MECHANISM OF OPTICAL RESOLUTIONS VIA DIASTEREOISOMERIC SALT FORMATION
Part 6[*] Thermoanalytical investigation of the optical resolution of racemic mandelic acid with *S*-(+)-2-benzylamino-butanol

D. Kozma[1], J. Sztatisz[2], K. Tomor[2], G. Pokol[2] and E. Fogassy[1]

[1]Department of Organic Chemical Technology, Technical University of Budapest
[2]Institute for General and Analytical Chemistry, Technical University of Budapest, Budapest
P.O. Box 91, H-1521, Hungary

Abstract

The optical resolution of racemic mandelic acid (I) by *S*-2-benzylamino-butanol (II) was performed in water, ethyl acetate, and water saturated ethyl acetate. It was found that the efficiency of the resolution is three times higher in water saturated ethyl acetate than in either water or ethyl acetate. The salt mixtures produced during the resolutions and the pure diastereoisomeric salts were analyzed by TG, DSC and X-ray powder diffraction measurements. The *R*-(–)-I·*S*-(+)-II salt has the higher melting point and heat of fusion value which indicates that this is the more stable salt. Though the general assumption is that diastereoisomeric salt pairs of successful optical resolutions form eutectic systems, the *R*-mandelic acid–*S*-2-benzylamino-butanol and the *S*-mandelic acid–*S*-2-benzylamino-butanol system was found to behave in a different way. Melting did not start at or near the estimated eutectic temperature. The difference can be explained either by miscibility in the solid phase (solid solution) or by a blocked interaction between the crystals of the two solid salts. This unusual behaviour of the salt pair should be responsible for the unusual difference in the efficiency of the resolutions performed in different solvents.

Keywords: 2-benzylamino-butanol, DSC, mandelic acid, melting phase diagram, optical resolution

Introduction

The optical resolution via diastereoisomeric salt formation is one of the most important ways to separate optical isomers of synthetic racemates [1, 2]. On reacting the racemate and a chiral resolving agent a diastereoisomeric salt pair is formed which can be separated by fractional crystallization.

---

*   D. Kozma, Cs. Novák, G. Pokol and E. Fogassy, Study of the Mechanism of Optical Resolutions via Diastereoisomeric Salt Formation Part 5. Thermoanalytical Investigation of the Optical Resolution of the N-methylamphetamine by Tartaric Acid, J. Thermal Anal., 47 (1996) 727.

$$F + 2R \xleftrightarrow{\ solvent\ } FR + \exists R$$
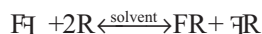
where F and ⊣ are the enantiomers of the racemate, R is the resolving agent.

The selection of the solvent is usually equally important as the selection of the resolving agent, since the efficiency of the resolution usually depends on it substantially.

Several solvents or solvent mixtures are tried during the optimization of a resolution [3] but usually only the solvent providing the most efficient resolution is reported [4]. That is why only a limited number of comparative data are available with different solvents on a given resolution and even in those cases usually without reporting the physicochemical data of the different precipitates.

As a part of an extended research program, in this paper we investigate the role of the solvent in the optical resolution of racemic mandelic acid (I) by optically active 2-benzylamino-butanol (II).

I.   II.
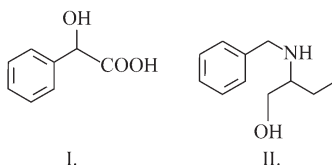
Experimental

All chemicals were purchased from Merck.

Optical resolution of racemic mandelic acid by S-(+)-benzylamino-butanol

1.52 g (0.01 mol) racemic mandelic acid and 1.79 g (0.01 mol) *S*-(+)-benzyl-amino-butanol were dissolved in the solvents (water, ethyl acetate (EtOAc), water saturated ethyl acetate, Table 1) to give a saturated solution at the boiling point of the solvent. On cooling back to room temperature in all cases white crystalline powder precipitated. The precipitate was filtered and dried. 3.31 g (0.01 mol) precipitated salt was considered 100% yield. 0.6 g portions of each salt were suspended in 2 ml of cc HCl and the liberated mandelic acid products were extracted three times with 30 ml of diethyl ether. After drying, the ether was evaporated leaving the mandelic acid back as a white residue. The optical 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 acids. (The results of the experiments were practically the same, when the resolutions were repeated by two days crystallization time with vigorous stirring.)

The optically pure diastereoisomeric salts were prepared from molar equivalent amounts of optically pure compounds in methanol, followed by the evaporation of the methanol in vacuum.

Table 1 Summary of the resolution experiments

Solvent	ml	Product code	Precipitate/g	Y^a	Mandelic acid $[\alpha]_D^{20}$	OP^a	S^a
Water	5	P1	0.79	0.24	−54.6	0.36	0.17
EtOAc	25	P2	2.20	0.66	−23.8	0.16	0.21
Water saturated EtOAc	20	P3	1.41	0.43	−104.0	0.68	0.58

[a]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: $S=OP\times Y$ [5]

The DSC curves were recorded and integrated with the aid of a DuPont 1090B Thermal Analysis System. Samples of 5.0–5.5 mg were run in open aluminum pans under argon atmosphere with a heating rate of 5 K min^{-1}. The temperature range of thermal decomposition was determined by thermogravimetric measurements (carried out on the same system).

A qualitative X-ray analysis of the products was carried out on a HZG-4/C Diffractometer, Carl Zeiss, Jena, using CuK$_\alpha$ (λ=0.15405 nm) radiation and Ni filter. The speed of the goniometer was 1° min^{-1}.

The melting processes were observed on a NU-10 microscope (Carl Zeiss, Jena).

Results and discussion

The optical resolution of racemic-I by S-II was performed in water, ethyl acetate, and water saturated ethyl acetate. Enantiomer separation took place in all cases, but a great difference between the efficiencies of the resolution performed in pure solvents or in water saturated ethyl acetate was observed (Table 1). 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: $S=OP\times Y$ [5]. In pure solvents the efficiency was low (about 0.2), while the S=0.58 value achieved in water saturated ethyl acetate is quite good. The great difference in the results of the resolutions can partly be explained by the solubility differences. The diastereoisomers are very soluble in water and hardly soluble in pure ethyl acetate. The medium solubility in water saturated ethyl acetate provides better conditions for the resolution.

If there is no solvation in thermodynamic equilibrium the S value should be constant for each diastereoisomeric salt pair, independently of the solvent [6]. If the yield of the precipitate increases, the optical purity of the precipitate decreases, as it was observed when water was replaced by ethyl acetate. Considering an experimental error of ±0.02 in the determination of S value, the efficiencies achieved by using pure solvents were practically the same.

To find reasonable explanation for the three times higher efficiency in the mixed solvent we carried out TG, DSC and X-ray powder diffraction measurements (Figs 1 and 2). The salt mixtures obtained in the resolutions and the pure diastereoisomeric salts were analyzed and compared.
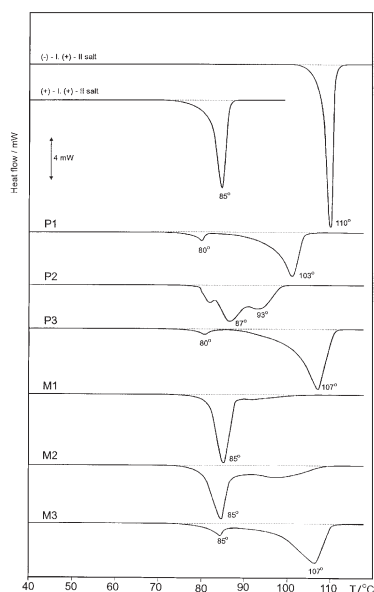
Fig. 1 DSC curves of the diastereoisomeric salt pair formed between mandelic acid and 2-benzylamino-butanol, the salts precipitated in the resolution (P1–P3) and the mechanical mixture of the pure salts (M1–M3). Heating rate: 5 K min^{-1}. Atmosphere: argon 10 l h^{-1}
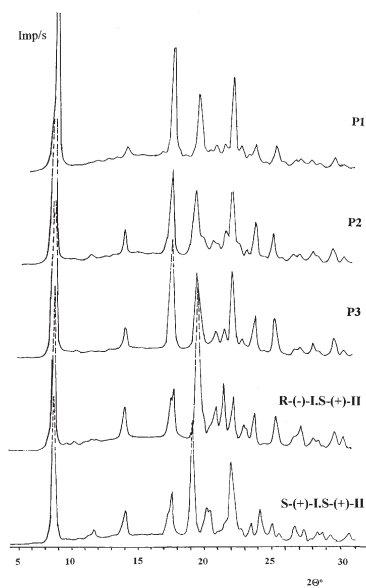

Fig. 2 X-ray powder diffractograms of the diastereoisomeric salt pair formed between mandelic acid and 2-benzylamino-butanol and the salts precipitated during the resolution (P1–P3)

The R-(–)-I·S-(+)-II salt has the higher melting point and heat of fusion value [R-(–)-I·S-(+)-II salt: mp.: 110°C, heat of fusion: 25.2 kJ mol^{-1}; S-(+)-I·S-(+)-II salt: mp.: 85°C, heat of fusion: 17.2 kJ mol^{-1}], which indicates that this salt is the more stable [7].

The mandelic acid liberated from the salts precipitated during the optical resolutions always contained R-(–)-I in excess, which is in agreement with the observation that always the more stable salt having the higher melting point precipitates [8].

The solvent is frequently incorporated in the crystal structure of one of the salts, enhancing the efficiency of the resolution by increasing the difference of the physico-chemical properties of the salt pair. In our model resolution the difference in the efficiency of the resolution could not be explained by the solvation (i.e., crystal solvate formation), since the TG measurements of the pure and the precipitated salts showed no mass loss before melting. The X-ray powder diffractograms of the pure and the precipitated salts (Fig. 2) indicated a high similarity of the salts.

Binary phase diagrams are widely applied in characterizing diastereoisomeric salt pairs [7, 9]. From the eutectic composition of conglomerate forming salt pairs even the efficiency of a resolution can be calculated [7]. The melting phase diagram can be calculated from the melting point and heat of fusion data of the two pure diastereoisomeric salts by the Schröder-van Laar equation [10] (Eq. (1)):

$$\ln x = \frac{\Delta H_a^f}{R}\left(\frac{1}{T_a^f} - \frac{1}{T^f}\right) \tag{1}$$

where x – the molar fraction of the diastereoisomer, T_a^f – melting point of the diastereoisomer (K), ΔH_a^f – heat of fusion of the diastereoisomer (J mol^{-1}), T^f – the melting temperature, i.e. end of fusion of a mixture with a molar fraction of x (K), R : the gas constant (J mol^{-1} K^{-1}).
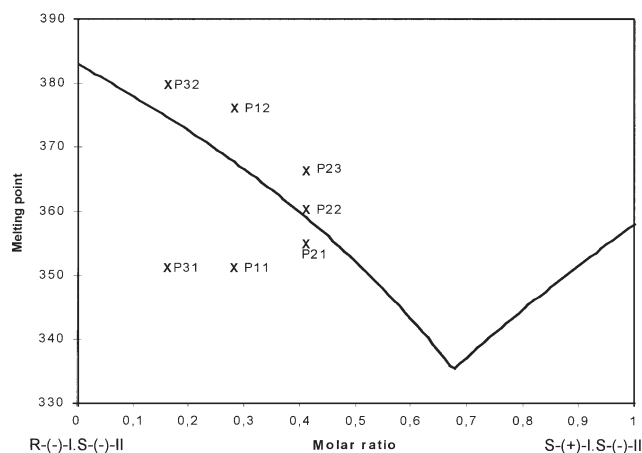

Fig. 3 Calculated melting phase diagram of the diastereoisomeric salt pair formed between mandelic acid and 2-benzylamino-butanol

For the application of the Schröder-van Laar equation three conditions should be valid:

1. the diastereoisomeric salts are immiscible in the solid state,
2. the molten diastereoisomeric salt mixture behave ideally,
3. the heat of fusion does not depend on the temperature.

Jacques and his co-workers investigated a large number of diastereoisomeric salt pairs and concluded that the diastereoisomeric salt pairs practically always satisfy these criteria [1].

In the calculated binary phase diagram of the diastereoisomeric salt pair the eutectic point is at $x_{eu}=0.3$, $T_{eu}=65°C$ (Fig. 3). At the first look the DSC curves of P1 and P3 – the salts with the higher optical purity – look like the DSC curve of a normal eutectic mixture having two peaks (Fig. 1). However the first peak of the curves at about 80°C is much higher than the calculated eutectic temperature. In two component eutectic mixtures the quantity of the eutectic should be between the quantity of the minor component and the double of that. Considering the calculated eutectic composition $x_{eu}=0.3$, in case of P1 the quantity of the eutectic should be 41.6, while for P3 it should be 20.8%. Even considering lower heat of fusion value for the eutectic the area under the first peaks on the DSC curves seems too small for such an amount of the material.

These facts indicate that the diastereoisomeric salt pair does not form a normal eutectic mixture in this case.

In a mortar 20:80 (M1), 50:50 (M2), 80:20 (M3) ratio mechanical mixtures of [R-(–)-I·S-(+)-II:S-(+)-I·S-(+)-II] were prepared from the pure diastereoisomeric salts. The DSC curves of M3 ($x=0.8$) and P3 ($x=0.84$) – which are of similar composition – resemble each other.

The molar fraction of P2 ($x=0.58$) is the closest to the $x=0.5$ value of M2. Their main peaks are around 86°C The first peak at 82°C could not be observed in the case of M2. On the DSC curve of M1 a peak could be observed around 85°C, there is no sample with similar composition among the precipitated salts.

To understand the melting process, the pure salts and the mechanical mixtures were heated under a microscope.

On the microscope hot stage the R-(–)-I·S-(+)-II salt melted at 109°C, while the S-(+)-I·S-(+)-II salt at 82°C. In case of M1 the first movement could be observed at 77, at 82°C most of the sample melted, in the drops some crystals could be observed. In one droplet only a few, in others a large number of crystals were seen, at 85°C some drops were already clear, but the last crystal disappeared only at 105–107°C. In M2 the first movements could also be observed at 77°C, at 81°C droplets of melt were observed with solid crystals in them, the last crystal disappeared at 107°C. During heating the first movement of M3 was observed at 76°C. At 82–83°C a few droplets of melt appeared with lots of floating crystals in them but the majority of the sample still had not changed. On heating the melt drops gradually became larger, and the number of the crystals inside the droplets continuously decreased. The last crystal disappeared at 107°C.

So, neither the precipitates nor the mechanical mixtures behave as a normal eutectic system. The first peak in the DSC curve is close to the melting point of the

lower melting salt, instead of emerging at the expected eutectic temperature. After this first melting process the remaining solid (i.e., the compound with the higher melting point) is dissolved in the melt.

There are two feasible explanation for this behaviour. The first is that the common assumption of total immiscibility in the solid phase is not valid in this case, and solid solutions exist in a certain composition range. The other is that the interaction between the two pure solid diastereoisomers is blocked and the solid mixture resembles an assembly of independent materials; when one of the phases starts to melt (near its melting point) the system returns to the eutectic behaviour.

The molten diastereoisomeric mixtures did not crystallize upon cooling back to room temperature, so it was also impossible to produce a normal eutectic mixture in this way.

Conclusions

Though the general assumption is that diastereoisomeric salt pairs of successful optical resolutions form eutectic systems, the *R*-mandelic acid–*S*-2-benzylamino-butanol and the *S*-mandelic acid–*S*-2-benzylamino-butanol system was found to behave in a different way. Melting did not start at or near the estimated eutectic temperature. The difference can be explained either by miscibility in the solid phase (solid solution) or by a blocked interaction between the crystals of the two solid salts.

We believe that somehow the unusual behaviour of the diastereoisomeric salt pair is responsible for the unusual difference in the efficiency of the resolutions, performed in different solvents.

* * *

References

 1 J. Jacques, A. Collet and S. H. Wilen, Enantiomers, Racemates and Resolutions, Wiley, New York 1981.
 2 R. A. Sheldon, Chirotechnology, Marcel Dekker, New York 1993.
 3 S. H. Wilen, A. Collet and J. Jacques, Tetrahedron, 33 (1977) 2725.
 4 P. Newman, Optical Resolution Procedures for Chemical Compounds, Vols 1–3, Optical Resolution. Information Center, Manhattan College, New York 1978-84.
 5 E. Fogassy, A. Lopata, F. Faigl, F. Darvas, M. Ács and L. Tőke, Tetrahedron Lett., 21 (1980) 647.
 6 F. J. J. Leusen, H. J. Bruins Slot, J. H. Noordik, A. D. van der Haest, H. Wynberg and A. Bruggink, Recl. Trav. Chim. Pays-Bas, 13 (1991) 110.
 7 D. Kozma, G. Pokol and M. Ács, J. Chem. Soc. Perkin Trans., 2 (1992) 435.
 8 D. Kozma, M. Ács and E. Fogassy, Tetrahedron, 50 (1994) 6907.
 9 D. Kozma, L. Poszávác, M. Ács, Gy. Pokol and E. Fogassy, J. Thermal Anal., 44 (1995) 339.
10 a. A. I. Schroder, Z. Phys. Chem., 11 (1893) 449.
    b. J. J. van Laar, Arch. Nederl., (1903) 264.