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A contribution to the mandelic acid phase diagram

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Abstract

Literature data on the mandelic acid phase diagram are reviewed and examined together with new own results in order to clarify the heterogeneous equilibria in the binary system of the mandelic acid enantiomers and the racemate in water. For this purpose the thermal stability and the melting and recrystallization behavior of racemic mandelic acid are studied using TG and DSC. A metastable racemic phase is prepared from the melt and solution and identified by means of DSC, XRPD and IR spectroscopy as a monotropic modification of the stable racemic compound. Problems associated with handling the metastable phase are addressed. Finally, a mandelic acid phase diagram modified by polymorphy of the racemate is suggested.
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1. Introduction

Due to its frequent application as agent for resolution of racemates and its use for production of certain drugs the chiral mandelic acid system has been often investigated. However, studying the literature gives rise to confusion and reveals inconsistent results both in the melting point phase diagram and concerning solubility data for racemic mandelic acid. The central issue seems to be the behavior of racemic mandelic acid that is normally described as a racemic compound [1] with a melting point of 118–121 °C [2] and a solubility in water of 15 g per 100 ml at room temperature [2]. A recent paper by the present authors is concerned with the binary melting point and the ternary solubility phase diagram of mandelic acid in water [3].

In the binary system of the mandelic acid enantiomers differences are reported with respect to the eutectic composition, usually given at a mole fraction of about 0.69 (0.69 ± 0.01) [4–7] but also with 0.75 [8] and with 0.63 and 0.6 in the earlier literatures [9,10]. Furthermore, some authors claim the existence of two different polymorphs of racemic mandelic acid. Additionally to the known modification they describe a low temperature form that is unsta-

ble with respect to the other one [6,11–13]. It could only be obtained from the melt, not from solution [11–13]. At room temperature the polymorphic phase transition occurred "overnight" [11]. It is remarkable that the measured IR spectrum [6] and X-ray powder diffraction (XRPD) pattern [11] exhibited similarities with the enantiomer characteristics.

Regarding the solubility of racemic mandelic acid in water, several authors [14–16] reported significantly higher values at temperatures above 25 °C, forming a further solubility curve that is shifted to higher solubilities at a given temperature, or vice versa, to lower saturation temperatures for a given mandelic acid–water mixture. Published solubility curves are shown in Fig. 1. Profir et al. [16] attributed the set of higher solubility data to the formation of a metastable mandelic acid conglomerate since the reported solid-state IR spectrum was found to be identical to that of the enantiomer. In our own published work [3,4] such a metastable phase was never detected. However, recent unpublished results give reason to discuss the phase behavior of mandelic acid from a theoretical and experimental background anew considering the references known.

The subject of this paper is to clarify the phase diagram of the mandelic acid system. First, heterogeneous equilibria in a compound forming system of enantiomers are depicted in a general way. Afterwards, literature references, own published and newly obtained results are examined with respect to heterogeneous equilibria in the mandelic acid phase

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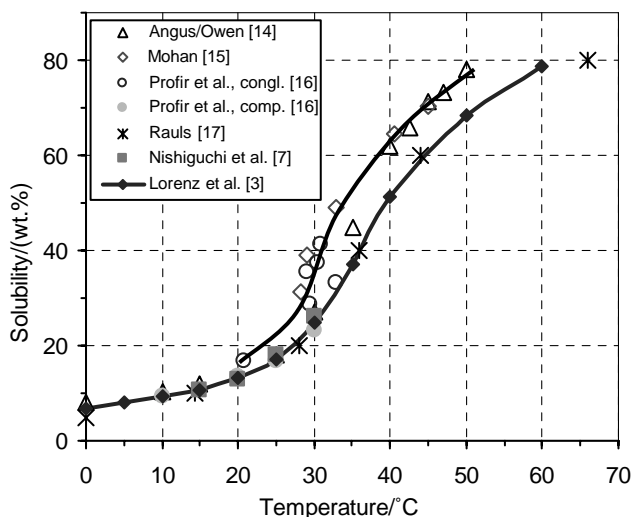*E-mail address:* lorenz@mpi-magdeburg.mpg.de (H. Lorenz).

Fig. 1. Solubility of racemic mandelic acid as function of temperature (own and literature data; wt.%: weight%; congl.: conglomerate; comp.: compound) [17].

diagram. Recent work refers to the thermal stability and the melting/recrystallization behavior of racemic mandelic acid and the preparation and characterization of the metastable racemic phase. Finally, a modified phase diagram for mandelic acid is introduced.

2. Heterogeneous equilibria in a compound forming chiral system

2.1. Binary system of enantiomers

A detailed review on heterogeneous equilibria between condensed phases in chiral systems is given by Coquerel [18]. Here, with respect to mandelic acid only the phase equilibria for a compound forming system are discussed without considering miscibility in the solid state and polymorphism of the enantiomers. The absence of solid solutions was confirmed for this system by means of a Tammann plot previously [3]. Polymorphism of the mandelic acid enantiomers has never been reported.

Fig. 2 shows the solid–liquid equilibria and possible solid–solid transitions that might occur in the mandelic acid system. Fig. 2a refers to polymorphism of the racemic compound RS, with T_τ the temperature of the polymorphic transition from the low temperature form RS_I to the high temperature form RS_{II}. Each polymorph has a domain in the phase diagram where it is the most stable form (enantiotropy). If the high temperature form is always the stable one compared to the other, the polymorphs are of monotropic type with the low temperature modification RS_I being a metastable form. In this case no two-phase invariant attributed to a polymorphic transition appears in the phase diagram; a possible transition $RS_I \rightarrow RS_{II}$ is irreversible. The liquidus curve of the metastable polymorph RS_I is located below the liquidus of the stable form RS_{II} with the (metastable) melting point $T_f(RS_I)$. It intersects the extended liquidus curves of the enantiomers at the (metastable) eutectic temperature $T_e(I)$. Further extension of the enantiomer liquidus lines intersecting at racemic composition depicts the position of a metastable conglomerate characterized by the lowest melting point in the system. Besides, a stable conglomerate can exist in a binary compound forming system of enantiomers (Fig. 2b). It is related to a three-phase eutectoid invariant (at T_ε), where a reversible transition between the racemic compound and the conglomerate occurs. In contrast to a polymorphic transition with two solid phases in equilibrium, at an eutectoid transition three solid phases are involved.

2.2. Ternary system of enantiomers in a solvent

Possible heterogeneous equilibria in a ternary system of two enantiomers in a solvent are illustrated in Fig. 3. The constraints made are the same as applied for the binary system above. Fig. 3a corresponds to the formation of a metastable conglomerate and a metastable polymorph of the racemic compound. As can be seen, both cases may explain higher solubilities measured for the racemate by some authors. A further possibility might be a solvated solid phase of the racemic compound precipitating from the solution as shown in Fig. 3b.
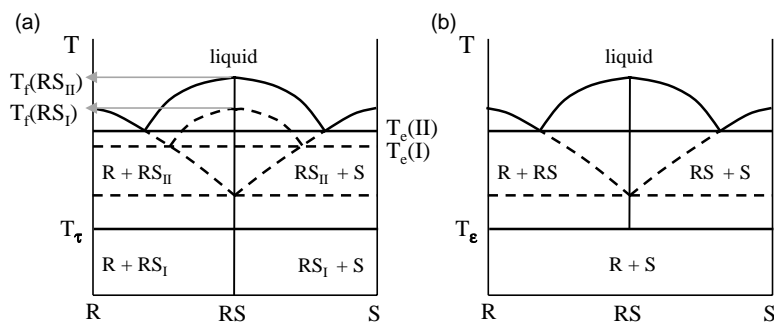

Fig. 2. Heterogeneous equilibria between condensed phases of enantiomers forming a racemic compound according to [18] (*R*, *S*: *R*- and *S*-enantiomer; *RS*: racemic compound; bold lines: stable equilibria; dashed lines: metastable equilibria; inside the phase diagram the stable solid phases are given).
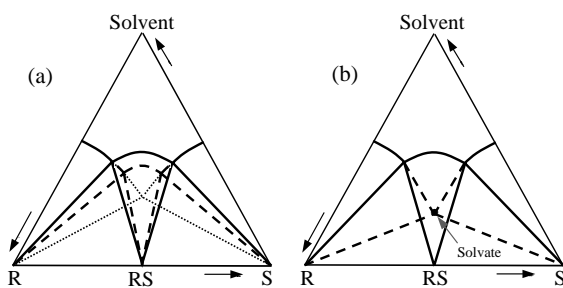
Fig. 3. Heterogeneous equilibria in a ternary system of compound forming enantiomers and a solvent (adapted to the mandelic acid system): (a) presence of a metastable conglomerate (dotted line) or/and a metastable polymorph of the racemic compound (dashed line); (b) solvate formation.

2.3. Problem of identification of heterogeneous equilibria

Various analytical methods (DSC, XRPD, IR spectroscopy) can be used to identify the present phases. However, when studying heterogeneous equilibria several experimental problems may account for different and ambiguous results. First, the formation of meta/unstable phases may cause a lack of reproducibility and difficulties in phase analysis due to insufficient stability of these phases. Further problems are very similar spectra in some cases [1] and, with respect to DSC, limits in detectability and different possibilities for interpretation of DSC curves [18].

3. Experimental work

Binary melting point data and solubilities in water have been determined and reported for the mandelic acid system in a previous work [3]. Here, additional experiments were performed to obtain and to study the nature of the metastable solid phase of racemic mandelic acid.

3.1. Stability studies and melting/recrystallization behavior

Racemic mandelic acid (Merck, >99%) was subjected to repeated heating and cooling cycles to study thermal stability and melting and recrystallization behavior. Experiments were carried out using a coupled TG–DSC unit (TG–DSC 111, Setaram, France) allowing to obtain mass and enthalpy change simultaneously. Measurement conditions were as follows: heating rate 5 K/min, temperature range 20–135 °C, He (5.0) as purge gas at 8 ml/min, 20 mg sample in open Al crucibles. The calorimetric resolution of the instrument is 0.4 μW, the detection limit 5–15 μW. The microbalance detection limit is 1 μg, the mass resolution 0.4 μg. Calibration procedures are described previously [4]. Comparable thermomicroscopic experiments were performed using a hot stage FP84HT (Mettler-Toledo GmbH, Germany) combined with a microscope (Axioskop2, Zeiss, Germany).

3.2. Preparation of the metastable phase

As reported in the literature different methods were applied to obtain the metastable solid phase of racemic mandelic acid.

Racemate was recrystallized *from the melt* in DSC and hot stage crucibles in amounts of some milligrams. Furthermore, samples between 250 mg and 1 g were kept in a drying oven at 125 °C for 15 min. The molten substance was rapidly cooled down at room temperature or quenched in liquid nitrogen. Material *from solution* was obtained by dissolving racemic mandelic acid (supplied from Merck and Aldrich) in water or ethanol and evaporating the solvent at room temperature and atmospheric pressure. For some experiments 1:1 mixtures of the enantiomers were used. In addition, recrystallization was performed from slightly enantiomerically enriched solutions and melts (enantiomeric excess (e.e.) 0.07–0.95%). Further material was prepared by freeze-drying from racemic solutions and sublimation under reduced pressure.

3.3. Phase analysis

Samples were characterized by DSC (DSC 111, Setaram, France) and thermooptical analysis using scanning rates between 1 and 5 K/min.

XRPD patterns were determined at room temperature using a Siemens D-5000 diffractometer with monochromatic Cu Kα radiation. The Bragg–Brentano geometry was applied for stable phases and thin-film geometry for metastable phases due to the low sample amount available. The sample was mounted on an Al sample holder and scanned from a diffraction angle of 3–50° with a step size of 0.05° and counting time of 10 s per step. Solid-state IR analyses were performed using a Perkin-Elmer System 2000 FT-IR in KBr-moulding technique.

4. Results

4.1. Thermal stability, melting/recrystallization behavior of racemic mandelic acid, phase analysis

Fig. 4 shows the results of multiple melting and recrystallization cycles of racemic mandelic acid under TG–DSC conditions. Each melting process is connected with a mass loss due to decomposition. The decomposition starts with formation of the melt phase, reaches a maximum rate at the final program temperature and significantly ends in the cooling cycle below about 109 °C. The mass loss in the first cycle was 1.05 wt.%, slightly decreasing in the following cycles due to the shrinking amount of mandelic acid left. Thus, the total mass loss after six melting/recrystallization cycles was 5.03 wt.%. It could be shown that the extent of decomposition clearly depends on the used heating rate and maximum temperature (duration and level of "thermal
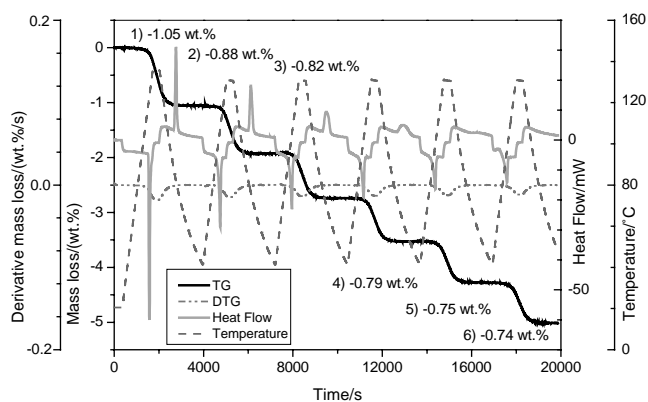
Fig. 4. Thermal stability of racemic mandelic acid (sample mass: 20.03 mg).

treatment"). Along with the mass loss the appropriate thermal effects and "melting temperatures" gradually decrease (Fig. 4). This is caused by the proceeding decomposition leading to an increasing impurity content in the mandelic acid sample. However, as the melting temperature is gradually lowered by about 2.5 K from the second to each higher cycle, the melting point of the phase crystallized from the raw material is measured at 107.4 °C (peak maximum) compared to 119.6 °C.

Fig. 5 compares the XRPD patterns obtained for racemic mandelic acid, (+)-mandelic acid and the phase crystallized from the melt. Typical reflexes characterizing the different species are indicated by thin dotted lines, e.g. the reflex at 6° is typical for the enantiomer, the reflex at 10.84° for the racemic compound. First, the racemic compound and the mandelic acid enantiomer are clearly distinguishable (Fig. 5c and d). They crystallize in various crystal systems and space groups and differ in the unit cell dimensions as well [19,20]. The XRPD pattern, measured for the racemic phase from the melt (Fig. 5b), differs both from the known racemic compound and the enantiomer, i.e. obviously a new phase

has been formed. It is not a conglomerate as the diffraction pattern must match that of the enantiomer. There is some similarity in particular to the main diffraction reflex at 6°, but reproducibly a slight shift is obtained for the new phase (6.14°). Also the reflexes at higher angles (≥24°) are significantly shifted. Time-resolved measurements indicated a stability of the phase of at least 4 days, afterwards transition to the stable racemic compound started. Fig. 5a presents the state of transition 1 month after preparation. Additional to the reflexes of the metastable phase diffraction peaks of the stable racemic compound appear. Even after 5 months the phase transition was not completed. The XRPD pattern measured for the new phase agrees well with data reported by Rose [11] for a DL-mandelic acid polymorph. Separately taken IR spectra confirm the results of the XRPD phase analysis. The IR spectrum of the new phase is very similar to that of the enantiomer. In fact, both differ significantly in the position of the absorption band at 863 cm^{-1} that is shifted to 877 cm^{-1} for the metastable phase. This is consistent with results depicted in [6] (band positions at 858 and 883 cm^{-1}). Further, a slight shift of the enantiomer band at 1248 cm^{-1}–1242 is detected in this work. Profir et al. [16] observed agreement of the IR spectra between 1025 and 1425 cm^{-1}. Thus, the metastable phase obtained from solution was identified as a conglomerate. Proof can be attained comparing also the lower range of wave numbers to avoid misinterpretation.

Due to the preparation procedure the purity of the metastable phase examined in this work was between 96 and 97 wt.% (purity determination by DSC [21]). The phase could only be obtained in small amounts, "bigger" sample volumes (>250 mg as described) were always identified as the stable racemate.

4.2. Metastable phase prepared from solution

To examine, if the metastable phase from the melt is identical to that characterized by higher solubilities, experiments were performed to gain it from solution, to separate and analyze it. Unfortunately, only once we succeeded in obtaining the phase stable enough to be characterized by DSC. Sometimes phase transition occurred already before/during the measurement. In Fig. 6 typical results of DSC analyses are presented comparing the heat flow curves of the stable and metastable phase. The latter melts at 108.5 °C (T_{onset}); the melting enthalpy was determined to 162 J/g. Considering the impurity content (e.e.) in the sample, for the pure material a melting point of 109 °C can be derived. This agrees with the melting temperature of the pure phase obtained from the melt that was estimated to 108.4 °C (average value of eight independent experiments). Fig. 6 further shows the DSC curve of a sample (sample 2) where the metastable phase was already partially transformed into the stable one. The remaining fraction of the metastable phase melts, the stable one recrystallizes from the melt and finally, melting of the stable racemate is observed.
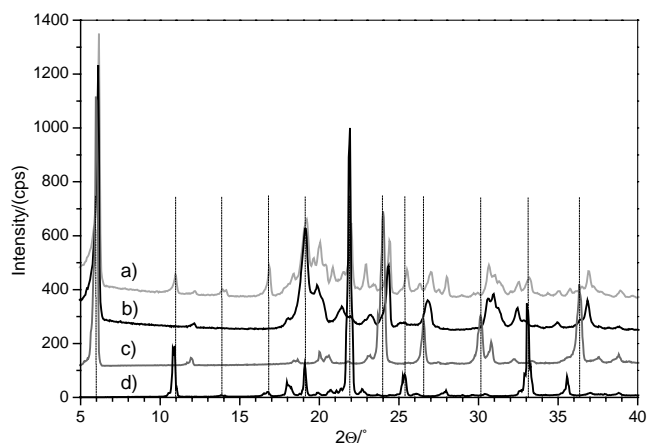

Fig. 5. Experimental XRPD patterns of mandelic acid species: (a) racemic phase from the melt (+1 month); (b) racemic phase from the melt; (c) (+)-mandelic acid; (d) racemic mandelic acid.
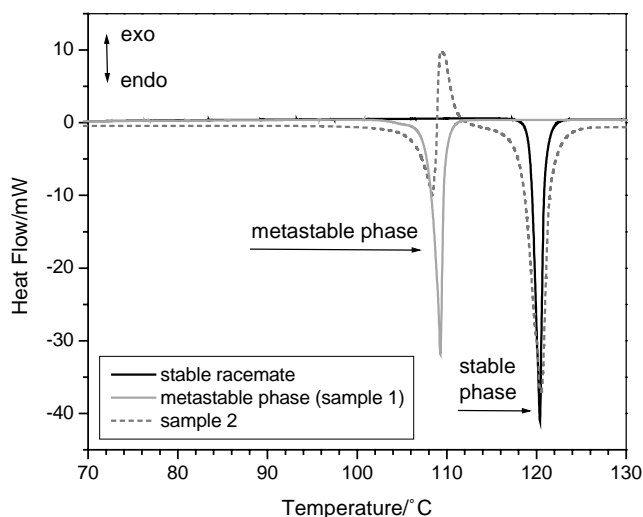
Fig. 6. DSC curves of stable and metastable phases of racemic mandelic acid (sample mass: 15.3–15.9 mg; e.e. in samples 1 and 2: 0.29 and 0.30%; heating rate: 1 K/min (sample 2: 2 K/min)).

The metastable phase was only obtained (analytically proven) from slightly enantiomerically enriched solutions (aqueous or ethanolic). Other experiments depicted in Section 3.2 (e.g. using a 1:1 mixture of the enantiomers, sublimation) were unsuccessful.

5. Discussion and conclusions

As described before, metastable equilibria can be derived from stable ones in the phase diagram. When considering the experimentally determined melting point of the metastable racemic phase, the heterogeneous equilibria in the binary mandelic acid system can consistently be described. The modified phase diagram is shown in Fig. 7.
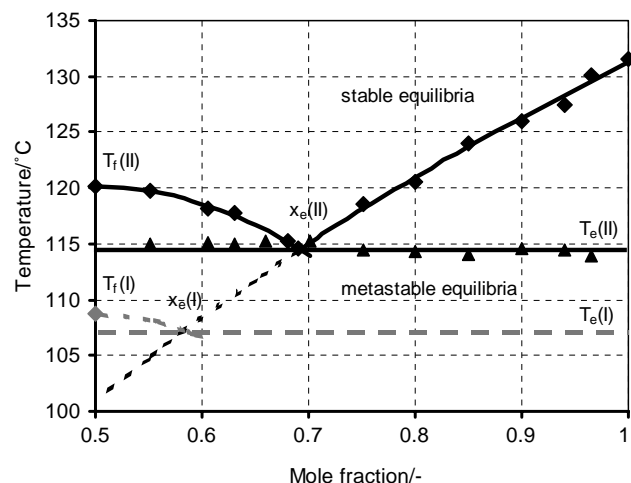

Fig. 7. Modified binary melting point phase diagram of the mandelic acid enantiomers (symbols: experimental data; bold lines: stable equilibria; dashed lines: metastable equilibria; liquidus curves: fitted according to the Schröder–van Laar or Prigogine–Defay equation).

There, the metastable phase with the melting point $T_f(I)$ is clearly identified as a monotropic modification of the racemic compound. It is the low temperature form that is metastable with respect to the stable known form. The melting point (108.7 °C) corresponds to literature data reported for a further racemic phase (108 °C [6,8], 107–108 °C [11], 105–106 °C [13]). Using the melting temperature and the melting enthalpy determined for this polymorph, the appropriate liquidus curve can be calculated according to the Prigogine–Defay equation (ideality assumed). The intersection with the extended liquidus line of the mandelic acid enantiomer indicates the position of the metastable eutectic in the system. One obtains an eutectic temperature of 107.3 °C ($T_e(I)$) and an eutectic composition of 0.584 ($x_e(I)$). Kuhnert-Brandstätter and Ulmer [6] depicted the eutectic at 106 °C and $x_e = 0.63$. Further, the stable eutectic at $x_e = 0.6$ reported by Adriani [10] might be attributed to the metastable polymorph present in the measurements. A metastable conglomerate in the system should have a melting point of about 101 °C (Fig. 7). In Fig. 6, a small additional thermal effect preceding the melting of the metastable phase (sample 1) is adumbrated. However, specifying requires the effect to be reproduced and further studied.

Fig. 8 presents the ternary phase diagram of the mandelic acid enantiomers in water. There, own solubility data (characterizing stable equilibria) are presented together with the higher solubilities reported in the literature for racemic mandelic acid. Confirming the results in the binary system, the data do not correlate with a hypothetical conglomerate; the measured solubilities are too low (e.g. the extension of the solubility isotherm at 20 °C does not meet the literature source). However, the deviations in the literature data support the presence of a metastable phase instead a stable one. The absence of a possible DL-mandelic acid hydrate (Fig. 3b) was experimentally approved by DSC analyses of random samples of the solid phase when determining solubility data. Hydrate phases of racemic mandelic acid are not described up to now. For the Mg- and Ba-salts low hydrate phases are reported but then hydrated enantiomer phases are known too [22]. However, the phase equilibria in the ternary mandelic acid system are not trivial. Simple linear fitting to construct the solubility isotherms of the enantiomer (Fig. 8) is obviously not sufficient in order to describe a system that significantly deviates from ideality. It was shown previously that the activity coefficients in aqueous solutions of mandelic acid depend on the temperature and the enantiomeric composition [3]. For clarification more data in the ternary system are required.

Most of the confusion and inconsistencies reported with respect to the mandelic acid phase diagram can be attributed to (1) the decompositon behavior of mandelic acid, making it difficult to determine the binary phase diagram with classical sample preparation methods that involve a previous melting cycle and/or (2) the presence of the metastable modification of the racemic compound. Hurd and Raterink [23] studied the thermal decomposition of mandelic acid up
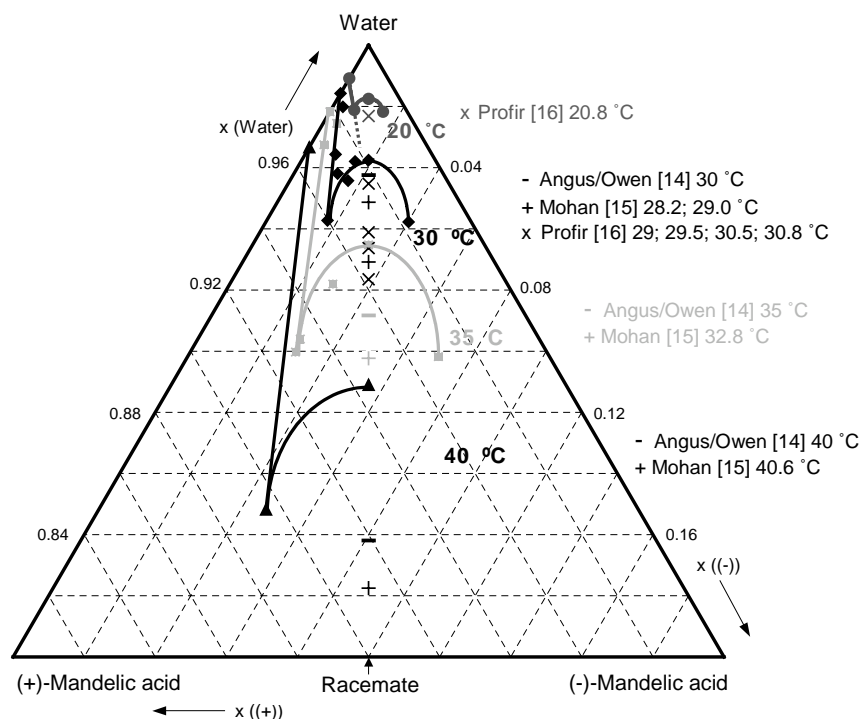
Fig. 8. Part of the ternary phase diagram of mandelic acid in water showing solubility isotherms between 20 and 40 °C (filled symbols: own data, stable equilibria; crosses, dashes: higher solubility data as reported in various literature sources; isotherm lines are guides to the eye; axes are given in mole fraction *x*).

to temperatures of 250 °C. They depicted condensation processes forming different esters and polymerization products. The presence of some esterified mandelic acid might account for stabilization of the recrystallized metastable phase. In the solution obviously the small excess of enantiomer supported the formation of the metastable polymorph, but did not stabilize it that strong as obtained for the phase from the melt. Kuhnert-Brandstätter and Ulmer [6] described a "seeding affinity" between the mandelic acid enantiomers and the unstable racemate, i.e. they always obtained the unstable phase from asymmetric mixtures. Profir and coworkers [16,24] observed the spontaneous formation of the metastable racemic phase from aqueous solution, especially when it was carefully filtered. Depending on the operating conditions the stability was between a few minutes and 8 h. They also emphasized the effect of the solvent on the formed phase [24]. The low stability makes the identification and characterization of the metastable polymorph difficult. Phase preparation, separation and analysis have to be carried out as close together as possible. Similarities in the crystal structure of the metastable racemic compound and the enantiomer most likely account for the resemblances in the XRPD patterns and IR spectra.

6. Summary and outlook

As a result of the presented work a modified phase diagram of the mandelic acid enantiomers was introduced. The

heterogeneous equilibria possible and present in the binary and also ternary system could be consistently discussed with regard to different literature sources. A metastable racemic phase obtained both from the melt and the solution was identified as a monotropic modification of the stable racemate. The stability of this polymorph could be affected to a certain extent by impurities like the mandelic acid enantiomer and the decomposition products formed during melting. To get more information about the nature of this polymorph, detailed phase analysis is required. Temperature-resolved XRPD experiments can help to analyze the polymorph in situ, i.e. immediately after recrystallization from the melt. If single crystals might be obtained with a sufficient stability, the structure can be determined by X-ray single-crystal diffraction in order to explain the similarities to the enantiomer spectra observed. The main problems in studying the mandelic acid system are both its thermal decomposition and the low stability of the monotropic modification, making it very difficult to obtain the metastable phase pure and sufficiently stable to work with.

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