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MECHANISM OF OPTICAL RESOLUTIONS VIA DIASTEREOISOMERIC SALT FORMATION

Part 7[*] Role of the solvents in the optical resolution of α-phenylethylamine by 2R,3R-tartaric acid

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Abstract

The optical resolution of α-phenylethylamine (**1**) by 2R,3R-tartaric acid (**2**) was studied in different solvents, the precipitated salts were subjected to thermoanalytical measurements and X-ray powder diffraction. The most efficient resolution can be accomplished by using methanol, the precipitate, an unsolvated salt containing the S-(–)-**1**·2R,3R-(+)-**2** salt in abundance, is not a simple mixture of the diastereoisomeric salt pair, but a new modification. In water, ethanol and acetonitrile a reversed, but less effective resolution can be accomplished by precipitation of a hydrate which contains the R-(+)-**1** in abundance. The precipitates from water and ethanol also proved to be new modifications. Only the precipitate from acetonitrile is the mixture of the diastereoisomeric salt pair, which can be expected in fractional crystallization of an eutectic forming diastereoisomeric salt pair. The number of different modifications found by changing the solvent in case of this particular salt pair seems surprisingly high, but may occur for other diastereoisomeric salt pairs, too. The existing but not investigated polymorphism can be the explanation for the sometimes very poor reproducibility of the preparative resolutions.

Keywords: diastereoisomeric salt formation, mechanism of optical resolutions

Introduction

The optical resolution of racemates via fractional crystallization of the diastereoisomeric salts formed between the enantiomers (F and ꟻ) and the optically active re-

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solving agent (R) is one of the most important ways for producing optically active isomers of chiral substances [1].

$$\mathrm{F}\text{ꟻ}+2\mathrm{R} \xleftrightarrow{\text{solvent}} \mathrm{FR}+\text{ꟻ}\mathrm{R}\downarrow$$

During development of a resolution process the selection of the solvent is usually as important as the selection of the resolving agent [2, 3]. The chemists who want to perform a new optical resolution are quite helpless in the selection of the solvent since in the literature usually only the solvent having given the most efficient separation is mentioned, only a few comparative data are available on resolutions in different solvents [3–7].

In this paper we investigate the optical resolution of α-phenylethylamine (**1**) by 2R,3R-tartaric acid (**2**) in different solvents and solvent mixtures.

Experimental

All chemicals were purchased from Merck.

General procedure for the optical resolution of racemic-α-phenylethylamine with 2R,3R-tartaric acid

4.8 g (0.04 mole) racemic-α-phenylethylamine and 6.0 g (0.04 mole) 2R,3R-tartaric acid was dissolved in the solvents to give saturated solution at the boiling point of the solvent. By cooling back to room temperature in all cases white crystalline powder precipitated. The precipitate was filtered and dried in air (temperature: 20–22°C, humidity: 50–65%) until the mass did not changed. The salts were suspended in 5 ml of aqueous NaOH and the liberated α-phenylethylamine were extracted three times with 30 ml of dichloromethane. After drying, the solvent was evaporated leaving the α-phenylethylamine back as an oily residue. $[\alpha]_D^{20}=\pm 30.0$ (c:0.5; ethanol) was considered as the specific rotation of the optically active α-phenylethylamine. 10.8 g was considered as 100% yield. The results are summarized in Table 1.

Preparation of the pure diastereoisomeric salts

The optically pure diastereoisomeric salts were prepared from molar equivalent amounts of optically pure compounds in 96% ethanol, followed by the evaporation of the solvent in vacuum. S-(–)-**1**·2R,3R-(+)-**2** melts at 188°C during thermal decomposition and does not contain any solvate. R-(+)-**1**·2R,3R-(+)-**2** melts at 183°C during thermal decomposition and contains 4.4% solvent which evaporates between 54–78°C during heating.

DSC curves were recorded and integrated with the aid of a DuPont 1090B Thermal Analysis System. Samples of 1–3 mg were run under argon atmosphere in open aluminium pans with a heating rate of 5 K min^{-1}. The temperature range of thermal decomposition was determined by thermogravimetric measurements (TG) (carried out on the same system). Evolved gas detection (EGD) was carried out on a DuPont

Table 1 Optical resolution of α-phenylethylamine by 2R,3R-tartaric acid in different solvents

Solvent/ml		Sign	Mass loss/%	Precipitated salt				S^b
				Mass/ g	Y^b/%	$[\alpha]_D^{20}$	OP^b/ %	
Methanol	50	MP	<0.1	3.6	33.4	–21.6	72.1	0.48
Water	30	WP	4.9	5.4	50.0	3.7	12.3	0.12
Acetonitrile	250	AP	2.0	9.5	88.0	1.39	4.6	0.08
Ethanol	50	EP	1.4	7.8	72.2	1.27	4.2	0.06
1:1 methanol:acetonitrile	80	MAP	<0.1	7.8	72.2	–6.1	20.4	0.30
1:1 methanol:water	35	MWP	1.4	6.4	59.3	–1.3	4.4	0.05

[a] mass loss between 30–85°C

[b] The efficiency (0<S<1) of the optical resolution has been defined as the product of the optical purity (0<OP<1) and the yield (0<0.5Y<1) of the precipitated salt: S=OP×Y [5]

916 TAE instrument, following the evolution of organic gases and vapours from the sample. A qualitative X-ray analysis of the products was carried out on a HZG-4/C Diffractometer, Carl Zeiss, Jena, using $CuK_{\alpha}(\lambda=0.15405$ nm) radiation and Ni filter. The speed of the goniometer was $1°$ min^{-1}.

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

Results and discussion

The optical resolution of R,S-**1** by 2R,3R-**2** has been only described in methanol, as a fairly efficient resolution [8]. For the study of the role of the solvent we accomplished the resolution in three additional single solvents: water, ethanol and acetonitrile, and after evaluating the preliminary results, in two solvent mixtures (1:1 ratio (v/v) mixture of metanol:acetonitrile and methanol:water).

The fractional crystallization of the diastereoisomeric salt pair yielded a white precipitate from every solvent, but none of them were optically pure. So -as usual in the first step of optical resolutions, the precipitates were salt mixtures in all the cases. In the salts precipitated from methanol containing solvents S-(–)-α-phenylethylamine was in abundance, while in all the other solvents the resolution reversed, the precipitated salts contained the R-(+)-**1** in abundance. The experimental results are summarized in Table 1.

All the precipitated salts were measured by TG, DSC and X-ray powder diffraction (Fig. 1.). The solvate containing salts were studied by EGD, as well. For comparison the pure diastereoisomeric salt pair were also studied.

The TG and DSC measurements of the salts revealed that the pure S-(–)-**1**·2R,3R-(+)-**2** salt does not contain any solvent. Salts precipitated from methanol and metanol:acetonitrile mixture contain very small amounts of the solvent, while the R-(+)-**1**·2R,3R-(+)-**2** salt and the precipitates from other solvents contain substantial, but different amounts of solvent evaporating from the substance between 30 and 85°C. Independently of the isomer content of the samples, on heating a rapid thermal decomposition starts between 170–175°C.

The EGD measurements proved that the solvate was water in every case. The organic solvents were not absolutized before use; the water of the precipitates probably comes from the water traces of the solvent or from the air of the laboratory.

These results clearly indicate that water free S-(–)-**1**·2R,3R-(+)-**2** precipitates if water in not present in the process. The trace of water in MP and MAP is due to small amounts of R-(+)-**1**·2R,3R-(+)-**2** hydrate contamination. The X-ray powder diffractograms proved that MP having a composition of 86:14 ratio of S-(–)-**1**·2R,3R-(+)-**2** and R-(+)-**1**·2R,3R-(+)-**2**, is not a simple mixture of the diastereoisomeric salt pair.

Its powder diffractograms show a very different pattern indicating another modification. Practically there is no water in MP, which means that here the R-(+)-**1**·2R,3R-(+)-**2** is in an unsolvated form.

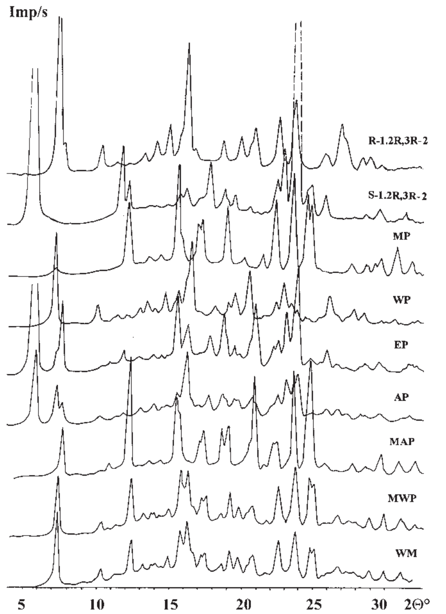

Fig. 1 X-ray powder diffractograms

Also a new diffraction pattern can be observed for MAP but the main peaks of MP can be recognised, which indicate that the precipitate from methanol:acetonitrile mixed solvent may be a mixture of the crystal form precipitating from methanol and a new polymorph. The later does not correspond to the diffraction pattern of AP, and may represent the anhydrous R-(+)-**1**·2R,3R-(+)-**2**.

Among the water containing precipitates only AP appears to be a mixture of the two pure diastereoisomeric salts, as it can be expected in fractional crystallization of a eutectic forming diastereoisomeric salt pair [9]. The precipitate from water and ethanol also exhibit a different diffraction pattern not only from the pure salts, but also from the other precipitates.

The powder diffractograms of the precipitate from the methanol-water solvent system, are practically identical with the powder diffractogram of the salt produced by evaporation of the mother liquor of the resolution accomplished in water (WM). These diffractograms also partly resemble that of MP to which their isomer content is similar.

Conclusions

In the separation of the optical isomers of racemic α-phenylethylamine by 2R,3R-tartaric acid the most efficient resolution can be accomplished by using methanol for the fractional crystallization of the diastereoisomeric salt pair. The precipitate, an unsolvated salt containing more then 70% S-(–)-**1**.2R,3R-(+)-**2** salt, is not a simple mixture of the diastereoisomeric salt pair, but a new modification. In water, ethanol and acetonitrile a reversed, but less effective resolution can be accomplished by precipitation of a hydrate. The achieved highest optical purity was 12.3% when the R-(+)-**1** was in abundance in the precipitate. The hydrated precipitates from water and ethanol proved to be new modifications. Only the precipitate from acetonitrile is the mixture of the diastereoisomeric salt pair, which can be expected during fractional crystallization of a eutectic forming diastereoisomeric salt pair.

From these results the relative stability of the salts can be deducted:

S-(–)-**1**·2R,3R-(+)-**2** > R-(+)-**1**·2R,3R-(+)-**2**·hydrate > R-(+)-**1**·2R,3R-(+)-**2**

This contradicts the conclusion of one of our recent papers [10] in which – by the analysis of a large number of diastereoisomeric salt pairs – we concluded that when one of the diastereoisomeric salts can precipitate as a solvate, the solvated salt will be the more stable. The formation of new modifications in the precipitate may be responsible for the deviation from this rule.

The different crystal forms of the diastereoisomeric salts were investigated only in a few cases [7, 11, 12]. The number of different modifications found by changing the solvent in case of this particular salt pair seems surprisingly high, but may occur for other diastereoisomeric salt pairs too. The existing but not investigated polymorphism can be the explanation for the sometimes very poor reproducibility of preparative resolutions.

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