Journal of Thermal Analysis, Vol. 47 (1996) 727-733

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

V. Thermoanalytical investigation of the optical resolution of the N-methylamphetamine by tartaric acid

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(Received January 26, 1996)

Abstract

The products obtained in the optical resolution of the N-methylamphetamine by the Pope-Peachy method, using half equivalent R, R-tartaric acid and half equivalent hydrochloric acid in absolute ethanol were investigated by thermoanalytical methods. The DSC measurements of the precipitated salts provide sufficient information for following the progress of the resolution. In this way, the results of the resolution can be estimated with the precision of about 5% optical purity.

Keywords: optical resolution, phase diagrams

Introduction

The optical resolution via diastereoisomeric salt formation has a great importance in the production of optically active chiral compounds both on lab scale and industrial scale [1, 2].

Thermoanalytical methods, especially Differential Scanning Calorimetry (DSC) have been widely used for chiral systems in the last twenty years [3–11]. DSC is usually applied to determine the melting phase diagram of the diastereoisomeric salt pairs taking part in the resolution process. The phase diagram reveals the relationship between the salt pairs [5]. Efficient resolution can usually be expected only in case of conglomerate forming salt pairs, when

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0368–4466/96/ $ 5.00

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the two salts crystallize separately, while in case of 1:1 molecular compound or solid solution formation a non-efficient resolution is expected. From the eutectic composition of a conglomerate forming salt pair, even the efficiency of a resolution can be estimated [10].

The melting phase diagram and the eutectic composition can be calculated from the DSC determined thermal data (T_{fus}, ΔH_{fus}) of the pure diastereoisomeric salts or of the 1:1 diastereoisomeric salt mixture produced from the racemate and the resolving agent. The latter method can facilitate the selection of the resolving agent [10].

In the published papers usually the pure diastereoisomeric salts or their mixtures are described, but less attention is paid to the analysis of samples from real resolution processes. In this work, we investigate the possibility of the use of DSC for following the progress of the resolution of N-methylamphetamine by R, R-tartaric acid by analysing samples from the real resolution process.

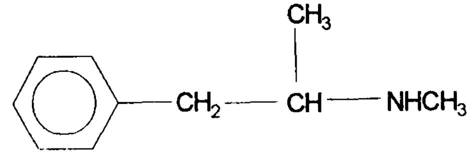
Experimental

1.49 g (0.01 mol) racemic N-methylamphetamine and 1.85 g (0.01 mol) racemic N-methylamphetamine hydrochloride were dissolved in 70 ml of abs. ethanol and the solution of 1.51 g (0.01 mol) R, R-tartaric acid in 10 ml of abs. ethanol was added. The mixtures were left undisturbed for 15 and 90 min, 24 h and for 5 days at room temperature, than the precipitates were filtered and dried. From 0.4 g of each salt the base was liberated by cc. NaOH and extracted from the aqueous phase by dichloromethane. The optical purity of the liberated base was determined by the measurement of the specific rotation by a Perkin Elmer 241 polarimeter. The specific rotation of the optically pure R-N-methylamphetamine is $[\alpha]_{\text{D}}^{20}$ –18.90 (c 0.1; 1N HCl).

The tartrate and hydrochloride content of the salts were determined by potentiometric titration using a RADIOMETER-85 TTT automatic titrator with 0.1 N NaOH and 0.1 N $AgNO_3$. 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 hermetically sealed aluminum pans 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).

Results and discussion

For this study, we selected a quite well known process which had been already extensively studied by our group [13–15]. The process is the optical resolution of the N-methylamphetamine (I) by the Pope-Peachy method, using half equivalent R, R-tartaric acid (II) and half equivalent hydrochloric acid in absolute ethanol.



I

According to the results of our previous studies, the solid salts do not contain solvates and neither of the pure diastereoisomeric salts nor the N-methylamphetamine hydrochloride decompose before melting if measured in closed DSC pan [11]. All samples from the resolutions were checked by TG; their thermal decomposition curves were similar to those of the pure salts. Both the diastereoisomeric salt pair and the hydrochloride salts form conglomerate, their thermal data are summarised in Table 1. There are quite large differences between the melting points and enthalpies of the diastereoisomeric salts, which indicate the possibility of an efficient resolution [11]. According to the data R-I. R,R-II is the more stable salt. The experimental results agree with the expectation, that the less soluble salt is in abundance in the precipitated product. At the beginning of the resolution nearly all the tartrate precipitates with low optical purity, then an enantiomeric exchange of N-methylamphetamine takes place between the precipitated tartrate and the hydrochloride in the mother liquor, which results in an enrichment of the more stable R-I.R,R-II salt in the solid phase. The process is fairly slow without stirring; the optical purity of the precipitated salt improves from an initial 25% up to 60.5% [15] in five days.

Table 1 Thermochemical data of the pure salts

	Melting point/°C	Heat of fusion/kJ mol^{-1}
S-I. R,R-II salt	114	35.88
R-I. R,R-II salt	164	49.09
R-I. HCl salt, S-I. HCl salt	173	25.6

Four parallel experiments were investigated. All of them were carried out exactly under the same conditions except crystallization times were different. The achieved enantiomeric purities are tabulated in Table 2. These independent small scale experiments can simulate a large scale experiment from which small amounts of samples are taken out at different times.

The DSC curves of the precipitated salts (PS) and those of the residue (MLR), which was produced by the evaporation of the mother liquor to dryness are displayed in Figs 1 and 2 respectively.

The anion content (tartrate and hydrochloride) of the salts were determined by potentiometric titration, which indicated that the anion content of the prod-

Table 2 Summary of the experimental results and the thermoanalytical data of the precipitated salt

Sample	Crystallization time	Precip. optical purity	Salt molar fraction	Calculated melting point/ °C	Measured melting point/ °C
PS1	15 min	25.0	0.625	149	150
PS2	90 min	27.0	0.635	150	151
PS3	24 hours	34.0	0.67	151	153
PS4	5 days	60.5	0.80	157	157

ucts did not change in time. PS is mainly tartrate containing 8–10 mol% hydrochloride, while MLR is mainly hydrochloride with 5–6% tartrate impurity. On the melting phase diagram calculated from the thermochemical data of the pure

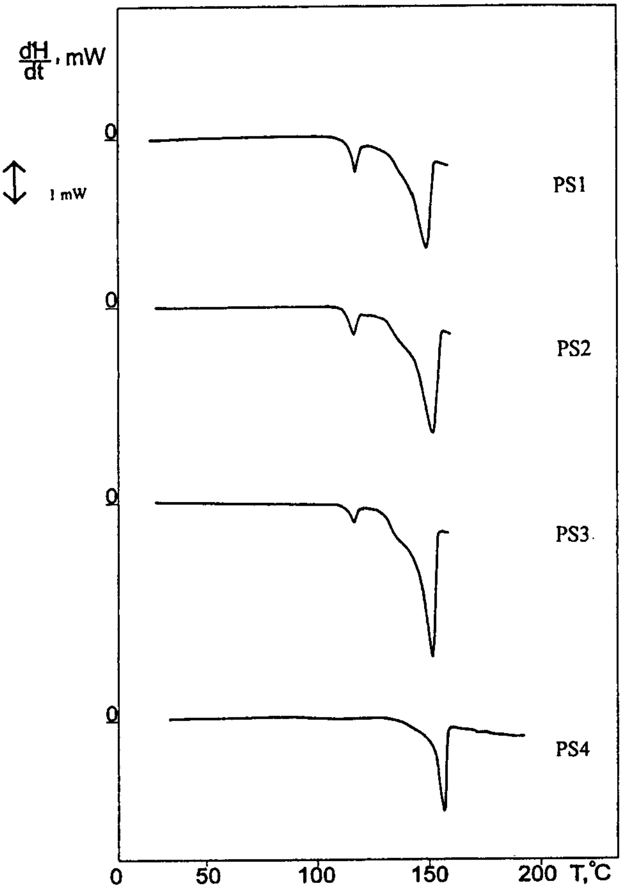


Fig. 1 The DSC curves of the precipitated salts

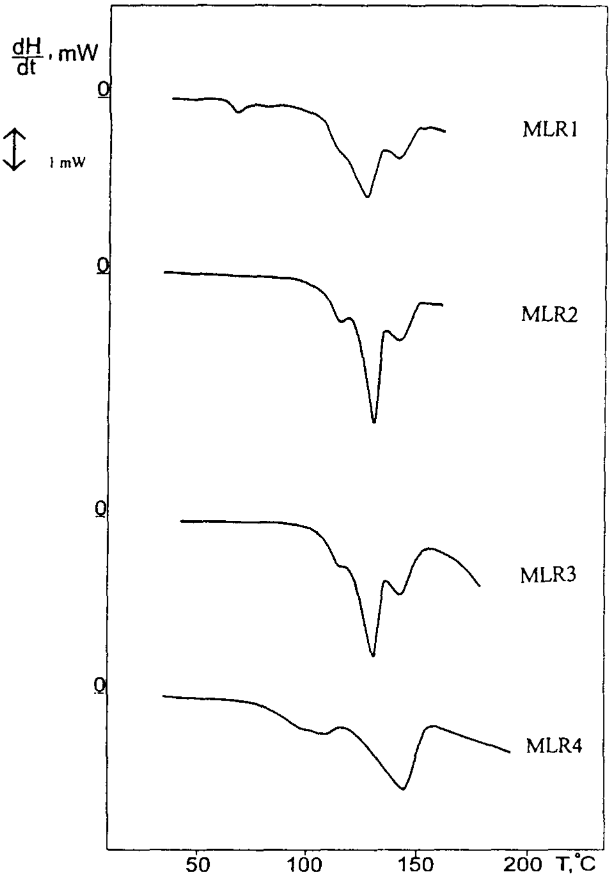


Fig. 2 The DSC curves of the residues

diastereoisomeric salts, the melting point of the eutectic is at 108°C, the calculated melting points i.e., the end of fusion which belong to the samples of different enantiomeric purity are between 149–157°C (Table 2).

Comprising the DSC curves of the precipitated salts it can be seen that the area under the first small peak became smaller with the increase of the enantiomeric purity and even disappeared in the case of the optically purest salt (PS4), but the temperature of the peak maximum is independent from the enantiomeric purity. That endotherm at 118°C behaved like eutectic peak (the melting point is independent from the composition). However, it could not be the eutectic of the two pure diastereoisomeric salts, because the eutectic temperature (T_{eu}) should be below the melting point of the lower melting S-I. R,R-II salt. According to the calculation by the Schröder VanLaar equation $T_{eu}=$ 108°C. The 10°C difference is much larger than the error of the calculation and the uncertainty of the DSC measurements. Besides, the area under the eutectic peak of a low optical purity diastereoisomeric salt pair should be much larger than the second peak representing the melting of the samples and here the reverse case occurs, which also prove that the first peak is not the eutectic of the diastereoisomeric salt pair. This small peak may represent eutectic formed by one of the tartrates and the hydrochloride.

The prolate shoulder at the beginning of the second large peak starting at about 130°C probably indicates the enantiomeric impurity. The maximum of the large peak may be assigned to the end of the fusion of the samples; it is shifted towards higher temperatures, which is in good agreement with the calculated melting phase diagram. A 4–5% increase of the optical purity raises the melting point by 1°C.

The DSC curves of the MLR samples are also similar. The MLR4 is the most different, but the optical purity of this sample also differs from the others. On the DSC curve of MLR1 there is a shoulder at 115°C on the large peak with a maximum at 126°C and there is a smaller overlapping peak at 140°C. In the case of MLR2 and MLR3 a well recognisable DSC peak occurs at 115°C, the large maximum is shifted up to 130°C, while the last peak up to 142°C. The DSC curve of MLR4 has a small prolate peak between 80–120°C with a maximum at 112°C. The second peak is a large, broad peak with a maximum at 146°C, which possibly corresponds to the peaks observed at 140 and 142°C in the case of the other samples. The area under the curve is larger and the maxima is shifted towards a higher temperature, which clearly indicates the enriched optical purity. We were not able to correlate the peaks on the MLR DSC curves with either the calculated melting phase diagram of methylamphetamine hydrochloride or the methylamphetamine tartrate. Possibly, the system formed here is much more complicated than a simple binary system.

Conclusion

The behaviour of the investigated system cannot entirely be described on the basis of the calculated melting phase diagram of the diastereoisomeric salt pair. This is probably because of the unpredictable effect of the hydrochloride salt, which may form ternary or quaternary equilibrium systems with the diastereoisomeric salt pair.

In order to follow the progress of the resolution, however, it seems enough to investigate the precipitated salts by DSC. The melting point characterised by the maximum of the second peak (end of the fusion of the sample) provide quite accurate information of the enantiomeric purity achieved during the process. In this way, the results of the resolution can be determined with a precision of about 5% optical purity. Since one measurement takes less than one hour and require only a very small amount of sample (c.a. 10 mg), it can be used efficiently for the analysis during industrial scale resolution too.

The authors are grateful for financial support to OTKA foundation (grant numbers: F7386 (D.K.), T14887 (E.F.)) and the Z. Magyary award for D.K.

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