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SELECTIVE REACTIONS OF ENANTIOMERIC-MIXTURES

Elemér Fogassy, Ferenc Faigl, Mária Ács*

Department of Organic Chemical Technology, Polytechnical
University, 1111 Budapest, Müegyetem rkp. 3-5. Hungary

Enantiomers in solution have a tendency to form associations of various compositions. This phenomenon is used to separate partially resolved mixtures of enantiomers.

Possibilities for improving separation by changing various parameters have been investigated. A new method for determination of optical purity is described.

Introduction

In non-ideal solutions of chiral molecules certain interactions have been observed between enantiomers[1,2]. The mirror-image isomers /D and L/ may associate with themselves and also with their antipodes. For dimers in solution the system is characterized by the equilibria:

$$\left\{ D + D \rightleftharpoons DD \qquad L + L \rightleftharpoons LL \qquad D + L \rightleftharpoons DL \right\} \quad DD + LL \rightleftharpoons 2DL$$

More than two molecules can associate and this can be represented by the general formula: D_nL_m. If n=m the "complex" is racemic, otherwise it is chiral. The relationship among associations can either be enantiomeric /DD and LL/ or diastereoisomeric /LL or DD and DL/. Consequently, in a mixture containing isomers in non-equivalent quantities, the numbers of diastereoisomeric and enantiomeric associations are not equal either. Since the rate constant for formation of diastereoisomeric "complexes" are also different for all types of reactions, the enantiomeric excess obtained via a "non-racemic antipode-mixture" of a chiral base /or acid/ can be separated from the racemic fraction by using an achiral agent.

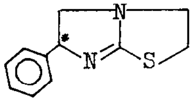
We have systematically investigated these types of enantiomeric separations.

A. Selective precipitation

The aqueous solution of the enantiomeric mixtures of the HCl salt of compound 1 was titrated against NaOH. The results of titration are given in a plot of the optical purity /OP/ versus initial optical purity /OP_o/, Fig.1.

The optical purity of the precipitated base is presented in line 1., the base remaining in the mother liquor in line 2. Data obtained indicate that the composition of the liberated mixture is closer to that of the racemate. The product remaining in solution is purer than the initial sample /i.e. the "racemic complex" is less soluble than the "enantiomeric complex"/.

The selective precipitation /from the aqueous solution of the HCl salt of the given compound/ is more effective in the case of the compound 3 than of the compound 1. We have examined how the selectivity /ΔOP/[x] depends /at standard initial optical purity: OP_o = 80%/ on the increasing temperature during the course of the selective precipitation of compound 3. The experimental data have proved that the complete dissociation /ΔOP=0/ could be observed only at about 100°C /Fig.2./.



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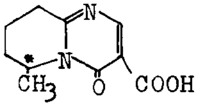

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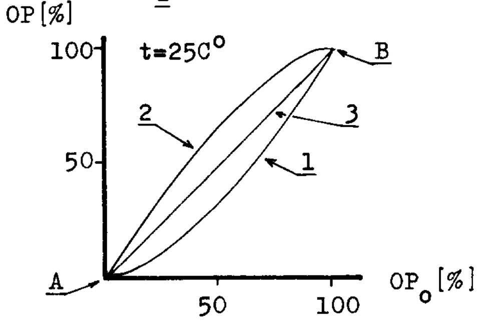

Fig.1.
Change in optical purity/OP/ vs. starting optical purity /OP_o/ during the course of the selective precipitation of compund 1.

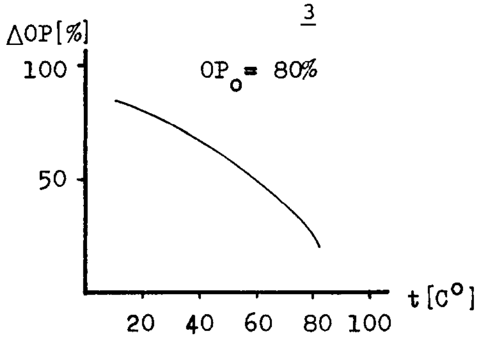

Fig.2.
Selectivity dependence on temperature during the course of the selective precipitation of compound 3.

B. Selective liberation combined with extraction /"selective extraction"/

Fig.3. shows the results of a selective separation of the enantiomers of compound 1 when titrated in the presence of a water- immiscible solvent in which the free base is soluble e.g. chloroform. The optical purity of the base in the organic layer is lower than that of the starting mixture if $OP_o < 50$ %; but it is higher when $OP_o > 50$%. The shape of the curve in Fig.3./ with a point of inflection at OP_o=50%/shows the formation of a stable enantiomer association /anomalous racemate[3]/, in which the isomer ratio 3:1 in the case of compound 1. This association is stable under the circumstances of a "selective extraction". The isomer composition can be determined easier by differentiating the function OP - OP_o, see Fig.3.

Based on our experiences /illustrated by the data obtained employing the compound 1/ we consider the "selective precipitation" as a more effective method for increasing the optical purity than the "selective extraction".

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[x] The selectivity /=ΔOP/ is defined as the difference between the starting /OP_o/ and achieved /OP/ optical purity: $\Delta OP = OP_o - OP$.

In all cases the efficiency depends on the initial optical purity and on the temperature.

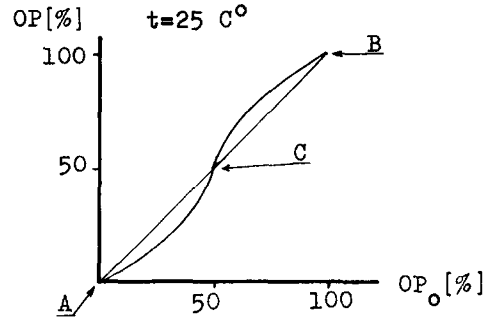

Fig.3.
Change in optical purity /OP/ vs. starting optical purity /OP$_o$/ during the course of the selective extraction of compound 1

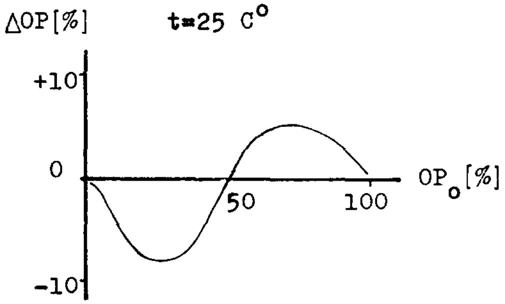

Fig. 4.
Selectivity dependence on starting optical purity /OP$_o$/ during the course of the selective extraction of compund 1

Repeated application of the "selective precipitation" or "selective extraction" results in the isolation of the enantiomeric excess and the racemic fraction from a non-racemic isomer mixture of a chiral base or acid. /The anomalous racemates can be destroyed using the selective precipitation/.

A new method to determine the optical purity

If the procedure is used for preparing the pure enantiomer from a mixture of unknown optical purity, measuring and plotting the optical rotational values $/[\alpha]^t/$ of the obtained samples versus of the actual initial rotational values $/[\alpha]_o^t/$ then we come, /e.g. in the case of the compound 1/, to a plot similar to the Fig.1. Hence the optical purity is defined as the ratio of the optical rotation of the given sample and of the pure enantiomer.

So with the help of the method of selective separation the value of the rotational maximum, and consequently the optical purity, can be determined. The curves plotted from the measured data /Fig.1.curve 1. or 2/ and the straight line 3 corresponding to the titration of an ideal solution, can intersect only at two points. Point "A" is characteristic for the racemic form, point "B" for the pure enantiomer. Comparing the value of the rotational maxima obtained using our method and traditional methods it is seen that our results are in a good agreement with those reported in references cited, see the table below.

Table
Comparison of the rotational maxima

Compound	method	$[\alpha]_D^{20}$ maximum experimentally determined	cited	ref.	concent-ration g/100 ml.	solvent
1	extraction	88,0°	85,3°	8	10	chloroform
2	extraction	108,0°	109,0°	9	2	chloroform
2	precipitation	110,0°	109,0°	9	2	chloroform
3	precipitation	164,0°	161,2°	10	2	1N HCl

Conclusions

The investigation of selective reactions of enantiomeric mixtures has preparative, analytical and theoretical significance in the area of optical resolution. In particular it is found that:

1.a. The existence of an anomalous racemate can greatly influence the results of a resolution[4,5].

  b. The pure enantiomer can easily be prepared from e.g. a partially resolved enantiomeric mixture[4].

2. The method for determination of optical purity presented in this paper is fundamentally simpler than other published methods.

3.a. The resolution by spontaneous or induced crystallization can be explained by the formation of chiral associations[1].

  b. The efficiency of a resolution accomplished by a given resolving agent, in a given solvent, can be predicted with the help of parameters characterizing the secondary bond /complex/ formation affinity of the said chiral compound[7].

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