Journal of chemical & engineering data

Article

pubs.acs.org/jced

Solid Phase Behavior in the Chiral Systems of Various 2-Hydroxy-2-phenylacetic Acid (Mandelic Acid) Derivatives

Jan von Langermann,*[,†,‡] Erik Temmel,[‡] Andreas Seidel-Morgenstern,[‡,§] and Heike Lorenz*[,‡]

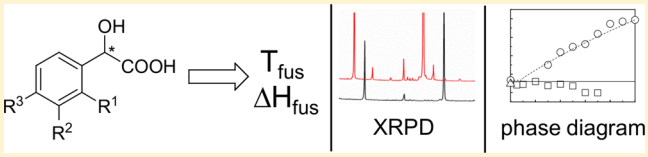
[†]Institute of Chemistry, University of Rostock, Albert-Einstein-Strasse 3A, 18059 Rostock, Germany

[‡]Max Planck Institute for Dynamics of Complex Technical Systems, Sandtorstrasse 1, 39106 Magdeburg, Germany

[§]Chemical Process Engineering, Otto von Guericke University Magdeburg, Universitätsplatz 2, 39106 Magdeburg, Germany

Supporting Information

ABSTRACT: The solid phase behavior of a series of monosubstituted F-, Cl-, Br-, I-, and CH_3- and two 2,4-halogen-disubstituted 2-hydroxy-2-phenylacetic acid (mandelic acid) derivatives was investigated. The study includes detailed information about melting temperature, melting enthalpy, X-ray diffraction data, as well as selected binary phase diagrams of the respective chiral systems. Aside from the known metastable conglomerate 2-chloromandelic acid, evidence for two more metastable conglomerates was found.



1. INTRODUCTION

Enantiomers are pairs of chiral molecules that are fully identical except its mirror-image symmetry. These closely related molecules possess identical physical-chemical properties, e.g., melting and boiling point, with the only exception that plane-polarized light is rotated to different directions. Aside from these fundamental physical-chemical properties enantiomers also show strong differences in biological activity.[1] While one enantiomer may result in the desired positive effect, its counterpart molecule could be harmful. A well-known example is the drug Contergan, which contained thalidomide as a racemic mixture and was used as a mild sedative for pregnant women.[2] While the target enantiomer, (+)-(*R*)-thalidomide, results in the desired effect, the other enantiomer, (−)-(*S*)-thalidomide, causes unfortunately strong teratogenic effect at the unborn child. As a result up to 20000 children were born worldwide with body deformities, which eventually forced pharmaceutical companies to remove the drug from the market in 1961 (Europe) and 1962 (Canada).

Consequently, nowadays almost all pharmaceuticals are provided as enantiopure preparations to prevent such negative effects. Unfortunately most chemical syntheses of chiral substances on industrial scale result in racemic mixtures, which require subsequent enantioseparation steps. Well-established techniques include chiral chromatography, enantioselective membrane separation, and crystallization.[3−5] From these methods crystallization has repeatedly proven its applicability and cost effectiveness, especially on an industrial scale.[6] However, detailed information about the physical−chemical properties of these substances, including their phase diagrams, is essential to plan and optimize crystallization processes.[7,8] Herein enantiomeric substances show three basic types of phase behavior (Figure 1).[1]

(a) Binary (Racemic) compounds, which represent the vast majority, show a crystalline racemate that consists of both enantiomers in equal and ordered quantities in its crystal structure. Within a binary phase diagram two symmetrical eutectics are found, shown in Figure 1A. Enantioselective crystallization is only feasible from enriched solutions, e.g., obtained via chromatography or partially selective synthesis.[9,10]

(b) Simple eutectics (conglomerates) are basically equimolecular mixtures of two crystalline enantiomers that are, in theory, separable via mechanical techniques. The corresponding phase diagram shows a single eutectic exactly at a mole fraction of 0.5, Figure 1B. Most importantly, pure enantiomers can be obtained directly from a racemic mixture, which represents a significant advantage from a crystallization separation point of view. Thus, conglomerates are typically preferred over racemic compounds.

(c) Solid solutions (pseudoracemates), which are relatively rare for chiral substances, show an extraordinary phase behavior. For this type any mixture of enantiomers forms a unique crystalline state with a stochastic distribution of the elementary building blocks, which also explains its designation as solid solutions. Phase diagrams show at the racemic composition a melting temperature maximum (I), a melting temperature minimum (III), or an identical melting temperature (II) as found for the enantiomers, Figure 1C. In theory such pseudoracemates are basically inseparable by classical crystallization processes. However, processes with a series of crystallization steps (fractional crystallization) may be used for enantioenrichment.[11,12]

In this study 18 substituted 2-hydroxy-2-phenylacetic acid (mandelic acid) derivatives were synthesized, in racemic and enantiomerically pure form, and their physical−chemical properties investigated and discussed in detail (Table 1). The

Received: September 16, 2014
Accepted: January 9, 2015

DOI: 10.1021/je500845d
J. Chem. Eng. Data XXXX, XXX, XXX−XXX

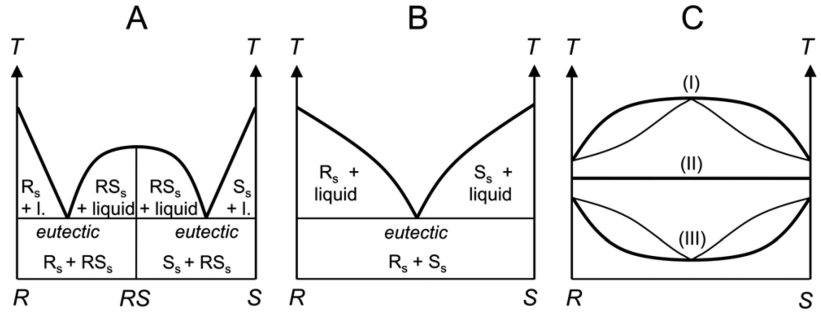


Figure 1. Schematic binary phase diagrams of chiral substances that form at racemic composition (A) a binary compound, (B) a simple eutectic, and (C) solid solutions; R_s – (*R*)-enantiomer, solid, S_s - (*S*)-enantiomer, solid, RS_s – racemic compound, solid, l. - liquid.

Table 1. Specifications of the Investigated Mandelic Acid Derivatives

entry	R^1	R^2	R^3	name	CAS no.	origin	final mole fraction purity	analysis method
1	H	H	H	mandelic acid	included as literature reference			
2	F	H	H	2-fluoromandelic acid	included as literature reference			
3	H	F	H	3-fluoromandelic acid	included as literature reference			
4	H	H	F	4-fluoromandelic acid	included as literature reference			
5	Cl	H	H	2-chloromandelic acid	racemic: 10421-85-9	synthesis	> 0.995	HPLC, DSC, XRPD
					(*S*)-enantiomer: 52950-19-3	synthesis	> 0.995	HPLC, DSC, XRPD
6	H	Cl	H	3-chloromandelic acid	racemic: 16273-37-3	synthesis	> 0.995	HPLC, DSC, XRPD
					(*S*)-enantiomer: 32222-43-8	synthesis	> 0.995	HPLC, DSC, XRPD
7	H	H	Cl	4-chloromandelic acid	racemic: 492-86-4	synthesis	> 0.995	HPLC, DSC, XRPD
					(*S*)-enantiomer: 76496-63-4	synthesis	> 0.995	HPLC, DSC, XRPD
8	Br	H	H	2-bromomandelic acid	racemic: 7157-15-5	synthesis	> 0.995	HPLC, DSC, XRPD
					(*S*)-enantiomer: 52923-26-9	synthesis	> 0.995	HPLC, DSC, XRPD
9	H	Br	H	3-bromomandelic acid	racemic: 49839-81-8	synthesis	> 0.995	HPLC, DSC, XRPD
					(*S*)-enantiomer: 52950-20-6	synthesis	> 0.995	HPLC, DSC, XRPD
10	H	H	Br	4-bromomandelic acid	racemic: 6940-50-7	synthesis	> 0.995	HPLC, DSC, XRPD
					(*S*)-enantiomer: 123484-90-2	synthesis	> 0.995	HPLC, DSC, XRPD
11	I	H	H	2-iodomandelic acid	racemic: 89942-35-8	synthesis	> 0.995	HPLC, DSC, XRPD
12	H	I	H	3-iodomandelic acid	racemic: 873963-87-2	synthesis	> 0.995	HPLC, DSC, XRPD
13	H	H	I	4-iodomandelic acid	racemic: 70466-89-6	synthesis	> 0.995	HPLC, DSC, XRPD
14	CH_3	H	H	2-methylmandelic acid	racemic: 85589-35-1	synthesis	> 0.995	HPLC, DSC, XRPD
15	H	CH_3	H	3-methylmandelic acid	racemic: 65148-70-1	synthesis	> 0.995	HPLC, DSC, XRPD
					(*S*)-enantiomer: 132748-42-6	synthesis	> 0.995	HPLC, DSC, XRPD
16	H	H	CH_3	4-methylmandelic acid	racemic: 18584-20-8	synthesis	> 0.995	HPLC, DSC, XRPD
					(*S*)-enantiomer: 75172-62-2	synthesis	> 0.995	HPLC, DSC, XRPD
17	Cl	H	F	2-chloro-4-fluoromandelic acid	racemic: 365525-72-0	synthesis	> 0.995	HPLC, DSC, XRPD
					(*S*)-enantiomer: 1630325-00-6	synthesis	> 0.995	HPLC, DSC, XRPD
18	F	H	Cl	4-chloro-2-fluoromandelic acid	racemic: 1214345-56-8	synthesis	> 0.995	HPLC, DSC, XRPD
					(*S*)-enantiomer: 1630519-50-4	synthesis	> 0.995	HPLC, DSC, XRPD

selected derivatives comprise o-, m-, and p-substituted compounds with halogen atoms Cl, Br, and I and a methyl group as potential substitutents (Table 1). This unique class of substances is considered as highly valuable intermediates for the direct synthesis of various pharmaceuticals.[13,14] Furthermore, mandelic acid and also its derivatives are used as chiral resolving agents. Despite its synthetic values detailed crystallization relevant physical-chemical data is only known for a few main mandelic acid derivatives. For example, 2-chloromandelic acid is an alternative intermediate for the synthesis of (*S*)-clopidogrel hydrogensulfate, a major pharmaceutical drug (commercially produced by Bristol-Myers Squibb and Sanofi, trade name: Plavix). The solid phase behavior of 2-chloromandelic acid was recently intensively studied in detail and its unusual behavior reported.[10,15−19] It was characterized as a racemic compound with a eutectic at a mole fraction of x = 0.56 and a corresponding eutectic temperature of 360.7 K. In addition, a metastable conglomerate was found with a eutectic temperature of ca. 356.2 K.[19] This detailed knowledge allows the use of other potential crystallization pathways via the conglomerate by avoiding a crystallization of the racemic compound. Another major example is 3-chloromandelic acid that exhibits different polymorphic forms for the racemic mixture and enantiomer.[20−22] These polymorphs can be transformed into each other by a careful selection of crystallization procedures.

2. EXPERIMENTAL SECTION

2.1. Chemicals. All monosubstituted derivatives of benzaldehyde, sodium cyanide, and sodium sulfate were obtained from Sigma-Aldrich, USA. 2-Chloro-4-fluoro and 4-chloro-2-fluorobenzaldehyde and the hydroxynitrile lyase from

DOI: 10.1021/je500845d
J. Chem. Eng. Data XXXX, XXX, XXX−XXX

Manihot esculenta were a gift from Julich Fine Chemicals (now Codexis), Germany/USA. Diisopropylether and poly(vinyl alcohol) (as Mowiol 18-88) was purchased from Fluka, Germany. Concentrated hydrochloric acid and concentrated acetic acid were obtained from Merck, Germany. Methanol was provided by Fisher Scientific, USA. Triethylammonium acetate was used as 1 mol·kg^{-1} solution from Calbiochem, (Merck Millipore, Germany). The immobilization reagent Sylgard 184 was a product sample from Dow Corning, USA. Deionized water was used throughout the study.

2.2. Synthesis of Mandelic Acid Derivatives. All required mandelic acid derivatives were synthesized from the respective benzaldehyde derivatives and HCN yielding the benzaldehyde cyanohydrin, which was hydrolyzed to form the final product (Figure 2). All reactions including or forming hydrogen cyanide were executed within a well ventilated fume hood with an electrochemical HCN-detector for self-protection.

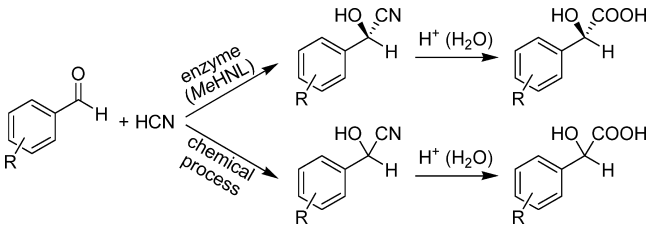


Figure 2. Synthesis of mandelic acid derivatives (enantiomerically pure and racemic mixture).

The required amount of sodium cyanide (5-fold excess) was dissolved in water and chilled to 5 °C. Afterward concentrated hydrochloric acid was slowly added to the cyanide mixture until pH < 2 was obtained. Throughout the whole procedure the solution temperature was kept below 10 °C to prevent evaporation of toxic hydrogen cyanide. The resulting aqueous solution was extracted 3 times with diisopropylether and the resulting diisopropylether-solutions were combined. (A) Enantiopure mandelic acid derivative: The respective benzaldehyde derivative and immobilized enzyme were added to the hydrogen cyanide solution and stirred overnight at room temperature. Immobilized enzyme was obtained as recently reported.[23] Afterward the immobilized enzyme was filtered off, the resulting solution dried with sodium sulfate and the solvent evaporated under reduced pressure. The resulting raw cyanohydrin was then refluxed with an excess of concentrated hydrochloric acid for 2 h. The resulting solution was allowed to cool to room temperature and evaporated to dryness. The resulting raw material derivative was then purified by recrystallization from toluene. If required multiple recrystallization steps were executed. (B) Racemic mandelic acid derivatives were obtained from a nonselective chemical reaction of the corresponding benzaldehyde derivative with hydrogen cyanide. For this purpose a biphasic system (50% (v/v)) consisting of 0.05 mol·kg^{-1} citrate-phosphate buffer pH 6 and the above-mentioned hydrogen cyanide solution was allowed to react at room temperature overnight. The resulting mixture was subjected to the identical purification protocol as described for the synthesis of enantiopure mandelic acid derivatives. Chemical identity as well as purity of the materials was determined via XRPD, NMR, DSC, and (chiral) HPLC analyses. A final mole fraction purity of > 0.995 was found within all shown investigations (see also Table 1). Exemplary analysis results are assembled in the Supporting Information (SI) file available with this article.

2.3. DSC Analysis. DSC experiments were performed with a DSC131 differential scanning calorimeter from Setaram (France). Pure samples were crushed into a fine powder, (0.010 to 0.015) g thereof given into an aluminum crucible, and then used for the determination of melting point and enthalpy. For the investigation of binary phase diagrams calculated amounts of racemate and enantiomer were cogrounded and dissolved in acetone. After evaporation of the solvent, the solid was crushed again into a fine powder and ca. 15 mg thereof used for DSC analysis.

DSC measurements were performed in closed aluminum crucibles at a heating rate of 2 K·min^{-1} in a temperature range from 30 to 140 (160 °C, if higher melting temperatures were found) and highly pure helium with a mole fraction purity of > 0.99999 % (5.0 purity) as purge gas. The DSC apparatus was regulary calibrated against temperature and enthalpy of fusion of water and highly pure standard materials (indium, tin, lead) also with respect to the heating rates applied. The determination of melting/liquidus and solidus temperatures from the DSC curves was executed as described in previous work.[24,25]

2.4. XRPD Analysis. All solid samples were analyzed throughout this study by X-ray powder diffraction (XRPD) to identify the present solid phases. For this purpose a X'Pert Pro diffractometer (PANalytical GmbH, Kassel, Germany) with Cu Kα radiation was used. Measurements covered a 2Theta-range from 3 to 40° with a step size of 0.0167° and a counting time of 50 s per step. Mostly samples were studied on (background-free) Si single crystal discs.

2.5. Induction of Metastable Conglomerates. 2-Bromomandelic acid or 2-chloro-4-fluoromandelic acid was grounded to a fine powder and then completely dissolved in acetone. A few very small crystals (typically 2−4 particles) of the metastable conglomerate of 2-chloromandelic acid were added and the resulting mixture covered with a punctured Parafilm, which facilitated a very slow evaporation process. After total evaporation of the solvent the resulting solid was carefully ground and then subjected to analysis with DSC and XRPD.

2.6. HPLC Analysis. The enantiomeric composition and purity of the investigated phases of mandelic acid and its derivatives was verified before DSC and XRPD measurements via High Performance Liquid Chromatography (HPLC). All chromatographic analyses were performed with an Agilent HP 1200 using the same chiral stationary phase column (Chirobiotic T 250·4.6 mm, particle size: 5 μm) and constant parameters to ensure comparability between the results. The eluent consisted of 80 % 1 % (m/v) triethylammonium acetate in H_2O and 20 % methanol and was adjusted to a pH of 4.02 with concentrated acetic acid. A temperature of 25 °C and a flow of 0.5 mL·min^{-1} were applied to achieve reasonable retention times. The samples were dissolved in the mobile phase and adjusted to a concentration of one weight percent (c_{inj} = 1 % (m/v)). A total of 5 μL of all solutions were injected into the system and investigated with a diode array detector (DAD) at 254 nm.

An exemplary chromatogram, retention times, and separation factors for all studied mandelic acid derivatives are reported in the SI, Figure SI-18 and Table SI-1. Regarding the shape of the chromatographic elution profiles of the racemic mixtures (see

DOI: 10.1021/je500845d
J. Chem. Eng. Data XXXX, XXX, XXX−XXX

Table 2. Melting Temperatures and Enthalpy of Melting of Mandelic Acid and Its Derivatives[a]

	enantiomer		racemic mixture[b]	
entry	melting temp, $T_{fus,E}$/K	melting enthalpy, $\Delta H_{f,us\ E}$/kJ·mol^{-1}	melting temp, $T_{fus,R}$/K	melting enthalpy, $\Delta H_{fus,\ R}$/kJ·mol^{-1}
1	404.7[24]	24.5	393.4[24]	25.6
			381.6[29] (metastable racemic compound)	24.6 (metastable racemic compound)
			380.2−381.2[30,31]	n.d.
2	361.8[28]	19.1	388.3[27,28]	31
	363.2[32]	20.9	390.2[32]	30.1
3	394.2[28]	22.3	368.4[27,28] ("I")	21 ("I")
			376.8 ("II")	23 ("II")
	394.2[32]	24.3	370.2[32]	24.7
4	425.8[28]	27.2	408.9[27,28]	30
	426.2[32]	30.6	403.2[32]	29.3
5	392.4[19]	24.6	(i) racemic compound: 363.4[19] ("form α") n.d.[19] ("form β") (ii) metastable conglomerate: 356.2[19]	(i) racemic compound: 23.2 ("form α") n.d. ("form β") (ii) metastable conglomerate: 21.2
	392.6[32]	24.7	358.7[32] ("conglomerate")	20.1 ("conglomerate")
	391.9[17]	24.9	(i) racemic compound: 363.1[17] ("form α") n.d.[17] ("form β") (ii) metastable conglomerate: 358.2 ("form γ")[17]	(i) racemic compound: 23.1 ("form α") n.d. ("form β") (ii) metastable conglomerate: 21.4 ("form γ")
6	378.8[21]	26.2	390.4[21]	28.0
	376.4[20] ("$(R)_1$", stable)	22.6 ("$(R)_1$")	391.1[20] ("$(RS)_1$")	27.9 ("$(RS)_1$")
	365.1 ("$(R)_2$", metastable)	14.6 ("$(R)_2$")	384.4 ("$(RS)_2$")	17.8 ("$(RS)_2$")
	380.2[32]	25.1	388.2[32]	27.2
7	392.7	27.1	393.2	16.2
	394.2[32]	23.0	394.2[32]	27.2
8	392.5	22.4	(a) racemic compound: 359.9 (b) metastable conglomerate: 357.9	(a) racemic compound: 22.3 (b) metastable conglomerate: 23.1
	395.2[32]	25.2	362.2 (racemic compound)[32]	20.5
9	376.2	23.0	392.7	30.1
	378.2[32]	24.7	394.2[32]	30.1
10	400.7	17.2	391.2	17.8
	404.7[32]	23.9	392.2[32]	23.9
11	n.d.	n.d.	382.1	25.0
12	n.d.	n.d.	370.1	24.6
13	n.d.	n.d.	415.3	30.4
14	n.d.	n.d.	376.9	21.5
15	382.8	29.2	365.5	25.6
16	404.6	22.4	416.9	25.6
17	405.9	20.1	(a) stable racemic compound: 370.7	(a) racemic compound: 18.2
			(b) metastable conglomerate: n.d.	(b) metastable conglomerate: n.d.
18	380.9	15.1	363.6	17.7

[a]n.d., not determined; standard uncertainties for own data, u, are $u(T_{fus}) = 0.45$ K and $u(\Delta H_{fus}) = 0.6$ kJ·mol^{-1}; compound **5** was investigated 15 times for reproducibility analysis, all other compounds were investigated at least twice. [b]In case that no phase information is given, a racemic compound is present as solid state form.

J. Chem. Eng. Data XXXX, XXX, XXX−XXX DOI: 10.1021/je500845d

the SI, Figure SI-18), there is evidence that the adsorption behavior of the enantiomers is based on different adsorption isotherms, which is remarkable for chiral compounds. It appears that the (*R*)-enantiomers exhibit a favorable Langmuir-isotherm for all derivatives tested. In contrary, a linear or even an unfavorable anti-Langmuir-isotherm can be observed for the (*S*)-enantiomers.

2.7. Reproducibility Analysis. The reproducibility of the chosen DSC technique was determined on the basis of its standard deviation by a series of measurements of different samples of racemic 2-chloromandelic acid (racemic compound). The standard deviation, s.d., was calculated as shown in eq 1.

$$\text{s. d.} = \sqrt{\frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{n-1}} \quad (1)$$

x_i is the observed value; $\bar{x}$ is the mean value; n is the number of samples

With a total number of 15 measurements (n = 15) for melting temperatures a standard deviation of ± 0.45 K was found. The melting enthalpies show a standard deviation of ± 0.6 kJ·mol^{-1} (n = 13). These values need to be considered throughout this study as a measure for accuracy of all reported values.

3. RESULTS AND DISCUSSION

3.1. Melting Temperatures and Melting Enthalpies of Mandelic Acid Derivatives. Table 2 summarizes the main results of DSC measurements of mandelic acid and its corresponding mandelic acid derivatives with a standard uncertainty u of $u(T_{fus})$ = 0.45 K and $u(\Delta H_{fus})$ = 0.6 kJ·mol^{-1}. The reported values represent measurements of enantiopure and racemic mandelic acid derivatives and include information about the presence of metastable conglomerates and further observed polymorphism. Noteworthy, a recent study indicates also the presence of other currently unknown polymorphs of racemic mandelic acid derivatives, which is in accordance with the already reported polymorphism behavior of 2-chloro- and 3-chloromandelic acid **5**, **6**.[26] Results for entries **7**−**18** were obtained in this study. The other entries comprehend literature data as comparison and completeness for mandelic acid **1**, all three monofluoro derivatives **2**−**4** and 2- and 3-chloromandelic acid **5**, **6**.

As shown in Table 2, all thermodynamic stable and a few metastable phases of mandelic acid and all its derivatives were characterized as racemic compounds. Another interesting behavior is the occurrence of metastable conglomerates, e.g., 2-chloromandelic acid **5**, which was recently characterized in detail.[17,19] In this study evidence for at least two other metastable conglomerates was found for 2-bromomandelic acid **8** and 2-chloro-4-fluoromandelic acid **17** (see also below). Such a behavior was expected since strong structural and chemical similarities to 2-chloromandelic acid are present. For these substances, also similar melting temperatures and enthalpies were found, e.g., enantiopure 2-chloromandelic acid **5** (T_{fus} = 392.4 K and ΔH_{fus} = 24.6 kJ·mol^{-1}) and enantiopure 2-bromomandelic acid **8** (T_{fus} = 392.5 K and ΔH_{fus} = 22.4 kJ·mol^{-1}). However, a clear tendency of the melting points or melting enthalpy between all similarly substituted mandelic acid derivatives was not observed, as shown for all racemic 3-substituted derivatives (**3**, **6**, **9**, and **12**). In addition, the melting points of all five racemic 4-substituted mandelic acid derivatives are not comparable, 408.9 (**4**), 393.2 (**7**), 391.2 (**10**), 415.3 (**13**), and 416.9 (**16**) K with the corresponding melting enthalpies of 30 (**4**), 16.2 (**7**), 17.8 (**10**), 30.4 (**13**), and 25.6 (**16**) kJ·mol^{-1}. Noteworthy, all 4-substituted derivatives always exhibit the highest melting temperature both for the enantiomer and racemic mixture.

Also all fluoro-substituted mandelic acid derivatives tend to be excluded from similarities, since probably other strong hydrogen bonds are formed in solid state in comparison to analogous chloro-substituted mandelic acid derivatives.[27,28] Unfortunately enantiopure iodine-substituted mandelic acid derivatives were not obtainable by synthesis, mostly due to size limitations by the iodine-substituent within the active site of the biocatalyst. Methyl-substituted mandelic acid derivatives (**14**, **15**, and **16**) were included in this study to compare the substitution-effect without the introduction of polar halogen-substituents.

3.2. XRPD-Phase Analysis Results. Analysis of the corresponding XRPD measurements reveals that at least a few similarities within the investigated mandelic acid derivatives library were found. The most prominent example is the occurrence of at least three very similar metastable conglomerates, as mentioned above. The metastable conglomerates of 2-chloromandelic acid **5**, 2-bromomandelic acid **8**, and 2-chloro-4-fluoromandelic acid **17** exhibit very similar X-ray diffraction results (Figure 3).

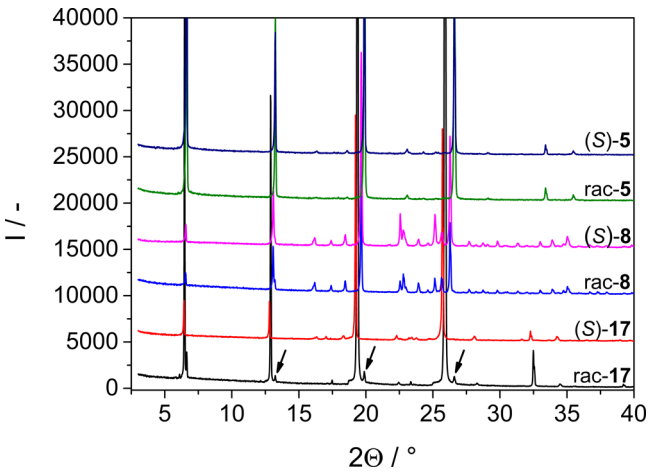


Figure 3. XRPD patterns of metastable conglomerates of 2-substituted mandelic acid derivatives; (*S*)-**5**, (*S*)-2-chloromandelic acid; rac-**5**, racemic 2-chloromandelic acid; (*S*)-**8**, (*S*)-2-bromomandelic acid; rac-**8**, racemic 2-bromomandelic acid; (*S*)-**17**, (*S*)-2-chloro-4-fluoromandelic acid; rac-**17**, racemic 2-chloro-4-fluoromandelic acid; *I*, intensity (arbitrary units); 2Θ, diffraction angle.

Slight deviations occur mainly only at the dominant reflections at 6.7, 13.4, 19.9, and 26.6° (values for derivative **5**), which also explain the very similar values of melting temperature and enthalpy for **5** and **8**. Both, an increase of the size of the substituent (2-chloro to 2-bromo) and the introduction of a second substituent (2-chloro to 2-chloro-4-fluoro) leads to shifts to smaller 2Theta values due to widening of the crystal lattice. The shown metastable conglomerates of **8** and **17** are unfortunately not directly obtainable from solution. For these derivatives seeding with a few crystals of metastable conglomerate **5** was required to induce the formation of the respective metastable conglomerate. In Figure 3 traces of the respective seeds of metastable **5** are still found in the XRPD

DOI: 10.1021/je500845d
J. Chem. Eng. Data XXXX, XXX, XXX−XXX

pattern of metastable **17**, as highlighted herein. The metastable conglomerate of **8** is relatively stable at ambient conditions, which allowed its investigation of the respective physical-chemical properties, but metastable racemic **17** was only sporadically obtained hereby. This indicates a significant lower stability of this solid phase. Presumable the presence of the additional fluoro-substituent at 4-position destabilizes the metastable conglomerate in favor of its stable racemic compound counterpart. In addition, the stable racemic compound of **17** shows the highest melting point (370.7 K; Table 2) compared to **5** and **8**. Furthermore, the presence of various other metastable conglomerates within this group of 2-substituted mandelic acid derivatives can be assumed.

In comparison, three similar 4-substituted derivatives (4-chloromandelic acid **7**, 4-bromomandelic acid **10** and 4-iodomandelic acid **13**) show hardly any similarities within XRPD-experiments (Figure 4). This indicates clearly that even for such highly similar substances various different crystal structures may occur.

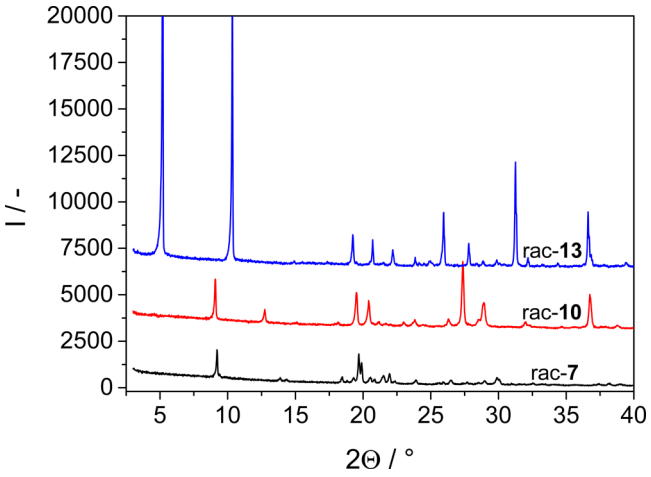


Figure 4. XRPD-results of racemic 4-chlorosubstituted mandelic acid derivatives; rac-**13**, racemic 4-iodomandelic acid; rac-**10**, racemic 4-bromomandelic acid; rac-**7**, 4-chloromandelic acid; *I*, intensity (arbitrary units); 2Θ, diffraction angle.

A similar behavior was found for the XRPD patterns of racemic 2,3 and 4-iodomandelic acid (**11**, **12**, **13**) derivatives (shown in the SI, Figure SI-7). Also considerably different melting temperatures ((382.1/370.1/415.3) K) and enthalpies of melting ((25/24.6/30.4) kJ·mol^{-1}) were observed. Herein differences in the crystal lattices, very likely due to diverse hydrogen-bonding patterns, are present, as also reported within the 2-, 3- and 4-fluoro-substituted mandelic acids (**2**, **3**, and **4**).[27,28] Further results of additional XRPD-measurements, both for the racemic and enantiopure composition of all investigated derivatives, are given in the SI.

3.3. Selected Binary Phase Diagrams. Strong differences within the investigated derivative library were also visualized by the determination of the respective binary melting phase diagram (as derived from DSC-analysis). As shown in Figure 5A and B, even small differences in halogen-substitution result in a significant different solid/liquid phase behavior. 2-Bromomandelic acid **8** exhibits a eutectic composition close to the racemic mixture at a mole fraction of about x = 0.54, while 3-bromomandelic acid **9** has a considerable higher eutectic composition of about x = 0.9. Noteworthy, the binary

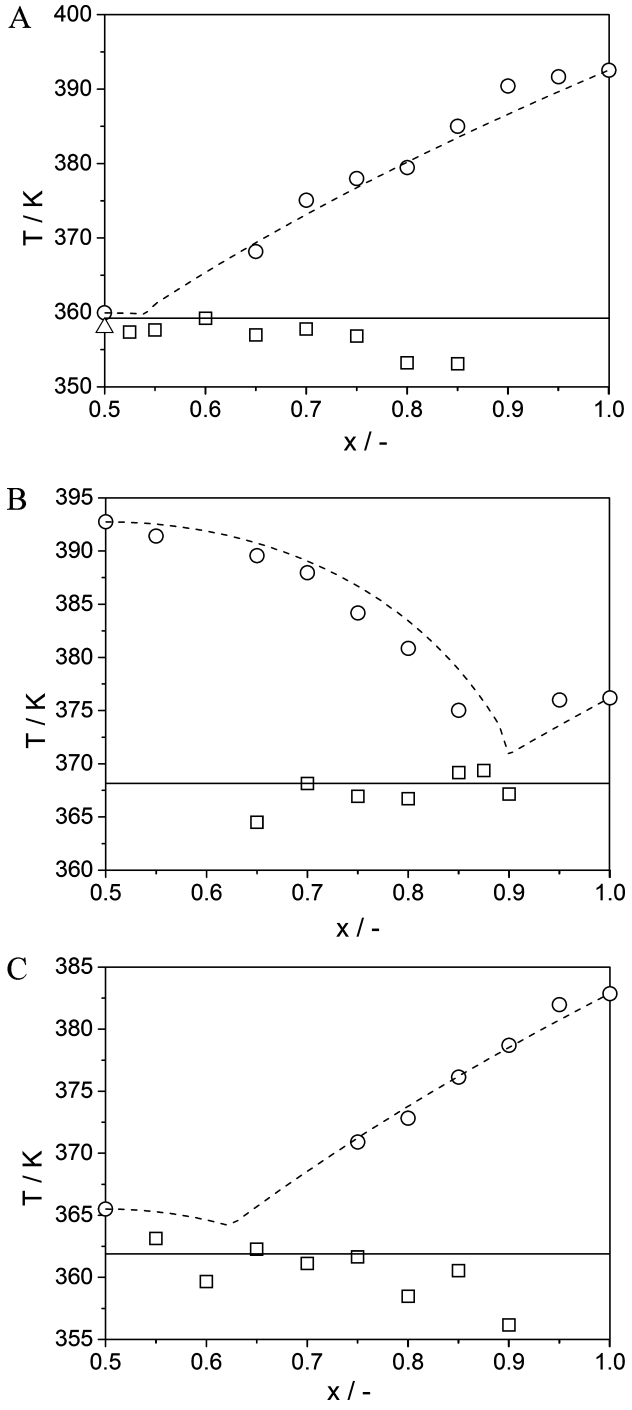


Figure 5. Exemplary binary melting point phase diagrams of (A) 2-bromomandelic acid **8** (racemic compound with a metastable conglomerate, triangle), (B) 3-bromomandelic acid **9** (racemic compound), and (C) 3-methylmandelic acid **15** (racemic compound). Detailed experimental data is available in the SI (Tables SI-2, -3, and -4). Panels A–C only show half of the full binary phase diagram, with the racemic composition on the left and the pure enantiomer (all (*S*) here) on the right side. The shown liquidus curves (dashed lines) are based on theoretical calculations using eqs 2 and 3 (see text). The eutectic temperatures are shown as straight lines.

phase diagrams of **8** and **9** show significant similarities to the binary phase diagrams of 2- and 3-chloromandelic acid **5**, **6**, which were recently investigated in detail.[19,20]

DOI: 10.1021/je500845d
J. Chem. Eng. Data XXXX, XXX, XXX−XXX

This comparison also includes the presence of an additional metastable conglomerate of **8**, indicated in Figure 5A by the triangle at the racemic composition below the circle representing the melting temperature of the racemic compound. Furthermore, an exchange of the substitution itself may result in various other solid phases. For example, strong differences were found between the structural very similar derivatives 3-bromo- and 3-methylmandelic acid **9** and **15**, Figure 5B and C. The binary phase diagram of **15** shows, in comparison to **9**, a relatively low eutectic composition around 0.62 (versus 0.9). In accordance to the results of other 3-halogen-substituted mandelic acid derivatives, a metastable conglomerate was not observed for **15** in this study. In addition, the shown phase diagrams partly exhibit a depression of the measured solidus temperatures, which may indicate a partial solid solution behavior (solvus line), e.g., wider deviations of the solidus temperatures close to the pure enantiomer side (Figure 5A and C) and the racemate side (Figure 5B). The eutectic compositions were calculated from the intersection of the liquidus lines of the enantiomer and the racemate according to simplified equations of Schröder−van Laar and Prigogine−Defay (eqs 2 and 3) with x, mole fraction; R, gas constant; $T_{fus,E}$, $T_{fus,R}$, melting temperature of enantiomer and racemic compound; $\Delta H_{fus,E}$, $\Delta H_{fus,R}$, enthalpy of fusion of enantiomer and racemic compound.[1]

$$\ln x = \frac{\Delta H_{fus,E}}{R}\left(\frac{1}{T_{fus,E}} - \frac{1}{T_{fus}}\right) \quad (2)$$

$$\ln 4x(1-x) = \frac{2\Delta H_{fus,R}}{R}\left(\frac{1}{T_{fus,R}} - \frac{1}{T_{fus}}\right) \quad (3)$$

The shown calculated liquidus lines describe the experimentally obtained liquidus temperatures sufficiently although the used equations principally only apply to ideal systems. We like to emphasize that liquidus and solidus lines are mainly presented here to qualitatively evaluate the solid/liquid phase behavior in the investigated chiral system.

4. CONCLUSIONS

The solid phase behavior of halogen- and methyl-substituted derivatives of mandelic acid was investigated. The results show clearly that the entire group of substances exhibit racemic compound behavior, while only a limited number of similarities between comparably substituted mandelic acid derivatives were found and described in this study. A noteworthy exclusion hereof is the presence of metastable conglomerates, which were found merely for 2-halogen-substituted derivatives.

■ ASSOCIATED CONTENT

Supporting Information

A summary of XRPD-results for all investigated mandelic acid derivatives, exemplary DSC curves, NMR and HPLC results are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*(Synthesis related) Phone: +49-3814986456. Fax: +49-3814986452. E-mail: jan.langermann@uni-rostock.de.

*(Solid phase behavior related) Phone: +49-3916110293. Fax: +49-3916110524. E-mail: lorenz@mpi-magdeburg.mpg.de.

Funding

Financial support by the European Union (EU-Project "INTENANT, Integrated Synthesis and Purification of Enantiomers"; NMP2-SL-2008-214129) and the German Federal Ministry of Education and Research (BMBF, Bundesministerium für Bildung and Forschung, Project No. 031A123) is highly acknowledged.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors want to thank Jacqueline Kaufmann, Luise Borchert, and Nora Doering for their help in the experimental work and Dr. Liane Hilfert for the help with NMR-analysis.

■ ABBREVIATIONS

HPLC, high performance liquid chromatography; DSC, differential scanning calorimetry; T_{fus}, melting temperature; ΔH_{fus}, melting enthalpy; XRPD, X-ray powder diffraction; x, mole fraction

■ REFERENCES

(1) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Krieger Publishing Company: Malabar, FL, 1981.

(2) Franks, M. E.; Macpherson, G. R.; Figg, W. D. *Lancet* **2004**, *363*, 1802−1811.

(3) Collins, A. N.; Sheldrake, G. N.; Crosby, J. *Chirality in Industry: The Commercial Manufacture and Applications of Optically Active Compounds*; John Wiley & Sons Ltd.: Hoboken, NJ, 1992.

(4) Subramanian, G. N.; Collet, A.; N, C. B. *Chiral Separation Techniques*, 2nd ed.; Wiley VCH: Weinheim, Germany, 2001.

(5) Toda, F. *Enantiomer Separation*, 1st ed.; Springer: Heidelberg, Germany, 2004.

(6) Lorenz, H.; Perlberg, A.; Sapoundjiev, D.; Elsner, M. P.; Seidel-Morgenstern, A. *Chem. Eng. Process.: Process Intensificat.* **2006**, *45*, 863−873.

(7) Coquerel, G. *Chem. Soc. Rev.* **2014**, *43*, 2286−2300.

(8) Lorenz, H.; Seidel-Morgenstern, A. *Angew. Chem. - Int. Ed.* **2014**, *53*, 1218−1250.

(9) Gedicke, K.; Kaspereit, M.; Beckmann, W.; Budde, U.; Lorenz, H.; Seidel-Morgenstern, A. *Chem. Eng. Res. Des.* **2007**, *85*, 928−936.

(10) von Langermann, J.; Tam, L. M.; Lorenz, H.; Seidel-Morgenstern, A. *Chem. Ing. Tech.* **2010**, *82*, 93−100.

(11) Temmel, E.; Wloch, S.; Müller, U.; Grawe, D.; Eilers, R.; Lorenz, H.; Seidel-Morgenstern, A. *Chem. Eng. Sci.* **2013**, *104*, 662−673.

(12) Binev, D.; Wloch, S.; Lorenz, H.; Seidel-Morgenstern, A. *1st Int. Workshop Ind. Pharm. Crystallisat. (HIW 2012)* **2012**, 127−135.

(13) Coppola, G. M.; Schuster, H. F. *a-Hydroxy Acids in Enantioselective Synthesis*; John Wiley & Sons: Hoboken, NJ, 1997.

(14) Gröger, H. *Adv. Synth. Catal.* **2001**, *343*, 547−558.

(15) Davey, R. J.; Sadiq, G.; Back, K.; Wilkinson, L.; Seaton, C. C. *Chem. Commun.* **2012**, *48*, 1976−1978.

(16) Gilks, S. E.; Davey, R. J.; Mughal, R. K.; Sadiq, G.; Black, L. *Cryst. Growth Des.* **2013**, *13*, 4323−4329.

(17) He, Q.; Rohani, S.; Zhu, J.; Gomaa, H. *Cryst. Growth Des.* **2010**, *10*, 5136−5145.

(18) He, Q.; Zhu, J.; Gomaa, H.; Jennings, M.; Rohani, S. *J. Pharm. Sci.* **2009**, *98*, 1835−1844.

(19) Lorenz, H.; Von Langermann, J.; Sadiq, G.; Seaton, C. C.; Davey, R. J.; Seidel-Morgenstern, A. *Cryst. Growth Des.* **2011**, *11*, 1549−1556.

(20) Le Minh, T.; Von Langermann, J.; Lorenz, H.; Seidel-Morgenstern, A. *J. Pharm. Sci.* **2010**, *99*, 4084−4095.

(21) Zhang, Y.; Ray, A.; Rohani, S. *Chem. Eng. Sci.* **2009**, *64*, 192−197.

DOI: 10.1021/je500845d
J. Chem. Eng. Data XXXX, XXX, XXX−XXX

(22) Coles, S. J.; Threlfall, T. L.; Tizzard, G. J. *Cryst. Growth Des.* **2014**, *14*, 1623−1628.
(23) von Langermann, J.; Wapenhensch, S. *Adv. Synth. Catal.* **2014**, *356* (14-15), 2989−2997.
(24) Lorenz, H.; Sapoundjiev, D.; Seidel-Morgenstern, A. *J. Chem. Eng. Data* **2002**, *47*, 1280−1284.
(25) Lorenz, H. *In Crystallization: Basic Concepts and Industrial Applications*; Beckmann, W., Ed.; Wiley-VCH: Weinheim, Germany, 2013; pp 33−74.
(26) Coles, S. J.; Ellis, A. L.; Leung, K.; Sarson, J.; Threlfall, T. L.; Tizzard, G. J. *CrystEngComm* **2014**, DOI: 10.1039/c4ce01832j.
(27) Larsen, S.; Marthi, K. *Acta Crystallogr. Sect. B* **1994**, *50*, 373−381.
(28) Larsen, S.; Marthi, K. *Acta Crystallogr. Sect. B* **1997**, *53*, 280−292.
(29) Lorenz, H.; Seidel-Morgenstern, A. *Thermochim. Acta* **2004**, *415*, 55−61.
(30) Kuhnert-Brandstätter, M.; Ulmer, R. *Mikrochim. Acta* **1974**, *62*, 927−935.
(31) Rose, H. A. *Anal. Chem.* **1952**, *24*, 1680−1681.
(32) Collet, A.; Jacques, J. N. *Bull. Soc. Chim. France* **1973**, *12*, 3330−3334.

DOI: 10.1021/je500845d
J. Chem. Eng. Data XXXX, XXX, XXX−XXX