SEPARATION OF OPTICAL ISOMERS VIA DIASTEREOISOMERIC SALT FORMATION

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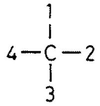
Abstract

The optical resolution processes were systematically investigated. The optimum of the parameters of the diastereoisomeric salt formation can be determined by using a thermodynamic equilibrium model. Based upon the conformational analysis of the structure for diastereoisomeric salts, a new method has been elaborated for designing optical resolutions.

Chiral stereoisomers have inherent interest, that is, their physical and chemical properties merit study; they are useful adjuvents in the elucidation of chemical reactions and of reaction mechanisms; and above all, their biological properties have driven chemists to seak them out and to prepare them for utilitarian purposes. In achiral circumstances the amounts of the generated mirror image molecules (optical isomers, enantiomers) are equal. Also synthetic methodology has been developing for the last twenty years, the procedures for separation of optical isomers (optical resolution) have remained practically unchanged since Pasteur. Resolutions are often tedious. The success or failure in separation are often unexplicable and "many experienced investigators in the field of organic chemistry, consequently continue to view resolutions as an art" [1]. There have been only few successful attempts for solving special problems in the field of designing different reactions resulting in optically active compounds, i.e. predicting the chiral agent to a given substrate, the solvent, the molar ratio, etc. [2, 3]. The classical resolutions involve crystallization techniques which remained the most frequent way to get optically active compounds starting from racemic mixtures. Diastereomeric salt forming acid-base reactions are central to such resolutions. The enantiomer separation is based upon the differences in physico-chemical properties of the formed diastereoisomers.

During the last fifteen years, we have studied a number of optical resolutions (Table) [3]. Most of the model compounds are synthetic molecules manufactured by the pharmaceutical industry as the intermediates or endproducts of different pharmacons. The aim of the investigations was to improve the technological conditions, e.g. the efficiency of the resolutions. In order to reach this goal we have applied different approaches, such as elaborating (thermodynamic) equilibrial model [4], application of mathematical statistics [2, 5, 6] the use of new preparative methods [7], etc.

a) Compounds having one chiral center

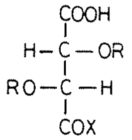


$$\begin{array}{c}1\\|\\4-\mathrm{C}-2\\|\\3\end{array}$$

No	Ligands 1	2	3	4
1	NH_2	COOH	CH_2CONH_2	H
2	OH	COOH	Ph	H
3	NH_2	Ph	Me	H
4	NH_2	CN	Ph	H
6	NH_2	$PhCH_2$	Me	H
8	NH_2	CN	3,4-$(MeO)_2$-$C_6H_3CH_2$	Me_3
7	NH_2	$\overset{*}{Fu}CH_2$	Me	H
9	NH_2	COOH	Ph	H

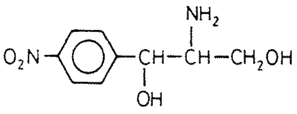
*2-Furyl

b) Compounds having two chiral centers



$$\begin{array}{c}\mathrm{COOH}\\|\\\mathrm{H}-\mathrm{C}-\mathrm{OR}\\|\\\mathrm{RO}-\mathrm{C}-\mathrm{H}\\|\\\mathrm{COX}\end{array}$$

No	R	X
9	H	OH
10	PhCO	OH
11	PhCO	NMe_2



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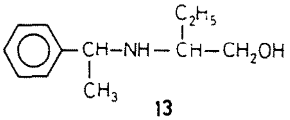

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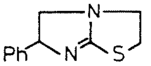
c) Compounds having the chiral center in their ring-systems



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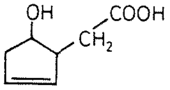
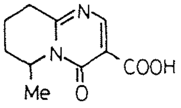


cis-15



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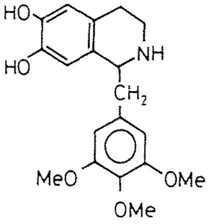

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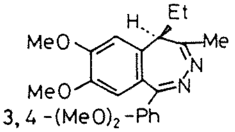
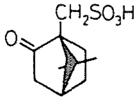
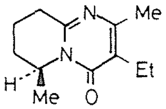


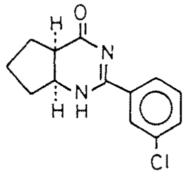
R-(+)-18



1*S*,4*R*-19



S-(+)-20



5*R*,6*S*-(−)-21

Table 1. Racemates and resolving agents

Optimation of optical resolutions

Equilibrium model of resolutions

In the reaction mixture of an optical resolution via diastereoisomeric salt formation, the following simultaneous equilibrial process can take place (Fig. 1):

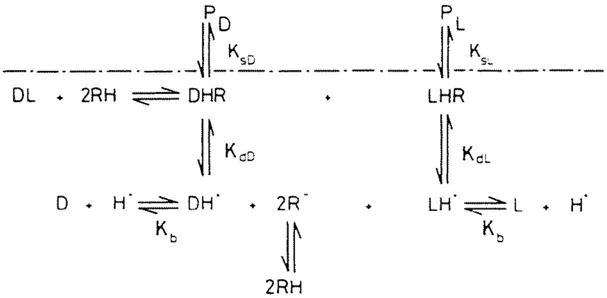


Fig. 1. General thermodynamic modell of optical resolutions Meaning of symbols: D and L enantiomers, RH resolving agent, P amount of preccipitated salt, K_s solubility constant, K_d dissociaton constant, K_b and K_a base and acid dissociation constant, D and L in index: diastereomeric salt containing the D or the L enantiomer

The relationship among the thermodynamic (such as solubility and dissociation) constants of the diastereoisomeric salts, the acid and base constants (for the racemate to be resolved and for the resolving agent) and reaction parameters (concentrations of reactants, pH) can be defined as follows.[4]

$$\left(\frac{1}{K_b}+\frac{K_{sL}K_{sD}}{K_bK_{bsD}K_{\alpha D}}\right)\cdot[D][H^+]-\frac{K_bK_{sD}K_{\alpha D}}{[D][H^+]}+$$

$$+\left(1+\frac{K_bK_{sL}K_{bL}}{K_bK_{sD}K_{dD}}\right)\cdot\frac{[D][H^+]}{[H^+]}-$$

$$-\frac{K_bK_{dD}K_{sD}}{K_{RH}}\cdot\frac{[H^+]}{[H^+][D]}-[D]_0-[L]_0+[RH]_0=0$$

$$\frac{Kw}{[H^+]}\cdot[H^+]+\frac{K_bK_{dD}K_{sD}}{[D][H^+]}-\left(\frac{1}{K_b}+\frac{K_{dL}K_{sL}}{K_bK_{sD}K_{dD}}\right)\cdot[D]\cdot[H^+]+[AH]_0=0$$

For using the equations the material and ionic balances must be taken into account. Applying the model the optimum of the efficiency for a given resolution can be calculated.

Selection of a new resolving agent

Frequently, the main problems of an enantiomer separation procedure is the selection of the proper resolving agent. With the aid of mathematical statistics, we have tried finding those factors which are playing important role in determining the success of the given resolution.

The model of the statistical approach was the enantiomer separation of a series of phenylglycine derivatives with d-tartaric acid. As a result of the calculations we concluded that the efficiency of a resolution in the case of phenylglycines is mainly influenced by the electronic properties symbolized by the Taft's substituent constants σ^* [6] of the ligands and the solvent polarity.

The model was extended to other resolution procedures resulting in an ability either the selection of a proper resolving agent or being aware of it one can determine the relative configuration of the more abundant enantiomer in the precipitating salt. In this theory we made a conformational analysis using Dreiding model and selecting the possible second order interactions for both diastereoisomeric salts, and using the Taft's σ^* constants we obtained the relative difference in the stability of the diastereoisomeric salts. The quality of the second order interactions is under investigation now by single crystal *X*-ray crystallography [8, 9]), *NMR*-spectroscopy. The relationship amond the stability, the solubility, the dissociation differences and the efficiency of optical resolution is studied by thermal analysis [10].

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