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ENANTIOMERIC ENRICHMENT OF PARTIALLY RESOLVED N-METHYL-AMPHETAMINE

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Abstract

The enantiomeric enrichment of N-methyl-amphetamine (MA) was tried by eight different preparative separation methods. The enrichment process was also studied by thermoanalitical methods (DSC,TG). There is no enantiomeric enrichment during fractional distillation and selective extraction of the liquid base. The enantiomeric mixture of MA·HCl can be enriched by crystallization or by sublimation. The most effective enrichment can be achieved by fractional crystallization or distillation of the reaction mixture after partial salt formation with hydrochloric acid. The separation is less effective in case of fractional steam distillation and selective extraction when the enantiomer and the racemate are distributed between two liquid phases. This supports the general experience that having a solid phase in the system makes enantiomer separation more efficient.

Keywords: enantiomeric enrichment, enantiomeric mixtures, N-methyl-amphetamine, partial salt formation, phase equilibrium

Introduction

Optical resolutions and enantioselective synthesis always result in partially resolved mixtures of enantiomers [1, 2], which can be further purified by enantiomeric enrichment without any chiral agent [3]. While fractional crystallization is dominant among the known enantiomeric enrichment processes, several other possibilities exist based on different phase equilibria [4]. In spite of the existence of several industrial applications, only few details are available of these alternative methods, their comparative applications for one model compound still have not been demonstrated.

In this paper we report a comparative study on the enantiomeric enrichment of N-methyl-amphetamine (MA)by different preparative methods and the thermo analitical study of the phases playing a role during the separation. MA is the key in-

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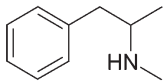
termediate of several chiral drugs, for example the anti-Parkinson agent Jumex®. The optically active form is prepared by optical resolution via diastereoisomeric salt formation with tartaric acid [5, 6].



MA

Materials and methods

All chemicals were purchased from Merck.

The specific rotations were measured on a Perkin Elmer 241 polarimeter.

The specific rotation of optically pure R-N-methylamphetamine is $[\alpha]_D^{20} = -18.90$ (c 0.1; 1 N HCl).

Enantiomeric enrichment experiments on the underivatized base

Fractional distillation

2 g of 73.3% *ee* ($[\alpha]_D^{20} = +13.8$) MA was distilled from a 70°C water bath at 2.5 Pa. The results are summarised in the 1st line of Table 2.

Selective extraction

2 g of 73.3% *ee* ($[\alpha]_D^{20} = +13.8$) MA was dissolved in 50 mL of chloroform and 50 mL of water. The mixture was stirred for 6 h at room temperature. Then the phases were separated, the aqueous phase was extracted three times with 50 mL of chloroform. Then the first organic phase and the combined organic phases were evaporated at atmospheric pressure. The results are summarised in the 2nd line of Table 2.

Enantiomeric enrichment experiments on MA·HCl

Mixture A: S-(+)-MA (*ee*:73.3%) was reacted with excess of 10 mass/mass% ethanolic HCl and the solution was evaporated in vacuum till dryness.

Fractional crystallization

2 g of Mixture A was recrystallized from 5 mL of abs. ethanol. The results are summarised in the 3rd line of Table 2.

Fractional sublimation

2 g of Mixture A was sublimed at 2.5 Pa in a 100–110°C oil bath. The results are summarised in the 4th line of Table 2.

Enantiomeric enrichment experiments using of non-stoichiometric amounts of achiral agent

Mixture B: 1.60 g (0.0086 mol) R-(-)-MA·HCl and 0.40 g (0.0027 mol) rac-MA (*ee*: 76.1%)

Mixture C: 1.60 g (0.011 mol) S-(+)-MA and 0.40 g (0.002 mol) rac-MA·HCl (*ee*: 84.6%)

Fractional crystallization

2 g of Mixture B (Mixture C) was recrystallized from 5 mL of abs. ethanol. The results are summarised in the 1st line of Table 3.

Fractional distillation

2 g of Mixture B (Mixture C) was distilled in a 70°C water bath at 2.5 Pa. The results are summarised in the 2nd line of Table 3.

Fractional steam distillation

2 g of Mixture B (Mixture C) was dissolved in 75 mL of water and 50 mL was distilled off at atmospheric pressure. The aqueous distillate was extracted three times with 50 mL of chloroform and the combined organic phases were evaporated at atmospheric pressure. The results are summarised in the 3rd line of Table 3.

Selective extraction

2 g of Mixture B (Mixture C) was dissolved in 50 mL of chloroform and 50 mL of water. The mixture was stirred for 6 h at room temperature. Then the phases were separated, the aqueous phase were extracted three times with 50 mL chloroform. Then the first organic phase and the combined organic phases were evaporated at atmospheric pressure. The results are summarised in the 4th line of Table 3.

DSC

DSC curves were recorded with a TA Instruments DSC 2920 Modulated DSC. Samples of 3.0–4.0 mg were analyzed in open aluminium pans under flowing argon (10 L h^{-1}) between 298–473 K with a heatig rate of 5 K min^{-1}.

Results and discussion

During enantiomeric enrichment the enantiomer in abundance should be separated from the racemate (Eq. (1)). The enantiomers can be separated as such, or in the form of an achiral salt. The role of the achiral derivative to transfer the liquid enantiomer into solid form which usually can be more effectively separated. The achiral agent can be applied in molar equivalent amounts (Eq. (2)) or in non-stoichiometric amounts (Eqs (3) and (4)).

$$EE\exists \leftrightarrow E+E\exists \quad (1)$$

$$EE\exists \cdot 3A \leftrightarrow EA+E\exists \cdot 2A \quad (2)$$

$$EE\exists + 2A \leftrightarrow E+E\exists \cdot 2A \quad (3)$$

$$EE\exists + A \leftrightarrow EA+E\exists \quad (4)$$

By using a non-stoichiometric amount of achiral salt forming agent, not only some reagent can be saved, but usually more efficient resolution can be achieved, since the differences are larger between the salt of the racemate and the pure enantiomer (Eq. (3)) or the salt of an enantiomer and the racemate (Eq. (4)) than between the enantiomer and the racemate. The possible enantiomer enrichment methods are summarised in Table 1.

Table 1 Possibilities for enantiomeric enrichment

Without an achiral agent or with stoichiometric amounts of achiral agent				
Enantiomer	Achiral salt	Phase 1	Phase 2	Method
liquid	–	liquid	vapour	fractional distillation
		liquid	liquid	selective extraction
solid	(solid)	solid	liquid	fractional crystallization
		solid	vapour	fractional sublimation
		liquid	liquid	selective extraction
		solid	solid	flotation
Non-stoichiometric amounts of achiral agent				
Enantiomer	Achiral salt	Phase 1	Phase 2	Method
liquid	solid	solid	liquid	fractional crystallization
		solid	vapour	fractional distillation
		liquid	vapour	fractional steam distillation
		liquid	liquid	selective extraction
solid	solid	solid	liquid	fractional crystallization
		solid	vapour	fractional sublimation
		liquid	liquid	selective extraction
		solid	solid	flotation

During separation the enantiomeric mixtures behave like the two-component mixtures of the enantiomer and the racemate. During enantiomeric enrichment by fractional crystallization in case of conglomerate formation always the pure enantiomer precipitates and the racemate remains in the mother liquor, in case of racemic molecular compound formation, depending on the enantiomer composition of the mixture, either the pure enantiomer or the racemate precipitates.

Table 2 Summary of the experiments with or without achiral salt forming agent

Method	MA (*ee*: 73.3%)					Mixture A (*ee*: 73.3%)				
	$[\alpha]_D^{20}$	*ee*/%	*m*/g	*Y*/%	*EEE*	$[\alpha]_D^{20}$	*ee*/%	*m*/g	*Y*/%	*EEE*
Distillation										
Residue	13.8	73.3	0.50	25.0	–	–	–	–	–	–
Distillate	13.8	73.3	1.40	70.0	–					
Extraction										
Organic phase	13.8	73.3	1.20	60.0	–	–	–	–	–	–
Aqueous phase	13.8	73.3	0.70	35.0	–					
Crystallization										
Precipitate	–	–	–	–	–	+17.7	93.6	0.83	41.5	53.0
Mother liquor						+10.8	60.3	1.15	57.5	–
Sublimation										
Sublimate	–	–	–	–	–	+13.5	71.2	1.78	89.0	–
Residue						+18.5	97.9	0.21	10.5	14.0

Table 3 Summary of the experiments with non–equivalent amounts of achiral agent

Method	MA (*ee*: 73.3%)					Mixture A (*ee*: 73.3%)				
	$[\alpha]_D^{20}$	*ee*/%	*m*/g	*Y*/%	*EEE*	$[\alpha]_D^{20}$	*ee*/%	*m*/g	*Y*/%	*EEE*
Crystallization										
Precipitat	–17.9	94.9	1.60	80.0	99.8	+18.5	97.9	0.38	20.0	23.1
Mother liquor	–	0.9*	–	20.0*	–	–	81.2*	–	80.0	–
Distillation										
Residue	–17.4	92.1	1.57	78.5	95.0	+18.1	95.6	0.40	20.0	22.6
Distillate	0.0	0.0	0.39	19.5	–	+15.4	81.7	1.55	77.5	–
Steam distillation										
Residue	–	76.3*	–	82.5*	82.7	–	90.3*	–	20.0*	21.3
Distillate	–14.3	75.3	0.35	17.5	–	+15.6	82.7	1.60	80.0	–
Extraction										
Organic phase	–13.9	73.8	0.36	18.0	–	+15.7	83.1	1.62	81.0	–
Aqueous phase	–	76.6*	–	82.0*	82.5	–	90.6*	–	19.0*	20.3

*calculated from the enantiomeric balance

The enantiomeric enrichment is always based on the distribution of the initial enantiomeric mixture between two separable phases. The degree of enrichment can be characterised by the term of Efficiency of the Enantiomeric Enrichment (*EEE*) [4]. This is defined as the ratio of the separable enantiomer content (enantiomeric excess) in the enriched and the initial enantiomeric mixture (Eq. (5)):

$$EEE = \frac{ee_e\, y}{ee_0} \tag{5}$$

where ee_e is the enantiomeric excess in the enriched phase (%); ee_0 the enantiomeric excess in the initial mixture (%) and y ratio of the amount of enriched and initial mixture (%).

The *EEE* value should be calculated only for the enriched phase ($ee_0 < ee_e$), so that *EEE* ranges from >0 to 100[7].

As MA is liquid at room temperature, we tried to achieve enantiomeric enrichment by distillation and extraction (Table 2).

Neither trial resulted in measurable enantiomer separation, which is in accordance with the theoretical considerations of Horeau *et al.* [8, 9]. They predicted that there is no significant difference in the boiling point of the racemate and the enantiomer.

The simplest solid achiral salt of the MA is its salt with hydrochloric acid. MA·HCl forms conglomerate [10], which is indicated by the DSC curves of enantiomeric mixtures having different *ee* (Fig. 1). Mixture A was subjected to enantiomeric enrichment by fractional crystalization and sublimation. The third possibility listed in Table 1, i.e. flotation was not tried since for conglomerates enantio-

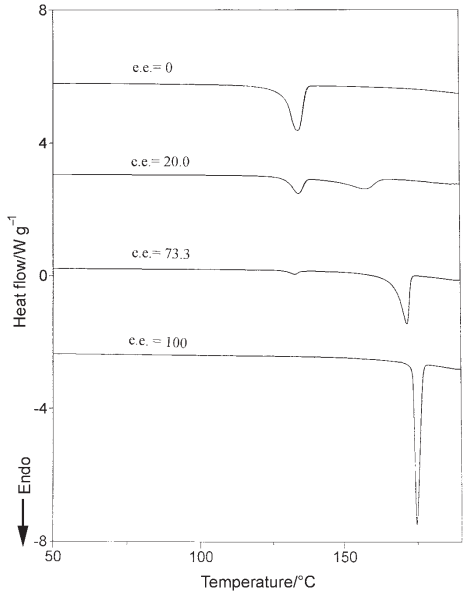


Fig. 1 DSC curves of MA·HCl salts with different *ee*

mer separation cannot be expected by this way [11]. Both separations were successful, the process produced the enantiomer in excess with more than 90% *ee*. The very high ee reached by sublimation was unfortunately accompanied by low yield. As can be seen from the *EEE* values in both cases large amounts of separable enantiomer remained in the other phase.

All the four methods listed in Table 1 for liquid enantiomers were tried on two samples by using non-stoichiometric amounts of achiral additive (Table 3).

The achiral additive was in all cases hydrochloric acid. Mixture B represents the case when the achiral additive was equal to that of the enantiomer in abundance (Eq. (4)). In Mixture C the amount of the achiral additive was equivalent to the racemate (Eq. (3)).

MA·HCl precipitates during fractional crystallization, remains in the residue by fractional distillation and steam distillation and goes to the aqueous phase by selective extraction with higher *ee* than the starting enantiomeric mixture. Always the phase transfer of the HCl salt was accompanied by enantiomeric enrichment which is in agreement with the fact that MA·HCl forms a conglomerate [10, 12]. Mixture C always results in higher optical purities in the enriched phase than Mixture B. In case of Mixture C the equilibrium shifted towards the formation of the more stable enantiomerically pure salt since there was not enough acid to react with all the enantiomer in excess. In spite of this the more effective enrichment was achieved in case of Mixture B since here the yield was always much higher.

Figure 2 shows the DSC and TG curves of Mixture C. These measurements can be considered as a micro-scale atmospheric version of enantiomeric enrichment by distillation. Between 60–110°C MA evaporates and the remainig MA·HCl melts

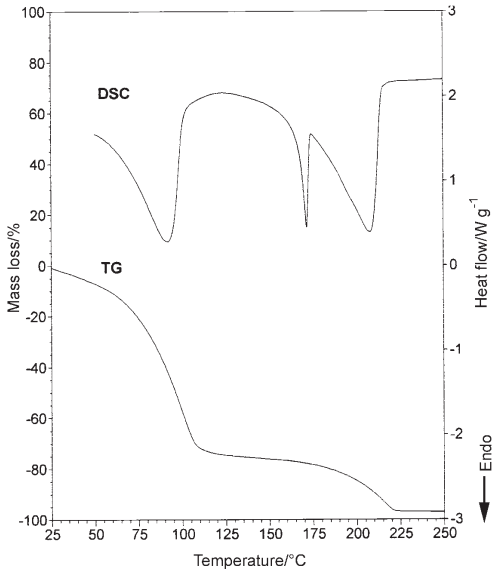


Fig. 2 DSC and TG curve of Mixture C

about 2°C lower than optically pure MA·HCl, indicating a substantial enantiomeric enrichment in the solid phase. The third peak corresponds to the thermal decomposition of the rest of the sample.

It is interesting that fractional distillation was nearly so efficient as fractional crystallization. Enantiomeric enrichment by fractional distillation after partial salt formation was described only once previously [13], no example of enantiomeric enrichment by fractional steam distillation has been published. The lower efficiency of steam distillation and selective extraction supports the assumed rule that enantiomer separation is always more efficient when one phase is solid [4].

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