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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):

$$(\pm)\,CH_3CH(Cl)COOH + (-)\,C_6H_5CH(CH_3)NH_2 \longrightarrow$$

$$(-)\,CH_3CH(Cl)COO^{\ominus}\ (-)\,C_6H_5CH(CH_3)NH_3^{\oplus} \quad \text{(1)}$$

P salt

$$+\ (+)\,CH_3CH(Cl)COO^{\ominus}\ (-)\,C_6H_5CH(CH_3)NH_3^{\oplus}$$

N salt

$$CH_3CH(Cl)COO^{\ominus}\ C_6H_5CH(CH_3)NH_3^{\oplus} + H_2SO_4 \rightarrow$$

$$CH_3CH(Cl)COOH + C_6H_5CH(CH_3)NH_3^{\oplus}\ HSO_4^{\ominus} \quad \text{(2)}$$

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]

the case of diastereomeric salts. Thus, if it be granted that as a first approximation molecular rotations of the salts are additive functions of those of the constituent ions, it becomes evident that a large value of $[\phi]$ of the common ion may mask variations in a weakly rotating counter ion.

In the following sections we attempt to justify our approach which attaches special importance to melting 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.

Table 1 illustrates clearly the value of examining rotations of the resolution substrate. The significance of the results is unambiguous, contrary to what would obtain in measuring diastereomer salt rotations. The choice of scale for the preliminary tests is predicated upon the requirements of the polarimetric measurements. Since α_D of modern photoelectric polarimeters are reproducible and significant at least to 0.005°, both examples in Table 2 illustrate the possibilities of working with very small quantities of resolved compounds. On the other hand, the data also suggest the potential for errors that may arise if small amounts of strongly rotating contaminants, resolving agents, for example, are imcompletely removed.

Table 1 clearly points up the fact that more is required than just obtaining a crystalline solid. In nine cases out of the 40 resolution attempts summarized in Table 1, crystalline solids yielded racemic acid upon recovery of the substrate. It is possible to summarise[3] the four situations that render resolutions mediated by diastereomers difficult as follows:

Situation (1) formation of non-crystalline diastereomers
Situation (2) too small differences in solubilities of diastereomers
Situation (3) formation of addition compounds, viz. double salts, between diastereomers
Situation (4) formation of solid solutions (isomorphism) between diastereomers

In fact, while the experimental data which illustrate these difficulties were obtained on diastereomeric *salts*, the same arguments apply, to some extent, to covalent diastereomeric compounds. However, with such compounds, *none* of these situations are true stumbling blocks to resolutions since separations by chromatography are feasible and often quite easy to achieve.

If covalent diastereomers are relatively easy to separate (in particular, we underscore the ease with which high pressure liquid chromatography with columns of high efficiency permits covalent diastereomer separation)[4] why not preferentially choose this route? Because their formation is not as easy as that of salts, nor is their decomposition. Moreover, the forward and reverse reactions described are more subject to racemization of chiral centers than is salt formation.

ω-Camphanic acid **1** illustrates another disadvantage occasionally found in resolutions mediated by covalent

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.

Table 2. Measurement of rotations of small samples

Case a

Molecular weight 150 ; $[\alpha]_D$ + 20°

Substrate taken : 150 mg (0.001 mole)

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

primary indicators that resolution has begun, do not tell one anything at all about its success, that is, about the enantiomeric enrichment[11] of a given sample unless the specific rotation of an enantiomerically pure sample is already known. For this information, one must have recourse to one of the known methods of determining enantiomeric purity. These methods are summarized in 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 of diastereomer mixtures—salts or covalent compounds—that are easily separable by common physical processes. One could then reword the title of this section to read: Finding the good diastereomer mixture. Unfortunately, at the present time this cannot yet be done directly in predictable fashion with any degree of success. All that one can do is to choose resolving agents suitable to the substrate.

How does one choose resolving agents? Table 1 implies that every conceivable resolving agent must be employed in preliminary resolution tests. That is patently untrue; many more chiral bases could have been tried. And, it turns out that there are by far more basic resolving agents known than any other type (Table 4).

One can consult recent reviews of resolutions[22,23] where useful types of resolving agents are listed or one can attempt to match the substrate to a known resolution through consultation of a compilation of resolutions.[24] Provided that one does not limit oneself to just one or two resolving agents in the preliminary tests, this is in fact the only realistic strategy at the beginning of a resolution empirical though it may be.

Table 4 gives an overview of the principal resolving agents of modern usage and the nature of the diastereomeric products formed in the corresponding resolutions. While statistical information has not been accumulated to confirm the contention, we have observed that diastereomer salt-forming resolutions remain the principal type employed.

Readers are also referred to the reviews of Boyle[23] and of Wilen[22] for particulars on specific resolving agents. New resolving agents or methods figuring prominently in the literature since 1971, or in current usage, are marked with an asterisk.

It is worthwhile to underline the continually increasing utility and advantages of synthetic resolving agents. These advantages are:

(1) The availability of both resolving agent enantiomers. This permits both substrate enantiomers to be obtained in mirror image resolutions.

(2) Synthetic resolving agents may be designed to have stronger acid–base properties and hence more easily form salts. For example, synthetic amine resolving

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

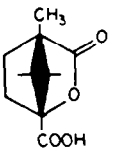
Table 4. Principal resolving agents of modern usage

Functional Group	Resolving Agent	Products	Reference
RCOOH, RSO_3H	Alkaloids: Brucine, strychnine, cinchonine, cinchonidine, quinine, quinidine ephedrine	Salts or amides (the latter with 1° amines only and then rarely)*	*(15)
	Synthetic amines: α-methylbenzylamine; 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		
	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	

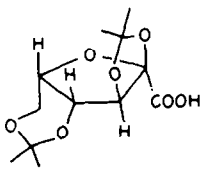
agents are all primary amines and hence are stronger bases than typical alkaloid resolving agents.

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]

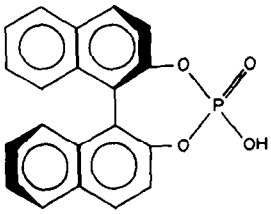
Availability and lower cost of synthetic resolving agents relative to those of naturally occurring resolving agents—especially for amines—often dictate their use when a choice is possible. Table 1 provides a good illustration. The choice of best resolving agents would seem to be morphine and (+)-α-(2-naphthyl)-ethylamine 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]

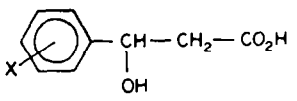
Detracting somewhat from these advantages is the fact that synthetic resolving agents must themselves be first resolved. Hence samples of these compounds may not be as enantiomerically pure as naturally occurring ones. Moreover, if they contain but one chiral center, they may be more easily racemized.†

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)



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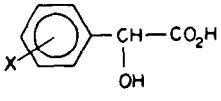

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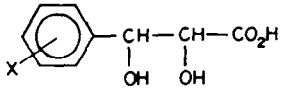

6

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, Br) are resolved by ephedrine.[29] In the last case, the less soluble ephedrine salt does not always correspond to the acid of the same absolute configuration (contrary to the very old rule of Winther[30]).

In contrast, in the analogous series of *threo*- and *erythro*-phenylglyceric acids 6, it was not possible to find a common resolving agent for the 8 cases examined (X=H, Cl).[31]

Let us now return to the role of the solvent.

In the most general case, a change in solvent affects the relative solubilities of the two diastereomers only to a minor extent. Deviations from ideality, if existent, operate in very similar ways on both species. We have seen that the horizontal lines in Table 1 show little variation. But there are cases where the role played by the solvent is large. For example, those where the salts crystallize only if they are solvated by a particular solvent, and where no crystallization takes place (neither of one nor the other isomer) in the absence of solvating molecules. For this reason, in certain exceptionally favorable cases, only one isomer crystallizes. Less rarely, one finds that both diastereomers crystallize yet only one of the two is solvated.

While the analysis of solvated salts is seldom carried out, we can point out, for example, that the bicarboxylic acid 7 gives salts with brucine in which the configuration of the less soluble isomer changes according to solvation. Another example of this phenomenon is the dimethyl-3-phenylpentanoic acid 8 (Fig. 1).

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

4. *Recrystallization of diastereomer mixtures*

Classical resolutions mediated by crystalline diastereomers depend usually upon solubility differences between the diastereomers produced in equal quantities. The solubilities of a three component system (two diastereomers and the solvent) such as that obtaining in a resolution are conveniently summarized in a ternary phase diagram. The Phase Rule, which governs such systems, limits their applicability to mixtures of two solid and one liquid components, i.e. three phases. It turns out that the most typical system is that incorporating a eutectic such as that shown in Fig. 2.

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

The solubility diagram (Fig. 2) describes solubilities of

†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).

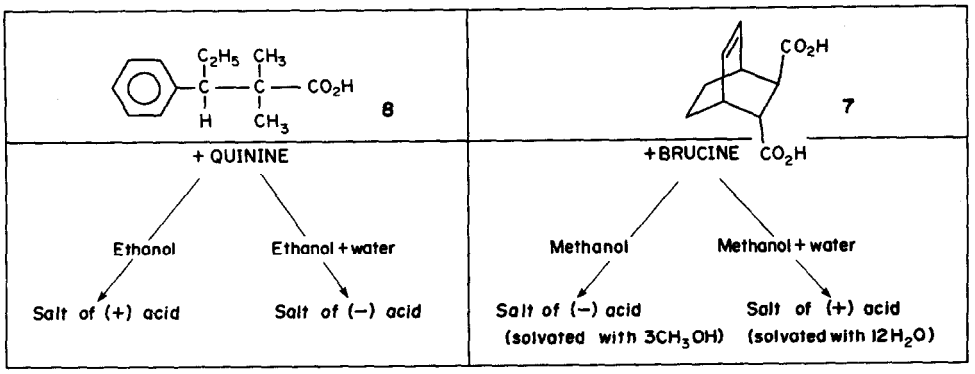

Fig. 1. Influence of solvation on the relative solubility of diastereomeric salts.

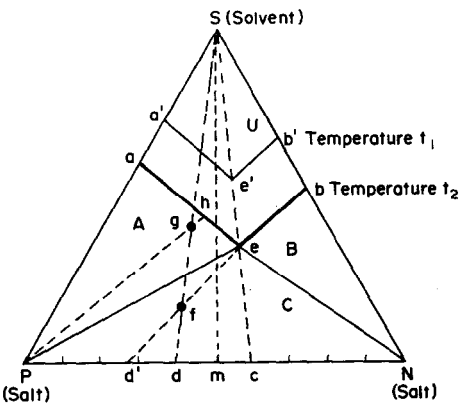

Fig. 2. Solubility diagram of a typical diastereomer mixture.

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.

formation) is exceptional, the incidence of situation 4, corresponding to formation of solid solutions, is more common and consequently is more serious. The case of the diastereomer mixture formed by mandelic acid and α-methylbenzylamine is described by the phase diagram shown in Fig. 3. Note the complete absence of a eutectic. Whether or not the isotherm contains an inflection, 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.

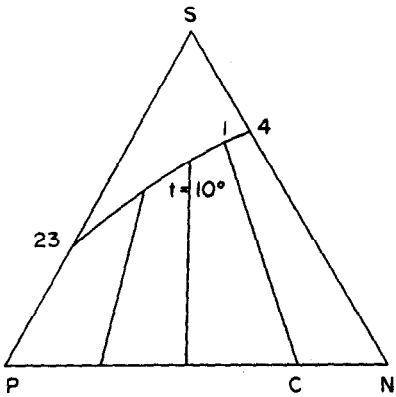

Fig. 3. Solubility diagram of α-methylbenzylamine mandelate salts in H_2O at 10°. Solubilities given in grams. The tie lines relate the composition of the precipitated solid to that of the saturated solution (e.g. C and l).

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

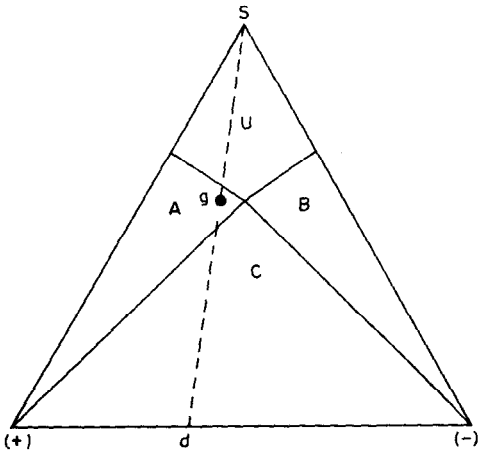

Fig. 4.

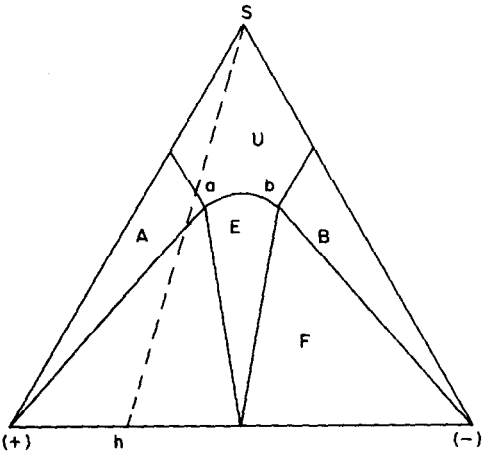

Fig. 5.

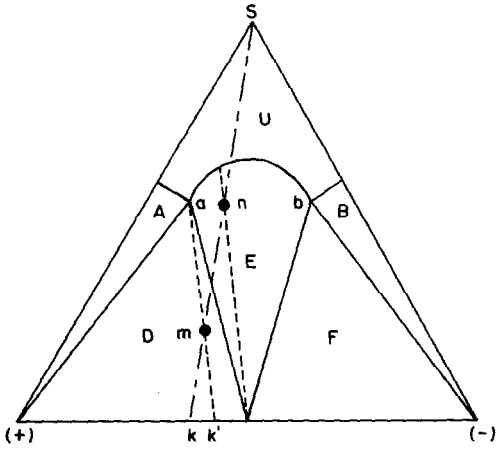

Fig. 6.

Fig. 4–6. Solubility diagrams of enantiomer mixtures.

two distinct phases yielding a eutectic. An accounting of the known systems, of ways of identifying conglomerates and even of predicting their incidence, has been given by Collet *et al.*[36] The importance of such an assessment follows from the fact that conglomerates are fundamentally the easiest enantiomer mixtures to resolve and to purify.

Consider Fig. 4. Any partially enriched mixture of

enantiomers forming a conglomerate, d for example, can be resolved by direct recrystallization. The same arguments as those made in connection with diastereomer mixtures (Fig. 2) obtain. With a dilute solution having a global composition given by g, a single recrystallization will directly yield crystals of pure (+)-enantiomer.

Unfortunately, compound formation (i.e. racemate formation) is by far more prevalent with enantiomers than with diastereomers. Figures 5 and 6 describe the solubility behavior of true racemates as these compounds are called. True racemates, an example being racemic tartaric acid, crystallize as a single phase containing equal numbers of (+) and (−) molecules in the crystal lattice (which is necessarily different from that of the enantiomers). The resolution of such enantiomer mixtures by recrystallization can be easy or hard depending upon the magnitude of the curved part, ab, of the solubility isotherm and the composition (enantiomeric purity) of the starting mixture.

Recalling that any argument which holds for the left side of the phase diagram holds for the right, any mixture of enantiomeric purity greater than that of the eutectic, e.g. h (Fig. 5) will be enriched by recrystallization just as in the case of conglomerates. A mixture of enantiomeric purity smaller than that of the eutectic, e.g. k (Fig. 6) recrystallizes to give a solid of composition k' of lower e.p. (case m) or, with more solvent (region E), crystallizes to give solid racemate (case n).

Clearly, one should begin such a recrystallization with a mixture having as high an e.p. as possible but in no case with less than is called for by the eutectic composition. The outcome quickly tells if one has erred but a foreknowledge of the nature of the racemate, of the location of the eutectic, and of the composition of the starting mixture would lead to a more rational and less empirical solution to the purification process.

Fortunately, the incidence of solid solution formation during recrystallization of enantiomer mixtures is small. This complication need not unduly concern us.

It is worthwhile emphasizing that *any* manipulation of partially resolved enantiomer mixture (any mixture other than 50:50) with solvent is potentially selective, even just washing solid with solvent. In this connection, note that the solubility of the eutectic is always greater than that of either enantiomer and of true racemate, hence washing an enantiomer mixture *other than* 50:50 with solvent leads to enrichment of the solid phase either in pure enantiomer or in racemate according to the nature of the racemic mixture and to the position of the eutectic in the case of a true racemate.

Such otherwise inocuous manipulation may lead to even substantial alteration of the enantiomer ratio and affect conclusions in mechanistic and asymmetric synthesis experiments.

An essential point that follows from this analysis is that a knowledge of the solubility behavior of an enantiomer mixture as exhibited by its ternary solubility diagram can greatly simplify a resolution that depends upon solubility differences. Alternatively, ignorance of the type of diagram a given system has can lead to failure of the resolution.

A technique other than direct recrystallization is available for the enrichment of enantiomer mixtures. It may be particularly useful in those instances where recrystallization reduces e.p. as in case n (Fig. 6). This technique involves *duplication* of partially resolved chiral substances (for example by converting an alcohol to the ester of a diacid, by preparing an anhydride from an acid, or forming a N,N-disubstituted urea from an amine) in such a way as to yield a mixture of *meso* and *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.†

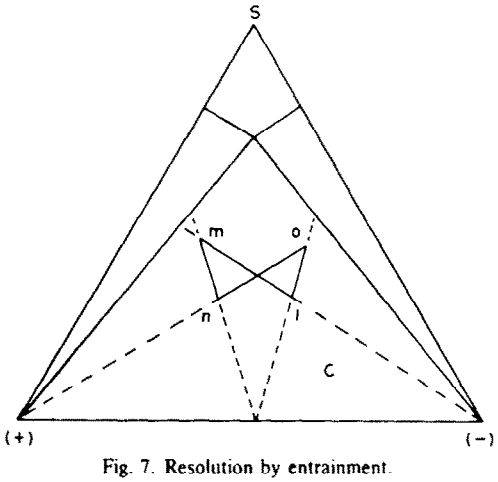

Fig. 7. Resolution by entrainment.

†In the foregoing analysis, readers will recognize ideas developed by Secor in his review[39] dealing with resolution by direct crystallization.

Measuring the rotation of the mother-liquors is the simplest way of following the process.

Resolution by entrainment is hardly a theoretical construct or a laboratory curiosity. A fair number of examples of entrainment have been described in the literature particularly in patents; in fact, this very 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 the liquidus of a binary mixture of diastereomers exhibiting eutectic formation, as is most common) is the Schröder–Van Laar equation[42]

$$\ln x = \frac{\Delta H_A^F}{R}\left(\frac{1}{T_A} - \frac{1}{T_F}\right) \tag{3}$$

where x = mol fraction of one enantiomer (or of one diastereomer in a binary mixture of two)

ΔH_A^F = molar heat of fusion of the pure enantiomer (or diastereomer)

T_A = melting point (°K) of the pure enantiomer (diasteromer)

T_F = melting point (°K), i.e. end of fusion, of the mixture of mol fraction x

R = Ideal gas constant (2 cal. mol^{-1} deg^{-1}).

The molar heat of fusion is directly obtainable from the area of an appropriate DSC trace as are the required melting points. Thus, a diagram such as that of Fig. 8, can be constructed with knowledge only of T_A and of ΔH_A^F. The corresponding DSC trace for a mixture of composition x is shown in Fig. 9. Similar traces are obtained for diastereomer mixtures.

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

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

where ΔH_R^F = molar heat of fussion of the true racemate

T_R = melting point (°K) of the true racemate

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

What all of this means is that availability of milligram quantities of racemic mixtures and of their enantiomer

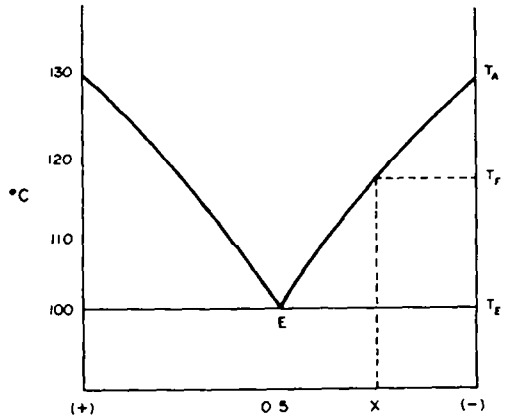

Fig. 8. Binary phase diagram of a conglomerate, calculated with T_A = 130°, ΔH_A^F = 7 kcal/mole. Note that the racemic mixture E melts 30° lower than do the pure enantiomers.

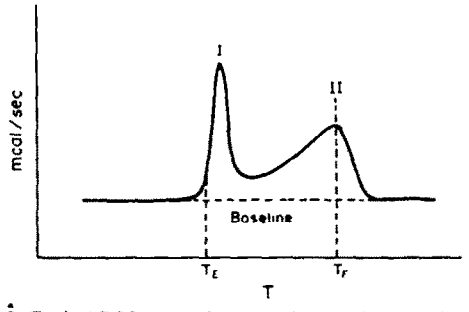

Fig. 9. Typical DSC trace of an enantiomer mixture (other than 50:50).

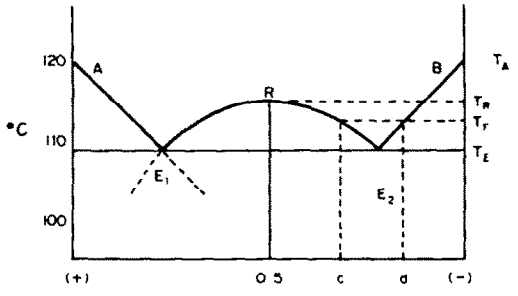

Fig. 10. Binary phase diagram of a true racemate, calculated with $T_A = 120°$, $T_R = 115°$, $\Delta H_A{}^F = 7$ kcal/mole and $\Delta H_R{}^F = 8.5$ kcal/mole.

constituents suffice for construction of binary phase diagrams such as those illustrated.

Now it is evident that samples of pure enantiomers are not usually available at the start of a resolution. What is useful in practice is to use those data that are available at the onset and to add to them after the resolution tests are concluded, and as the resolution progresses. In the more difficult cases, complete resolution on a very small scale, by chromatography (HLPC or thin layer) of covalent diastereomers if need be, would yield the required samples of enantiomers to generate the phase diagrams.

Beyond this, a fusion determination of a partially resolved mixture of a chiral substance locates the mixture on the phase diagram, incidentally yielding its enantiomeric purity, and suggests the procedure for further enrichment by recrystallization. Note that in the case exemplified by Fig. 10, the composition of a sample whose fusion ends at T_F must be established by addition of a small amount of either racemate or pure B. If the melting point (end of fusion) rises in the latter case the composition is d; if it drops, the composition is c.

None of this is meant to suggest that there are not complications which can preclude the approach suggested. For example, the incidence of polymorphism is actually quite common among organic compounds. This yields additional peaks in DSC traces which may be difficult to interpret.

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

For most resolutions, however, the approach suggested is practical. The various recommendations made here are summarized in the concluding section.

7. *Conclusions and recommendations*

Just as one cannot provide recipes for as yet untried resolutions, one cannot completely eliminate tedium in resolutions. Yet one can proceed with confidence.

The following observations follow from the foregoing analysis of resolution steps:

(1) A wide range of resolving agents should be 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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[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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