SELECTIVITY

a Computer Program for the Determination of the Enantioselectivity (*E*-Value) in the Kinetic Resolution of Enantiomers

Kurt Faber, Wolfgang Kroutil

Department of Chemistry, University of Graz, Heinrichstrasse 28, A-8010 Graz, Austria.
<Kurt.Faber@Uni-Graz.at> <Wolfgang.Kroutil@Uni-Graz.at>

When a racemic substrate is subjected to an enzymatic reaction (e.g. hydrolysis), chiral discrimination of the enantiomers occurs [1,2]. It should be noted that the chirality does not necessarily have to be of a central type, but also can be axial or planar to be 'recognized' by enzymes. Due to the chirality of the active site of the enzyme, one enantiomer fits better into the active site than its counterpart and is therefore converted at a higher rate. As a consequence, each of the enantiomers from a kinetic resolution of a racemate can be obtained in only 50% yield. To ensure a high selectivity for both enantiomers, the difference in the reaction rates of the individual enantiomers should be as large as possible. In some rare ideal cases it is so extreme that the 'good' enantiomer is transformed quickly and the other is not converted at all. Then the enzymatic reaction will cease automatically at 50% conversion, when there is nothing left of the more reactive enantiomer.

In practice, however, most cases of enzymatic resolution of a racemic substrate do not show this ideal situation. In such cases the difference in - or better the ratio of - the reaction rates of enantiomers is not infinite, but measurable. What one observes in these cases, is not a complete standstill of the reaction at 50% conversion but a marked decrease in reaction rate at around this point. In such cases one encounters some crucial dependencies:

- The velocity of the transformation of each enantiomer varies with the degree of conversion, since the ratio of the two enantiomers does not remain constant during the reaction.
- Consequently, the optical purity of both substrate ($e.e._S$) and product ($e.e._P$) becomes a function of the extent of conversion.

A very useful treatment of the kinetics of enzymatic resolution, describing the dependency of the conversion (c) and the enantiomeric excess of substrate ($e.e._S$) and product ($e.e._P$), was developed by C. J. Sih in 1982 [3] on a theoretical basis laid by K. B. Sharpless [4] and K. Fajans [5]. The parameter describing the selectivity of a kinetic resolution was introduced as the dimensionless

'Enantiomeric Ratio' (E), which remains constant throughout the reaction and is only determined by the 'environment' of the system. A related alternative method has been proposed more recently [6, 7].

For irreversible reactions, such as an ester hydrolysis in an aqueous medium or acyl transfer reactions using enol esters or acid anhydrides as acyl donors, the selectivity of the reaction - expressed as the Enantiomeric Ratio (*E*) [8] - can be mathematically linked to the conversion (c) of the reaction, and the optical purities of substrate ($e.e._S$) and product ($e.e._P$).

The dependence of the enantioselectivity and the conversion of the reaction is

for the product:

$$E = \frac{\ln [1-c\,(1+e.e._P)]}{\ln [1-c\,(1-e.e._P)]}$$

for the substrate:

$$E = \frac{\ln [(1-c)\,(1-e.e._S)]}{\ln [(1-c)\,(1+e.e._S)]}$$

c = conversion, $e.e._S$, $e.e._P$ = enantiomeric excess of substrate (S) and product (P);
E = Enantiomeric Ratio [8].

The above mentioned equations give reliable results except for very low and very high extents of conversion, where accurate measurement is restricted by errors derived from sample manipulation. In such cases, the following equation is recommended instead, because only values for the optical purities of substrate and product need be measured. The latter are *relative* quantities in contrast to the conversion, which is an *absolute* quantity [8].

$$E = \frac{\ln \dfrac{[e.e._P\,(1 - e.e._S)]}{(e.e._P + e.e._S)}}{\ln \dfrac{[e.e._P\,(1 + e.e._S)]}{(e.e._P + e.e._S)}}$$

Using the equations discussed above, the expected optical purity of substrate and product from a kinetic resolution can be calculated for a chosen point of conversion and the Enantiomeric Ratio (*E*) can be determined as a convenient constant value for the 'enantioselectivity' of an enzymatic resolution. As a rule of thumb, Enantiomeric Ratios below 15 are unacceptable for practical purposes. They can be regarded as moderate to good from 15-30, and above this value they are excellent. It must be emphasized that values of $E > 200$ cannot be accurately determined due to the inaccuracies emerging from the determination of the enantiomeric excess (e.g. by NMR, HPLC or

GC) due to the fact that in this range even a very small variation of $e.e._S$ or $e.e._P$ causes a significant change in the numerical value of *E*. It should be noted that in chemo-catalysis the stereoselectivity factor (s) [9] is more widely used. Since it is mathematically identical and thus synonymous to the *E*-value, the SELECTIVITY program can be likewise applied.

Recommended Reading:

1 K. Faber, *Biotransformations in Organic Chemistry*, 6th edition, pp. 38-43. Springer, Heidelberg, **2011**.

2 C. J. Sih, S.-H. Wu, *Topics Stereochem.* **1989**, *19*, 63.

3 C.-S. Chen, Y. Fujimoto, G. Girdaukas, C. J. Sih, *J. Am. Chem. Soc.* **1982**, *104*, 7294.

4 V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, *103*, 6237.

5 G. Bredig, K. Fajans, *Ber. dtsch. chem. Ges.* **1908**, *41*, 752.

6 A. J. J. Straathof, J. L. L. Rakels, J. J. Heijnen, *Biocatalysis* **1992**, *7*, 13.

7 J. B. A. van Tol, J. A. Jongejan, A. Geerlof, J. A. Duine, *Rec. Trav. Chim. Pays-Bas* **1991**, *110*, 255.

8 J. L. L. Rakels, A. J. J. Straathof, J. J. Heijnen, *Enzyme Microb. Technol.* **1993**, *15*, 1051.

9 H. B. Kagan, J. C. Fiaud, *Topics Stereochem.* **1988**, *18*, 249; R. E. Gawley, *J. Org. Chem.* **2006**, *71*, 2411; K. Faber, *Enantiomer* **1997**, *2*, 411.