KINETIC RESOLUTION OF RACEMATES UNDER CHIRAL CATALYSIS: CONNECTING THE DOTS

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ABSTRACT

The current theory of the titled phenomenon is apparently based on an inconsistent use of concentration units, as employed in the derivation of the fundamental equations. Thus, manifestly, whilst the relation between extent of conversion and e.e. is derived with mole fractions, the succeeding kinetic equations employ units of molarity. This invalidates the derivation in the general case. Fortuitously, however, it is applicable in the majority of simple cases, wherein the total number of moles involved in the reaction remains constant. Herein is presented a rigorous approach which is generally valid.

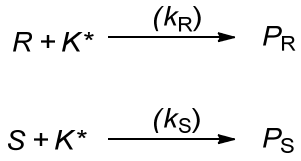
INTRODUCTION

Of the many methods available for the separation of the enantiomeric constituents of a racemate, kinetic resolution offers distinct advantages, particularly when effected with a chiral catalyst.[1,2] Primarily, kinetic resolution avoids the formation of diastereomeric derivatives, their tedious separation and their re-conversion to the resolved substrate enantiomers. Kinetic resolution involves the enantioselective modification of one of the enantiomers (Scheme 1), which can then be separated from the unreacted enantiomer by

achiral means (crystallization, chromatography, etc.). However, the process is complicated by the fact that the enantioselectivity is rarely total ($k_R/k_S \neq \infty$ or 0), so that both the enantiomers are modified concurrently, albeit at different rates.

An enduring problem with kinetic resolution is that, even if the enantioselectivity is high (k_R/k_S is very large or very small), the concentration of the less reactive enantiomer gradually rises during the process; its reaction then competes with that of the other enantiomer at some stage, determined by the enantioselectivity factor (k_R/k_S). Despite this, intriguingly, the enantiomeric excess (e.e.) of the slow-reacting enantiomer increases during the process, essentially because the total concentration of the substrate ([*R*] + [*S*]) decreases. Thus, the success of the process hangs on a subtle balance between enantioselectivity and extent of conversion.

In other words, the e.e. of the unreacted enantiomer is higher towards the end of the process, but at a cost in terms of yield (as both enantiomers have been largely converted to products); the difference in concentrations of the enantiomers (|[*R*] - [*S*]|) indeed 'peaks' at an intermediate stage, but does not manifest as high e.e., as ([*R*] + [*S*]) is relatively large. Thus, kinetic resolution is best suited to obtaining chiral compounds in high e.e., but modest yields.



Scheme 1. Reactions in a kinetic resolution of a racemate composed of *R* and *S* enantiomers by a chiral catalyst *K**; k_R and k_S are the respective rate constants for the formation of products P_R and P_S

In view of the manifest advantages of kinetic resolution, and the need to maximize its efficiency in practical terms, its theoretical basis has been of much interest. In particular, the dependence of the e.e. obtained on the enantioselectivity factor (k_R/k_S) and the extent of conversion has been much sought after, as it indicates at what stage the process can be terminated for an appropriate balance between e.e. and yield.

Although a qualitative view of kinetic resolution can be reached in straightforward fashion (*vide supra*), a rigorous quantitative theory would be essential to understanding its characteristic strengths and limitations. In fact, the current theory – although apparently applicable to the majority of cases – has several unexplained features which introduce an element of fortuitousness, as argued below. A complete rigorous derivation that is generally valid is also set out.

RESULTS AND DISCUSSION

The key equations currently employed are set out below. Eqs. 1 and 2 relate the extent of conversion C and the e.e. of (residual) substrate to the concentration of the enantiomers ([R] and [S]). It should be noted that this is based on the assumption that the initial concentrations of the enantiomers are equal to 0.5: $[R_o] = [S_o] = 0.5$. This clearly implies that the concentrations are expressed as mole fractions. This is further supported by the definition of the extent of conversion: $0<C<1$ and ([R] + [S]) = (1-C). These relations imply that C is none other than the total yield of product expressed in mole fractions, [R] and [S] being also in mole fractions.

$$[S] = [(1-C)(1 + \text{e.e.})]/2 \qquad (1)$$

$$[R] = [(1-C)(1 - \text{e.e.})]/2 \qquad (2)$$

The mole fractions of *R* and *S* would be defined as in eqs. 3 and 4, wherein $\sum[P]$ represents the total yield of all products, the subscript 'mf' indicating mole fractions henceforth. Thus, $\sum[P] = ([P_R] + [P_S])$, P_R and P_S being the products formed from *R* and *S* substrate enantiomers respectively. (Note that the reaction may or may not be stereospecific, *i.e.* it is irrelevant whether the same or different products are formed from the two substrate enantiomers, as $\sum[P]$ refers to the sum total of products.)

$$[S]_{mf} = [S]/([S] + [R] + \sum[P]) \qquad (3)$$

$$[R]_{mf} = [R]/([S] + [R] + \sum[P]) \qquad (4)$$

$$\sum[P]_{mf} = \sum[P]/([S] + [R] + \sum[P]) \qquad (5)$$

Eq. 5 defines the mole fraction of all the products taken as a sum. As defined above, we now note that $\sum[P]_{mf} = C$. Thus, $([S]_{mf} + [R]_{mf} + \sum[P]_{mf}) = ([S]_{mf} + [R]_{mf} + C) = 1$, so $([S]_{mf} + [R]_{mf}) = (1\text{-}C)$. This justifies the above argument that $([R] + [S]) = (1\text{-}C)$ only when all the concentrations including *C* are in mole fractions.

Also, in light of the above discussion, eqs. 1 and 2 would now need to be recast as eqs. 6 and 7 respectively, with the concentrations expressed in mole fractions.

$$[S]_{mf} = [(1\text{-}C)(1 + \text{e.e.})]/2 \qquad (6)$$

$$[R]_{mf} = [(1\text{-}C)(1 - \text{e.e.})]/2 \qquad (7)$$

The enantioselectivity factor ($\mathbf{s} = k_R/k_S$) is derived from the ratio of the yields of product formed. This is obtained *via* the integrated rate equations for the pseudo first order reactions of the two enantiomers at time *t*, as in eqs. 8 and 9; these lead to the enantioselectivity factor in eq. 10.

$$[P_R] = \ln([R]/[R_o]) = -k_R t \qquad (8)$$

$$[P_S] = \ln([S]/[S_o]) = -k_S t \qquad (9)$$

$$\mathbf{s} = k_R/k_S = \{\ln([R]/[R_o])\}/\{\ln([S]/[S_o])\} \qquad (10)$$

However, the problem now is that these would, generally, express the concentrations in units of molarity (*M*) rather than in mole fractions. For this reason, eq. 10 cannot – in general – be combined with eqs. 6 and 7. The relation between $([S]/[S_o])$ and $([S]_{mf}/[S_o]_{mf})$, and between $([R]/[R_o])$ and $([R]_{mf}/[R_o]_{mf})$ can be derived as follows.

Eqs. 11 and 12 follow from eqs. 3 and 4 respectively, noting that $[R_o]_{mf} = [S_o]_{mf} = 0.5$. Eq. 13 derives from the fact that the starting mixture is a racemate (hence $[R_o] = [S_o]$), and the requirements of mass balance. Thus, the total number of moles of all species present, *i.e.* unreacted *S*, *R* and products ($P_R + P_S$) should sum up to the starting count ($[R_o] + [S_o]$).

$$([S]_{mf}/[S_o]_{mf}) = 2\{[S]/([S] + [R] + \sum[P])\} \qquad (11)$$

$$([R]_{mf}/[R_o]_{mf}) = 2\{[R]/([S] + [R] + \sum[P])\} \qquad (12)$$

$$[R_o] = [S_o] = ([S] + [R] + \sum[P])/2 \qquad (13)$$

Interestingly, combining eqs. 11, 12 and 13 apparently leads to eqs. 14 and 15, which with eqs. 6, 7 and 10 leads to eq. 16. This relates the stereoselectivity factor **s** to the extent of conversion *C* and the e.e.

$$([S]_{mf}/[S_o]_{mf}) = ([S]/[S_o]) \qquad (14)$$

$$([R]_{mf}/[R_o]_{mf}) = ([R]/[R_o]) \qquad (15)$$

$$\mathbf{s} = \{\ln[(1-C)(1 - \text{e.e.})]\}/\{\ln[(1-C)(1 + \text{e.e.})]\} \qquad (16)$$

However, the validity of eq. 13 cannot be assumed in the general case, as it depends on there being no change in the total number of moles in the reaction mixture. This condition will be met as long as a molecule of *R* produces a molecule of P_R, and a molecule of *S* produces a molecule of P_S. This indeed corresponds to the majority of known strategies employed in kinetic resolution, so the unstated assumption represented by eqs. 14 and 15 is apparently justified.

Interestingly, however, cases may be envisaged wherein there is a change in the number of moles present in the reaction mixture (without prejudice to the overall mass balance). This may happen, for instance, in the case of a fragmentation reaction, which would produce two molecules of product (different or not) from one of *R* or *S*. Alternatively, condensation reactions represent an example involving a decrease in the number of moles.

In such cases, eq. 13 would not be valid, thus also invalidating eqs. 14-16. Eqs. 14 and 15 would then be replaced by a complex relation of the type given by eqs. 17 and 18 respectively, where *n* is the number of product molecules formed from a single molecule of *R* or *S*. Apparently, no simple approach to an analog of eq. 16 is possible.

$$([S]_{mf}/[S_o]_{mf}) = 2[S]/\{n([R]_o + [S]_o) - (n-1)([R] + [S])\} \quad (17)$$

$$([R]_{mf}/[R_o]_{mf}) = 2[R]/\{n([R]_o + [S]_o) - (n-1)([R] + [S])\} \quad (18)$$

CONCLUSION

In conclusion, the current theory of kinetic resolution appears to be valid by happenstance, and its elaboration to the general case cannot be assumed. The theory

should be used with caution as it is apparently inapplicable in the case of processes that occur with a change in the number of molecules.

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