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Mathematical Treatment of Kinetic Resolution of Chirally Labile Substrates†

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Abstract: Kinetic resolution of chirally unstable compounds prone to racemize has been quantitatively analyzed. Enantiomeric purities of the products as a function of conversion can be graphically displayed. This approach may be useful for designing an efficient asymmetric reaction.

Since enantiomers react at different rates under chiral conditions, racemates can be kinetically resolved by appropriate reactions using chiral reagents or catalysts as well as enzymes.[1] Each enantiomer is transformed to a single or plural, chiral or achiral compound, depending on the reaction system. When the enantiomeric substrate is chirally labile, dynamic kinetic resolution utilizing in situ racemization is possible. Scheme I illustrates the simplest framework, in which interconvertible enantiomeric substrates form stereospecifically the corresponding chiral products.[2] The substrates S_R and S_S and products P_R and P_S are enantiomeric. Typical examples are seen in the asymmetric cyclization of 1,2-diarylethylenes to helicenes by irradiation with circularly polarized light,[3] the coupling of secondary alkyl Grignard reagents and organic halides caused by chiral phosphine-nickel catalysts,[4] the condensation of a secondary allylic Grignard reagent and a chiral boronic ester,[5] the enzymatic hydrolysis of ketorolac esters, hydantoins, or oxazolinones,[6] and the lipase catalyzed acetylation of cyanohydrins.[7] Such a second-order stereoselective reaction may convert a racemic compound to a highly enantiomerically pure product in 100% yield instead of the 50%, maximum obtainable with chirally rigid substrates, offering a tangible synthetic advantage. This type of transformation is characterized by a pair of competitive reactions which are closely interrelated by the stereoinversion of the substrates. The efficiency of the resolution is highly influenced by the kinetic parameters of the parallel reactions and racemization. Here we describe the quantitative analysis of the dynamic kinetic resolution.[8]

Scheme I

$$\begin{tikzcd}
S_R \arrow[r, "k_R"] \arrow[d, shift right, "k_{inv}"'] & P_R \\
S_S \arrow[r, "k_S"] \arrow[u, shift right, "k_{inv}"'] & P_S
\end{tikzcd}$$

In the mathematical treatment of Scheme I, four assumptions are set: (1) S_R reacts faster than S_S and hence P_R is the prevailing enantiomeric product; (2) reaction rates, k_R (k_{fast}) and k_S (k_{slow}), and stereoinversion

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†Dedicated with respect to Professor Shun-ichi Yamada on the occasion of his 77th birthday.

of the substrate, k_{inv}, are pseudo-first order in substrate concentration;[9] (3) S_R and S_S racemize at the same rate; (4) the reaction is irreversible and P_R and P_S are stable under the reaction conditions. Then the rate of substrate consumption can be expressed as eqs 1 and 2, since S_R is consumed at k_R and k_{inv} and supplied from S_S at k_{inv}.

$$-\frac{d[S_R]}{dt} = (k_R + k_{\text{inv}})[S_R] - k_{\text{inv}}[S_S] \tag{1}$$

$$-\frac{d[S_S]}{dt} = (k_S + k_{\text{inv}})[S_S] - k_{\text{inv}}[S_R] \tag{2}$$

Integration of these second linear differential equations by transformation affords eqs 3 and 4 stating the substrate quantities as a function of time elapsed:

$$S_R(t) = C_1 e^{\lambda_1 t} + C_2 e^{\lambda_2 t} \tag{3}$$

$$S_S(t) = C_3 e^{\lambda_1 t} + C_4 e^{\lambda_2 t} \tag{4}$$

Further integration of these equations gives eqs 5 and 6 that describe the product quantities at time t.

$$P_R(t) = \int k_R S_R(t)dt = k_R\left[\frac{C_1}{\lambda_1}\left(e^{\lambda_1 t} - 1\right) + \frac{C_2}{\lambda_2}\left(e^{\lambda_2 t} - 1\right)\right] \tag{5}$$

$$P_S(t) = \int k_S S_S(t)dt = k_S\left[\frac{C_3}{\lambda_1}\left(e^{\lambda_1 t} - 1\right) + \frac{C_4}{\lambda_2}\left(e^{\lambda_2 t} - 1\right)\right] \tag{6}$$

Here, C_1, C_2, C_3, λ_1, and λ_2 are coefficients correlating with the rate constants, k_R, k_S, and k_{inv} (see Computational Procedure).

The amounts of the four components in Scheme I, $S_R(t)$, $S_S(t)$, $P_R(t)$, and $P_S(t)$, are now represented as the time functional equations by using the parameters, k_R, k_S, and k_{inv}. Thus the selectivity profiles, the enantiomeric excess (ee) of the unreacted slow-reacting substrate [$ee_S(t)$], and the ee of the product P_R [$ee_P(t)$], and conversion [convn(t)] can be expressed by eqs 7–9, respectively. Accordingly, experimental determination of the k_{inv}/k_R and k_R/k_S ratios allows graphic representation of the time-dependent values.

$$ee_S(t) = \frac{S_S(t) - S_R(t)}{S_R(t) + S_S(t)} \tag{7}$$

$$ee_P(t) = \frac{P_R(t) - P_S(t)}{P_R(t) + P_S(t)} \tag{8}$$

$$\text{convn}\,(t) = \frac{P_R(t) + P_S(t)}{S_R(0) + S_S(0)} \qquad (9)$$

The rate ratio k_R/k_S is equivalent to the product ratio when S_R and S_S are present in equal amounts. The actual S_R/S_S ratio, however, usually deviates from unity as the reaction proceeds except for the case where the stereoinversion, $S_R \rightleftharpoons S_S$, is infinitely faster than the reaction.[3,10] In any event the k_R/k_S ratio can be approached from the product ratio with a very low conversion. The enantiomeric purities of the unreacted substrate and product are highly affected by the relative ease of the reaction and stereoinversion. When k_{inv} is not large enough with respect to k_R, the value tends to significantly decrease from the initial value, eep^0, which is the maximum enantiomeric purity in a given reaction system and corresponds to $(k_R - k_S)/(k_R + k_S)$. Eq 10 expresses the limiting eep attained at 100% conversion, which is the minimal ee value throughout the reaction:

$$\text{ee}_P^{\;100} = \lim_{t \to \infty} \frac{P_R(t) - P_S(t)}{P_R(t) + P_S(t)} = \frac{\dfrac{k_{\text{inv}}}{k_R}\left(\dfrac{k_R}{k_S} - 1\right)}{1 + \dfrac{k_{\text{inv}}}{k_R}\left(\dfrac{k_R}{k_S} + 1\right)} \qquad (10)$$

and therefore,

$$\frac{k_{\text{inv}}}{k_R} = \frac{\text{ee}_P^{\;100}}{\left(\dfrac{k_R}{k_S} - 1\right) - \text{ee}_P^{\;100}\left(\dfrac{k_R}{k_S} + 1\right)} \qquad (11)$$

The k_{inv}/k_R ratio is obtained by putting k_R/k_S, which is approximated by P_R/P_S ratio at a low conversion, and eep^{100} into eq 11. Thus the mathematical equations can be correlated with the experimentally available k_R/k_S and k_{inv}/k_R ratios, deducing the overall profile of the stereoselectivity as a function of conversion.

Visualization of the time-dependent behavior helps to further understand the dynamic features of a given kinetic resolution. Figure 1 illustrates time-parametrically plotted curves derived from eq 8 with some imaginary k_R/k_S and k_{inv}/k_R ratios. It shows simulated variations of product ee in stereoselective reactions with $k_{\text{fast}}/k_{\text{slow}}$ ranging from 6/4 to 99/1. Figure 2 displays the relationship of k_{inv}/k_R, k_R/k_S, and eep^{100} by a 3D-graph. The top corner denotes the ideal situation giving a high degree of enantioselection. It is obvious that high k_R/k_S, k_{inv}/k_R, and eep^0 values are desirable to obtain a high enantiomeric purity of the product through dynamic kinetic resolution. As the rate ratios k_{inv}/k_R and k_R/k_S decrease, eep^{100} is lowered from eep^0 to a considerable extent. Only with $k_{\text{inv}}/k_R = \infty$, will ee remain constant throughout the reaction.

When S_R and S_S are not interconvertible ($k_{\text{inv}} = 0$ as a limited case), the two parallel reactions in Scheme I become independent. Since the above mathematical treatment is valid with $k_{\text{inv}}/k_R > 0$, parametric plotting of ee_S and eep as a function of convn with k_{inv} close to 0 affords the selectivity profile expressed by Figure 3. These are essentially identical with those given by Sharpless and Sih.[11]

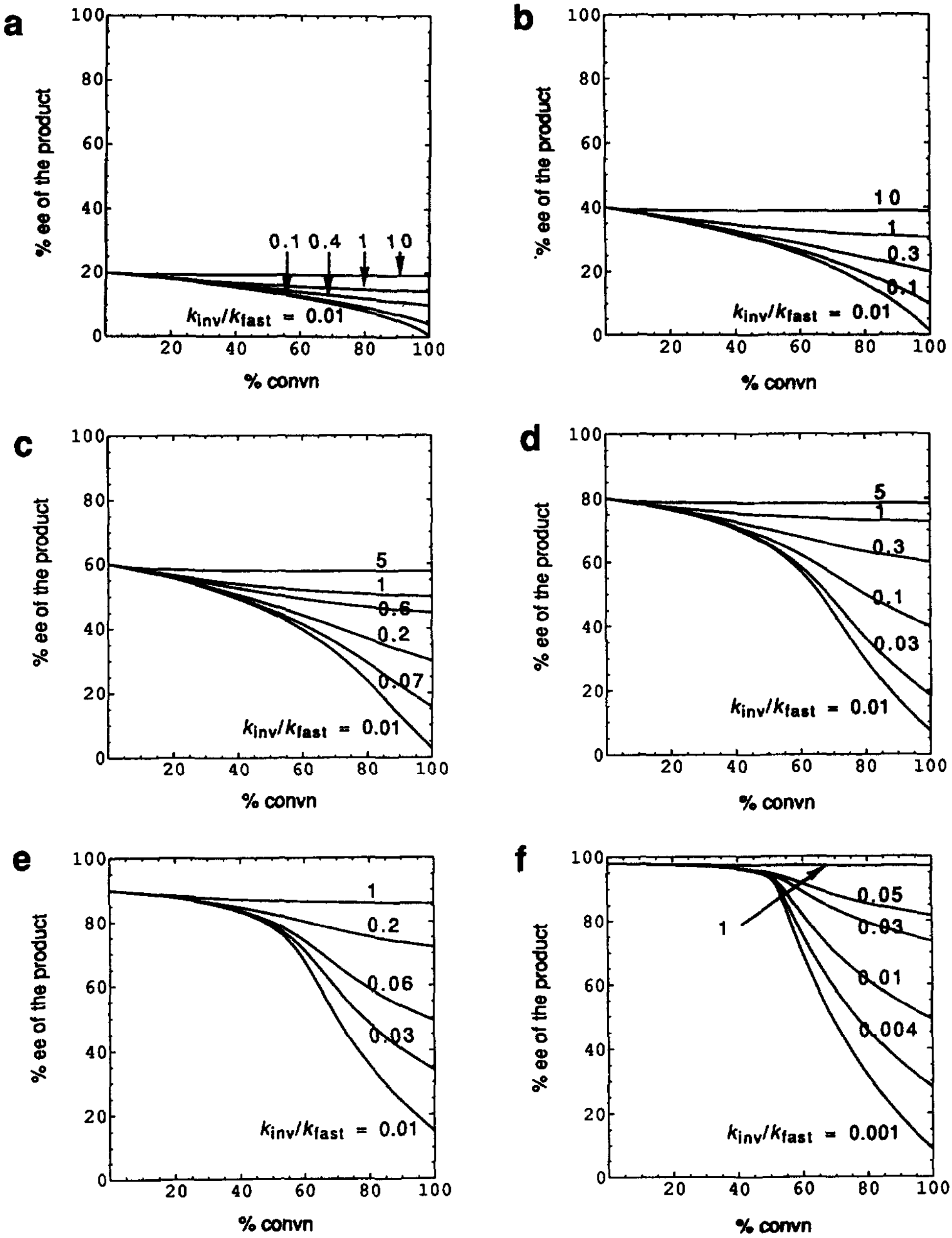

Figure 1. Simulation of variations of enantiomeric purities of the product as a function of conversion with imaginary k_R/k_S (k_{fast}/k_{slow}), and k_{inv}/k_R parameters. **a**: k_{fast}/k_{slow} = 6/4. **b**: k_{fast}/k_{slow} = 7/3. **c**: k_{fast}/k_{slow} = 8/2. **d**: k_{fast}/k_{slow} = 9/1. **e**: k_{fast}/k_{slow} = 95/5. **f**: k_{fast}/k_{slow} = 99/1.

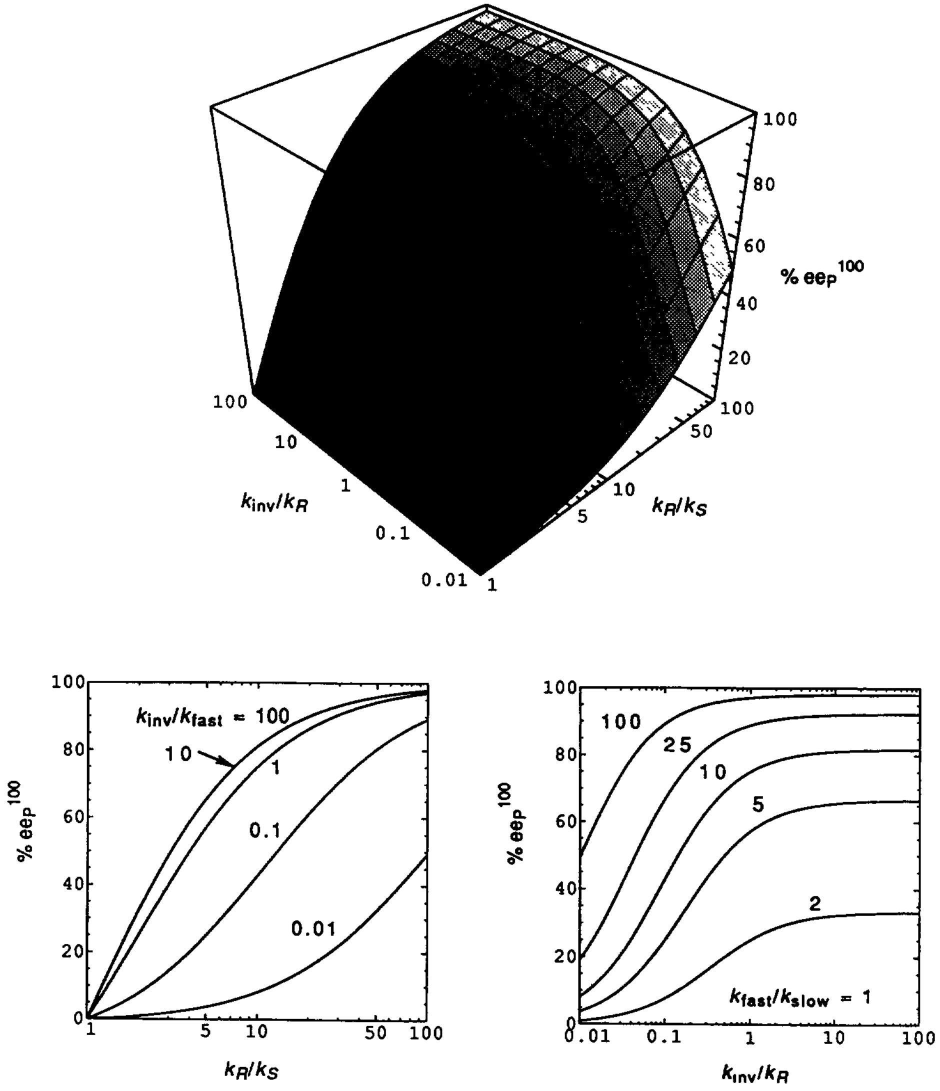

Figure 2. Three-dimensional graphic demonstration of the relationship of k_{inv}/k_R, k_R/k_S, and eep^{100}.

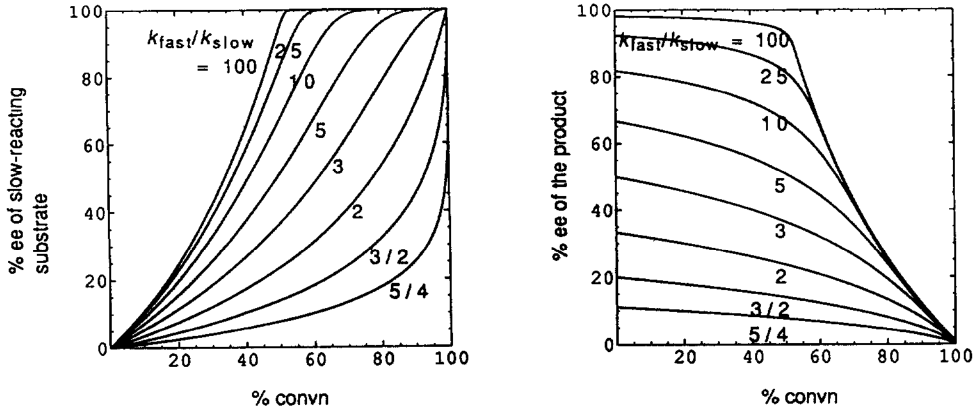

Figure 3. Simulation of enantiomeric purities as a function of conversion with imaginary k_R/k_S parameters (100, 25, 10, 5, 3, 2, 3/2, 5/4) and k_{inv}/k_R (0.0001). Left: ee of the slow-reacting substrate (ee$_S$). Right: ee of the product (ee$_P$).

Dynamic kinetic resolution of a chirally unstable racemic compound can allow preferential formation of a chiral product of high enantiomeric purity in high yield. Such a mathematical treatment is helpful in determining the optimum experimental conditions for a high degree of enantioselection, by varying the k_{inv}/k_{fast} rate ratios. This has already been demonstrated in the BINAP–Ru(II) catalyzed hydrogenation of 2-substituted 3-oxo carboxylic esters forming four stereoisomeric products.[13] Here we have presented the general equations for simpler, more common reaction systems.

Computational Procedure

Graphical expression of the mathematical equations in Figures 1–3 was aided by the Mathematica program on an Apple Macintosh computer. Correlation of C_1, C_2, C_3, C_4, λ_1, and λ_2 with k_R, k_S, and k_{inv} was done as follows. Unique values, λ^1 and λ^2, in the matrix representation 12 are expressed by eq 13.

$$\begin{pmatrix} -(k_R + k_{inv}) & k_{inv} \\ k_{inv} & -(k_S + k_{inv}) \end{pmatrix} = \begin{pmatrix} a & b \\ c & d \end{pmatrix} \tag{12}$$

$$\lambda_1, \lambda_2 = \frac{1}{2}\left\{(a+d) \pm \sqrt{(a+d)^2 - 4(ad - bc)}\right\} \tag{13}$$

The kinetic behavior of $S_R(t)$ and $S_S(t)$ is highly dependent on whether λ is a real or imaginary number and positive or negative. In the dynamic kinetic resolution of Scheme I where both the reaction rates, k_R and k_S, and the inversion rate k_{inv} are greater than 0, λ^1 and λ^2 are deduced, from eqs 12 and 13, to be negative real numbers.

C_1, C_2, C_3, and C_4 can be correlated with α and β, solutions of eq 14, as shown in eqs 15 and 16.

$$bx^2 + (a - d)x - c = 0 \tag{14}$$

$$C_3 = \alpha C_1 \tag{15}$$

$$C_4 = \beta C_2 \tag{16}$$

Initial quantities of the substrates are expressed by $S_R(0) = C_1 + C_2$ and $S_S(0) = C_3 + C_4$, respectively, by substitution of t = 0 into eqs 3 and 4. On the assumption of $S_R(0) = S_S(0) = 1$, these equations afford:

$$C_1 = \frac{\beta - 1}{\beta - \alpha} \tag{17}$$

$$C_2 = \frac{1 - \alpha}{\beta - \alpha} \tag{18}$$

$$C_3 = \frac{\alpha(\beta - 1)}{\beta - \alpha} \tag{19}$$

$$C_4 = \frac{\beta(1 - \alpha)}{\beta - \alpha} \tag{20}$$

Substitution of *a*, *b*, *c*, and *d*, which are correlated with k_R, k_S, and k_{inv} by eq 12, into eq 13 and eqs 17–20, affords:

$$\lambda_1 = \frac{1}{2}\left(-(k_R + k_S) - 2k_{\text{inv}} + \sqrt{(k_R - k_S)^2 + 4k_{\text{inv}}^2}\right) \tag{21}$$

$$\lambda_2 = \frac{1}{2}\left(-(k_R + k_S) - 2k_{\text{inv}} - \sqrt{(k_R - k_S)^2 + 4k_{\text{inv}}^2}\right) \tag{22}$$

$$C_1 = \frac{-(k_R - k_S) + 2k_{\text{inv}} + \sqrt{(k_R - k_S)^2 + 4k_{\text{inv}}^2}}{2\sqrt{(k_R - k_S)^2 + 4k_{\text{inv}}^2}} \tag{23}$$

$$C_2 = \frac{(k_R - k_S) - 2k_{\text{inv}} + \sqrt{(k_R - k_S)^2 + 4k_{\text{inv}}^2}}{2\sqrt{(k_R - k_S)^2 + 4k_{\text{inv}}^2}} \tag{24}$$

$$C_3 = \frac{(k_R - k_S) + 2k_{\text{inv}} + \sqrt{(k_R - k_S)^2 + 4k_{\text{inv}}^2}}{2\sqrt{(k_R - k_S)^2 + 4k_{\text{inv}}^2}} \tag{25}$$

$$C_4 = \frac{-(k_R - k_S) - 2k_{\text{inv}} + \sqrt{(k_R - k_S)^2 + 4k_{\text{inv}}^2}}{2\sqrt{(k_R - k_S)^2 + 4k_{\text{inv}}^2}} \tag{26}$$

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