Enantiomers, Racemates, and Resolutions

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It is known that certain racemates may be resolved by inclusion in an enantiomorphous crystal (Section 5.1.8). According to Mislow, the above results correspond to the inverse of this type or resolution since racemic 7 constitutes the host molecules which are resolved by inclusion of optically active guest molecules in their lattice.

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Formation and Sepa of Diastereomers

In the preceding chapter we have principally examin of enantiomers that do not require the intervention examine those processes which depend on the form *pounds* derived from the enantiomers to be separa stereomer pairs may have significantly different phys the basis of their separation from one another. We c *line* diastereomeric compounds. We examine two br *dissociable compounds*, or *complexes*, and *covalent* is convenient even if somewhat arbitrary.

The number of resolutions mediated by diastere ture is quite large, and we have not felt it necessary us. The cases cited are representative and cover the functional groups.

While covalent diastereomers are increasingly s the separation of other types of diastereomeric su crystallization techniques that are based upon differe chapter we apply several of general concepts develo those involving the use of phase diagrams.

Before taking up these matters, let us briefly ex diastereomer specification and of the way in which t from diastereomers may be distinguished.

The bimolecular combination of two chiral sub four diastereomers (Scheme 1). We have adopted t letter *p* is used to designate the diastereomers result constituents having like *sign* of rotation and the lette mers formed from constituents of unlike sign. Th suggestion made by I. Ugi (*Z. Naturforsch.*, 1965, pounds possessing but two chiral centers and which is Cahn, Ingold, and Prelog: $RR = SS = p$ and $RS =$ which is applicable to all types of dissociable as well no account is taken of the absolute configurations o

The p and n designations take into account only the signs of the rotations of species A and B.* In the case of diastereomeric salts, for example, reference may be made to Tables 1 and 2 in Section 5.1, which give the signs of the rotatory power of the principal alkaloids and the naturally occurring acids used in resolutions.

SCHEME 1

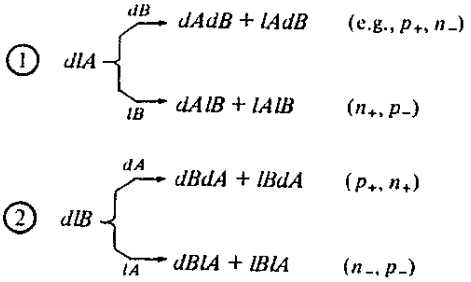
① $dAdB = p_+$ (or p_-) ③ $dAlB = n_+$ (or n_-)

② $lAlB = p_-$ (or p_+) ④ $lAdB = n_-$ (or n_+)

Given the above, the four diastereomers $[AB]$ are found to consist of two enantiomeric p compounds, p_+ and p_- and, by the same token, two enantiomeric n compounds, n_+ and n_-. It should be evident that the sign of rotation of a given diastereomer p or n is not necessarily related directly to those of its constituents A and B. In Scheme 1, the diastereomers $dAdB$ and $dAlB$ have been arbitrarily designated as p_+ and n_+; they could just as well (experimentally) have been found to be p_- and n_-, or even p_- and n_+, for example.

In a resolution, which brings into play a racemic substrate and a resolving agent which is by definition a single enantiomer, the formation of diastereomers leads to a mixture of only *two* compounds: p and n. It is important to observe, as Scheme 2 makes clear, that the mixtures derived from racemic A and optically active B (case ①) are not identical to those derived from the inverse operation, namely, racemic B and optically active A (case ②). In one case, the diastereomers p and n have the same sign, while in the other they have unlike signs.

SCHEME 2



The consequence of this lack of symmetry between the two cases is taken up in Section 5.1.16. In the sections which follow, we generally deal with mixtures of diastereomeric pairs (p,n) without need of further specification of their sign of rotation.

* In those cases – fortunately relatively rare – in which the sign inverts upon a change in solvent, it is necessary to stipulate the solvent used (preferably that solvent in which the salts are best formed).

5.1 DISSOCIABLE COMPOUNDS AND COMPLEXES

The most widely used resolution method remains the forma crystalline diastereomeric *salts* between racemic substrate resolving agents. Other usable dissociable crystalline combi theless; these are Lewis acid–base complexes, inclusion c racemates. These diverse addition compounds have in comm They are obtained generally by simple mixing of the constitu solvent. Regeneration of the constituents is most often imme agent is almost always recovered in a form that allows its reus

The resolution method consisting of the formation of a acid and an optically active base was discovered by Pasteur[1–3]

> I have shown that the absolute identity of the physical ar ties of nonsuperposable right and left bodies ceased to ex stances were put in the presence of [optically] active bo and left tartrates of the same [optically] active organi distinct in their crystalline forms, in their solubility, etc. . hoped that one could take advantage of this difference to taric acids which comprise the racemate: after much attempted on various bases, this is the service done by the and cinchonicine. When, for example, one prepares the ra cine [i.e., in modern terms the cinchotoxine salt of rac then for a given concentration of the solution it is alway first crystallization consists for the most part of left tartra the right tartrate remains in the mother liquor. A simila with quinicine; however, in this case it is the right tartrat first. Thus, when a binary composition analogous to that suspected, its resolution should be attempted by placing i an [optically] active product which, as a consequence o similarity of the properties of the combinations which it make from the components of the complex group, will a of the latter.

The process may be summarized by Scheme 1, which corresp of a racemic acid $dlAH$ with an optically active base to form inverse (racemic base and active acid).

SCHEME 1

$$dlAH \xrightarrow{dB} \underset{p \text{ salt}}{\{dA^-, dBH^+\}} + \underset{n \text{ salt}}{\{lA^-, dBH^+\}}$$

When they are prepared separately from previously reso n and p have different crystalline forms and frequently als solvation. The possibility of separating such diastereomeri allowed to crystallize from a mixture of a racemate and an op agent presupposes the occurrence of a number of condition which we examine in the following sections: salts p and n, c

must be crystalline; their solubilities must differ; they must not cocrystallize (form solid solutions); and they must not form double salts (addition compounds [p, n]).

While any optically active acid or base is in principle usable, its use as a resolving agent is limited by its availability and cost.

The naturally occurring alkaloids, which were virtually exclusively utilized for about 100 years, are still much utilized in the resolution of acids. They are gradually being displaced by synthetic bases and by derivatives of natural products. The totally synthetic bases are, most often, primary amines and consequently are stronger bases than the common alkaloidal resolving agents, which are all tertiary amines and this may in some instances facilitate salt formation. On the other hand, synthetic bases all have the disadvantage that they themselves need to be resolved. This resolution, however, furnishes both enantiomers, which are thus available for use as resolving agents, quite unlike what obtains with alkaloids.*

The use of diastereomeric salts in resolutions of acids or bases in preference to that of covalent diastereomers is traditional. It stems from the simplicity with which diastereomeric salts are formed and from the ease of their cleavage to resolution substrates.

The frequency of use of the several basic resolving agents is quite unequal. For some 230 cases of resolutions of acids described in the literature between 1960 and 1970,[4] about one third were carried out with brucine and quinine. During the same interval, tartaric acid and its derivatives accounted for about half of all resolving agents used in the resolution of bases.

The cost of a resolving agent is also of some interest, although it is clearly not an independent variable since one does not necessarily have the option of choice. Brucine, cinchonidine, cinchonine, strychnine, dehydroabietylamine, (+)- and (−)-ephedrine, (−)-2-amino-1-butanol, (+)- and (−)-α-methylbenzylamine, (+)-amphetamine, and (+)-deoxyephedrine are the least expensive bases available commercially; each cost less than $100 per mole in 1979.

Comparable least expensive resolving acids commercially available are: (+)-camphor-10-sulfonic acid, (+)-camphoric acid, (−)-dibenzoyltartaric acid, diacetoneketogulonic acid, (+)- and (−)-mandelic acid, (−)-malic acid, and (+)- and (−)-tartaric acid. Each of these cost less than $90 per mole in 1979.

Tables 1 and 2 list the principal bases and acids used as resolving agents through salt formation. Virtually all are commercially available. The leading firms furnishing organic compounds for laboratory use also supply most of the resolving agents on a relatively small scale and at relatively high prices. There are also suppliers more or less specialized in certain types of compounds (e.g., alkaloids, camphor derivatives, or synthetic amines for pharmaceutical use) who may furnish kilogram quantities of some resolving agents at lower prices.

The practical aspects of the use of resolving agents, which are only briefly given in the following sections, are taken up in Chapter 7. The purification of resolving agents and the cleavage of diastereomeric salts are discussed in Section 7.4.

*Quinine and quinidine, on one hand, and cinchonidine and cinchonine, on the other, may be considered as pairs of quasi-enantiomers. Their use in the resolution of acids so as to lead to both substrate enantiomers is discussed in Section 5.3.2.

Table 1 Principal bases used as resolving agents via salt formation

Formula No.	Name	Mol. Formula	Mol. Weight	$[\alpha]_D$ (deg)
1	Brucine	$C_{23}H_{26}N_2O_4$	394.4	− 127 ($CHCl_3$)
2	Strychnine	$C_{21}H_{22}N_2O_2$	354.4	− 139 ($CHCl_3$)
3	Quinine	$C_{20}H_{24}N_2O_2$	324.4	− 117 ($CHCl_3$)
4	Quinidine	$C_{20}H_{24}N_2O_2$	324.4	+ 230 ($CHCl_3$)
5	Cinchonidine	$C_{19}H_{22}N_2O$	294.4	− 109 (EtOH)
6	Cinchonine	$C_{19}H_{22}N_2O$	294.4	+ 229 (EtOH)
9	Yohimbine	$C_{21}H_{26}N_2O_3$	354.4	+ 108 (py)
10	Morphine	$C_{17}H_{19}NO_3$	285.3	− 132 (MeOH)
11	Dehydroabietylamine	$C_{20}H_{31}N$	285.5	+ 46 (MeOH)
13	Ephedrine (−), (+)	$C_{10}H_{15}NO$	165.2	± 6.3 (EtOH)
14	Deoxyephedrine (+), (−)	$C_{10}H_{15}N$	149.2	± 17.9 (H_2O, hydrochloride)
15	Amphetamine (+), (−)	$C_9H_{13}N$	135.2	± 38 (C_6H_6)

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