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Interactive analysis of selectivity in kinetic resolutions

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Abstract

Kinetic resolution is a widely used technique, but the mathematical description is awkward to manipulate. This can lead to errors in calculations, and can also make it difficult to assess the effects of the uncertainty in the measurements on the calculated values. This paper presents a convenient method for handling the data generated by kinetic resolution studies. © 1999 Elsevier Science Ltd. All rights reserved.

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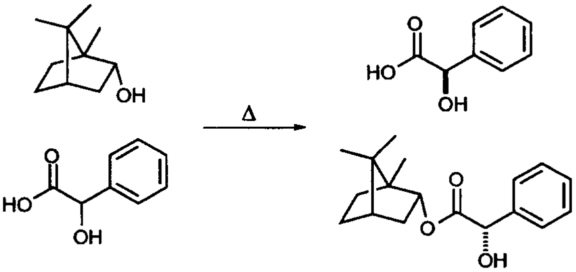
Kinetic resolution is an important technique, which is very widely used. A racemic starting material is reacted with a chiral reagent, but the reaction is not allowed to go to completion. When the reaction is stopped, both the product and the starting material will be enantiomerically enriched. A reaction which may be an early example of this process is illustrated in Scheme 1.[1]



Scheme 1. An early example of kinetic resolution? Mandelic acid and borneol[1]

Many newer papers describe kinetic resolution results, and a number of examples have been published this year.[2] The mathematical analysis of reactions of this type has been reviewed by Kagan and Fiaud[3] and the crucial equation is for the selectivity of the reagent, S. In order for the kinetic resolution to occur, the rates of reaction of the two enantiomeric starting materials must be different. S is defined as the ratio

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of these rates, and can be related to the enantiomeric excess of the unreacted starting material and the conversion (c) by Eq. 1.

$$S = \frac{\ln[(1-c)(1-ee)]}{\ln[(1-c)(1+ee)]} \qquad (1)$$

Eq. 1[†] is non-linear, and its complexity makes it difficult to estimate the results, and so to assess whether or not a calculation is giving reasonable answers. There is a trade off between the enantiomeric excess which can be obtained in a reaction and the yield (conversion) of the reaction. It is not immediately obvious whether a reagent which gives 99% ee and 60% conversion is better or worse than a reagent which gives only 97% ee but 70% conversion.

The application of this equation to find S is straightforward provided that c and ee are known. If S has been found by a separate experiment, it is less easy to calculate the expected enantiomeric excess for different conversions. It is also difficult to analyse the uncertainty in the calculation of S. Any measurement will have some uncertainty associated with it. If an enantiomeric excess is measured with a precision of ±1%, what will the corresponding uncertainty be in S? These questions are likely to remain unanswered, unless there is a straightforward way of manipulating the data. In this communication, we describe a Java applet, KinRes, which makes this possible.

Java is a computer language which can be used to write programs which can be run within web-browsers.[4] This means that a Java applet should be able to run on any computer with a suitable web-browser, and not be limited to particular makes of computers. The applet has been tested on a variety of machines, and runs successfully on every computer tested which was able to run a suitable web-browser.[5] The program is available on the URL: http://www.ch.cam.ac.uk/MMRG/kinres/.

Opening this web page should produce a display similar to that in Fig. 1. The details of the display vary slightly from computer to computer. If a number is typed in any of the three boxes, to assign a value to S, ee, or c, then a graph of the variation of the other two quantities with respect to each other is plotted for this value. If two values are entered, then the third quantity is calculated and the result displayed. A graph of the variation of the two values which are entered is drawn for the calculated value of the third variable.

If a single value for S is entered, or a value for each of ee and c, then the graph results are recorded in the box at the lower left hand corner of the screen, so that the results of different experiments may be compared. Fig. 1 shows a series of lines, each of which is based on a circled point corresponding to 95% conversion and differing enantiomeric excesses, ranging from 50% to 99%. The selectivity, S, is calculated to vary from 1.42 to 3.29 for these results.

At the top of the graph, where the point measured is on a part of the line which is almost horizontal, a small error in the measurement of ee, would lead to a large difference in S. A conversion of 95% and an ee of 99% corresponds to a selectivity S of 3.29. If the ee is mis-measured as 98%, S falls to 2.98, a change of 10%. If the ee is measured as 99.5%, an error of half of 1%, the change in S is also 10%, this time getting larger.

Where the graph is steeper, errors in ee have a less dramatic effect but errors in the measurement of conversion will now greatly effect the measurement of S. These graphs, therefore, provide a rapid way of testing how sensitive the calculated values of S are to errors in the experiment. It is not uncommon for papers to calculate S based on just one measurement. It is clear from the above analysis that this gives

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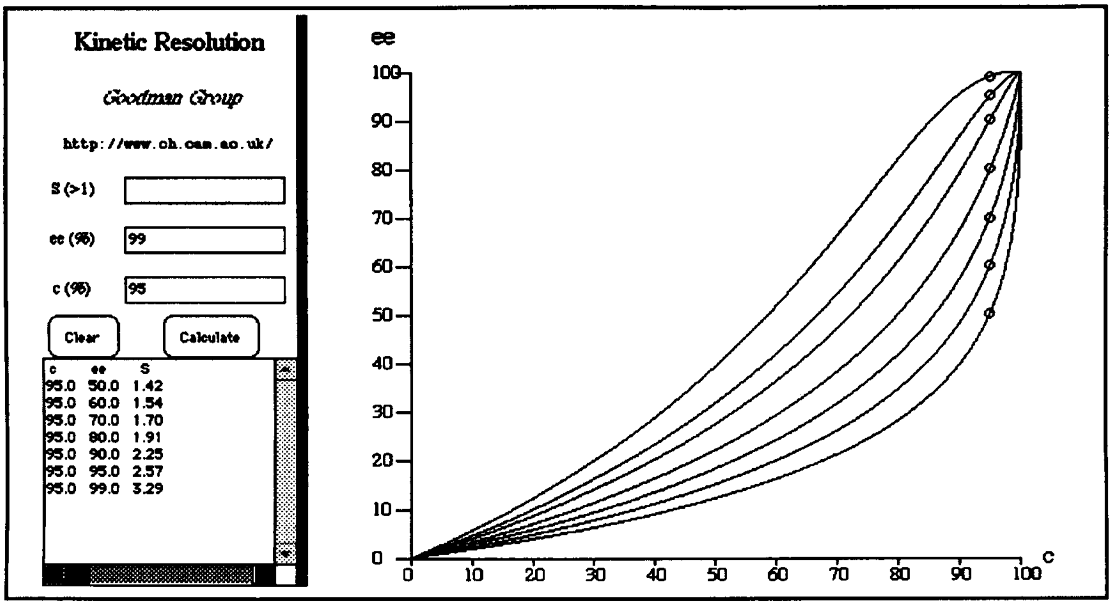
[†] The enantiomeric excess of the starting material is given as ee. The conversion, c, is the amount of the product divided by the initial amount of the racemic starting material.



Kinetic Resolution

Goodman Group

http://www.ch.cam.ac.uk/

S (>1)

ee (%) 99

c (%) 95

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c     ee    S
95.0  50.0  1.42
95.0  60.0  1.54
95.0  70.0  1.70
95.0  80.0  1.91
95.0  90.0  2.25
95.0  95.0  2.57
95.0  99.0  3.29
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Figure 1. The appearance of the applet KinRes after several pairs of values for ee and conversion have been added

a large uncertainty in the value of S which is calculated, and so should be used to assess the efficacy of new reagents with care.

There are a number of assumptions in the calculation of Eq. 1. In particular, it is assumed that the reactions are of the first order, with respect to the substrates. If this is not the case, then a different form of the equation should be used. KinRes can also be used to test whether this is necessary, by plotting lines for different conversion and enantiomeric excess pairs of measurements in order to assess whether all of the points fall on the same line, after experimental error has been taken into account.

The reaction illustrated in Scheme 1 is not necessarily a kinetic resolution. It may be that the reaction is under thermodynamic control and not kinetic control. If this is the case, then the calculation of a selectivity, S, would not give a reliable method for predicting the enantiomeric excesses which may be expected at other conversions. The paper also reports that mandelic acid may racemise under the reaction conditions and so the process could be regarded as a dynamic kinetic resolution.[6] If this is the case, then the calculation of S will not be a useful way of analysing the response of the reaction to different conditions. In both of these cases, however, the use of the KinRes applet with two or more experimental results, would make it clear whether or not Eq. 1 was appropriate for the analysis.

In summary, a program is available which can be run over the internet on a wide range of computers and web-browsers, which makes the analysis of the results of kinetic resolution experiments much easier. This should be a useful tool for studies of this type.

Acknowledgements

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4. http://www.javasoft.com/. The applet is written using Java 1.0 exclusively, and so runs on a wide range of web browsers.
5. Machines tested included Apple Macintoshes, PCs (Windows 95, Windows 98, Windows NT), SGI workstations (IRIX 5.3 and IRIX 6.X). Web browsers included Netscape 3.0.4, Netscape 4.0, Internet Explorer 5.0.
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