

# STUDY OF THE MECHANISM OF OPTICAL RESOLUTIONS VIA DIASTEREOISOMERIC SALT FORMATION

## 2. Thermoanalytical and X-ray study of solid solution formation during the resolution of racemic malic acid by R- $\alpha$ -phenylethylamine\*

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### Abstract

Racemic malic acid (I) was resolved by R- $\alpha$ -phenylethylamine(II). The S-(-)-I.R-(+)-II diastereoisomer was in excess in the precipitated salt. DSC curves and X-ray powder diffractograms proved that the diastereoisomeric salt mixture precipitated during the resolution was isomorphous with the optically pure S-(-)-I.R-(+)-II salt. The diastereoisomeric salt mixture containing the R-(-)-I.R-(+)-II salt in abundance bound crystal solvate (water or methanol) when produced by the total evaporation of the mother liquor, while the optically pure R-(-)-I.R-(+)-II salt crystallized without solvate. It is generally assumed that solid solution formation takes place when the two diastereoisomers are alike and the high similarity results in less efficient enantiomer separation.

This paper demonstrates that efficient resolution can be accomplished in case of solid solution formation too. The diastereoisomeric salt mixtures can crystallize in isomorphic form even when the physico-chemical properties of the optically pure diastereoisomeric salts are quite different.

**Keywords:**  $\alpha$ -phenylethylamine, optical resolution, racemic malic acid

### Introduction

The optical resolution via diastereoisomeric salt formation is of great practical importance in the preparation of optical isomers [1]. It is generally ac-

\* Part 1. D. Kozma, Z. Madarász, M. Ács, E. Fogassy, *Tetrahedron: Asymmetry* 1994, 5, 193.

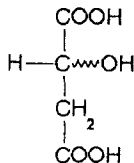
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cepted that diastereoisomeric salt pairs, similarly to other two component systems can crystallize in three main forms, which determine the course of the resolution process [2, 3]. When 1:1 double salts are formed there is no enantiomer separation since the two diastereoisomers of the salt pair crystallize together. Efficient resolution is expected only in case of conglomerate formation when the salts crystallize separately and the precipitated product is the mixture of the two salts with the abundance of the more stable and less soluble salt [4].

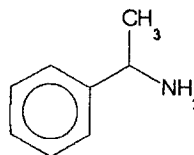
When the diastereoisomeric salts crystallize in isomorphic forms then, independently from the enantiomeric composition, solid solution formation takes place. It is assumed that solid solution formation is more frequent among diastereoisomeric salts than among enantiomers from which they are derived [2, 3], but the existence of solid solution forming diastereoisomeric salts has been proven only in two cases [5]. Solid solution formation is suspected during optical resolutions via diastereoisomeric salt formation when 'abnormally high (e.g. more than four)' recrystallization of the precipitated diastereoisomeric salt are required for an efficient resolution [3].

In the last twenty years a number of optical resolutions were analysed by physico-chemical methods including structural determinations [6]. Most of the works were based on the comparison of the properties and structures of the two pure diastereoisomeric salts, without the investigation of samples from real resolution processes. The background of this approach is the assumption of conglomerate formation in each case of efficient resolution.

In a recent paper we discussed the mechanism of the optical resolution of mandelic acid by cinchonine in water, which is an efficient resolution, but it did not involve conglomerate formation [7]. As a part of an extensive study on the mechanism of optical resolutions via diastereoisomeric salt formation, in this paper we report a thermoanalytical and X-ray diffraction study on the mechanism of the optical resolution of malic acid(I) by R- $\alpha$ -phenylethylamine(II).



I



II

## Results and discussion

The resolution of racemic  $\alpha$ -phenylethylamine by malic acid is a well known process [8], but the resolution of malic acid by  $\alpha$ -phenylethylamine has not been described yet. Newman [9] falsely cited the work of Bachelor and Miana

[10] as a resolution of I by II; that paper only describes the recovery of malic acid from diastereoisomeric salt formed during the resolution of  $\alpha$ -phenylethylamine by optically active malic acid.

The experiments has proven that the resolution of II by I can be reversed. We resolved racemic malic acid by R- $\alpha$ -phenylethylamine in water (Table 1). In the precipitated salt the S-(-)-I.R-(+)-II diastereoisomer was in abundance. Optically completely pure diastereoisomeric salt (S3) was produced by the repeated recrystallization of the precipitated salt from water. From the mother liquor another portion of the S-(-)-I.R-(+)-II salt was collected with low optical purity (SM1). Then the mother liquor was evaporated to dryness, yielding the R-(+)-I.R-(+)-II salt (M1) with about 70% optical purity.

**Table 1** Summary of the resolution experiments

Solvent	Sample	<i>a</i> /g	<i>b</i> /g	$c[\alpha]_D^{20}$	<i>d</i> /OP%	<i>S</i>	$T_{fus}/^{\circ}\text{C}$
water	S1	220	68.6	-1.23	52.8	0.33	172
	S2	65	44.6	-2.08	89.3	0.38	178
	S3	40.6	33.5	-2.33	100	0.35	178
	SM1		19.5	-0.48	20.6	-	168
	M1		118.3	1.62	69.5	-	119/148
methanol	P1	11	4.33	-1.04	44.6	0.35	171
	R1			1.28	54.9	-	118/150

*a* – weight of the starting material; *b* – weight of the precipitated salt or residue; *c* – specific rotation of the malic acid liberated from the salts; *d* – optical purity of the salts, calculated from the specific rotation of the malic acid

The resolution was accomplished in methanol too with about the same efficiency [11] (S). Here the precipitated salt (P1) was not recrystallized further (Table 1).

All the salts prepared during the resolutions and the pure diastereoisomeric salts prepared for reference were investigated in TG, DSC and X-ray powder diffraction.

None of the optically pure salts crystallized with solvate. The S-(-)-I.R-(+)-II is the more stable, since it has a higher melting point (177°C), which is in agreement with our experimental results as always the precipitation of the more stable salt can be expected [4, 12]. The R-(+)-I.R-(+)-II salt melt at 152°C. In a recent paper we stated that at least 20°C difference in the melting points of the diastereoisomeric salt pair is needed for an efficient resolution [12]. Here the 25°C difference between the melting points correspond to the medium efficiency of this resolution. The decomposition of the S-(-)-I.R-(+)-II salt started parallelly with melting, the heat of fusion ( $\Delta H_{fus}$ ) could not be determined.

The DSC curves of the precipitated salts including the recrystallized products showed one melting peak, they are quite similar to each other (Fig. 1). The

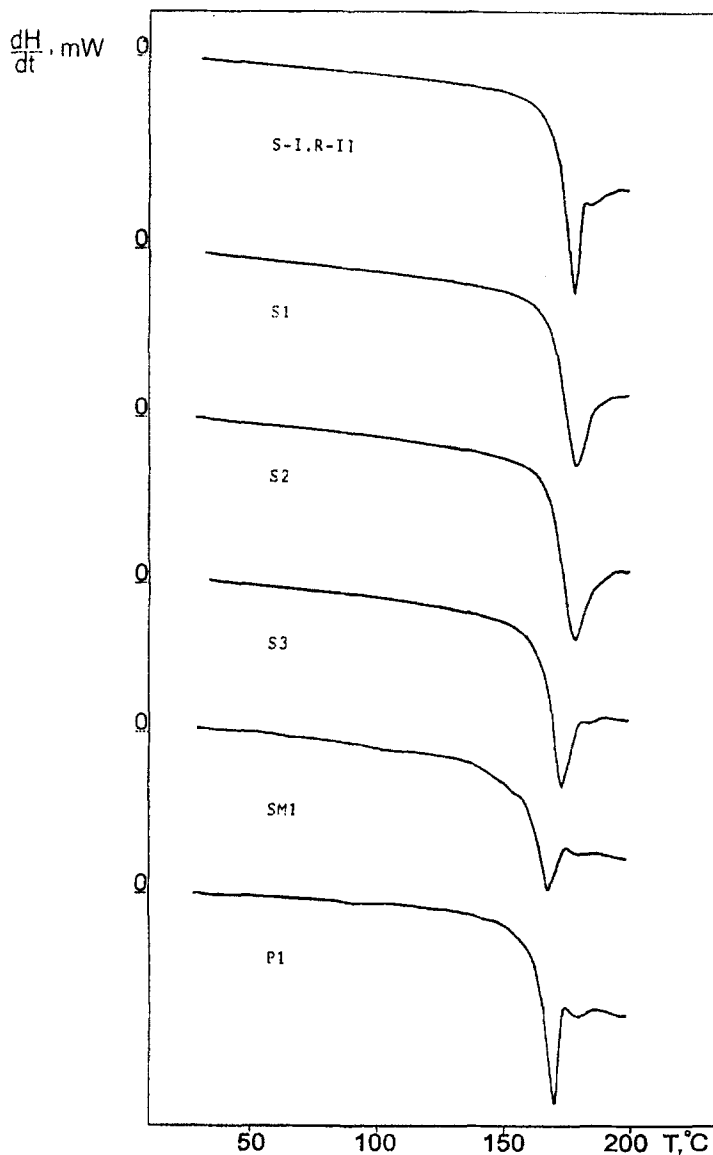


Fig. 1 DSC curves of the precipitated salts and the S-(+)-I.R-(+)-II salt

maxima of the melting peaks can be considered as the melting points of the samples [13], but the peak could not be integrated for calculation of the heat of fusion because of thermal decomposition overlapping the melting endotherm.

Since the resolution was quite efficient first we assumed that conglomerate formation took place, but the one peak DSC curves did not support that assump-

tion [4]. In case of conglomerate formation a DSC curve with two peaks are expected; the first peak belongs to the melting of the eutectic while the second one to the melting of the rest of the sample. For samples of low optical purity (for example S1, S2), the area under the first peak should be larger, than the area under the second peak or the area under the first peak of salt of a larger optical purity. The eutectic melting point should be lower than the melting point of the less stable salt, in our case below 152°C.

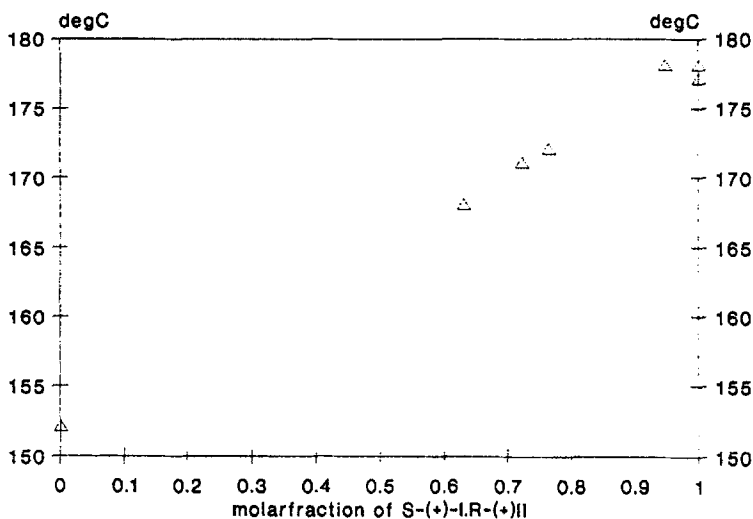


Fig. 2 Melting phase diagram of the salt pair

Two peaks could not be observed in any case and the total overlap of the two peaks is not likely either since the onset of the peaks is higher than 152°C. A single DSC melting peak of the precipitated diastereoisomeric salt could be expected in case of double salt formation or in case of solid solution. The formation of 1:1 double salt can be excluded since the resolution was efficient. The binary phase diagram plotted from the melting point data of the precipitated salts and the pure salts are fairly linear (Fig. 2), which indicates a solid solution formation. (The linearity of the melting phase diagram make it possible to estimate the optical purity of the precipitated salt by DSC measurements of small samples, being much is more simple than the determination of the optical purity by the measurement of specific rotation of the malic acid liberated from the salts.)

The X-ray powder diffractograms of the precipitated salts and the pure salts can be seen on Fig. 3. The powder diffraction pattern of the precipitated salts are very similar to each other and to the more stable S-(+)-I.R-(+)-II salt, while they differ markedly from the diffraction pattern of the R-(+)-I.R-(+)-II salt. The identical diffractograms prove that the precipitated salt are isomorphous

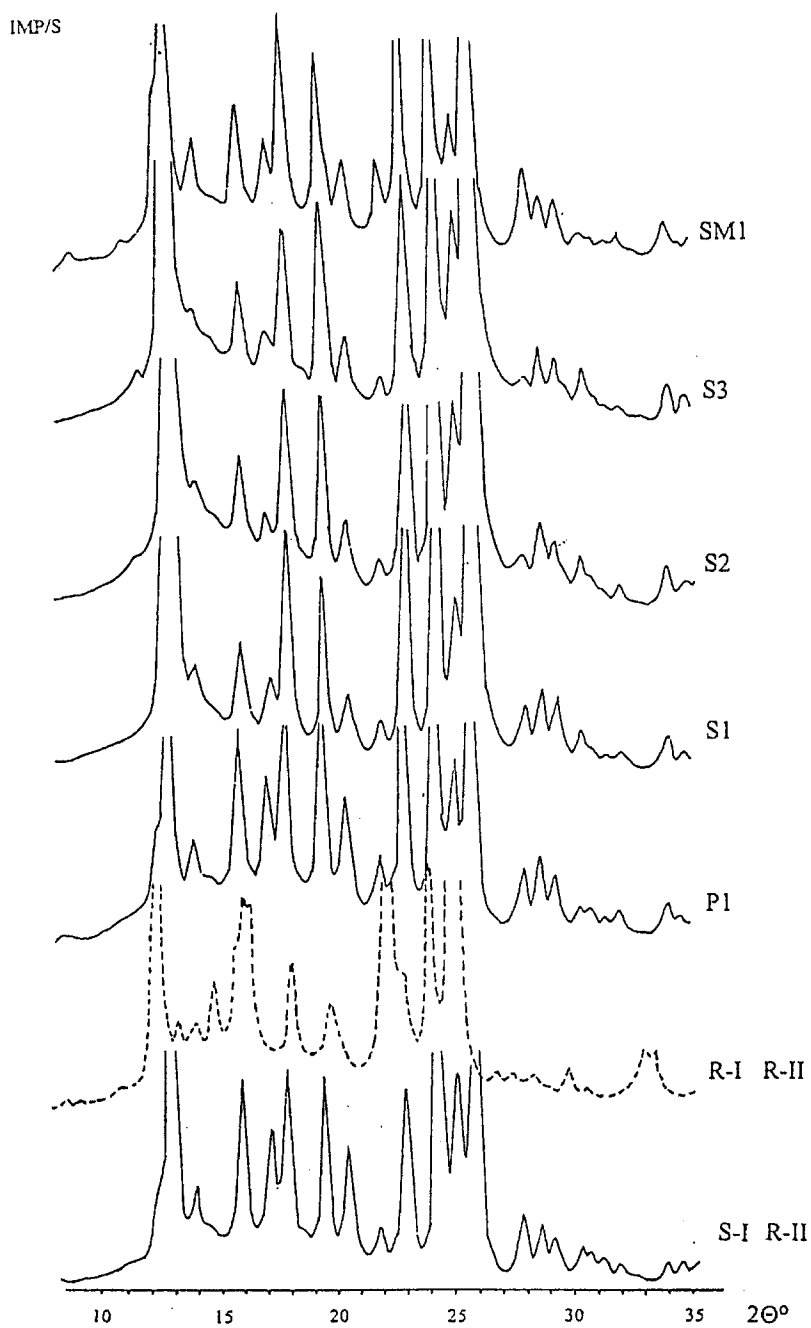


Fig. 3 X-ray powder diffractograms of the precipitated and the optically pure salts

with each other and with the S-(+)-I.R-(+)-II salt. Consequently, taking into account of the binary phase diagram, too, solid solution formation takes place during the resolution either in water or in methanol, at least in case of the precipitating salts.

The residues produced by the total evaporation of the mother liquor were also investigated. The TG measurements indicated 5% weight loss from both residues between 90 and 130°C, corresponding to ca. 0.75 molar equivalent amount of water for M1 and R1, respectively and 0.4 molar equivalent amount of methanol per salt molecule. The DSC curves of the residues (Fig. 4) are similar, both contain two peaks. The first peak between 90–130°C with a max-

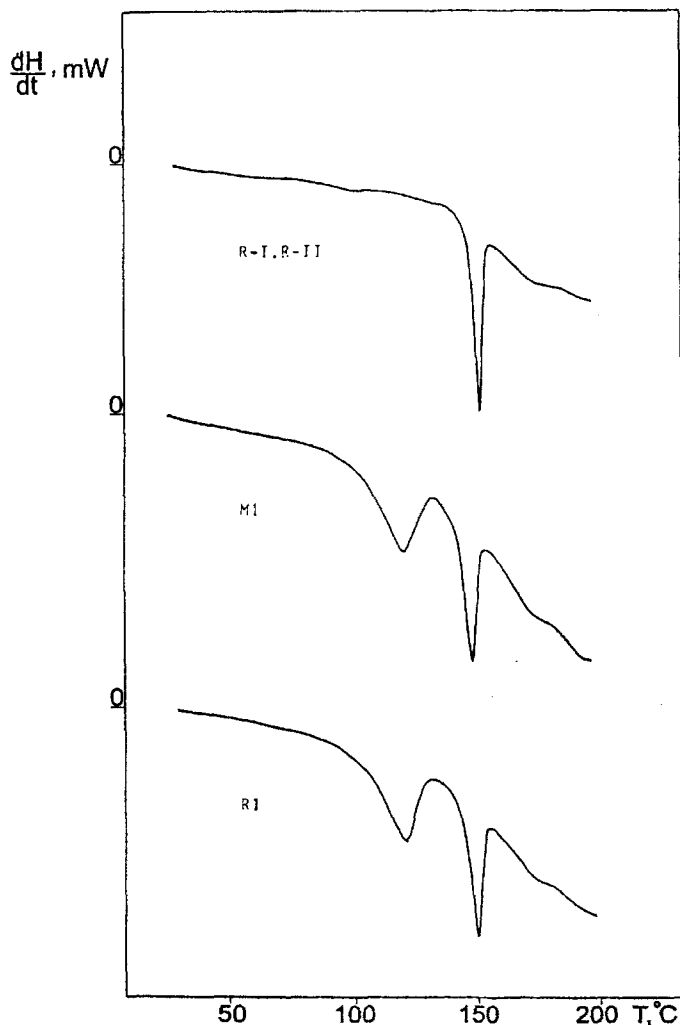


Fig. 4 DSC curves of the residues produced by the evaporation of the mother liquor to dryness and the S-(+)-I.R-(+)-II salt

ima around 122°C correspond to the loss of solvent bound as crystal solvate. It could not be solvent sticking to the surface as the temperature of evolution is higher (in case of methanol much higher) than the boiling point of the solvents.

IMP/S

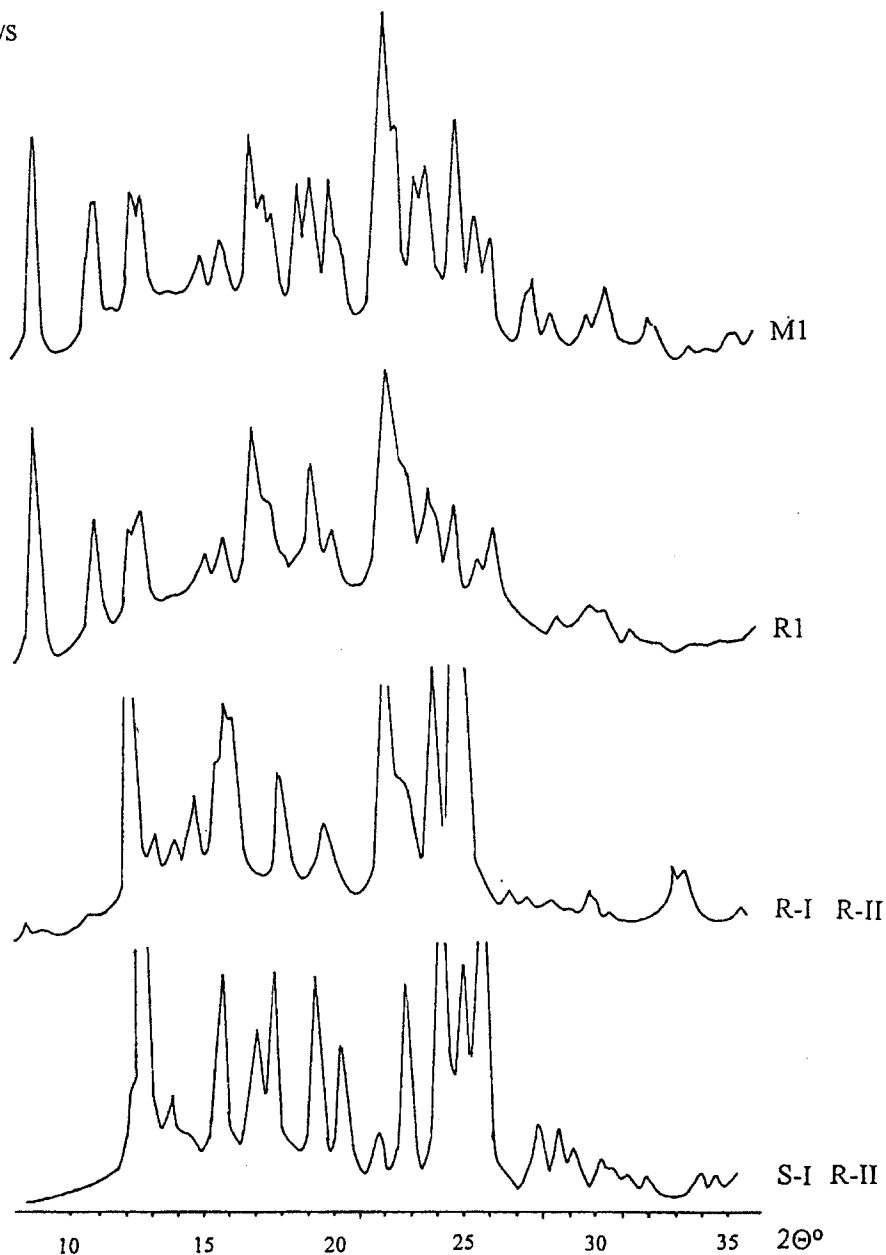


Fig. 5 X-ray powder diffractograms of the residues produced by the evaporation of the mother liquor to dryness and the optically pure salts



The second peaks, which correspond to the melting of the samples, are also very similar to each other. Eutectic could not be observed in neither case.

The X-ray powder diffractograms of M1 and R1 (Fig. 5) are different from those of the pure salts, because of the solvate content. Significant differences can be observed in the powder diffractograms of the residues, but basically they are quite similar, indicating that the two solvents are bonded in a similar manner. The solvation of the residues is unusual since in all the known examples of optical resolutions when solvation takes place the precipitating salt contain the solvate.

The whole binary phase diagram of the real resolution process could not be determined, since the residues produced by evaporation not by precipitation, they represent different systems. The determination of binary or ternary phase diagram by measurements of mixed pure salts are also lead to different phase diagrams, since the mechanical mixture of the salts are different from the precipitated salt mixtures.

## Conclusions

In the optical resolution of racemic malic acid by R- $\alpha$ -phenylethylamine, the formation of a solid solution has been proven by DSC and X-ray diffraction study. This finding is not really surprising, as it was assumed earlier that isomorphism frequently takes place among diastereoisomeric salts. Solid solution formation can take place when the two diastereoisomers are structurally similar and the high similarity was supposed to hinder the enantiomer separation or render it less efficient. This study demonstrates that an efficient resolution can be accomplished in case of solid solution formation, too. The diastereoisomeric salt mixtures can crystallize in isomorphic form even when the physico-chemical properties of the optically pure diastereoisomeric salts are quite different.

## Experimental

All chemicals were purchased from Aldrich.

Optical resolution of racemic-malic acid by  $\alpha$ -phenylethylamine in water: 115.6 g (0.863 mol) of racemic malic acid was dissolved in 500 ml of hot water and 104.4 g (0.863 mol) of R- $\alpha$ -phenylethylamine was added. By cooling back to room temperature large transparent crystals precipitated. The precipitated salt was filtered off and dried, yielding 68.6 g salt (S1). From the 663 g mother liquor 330 g water was evaporated in vacuo. From the obtained concentrated solution 19.5 g salt (SM1) precipitated. The mother liquor was evaporated to dryness resulting in 118.4 g light brown residue (M1). 65 g of S1 was recrystallized from 180 ml of hot water giving 44.6 g salt (S2). 40.6 g S2 was recrystallized from 120 ml of hot water; 33.5 g salt (S3) was obtained. About

1 g portions of every fraction were acidified by cHCl and the liberated malic acid was extracted by diethyl-ether, for the determination of specific rotation.  $[\alpha]_D^{20} = \pm 2.33$  (c:1, water) [14] was considered as the specific rotation of the optically pure malic acid. The results are summarised in Table 1.

Optical resolution of racemic-malic acid by  $\alpha$ -phenylethylamine in methanol: The resolution was accomplished in 0.043 mol scale in 25 ml of absolute methanol, similarly to the resolution in water except the precipitated salt (P1) was not recrystallized. The results are summarised in Table 1.

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 vacuo.

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

The DSC curves were recorded and integrated with the aid of a DuPont 1090B Thermal Analysis System. Samples of 1–3 mg were run in open or hermetically sealed aluminium pans with a heating rate of  $5 \text{ K min}^{-1}$ . 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  $\text{CuK}\alpha$  ( $\lambda = 0.15405 \text{ nm}$ ) radiation and Ni filter. The speed of the goniometer was  $1^\circ \text{ min}^{-1}$ .

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