active forms of the catalyst react with the substrate and the reactant, forming transient complexes denoted by³ *R-Sub-Rea* and *S-Sub-Rea*. These are in equilibrium with *Sub* and *Rea*, thus obeying

$$\frac{[R-Sub-Rea]}{[R] [Sub] [Rea]} = \frac{[S-Sub-Rea]}{[S] [Sub] [Rea]} = K_{\text{assoc}} \quad (7)$$

Finally the complexes decompose in irreversible first order reactions:



with $(R)Prod$ and $(S)Prod$ standing for the two enantiomers of the product (*e.g.*, of 1-phenyl-1-propanol). For the sake of simplicity, it is assumed that the enantiomeric selectivity of the reactions (8) and (9) is 100%, *i.e.*, that no $(S)Prod$ is formed from *R-Sub-Rea* and no $(R)Prod$ from *S-Rea-Sub*.

The enantiomeric excess of the products is

$$ee_{\text{prod}} = \frac{[(R)Prod] - [(S)Prod]}{[(R)Prod] + [(S)Prod]} \quad (10)$$

Now, because of the equilibria (7) and the fact that the concentrations of $[R]$, $[Sub]$ and $[Rea]$ are time-independent, the rates of the reactions (8) and (9) are also time-independent. Therefore, $[(R)Prod]$ and $[(S)Prod]$ linearly increase with time and are proportional to $[R-Sub-Rea]$ and $[S-Sub-Rea]$, respectively. Consequently,

$$\begin{aligned}
 ee_{\text{prod}} &= \frac{[R\text{-Sub-Rea}] - [S\text{-Sub-Rea}]}{[R\text{-Sub-Rea}] + [S\text{-Sub-Rea}]} \\
 &= \frac{K_{\text{assoc}} [R] [Rea] [Sub] - K_{\text{assoc}} [S] [Rea] [Sub]}{K_{\text{assoc}} [R] [Rea] [Sub] + K_{\text{assoc}} [S] [Rea] [Sub]} \\
 &= \frac{[R] - [S]}{[R] + [S]} = ee_{\text{act.cat}}
 \end{aligned} \tag{11}$$

Hence, the enantiomeric excess of the product is the same as the enantiomeric excess of the active form of the catalyst. This latter value may, however, significantly differ from the enantiomeric excess of the catalyst added to the system. This is shown in the subsequent section.

THE MODEL

Denote for brevity $2/K_{\text{homo}}$ and $1/K_{\text{hetero}}$ by K_1 and K_2 , respectively. Then by combining Eqs. (4) and (5) with (1) and (2) one obtains

$$R_0 = [R] + K_1 [R]^2 + K_2 [R] [S] \tag{12}$$

$$S_0 = [S] + K_1 [S]^2 + K_2 [R] [S] \tag{13}$$

which on substitution back into Eq. (3) gives

$$\begin{aligned}
 ee_{\text{ini}} &= \frac{[R] - [S] + K_1 ([R]^2 - [S]^2)}{[R] + [S] + K_1 ([R]^2 + [S]^2) + 2K_2 [R] [S]} \\
 &= \frac{[R] - [S] + K_1 ([R] - [S]) ([R] + [S])}{[R] + [S] + K_1 ([R] + [S])^2 + 2(K_2 - K_1) [R] [S]} \\
 &= \frac{[R] - [S]}{[R] + [S]} \cdot \frac{1 + K_1 ([R] + [S])}{1 + K_1 ([R] + [S]) + 2(K_2 - K_1) [R] [S]/([R] + [S])} \\
 &= ee_{\text{act.cat}} \frac{1 + K_1 ([R] + [S])}{1 + K_1 ([R] + [S]) + 2(K_2 - K_1) [R] [S]/([R] + [S])}
 \end{aligned}$$

This immediately implies

$$\begin{aligned}
 ee_{\text{act.cat}} &= ee_{\text{ini}} \frac{1 + K_1 ([R] + [S]) + 2(K_2 - K_1) [R] [S]/([R] + [S])}{1 + K_1 ([R] + [S])} \\
 &= ee_{\text{ini}} \left[1 + \frac{2(K_2 - K_1) [R] [S]/([R] + [S])}{1 + K_1 ([R] + [S])} \right]
 \end{aligned}$$

Bearing in mind Eq. (11), one arrives at the final expression, relating the initial enantiomeric excesses of the catalyst with the enantiomeric excess of the product:

$$ee_{\text{prod}} = ee_{\text{ini}} \left[1 + \frac{2(K_2 - K_1) [R] [S]/([R] + [S])}{1 + K_1 ([R] + [S])} \right] \quad (14)$$

DISCUSSION

From a formal point of view, the problem encountered in this work is the finding of the mathematical dependence of the enantiomeric excess of the products ee_{prod} , Eq. (10), on the initial enantiomeric excess ee_{ini} , Eq. (3). In principle, this can be achieved by solving the system of Eqs. (12)–(13) in the unknowns $[R]$ and $[S]$, by substituting these solutions into Eq. (6) and by taking into account relation (11). Unfortunately, finding explicit expressions for the solutions of (12)–(13) is not a feasible mathematical task. Therefore, a different, less straightforward strategy is required. The approach elaborated in this work is based on Eq. (14).

The terms $[R][S]/([R] + [S])$ and $1 + K_1 ([R] + [S])$, occurring on the right-hand side of Eq. (14), are necessarily positive-valued. Therefore, from Eq. (14), one can immediately see that chiral amplification (*i.e.*, $ee_{\text{prod}} \geq ee_{\text{ini}}$) will occur if, and only if, $K_2 > K_1$, that is whenever

$$K_{\text{homo}} > 2 K_{\text{hetero}} \quad (15)$$

The measured values of K_{homo} and K_{hetero} (see above) satisfy well condition (15).

If $K_2 < K_1$, then chiral attenuation is to be expected, the enantiomeric excess of the product is smaller than the initial enantiomeric excess of the catalyst. The critical case is $K_2 = K_1$ when the product has the same enantiomeric excess as the added catalyst.

In any satisfactory model of chiral amplification the following two boundary conditions must be obeyed:

- (a) if $ee_{\text{ini}} = 0$ then $ee_{\text{prod}} = 0$, and
- (b) if $ee_{\text{ini}} = 1$ then $ee_{\text{prod}} = 1$.

Indeed, if $ee_{\text{ini}} = 0$ then by Eq. (3), $R_0 = S_0$. Then the difference of Eqs. (12) and (13) yields $([R] - [S])(1 + K_1([R] + [S])) = 0$ implying $[R] - [S] = 0$. Then from Eq. (6) one gets $ee_{\text{act.cat}} = 0$ which by Eq. (11) results in $ee_{\text{prod}} = 0$.

If, in turn, $ee_{\text{ini}} = 1$ then by Eq. (3), $S_0 = 0$. Then from Eq. (13), $[S](1 + K_1[S] + [K_2][R]) = 0$ implying $[S] = 0$. Then from Eq. (6) one gets $ee_{\text{act.cat}} = 1$. Condition $ee_{\text{prod}} = 1$ follows from relation (11).

Two further limit cases deserve to be considered.

Case 1: the heterochiral dimer RS is significantly more stable than the

homochiral dimers R_2 and S_2 ; $K_2 \rightarrow \infty$. Then, assuming $R_0 > S_0$, the entire amount of the S -catalyst will be turned into the inactive heterochiral dimer. The remaining active form of the catalyst will be the pure R -enantiomer and, consequently, $ee_{\text{prod}} = 1$.

Case 2: the heterochiral dimer RS is significantly less stable than the homochiral dimers R_2 and S_2 ; $K_2 \rightarrow 0$. Then, by using Eqs. (1) and (11),

$$ee_{\text{prod}} = \frac{\sqrt{K_{\text{homo}} + 8 R_0} - \sqrt{K_{\text{homo}} + 8 S_0}}{\sqrt{K_{\text{homo}} + 8 R_0} + \sqrt{K_{\text{homo}} + 8 S_0} + 2\sqrt{K_{\text{homo}}}}$$

Subcase 2a: the homochiral dimers are also very unstable; $K_{\text{homo}} \rightarrow 0$. Then,

$$ee_{\text{prod}} = \frac{\sqrt{R_0} - \sqrt{S_0}}{\sqrt{R_0} + \sqrt{S_0}}$$

Subcase 2b: the homochiral dimers are very stable; $K_{\text{homo}} \rightarrow \infty$. Then, $ee_{\text{prod}} = ee_{\text{ini}}$.

ИЗВОД

ЈЕДНОСТАВНИ МОДЕЛ ЗА ХИРАЛНУ АМПЛИФИКАЦИЈУ У РЕАКЦИЈИ АЛДЕХИДА СА ДИАЛКИЛЦИНКОМ, КАТАЛИЗОВАНОЈ АМИНОАЛКОХОЛОМ

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Предложено је једноставно објашњење недавно откривене хиралне амплификације у реакцији алкиловања бензалдехида помоћу диалкилцинка, катализоване (диметиламино)изоборнеолом. Наш модел је сличан моделу који су разрадили Nojori и сарадници, мада је од њиховог нешто једноставнији.

(Примљено 2. марта 1999)

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