STRATEGIES IN OPTICAL RESOLUTIONS

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Even in this day of phenomenal success with the synthesis of chiral multifunctional compounds, and of powerful control of stereochemical variables during such syntheses, the successful resolution of even simple organic compounds is occasionally difficult to achieve. In any event, resolutions are often tedious. The reasons for the lack of success in resolutions are unclear; and many experienced investigators in the field of organic chemistry consequently continue to view resolutions as an art.

In fact, it is today possible to carry out resolutions of organic compounds bearing functional groups quite rationally and with a high probability of success. In this article we outline an approach to resolutions that is based in part on an improved understanding of factors that govern resolutions and in part on an effective *modus operandi* employed in groups which carry out resolutions regularly.

We limit this analysis principally to classical resolutions, i.e. those involving crystallization techniques. This is the type which today remains the most common optical activation route. Salt-forming acid–base reactions are central to such resolutions for they suffice in the overwhelming majority of cases. Such resolutions are exemplified by eqns (1) and (2):

$$(\pm)\,CH_3\underset{Cl}{CH}\text{–}COOH + (-)C_6H_5\underset{CH_3}{CH}\text{–}NH_2 \longrightarrow$$

$$(-)CH_3\underset{Cl}{CHCOO^{\ominus}}\ \ (-)C_6H_5\underset{CH_3}{CHNH_3^{\oplus}} \qquad (1)$$

P salt

$$+\ (+)CH_3\underset{Cl}{CHCOO^{\ominus}}\ \ (-)C_6H_5\underset{CH_3}{CHNH_3^{\oplus}}$$

N salt

$$CH_3\underset{Cl}{CHCOO^{\ominus}}\ \ C_6H_5\underset{CH_3}{CH}\text{–}NH_3^{\oplus} + H_2SO_4 \rightarrow$$

$$CH_3\underset{Cl}{CHCOOH} + C_6H_5\underset{CH_3}{CHNH_3^{\oplus}}\ \ HSO_4^{\ominus} \qquad (2)$$

which describe the resolution of racemic 2-chloropropanoic acid with the synthetic resolving agent (−)-α-methylbenzylamine.

Equation (1) describes the formation of a mixture of diastereomteric salts whose separation depends upon solubility differences of the P salt (substrate and resolving agent of like sign) and the N salt (substrate and resolving agent of unlike sign)‡. Alternatively, diastereomers produced may be covalent compounds such as esters or amides in which case their separation may be carried out also by chromatographic techniques, in particular thin layer and liquid chromatography. Equation (2) describes the isolation of resolved 2-chloropropanoic acid from one of the separated diastereomeric salts.

What is required in carrying out resolutions such as that of 2-chloropropanoic acid is:

(1) A systematic approach carried out with patience
(2) A reasonably large collection of resolving agents
(3) An understanding of phase and solubility behaviour of stereoisomers to guide one during resolutions.

Before proceeding, let us say what we think is unsystematic. A resolution carried out with one resolving agent—whether one that is on-the-shelf, or in-the-stock room, or one chosen by analogy—followed by a second resolution in the event of failure of the first and so on, is deemed unsystematic. This approach may work; we do not claim that it is always doomed to failure. But it leaves matters too much to chance.

The way in which resolutions are monitored is important as well. It is known that the progress of a resolution can be followed by measurement of optical rotations or of m.ps either on the isolated diastereomers or on the enantiomers derived from the diastereomers.

However, the rotatory power alone is but a poor indicator of the progress of a resolution particularly in

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‡This convenient nomenclature derives from a proposal made by Ugi.[1]

points as criteria of purity expecially those of partially resolved enantiomers.

1. *Trial resolutions*

Let us examine the resolution of an organic acid that illustrates the systematic approach advocated. In his resolution of α-(2-thianaphthenyl)-propionic acid, Sjöberg[2] began by carrying out a number of preliminary tests on a small scale to learn which resolving agent to use. The preliminary tests were carried out with 0.001 mole of acid and 0.001 mole of base which were dissolved together by heating the mixture with small amounts of solvent.

Where crystalline product does not precipitate spontaneously on standing or upon cooling, this may be due to the presence of too much solvent. A few drops of the solution placed on a watch glass rapidly evaporates and this, coaxed by scratching, may elicit crystal formation. Note that *solvated* salts, particularly *hydrates* formed through addition of water or hydrophilic solvents such as alcohol, acetone, etc. often are produced and these sometimes crystallize more easily than "anhydrous" salts.

Table 1 summarizes the results obtained by Sjöberg after isolation of the crystals, liberation of the acid by acidification with concentrated mineral acid, extraction of the free acid with ether and determination of the specific rotation of the isolated acid in a common solvent. It is evident in the example that seven out of ten of the resolving agents gave little or no evidence of resolution. This may or may not be typical; negative results in resolutions—as in other types of chemical reactions—are rarely reported. Nonetheless, the "wrong" choice of as many as seven resolving agents may well have led another investigator to abandon the resolution or to attempt an alternative approach to the optical activation. It must be added—so as not to discourage apprentice or novice resolvers—that fortunately a study as extensive as that illustrated here is not always necessary.

ples in Table 2 illustrate the possibilities of w
very small quantities of resolved compoun
other hand, the data also suggest the potentia
that may arise if small amounts of strong
contaminants, resolving agents, for examp
completely removed.

Table 1 clearly points up the fact that more
than just obtaining a crystalline solid. In nin
of the 40 resolution attempts summarized
crystalline solids yielded racemic acid upon
the substrate. It is possible to summarise[3] t
uations that render resolutions mediated
tereomers difficult as follows:

Situation (1) formation of non-crystal
tereomers
Situation (2) too small differences in so
diastereomers
Situation (3) formation of addition comp
double salts, between diaster
Situation (4) formation of solid solutio
phism) between diastereome

In fact, while the experimental data whi
these difficulties were obtained on diastereo
the same arguments apply, to some extent,
diastereomeric compounds. However, with
pounds, *none* of these situations are tru
blocks to resolutions since separations by
graphy are feasible and often quite easy to

If covalent diastereomers are relatively
parate (in particular, we underscore the ease
high pressure liquid chromatography with
high efficiency permits covalent diaster
aration)[4] why not preferentially choose this
cause their formation is not as easy as that of
their decomposition. Moreover, the forward
reactions described are more subject to rac
chiral centers than is salt formation.

ω-Camphanic acid 1 illustrates another c
occasionally found in resolutions mediated

Table 1. Preliminary tests on the resolution of α-(2-thianaphthenyl)-propionic acid

Base	$[\alpha]_D$ of acid in abs. ethanol			
	From methanol	From ethanol	From acetone	From ethyl acetate
Cinchonine	Oil	Oil	Oil	+ 2°
Cinchonidine	− 2°	+13°	+ 4°	+ 4°
Quinine	± 0°	± 0°	±0°	± 0°
Quinidine	Oil	Oil	Oil	Oil
Brucine	− 2°	± 0	− 2°	± 0
Strychnine	Oil	Oil	Oil	Oil
Morphine	+23°	± 0	+20°	+26°
Ephedrine	Oil	Oil	Oil	Oil
(+)-α-Phenylethylamine	− 2°	− 3°	± 0	± 0
(+)-α-(2-Naphthyl)-ethylamine	−21°	− 8°	− 5°	−26°

From B. Sjöberg, *Arkiv. Kemi.* 12. 568 (1958), by permission of the Royal Swedish Academy of Science.

Substrate recovered from the diastereomer mixture : 30 mg

(40% of 0.0005 mole maximum)

Rotation observed : α_D = +0.30° (c=0.030g/2.0ml = 1.5g/100ml)

if optically pure

Case b

Molecular weight 450 ; $[\alpha]_D$ + 20°

Substrate taken : 45 mg (0.0001 mole)

Substrate recovered : 9 mg

Rotation observed : α_D = +0.09° (c=0.009g/2.0ml) if optically pure

diastereomers. While easily produced from camphoric acid[5] and quite useful in the resolution of alcohols and phenols,[6] it cannot be reused since hydrolysis of the covalent diastereomers cleaves the lactone ring of 1. It is nonetheless true that for the preparation of small samples of chiral compounds of high enantiomeric purity (e.p.) use of covalent diastereomers may be ideal.

Returning to Table 1, we see now how the results described by Sjöberg could be explained:

Formation of oils: situation 1.
Recovery of acid of $[\alpha]_D = 0$: situation 3; possibly 2 or 4.
Small rotations (low e.p.): situation 2 or 4.

Sufficient data are not available to ascribe specific causes to each example of Table 1. However, the two principal obstacles to resolutions remain, in a general sense, formation of addition compounds (situation 3) and co-crystallization of diastereomers (situation 4).

Let us briefly examine these two situations. The formation of "double salts" or of "partial racemates" was the object of a number of studies at the turn of the century which merit reinvestigation and extension.

Several types of definite combinations of diastereomeric salts can exist in principle. Given a racemic acid (±)-A and an active base (+)-B, compounds of formula

$$[(+)\text{-A}, (+)\text{-B}]_n \cdot [(-)\text{-A}, (+)\text{-B}]_m$$

may be called double salts. Where $n = m$, a racemic substance and an optically active compound may yield a stable combination of such low solubility as to preclude all resolutions. It is particularly cases such as these which have been studied.[7]

On the other hand, note that in a certain number of cases of this type a *transition temperature* exists which imposes limits to the existence of such addition compounds. For example, Ladenburg,[7] has shown that resolution of 3-methylpiperidine with (+)-tartaric acid is possible only *below* 39°;[8] above this temperature, a double salt is formed between (+)-tartaric acid and the racemic amine which precludes resolution. In other cases the opposite is true. With the hydrogen tartrates of brucine for example, the double salt formed by racemic tartaric acid and brucine is stable only *below* 44° and resolution is possible at a higher temperature.

If n is different from m, a partial resolution is possible. But the enantiomeric purity attainable cannot exceed that which is deduced from the stoichiometry of the salts formed, viz. 33.3% for $n = 2$ and $m = 1$; 50% for $n = 3$ and $m = 1$, 20% for $n = 3$ and $m = 2$, etc.

In fact, experimental data on this subject are almost totally lacking. Nonetheless, one can cite the observation of Matell:[9] in the resolution of α-(2-naphthoxy)-*n*-valeric acid, brucine yields a salt from which an acid $[\alpha]_D$ = +25° can be generated. The rotation is unchanged by recrystallization. Since the specific rotation of the pure acid, as obtained employing a different resolving agent, is 73.6°, Matell believes that the brucine salt is formed in the proportions $n = 2$ and $m = 1$ consistent with the observed rotatory power. Examples such as this merit confirmation.

Finally, the formation of solid solutions (situation 4) is anything but rare among diastereoisomeric salts. We will have occasion to return to this point. The formation of solid solutions can undoubtedly be explained as follows: diastereoseomeric salts perforce contain identical moieties (a common counter ion) which make them partially identical. By increasing the degree of similarity, as defined by the overlapping volumes of Kitaigorodskii,[10] the occurence of crystalline isomorphism is increased.

In any event, the consequences of the formation of double salts (situation 3) and the co-crystallization of diastereomeric salts (situation 4) are not of equal importance.

In situation 3, either resolution cannot even be *begun*, or much more rarely, resolution stops completely upon attainment of a partial enantiomeric purity. In the fairly frequent instance of co-crystallization, resolution is possible, but it often is *completed* with only a low enantiomeric yield.

2. *Enantiomeric purity determination*

We have already seen how one systematically begins a resolution. Indeed it is important to get it underway and to get some idea of how well it is going. Does substrate rotation (Table 1) provide this information? In a relative sense yes; hence it is easy to tell which resolving agent and solvent to use. But the rotations, which are the

Table 3. Note that the methods are applicable either to enantiomer mixtures (substrates, in the context of resolutions) or diastereomer mixtures (resolution intermediates). The first four of the processes are the most common due to their ease of application. Contrary to what appears to be general practice, none of the first three methods are as easy to apply—at least in the context of a resolution—as is method 4 provided that the samples are crystalline or can be induced to crystallize at low temperature. Liquid compounds can be analyzed in the form of solid derivatives.

Differential scanning microcalorimetry (DSC) is a generally useful process because it permits one to relate an enantiomerically enriched sample to the binary phase diagram for the two enantiomers. Construction of such a diagram (or of part of the diagram) requires few data, and can be rapidly carried out. At the same time, calorimetry permits the determination, with high precision, of the enantiomeric purity of the enantiomers obtained at the conclusion of a resolution. The measurements here are based upon a different principle, namely analysis of the fusion peak, and do not involve the phase diagrams.[12,13]

Specifics will be given in Section 6 (see below).

3. *Finding a good resolving agent*

Formation of diastereomeric salts which possess sufficiently different solubilities to make possible their separation depends upon the sucess of two operations: one must choose a good resolving agent and one must choose a good solvent. However, these two requirements do not have equal weight. As we will see, the solvent is really important only to the extent in which it is involved in *selective solvation* of one or the other of the diastereomeric salts.

In fact, the crucial step in a resolution is the creation

suitable to the substrate.

How does one choose resolving ag
implies that every conceivable resolving
employed in preliminary resolution tests.
untrue; many more chiral bases could b
And, it turns out that there are by far
solving agents known than any other typ

One can consult recent reviews of
where useful types of resolving agents a
can attempt to match the substrate to a k
through consultation of a compilation o
Provided that one does not limit oneself
two resolving agents in the preliminary
fact the only realistic strategy at the
resolution empirical though it may be.

Table 4 gives an overview of the pri
agents of modern usage and the natu
tereomeric products formed in the corres
tions. While statistical information ha
cumulated to confirm the contention, we
that diastereomer salt-forming resoluti
principal type employed.

Readers are also referred to the revi
and of Wilen[22] for particulars on sp
agents. New resolving agents or m
prominently in the literature since 1971, or
are marked with an asterisk.

It is worthwhile to underline the contin
utility and advantages of synthetic re
These advantages are:

(1) The availability of both resolvi
tiomers. This permits both substrate en
obtained in mirror image resolutions.

(2) Synthetic resolving agents may
have stronger acid–base properties and he
form salts. For example, synthetic a

Table 3. Methods of determining enantiomeric purity (14)

Basis of Measurement	Nature of Measurement	Application (*)
1. Enantiotopic nuclei	a) NMR in chiral solvents	E
	b) NMR with chiral shift reagents	E
	c) NMR of salts in presence of chiral counter ions	D
2. Diastereotopic nuclei	a) NMR in achiral solvents	D
3. Diastereomeric interaction	a) Chromatography on chiral stationary phases	E
	b) Chromatography on achiral stationary phases	D
4. Fusion properties	Differential scanning calorimetry (DSC)	E or D
5. Isotope dilution	Isotope analysis	E
6. Enzyme specificity	Quantitative enzyme catalyzed reaction	E

(*) D = Analysis of diastereomer mixtures

E = Analysis of enantiomer mixtures

	ephedrine	with 1°	
	Synthetic amines: α-methyl-benzylamine; α-(1-naphthyl)-ethylamine; α-(2-naphthyl)-ethylamine; amphetamine; deoxyephidrine; threo-2-amino-1-(p-nitrophenyl)-1,3-propanediol and threo-2-(N,N-dimethylamino)-1-(p-nitrophenyl)-1,3-propanediol	amines only and then rarely)*	*(15)
	Other amines: Dehydroabietylamine; menthylamine		
	Alcohols: (-)Menthol	Esters(*)	
Amine	Carboxylic acids: tartaric acid; O,O'-dibenzoyltartaric acid; mandelic acid; di-O-isopropylidene-2-oxo-L-gulonic acid 2 (*)	Salts or amides (rarely)	*(16)
	Sulfonic acids: camphor-10-sulfonic acid; 3-bromocamphor-9-sulfonic acid		
	Other acids: 2,2'-(1,1'-Binaphthyl)-phosphoric acid 3 (*)	Salts	*(17)
Alcohols	As hydrogen phthalate, glycolic acid, or less commonly hydrogen succinate derivatives; same resolving agents as acids	Salts or esters	
	Acids: Menthoxyacetic acid; ω-camphanic acid 1 (*); 3β-acetoxy-Δ^5-etienic acid	Esters(*)	*(6)
	Isocyanates: α-methylbenzyl isocyanate; α-(1-naphthyl)-ethylisocyanate (*)	Urethanes(*)	*(18)
Carbonyl	As oximino carboxylic acids: =N-O-CH_2COOH; same resolving agents as acids (*)	Salts	*(19)
	O-amino hydroxyacids (*)	Oximino derivatives	*(20)
	Ephedrine (*)	Oxazolidines	*(21)
	Hydrazides: Menthydrazide	Menthydrazones	
	Diols or dithiols: 2,3-butanediol; 2,3-butanedithiol	Ketals or thioketals	

agents are all primary amines and hence are stronger bases than typical alkaloid resolving agents.

The only known exceptions to the first advantage are the cinchonine–cinchonidine and quinine–quinidine quasi-enantiomeric pairs. By virtue of the inverted configuration of the asymmetric carbon adjacent to the more basic of the two nitrogens in each molecule, members of each pair often serve as if they were enantiomers in resolutions.[25] For example, the synthetic acidic resolving agent 2,2'-(1,1'-binaphthyl)-phosphoric acid 3 is resolved with cinchonine. Cinchonidine affords the enantiomer.[17]

Availability and lower cost of synthetic resolving agents relative to those of naturally occurring resolving agents—especially for amines—often dictate their use when a choice is possible. Table 1 provides a good illustration. The choice of best resolving agents would seem to be morphine and (+)-α-(2-naphthyl)-ethylamine to provide both enantiomers of α-(2-thianaphthenyl)-propionic acid. In fact, due to the cost and difficulty of

(+)1 (−)2 (−)3

obtaining morphine this resolving agent is replaced by (−)-α-(2-naphthyl)-ethylamine.

The importance of the second advantage listed is seen in the recent development of the strong acid resolving agent 3 which permitted a variety of weakly basic amines to be resolved which had resisted resolution with other acidic resolving agents.[17]

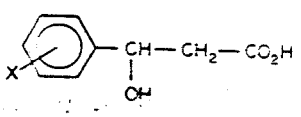
Detracting somewhat from these advantages is the fact that synthetic resolving agents must themselves be first resolved. Hence samples of these compounds may not be as enantiomerically pure as naturally occurring ones. Moreover, if they contain but one chiral center, they may be more easily racemized.†

If compound (±)-A is resolved with (−)-B, it is sometimes the case that (±)-B can be resolved with one of the enantiomers of A. These are called *reciprocal* resolutions. It seems worthwhile reiterating the admonition that reciprocal resolutions need not succeed in principle.[26] Surprisingly, resolutions conceived with reciprocity as operative principle continue to be proposed.[27]

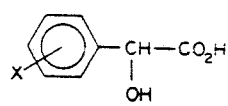
Finally, while the choice of a good resolving agent nowadays remains mostly a matter of guesswork or of perspicacity, there are nevertheless some instances where the chemist can operate less blindly than in the past.

It is now possible to document cases of resolutions of compounds having major structural and conformational similarities in which the *same* resolving agent works for most, if not all, cases.

Thus, the phenylhydracylic acid 4 (X = H)



4



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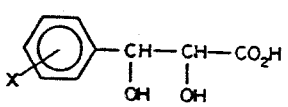


6

and 8 out of 9 of its halogenated derivatives (X = F, Cl, Br) are resolved by brucine.[28] Likewise, mandelic acid 5 and all of its halogenated derivatives (X=F, Cl resolved by ephedrine.[29] In the last case, the les ephedrine salt does not always correspond to th the same absolute configuration (contrary to the rule of Winther[30]).

In contrast, in the analogous series of *thr erythro*-phenylglyceric acids 6, it was not possibl a common resolving agent for the 8 cases e (X=H, Cl).[31]

Let us now return to the role of the solvent.

In the most general case, a change in solven the relative solubilities of the two diastereomers a minor extent. Deviations from ideality, if e operate in very similar ways on both species. W seen that the horizontal lines in Table 1 sho variation. But there are cases where the role pl the solvent is large. For example, those where t crystallize only if they are solvated by a pa solvent, and where no crystallization takes place (of one nor the other isomer) in the absence of so molecules. For this reason, in certain excep favorable cases, only one isomer crystallizes rarely, one finds that both diastereomers crystalli only one of the two is solvated.

While the analysis of solvated salts is seldom out, we can point out, for example, tha bicarboxylic acid 7 gives salts with brucine in wh configuration of the less soluble isomer chang cording to solvation. Another example of phenomenon is the dimethyl-3-phenylpentanoic (Fig. 1).

The few known cases in which it is possible to salts of either enantiomer with *the same* al according to solvent employed must be due t existence of this phenomenon.[32]

4. *Recrystallization of diastereomer mixtures*

Classical resolutions mediated by crystalline tereomers depend usually upon solubility differ between the diastereomers produced in equal quan The solubilities of a three component system diastereomers and the solvent) such as that obtainin resolution are conveniently summarized in a te phase diagram. The Phase Rule, which governs systems, limits their applicability to mixtures of two and one liquid components, i.e. three phases. It turn that the most typical system is that incorporati eutectic such as that shown in Fig. 2.

To simplify matters, in the following discussion will not consider cases in which the salts (or enantiomers themselves) are *solvated*. Here, the sibility of reversibly effecting transformations leadi changes in or to the disappearance of solvation (abov below a given transition temperature) raises the portance of temperature to a level which it does not in usual cases.

The solubility diagram (Fig. 2) describes solubilitie

†The oft-repeated proposition according to which the enantiomeric purity of a resolved substance cannot exceed that of the resolving agent is not exact. Suppose that in the resolution of compound (±)-A one employs resolving agent (−)-B contaminated by some (+)-B. The isolated diastereomer, say salt (+)-A(−)-B will perforce contain some (−)-A(+)-B and be of less than optimal optical purity. However, the optical purity of this enantiomeric pair of salts will increase or decrease upon recrystallization depending upon its composition relative to that of the eutectic and in accord with the solubility behavior expected of mixtures of enantiomers (see Section 5).

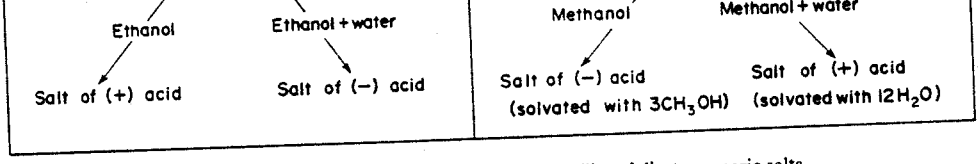


Fig. 1. Influence of solvation on the relative solubility of diastereomeric salts.

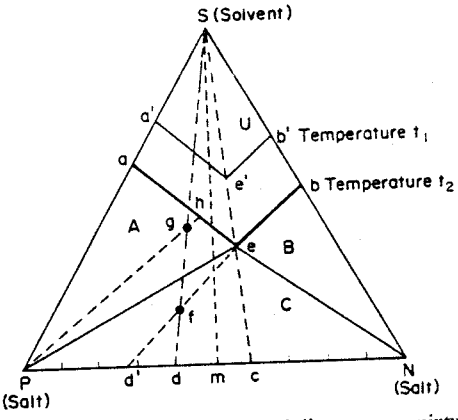


Fig. 2. Solubility diagram of a typical diastereomer mixture.

each diastereomer in pure solvent (points a and b) and of diastereomer mixtures in the same solvent (isotherms ae and be). At lower temperature, parallel (or nearly so) isotherms (a'e' and b'e') similarly yield the compositions of saturated solutions of all possible mixtures of P and N salts. It is significant that for many organic mixtures, *the eutectic composition is practically independent of temperature.*[33] A tie line originating at S and passing through e' will necessarily also pass through, or near e. Since solubilities are temperature dependent, greater absolute recoveries can usually be obtained at lower temperatures. On the other hand, the cost of this greater recovery will be poorer separation: solubility decreases are proportional to diastereomer purity as can be inferred from the phase diagram.

The phase diagram describes four regions, one an unsaturated solution of P and N in solvent labelled U, a region labelled A in which pure P is in equilibrium with solvent containing dissolved P and N in proportion described by the ae isotherm and a reciprocal region labelled B in which pure N is in equilibrium with solvent containing dissolved P + N in proportion described by the be isotherm. The region labelled C describes a saturated solution of fixed composition (the relative proportions of P and N in solution are given by the distances cN and cP, respectively) in equilibrium with solid P and solid N.

The recrystallization of a crystalline diastereomer mixture such as that initially obtained in a resolution trial (and hence enriched in one enantiomer) can be easily followed on the diagram. Suppose the solid precipitated has a composition given by point d (enantiomeric purity = (dN-dP/PN) = (dm/mP) = 20%; the argument is not altered if the e.p. = 0%). The outcome of the recrystallization now depends strictly upon the amount of solvent taken. With little solvent, represented by point f (solvent/solid mixture = df/fS), warming of a mixture until all solid is dissolved and allowing the temperature to return to t_2 (equilibrium), some of the solid will precipitate. Its composition is given by d'. The solid is still a mixture of the two diastereomers but it is enriched in P. Repetition of this process rapidly yields pure P provided that the diagram is not too symmetrical and that solubilities are not too low. The latter point follows from the relative steepness of the line passing through e' and f relative to that of the efd' line.

If the *same* sample of composition d had been recrystallized with more solvent (still along line dS) a global composition described by point g might be attained. Since this solution, upon reestablishment of equilibrium, falls in region A, the solid crystallizing necessarily must have composition P. That is, pure diastereomer P is obtained directly. The mother liquor remaining will have a composition given by point h.

When solubilities of the two diastereomeric salts are more nearly equal, the ternary diagrams are more nearly symmetrical, with the eutectic falling close to the line passing through the 50:50 P + N composition. A consequence of this is that a 50:50 mixture of P + N cannot be separated under any set of conditions described by the ternary diagram (at least under equilibrium conditions).† From what has been stated above, changing the temperature would avail nothing (except, as already mentioned, in the case of polymorphism with transition temperatures). This reproduces situation 2 of section 1.

The upshot of all of this is that when diastereomer mixtures behave as in Fig. 2, recrystallization always leads to enrichment. So long as the diagram is unsymmetrical, this is true even of a 50:50 mixture. For a system such as that described by Fig. 2 enrichment naturally proceeds on that side of the eutectic containing the less soluble diastereomer, the P salt in the example. But how realistic is all this? Do most diastereomer mixtures exhibit ideal behavior, i.e. form eutectics? Fortunately, the answer appears to be yes.[34] However, intervention of situations 3 and 4 of section 1 corresponds to other phase diagrams which are less favorable to separation. While situation 3 (compound

†As in the case of enantiomers (see below) the entrainment of a crystallization (out of equilibrium, for example, by seeding with a single pure salt) can sometimes considerably facilitate separations.

separation of diastereomers exhibiting this kind of behavior becomes extremely difficult, this in spite of considerable difference in solubility between the diastereomeric salts. While few systems are known whose solubility diagrams look like Fig. 3, formation of solid solutions in *part* of the diagram appears to be quite common. One of the principal conclusions of a recent study[3] is that solid solutions are frequently formed when diastereomer salt mixtures are recrystallized.

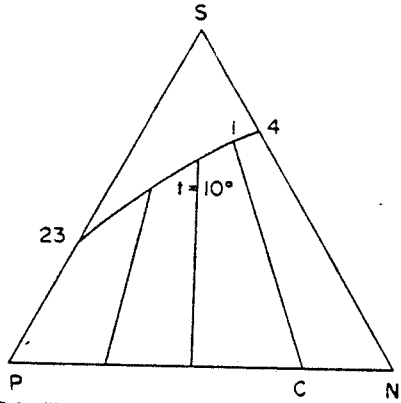


Fig. 3. Solubility diagram of α-methylbenzylamine mandelate salts in H_2O at 10°. Solubilities given in grams. The tie lines relate the composition of the precipitated solid to that of the saturated solution (e.g. C and l).

The way to overcome this problem is to cleave the diastereomer salt mixture back to the resolution substrate, an enantiomer mixture, and to attempt its optical enrichment.[3] Section 5 discusses recrystallization of enantiomer mixtures.

5. *Recrystallization of enantiomer mixtures*

The phase diagrams which describe and summarize the solubility behavior of enantiomer mixtures are fundamentally like those we have seen and discussed in Section 4 of this paper. Figures 4 and 5 illustrate the two most common types. Surprisingly, experimental data illustrating such solubility behavior are of very recent origin.[33]

The principal differences between these diagrams and those for diastereomer mixtures are:

(1) The symmetry of the enantiomer mixture diagrams.

(2) The greater incidence of systems exhibiting compound formation.

Figure 4, the analog of the most common type of diastereomer mixture solubility behavior (Fig. 2.) is by far rarer for enantiomer mixtures. This is the case of conglomerates, mechanical 1:1 mixtures of (+) and (−) crystals, which brings to mind the first resolution performed by Pasteur.[35] Indeed, mechanical separation of this type (so-called spontaneous resolution) or, as we will see further on, resolution by entrainment, is only possible with enantiomer mixtures which crystallize as

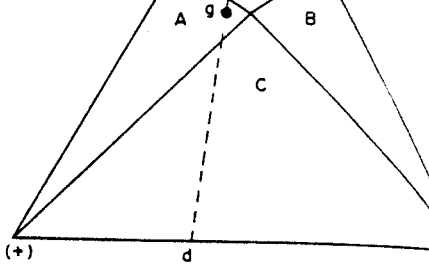


Fig. 4.

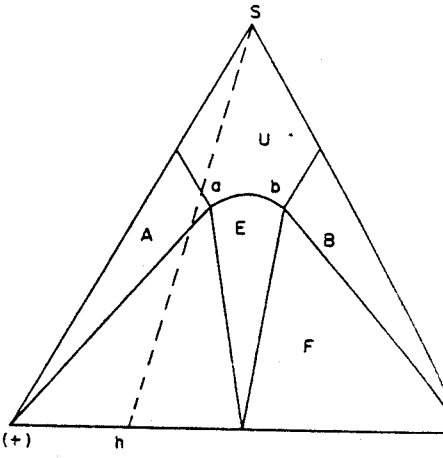


Fig. 5.

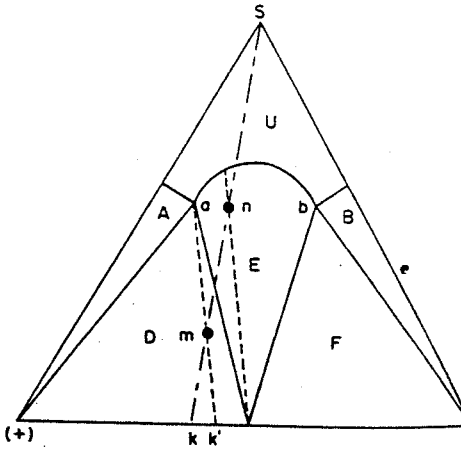


Fig. 6.

Fig. 4–6. Solubility diagrams of enantiomer mixture

two distinct phases yielding a eutectic. An account the known systems, of ways of identifying glomerates and even of predicting their incidenc been given by Collet *et al.*[36] The importance of su assessment follows from the fact that conglomerat fundamentally the easiest enantiomer mixtures to r and to purify.

Consider Fig. 4. Any partially enriched mixtu

is by far more prevalent with enantiomers
iastereomers. Figures 5 and 6 describe the
ehavior of true racemates as these com-
called. True racemates, an example being
taric acid, crystallize as a single phase
equal numbers of (+) and (−) molecules in
lattice (which is necessarily different from
e enantiomers). The resolution of such
mixtures by recrystallization can be easy or
ding upon the magnitude of the curved part,
solubility isotherm and the composition
ic purity) of the starting mixture.

that any argument which holds for the left
hase diagram holds for the right, any mixture
eric purity greater than that of the eutectic,
5) will be enriched by recrystallization just as
of conglomerates. A mixture of enantiomeric
ler than that of the eutectic, e.g. k (Fig. 6)
es to give a solid of composition k′ of lower
n) or, with more solvent (region E), crys-
ive solid racemate (case n).

one should begin such a recrystallization with
aving as high an e.p. as possible but in no
less than is called for by the eutectic
n. The outcome quickly tells if one has erred
nowledge of the nature of the racemate, of the
the eutectic, and of the composition of the
xture would lead to a more rational and less
olution to the purification process.

ely, the incidence of solid solution formation
ystallization of enantiomer mixtures is small.
ication need not unduly concern us.

hwhile emphasizing that *any* manipulation of
solved enantiomer mixture (any mixture other
) with solvent is potentially selective, even
g solid with solvent. In this connection, note
ubility of the eutectic is always greater than
er enantiomer and of true racemate, hence
enantiomer mixture *other than* 50:50 with
ds to enrichment of the solid phase either in
omer or in racemate according to the nature
nic mixture and to the position of the eutectic
of a true racemate.

erwise inocuous manipulation may lead to
antial alteration of the enantiomer ratio and
lusions in mechanistic and asymmetric syn-
riments.

tial point that follows from this analysis is
owledge of the solubility behavior of an
mixture as exhibited by its ternary solubility
n greatly simplify a resolution that depends
ility differences. Alternatively, ignorance of
f diagram a given system has can lead to
he resolution.

ique other than direct recrystallization is
r the enrichment of enantiomer mixtures. It

threo diastereomers. Separation and elimination of the *meso* isomer by washing or recrystallization raises the enantiomeric purity of the chiral substance recovered from the *threo* diastereomer.[37]

A second potentially useful enrichment technique involves subjecting a partially resolved chiral substance to homocompetitive reactions with an insufficient amount of a chiral reagent. Differences in reaction rate lead to enrichment or reduction in e.p. of the residual substrate depending upon the configuration of the chiral reagent used but in a predictable fashion. This technique is particularly useful to determine the maximum rotatory power of a chiral substance by raising the e.p. from a high level to a new e.p. which, e.g. may be as high as 99.9%.[38]

Finally, solubility diagrams such as Fig. 4 permit a facile explanation of the resolution by entrainment, one of the simplest resolution processes known.

Resolution by entrainment occurs only with conglomerates and takes place entirely in region C of the diagram (Fig. 7), in which supersaturation by the two enantiomers may occur. Thus, a supersaturated solution of racemate containing a slight excess (*ca.* 10%) of (−)-enantiomer and maintained at constant temperature constitutes proper initial conditions (point 1 on Fig. 7); after seeding with (−)-enantiomer, the composition of the solution gradually changes from 1 to m as pure (−) crystallizes. This crystallization is attended by gradual changes in the optical rotation of the solution, which is first (−), then zero, then (+). Ideally, the m end point is chosen to be symmetrical to 1 with respect to the optical rotation.

When the composition m has been attained, (−) crystals are collected and an equivalent weight of racemate is added to the solution, dissolved by heating and then cooled. A supersaturated solution of composition n (symmetrical to 1) is thus obtained and (+)-enantiomer is induced to crystallize until the solution attains composition o; (+)-crystals are collected, more racemate is added and the process repeated.†

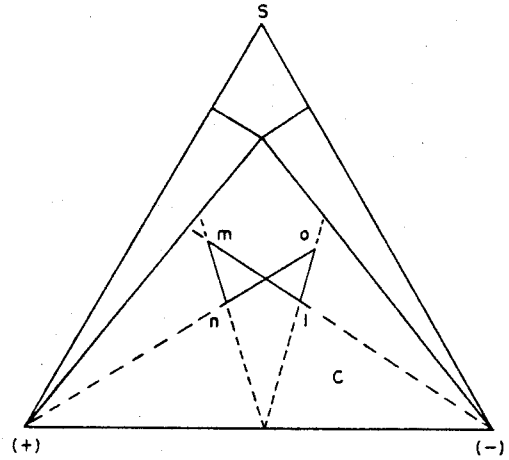


Fig. 7. Resolution by entrainment.

foregoing analysis, readers will recognize ideas
y Secor in his review[39] dealing with resolution by
llization.

economical process is of considerable importance industrially.[40]

6. *Utility of binary phase diagrams in resolutions*

Granted that it is useful to have a solubility diagram of the system being resolved, how useful is this fact in a real situation, when little or no information is available at the onset?

It turns out that the essential information provided by solubility diagrams is of two kinds:

(1) Their form, i.e. number of eutectics and compounds formed between the components and occurrence of solid solutions and

(2) The actual composition of eutectics and compounds formed by enantiomer mixtures in solution.

The crucial point that answers the question in the first paragraph above is that ternary solubility diagrams in general are directly related to classic binary phase diagrams. That is, they have the same form. Chiral compounds whose enantiomer mixtures yield only a eutectic upon melting, only exhibit a eutectic when dissolved. And chiral compounds whose racemates are compounds, i.e. true racemates, exhibit solubility minima corresponding to these compounds in solution in addition to eutectic points.

Moreover, and equally important, the composition of eutectics in systems which are solutions of enantiomer mixtures (or of diastereomer mixtures) closely reflects the composition of eutectics in the corresponding binary phase diagrams. The evidence for this comes from the few systems that have been carefully investigated in the past several years.[3,33] Thus binary phase diagrams are directly useful in resolution processes as alternatives to solubility diagrams. Even solid solution formation is recognizable in binary phase diagrams.[3]

Why should binary phase diagrams be any more practical aids in resolution than the tertiary diagrams already described? Because they are inherently simpler and because their principal features are easy to determine.

All required features of binary phase diagrams of conglomerates and of true racemates, or even of diastereomer mixtures exhibiting eutectics, can be *calculated* from relatively few data on the basis of the Schröder–Van Laar or Prigogine–Defay equations. This has been known for a long time but not much applied because of the difficulty of measuring heats of fusion, particularly on very small samples.

The introduction of commercial differential scanning microcalorimeters has changed all of this. With a sample weighing as little as 0.1 mg, the heat of fusion of compounds (true racemate, enantiomer or eutectic mixture) can be rapidly determined to a precision of 1–2% and the fusion temperature accurately measured as well. In the case of a conglomerate, these data suffice to calculate the binary phase diagram. Such calculated diagrams, which are based upon the assumption (actually observed[41]) that enantiomer mixtures behave ideally, are sufficiently accurate reflections of diagrams constructed point by point from experimental data to be useful in guiding resolutions. The equation permitting the calculation of the liquidus of a phase diagram of a conglomerate (or even

where x = mol fraction of one enantiomer (or of
diastereomer in a binary mixture of two)
ΔH_A^F = molar heat of fusion of the pure enantiomer
diastereomer)
T_A = melting point (°K) of the pure enantiom
(diasteromer)
T_F = melting point (°K), i.e. end of fusion of
mixture of mol fraction x
R = Ideal gas constant (2 cal. mol^{-1} deg^{-1}).

The molar heat of fusion is directly obtainable fr
the area of an appropriate DSC trace as are the requir
melting points. Thus, a diagram such as that of Fig.
can be constructed with knowledge only of T_A and
ΔH_A^F. The corresponding DSC trace for a mixture
composition x is shown in Fig. 9. Similar traces a
obtained for diastereomer mixtures.

Where the racemic mixture exhibits compound fo
mation as illustrated in Fig. 10, liquidus curves AE_1 (a
perforce BE_2) can be calculated as well by means
eqn 3. Liquidus curve E_1RE_2 is similarly calculab
with the Prigogine–Defay relationship:[43]

$$\ln 4x(1-x) = \frac{2\Delta H_R^F}{R}\left(\frac{1}{T_R} - \frac{1}{T_F}\right)$$

where ΔH_R^F = molar heat of fussion of the true racemat
T_R = melting point (°K) of the true racemate

In the case of a true racemate, the intersection of th
two calculated liquidus curves yields the composit
and the fusion temperature of the eutectic. DSC curve
of true racemates do not differ markedly from those
conglomerates. Recall that racemic mixtures which yie
fusion maxima behave like ordinary compounds o
fusion. In these cases, peak II of Fig. 9 would cor
respond to that for the compound R at composition c fa
example.

What all of this means is that availability of milligra
quantities of racemic mixtures and of their enantiome

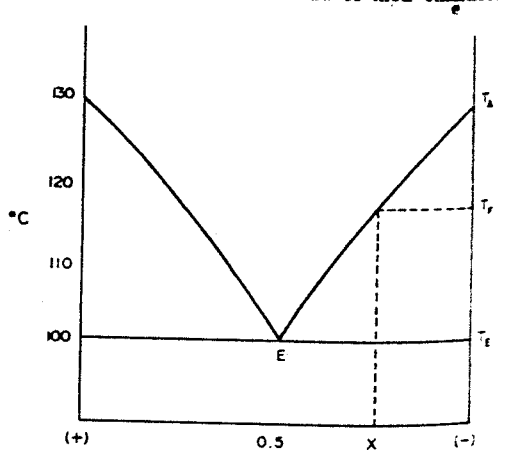
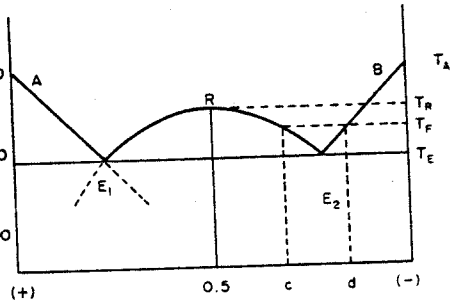


Fig. 8. Binary phase diagram of a conglomerate, calculated with T_A = 130°, ΔH_A^F = 7 kcal/mole. Note that the racemic mixture E melts 30° lower than do the pure enantiomers.

T

ypical DSC trace of an enantiomer mixture (other than 50:50).



Binary phase diagram of a true racemate, calculated with 0°, $T_R = 115°$, $\Delta H_A^F = 7$ kcal/mole and $\Delta H_R^F = 8.5$ kcal/mole.

tuents suffice for construction of binary phase ms such as those illustrated.

w it is evident that samples of pure enantiomers are sually available at the start of a resolution. What is l in practice is to use those data that are available at set and to add to them after the resolution tests are uded, and as the resolution progresses. In the more ılt cases, complete resolution on a very small scale, romatography (HLPC or thin layer) of covalent ereomers if need be, would yield the required les of enantiomers to generate the phase diagrams. yond this, a fusion determination of a partially ved mixture of a chiral substance locates the ure on the phase diagram, incidentally yielding its tiomeric purity, and suggests the procedure for er enrichment by recrystallization. Note that in the exemplified by Fig. 10, the composition of a sample se fusion ends at T_F must be established by addition small amount of either racemate or pure B. If the ting point (end of fusion) rises in the latter case the position is d; if it drops, the composition is c.

one of this is meant to suggest that there are not plications which can preclude the approach sug- ted. For example, the incidence of polymorphism is ually quite common among organic compounds. This ids additional peaks in DSC traces which may be icult to interpret.

Also, eutectic peaks are sometimes not observed. The ence of a significant eutectic peak in a DSC trace, cept at the very extremes of composition (abcissa) ere its area is expected to be so small as to preclude servation, is indicative of solid solution formation. is can be confirmed by measurement of heats of sion of the eutectic present in mixtures which vanish here solid solution formation begins. This phenomenon particularly common in diastereomer salt mixtures (see ef. 3 for an example).

(1) A wide range of resolving agents are available and utilized in resolution trials. Finding a good resolving agent is the first step in the resolution process. It is also the most empirical of all the steps.

(2) Efficient separation of enantiomers under equilibrium conditions requires close control of solvent amount and of temperature. These factors are at least as important as choice of solvent in a resolution.

Enantiomer mixtures are among the most ideal in their behavior. Solvent selection is relatively unimportant in the recrystallization of such mixtures.

(3) Resolutions achieved through recrystallization of enriched enantiomer mixtures need to be recognized as useful alternatives to separation through recrystallization of diastereomer mixtures. In some cases, the former approach is clearly superior.

(4) Successful resolutions require the early recognition of the nature of the racemic form of the substrate: binary phase diagrams of enantiomer mixtures are valuable signposts in resolutions.

(5) Examination of the fusion process of enantiomer mixtures is the simplest and fastest method for monitoring resolution progress available at the present time.

The emphasis here is on a fusion procedure that accurately identifies beginning and termination of melting. Observations of relative proportions of eutectic and enantiomer fusion peaks also assists in planning resolution steps. Differential scanning microcalorimetry is recommended as the most sensitive and efficient technique meeting the requirements.

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[4]For an early example see M. Koreeda, G. Weiss and K. Nakanishi, *J. Am. Chem. Soc.* **95**, 239 (1973).
[5](−)-Camphoric acid is treated with PCl_5 (2 h, 130°). This is followed by addition of 1 eq. bromine and heating to nearly complete discoloration of the mixture. (+)-Bromocamphoric anhydride is isolated by pouring the mixture into ice-cold water. The anhydride is hydrolyzed (10 min in boiling water containing 10% dioxane) and neutralized (2 eq. NaOH). Acidification, extraction and crystallization (toluene) affords (+)-camphanic acid in *ca.* 50% overall yield.
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$$op = \frac{(R-S)}{(R+S)} \cdot 100$$