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# Mechanistic Implications of Pseudo Zero Order Kinetics in Kinetic Resolutions

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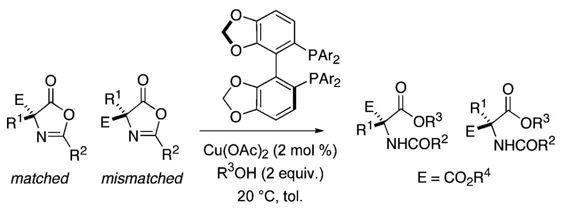
Kinetic resolutions offer a practical route to enantiopure compounds via asymmetric catalysis.[1] Such multistep competitive reaction systems present a more complex kinetic scenario than does a single-substrate catalytic network, but in most cases, kinetic resolutions have been treated as the simplified first order system shown in Scheme 1, with the efficiency of the resolution characterized by the selectivity factor, $k_{\mathrm{rel}}$.[2] Results are most commonly presented by consideration of how enantiomeric excess of substrate ($\mathrm{ee}_{\mathrm{sm}}$) or product ($\mathrm{ee}_{\mathrm{prod}}$) evolves as a function of substrate conversion (*c*). Temporal concentration or rate profiles are not typically reported.

A number of recent studies of kinetic resolutions have treated more complex catalytic reaction mechanisms. In particular, the consequences of pseudo zero order dependence on substrate concentration in reactions using enantioimpure catalysts have been exploited by Blackmond[4] and by Lloyd-Jones.[5]

Most recently, a report showed that kinetic resolution of azlactones via Cu-catalyzed alcoholysis (eq 1) can follow a relationship for $k_{\mathrm{rel}}$ derived for a true mathematical zero order dependency on substrate concentration rather than the first order expression of Scheme 1.[6] Graphical analysis was used to demonstrate that in this case the product enantioselectivity (ee) remains constant with conversion until the matched enantiomer is consumed, affording an apparent enhancement of selectivity over a true mathematical first order dependency, where product ee erodes with conversion. Citing the many observations of zero order kinetics in catalysis, these authors asserted that higher selectivity will be easier to achieve in such cases compared to first order reactions.



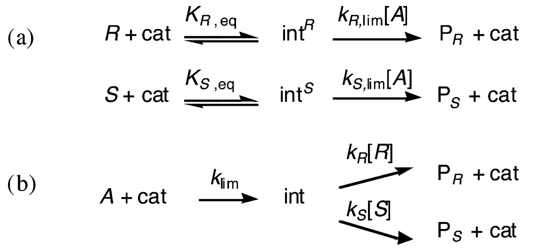
(1)

We report herein reaction simulations and experimental data illustrating that a noneroding product ee versus conversion profile, as reported in ref 6, is not a general consequence of pseudo zero order dependency of the global reaction rate on the substrate concentration. Instead, such behavior only occurs under specific mechanistic constraints that cannot be expected to apply in many observed cases of pseudo zero order behavior. Furthermore, we describe how the analysis of rate behavior in addition to selectivity can yield significant additional mechanistic information about kinetic resolutions.

***Scheme 1.*** First Order, Noncatalytic Kinetic Resolution[3]

$$R \xrightarrow{k_R} P_R \qquad S \xrightarrow{k_S} P_S \qquad k_{rel} = \frac{k_R}{k_S} = \frac{\ln\left[(1-c)(1-ee_{sm})\right]}{\ln\left[(1-c)(1+ee_{sm})\right]}$$

***Scheme 2.*** Generic Regimes for Catalytic Kinetic Resolution; $k_{\mathrm{lim}}$ is the Rate-Limiting Step Rate Constant in Each Case



The observation of pseudo zero order substrate dependency in catalytic kinetic resolution reactions typically arises due to one of the two generic mechanisms outlined in Scheme 2. Either a strong pre-equilibrium binding resulting in a "saturated" intermediate species precedes rate-limiting product formation (Scheme 2a) or reaction of the substrate occurs after a rate-limiting step involving the catalyst and another reagent (Scheme 2b). The alcoholysis reaction of ref 6 (eq 1) was suggested to follow pathway 2a, while an example of pathway 2b is provided by the (salen)Mn-catalyzed epoxidation of allylic alcohols.[7]

For reactions obeying Scheme 2a, the impact of enantiomer binding strength ($K_{\mathrm{eq}}$) on the efficiency of kinetic resolution is illustrated in Figure 1 for several limiting cases (see Supporting Information for mathematical and modeling details). When neither enantiomer binds strongly (Case i, $K_{\mathrm{R,eq}} \approx K_{\mathrm{S,eq}} = \mathrm{low}$), the product ee versus conversion profile corresponds to that for simple first order kinetics given in Scheme 1.

Similarly, we show that under conditions of pseudo zero order dependency on substrate, when *both enantiomers* bind strongly,

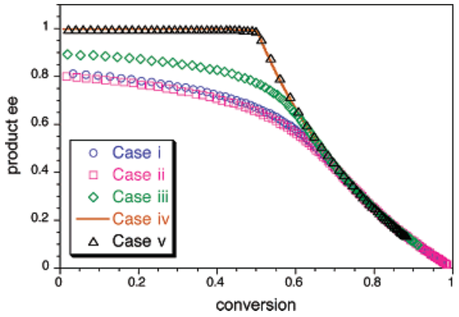


***Figure 1.*** Simulations of kinetic resolutions for a racemic mixture of *R* and *S* according to the mechanism of Scheme 2a. See text for conditions of Cases i−v and the Supporting Information for details of the simulations.

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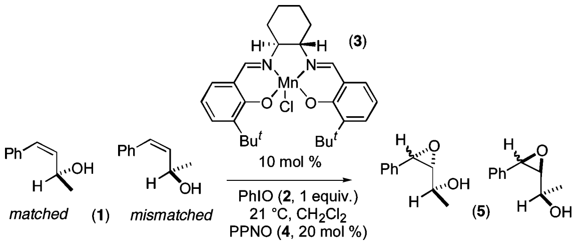
the plot of product ee versus conversion curve retains the form observed for first order kinetics, regardless of whether the binding is equal (Case ii, $K_{R,eq} \approx K_{S,eq}$ = high) or unequal (Case iii, $K_{R,eq}$, $K_{S,eq}$ = high; $K_{R,eq} \neq K_{S,eq}$). Figure 1 shows that product ee does not erode prior to 50% conversion *only* when binding is sufficiently differentiated such that *only one* of the two parallel pathways exhibits zero order kinetics in [substrate] (Cases iv and v).

Under the conditions of Cases iv and v, differential binding allows the more stable intermediate to occupy a large fraction of the catalyst, preventing the more weakly binding enantiomer from competing effectively for the catalyst until complete conversion of the matched enantiomer. This phenomenon may be observed both in the case where the more stable intermediate reacts faster, as in Case iv ($K_{R,eq}$ = high; $K_{S,eq}$ = low; $k_{R,lim} > k_{S,lim}$), and in the case where it reacts more slowly, as in Case v ($K_{R,eq}$ = high; $K_{S,eq}$ = low; $k_{R,lim} < k_{S,lim}$). Studying the global kinetics in examples showing Case iv or Case v behavior will allow differentiation between these possibilities.

It is also important to note that this noneroding product ee profile necessarily leads to near-perfect selectivity until full consumption of the strong binding enantiomer. The nonperfect but noneroding product ee profiles produced in ref 6 by simulation of true mathematical zero order kinetics are thus not chemically meaningful, suggesting that the nonperfect, noneroding product ee profiles observed experimentally in ref 6 require further rationalization. One possibility is that two separate catalyst species, both exhibiting Case iv or v behavior but with different net reactivities and opposite selectivities, may operate in that system. The suggestion by the authors of ref 6 that the slow- and fast-reacting enantiomers exhibit different coordination modes may in fact signify that *R* and *S* substrates each bind strongly to separate catalyst species.[8]

Scheme 2b shows a further mechanistic possibility for pseudo zero order kinetics in substrate concentration that holds for the example of kinetic resolution[7] in the (salen)Mn-catalyzed epoxidation of alkenes shown in eq 2, where Mn═O generation is rate limiting.[7b,c] While the *global* rate has a zero order dependency on substrate (alkene **1**) concentration, the *local* dependency at the stage of enantioselection remains first order (Scheme 2b, $k_R[R]$ versus $k_S[S]$). The experimental data (ee and conversion of **1**) should and does give a linear correlation plotting the standard first order equation in Scheme 1, the selectivity factor ($s = k_{rel}$) being given by the slope of the plot in Figure 2a. In contrast, the "zero order" expression developed in ref 6 is inappropriate, giving a curved relationship (Figure 2b) devoid of chemical meaning. Thus the observation of zero order dependency on substrate concentration does not result in an apparent enhancement of selectivity in kinetic resolutions following the mechanism presented in Scheme 2b (see Supporting Information).



(2)

The work presented herein provides simulations and experimental results to demonstrate that a constant product ee versus conversion profile in kinetic resolution is not a general consequence of pseudo zero order kinetics in [substrate]. This behavior arises only from a case of saturation kinetics in *one* enantiomeric substrate on only *one* of the two parallel pathways in a kinetic resolution following a mechanism such as that given in Scheme 2a. For a resolution involving a single catalyst species, this will be limited to reactions of near-perfect selectivity (cf. Cases iv and v, Figure 1).

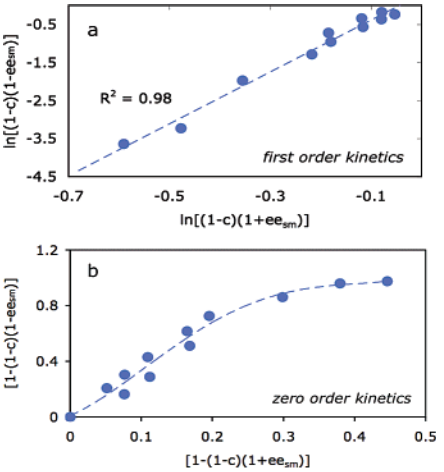


***Figure 2.*** Experimental conversion and enantioselectivity of starting material from the reaction of eq 2. (a) Expression for first order kinetics according to the equation in Scheme 1; (b) expression for zero order kinetics according to eq 1 of ref 6. The first order fit in part (a) gives a $k_{rel} \approx 6.0$.

In conclusion, these findings demonstrate that observation of a noneroding product ee versus conversion profile can provide additional mechanistic information concerning relative enantiomer binding strengths and reactivity of intermediate species and can hint at the possibility of turnover by multiple catalyst species. The combined analysis of global kinetics and ee versus conversion profiles can provide significant mechanistic detail as well as help distinguish between proposed mechanisms in kinetic resolution.

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**Supporting Information Available:** Mathematical details and simulation results for the five cases in Figure 1 for Scheme 2a; simulations for reactions following Scheme 2b; details of the experiments in Figure 2 (9 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley & Sons: New York, 1988; Vol. 18, p 249.
(2) Reference 1 also treats reactions that are second order in the enantiomeric substrate concentration.
(3) This equation for $k_{rel}$ holds for experiments initiated with a strictly racemic mixture of enantiomers.
(4) Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 545.
(5) Dominguez, B.; Hodnett, N. S.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 4289.
(6) Tokunaga, M.; Kiyosu, J.; Obora, Y.; Tsuji, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4481.
(7) (a) Adam, W.; Humpf, H. U.; Roschmann, K. J.; Saha-Moller, C. R. *J. Org. Chem.* **2001**, *66*, 5796. (b) Finney, N. S.; Pospisil, P. J.; Chang, S.; Palucki, M.; Konsler, R. G.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1720. (c) Hughes, D. L.; Smith, G. B.; Dezeny, G. C.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2222. (d) Linde, C.; Arnold, M.; Norrby, P.-O.; Akermark, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1723. (e) Linker, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2060.
(8) See Supporting Information for simulations of two-catalyst cases that reproduce the experimental results of ref 6.

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