Mathematical Description of Kinetic Resolution with an Enantiomerically Impure Catalyst and Nonracemic Substrate

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Kinetic resolution is an important method in organic chemistry; catalytic kinetic resolution is especially attractive because a smaller amount of the optically active material is required. In principle, a naturally occurring catalyst (enzyme)[1] or a synthetic catalyst can be employed. Possible disadvantages of an enzymatic catalyst include limited scope of reactions and substrates; therefore, there is an increasing effort targeted at the design of chemical catalysts for kinetic resolution.[2] The most useful parameter in comparing different catalysts is the *selectivity factor S*, which is the ratio of the rate constants for the reaction of the catalyst with the two enantiomers of the substrate ($S = (k_1/k_2)$, see below). Mathematical treatment of kinetic resolution should provide a way to calculate S from experimental observables, and for enantiomerically pure catalysts the equations are well-known from the work of Kagan and others.[3,9]

Depending on the source of the chiral building block, a synthetic catalyst may be prepared contaminated with the undesired enantiomer.[4] Although mathematical treatments of many much more complicated cases of kinetic resolution have appeared,[5] catalytic kinetic resolution with an enantiomerically impure catalyst has not been described. Furthermore, if the selectivity of a given kinetic resolution is not very high, or if very high enantiomeric excess is desired, the resolution might be conducted more than once. In such a case, the second and subsequent resolutions start with a mixture of substrate enantiomers that is not a racemate. Kinetic resolution of a nonracemic mixture can also be used in mechanistic studies.[6] Therefore, reactions involving nonracemic starting materials should be described as well.

Below, a mixture of the Major (Maj) and a Minor (Min) enantiomers of the catalyst is used to resolve a mixture of enantiomers A and O, where A reacts fast (k_1) with the major enantiomer of the catalyst and O reacts with it slowly (k_2). AP and OP are the products obtained from A and O, respectively. The reactions are first-order in substrate and catalyst.

$$A + Maj \xrightarrow{k_1} AP \qquad (1)$$

$$A + Min \xrightarrow{k_2} AP$$

$$O + Maj \xrightarrow{k_2} OP$$

$$O + Min \xrightarrow{k_1} OP$$

The differential description of eqs 1 is given by (2),

$$-\frac{d[A]}{d[t]} = k_1[A][Maj] + k_2[A][Min] \qquad (2)$$

$$-\frac{d[O]}{d[t]} = k_2[O][Maj] + k_1[O][Min]$$

which upon separation of variables yields (3). This transformation assumes that the concentration of the catalyst is constant over the course of the reaction.

$$-\frac{1}{k_1[Maj] + k_2[Min]} \int_{A_0}^{A_t} \frac{d[A]}{[A]} = \int_{t=0}^{t} dt \qquad (3)$$

$$-\frac{1}{k_2[Maj] + k_1[Min]} \int_{O_0}^{O_t} \frac{d[O]}{[O]} = \int_{t=0}^{t} dt$$

Since the right sides of the two equations in (3) are equal, integration transforms it to (4).

$$\frac{1}{k_1[Maj] + k_2[Min]} \ln \frac{[A_t]}{[A_0]} =$$

$$\frac{1}{k_2[Maj] + k_1[Min]} \ln \frac{[O_t]}{[O_0]} \qquad (4)$$

Equation 4 is linear in k_1 and k_2, and the expression (5) for selectivity $S = (k_1/k_2)$ can be readily

$$S = \frac{k_1}{k_2} = \frac{[Maj] \ln \dfrac{[A_t]}{[A_0]} - [Min] \ln \dfrac{[O_t]}{[O_0]}}{[Maj] \ln \dfrac{[O_t]}{[O_0]} - [Min] \ln \dfrac{[A_t]}{[A_0]}} \qquad (5)$$

derived from it. To be more useful, the equation should employ either the enantiomeric excess of the recovered

(1) Sih, C. J.; Wu, S.-H. *Top. Stereochem.* **1989**, *19*, 63. Guo, Z.-W.; Wu, S.-H.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *Am. Chem. Soc.* **1990**, *112*, 4942. Guo, Z.-W. *J. Org. Chem.* **1993**, *58*, 5748. Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114.

(2) For recent examples, see: (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Fujimura, O.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 2499. Fujimura, O.; De la Mata, F. J.; Grubbs, R. H. *Organometallics* **1996**, *15*, 1865. (c) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492. (d) Hashiguchi, S.; Fujii, A.; Haack, K. J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288. (e) Vedejs, E.; Chen, X. H. *J. Am. Chem. Soc.* **1996**, *118*, 1809.

(3) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249. Kagan, H. B. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 203.

(4) For example, see ref 2b.

(5) (a) Brandt, J.; Jochum, C.; Ugi, I. *Tetrahedron* **1977**, *33*, 1353. (b) Dynamic kinetic resolution: Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36. Kitamura, M.; Tokunaga, M.; Noyori, R. *Tetrahedron* **1993**, *49*, 1853. (c) *Meso/dl* stereoisomeric mixtures: Ward, D. E.; How, D.; Liu, Y. *J. Am. Chem. Soc.* **1997**, *119*, 1884 and references therein. (d) Sequential kinetic resolution: Baba, S. E.; Sartor, K.; Poulin, J.-C.; Kagan, H. B. *Bull. Soc. Chem. Fr.* **1994**, *131*, 525. (e) Kinetic analysis by progress curve evaluation: Rakels, J. L. L.; Romein, B.; Straathof, A. J. J.; Heijnen, J. J. *Biotechnol. Bioeng.* **1994**, *43*, 411. See also: Lu, Y.; Zhao, X.; Chen, Z.-N. *Tetrahedron: Asymmetry* **1995**, *6*, 1093. (f) Nonlinear effects due to enantiomeric impurity of the ligand L in ML$_x$ catalyst: Kagan, H. B.; Girard, C.; Guillaneux, D.; Rainford, D.; Samuel, O.; Zhang, S. Y.; Zhao, S. H. *Acta Chem. Scand.* **1996**, *50*, 345; Blackmond, D. G. *J. Am. Chem. Soc.* **1997**, *119*, 12934 and references therein.
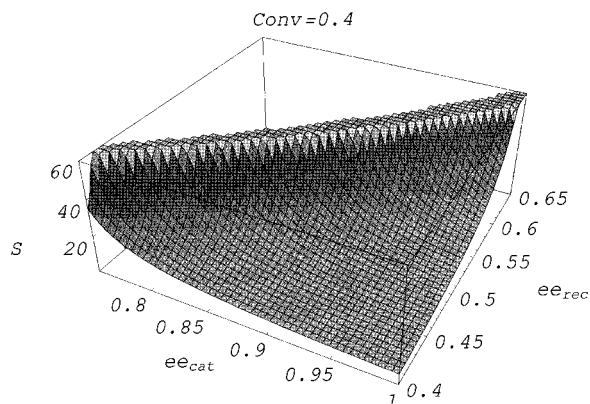
(6) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1996**, *118*, 235. Approximate treatment was used.

Figure 1. Three-dimensional selectivity surface at Conv = 0.4 vs $ee_{cat.}$ and ee_{rec} calculated using eq 9. The surface was clipped at $S = 60$ for clarity.

mixture of A and O (ee_{rec}) or the enantiomeric excess of the obtained product (ee_{prod}) at a given conversion (Conv) rather than time-dependent quantities $[A_t]$ and $[O_t]$. The expressions (6) used for this transformation can be obtained in a straightforward manner from the definitions of Conv, ee_{rec}, and ee_{prod}. To make the equations simple, Conv and all the enantiomeric excesses are expressed as fractions of unity. When the starting material is not racemic, ee_{SMf} describes the enantiomeric excess of the faster-reacting enantiomer.[7]

$$ee_{cat.} = \frac{[Maj] - [Min]}{[Maj] + [Min]}$$

$$\frac{[A_t]}{[A_0]} = \frac{(1 - Conv)(1 - ee_{rec})}{1 + ee_{SMf}} \quad or \quad \frac{[A_t]}{[A_0]} = 1 -$$
$$\frac{Conv(1 + ee_{prod})}{1 + ee_{SMf}} \quad (6)$$

$$\frac{[O_t]}{[O_0]} = \frac{(1 - Conv)(1 + ee_{rec})}{1 - ee_{SMf}} \quad or \quad \frac{[O_t]}{[O_0]} = 1 -$$
$$\frac{Conv(1 - ee_{prod})}{1 - ee_{SMf}}$$

Since the substrate of kinetic resolution can be either racemic or not, and the catalyst can be either enantiomerically pure or just enantiomerically enriched, there are four possible combinations of interest. No assumptions about enantiomeric composition of the starting material or the catalyst have been made in the derivation of (5). Therefore, it can be used to calculate selectivity S in any of the four cases. Two of these cases have already been treated in the literature:

(a) Racemic starting material, enantiomerically pure catalyst.[3]

$$S = \frac{\ln((1 - Conv)(1 - ee_{rec}))}{\ln((1 - Conv)(1 + ee_{rec}))} \quad and \quad S =$$
$$\frac{\ln(1 - Conv(1 + ee_{prod}))}{\ln(1 - Conv(1 - ee_{prod}))} \quad (7)$$

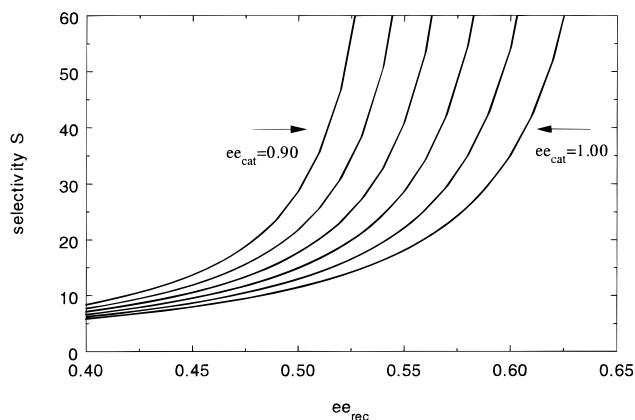(b) Nonracemic starting material, enantiomerically pure catalyst.[7-9]

Figure 2. Cross-sections of the selectivity surface in Figure 1 at $ee_{cat.}$ = 0.90, 0.92, 0.94, 0.96, 0.98, and 1.00 (from left to right, respectively).

This case has been treated both theoretically and experimentally by Sih and co-workers.[8] When ee_{SMf} is the initial enantiomeric excess of the faster-reacting enantiomer in the starting material, known expressions are obtained.

$$S = \frac{\ln\dfrac{((1 - Conv)(1 - ee_{rec}))}{1 + ee_{SMf}}}{\ln\dfrac{((1 - Conv)(1 + ee_{rec}))}{1 - ee_{SMf}}} \quad and \quad S =$$
$$\frac{\ln\left(1 - \dfrac{Conv(1 + ee_{prod})}{1 + ee_{SMf}}\right)}{\ln\left(1 - \dfrac{Conv(1 - ee_{prod})}{1 - ee_{SMf}}\right)} \quad (8)$$

Analytical solutions for the following cases have not been obtained previously:

(c) Racemic starting material, enantiomerically impure catalyst.

The enantiomeric excess of the catalyst $ee_{cat.}$ is required to calculate S. Substitution into eq 5 gives (9) and (10) (Chart 1).

When $ee_{cat.} = 1$ (that is, enantiomerically pure catalyst), eqs 9 and 10 reduce to the known eqs 7 and 8.

(d) Nonracemic starting material, enantiomerically impure catalyst.[7]

Expressions (11) and (12) are obtained for this case from (5). They reduce to (7), (8), (9), or (10) under the appropriate conditions.

To compare different kinetic resolution catalysts, one has to correct for the ee of the catalyst. Figure 1, Figure 2, and Table 1 summarize the selectivity (S) values for various $ee_{cat.}$ and ee_{rec} calculated using eq 9 at Conv = 0.4. Figure 1 describes the overall three-dimensional selectivity surface. Figure 2 gives two-dimensional cross-sections of that surface at selected $ee_{cat.}$, and Table 1 gives numerical values for curves in Figure 2.

(7) If the slower-reacting enantiomer is present with an enantiomeric excess of ee_{SMs}, $-ee_{SMs}$ should be used in place of ee_{SMf}.

(8) Chen, C.-S., Fujimoto, Y., Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294. Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695.

(9) Note that there is a typographical error in eq 12 of ref 3—the minus sign in the numerator of the left fraction should be changed to a plus sign, as it is here and in ref 8.

Chart 1

$$S = \frac{(1 + ee_{cat.}) \ln ((1 - \text{Conv})(1 - ee_{rec})) - (1 - ee_{cat.}) \ln ((1 - \text{Conv})(1 + ee_{rec}))}{(1 + ee_{cat.}) \ln ((1 - \text{Conv})(1 + ee_{rec})) - (1 - ee_{cat.}) \ln ((1 - \text{Conv})(1 - ee_{rec}))} \tag{9}$$

$$S = \frac{(1 + ee_{cat.}) \ln (1 - \text{Conv}(1 + ee_{prod})) - (1 - ee_{cat.}) \ln (1 - \text{Conv}(1 - ee_{prod}))}{(1 + ee_{cat.}) \ln (1 - \text{Conv}(1 - ee_{prod})) - (1 - ee_{cat.}) \ln (1 - \text{Conv}(1 - ee_{prod}))} \tag{10}$$

$$S = \frac{(1 + ee_{cat.}) \ln \dfrac{((1 - \text{Conv})(1 - ee_{rec}))}{1 + ee_{SMf}} - (1 - ee_{cat.}) \ln \dfrac{((1 - \text{Conv})(1 + ee_{rec}))}{1 - ee_{SMf}}}{(1 + ee_{cat.}) \ln \dfrac{((1 - \text{Conv})(1 + ee_{rec}))}{1 - ee_{SMf}} - (1 - ee_{cat.}) \ln \dfrac{((1 - \text{Conv})(1 - ee_{rec}))}{1 + ee_{SMf}}} \tag{11}$$

$$S = \frac{(1 + ee_{cat.}) \ln \left(1 - \dfrac{\text{Conv}(1 + ee_{prod})}{1 + ee_{SMf}}\right) - (1 - ee_{cat.}) \ln \left(1 - \dfrac{\text{Conv}(1 - ee_{prod})}{1 - ee_{SMf}}\right)}{(1 + ee_{cat.}) \ln \left(1 - \dfrac{\text{Conv}(1 - ee_{prod})}{1 - ee_{SMf}}\right) - (1 - ee_{cat.}) \ln \left(1 - \dfrac{\text{Conv}(1 + ee_{prod})}{1 + ee_{SMf}}\right)} \tag{12}$$

Table 1.   Selectivities at Conv = 0.4 Calculated Using (9)

ee_{rec}	$ee_{cat.}$					
	1.00	0.98	0.96	0.94	0.92	0.90
0.40	5.86	6.22	6.63	7.12	7.70	8.40
0.50	11.43	12.91	14.88	17.63	21.73	28.54
0.54	18.04	22.05	28.52	40.75	72.51	356.85

The selectivity surface is rather flat in the region of low selectivity, but it becomes very steep as the selectivity of the catalyst increases. The selectivity value calculated for a given ee_{rec} is measurably different even for catalysts with $ee_{cat.} = 1.00$ and $ee_{cat.} = 0.98$, and the difference becomes very large for highly selective catalysts. In the case of a reaction where $ee_{cat.} = 0.94$ and the starting material is recovered with $ee_{rec} = 0.54$ (Conv = 0.4), eq 7, which assumes enantiomerically pure catalyst ($ee_{cat.} = 1$), and eq 9 predict very different selectivities. Ignoring enantiomeric impurity of the catalyst and using (7) gives $S = 18$, whereas the true selectivity of the catalyst

from (9) is 41. The selectivity values calculated are clearly very sensitive to errors in $ee_{cat.}$ and ee_{rec} (or ee_{prod}). The sensitivity increases as $ee_{cat.}$ decreases, and for low $ee_{cat.}$ values eqs 9−12 should be used with caution.

In conclusion, failure to correct for the ee of the catalyst leads to an underestimation of the selectivity and, therefore, to an overly pessimistic evaluation of the catalyst. If the catalyst is synthesized in enantiomerically impure form, laborious purification is not needed to evaluate its selectivity. Equations 9−12 are analytical solutions of (5) and therefore describe the system exactly.