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Optical Resolution of Mandelic Acid by Cinchonine in Different Solvents

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Abstract: During optical resolution of racemic mandelic acid by cinchonine the S-mandelate as a hydrate, the R-mandelate or the R-mandelate with ethylacetate solvate precipitates depending on the solvent .

The resolution of racemic mandelic acid (I) by cinchonine (II) was accomplished in the last century[1-3], water served as a solvent for the preferential crystallization of the diastereoisomeric salts. As a part of our extended study of optical resolutions by mandelic acid and resolutions of the mandelic acid, we reinvestigated this resolution. In an ideal case the solvent does not have great influence on the efficiency of resolution[4,5], but when the diastereoisomers incorporate solvate the resolution process changes. The diastereoisomeric salts of mandelic acid can often contain crystal solvate [6-9]. To investigate the role of the crystal solvate, we performed the resolution of mandelic acid by cinchonine in different solvents. The experimental results are summarized in Table 1[10].

Table 1. Experimental results

	Solvent[12]	vol. (ml)	Precipitating config. of I.	salt yield %	optical purity %	S[11]	Solvate
1.	water	50	S-(+)	100	28	0.28	water
2.	4:1 (v/v) water:ethanol	25	S-(+)	55	13	0.07	water
3.	2:1 (v/v) water:ethanol	15	R-(-)	88	9	0.08	no solvate
4.	waterfree ethylacetate	110	R-(-)	82	36	0.30	ethylacetate
5.	water saturated ethylacetate	30	R-(-)	73	61	0.45	ethylacetate

It is easy to reproduce the resolution from water[3]. The precipitated salt contains the S-(+)-mandelic acid in excess. The precipitated salt contains water as a crystal solvate, that was not reported in the previous papers. A similar resolution could be accomplished from 4:1 water:ethanol mixtures, but both the optical purity and yield decreased. When the water content of the solvent mixture was decreased to 2:1 water:ethanol, the resolution reversed. In this case the precipitated salt contained the other isomer, the R-(-)-mandelic acid in excess, without any crystal solvate. The resolution was also performed in waterfree and water saturated ethylacetate. Also in this case the salt with R-(-)-mandelic acid in excess precipitated, containing in both cases ethylacetate as crystal solvate. The resolution in water saturated ethylacetate was the most efficient.

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Three solvents were used in five different combinations and the resolutions in these five solvents/solvent mixtures are markedly different. The precipitated salts differ in configuration of the mandelic acid and in crystal solvate.

Water was present in four cases, but it is incorporated in the precipitating salt only when it was in abundance. On the contrary the R-phenyl-glycinol R-mandelic acid salt[6] crystallizes with crystal water even when only traces of water are present.

The unsolvated precipitate in case 3 has the least optical purity, which indicates that the crystal solvate content of the diastereoisomeric salt can increase the difference between the diastereoisomeric salts, which may increase the efficiency of the resolution. The low efficiency is in accordance with our previous structural study of the unsolvated diastereoisomeric salt pair, when only very little differences were found between the second order interactions of the salt pair[13].

The changes in the configuration of the mandelic acid in the precipitate by the alteration of the solvent may have importance from the practical view of the optical resolution of mandelic acid.

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10) 0.76 g (0.005 mol) racemic-mandelic acid and 1.47 g (0.005 mol) cinchonine were dissolved in given amounts of hot solvent (see Table 1.). By cooling back to room temperature in all cases white crystalline powder precipitated. The precipitate were filtered and dried. 1.12 g (0.0025 mol) precipitated salt was considered 100 % yield. The solvate content of the salt were checked by TGA. In case 2 the solvate proved water, in case 5 the solvate proved ethylacetate by TEA measurements. The TGA and TEA measurements were performed on a DuPont 1090B Thermal Analysis System. 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, the ether were evaporated leaving the mandelic acid back as a white residue. The optical rotation of the mandelic acid were 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.

11)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 ($0<Y<1$) of the precipitated salt: $S= OP \times Y$, in Fogassy,E.; Lopata,A.; Faigl,F.; Darvas,F.; Ács,M; Tôke,L. Tetrahedron Lett., **1980**,21, 647

12) The ethanol is not suitable solvent for the resolution because the salts are very soluble in it.

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