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Enantiomeric Enrichment by the Use of Density Differences between Racemic Compounds and Optically Active Enantiomers

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***Abstract**: A new method for enantiomeric enrichment has been elaborated. Enantiomeric mixtures in an inert solvent having a difference between the densities of the racemate and the optically pure enantiomer separate into upper and lower layers having different optical purity.*

Asymmetric syntheses and optical resolutions never completely result in optically pure enantiomers.[1,2] The optically active enantiomer can be separated from an enantiomeric mixture during enantiomeric enrichment without any chiral agent. The enantiomeric enrichment is usually accomplished by recrystallization from a solvent, crystallization from melt or selective methods.[1-4] During these processes the enantiomeric mixtures behave as a mixture of the optically active (or racemic) compound and the eutectics. As a result of this complete separation into optically active and racemic compound can be achieved in the case of conglomerate formation when the eutectic molarfraction is 0.5. In the case of the most common[5,6] molecular compound formation such complete separation is not possible since the non-racemic eutectic could not be separated further by solid-liquid phase transition.

The effect of the eutectic can be eliminated only when there is no solid-liquid phase transition. The enantiomeric mixture of a racemic compound forming substances can be considered as a mechanical mixture of the optically active enantiomer and the racemic compound, as they have different densities we assumed that difference may be used for enantiomeric enrichment without any phase transition.

Table 1. The summary of the successful experimental results

Starting	mixture mg	OR $[\alpha]_D^{20}$	OP %	Solid Phase	Yield mg	%	OR $[\alpha]_D^{20}$	OP %
phenylethyl-ammonium-hydrogen-fumarate $d = 1.39\ g/cm^3$	500	2.2	40	upper	90	18	1.6	29
				middle	90	18	1.8	32
				lower	290	58	2.6	46
	500	2.8	50	upper	320	64	2.5	45
				lower	170	34	3.4	61
	500	3.9	70	upper	240	48	3.2	57
				lower	250	50	4.2	75
phenylalanine $d = 1.35\ g/cm^3$	1000	-17.5	50	upper	440	44	-31.5	90
				lower	550	55	-4.4	13
aminodiol $d = 1.46\ g/cm^3$	1000	10.4	33	upper	100	10	3.4	11
				middle	610	61	8.0	26
				lower	280	28	15.4	50

d: *density of the liquid phase;* aminodiol:*2-amino-1,3-hydroxy-1-(4-nitro-phenyl)-propane*

The experiments were accomplished similarly as the crystallographers measure the densities by flotation. The finely pulverised enantiomeric mixture[7] and an inert solvent were placed into a test tube, the mixture was stirred to remove the air bubbles from the powder and after standing undisturbed for one or two hours the layers were separated, from which the solid was removed by filtration. The density of the liquid phase was adjusted between the densities of the racemate and the enantiomer by mixing chlorobenzene (d=1.106 $^{g}/_{cm^3}$) and bromobenzene (d= 1.495$^{g}/_{cm^3}$).

In the case of the three model compounds listed in Table 1 the enantiomer separation proved successful. The phenylethyl-ammonium-hydrogen-fumarate enantiomer enriched in the lower phase, while in the upper phase the optical purity was lower than the starting enantiomeric mixture, the efficiency of the separation is not really high. In the first experiment when the optical purity was 40% the mixture was separated into three parts, similarly to the 2-amino-1,3-hydroxy-1-(4-nitro-phenyl)-propane (aminodiol), which gave slightly more efficient separation. The separation was really efficient only in the case of phenylalanine, the enantiomer with 90 % optical purity accumulated in the upper phase. In spite of at least 2 % difference reported between the densities of racemic and active form of mandelic acid,[8] we were not able to achieve enantiomeric enrichment on 50% optical purity mandelic acid by this method.

Complete separation was not achieved in any of the cases, which possibly indicates that even the fine particles of the enantiomeric mixture are still aggregates of the crystals of racemate and optically active enantiomer. The increase inefficiency of the separation by the decrease of the particle size is limited, since by decrease of the particle size the decantation times increased by the second power. The separation of the layers is much easier at larger scale and the solvent can be recovered without loss, which can make that new enantiomer enrichment method a simple, environmentally friendly industrial process.[9]

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References and Notes

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7.) The enantiomeric mixtures for the model experiments were produced by the complete evaporation of ethanolic solution of calculated amounts of optically active enantiomer and racemic compound. The optical purity was checked by the measurement of the specific rotation on a Perkin-Elmer 241 polarimeter. The specific rotation of the optically active forms: phenylethyl-ammonium-hydrogene-fumarate $[\alpha]_D^{20}$= ±5.6 (c:1;ethanol); phenylalanine $[\alpha]_D^{20}$= ±35.0 (c:1;water); 2-amino-1,3-hydroxy-1-(4-nitro-phenyl)-propane $[\alpha]_D^{20}$= ± 31.1 (c:1;6NHCl)

8.) ref 1. 29 pp.

9.) Parallel with our experimental work a new method of optical resolution by foam flotation has been published. Armstrong,D.W.,Zhou,E.Y.,Chen,S., Le,K. Tang,Y, Anal.Chem., 1994, **66**, 4278

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