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Solid-Phase and Oscillating Solution Crystallization Behavior of (+)- and (−)-*N*-Methylephedrine

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ABSTRACT

This work involves the study of the solid-phase and solution crystallization behavior of the *N*-methylephedrine enantiomers. A systematic investigation of the melt phase diagram of the enantiomeric *N*-methylephedrine system was performed considering polymorphism. Two monotropically related modifications of the enantiomer were found. Solubilities and the ternary solubility phase diagrams of *N*-methylephedrine enantiomers in 2 solvents [isopropanol:water, 1:3 (Vol) and (2R, 3R)-diethyl tartrate] were determined in the temperature ranges between 15°C and 25°C, and 25°C and 40°C, respectively. Preferential nucleation and crystallization experiments at higher supersaturation leading to an unusual oscillatory crystallization behavior as well as a successful preferential crystallization experiment at lower supersaturation are presented and discussed.

Introduction

The significance of enantioseparation has increased due to the fact that FDA more and more restricts the introduction of racemic drugs. As a result, the manufacture of pure enantiomer drugs is of large concern for the pharmaceutical industry.[1,2] Apart from the asymmetric synthesis of optically pure substances, most of the drugs produced in the pharmaceutical industry during the chemical synthesis of chiral systems are 50:50 mixtures of both enantiomers. Usually, only one of the enantiomers shows the wanted physiological effect, what made it necessary to resolve racemic mixtures and compounds into single enantiomers. Among the existing processes applied for resolution, preferential crystallization is an efficient and cheap method for large-scale enantiomeric separation of chiral compounds.[3,4] Nevertheless, it requires that the racemic mixture crystallizes as a stable conglomerate, with a physical mixture of crystals comprising only of S and R with no measurable solid solution.[5] The same applies to preferential nucleation as a further technique to provide pure enantiomers from racemic mixtures[3,6] However, only 5%-10% of the racemic mixtures crystallize as a conglomerate system; racemic compounds account for the majority (90%-95%) of cases, and pseudoracemates (solid solutions) are seldomly established in literature.[5]

The studied model substance in this work is *N*-methylephedrine (NME). This chiral substance has previously been investigated by Wang et al.[7] and reported to exhibit conglomerate system properties. NME belongs to the class of ephedrines. A significant plant species of Ephedra-Ephedra sinica (Ma Huang) has long ago been used in traditional Chinese herbal medicine for diaphoretic, antiasthmatic, and diuretic effects.[8] (−)-ephedrine and (+)-pseudoephedrine account for the huge majority of the alkaloid content in the ephedra-containing products.[9] Recently, Ma Huang and ephedrine-containing products have been used as an appetite suppressant, as a stimulant, and as an aphrodisiac. Other herbal uses of Ma Huang include the treatment of low blood pressure, arthralgia, edema, enuresis, narcolepsy, cold and flu symptoms, asthma, and upper respiratory infections.[10] Moreover, ephedrine herbal preparations provide modest, short-term weight loss (<1 kg/month); however, there are few data to support the use of these preparations for a

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long-term weight loss or for the enhancement of athletic performance.[11]

Since the NME system is reported to be a conglomerate,[7] the application of preferential crystallization and nucleation is principally feasible for resolving the racemate. However, several limitations are known that complicate or constrict the separation process, such as polymorphy or other solid phases (e.g., competing polymorphs or a metastable racemic compound present), partial solid solutions, R-S epitaxial growth, or irreversible adsorption of the counter-enantiomer on selected crystal faces.[3] Examples are depicted by Courvoisier et al., Druot et al., Green et al., and Davey et al.[12-15]

In the NME system, Wiehler[16] and first own data already indicated complications in the phase diagram (possible additional solid phases), and also in preferential crystallization results showed poor enantiomeric excesses and yield. Therefore, this contribution is aimed at a comprehensive review of the solid-phase behavior and verifying the feasibility and performance of preferential crystallization for racemate resolution of NME. In addition, preferential nucleation experiments in a chiral solvent were included to check its suitability for enantioselective crystallization.

In the following, first a detailed solid-phase study will be presented using combined differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) analyses to ascertain the existence of a new polymorph. In this connection, the melt-phase diagram of the NME enantiomers will be established. Afterward, for solution crystallization experiments, solubility data of NME enantiomers and selected mixtures in 2 solvents, isopropanol/water, 1:3 (Vol) and (2R, 3R)-diethyl tartrate, will be shown and the ternary solubility phase diagrams derived. The chiral (2R, 3R)-diethyl tartrate was selected as solvent for preferential nucleation experiments, achiral isopropanol/water, 1:3 (Vol) as an appropriate solvent for preferential crystallization, respectively. Based on the phase diagrams and preliminary nucleation experiments, resolution procedures were deduced and preferential nucleation and crystallization resolutions performed. The related results are finally presented and discussed.

Experimental Section

Materials

(+)-(1S, 2R)-*N*-methylephedrine [(+)-NME] and (−)-(1R, 2S)-*N*-methylephedrine [(−)-NME] were supplied from Aldrich Chemical Company with purities of >99%. As solvents (+)-(2R, 3R)-diethyl tartrate and isopropanol (Merck KGaA, Darmstadt, Germany) with purities of >99% and deionized water (Millipore machine, Schwalbach, Germany) were used.

Phase Analyses

X-Ray Powder Diffraction

The solid phases of all samples were analyzed by XRPD to identify the polymorphic form present. The crystalline materials were characterized on a PANalytical X'Pert Pro diffractometer with Cu Kα radiation at 40 mA and 40 kV. The scanned 2θ region was 3°-40° with a step size of 0.017° and counting time of 50 s per step.

Differential Scanning Calorimetry

The melting behavior of the pure substances and different mixtures of the enantiomers was determined using a Setaram DSC 131 and DSC 111. Between 3- to 10-mg samples were used for the DSC measurements at a heating rate of 1 K/min, a temperature range between 25 and 130°C, and 8 mL/min helium as a purge gas.

HPLC

The enantiomeric compositions of the liquid and solid phases were analyzed by HPLC. A Eurocel OD stationary phase (column: 250 mm × 4.6 mm, 5 μm particles; Knauer, Germany) was applied. The eluent was 85% n-Hexane and 15% isopropanol with 0.1 vol% diethylamine. The chromatographic separation was performed at 25°C and an eluent flow rate of 1 mL/min. The wavelength used was 254 nm.

Polarimetry and Refractive Index Measurements

The enantiomeric compositions and total concentration of the liquid for the preferential crystallization experiments were analyzed by offline polarimetry (PerkinElmer Polarimeter 341 at wavelength of 325 nm, length of the cell: 100 mm) and offline refractive index measurements (Mettler-Toledo RE 40), both at 25°C.

Melting Behavior and Phase Identification

To prepare the stable modifications of NME, about 100 mg of differently composed mixtures of the enantiomers were dissolved in 2-3 mL isopropanol. The solvent was evaporated at room temperature, and the recrystallized solid was gently reduced to small particles. About 5-10 mg thereof was used for the DSC measurement as described previously.

To prepare metastable modifications of NME, about 50 mg of the pure enantiomers and various mixtures of both were molten and recrystallized by crash cooling at 0°C. After sample preparation, the obtained solids were analyzed by DSC and simultaneously subjected to XRPD analysis.

Solubility Measurements for N-Methylephedrine in Isopropanol:Water, 1:3 (Vol)

An isothermal measurement technique was used to determine solubilities of the (−)- and (+)-enantiomer and the racemic mixture of NME in isopropanol:water, 1:3 (Vol). Calculated amounts of the enantiomers were weighed and placed in small closed glass vessels. Definite amounts of solvent, not sufficient to dissolve the entire solid, were added with a syringe. The suspensions were stirred at constant and controlled temperature using a thermostated double-jacketed device. After ~24 h, the suspensions were filtered and the liquid phase mass and the dry residue mass after evaporation (m_{liquid}; m_{dry}) were determined at room temperature. The solubility was calculated in weight percent w (wt.-%) by:

$$w[wt.-\%] = \frac{m_{dry}}{m_{liquid}} \cdot 100 \quad (1)$$

The filtration equipment was tempered to ensure that no nucleation takes place during solid/liquid separation.

The error analysis determination for the solubility measurement of NME in isopropanol/water system for the absolute error was within ±0.14 wt.-%, and the relative error was smaller than 6%.

Solubility Measurements for N-Methylephedrine in (2R, 3R)-Diethyl Tartrate

The classical isothermal method was also applied here, and the same procedure as the one described previously was followed. The exception here is the analytical method used to determine the concentrations and enantiomeric compositions. For analysis, the saturated solution was filtered with a glass filter (pore size, 10 μm), and samples of 1-3 mL were withdrawn from the filtrate for double analysis. The concentrations and the enantiomeric excess were

determined by means of HPLC after dilution with isopropanol. Reproducibility of the solubility measurements was investigated at the lowest and the highest temperatures considered by performing 6 experiments under the same conditions. Standard deviation was determined to be 0.24 and 0.45 wt.-% at 25°C and 40°C, respectively.

Preliminary Nucleation Experiments for N-*Methylephedrine in (2R, 3R)-Diethyl Tartrate*

Preliminary nucleation (induction time) experiments were performed for the racemic mixture of NME, (+)-NME and (−)-NME in (2R,3R)-diethyl tartrate at 35°C. The experiments were carried out in a magnetically stirred double-jacketed glass vessel of 50 mL. Saturated solutions of about 10 g (35°C) were prepared for all the samples. The various saturated solutions were crash cooled to 1.0°C, and the induction time, $t_{ind,}$ at this temperature for appearance of first crystals, was determined by visual observation. The reproducibility of the nucleation measurements was studied by repeating 3 experiments under same conditions.

Preferential Nucleation Experiments for N-*Methylephedrine in (2R, 3R)-Diethyl Tartrate*

Preferential nucleation experiments have been performed for the racemic mixture of NME in (2R, 3R)-diethyl tartrate. Fifty grams of initial solutions were prepared according to solubility data at T_{sat} = 35°C, that is, concentration was w_{sat} = 49.20 wt.-%. The solutions were heated to 38°C and maintained for about 60 min at that temperature to ensure that even the smallest crystals were fully dissolved. The temperature was then decreased to a final crystallization temperature of 25°C with a cooling rate of 10 K/h. At certain times, liquid phase samples were collected for offline HPLC analyses of the enantiomeric excess in the solution. To obtain solid-free samples, a syringe with a filter was used.

Preferential Crystallization Experiments for N-*Methylephedrine in Isopropanol:Water, 1:3 (Vol)*

Two isothermal preferential crystallization experiments were performed. The crystallization process was monitored by offline HPLC and refractive index measurements. For the first experiment, 50 g of the initial solution according to solubility data [T_{sat} = ~20°C, w_{sat} = 3.8 wt.-%, initial composition (−)-NME/(+)-NME = ~51.5/48.5] was prepared. The stirred solution was heated to 28°C, and to ensure that all particles are dissolved, the mixture was maintained for about 60 min at that temperature. After cooling down to the crystallization temperature of T_C = 18.5°C (what is ~12% of the metastable zone width[7] of the racemic mixture), 50 mg of (−)-NME seed crystal powder (purity > 99%) was added. During the experiment, at definite time intervals, several liquid samples of ~1 g were withdrawn with a syringe with a filter to follow the crystallization progress. The samples were analyzed by offline polarimetry refractive index measurements. The second experiment was performed under similar conditions [initial composition (−)-NME/(+)-NME = ~50.25/49.75] but at lower crystallization temperature (T_C = 17°C) and thus higher initial supersaturation (~23% of the metastable zone width[7]).

Results and Discussion

Identification and Verification of the Solid-State Nature of N-*Methylephedrine and Its Melt Equilibria*

In the literature for the NME enantiomers, a simple conglomerate-forming system is reported without the description of any complications.[7] Wiehler[16] determined the melting temperature and enthalpy of the pure enantiomers with a reproducible behavior for several melting and recrystallization cycles. Decomposition of the NME enantiomers was never observed. However, for enantiomer mixtures after the first melting, subsequent melting and recrystallization steps provided a significant lower melting temperature (~5 K) for the solidus line. As a possible explanation, the authors proposed the formation of a metastable racemic compound. To verify the solid-state nature of NME and the corresponding melt phase equilibria of the chiral system, the solid phases before and after melting of different mixtures of NME enantiomers and their melting behavior were studied by DSC and XRPD measurements and will be elaborated in the following.

X-Ray Powder Diffraction Patterns for the Commercially Available and the Recrystallized Melt of the Enantiomers

In Figure 1, the XRPD patterns for the pure, commercially available (−)-NME and (+)-NME and the related recrystallized melt (already designated as (−)-NME_Modification II) are shown. Reference patterns simulated from the crystal structures reported for (−)-NME[17] and (+)-NME[18] are depicted as well. Surprisingly, the reference XRPD patterns for (+)- and (−)-NME are different from each other, suggesting that there might be polymorphism in the enantiomeric NME system.

It can be derived that the XRPD patterns of the commercially available (−)-NME and the subsequently recrystallized melt show significant different reflex positions. Thus, the enantiomers of NME exist in 2 different modifications, one obviously stable at room temperature (modification I) and one that forms after fast cooling from the melt (modification II). Significant reflex positions in the XRPD patterns are 12°, 12.5°, 15.6°, 16°, 19.2°, 20°, 22°, 24.3°, 25.2°, 27°, and 28.6° for the commercially available (−)-NME (modification I) and 8.5°, 11.4°, 17°, 18.5°, 22.8°, 23.4°, 26°, and 26.9° for the recrystallized melt (modification II).

When comparing them to the reference patterns, it becomes obvious that the powder patterns of the commercially available (−)-NME and (+)-NME correspond to the reference pattern of (−)-NME[17] and also to the powder pattern reported in former studies.[7,16] The XRPD pattern of the recrystallized (−)-NME mimics that of the (+)-NME reference pattern,[18] which verifies that both characterize modification II of NME.

The XRPD pattern for the racemic mixture of the commercially available NME enantiomers (not shown here) corresponds to the reference pattern of (−)-NME.[17] In case of a recrystallized racemic mixture, measured reflex positions correspond to the reference

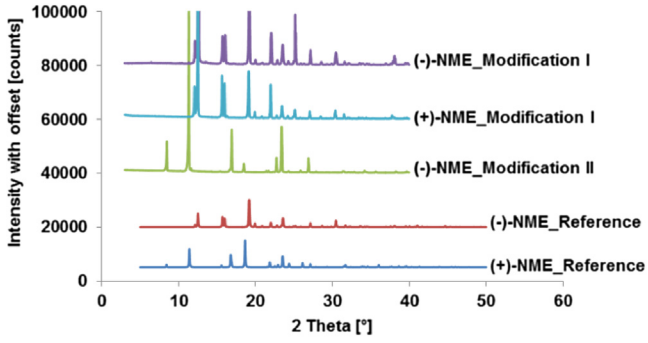

Figure 1. XRPD patterns (own measurements) obtained for the *N*-methylephedrine modifications: modification I [commercially available (−)-NME and (+)-NME] and modification II [recrystallized melt of (−)-NME]. Reference patterns for (−)-NME and (+)-NME were simulated from structural data (Cambridge Crystallographic Data Centre [CCDC] deposition numbers "CCDC 603318"[17] and "CCDC 293361,"[18] respectively).

pattern given for (+)-NME.[18] As a result, it can be derived that the enantiomers of both modifications form conglomerates in mixtures.

In a few cases, the XRPD pattern of the recrystallized racemic mixture revealed additional reflex positions that could not be allocated to the XRPD patterns of the stable or metastable NME enantiomers. Identification was not successful based on the very fast phase transformation into the stable modification.

Differential Scanning Calorimetry Measurements for the Enantiomer and the Racemic Mixture of Both Modifications

Sharp melting points were observed for the commercially available substances at 87.7°C for the (+)-NME and (−)-NME enantiomers (modification I) and at 62.5°C for the racemic mixture with melting enthalpies of 27.8 and 25.5 kJ/mol, respectively. Furthermore, sharp melting points were measured for the recrystallized melts at 86.5°C for the pure (−)-NME enantiomer (modification II) and at 61.7°C for the corresponding racemic mixture with melting enthalpies of 26.3 and 23.5 kJ/mol, respectively.

According to heat-of-fusion rule of Burger and Ramberger,[19] modifications I and II are in a monotropic relationship, with modification I the stable form and modification II metastable with respect to form I over the entire temperature range. The produced metastable modification II of the enantiomer showed a physical stability of more than 1 day, the corresponding racemic mixture of less than 30 min. Always transformation into stable modification I was confirmed.

Melt Phase Diagram of the N-*Methylephedrine Enantiomers*

In Figure 2, the measured melting data in the NME system are shown for the first and second melting, each representing the melt phase diagram of the NME enantiomers. "Ideal" liquidus curves have been calculated using the simplified Schröder-van Laar equation (Eq. 2)[5]

$$\ln(x_{En}) = \frac{\Delta H^{f}_{En}}{R} \cdot \left(\frac{1}{T^{f}_{En}} - \frac{1}{T} \right) \qquad (2)$$

with ΔH^{f}_{En} and T^{f}_{En} being the melting enthalpy and melting temperature of NME modifications I and II.

In Figure 2, stable equilibria are indicated by black lines and metastable equilibria by gray lines, that is the related data points by black or gray circles, respectively. There, the liquidus

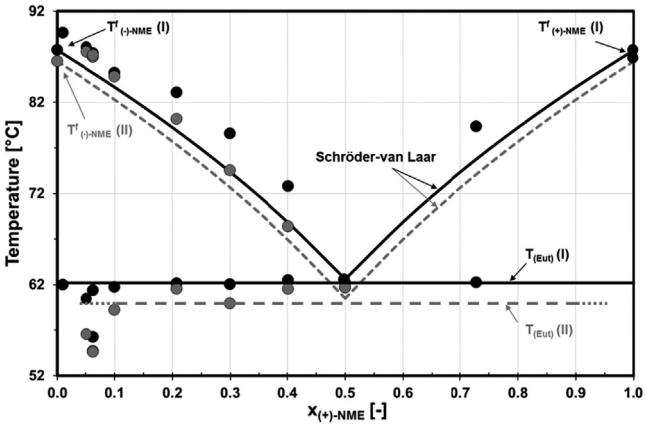

Figure 2. Melt phase diagram of the *N*-methylephedrine enantiomers. Melting data for first melting (modification I) in black circles and second melting (modification II) in gray circles. Calculated liquidus lines represent ideal behavior in the system and are used for comparison purposes.

temperatures of stable equilibria exceed those of metastable equilibria by 1-5 K. Furthermore, the associated solidus lines differ by ~2 K. Both results correspond to the mentioned findings of Wiehler[16] and explain it well. Although the eutectic temperature, $T_{(Eut)}$, and therewith the melting point of the racemic mixture of NME is almost perfectly predicted, the calculated liquidus lines deviate clearly from the data measured indicating a certain nonideal behavior of the system.

It should be noted that, as indicated by data points on the (−)-NME side of the phase diagram, solubility at solid state of particularly modification II of NME enantiomers in a rather narrow region is possible but could not be verified within this study. For that reason, the end of the corresponding solidus line is let open in Figure 2. The results obtained from DSC and XRPD measurements confirm polymorphism (monotropy) in the NME system and prove for both polymorphs conglomerate behavior.

Solubilities and Ternary Solubility Phase Diagrams

Table 1 shows the solubility data of the enantiomer and racemic mixture of NME in isopropanol:water, 1:3 (Vol) and (2R, 3R)-diethyl tartrate, respectively. The resulting ternary solubility phase diagrams are presented in Figures 3 and 4.

Comparatively, much less amount of NME enantiomer and racemic mixture is soluble in isopropanol:water, 1:3 (Vol) than in (2R, 3R)-diethyl tartrate. The solubilities differ from each other in more than 1 magnitude. However, in both solvents, a strong effect of temperature on solubility is observed, slightly more pronounced for (2R, 3R)-diethyl tartrate as solvent. As expected, solubilities of the racemic mixture exceed those of the enantiomer in both solvents. In case of the solvent system isopropanol:water, 1:3 (Vol) the solubility data correspond well with the literature data.[7]

As can be seen, the solubility isotherms differ significantly in shape. In ideal conditions, the solubility of the racemic mixture is expected to be twice the solubility of the enantiomers, which implies that the solubility ratio (α_{mol}) is equal to 2 according to the "double solubility" rule proposed by Meyerhoffer.[21] Table 1 depicts the corresponding calculated solubility ratios (α_{mol}). The α_{mol} value of NME in (2R, 3R)-diethyl tartrate is lower than 2 (1.7 and 1.5 at 25°C and 40°C, respectively). When the α_{mol} values are lower than 2, it implies a decrease in solubility of one enantiomer in the presence of the other enantiomer. In the case of isopropanol:water, 1:3 (Vol) as solvent, the ratio exceeds 2 (2.2 and 3.1 at 15°C and 25°C, respectively). Consequently, the solubility of one enantiomer increases considerably by the presence of the other one.

Preferential Nucleation Experiments

In the preliminary nucleation experiments, a pronounced delay of the appearance of first crystals for the racemic mixture of NME was observed. The induction time, $t_{ind,}$ was determined to be 500 ± 0.76 s, longer compared to (+)-NME with 364 ± 0.58 s and (−)-NME with 240 ± 0.57 s, respectively. This nucleation delay behavior of the racemic mixture of NME was expected based on the α_{mol} values determined to be ~1.5-1.7 for this system. Wang et al.[22] reported that classical nucleation theory can explain this observed phenomenon. According to this theory, the induction time of the racemic mixture will depend on the concentrations of the 2 enantiomers. The solubility of the racemate is larger than that of the enantiomer, but the α_{mol} value is smaller than 2. In this situation, though more molecules are in solution, both (+)-NME and (−)-NME molecules are required to arrange in equal quantities to form racemic NME. Consequently, the effective concentration to form homochiral nuclei is in reality only half the total concentration. Since α_{mol} <2, the effective enantiomer concentration

Table 1
Solubilities of the (−)-Enantiomer and the Racemic Mixture of *N*-Methylephedrine in Isopropanol:Water, 1:3 (Vol) and (2R,3R)-Diethyl Tartrate as a Function of Temperature (Own and Literature Data[7])

Isopropanol:Water; 1:3 (Vol)						(2R, 3R)-Diethyl Tartrate			
t in °C	Enantiomer		Racemic Mixture		Solubility Ratio	t in °C	Enantiomer	Racemic Mixture	Solubility Ratio
	wt.-%	wt.-%	wt.-%	wt.-%	α_{mol}		wt.-%	wt.-%	α_{mol}
15	1.2	1.1[7]	2.6	2.7[7]	2.2	25	23.7	42.0	1.7
20	1.3	1.4[7]	3.8	3.6[7]	2.9	30	28.0	46.5	1.6
25	1.6	1.7[7]	4.7	4.9[7]	3.1	35	30.3	49.2	1.6
30		2.2[7]		6.3[7]		40	36.3	55.6	1.5

Solubility ratio, α_{Mol}, as ratio of mol fraction solubilities of the racemic mixture to the enantiomer.

[(+)-NME:(−)-NME = 0.5:0.5] is smaller than that of the pure enantiomer. Hence, the induction time of the racemate should exceed that of the pure enantiomer. According to the results obtained from these preliminary nucleation experiments, (−)-NME with the shortest induction time might selectively nucleate first (preferential nucleation) when cooling a racemic mixture of NME in (2R,3R)-diethyl tartrate solution. This is considered as a possible resolution method.

On the basis of the measured solubility and the preliminary nucleation data, primary resolution experiments of racemic mixture of NME in (2R,3R)-diethyl tartrate were designed and performed. In Figure 5, the enantiomeric excess is presented as a function of time for a preferential nucleation experiment of NME in (2R,3R)-diethyl tartrate.

The sudden jump of the enantiomeric excess to almost 9% ee of (+)-NME in the solution indicates a rapid crystallization of (−)-NME after nucleation. The vertical dashed line designates the maximum enantiomeric excess point reached. Afterward, the counter-enantiomer (+)-NME started crystallizing, the solution composition thus tended in the direction of the racemic composition (ee = 0%). After the composition reached 0% ee, further crystallization of (+)-NME gave rise to (−)-NME in the liquid phase to a minimum point of approximately −6% ee at about 15 min after onset of nucleation. At this point again (−)-NME nucleates and crystallizes leading to an opposite trend of the enantiomeric excess in the solution, finally, becoming equal in amount of enantiomeric excess of both enantiomers. The whole process came to an end, as the liquid hold up finished.

The observed nucleation behavior of NME is exceptional in the fact that an oscillating behavior of the resolution trajectory is obtained, that is, one phase crystallizes followed by nucleation and crystallization of the other one. This makes the resolution difficult and not attractive for application.

Preferential Crystallization

In Figure 6, the enantiomeric excess of the solution and the masses of the enantiomers crystallized are shown as a function of time for 2 exemplary preferential crystallization experiments differing in the level of initial supersaturation. The enantiomeric excesses and the crystallized masses of the enantiomers in the

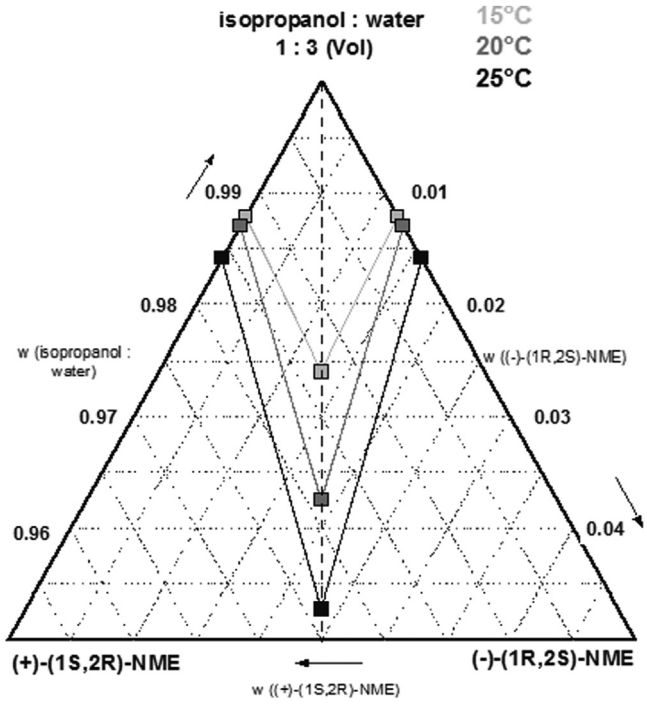

Figure 3. Ternary solubility phase diagram of *N*-methylephedrine enantiomers in isopropanol:water, 1:3 (Vol) including solubility isotherms at 15°C, 20°C, and 25°C; axes in weight fractions; *w* (+)-NME and *w* (−)-NME ≤0.05, lines are guide to the eye.

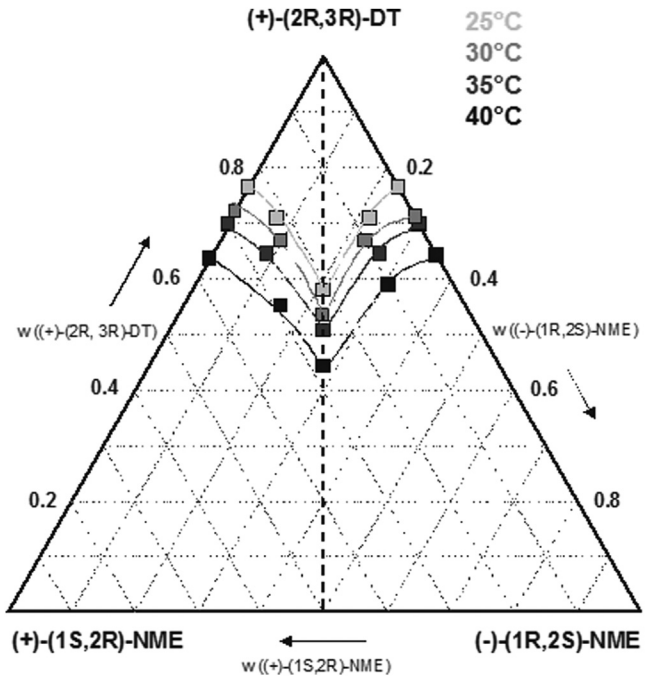

Figure 4. Ternary phase diagram of the *N*-methylephedrine enantiomers in (2R, 3R)-diethyl tartrate including solubility isotherms between 25°C and 40°C; axes in weight fractions; *w* (+)-NME and *w* (−)-NME ≤1.0; lines are guide to the eye.[20]

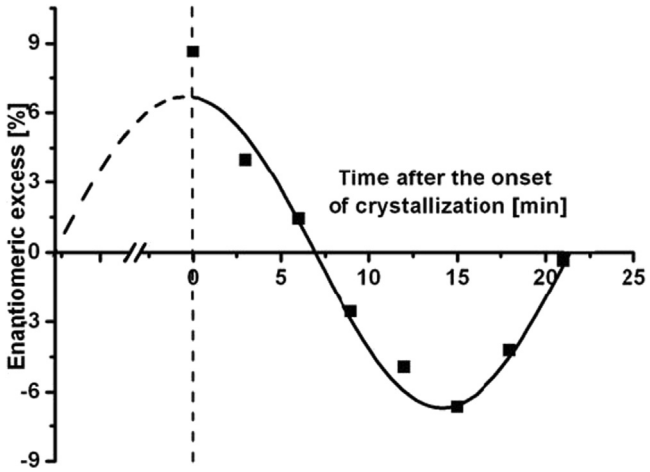

Figure 5. Enantiomeric excess as a function of time for a preferential nucleation experiment of racemic NME in (2R,3R)-diethyl tartrate. Dotted line through the maximum enantiomeric excess point is shown.

product were calculated according to the offline data (polarimeter and refractive index measurements).

In the first experiment (Fig. 6, left) after cooling down the clear solution and seeding with (−)-NME seed crystals (modification I), the enantiomeric excess increased to approximately +2%, that is, the eutectic line was crossed and exceeded significantly. The calculated mass for (−)-NME (modification I) increased due to crystallization and the calculated mass of (+)-NME remained almost 0 for the first ~18 min (a → b, Fig. 6, left). After ~18 min, (+)-NME nucleated and crystallized caused by the steadily increasing supersaturation with respect to the enantiomer remaining in solution. The enantiomeric excess decreased to 0%, as the calculated masses of both enantiomers increased continuously (b → c). This crystallization behavior is typically for enantioseparation by preferential crystallization and was also observed in previous works of our group, for example, for the threonine system studied.[23-25]

The second experiment (Fig. 6, right) was performed under similar conditions as the first one. The initial enantiomeric excess was slightly smaller, but the initial supersaturation of the counter-enantiomer was significantly higher (3 K vs. 1.5 K in terms of temperature). After cooling down the clear solution and seeding with (−)-NME crystals (modification I) the enantiomeric excess increased as result of (−)-NME crystallization and the eutectic line is crossed reaching a maximum ee of almost +1%. However, as indicated by the masses of (−)-NME and (+)-NME formed, simultaneously to (−)-NME at a lower extent also (+)-NME crystallized (a → b, Fig. 6, right). Afterward, the enantiomeric excess decreased steeply to almost −1.5% (b → c) and after ~20 min reversed again the slope and increased slowly to nearly 0, that is racemic composition (c → d). The calculated masses of both enantiomers increased continuously in both sections with different slopes, that is, much more quickly between b → c [with crystallization rate of (+)-NME exceeding that of (−)-NME] and rather weakly between c → d [with a slightly higher crystallization rate of (−)-NME compared to (+)-NME].

Thus, the second experiment has shown clearly an oscillatory behavior in preferential crystallization. Even in all sections, a → b → c → d both enantiomers crystallized concurrently, the rate of crystallization of the 2 enantiomers differed providing always one enantiomer preferentially. This crystallization behavior is clearly different from the first experiment. An explanation could be the influence of the polymorphic modifications, that is, at first (−)-NME (modification I) crystallized preferentially according to seeding with this species, followed by nucleation of (+)-NME (modification II) as a result of the high supersaturation in the experiment (double that of experiment 1). Due to its increasing supersaturation with respect to (+)-NME, finally again the counter (−)-enantiomer crystallized at elevated rate and the solution ee approaches the equilibrium value of 0%.

The final solid phases in both experiments were (+)- and (−)-NME in the stable modification I.

Conclusions and Summary

In this work, the solid-phase and solution crystallization behavior of the NME enantiomers have been studied via detailed phase equilibria measurements in melt and solution as well as exemplary preferential nucleation and crystallization experiments.

Two NME polymorphs have been allocated and characterized by both XRPD pattern and DSC measurements. The NME polymorphs are in monotropic relationship with each other. Both

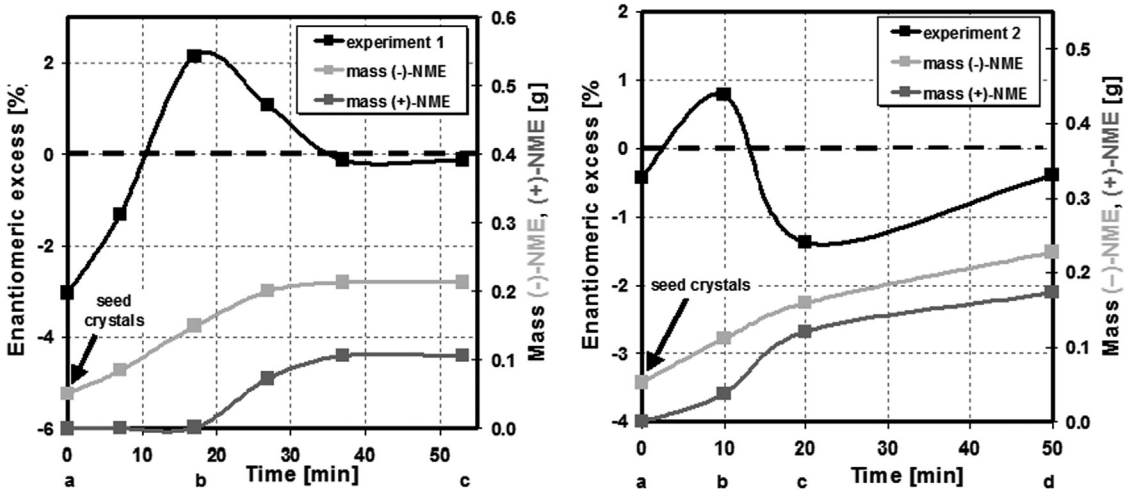

Figure 6. Enantiomeric excess of the mother liquor (black) and calculated masses of (−)-NME and (+)-NME produced (light gray and middle gray) as a function of time after seeding for preferential crystallization experiments 1 (left) and 2 (right). [The enantiomeric excess (+)-ee or (−)-ee corresponds to the optical rotation, for example (+)-NME or (−)-NME in excess in the mother liquor.]

modifications show conglomerate behavior in the binary enantiomeric system, verified by the melt phase diagram determined. The possible appearance of the metastable modification can explain the ambiguous results reported early on by Wiehler.[16]

In the preferential nucleation and crystallization experiments performed at higher supersaturation, an oscillatory crystallization behavior was observed, characterized by alternating preferential crystallization of the 2 NME enantiomers. Such a behavior was already described for other chiral systems. For instance, Gervais et al.[26] and Potter et al.[27] reported on a similar oscillating behavior in solution for (+)-/(−)-5-ethyl-5-methylhydantoin and the (+)- and (−)-enantiomers of 2-azabicyclo[2.2.1]hept-5-en-3-one in preferential crystallization attempts, respectively. In the first case, they attributed this phenomenon to diffusion limitation during growth of the pure enantiomer phase as a result of missing stirring the solution that lead to an increase in supersaturation and thus nucleation of the counter-enantiomer. In addition, in the second case, the phenomenon was explained by the high α values (α = solubility of racemic mixture/solubility of one enantiomer) in the system and by the formation of "twins" (actually epitaxy) between the crystals of the 2 enantiomers. They attributed this phenomenon to be caused by a higher supersaturation and lower diffusion during nucleation and growth of the crystal.

In our case, the oscillatory resolution behavior obtained most probably is caused by the appearance of the metastable modification of the NME enantiomer that interferes with the resolution. The determined melt phase diagram of the NME enantiomers and the preferential nucleation experiments both confirm appearance of modification II at higher supersaturation conditions (e.g., achieved by crash cooling of the melts). In addition, in preferential crystallization experiment 2, the significantly higher initial supersaturation (almost double that of reference experiment 1) resulted in an oscillatory crystallization. The observed behavior can basically be explained by the Ostwald's rule of stages,[28] meaning that the metastable form always crystallizes first followed by the thermodynamically stable form.

However, with preferential crystallization experiment 1, the results have also shown that at sufficiently low supersaturation, preferential crystallization can be successfully performed also in this system. To improve the outcome quantifying yields and purities, much more work is required.

The same refers to deeper insights into the mechanisms of the oscillatory crystallization behavior of the NME system, which necessitates detailed fundamental studies on the crystal behavior level and comprehensive solid-phase analysis.

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