University of Groningen

Dutch Resolution

Broxterman, Quirinus B.; Echten, Erik van; Hulshof, Lumbertus A.; Kaptein, Bernard; Kellogg, Richard M.; Minnaard, Adriaan J.; Vries, Ton R.; Wynberg, Hans

Published in:
Chimica Oggi-Chemistry Today

DOI:
[10.1002/chin.199907313](https://doi.org/10.1002/chin.199907313)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
1999

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Broxterman, Q. B., Echten, E. V., Hulshof, L. A., Kaptein, B., Kellogg, R. M., Minnaard, A. J., Vries, T. R., & Wynberg, H. (1999). Dutch Resolution: Dutch Resolution, a New Technology in Classical Resolution. *Chimica Oggi-Chemistry Today*, 30(7), 34-37. <https://doi.org/10.1002/chin.199907313>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Using the novel technology described, resolution of racemates can be considered as a reliable method to produce enantiomerically pure product

QUIRINUS B. BROXTERMAN^{a*}
ERIK VAN ECHTEN^b
LUMBERTUS A. HULSHOF^c
BERNARD KAPTEIN^a
RICHARD M. KELLOGG^b
ADRIAAN J. MINNAARD^a
TON R. VRIES^b
HANS WYNBERG^b

a. DSM Research, Organic Chemistry & Biotechnology Section
P.O. Box 18
6160 MD Geleen,
The Netherlands

b. Syncom BV
P.O. Box 2253
9704 CG Groningen,
The Netherlands

c. DSM Andeno
P.O. Box 81
5900 AB Venlo, The Netherlands

* corresponding author

ABSTRACT

A new method for the resolution of racemates through diastereomeric salt formation is presented. An essential feature of this new method is the use of mixtures of resolving agents. The application of certain mixtures results in an efficient and fast crystallisation of enantiomerically enriched salts. It turns out that these salts still contain a mixture of the resolving agents. Via this new method, referred to as the Dutch Resolution (DR) technology, the success rate in identifying and performing adequate resolutions of racemates has been greatly improved.

"DUTCH RESOLUTION", A NEW TECHNOLOGY IN CLASSICAL RESOLUTION

INTRODUCTION (1)

Exactly 150 years ago this year, Louis Pasteur described for the first time the resolution of a salt of tartaric acid. This accomplishment forms a cornerstone of stereochemistry (2). Conversion of a racemic mixture into a mixture of diastereomers using an enantiomerically pure resolving agent, and subsequent separation of the diastereomers (3), is known as the "classical method of resolution" (4). Although classical resolution is still the most important industrial method for the preparation of enantiopure

compounds, despite 150 years of experience it remains a method of trial and error.

The treatment of racemic α -phenethylamine with L-(+)-tartaric acid is a typical textbook example (Scheme 1). Of the two diastereomeric salts formed, the (-,+) salt (n-salt) has the lowest solubility and precipitates while the (+,+) salt (p-salt) remains in solution (5). The precipitated salt is isolated and subsequently converted into the desired enantiomerically enriched (-)- α -phenethylamine and the resolving agent, which can be reused.

Scheme 1

Have you renewed your subscription to CHIMICAoggi?
Don't stand the chance of missing
KEY issues within the year!

Figure 1

The formation of crystalline diastereomeric salts of different solubility can be visualised by a ternary phase diagram (Figure 1) with the pure p- and n-salt at the corners of the baseline and pure solvent at the top of the diagram.

In this so called conglomerate resolution, the positioning of the eutecticum **E** (i.e. the eutectic composition X_E) is of considerable importance since it determines the efficacy of a resolution. An ideal resolution of a racemate (i.e. X_{rac}) is performed starting at point **R** in the diagram yielding the maximum amount of pure n-salt and leaving a saturated solution of p- and n-salt of eutectic composition (**E**).

In practice, the usual approach in finding a suitable resolving agent for a given substrate consists of trying a number of resolving agents in a number of solvents. The precipitate is isolated, and the yield and e.e. of resolved racemate are determined.

Problems encountered in developing classical resolutions are caused by the following reasons:

- Crystals are not obtained (unsaturated or super-saturated solutions, or formation of oils that crystallise slowly).
- An unfavourable position of the eutecticum (i.e. near a 50:50 composition) leads to low yields of enantiomerically pure material.
- "Solid solution" behaviour requires frequent recrystallisations to obtain high e.e.'s.
- Double salt formation can lead to incorporation of both enantiomers of the substrate.

All these complications result in a low success rate for typical resolution experiments, as described by Jacques, Collett and Wilen (6). We here describe a new approach to this problem which leads to a much higher success rate.

A COMBINATORIAL RESOLUTION

The application of a mixture containing eleven enantiomerically pure carboxylic acids in the

resolution of racemic *m*-Cl-phenethylamine resulted in rapid precipitation of a crystalline salt. Surprised by this result, we realised that in this way a number of resolving agents could be screened in one trial, leaving only the choice of the solvent. This approach (7) should lead to a quick selection of the appropriate resolving agent. Analysis of the salt showed that it contained *m*-Cl-phenethylamine in optically enriched form and, moreover, not one but *three* of the resolving agents applied. Thus, although one could expect the least soluble salt to precipitate from the solution, a mixture of several resolving agents was found instead. A closer look revealed that not a mixture of crystals had been obtained, as expected, but a "mixed crystal" containing the resolving agents in non-stoichiometric amounts.

In the hope that a synergistic effect would occur on the application of mixtures of resolving agents instead of one agent at a time a large number of racemic acids and amines was subjected to resolution. Every resolution was carried out using a mixture of three or four resolving agents.

To our surprise, it turned out that with more than 90 of about a hundred substrates used, rapid precipitation of a salt took place.

The isolated salts almost invariably consisted of the substrate in reasonable to high e.e. and a mixture of the resolving agents employed, in non-stoichiometric amounts. In cases where the e.e. was only moderate, one or two recrystallisations were generally sufficient to obtain the desired high e.e.. In these recrystallisations, the ratio of the resolving agents present in the salt changed only slightly. A condensed selection of the large number of racemates resolved using this method is shown in Scheme 2.

Scheme 2

X-RAY STRUCTURE OF A "MIXED" CRYSTAL

Analysis of the salts isolated is routinely done by NMR, GC or HPLC. Although the amounts of the various resolving agents present can easily be determined this way, it does not show how the components are distributed in the crystal. In order to get more insight in the distribution of the different resolving agents in the crystalline phase, the crystal structure was examined more closely. As an example, the resolution of rac-ephedrine was chosen, using a mixture of phencyphos, chlocyphos and anicyphos. These resolving agents belong to an entire family of chiral phosphoric acids, developed by some of us twelve years ago (8). The resolution afforded a salt containing, apart from (1*R*,2*S*)-ephedrine, both phencyphos and chlocyphos in non-stoichiometric

Scheme 3

amounts (Scheme 3). X-ray diffraction of a suitable crystal revealed that these acids were randomly distributed in the crystal. In other words, phenicyphos and chlocyphos are randomly distributed over the positions of the phosphate anion in the crystal lattice.

A FAMILY APPROACH

In the course of this work it became apparent that some combinations of resolving agents were better than others. In particular the use of homochiral families that differ only in a substituent proved to be especially effective. Other variations are possible some of which are described in the original article (1). Several families

Scheme 4

currently in use are depicted in Scheme 4.

In the development of a resolution protocol for a given racemate, different families can be tested separately or together. The combination of resolving agents found in the precipitated salt is then used to repeat the experiment. On occasion a single resolving agent is found in the precipitate. Logically, this resolving agent is then applied further on.

A typical resolution experiment is shown in Scheme 5. To a solution of the racemic amine in an appropriate solvent is added one equivalent of a mixture of three enantiomerically pure phosphoric acids in a ratio of 1:1:1. This ratio is arbitrarily chosen, and can be changed in follow-up experiments, based on insight from the results of the first experiments. The precipitate formed is filtered off, washed and analysed. In this particular case, it contains the

Scheme 5

nearly enantiomerically pure amine and the phosphoric acids in a ratio of 5:5:1.

The family approach certainly does not exclude the use of other combinations. For instance, it turned out to be possible to use a racemic resolving agent as part of a mix. In another example, using one of the family members with opposite absolute configuration also gave a satisfactory resolution result. Even an achiral agent could be used as part of the resolution mix, e.g. a combination of enantiomerically pure mandelic acid with phenylacetic acid.

Therefore, instead of performing a rapid combinatorial screening of a mixture of resolving agents, we unexpectedly found that certain mixtures give much better results than the resolving agents alone. Precipitation of a salt is much more rapid and formation of an oil is less a problem. The enantiomeric excesses are nearly invariably good. Although the development of a resolution for a racemic substrate still has trial and error aspects, the chance of success has been strongly increased.

APPROACH TOWARDS UNDERSTANDING THE TECHNOLOGY

Research is in progress to obtain more insight in the physical background of this new resolution technique. For example, in order to understand the thermodynamic origin of this type of resolution, we are studying the changes in solubility behaviour and

Figure 2

eutectic composition as a result of the mix composition. Whereas a classical resolution with a single resolving agent can be described by a ternary phase diagram, as depicted in Figure 1, resolution with a mix of n components can be described with a $(n+1)$ dimensional phase diagram (at constant temperature). For a two-component mix this can be visualised by a pyramidal phase diagram (Figure 2). The left and right side of this diagram represent the

phase diagram of the resolution with one of the two resolving agents, and the front and back side represent the phase diagram of the two (pure) enantiomers with the mixture of resolving agents.

CONCLUSION

The application of mixtures of resolving agents in the resolution of racemates has significantly decreased some of the problems associated with classical resolution. In nearly all cases a precipitate is rapidly formed without the nuisance of oil formation. E.e.'s are nearly invariably good or can be improved by few recrystallisations. This means that - using the method described - resolution of racemates can be considered as a reliable method to produce enantiomerically pure product. Moreover, the time required to identify an adequate resolving agent (i.e. a mix of resolving agents) is now dramatically reduced - "from months to days".

This new concept is of commercial value. These days, there is an enormous increase in the pressure to reduce time-to-market for new Life Sciences molecules, especially for new drugs. Therefore, if a new drug development program requires rapid generation of a quantity of enantiomerically pure material out of the corresponding racemate, this method can materially shorten the time required to do so. The method also can offer a solution in case of failure to find an adequate single resolving agent. We

think that in principle the method can be scaled up to full plant-scale. Therefore, it is not necessary *per se* to develop a completely new method to prepare the enantiomerically pure product of interest (e.g. an asymmetric synthetic route) once it has been decided to produce the product on larger scale. In order to emphasise the difference between classical methods using single resolving agents and the use of mixes, we have introduced the term *Dutch Resolution* (DR-technology) for the application of this technology. DR-technology is now applied by SYNCOM and DSM-Andeno/RESCOM^{TM}, both located in the Netherlands.

REFERENCES