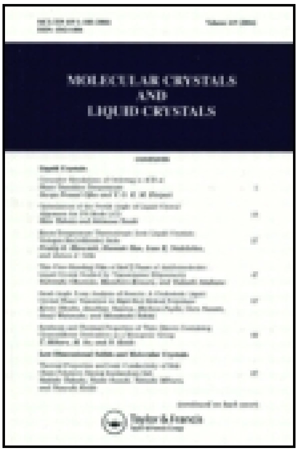

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Study of the Mechanism of Optical Resolutions Via Diastereoisomeric Salt Formation Part 3. Two Consecutive 1:X Double Salt Formations During an Optical Resolution Via Diastereoisomeric Salt Formation

Dávid Kozma [a] & Elemér Fogassy [a]

[a] Department of Organic Chemical Technology, Technical University of Budapest, Budapest, POB 91, H-1521, Hungary

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STUDY OF THE MECHANISM OF OPTICAL RESOLUTIONS VIA DIASTEREOISOMERIC SALT FORMATION PART 3*

TWO CONSECUTIVE 1:X DOUBLE SALT FORMATIONS DURING AN OPTICAL RESOLUTION VIA DIASTEREOISOMERIC SALT FORMATION

DÁVID KOZMA AND ELEMÉR FOGASSY
Department of Organic Chemical Technology, Technical University of Budapest, Budapest POB 91, H-1521 Hungary

Abstract The optical resolution of mandelic acid with cinchonine in water happens by consecutive formation of two different hydrated 1:x double salts, the two salts have different enantiomeric purity, they bound the water with different strength, but their solvent contents are the same.

INTRODUCTION

The optical resolutions via diastereoisomeric salt formation are usually classified into three main groups according to the behaviour of the diastereoisomeric salt pairs taking part in the process[1]. In case of isomorphism of the two salts (solid solution formation) efficient resolution can not be achieved. At an efficient resolution conglomerate formation is always assumed, the two diastereoisomeric salts crystallize separately. There is no isomer separation when 1:1 double salts (molecular compound) formed. In case of 1:x double salt formation a partial resolution with a constant result is expected, but such cases still never have been proved, the demonstration of their existence is regarded questionable by Jacques et.al.[1a]

The research on optical resolution nowadays is focused on the structural study of the pure diastereoisomeric salts of successful resolutions trying to find explanations among second order interactions for the solubility and other physico-chemical difference of the salt pair (for example 2-7).

It is well known that the mandelic acid can be resolved efficiently by cinchonine.[8,9] The crystal structure of cinchoninium-R-mandelate and cinchoninium-S-

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[*] Part 2. D. Kozma, K. Tomor, Cs Novák, Gy. Pokol, E. Fogassy, Solid Solution Formation during the Resolution of Racemic malic acid by R-α-phenylethylamine, submitted to J.Therm.Anal.

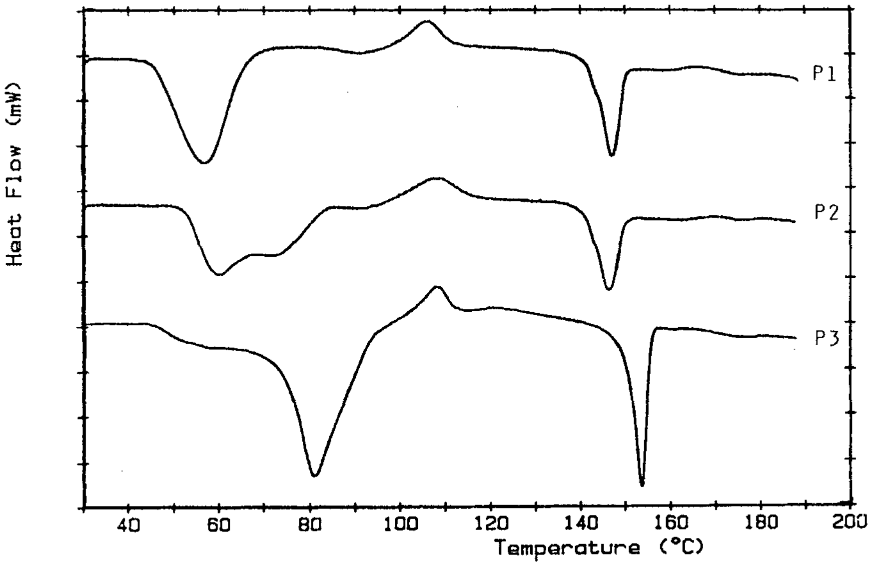
mandelate[10] was published, the differences in the heat of fusion and entropies of the two diastereoisomeric salts were related to their structural differences, but that does not really correspond to the real resolution process since during the resolution different kinds of solvation take place[11]. In this paper we report the reinvestigation of that resolution in water.

RESULTS AND DISCUSSIONS

The experiments were performed similarly described by McKenzie[9]. In the first step of the resolution a diastereoisomeric salt mixture precipitates (P1) containing 25.3% optical purity (o.p.) S-mandelic acid. The first recrystallization of P1 increased the o.p. to 77.6% (P2), while the second recrystallization upto 90.1% (P3). All salts were subjected to thermoanalitycal[12] and X-ray powder diffraction measurements.

The thermogravimetric (TGA) curves indicated that all the three samples contain water as crystal solvent in 6.7%, which correspond about 1.75 mole water for each salt molecule, and there were no substantial thermal decomposition before melting of the dehydrated salts. There were differences in the temperature of the loss of water of the samples.

FIGURE 1. DSC traces of the precipitated salts



All the DSC curves have similar features (Fig.1.). The first endothermic peaks correspond to the loss of water. The exothermic peaks around 105-110 °C correspond to the recrystallization of the dehydrated salts during melting, which can be observed as slight movement of the crystals under microscope. The large endothermic peaks at 155-165 °C correspond to the melting of the salts. Those peaks are shifted in the direction of higher temperatures by increasing optical purity. The maxima of the dehydration peaks are 60 °C at P1, 80 °C at P3. The DSC trace of the dehydration of P2 is a large peak with two maxima around 60 and 80 °C.

The thermoanalytical measurements clearly indicate that there are two different modifications of the precipitating salts. The differences are in the strength of the solvation but not in the degree of solvation. The higher optical purity form bound the water more strongly. The existence of the two forms were also conformed by X-ray powder diffractograms (Table 1.). The powder diffraction pattern of P1 and P3 are different, while the diffractogram of P2 contains lines from both forms.

TABLE 1. X-ray powder diffracrograms of the precipitated salts

P1		P2		P3	
d (Å)	I/I_0	d (Å)	I/I_0	d (Å)	I/I_0
8.630	37.1	8.608	56.5	8.630	33.9
		6.511	52.2	6.511	24.2
5.580	48.1	5.680	34.8		
		5.505	69.6	5.522	100
5.340	70.4	5.372	91.3	5.340	54.8
5.246	55.5	5.246	73.9	5.246	54.8
4.874	59.3	4.887	100		
4.720	40.7	4.732	47.8		
4.270	55.5	4.280	65.2	4.270	55.0
4.191	59.2	4.191	69.6	4.181	69.4
		3.738	43.5	3.731	53.2
3.648	100	3.655	82.6		
		3.479	39.1	3.493	29.0
		3.272	43.5	3.272	32.3

The DSC peak of dehydration of P3 starts at 50 °C that indicate some P1 impurity. The question arises whether the main part of P3 is the pure S-mandelate hydrate or a hydrated 1:x double salt containing the S-mandelate in large excess. We tried to prepare the S-mandelate hydrate as a reference material several times by recrystallization of the S-mandelate from water, but solvate had never been built into the pure salt. The impossibility of the formation of optically pure S-mandelate hydrate settles the question, the P3 must be mainly a 1:x double salt.

The existence of those two non identical forms of precipitating salt can be explained only by the consecutive formation of two different 1:x double salt. Such route has never been described for resolutions.

The formation of the second double salt makes it possible to achieve an efficient enantiomer separation. The experiments call the attention that an efficient resolution can happen not only in case of conglomerate formation, for the analysis of an optical resolution it is not enough to investigate of the pure diastereoisomeric salts, but the samples from the real resolution processes also should be analysed.

EXPERIMENTAL

The DSC curves were recorded and integrated with a DuPont 1090B Thermal Analysis System. Samples of 2-3 mg were run in hermetically sealed aluminium pans with a heating rate of 5 K/min. The temperature range of thermal decomposition was determined by thermogravimetric measurements (carried out on the same system).
The X-ray powder diffractograms were recorded on a HZ6-4C diffractometer with Ni filtered Cu radiation (40 kW, 20 mA)

Description of the resolution experiments

1.976 g (0.013 mol) racemic mandelic acid and 3.822 g (0.013 mol) cinchonine were dissolved in 100 ml of boiling water. By cooling back white crystalline salt precipitated. The precipitate was filtered at room temperature and dried. The precipitated salts were recrystallized two times from water. Small parts of the salts were suspended in 2-5 ml of cc HCl and the liberated mandelic acids were extracted three times with 30 ml of diethyl-ether. After drying on Na_2SO_4 the ether were evaporated leaving the mandelic acid back as a white residue. The specific rotation of the mandelic acid was measured on a Perkin Elmer 241 polarimeter. $[\alpha]_D^{20} = \pm 154$ (c:0.5;water) were considered as the specific rotation of the optically active mandelic acid. The results of the experiment are summarised in Table 2.

TABLE 2. Summary of the experimental results

Resolution step	Weight of starting material g	Water used g	Yield of precipitated salt		Optical purity %
			g	%	
1st (P1)	5.80	100	3.21	55.3	26.3
2nd (P2)	2.50	70	1.05	42.0	77.6
3rd (P3)	0.60	25	0.29	48.3	90.1

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