

THE RESOLUTION OF RACEMIC MIXTURES

A Senior Thesis

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## INTRODUCTION

In nature, due to selective synthesis or destruction by living organisms, optically active compounds are fairly numerous. However, there also exists a large number of racemic mixtures of optically active compounds. The components of these mixtures usually have the same physical and chemical properties making them difficult to separate by ordinary means. Thus, indirect methods must be used to effect the resolution of these inactive substances into their optically active components.

## HISTORICAL BACKGROUND

In his treatise on light, in the latter part of the seventeenth century, the Dutch physicist Christian Huygens (1629-95) observed that when light is passed through a crystal of Iceland spar, "the waves of light acquire a certain form and disposition."<sup>32</sup> The term polarization however, was not applied to this effect until the early part of the nineteenth century.

Although during this time the optical activities of a large number of crystalline substances were thoroughly investigated, it was 1815 before Jean Baptiste Biot (1774-1862) made the important discovery that certain naturally occurring organic compounds such as, oil of turpentine, solutions of sugar, camphor, and tartaric acid possess the power to rotate a plane of polarized light in either a molten or a dissolved state. From the important fact that dissolving or melting of these substances did not destroy their ability to rotate polarized light, Biot postulated that this ability must be inherent in the molecules themselves.

6, 32

The separation, or resolution, of an optically inactive compound into its optically active components was first achieved in 1848 by Louis Pasteur while working on the crystal structure of the sodium ammonium salt of optically inactive racemic acid (tartaric acid). He found two mirror image crystals with small faces which were not perfectly symmetrically situated to the other crystalline faces, in other words, two hemihedral

mirror image crystals were formed. These could be separated by hand and would produce optical activity.

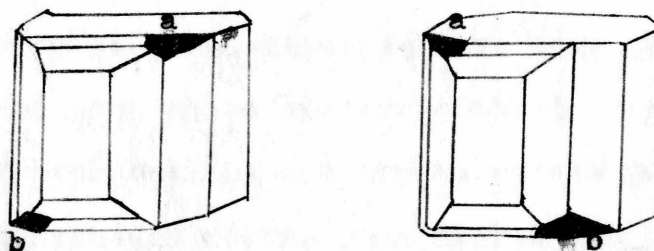


Figure 1

The hemihedral mirror image crystals of sodium  
35  
ammonium tartarate.

#### THEORY OF OPTICAL ACTIVITY

Without benefit of the modern theories on structure, Pasteur put forth an explanation of optical activity based on crystallography relations. He also predicted that the phenomena would have to be accounted for by some asymmetrical space arrangement of the atoms in the molecules and today the theory is based on just such a conception. The four valences of carbon are directed toward a  
9  
tetrahedron making it possible to have an asymmetric

molecule existing in two forms by attaching four different groups to these corners. The configuration of these two forms is so arranged that it is impossible to superimpose one form upon another. In most cases the antipodes have like physical and chemical properties and are alike in every way except each has the ability to rotate polarized light, although to the same degree, in opposite directions.

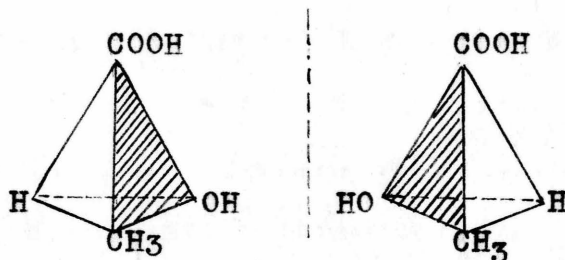


Figure 2

d-lactic acid and l-lactic acid

By means of quantum mechanics, much of the question of optical activity can be said to be solved in principle; <sup>28</sup> however, this is beyond the scope of the present discussion and only the most essential factors of this problem will be discussed here.

The path followed by a beam of light may be predicted by the laws governing waves. Light waves of a single wave length are obtained by using filters or a separate light source. These waves vibrate at random, in many planes, and may be filtered into parallel planes of polarized light by the use of either a Nicol prism or a sheet of transparent material similar to cellulose acetate. 17

The ability of an optically active compound to rotate this polarized light depends upon various physical and chemical factors such as structure of the molecule, <sup>37</sup> temperature, <sup>14</sup> nature of the solute and solvent, <sup>41</sup> concentration, <sup>16</sup> and the wave length of light used. <sup>15</sup> Results give evidence that there is little or no regularity connected to these above factors and the specific rotation of the compound. Thus, no general statement can be made relating the specific rotation to these factors and therefore, each individual substance behavior must be found by experimental methods.

## TYPES OF RESOLUTION

## a. Mechanical separation

If a racemic modification, usually a metal salt, is permitted to crystallize under the proper conditions, two types of hemihedral crystals will be formed which are mirror images of each other. The separation of the two variations of crystals with the aid of a magnifying glass and tweezers is the resolution of the mixture, since the crystals of one type are d-isomers and crystals of the other are l-isomers. Pasteur<sup>34</sup> first effected the resolution of tartaric acid by the use of the double salt of sodium ammonium tartarate. Equal weights of racemic acid were saturated, one with soda, the other with ammonia, and the solution mixed. The liquid upon cooling, deposited fine hemihedral crystals which were separated by mechanical means. In this, Pasteur was exceedingly fortunate for it is now known that the hemihedism of the double tartarate is dependent upon a critical temperature factor.

7  
Only nine other compounds have been found



to date that give the requisite hemihedral crystals since Pasteur's initial resolution of tartaric acid. Therefore, the mechanical method of resolution is extremely limited in its application and its salient points lie only in its historical significance.

b. Conversion to diastereoisomers

The conversion of the racemic mixture to diastereoisomers by the use of naturally occurring optically active reagents, also developed by Pasteur, is a far more practical method with wider application. The separation depends upon the fact that diastereoisomers are not antipodes and thus have different physical properties.

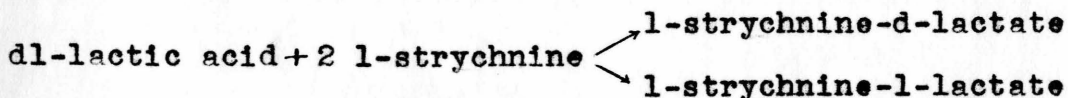
In considering a general example, if a racemic dl-acid is neutralized with an l-base, two salts are formed, namely, the ll-salt and the dl-salt. Since these are not antipodes they may be separated by whichever means suggests itself by the extent of the differences of their physical properties. Actually however, this general method has encountered difficulties which has necessitated developments in technique and procedure to effect

a successful resolution of the racemate.

In practice, it is customary to have the semi-permanent linkage between the resolving agents be of such order as to withstand the operation of fractional crystallization, yet be easily broken without doing damage to the active substance. The diastereoisomeric derivatives are also chosen so that at least one form is capable of crystallization in the solvent. Although some diastereoisomers in the liquid form have been partially separated by fractional distillation, the proximity of their vapor pressure makes this practice unsatisfactory.

#### 1. Acids and bases

The resolution of a racemic acid can be best illustrated by the resolution of dl-lactic acid by the use of the optically active alkaloid strychnine. <sup>40</sup> The reaction is:



The solubility of these diastereoisomers differs sufficiently to make their separation by fractional

crystallization a relatively easy matter. The two active acids are then regenerated by displacement of lactic acid with dilute HCl.

l-strychnine-d-lactate+HCl → d-lactic acid+l-strychnine-HCl

l-strychnine-l-lactate+HCl → l-lactic acid+l-strychnine-HCl

TABLE I 10  
Bases Commonly Used as Resolving Agents for Acids

Brucine	α-Phenylethylamine
Cinchonidine	Phenyl oxynapthyl methylamine
Cinchonine	Quinidine
Hydroxyhydrindamine	Quinine
Menthylamine	Strychnine
Morphine	ψ Ephedrine

The method for the resolution of racemic bases by the conversion to diastereoisomers is analagous to the method described above for the resolution of racemic acids.

TABLE II 10  
Acids Commonly Used as Resolving Agents for Bases

α-Bromo camphor-7-sulfonic acid	Camphoric acid
Camphor-10-sulfonic acid	Helicin
Diacetyl tartaric acid	Malic acid
2,2'Dinitro-6,6'diphenic acid	Quinic acid
Menthoxyacetic acid	Tartaric acid

In the resolution of acids and bases, difficulty is often encountered in isolating the

insoluble diastereoisomer from the more soluble diastereoisomer. In the general reaction:



The more soluble salt, l-acid-l-base may be contaminated with a small amount of d-acid-l-base and it is therefore difficult to effect a complete resolution of the l-acid. Marchwald<sup>30</sup> overcame this difficulty by taking advantage of the fact that the salts l-acid-d-base and d-acid-d-base as well as d-acid-l-base and l-acid-l-base are enantiomorphous. Hence, if the solution of partially resolved acid obtained above, l-acid contaminated with d-acid is freed from l-base and then is combined with the antipode of the base, the salt of the l-acid, will be the least soluble because it has the same solubility as its enantiomorph, and thus obtained in a pure state. The main difficulty with Marchwald's method is that it requires the use of the rare dl-isomers of an optically active acid or base. These are not at all plentiful and therefore this method is little used. In an ingenious modification of this method, Ingersoll,

in certain cases, was able to replace the second optical base by a racemic mixture of the base. The procedure was as follows: An acid (dA) was combined with a racemic base (dlB). The lB.dA separated first by crystallization from which the pure l-base was liberated. Then with the separation of dA + dlB  $\rightarrow$  two lB.dA + dB.dA. The mother liquid when treated with an alkali gave the partially resolved base (dB + dlB). This partially resolved base was then completely resolved in one of two ways. By the first method, the partially resolved base was combined with an equivalent amount of the racemic dl-acid, forming four salts, dB.lA, dlB.dlA, lB.lA, and dB.dA. The dB.lA is enantiomorphic with the lB.dA salt and therefore by careful crystallization, the dB.lA salt was obtained, which on hydrolysis gives the pure d-base, provided, of course, the dB.dA and lB.dA salts are more soluble than dB.lA and lB.dA salts.

In the second procedure, the pure l-base,

obtained above, is combined with excess of the dl-acid. The lB.dA salt crystallized out and the mother liquor contained the excess l-acid plus the rest of the lB.dA salt. To this is added an equivalent amount of the partially resolved base (dB + dlB). The same salts are again formed, dB.lA, dlB.dlA, lB.lA, and dB.dA. Then with the separation of the other two salts and through hydrolysis a pure l-acid is formed; thus, both forms of active base and active acid are obtained.

Two conditions must be met before the above system will be workable. One, that the acid and base must be mutually resolvable, and the second that the desired active salt must be less soluble than the racemic salt dlB.dlA.

The possible salts resulting from the combination of a racemic acid and a partially active base in all possible orders of their solubilities are as follows:

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TABLE III  
Possible Orders of Solubilities of Racemic Salts

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1. (dBdA or lB1A) < (dB1A or lBdA) < (dlBdlA)\*
2. (dB1A or lBdA) < (dBdA or lB1A) < (dlBdlA)\*
3. (dBdA or lB1A) < (dlBdlA)\* < (dB1A or lBdA)
4. (dB1A or lBdA) < (dlBdlA)\* < (dBdA or lB1A)
5. (dlBdlA)\* < (dBdA or lB1A) < (dB1A or lBdA)
6. (dlBdlA)\* < (dB1A or lBdA) < (dBdA or lB1A)
7. (dBdlA or lBdlA) < (dlBdlA)\*
8. (dlBdlA)\* < (dBdlA or lBdlA)

\* racemic salts

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The possibilities are the same for the reactions with the racemic base and a partially resolved acid with the exceptions of 7 and 8. In this case the salt would be of the dlBdA or dlB1A type. Thus, in cases 1, 2, 3, 4, and 7 a successful completion of the resolution is possible. However, in the cases 5, 6, and 8 the resolution will be difficult. Hence, it is clear that each of these methods depend for its success on a favorable order of the soluble salts involved.

## 2. Alcohols

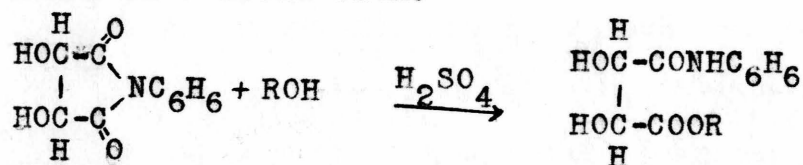
Nearly one hundred and fifty alcohols and phenols have been recorded in the literature<sup>25</sup> as having been resolved. Among all the methods used for their resolution, the most general and the most useful method is the conversion to diastereoisomeric derivatives. In practice, to form a linkage of sufficient strength that will not be broken by the fractional crystallization process, this is accomplished most commonly by the esterification with an acid or an acid derivative by one of two principal methods.

In the first method the racemic alcohol is esterified with an active acid so chosen that at least one of the diastereoisomeric esters is capable of forming a solid which can be separated. The other method is the esterification of the racemic alcohol with a dibasic acid. The ester is then resolved with an alkaloid as a racemic acid and the optically active component is regenerated when the separated esters are saponified.

In the successful resolution of racemic alcohols through the formation of simple esters



the following types of agents have been used:  
 d- and l-mandelic acid,<sup>33</sup> l-menthoxy-acetic acid,<sup>39</sup>  
 l-menthylglycine,<sup>5</sup> and tartranitic acid.<sup>3</sup> Other  
 types of resolving agents that have been used with  
 limited success are l-menthylisocyanate,<sup>25</sup> and  
 d-camphoric acid.<sup>25</sup> To consider a typical example  
 of this method of resolution, using a tartranitic  
 acid type,<sup>3</sup> Barrow and Atkinson formed esters by  
 heating d-tartanil, secondary n-octyl alcohol and  
 a trace of concentrated sulfuric acid for twenty-four  
 hours on a steam bath.



The ester was separated by fractional crystallization and the active alcohols regenerated in a steam bath with aqueous potassium hydroxide.

Resolution through the salts of the acid esters is usually accomplished by converting the inactive alcohol to an acid ester with acid sulfate, acid phthalate, or succinates, the latter two being the most commonly used. Esters of nearly all types of primary and secondary alcohols can be prepared with phthalates and hence, have a wide use. The

resolution from this point on is similar to that of an acid. Excellent yields are obtained and the resolving agent is usually recovered. An example of this method will be discussed further in the experimental part of this paper.

### 3. Aldehydes and ketones

The usual method of resolution of aldehydes and ketones is by combining a hydrazine with the ketones or aldehydes forming two hydrazones which can be separated by fractional crystallization. The active components are then obtained by hydrolysis.<sup>4</sup> Some of the types of resolving agents used to separate externally compensated aldehydes and ketones are: 1-menthylhydrazine, d-isomylhydrazine, 1-methylsemicarbazide, and d-alpha-phenylethylsemicarbazide.  
11

### 4. Amino acids

Since due to their amphoteric nature, amino acids will not usually form stable salts with optically active acids and bases, a method similar to that for resolving alcohols must be used.

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In the one method,<sup>35</sup> the amino acid is converted into its benzoyl derivative, thus the product loses its basic character permitting it to be resolved as a racemic acid. Another method,<sup>22</sup> described by Holmes and Adams which contains several advantages over the above method and is more widely used, makes use of an optically active chloride. Diastereoisomeric amides of the type  $RCONHCR'-COOH$  are formed. These are then separated by fractional crystallization and hydrolyzed.

Separation of the optically active racemates into the optically active components by means of converting them to diastereoisomers, has been shown to be the most practical and most universally used method. Although there are many different methods for accomplishing this type of resolution, most are variations of procedure and improvements in laboratory technique.

- c. Methods of resolution due to differential interaction between the racemic mixtures and the resolving agent
1. Micro biological separation

This method, the third originated by

Pasteur, was discovered when he observed that organisms in cultures of yeast and of certain molds, *penicillium glaucum*, destroyed the d-ammonium tartarate more rapidly than the l-ammonium tartarate, thereby resolving the tartrate. Although this method has been of great interest in the biochemical field, and a large number of active alcohols have been prepared this way, the use of this method is limited by its many apparent disadvantages. The most obvious of these disadvantages is that one of the antipodes must be sacrificed in order to gain the other. Even at this, the chances are that the isomer recovered will not be pure. Further, to be effective, usually very dilute solutions are necessary and the time consumed for this operation runs from two to sixty days.

Racemic mixtures have been resolved by feeding and injecting into the blood stream of animals when it was found that certain racemic substances would be unequally effected by the living organisms in the animals. Still other racemic compounds have been resolved by employing

purified enzyme preparations under controlled  
26  
conditions.

Biochemical resolutions can only be used profitably in a few instances where other methods are not available or fail to give results.

## 2. Preferential crystallization due to inoculation

If in a solution of a racemic mixture, some way can be found to crystallize out one of the active components leaving the other behind, the separation of the racemate will have been accomplished.

Pasteur first observed that a concentrated solution of inactive ammonium hydrogen malate, first deposited, on evaporation, crystals which were similar to the form of the active salt. This was later shown that the salt deposited actually consisted of three parts of the l-salt and one part of the d-salt, thus a partial resolution has been effected.

38  
Purdie resolved inactive lactic acid by inoculating a concentrated aqueous solution of the zinc ammonium salt with a crystal of the active salt.

A spontaneous resolution of atropine sulfate,  
1  
by Anderson and Hill occurred when crystallizing

this dl-salt from alcohol yielding l-hyoscyaine sulfate. They postulated that it was inoculated by the l-hyoscyaine in the atmosphere of the laboratory.

Due to the small number of racemic mixtures that can be separated by this method its use is limited.

### 3. Kinetic crystallization

It often occurs that when the two active components of the racemic mixture are brought into contact with the resolving agent they do not combine at the same rate. Such is the reaction between l-menthol and d-mandelic acid; thus, when one equivalent of dl-mandelic acid is esterified with less than one equivalent of l-menthol, the l-menthol-d-mandelic consists of the larger amount of the yield. If one equivalent of l-menthol has been used instead, the reaction could not have been permitted to go to completion to obtain the same results.<sup>12</sup> The degree of separation by this method will depend upon the differences in the reaction of the isomers with the resolving agent. If one isomer reacted completely

with the resolving agent and the other did not, there would be a complete resolution into an active component. Unfortunately, the differences in the rate are usually rather small, thus the procedure would have to be repeated many times if a pure isomer is to be obtained.

#### 4. Adsorption and fractional distillation methods

The difference of degree of adsorption which an asymmetrical crystal, such as d- or l- quartz, shows for the two antipodes, has suggested a method of resolution based on this fact.

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Henderson and Rule were able to effect a complete resolution of dl-phenylenebisiminocamphor, by allowing a dilute solution in light petroleum ether containing fifteen to twenty-five percent benzene to flow through an upright adsorption tube packed with d-lactose using the same solvent mixture. The d-<sup>d</sup>iminocamphor was more strongly absorbed on the d-lactose than the l-iminocamphor, hence the product contained at the top section will be dextroserotatory and that at the bottom will be laevorotatory.

By converting liquid racemic mixtures into volatile diastereoisomers, Hass has been able to accomplish partial resolution of the mixture by fractional distillation.<sup>20</sup>

Although numerous attempts to effect a complete resolution by this method have been tried,<sup>19</sup> the results of most have been disappointing and in a good many cases the results have been nonreproducible.

18, 27, 29

#### EXPERIMENTAL

The resolution of dl-2-octanol may be divided into the following phases: preparation of the ester, the formation of the diastereoisomeric salt, separation of the salt, freeing the active ester from its salt and its purification, hydrolyzing the ester into the active alcohol.

##### a. Preparation of secondary octyl hydrogen phthalate

A mixture of 130 grams (1 mole) of secondary octyl alcohol and 148 grams of new phthalic anhydride were heated for twelve hours at 112° C, with mechanical stirring throughout the entire operation. The mixture was allowed to cool,



then poured into a solution of 150 grams of sodium carbonate in eight liters of water and mechanically stirred. This solution was not clear, thus it had to be extracted with benzene in order to remove excess alcohol, phthalic anhydride, and any neutral ester formed. A slight excess of hydrogen chloride was added to the clear solution and permitted to stand overnight.

The octyl hydrogen phthalate was then filtered, ground in a mortar, filtered again, washed and dried. The dry ester was then recrystallized from about two-thirds of its weight of petroleum ether. This gave a yield of 252 grams of the octyl hydrogen phthalate, or about 91%, which had a melting point of 55° C.

b. Formation of the diastereoisomeric salt

To a warm solution of 252 grams of the ester and 550 cc of anhydrous acetone, 357 grams of dry powdered brucine was added and mechanically mixed intermittently over a period of several days for a total of twelve hours. This solution was kept at constant volume by constant addition of acetone. This solution never became clear.

c. Separation of the salt

The solution was permitted to stand overnight in a cool place. The d-octyl hydrogen phthalate brucine salt crystallized out and the l-octyl hydrogen phthalate brucine salt remained in the solution. The solution was filtered and the crystals were washed with 250 cc of acetone.

d. Freeing the active ester from its salt and its purification

The combined filterings and washings of the above were then concentrated to about half their original volume and poured into a solution of 100 cc of concentrated HCl to one and a half liters of water while still warm. This caused the precipitation of l-octyl hydrogen phthalate as an oil which solidified upon standing overnight. These were filtered and washed thoroughly with cold water.

The crystals of d-octyl hydrogen phthalate brucine salt were dissolved in about 200 cc of hot ethyl alcohol and decomposed by pouring this solution into dilute HCl. After

maximum crystallization and complete settling out, they were filtered and thoroughly washed with cold water.

Both esters were then crystallized, separately, three times from twice their weight of 90% acetic acid to remove any small portion of dl-octyl hydrogen phthalate, the racemic form being considerably more soluble than the active form in the acetic acid. The yields were 105 grams of the d- and 52 grams of the l-octyl hydrogen phthalate with a melting point of 74°C.

Alcohols of reduced optical rotatory power were obtained by adding water to the filtrates of the above and recovering the impure d- and l-octyl hydrogen phthalate crystals that were precipitated.

e. Hydrolyzing the esters into the active alcohols

The octyl hydrogen phthalates were then steam distilled in a solution of 80 grams of sodium hydroxide to 400 cc of water. The free alcohols being insoluble in water were separated and dried over anhydrous potassium carbonate. They were then

purified by distillation giving a yield of 45 grams of d-octyl alcohol and 22 grams of l-alcohol, with a boiling point of 193 degrees corrected. The optical activities of the alcohols were measured in a polarimeter with the following specific rotation.

$$[\alpha]_D^{24^\circ} = \pm 9.1^\circ$$

#### SUMMARY

It has been the purpose of this paper to place in review the several most used methods for resolving externally compensated mixtures into their active components. The salient points of each have been shown whenever possible by actual or general type examples and comments, when they could be justified, have been made on each.

There is also included an experimental part, the resolving of secondary octyl alcohol by one of the methods suggested in this review.

It is apparent that even the simplest

methods suggested to effect these resolutions are a difficult and tedious undertaking even for a comparatively skilled worker.

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