Resolutions with families of resolving agents
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Chapter 2

Resolutions via diastereomeric salt formation

This Chapter gives an overview of theoretical and practical aspects that come into play when using resolutions via diastereomeric salt formation. Some basic principles are given, as well as a thorough description of how to perform a resolution in practice. Subsequently, some basics of crystal growth are explained and the Chapter ends with a description of Dutch Resolution.
2.1 Principles and definitions

2.1.1 Racemate types

There are three known solid forms of racemates, namely conglomerates, racemic compounds and solid solutions. The type of solid racemate found can be temperature dependent (see also Box 2.1).

A conglomerate is an equimolar mixture of two crystalline enantiomers that can, in principle, be mechanically separated. The most famous example is most likely sodium ammonium tartrate. Pasteur was able to resolve the racemic mixture by ‘crystal picking’, using a pair of tweezers. It turned out that he was quite lucky (Box 2.1), and he obtained crystals with a well-defined morphology that clearly revealed the difference between left- and right-handedness (Figure 2.1).

![Figure 2.1](image)

**Figure 2.1** The two enantiomers of sodium ammonium tartrate as observed by Pasteur

The melting point phase diagram characteristic for a conglomerate is illustrated in Figure 2.2. The lowest melting point is always found for the 50:50 mixture of enantiomers. This point is called the eutectic point (E).

![Figure 2.2](image)

**Figure 2.2** Melting point phase diagram of a conglomerate
In principle, a conglomerate can be resolved without the aid of a resolving agent via spontaneous resolution. Resolution by means of recrystallization of a slightly enriched enantiomeric mixture is also possible. Moreover, it is sometimes possible to resolve a conglomerate by recrystallization from an optically active solvent. The resolution of conglomerates was thoroughly studied by Lahav et al., who discovered the use of so called ‘tailor-made additives’. These additives are compounds that are structurally very similar to the conglomerate. Use of a few percent of an enantiomerically pure additive inhibited the crystallization of one enantiomer dramatically. The enantiomerically pure additives were selectively adsorbed on certain crystal faces, causing a severe change in crystal morphology (Figure 2.3).

Figure 2.3 Examples of habit modification under the influence of tailor-made additives

In the first row the morphology of L-asparagine is shown, looking along the three axes. The next three rows show how the crystal habit changes considerably under the influence of three tailor-made additives, in this case L-glutamine, L-serine and L-aspartic acid, respectively. Chaplin et al. reported the use of a structurally dissimilar compound as additive in the resolution of a conglomerate.

It is assumed that less than 10% of racemic compounds form conglomerates as solids. Jacques et al. listed over 200 conglomerates, in which he also gave the results of earlier
New conglomerates are continuously being discovered. The factors that lead to the formation of a conglomerate are poorly understood, if at all. There are quite a few amino acids that are conglomerates. In addition, salts more often form conglomerates than neutral compounds. Of a number of reports, the work of Saigo and co-workers is highly pertinent in this area. He described the search for salts that form conglomerates for several racemic amines and amino acids.

In 1895, Wallach maintained that racemic crystals tend to be more densely packed than their chiral counterparts and that the avoidance of tight packing is the driving force for the formation of conglomerates. Although Wallach’s rule is still under debate, it is probably the only plausible explanation to date for the fairly rare occurrence of conglomerates.

*Racemic compounds* constitute the second class of solid racemates. These possess a crystal form in which the two enantiomers coexist in the same unit cell, in an ordered fashion. This type of racemate is often found in resolutions. The binary phase diagram of a racemic compound can look like that shown in Figure 2.4.

![Figure 2.4 Binary phase diagram of a racemic compound](image)

It is clear from Figure 2.4 that the melting point of the racemate of a racemic compound is higher than that of the enantiomerically pure compounds, contrary to the situation described for conglomerates.

*Solid solutions* are the third class of solid racemates. The enantiomers of these compounds coexist within the unit cell, but in an unordered manner. In other words, the crystal lattice does not discriminate between the enantiomers. If a compound forms a full solid solution, resolution is not possible for that particular system. A solid solution is sometimes referred to as pseudoracemate, although this term is in our opinion, quite confusing, and we shall avoid using it.

Often a combination of the racemate types is found, and *end solid solution* behavior is observed. In practice this means that it is difficult to reach the diastereomerically pure end
stage of a resolution. The prerequisites for a resolution to end up in a solid solution are not well understood.\[17\]

There are three types of solid solutions, as described by Roozenboom.\[18\] The three types are characterized by their melting point phase diagrams, as is illustrated in Figure 2.5. In an ideal solid solution (Roozenboom type I, on the left), the melting point (among other physical properties) is independent of the composition. Type II (in the middle) exhibits a maximum melting point for the racemate, whereas type III (on the right) has a minimum melting point for the racemate.

![Figure 2.5 Roozenboom type I, II and III solid solutions](image)

### 2.1.2 Resolvability and eutectic point

In a resolution process whereby a salt is formed, a racemic acid or base is brought into reaction with an enantiomerically pure resolving agent, forming diastereomers. Due to the difference in physical properties, there is usually a difference in solubility of the diastereomers. If so, it is possible, at least in principle, to separate the two diastereomers via fractional crystallization. To compare resolution processes, Fogassy\[19\] introduced the so-called S-factor, or resolvability, which is calculated by multiplying the chemical yield of the first obtained salt by the enantiomeric excess ($ee$) thereof:

$$S = 2 \cdot \text{yield} \cdot ee$$

The actual yield cannot be higher than 0.50 (or 50%), which is the reason for the factor 2. The enantiomeric excess can range between 0 and 1.0 (or 100%). Subsequently, the S-factor is always between 0 and 1, where unity corresponds to complete separation. The S-factor can also be approximated from the solubilities $k_{\text{more}}$ and $k_{\text{less}}$ of the two diastereomers: \[20\]

$$S_{\text{max}} \approx \frac{k_{\text{more}} - k_{\text{less}}}{k_{\text{more}}}$$
If a resolution is carried out under equilibrium conditions, the composition of the mother liquor is the composition of maximum solubility. This composition has the lowest melting point in a binary phase diagram and is referred to as the eutectic point. For an optimal resolution, the eutectic composition should be as close as possible to diastereomeric purity in the mother liquor.

From the eutectic composition $x_{eut}$, the theoretical maximum S-factor can be calculated:1,2

$$S_{max} = \frac{1 - 2 \cdot x_{eut}}{1 - x_{eut}}$$

This formula can be rewritten as:

$$x_{eut} = \frac{1 - S_{max}}{2 - S_{max}}$$

It is often observed that the maximum S-factor is not reached in a given resolution process. This can occur if an equilibrium is not established.

If $S_{max}$ is determined from the eutectic point, the maximum yield obtainable in one crystallization $R_{max}$ can be calculated by:

$$R_{max} = \frac{0.5 - x_{eut}}{1 - x_{eut}} \cdot 100\%$$

### 2.1.3 Supersaturation and meta-stable zone width

Normally, crystallizations are performed from a clear, homogeneous and well-mixed (isotropic) solution. The reagents are mixed in the appropriate solvent and heated until a clear solution is formed. Upon cooling the mixture, it will remain clear below the equilibrium dissolution temperature. This phenomenon is called *supersaturation*. Supersaturation is the driving force for the crystallization and can be expressed at a given temperature as shown below where $c$ is the concentration and $c_{eq}$ the equilibrium dissolution concentration at that temperature.

$$\beta = \frac{c}{c_{eq}}$$
Also, supersaturation can be expressed as $\sigma$:

$$\sigma = \frac{c - c_{eq}}{c_{eq}}$$

The higher the supersaturation of the solution, the sooner crystallization will start. Also, the crystallization rate is then likely to be higher. The supersaturation has an impact on the growth rate and growth mechanism of a crystal and the particle size.

The temperature range between the equilibrium dissolution temperature and the crystallization temperature is called the *meta-stable zone width*. This meta-stable zone width depends on the rate of cooling, so it can also be expressed as a temperature zone in which no crystallization occurs although the solution is supersaturated. If one waits long enough, crystallization will eventually start, since the solution is supersaturated. In the meta-stable zone, the driving force (difference between chemical potential of the solution phase and solid phase) is so small that no crystallization occurs within reasonable timeframes. However, at a certain cooling rate the meta-stable zone width is well defined.

### 2.1.4 Marckwald principle versus reciprocal resolutions

The Marckwald principle is the phenomenon that both enantiomers of a resolving agent give access to each enantiomer of the racemate to be resolved. These processes are mirror image related and can be carried out under the same circumstances.

The Marckwald principle can be applied in every resolution: the enantiomer that is present in the more soluble diastereomer (in the mother liquor) is liberated from the resolving agent and subsequently resolved with the enantiomer of the resolving agent. In the case natural resolving agents such as alkaloids are used, this cannot be done, since usually only one enantiomer is available.

This principle is easily confused with *reciprocal resolutions*. This means that if a given racemate can be resolved with a single enantiomer of a resolving agent, it is possible to resolve a racemic mixture of this resolving agent with one enantiomer of the racemate. These processes are not mirror image related.

### 2.2 Practice

In principle, the practical aspects of a resolution process are rather simple. However, among chemists it is often thought that the capability to perform a resolution is also a matter of art and most of all, experience. In this section, some of the basic experimental features are
outlined. In their book on resolutions, Jacques, Collet and Wilen devoted a whole chapter to experimental aspects and art of resolutions.23

2.2.1 Carrying out an experiment

In a nutshell, a small-scale resolution experiment wherein acid-base interactions are involved consists of only a few steps: the racemate and the resolving agent are mixed in a suitable solvent and heated until a clear solution is obtained. In general, one attempts to dissolve as much material as possible within a reasonable volume suitable for the glassware used. The clear solution is allowed to cool and if a salt precipitates, this is removed by filtration. The salt is either analyzed as such or the material to be resolved is liberated from the resolving agent and analyzed subsequently.

If the compound of interest has not been resolved before, the easiest way to screen a resolution is via a resolution matrix, in which various resolving agents are employed in different solvents.24 An example of a resolution table (matrix) is shown in Table 2.1.

Table 2.1 Typical resolution matrix

<table>
<thead>
<tr>
<th>Resolving agent</th>
<th>Solvent P</th>
<th>Solvent Q</th>
<th>Solvent R</th>
<th>Solvent S</th>
<th>Clear?</th>
<th>Yield</th>
<th>Ee</th>
<th>S-factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes/no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes/no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes/no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes/no</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Usually 1 mmol quantities of both racemate and resolving agent suffice. In the resolution matrix it is indicated whether a clear solution was obtained for which volume of which particular solvent. In addition, it is noted whether salts were obtained and what their consistency was. Also, the yield and ee of the precipitated salt are listed and the S-factor is calculated. From these preliminary results conditions for a larger scale experiment can be derived.

If salts are not obtained, other resolving agents should be screened, together with more apolar solvents and/or higher concentrations.

Resolutions are frequently carried out in polar solvents, such as methanol, ethanol, isopropanol or methyl ethyl ketone, with or without the addition of water. In some cases, more apolar solvents such as ethyl acetate or toluene are necessary. In their book, Jacques,
Collet and Wilen listed some of the general trends in solvent use in relation to the resolving agent used.25

2.2.2 Commonly used resolving agents
For the resolution of racemic acids, several naturally occurring alkaloids, such as brucine, cinchonine or quinine are available. A disadvantage of these alkaloids, in addition to their toxicity, is the fact that only one enantiomer is available. The alkaloids (−)-quinine and (−)-quinidine form an unusual exception, for those are ‘pseudoenantiomers’.

Other basic resolving agents are phenylethylamine and ephedrine. In Figure 2.6 the structures of some of the commonly used basic resolving agents are shown.

For the resolution of racemic amines, the choice of acidic resolving agents is somewhat limited. Tartaric acid and its diaroyl derivatives are widely used and are relatively cheap. Both enantiomers are commercially available. Other commonly used acidic resolving agents are mandelic acid, the camphor sulphonic acids and some N-acetylated amino acids. The structures of some commonly used acidic resolving agents are shown in Figure 2.7.
The choice of a resolving agent is not trivial; it also depends on experience and on known resolutions with related compounds. In our experience, it is not true that a certain resolving agent will necessarily resolve structurally related compounds, as is maintained by Kozma et al.\textsuperscript{26}

It is assumed that if the racemate and the resolving agents are structurally very similar, a very efficient resolution can be achieved.\textsuperscript{27} The main cause could be the formation of quasi-racemic diastereomeric salts, \textit{e.g.} in the resolution of phenylglycine with \textit{N}-acetylphenylglycine as resolving agent.

Despite all the effort undertaken to predict which resolving agents should be used for a given substrate,\textsuperscript{28} the choice of resolving agents still has trial-and-error aspects.

\subsection{Stoichiometry; Peachy-Pope resolutions}

For the first screening of a new resolution, a stoichiometry of 1:1 is convenient, meaning 1 molar equivalent of resolving agent \textit{versus} 1 molar equivalent of racemate. In principle, however, only 0.5 equivalent of resolving agent should suffice, knowing that only the less soluble combination of resolving agent and racemate will crystallize. However, when using 0.5 equivalents of resolving agent, both diastereomeric salts will be less supersaturated compared to the same resolution at the same concentration with 1 equivalent of resolving agent. If the less-soluble salt is still supersaturated, it will crystallize, but in a lower yield and higher \textit{ee}. The more soluble salt is more likely to become undersaturated and will hence not crystallize. Therefore, usually a slight improvement in results is obtained if less than one equivalent of resolving agent is used. Especially when a resolution is to be optimized for
large scale experiments and/or the resolving agent is rare or expensive, it is worthwhile to investigate the influence of stoichiometry on the resolution efficiency (S-factor). In practice, the use of 0.7 equivalents is usually the best option, since it combines the advantage of lower supersaturation with acceptable yields.

Another way of performing a resolution with only 0.5 equivalent of resolving agent is the method developed by Peachy and Pope, first described in 1899.29 In this method, 0.5 equivalent of resolving agent is used and the excess of racemic acid or base is neutralized by the addition of the necessary amount of an achiral acid or base. In this way, a neutral system is obtained. An example is the resolution of trans-1,2-cyclohexanediynamine with 0.5 equivalent of tartaric acid and 0.5 equivalent of propanoic acid as the chiral acid.30,31

2.2.4 Recovery of enantiomers from diastereomers
After a resolution experiment it is necessary to separate the resolving agents from the enantiomerically pure compound. This recovery process should be simple and selective, it should not cause racemization of the resolved material, and it should allow for the recovery of the resolving agent. The method of choice depends on the system. Generally, standard organic extraction procedures are used and the method of choice is a matter of common sense and knowledge of solubilities of the various compounds in the solvents used.

If an amine has been resolved with an acidic resolving agent, it is usually possible to stir the salt with dilute base (e.g. NaOH, NH₄OH or Na₂CO₃) and extract the amine with an organic solvent. After acidification of the aqueous phase and subsequent extraction, the acidic resolving agent can be recovered. However, sometimes it is more convenient to acidify the salt, such as with resolutions using the cyclic phosphoric acids.32 Upon acidification the phosphoric acid precipitates from the aqueous phase and can be removed by filtration. Afterwards, the mother liquor is made basic and extracted with an organic solvent to furnish the free amine.

When a racemic acid is resolved with a basic resolving agent, the salt is usually treated with aqueous acid, after which the acid is extracted with an organic solvent.

If standard procedures fail, other methods such as ion exchange resins can be used. These are especially useful if both components are water-soluble.

2.2.5 Other resolution methods
Since the physical properties of diastereomers differ, it is possible to take advantage of factors other than solubility to carry out a resolution of a racemate. If the racemate is volatile enough, one of the enantiomers can be distilled off in excess, in the case of using 0.5 molar equivalent of resolving agent. Without solvent the resolving agent will associate with the
racemate, and the enantiomer that is not, or only poorly, bound can be distilled off. This method has been applied to several amines by Kozma et al.\textsuperscript{33} It is limited in use to volatile racemates and to relatively small scale experiments.

In some cases it is possible to carry out a resolution \textit{via} an inclusion compound. A chiral host molecule is used to complex (hydrogen bonds) preferably one of the enantiomers of the racemate and crystallize. Several racemic alcohols have been resolved in this way.\textsuperscript{34} It is often assumed that a salt is formed during a resolution \textit{via} crystallization and this has led to several resolutions \textit{via} inclusion compounds being overlooked.\textsuperscript{35}

Other resolution methods that have been less frequently employed are resolution by liquid-liquid extraction,\textsuperscript{36} supercritical extraction\textsuperscript{37} or sublimation.\textsuperscript{38} Preparative HPLC is also often used, from relatively small amounts on a lab-scale to kilograms on an industrial scale.\textsuperscript{39}

### 2.3 Factors that influence the resolution efficiency

#### 2.3.1 Solubility difference; eutectic point

The main key to a successful resolution by crystallization is a large difference in solubility of the diastereomers. However, the respective solubilities of the diastereomers are usually not known beforehand. It is important to realize that the solvent used is in principle not responsible for the success of a resolution. The ratio between the solubilities is theoretically independent of the solvent used, provided that the solvation of both diastereomers is identical (ideal behavior).\textsuperscript{40} Sometimes, solvates are formed in a particular solvent (\textit{e.g.} hydrates in water),\textsuperscript{41} which give rise to different results. Hence, it is always useful to screen several (combinations of) solvents. Moreover, the temperature dependency of the solubilities of the two diastereomers is not identical (see Section 2.3.4).

The position of the eutectic point is also independent of the solvent. If the position of the eutectic is very unfavorable, \textit{i.e.} close to the racemic composition, it will not be possible to achieve a high resolution efficiency. In such a case it is better to switch to another resolving agent.

#### 2.3.2 Concentration; supersaturation

If the first salt of a resolution experiment is obtained in a yield higher than 50%, the \textit{ee} can never be 100% in a racemization free process. The solution was probably too concentrated. It is always useful to screen the resolution at different concentrations. As a rule, the lower the concentration, the higher the \textit{ee}, but the lower the yield. The optimal concentration can also be calculated from the ternary phase diagram, which is a diagram that combines both diastereomers with their solubilities.
Related to concentration is, of course, the degree of supersaturation. At high supersaturations, the solution is prone to nucleate. The nucleation rate will be much higher than the crystal growth rate and this usually leads to low resolution efficiencies, because of the tendency towards the formation of amorphous powders.

2.3.3 Stirring; seeding

In principle, it is better to stir during a resolution by crystallization. In this way, the nuclei that are formed are equally divided over the reaction flask and this leads to uniform results. Also, the reproducibility of stirred resolutions is usually better. Furthermore, stirring promotes the establishment of a thermodynamic equilibrium. On the other hand, when performing preliminary experiments in small test tubes, it is sometimes better to evaporate the solvent slowly, since the solubilities of the diastereomers are not known. Concentration gradients are common for this method. The higher the stirring speed, the smaller the crystals will be. If crystals are needed for X-ray or if a study of the morphology is necessary, it is better not to stir.

If diastereomERICALLY pure material is available from previous experiments, this can be used to seed the resolution. This usually leads to better results. Seeding is only useful when performed in the meta-stable zone width (see Section 2.1.3), because only then can the nucleation be influenced. In practice, if the seeds do not dissolve immediately, the seeding will be effective.

The resolution of \(N\)-methylamphetamine with tartaric acid under Peachy-Pope conditions was examined under different circumstances: with and without stirring and with seeding and stirring (Figure 2.8).42

![Figure 2.8 Resolution efficiency as a function of stirring and/or seeding](image)
The maximum resolution efficiency (S-factor) is established much faster when the resolution is stirred, which means that a thermodynamic equilibrium is established more rapidly. Seeding improved the S-factor only marginally in this experiment.

### 2.3.4 Temperature

Since the solubility of a diastereomer is in general dependent on the temperature, it is not unlikely that the resolution efficiency will also be temperature dependent. Usually, resolution mixtures are allowed to cool to room temperature and subsequently filtered at that temperature. In principle, it would be better to screen a resolution at different temperatures, especially when a low resolution efficiency is obtained after filtration at room temperature. Since the temperature dependency of the solubility of both diastereomers can be different, performing the resolution at elevated temperatures can lead to striking improvements of the resolution. This was illustrated in the resolution of pipecolic acid xylydes with tartaric acid and O,O'-dibenzoyltartaric acid. The optimum temperatures of these resolutions turned out to be in the range of 45-50°C.

### 2.4 Basics of crystal growth

As explained before, classical resolution started with the observation of Pasteur that left- and right-handed sodium ammonium tartrate have different appearances, or in other words, display a different morphology or crystal habit. The packing of enantiomerically pure molecules in a crystal is different from that of racemates. For enantiomerically pure compounds, the crystal lattice needs to be enantiomorphous, whereas the lattice of the racemate needs inverse elements of symmetry, which transform an object into its mirror image. The adjective enantiomorphous is generally applied to macroscopic objects, whereas the equivalent enantiomeric is used for single molecules.

There are 230 different ways of arranging molecules repetitively in a crystal lattice. Of all these possible 230 space groups that are available for solids, only 66 lack inverse symmetry elements and can thus be applied to crystal lattices of enantiomers. However, only a few of these 66 groups are commonly found, the most important ones being $P2_12_1$, $P2_1$, and $C2$.

#### 2.4.1 Nucleation

The birth of new crystals is called nucleation. The driving force for nucleation is the supersaturated solution. Before the actual nucleation is observed, clusters (‘embryos’) are formed in solution (Figure 2.9).
The formation of these clusters is a reversible process. The free energy needed to form a cluster of volume $V$ and area $S$, the energy required is given by:

$$
\Delta G = -\frac{V}{\Omega}k_B T \ln \beta + S \gamma
$$

$\Omega$ = volume of a molecule inside the crystal
$\gamma$ = interfacial free energy between nucleus and solution
$k_B$ = Boltzmann constant
$\beta$ = supersaturation (see Section 2.1.3)

The first term of this equation is a volume term and the second a surface term. It is assumed that $\gamma$ has the same value over the whole nucleus surface and for a spherical nucleus the equation can be rewritten to:

$$
\Delta G = -(4\pi r^3/3\Omega)k_B T \ln \beta + 4\pi r^2 \gamma
$$

The energy $\Delta G$ is shown in Figure 2.10 as a function of radius $r$. If both volume and surface terms are added, $\Delta G$ passes through a maximum at a certain value of $r$, the critical radius $r^*$. 
It follows that \( r^* \) can be expressed through the following equation:

\[
r^* = \frac{2\Omega \gamma}{k_B \ln \beta}
\]

The corresponding critical activation free energy for nucleation is:

\[
\Delta G^* = \frac{16\pi \Omega^2 \gamma^3}{3(k_B T \ln \beta)^3}
\]

This means that aggregates smaller than \( r_c \) will fall apart, whereas aggregates that exceed \( r_c \) in radius will form nuclei. The size of \( r_c \) is beyond limits of detection even by dynamic light scattering and depends on the compound used. A clear solution does not necessarily mean that no seeds with \( r > r_c \) are present. Therefore, prolonged heating to dissolve everything completely is always necessary to achieve reproducible results.

There are two main types of nucleation, namely primary and secondary. Primary nucleation is divided into homogeneous and heterogeneous nucleation. Primary homogeneous nucleation is the formation of critical-sized clusters, whereas heterogeneous primary nucleation is mainly caused by dust, dirt or interaction with the container walls.
Secondary nucleation is due to the presence of existing crystals and the interaction of these crystals with the container walls and the stirrer. In practice, it is almost impossible to achieve solely homogeneous primary nucleation.

Nucleation is a statistical process, which means that the probability of forming new nuclei is higher in a larger amount of material than in a small amount. The time required for a given supersaturated solution to nucleate at constant conditions is called nucleation induction time. The higher the supersaturation, the shorter the nucleation induction time will be, or the less time is needed to form a critical sized cluster.

### 2.4.2 Crystal growth

Crystal growth involves the incorporation of growth units into the crystal lattice, once the lattice has developed from a nucleus. These growth units can be molecules, atoms or ions, depending on the type of substance. The crystal growth rate is dependent on the supersaturation and the area of the crystal exposed to the growth. On a microscopic level, the growth can follow two mechanisms: via two-dimensional nucleation or via screw dislocations.

The two-dimensional step-mechanism is shown schematically in Figure 2.11. In this picture it is assumed that the crystal possesses a simple cubic lattice. The small cubicle represents a growth unit, which is added to the layer that already exists. By repeated addition of these growth units, a line is formed. It is clear that the creation of a new ‘terrace’ costs more energy than the addition of one growth unit.

At lower supersaturations this process is slow, since it is difficult to generate a new layer on the already existing layers.

![Figure 2.11 Step mechanism of crystal growth](image)

The second mechanism that is pointed out here is the screw dislocation, as is shown in Figure 2.12. A rectangle with corners A, B and C is shifted one growth unit upwards, creating the screw dislocation. As a result, the crystal will acquire a spiral structure.
This mechanism is also possible at low supersaturations, since the spiral is an always present starting point for nucleation.

The most important properties of crystals are average size/size distribution, shape, polymorphism, ability to filter from solution and the strength of the crystal. These properties are determined by the way the crystals are grown.

2.4.3 Crystal habit

The macroscopic shape of a crystal is called morphology or crystal habit. The overall form of a crystal depends on the crystal planes (or faces) and the relative growth rates of these planes. The morphology of the crystal is largely dependent on the growth conditions, such as solvent, crystallization rate and the presence of impurities. The largest faces formed on a crystal are the slowest growing. The growth vector of a certain face is perpendicular to the face and goes through the middle point of the crystal. This is shown in Figure 2.13, the growth vector \( a \) of the largest face is shorter than vector \( b \) of a smaller face, which is therefore growing faster than the largest face.
2.5 Dutch Resolution

In 1998, a paper was published by Vries et al., in which a new approach to the classical resolution of racemates was introduced. The use of mixtures of structurally related resolving agents led often to high ee values than in the case of using a single resolving agent. A striking observation was the fact that the resolving agents were present in a non-stoichiometric ratio in the salt. The initial idea was to use a mixture of several resolving agents in order to screen for the least soluble resolving agent with the highest ee. To the authors’ surprise, when using 11 resolving agents, a salt precipitated in which 3 structurally related resolving agents were present. This was the beginning of an enormous number of resolution experiments. The new method was named ‘Dutch Resolution’ and was patented. This new resolution method gained considerable attention from the chemical community.

Several families of structurally related resolving agents were described, including the mandelic acids (M-mix), benzyol tartaric acids (T-mix), cyclic phosphoric acids (P-mix) and phenylethylamines (PE-I-mix), which are shown in Figure 2.14. With these families some compounds were resolved which were impossible to resolve until then.

Figure 2.14 Families of resolving agents

In general, the family members differ in the substituents on the aromatic ring, but other variations are also possible. At that point, no clear rationale as to which substituents should be used was available. Also, no explanation was given for the high ee values.

The use of families of structurally related resolving agents was extended to the use of a mixture of chiral ligands used for the asymmetric borane reduction of acetophenone. A small improvement in ee was observed.
2.6 Concluding remarks

Resolutions via crystallization are used on a daily basis in many labs, but the physical background is usually poorly understood. In this chapter I have tried to provide the organic chemist involved in resolutions via crystallization with a short overview of the processes that play a role and with a number of useful formulae. A deeper insight into these interesting phenomena will help the chemist to understand the, at first sight sometimes illogical, events that take place.

In the following chapters of this thesis, the main focus will be on the synthesis of new families of resolving agents and the understanding of Dutch Resolution. The processes and formulae explained here will be a foundation for the rest of the thesis.

2.7 References


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14 (a) Wallach, O. Liebigs Ann. Chem. 1895, 286, 90; (b) Wallach’s rule was tested for 36 pairs of racemic and chiral crystals by: Jacques, J.; Collet, A.; Wilen, S.H. Ref. 1b, 93-100.


20 Ref. 1a, 11-14.


22 (a) Marckwald, W. Ber. 1896, 29, 42; (b) Marckwald, W. Ber. 1896, 29, 43.

23 Ref. 1b, 378-435.


25 Ref 1b, 384-385.


42 Ref. 1a, 19-20.


Resolutions via diastereomeric salt formation


