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Best practice considerations for using the selectivity factor, *s*, as a metric for the efficiency of kinetic resolutions

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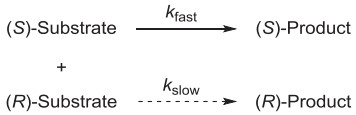
ABSTRACT

The suitability of using the selectivity factor, *s*, as a metric for kinetic resolution reactions and the errors associated with its measurement are considered. Investigation of the analytical error associated with HPLC analysis of a kinetic resolution reveals that one of the largest potential sources of variation arises from the ability of a practitioner to integrate the peaks from a single analysis. The consequences of this error on the reliability of reported *s* values are discussed, and some general rules for good practice regarding the use and reporting of *s* as a metric are suggested.

1. Introduction

Kinetic resolution (KR) is a widely-used process in academia and industry for separating the enantiomers of a substrate from a racemic or scalemic mixture (Scheme 1).[1] The principle of KR relies on the reaction of a chiral reagent or chiral catalyst-derived species with each enantiomer of the substrate taking place *via* diastereomeric transition states. The difference in free energy between these two transition states ($\Delta\Delta G^{\ddagger}$) dictates the difference in rate constants (k) for the reaction of each enantiomer. Effective KR protocols have been developed for numerous substrate classes using many different types of reaction including acylation, oxidation, silylation, nucleophilic ring-opening, and cycloadditions amongst others.[1]

The most commonly-applied metric to assess the efficiency of a given KR is the selectivity factor (s), which is defined as the rate constant for the reaction of the fast-reacting enantiomer divided by the rate constant for the slow-reacting enantiomer (eq. (1)). Consequentially, s can also be related to the difference in free energy between the diastereomeric transition states ($\Delta\Delta G^{\ddagger}$).



Scheme 1. General KR reaction.

$$s = \frac{k_{fast}}{k_{slow}} = e^{\Delta\Delta G^{\ddagger}/RT} \quad (1)$$

While the direct measurement of such kinetic parameters is practically challenging, s is usually more conveniently calculated using the reaction conversion (c) and the % enantiomeric excess (ee) of either the recovered substrate or the reaction product (eq. (2) or eq. (3), respectively) as originally outlined by Sih and co-workers[2a] for enzymatic KRs, and Kagan and Fiaud[2b] for general cases.[3] The reaction conversion (c) can itself be conveniently calculated using the ee of recovered substrate and product (eq. (4)). Importantly, calculation of s using these equations requires the KR to be irreversible and first-order in substrate for the selectivity-determining step, with more detailed kinetic analysis required to interrogate processes with more complex rate laws.[4,5]

$$s = \frac{\ln[(1-c)(1-ee_{substrate})]}{\ln[(1-c)(1+ee_{substrate})]} \quad (2)$$

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$$s = \frac{\ln\left[1 - c\left(1 + ee_{product}\right)\right]}{\ln\left[1 - c\left(1 - ee_{product}\right)\right]} \quad (3)$$

$$c = \frac{ee_{substrate}}{ee_{substrate} + ee_{product}} \quad (4)$$

The distinct rate constants for the reaction of each enantiomer of substrate mean that the relative concentrations, and hence relative *rates* of reaction, of each enantiomer vary throughout the course of a KR. The non-linear relationship between conversion and ee in a KR makes comparison of two different reactions using only these parameters difficult. Therefore *s*, if used correctly, is a particularly useful metric for comparing different KRs, as for a given process *s* should remain constant and be independent of the reaction conversion.[6] However, the logarithmic nature of *s* makes direct comparison of values for different KRs non-intuitive. For example, while the difference in synthetic utility for two reactions that give yields of 50% and 90% is readily understood, the same is not the case for KRs with $s = 50$ and 90. Moreover, the non-linear nature of the equations used to calculate *s* means that small inaccuracies in measuring either conversion or ee can lead to large variations in *s*. It is commonly appreciated that an enantioselective reaction reported as giving 99% ee and 70% yield will have small errors associated with measuring these values[7]; however the magnitude of error in *s* calculated for a KR measured to give 99% ee at, for example, 52% conversion is not as easily inferred. To exemplify this point, uncertainty in the measurement of ee within the range 98.5–99.5% ee for a KR at 52% conversion results in variation in the calculated value of *s* in the range of 102–138; while the same uncertainty in ee for a KR at 55% conversion results in a smaller spread of *s* values in the range of 44–57.

A convenient visual comparison of reactions with different *s* values is obtained by plotting conversion against either substrate or product ee (Figs. 1 and 2). For each value of *s*, the ee of substrate increases throughout the reaction (Fig. 1), while the ee of product starts at a maximum value and decreases, tending towards 0 at 100% conversion (Fig. 2). The initial maximum ee of product is inherently limited by *s* (eq. (1)). For example, in a KR with $s = 10$, the maximum ee of product is determined by the ratio of rate constants for the reaction of each enantiomer, leading to an initial ee of ~82% (91:9 er). In contrast, the ee of substrate continues to increase over the full reaction course, allowing the isolation of highly enantioenriched material even for KRs with only a modest *s*.

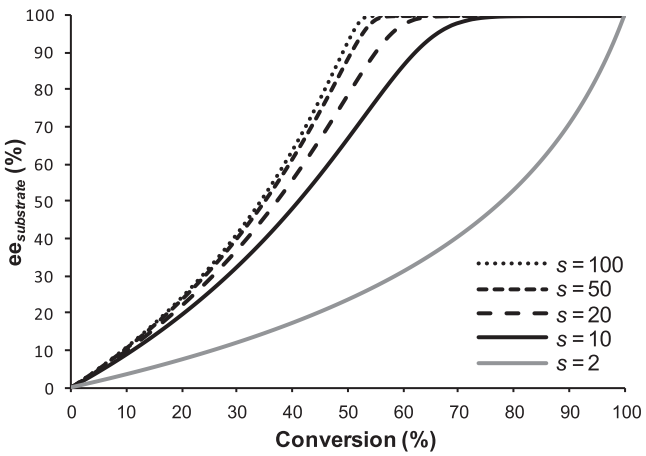

Fig. 1. Evolution of %ee of substrate with reaction conversion.

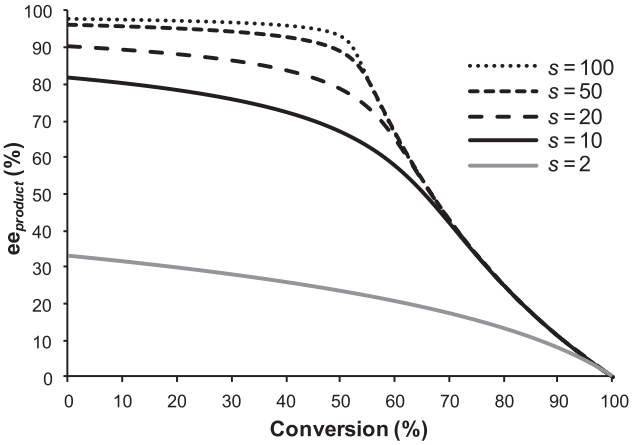

Fig. 2. Evolution of %ee of product with reaction conversion.

For example, in a KR with $s = 10$, the unreacted substrate can be recovered at 72% conversion (maximum 28% yield) in 99% ee. Such plots also highlight the errors associated in calculating *s*,[4,5] with only small inaccuracies in measuring either conversion or ee leading to potentially large difference in the calculated value of *s*, a problem that is expected to be particularly exacerbated for high *s* values.

The power of modern catalytic methods has led to numerous advances in kinetic resolutions to provide a range of highly effective resolution processes. However, based upon our experience from a practical perspective, as well as informative referee comments, the use of *s* as a metric for kinetic resolutions is often misrepresented. In particular, the suitability and accuracy of reporting *s* values often does not take errors into consideration, particularly for values of $s > 50$. Herein, we first outline suggested experiments and analyses to ensure that *s* is an appropriate metric for a given KR. From a practical perspective we propose a simple approach to estimating the analytical and operational error in measuring conversion and ee, and highlight the implications these have on the calculation of *s*. Considering these errors in the context of synthetic applicability, suggested boundaries for reporting *s* values to an appropriate number of significant figures are put forward. These general guidelines should aid in the comparison and use of *s* to evaluate the effectiveness of a KR.

2. Results and discussion

2.1. Nomenclature

There is currently no universally accepted abbreviation for "selectivity factor" in KRs, with *s* (italics), S, **s** (bold) and k_{rel} all having been used in the literature, while the abbreviation *E* is commonly used for enzymatic KRs. We favour the abbreviation *s* (lowercase, italics), as it is most commonly used, is clear in all typefaces, and importantly avoids ambiguity with the main text and/or stereochemical descriptors. For clarity in schemes, and axis and column titles the use of ***s*** (lowercase, italics, and bold) may also be appropriate on the grounds of stylistic discretion.

2.2. Practical considerations

In a typical small-scale KR performed as part of a method development, or for assessing substrate scope, it is likely that both the experiment and analysis will be performed only once.[6,7] It is therefore important to consider the potential analytical errors

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