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Non-equimolar discrete compounds in binary chiral systems of organic substances†

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Since knowledge on the occurrence of non-equimolar discrete compounds in binary systems containing chiral molecules is very limited, this study reviews and systematizes the current state of investigating such systems and summarizes the results on two example systems studied in detail by the authors. In particular, the identification and verification of the non-equimolar discrete compounds compared to other discrete solid phases occurring in the two systems are discussed by presenting the results of related SCXRD, PXRD, TRPXRD, DSC, IR, and HSM studies. The (*S*)-malic acid–(*R*)-malic acid system has been found to contain non-equimolar 1 : 3 and 3 : 1 stable (S_3R and SR_3) and metastable (3*S*1*R* and 1*S*3*R*) discrete compounds, along with the equimolar compounds *RS*I and *RS*II (known monoclinic modifications) and the recently discovered *RS*III modification. Polymorphic transformations of the discrete phases are debated, and the crystal structure of the stable compound S_3R is identified (S. G. *P*1). The L-valine–L-isoleucine system has been stated to contain a non-equimolar 2 : 1 discrete compound, V_2I, that could independently be proven by the ternary solubility diagram in water and its crystal structure solved (S. G. *C*2). The results obtained are discussed in conjunction with the findings reported in the literature. In order to systematize the variety of terms used for the description of discrete phases in binary chiral systems of organic substances, a systematization of equimolar and non-equimolar compounds based on chemical and crystallographic characteristics is proposed.

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1. Introduction

When studying the limits of solid solutions and the polymorph diversity of organic compounds, several geometric and chemical factors are taken into account, such as dimensions, shape, and symmetry of a molecule, as well as the type of intermolecular bonding.[1–3] In the last decades, further geometrical (stereochemical) factors – the molecule chirality and its configuration[4] – have been found to be essential for the analysis of molecular packing in crystal structures of enantiomeric compounds.[5,6] An avalanche-like growing interest in a rather abundant class of organic substances that contain chiral molecules is prompted by their numerous applications in the pharmaceutical industry, medicine, biochemistry[7–11] and even in geology,[12–16] where they are used, for example, for sediment rock dating; the last method is based on interrelations between levorotatory and dextrorotatory enantiomers in fossilized organic matter.[13,16] Industrial use and treatment of biochemically active chiral compounds requires development and improvement of synthesis techniques and also of methods for chiral resolution and

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purification. This requires, in its turn, a fundamental knowledge and understanding of the phase equilibria and crystal chemistry in chiral systems.[6–20]

The three general types of phase diagrams known for chiral systems are shown in Fig. 1 (upper part).[5,21] These are diagrams containing a eutectic (Fig. 1a), a binary compound (Fig. 1b), and (complete) solid solutions (Fig. 1c). The exact type of phase diagram is determined by the nature of the equimolar (1 : 1) mixture of enantiomers. The diagram of the first type corresponds to a physical mixture of enantiomers, or conglomerate, *S* + *R*; the second type to a binary compound (racemic compound[5]), *RS*; and the third type to a solid solution, *S*,*R*. Schematic representations of the equimolar compositions that correspond to the three types mentioned are illustrated in Fig. 1 (bottom part). The maximum of the liquidus line of the racemic compound can lie above or below the melting points of the enantiomers or even be equal to them (Fig. 1b). So, the diagrams of the second type can be further divided into three subtypes.[5,6,22] Analogous subtypes are allocated for the diagrams containing solid solutions (Fig. 1c). According to J. Jacques *et al.*,[5] a majority of binary systems (~90%) belongs to the second type, while the first type systems are much less frequent (~10%), with the third type being the rarest.

A diagram of each type may be further complicated due to polymorphism of the system components and/or equimolar compounds. Moreover, the diagrams of the first two types can be additionally diversified due to the formation of limited solid solutions.[19] For example, in very recent work,[23] C. Brandel *et al.* described the complex behavior of the diprophylline enantiomers, a system where solid solutions form in addition to the polymorphism of both the equimolar compound and the enantiomer.[23] Possible phase diagram arrangements that can result from such complications are discussed in detail by G. Coquerel.[6] However, all the diagrams presented there correspond to binary systems of the same group, *viz.* systems consisting of enantiomers of the same chemical compound.

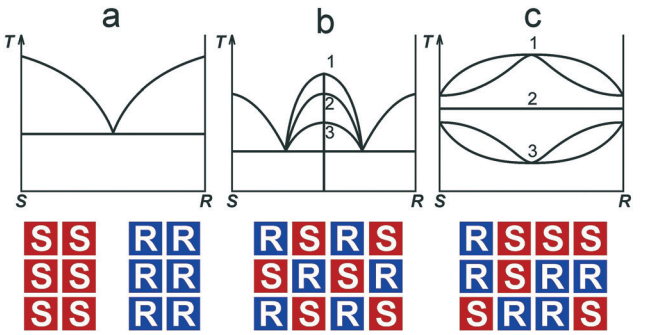

Fig. 1 Three basic types of phase diagrams characterizing binary systems formed by *S*- and *R*-enantiomers. *At the top*: diagrams of the systems containing a conglomerate (a), a racemic compound (b), and solid solutions (c). Subtypes 1, 2, and 3 of racemic compounds have melting points that lie above, are equal to, or lie below the melting points of the enantiomers; subtypes 1, 2, and 3 of the solid solutions are presented in the following order: a non-ideal solution having a maximum, an ideal solution, and a non-ideal solution having a minimum.[5] *At the bottom*: schematic representations of molecular packing in the equimolar phases corresponding to the diagrams above.

In the published literature, there are sparse data on two other groups of binary systems containing chiral molecules. One group includes systems of diastereomers and the other systems of enantiomers of different compounds. Examples of our investigations of the solid phases existing in binary systems of the three above groups are summarized in Table 1.

The three systems of the first group[24–30] contain enantiomers of the same compound. The system formed by the *S*-

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Table 1 The solid phases formed in exemplary chiral systems of 3 groups: systems of enantiomers of the same and different compounds and diastereomers of the same compound (results of our research group, except ref. 24)

Molecular components	System	Number of chiral centers	Solid phase characteristics	Ref.
Systems of enantiomers of the same compound				
Enantiomers	(*S*)-E3ClMA–(*R*)-E3ClMA	1 and 1	Eutectic mixture and limited solid solutions	24, 25
Enantiomers	(*S*)-Malic acid–(*R*)-malic acid	1 and 1	Equimolar (*RS*) and non-equimolar (S_3R and SR_3) discrete compounds and limited solid solutions	26, 27, 28, 29
Enantiomers	L-Thr–D-Thr (L-*a*Thr–D-*a*Thr)	2 and 2	Eutectic mixture	30
Systems of diastereomers of the same compound				
Diastereomers	D-Thr–L-*a*Thr (L-Thr–D-*a*Thr)	2 and 2	Eutectic mixtures	31
Diastereomers	L-Thr–L-*a*Thr (D-Thr–D-*a*Thr)	2 and 2	Complete miscibility	32, 33
The system of enantiomers of different compounds				
Enantiomers of different compounds	L-Val–L-Ile (D-Val–D-Ile)	1 and 2	Non-equimolar discrete compound (V_2I) and limited solid solutions	34, 35

Designations: E3ClMA – ethanolamine salt of 3-chloromandelic acid; Thr and *a*Thr – threonine and *allo*-threonine; Val – valine; Ile – isoleucine.

and *R*-enantiomers of the ethanolamine salt of 3-chloromandelic acid (E3ClMA) is an example of a eutectic system with partial miscibility between the components.[24,25] The system of malic acid *S*- and *R*-enantiomers belongs to the type 2 systems showing different polymorphs of the racemic compound and limited solid solutions.[26–29] Moreover, the system is complicated by the presence of two non-equimolar discrete compounds, $S:R = 1:3$ and $3:1$.[29] The system of L- and D-enantiomers of threonine is a eutectic system free from solid solutions.[30] Two shown systems of the second group are formed by diastereomers of the same compound. D- and L-*allo*-diastereomers of threonine form a eutectic system,[31] where, in contrast to the L- and D-threonine system, the eutectic point must be shifted from the equimolar composition. L- and L-*allo*-diastereomers of threonine show full miscibility in the solid state,[32,33] and the phase diagram is asymmetric due to different components' melting points/solubilities.[32] The third groups' system studied consists of enantiomers of different compounds: L-valine and L-isoleucine. This system is characterized by the occurrence of a non-equimolar discrete compound Val : Ile = 2 : 1 and limited solid solutions.[34,35]

Polymorphism of enantiomers and their equimolar compounds is rather common among chiral systems.[6] However, the systems (*S*)-malic acid–(*R*)-malic acid and L-valine–L-isoleucine show relatively rarely reported additional phase behaviours as limited solid solutions and, in particular, non-equimolar discrete compounds. Both, as well as literature data concerning these and similar systems, will be presented in this paper. A discrete compound as used here is a solid phase with fixed stoichiometry (equimolar or not but stoichiometric) having a crystal structure different from the compound components and, hence, clearly differs from solid solutions.

The paper is structured as follows. After introducing in section 2 the materials and experimental methods used in our own studies, in section 3, the systems of enantiomers of the same compound containing non-equimolar discrete phases are reviewed and followed by a detailed discussion of the (*S*)-malic acid–(*R*)-malic acid example. Section 4 refers to the systems of enantiomers of different compounds containing equimolar and non-equimolar discrete solid phases with a special emphasis on the L-Val–L-Ile system. For both exemplary systems, particular focus is set on discrete compounds described recently. In section 5, a systematization of the discrete compounds occurring in binary chiral systems of organic substances is suggested. Finally, the main results are summarized, and conclusions are drawn.

2. Materials and methods

2.1 Materials

System 1: (*S*)-malic acid–(*R*)-malic acid. The starting reactants were *S*- and *R*-enantiomers and racemates of the *RS*I modification with 98% purity, which are available from Merck Schuchardt OHG, Hohebrunn, Germany. The reactants were used for preparing samples of quenched mixtures and growing samples of different compositions from aqueous, ethanol, acetone, and isopropanol solutions. The sample preparation techniques are described in detail elsewhere.[27–29]

System 2: L(+)-valine–L(+)-isoleucine. The starting substances were L-valine and L-isoleucine with a 99% purity, which are available from Alfa Aesar, Massachusetts, USA, as well as deionized water as solvent. These reactants were used for sample preparation by means of isothermal evaporation and cooling techniques, as well as grinding of mixtures with various compositions. The sample preparation techniques are described in detail elsewhere.[34,35]

2.2 Experimental techniques

High-performance liquid chromatography (HPLC). An analytical HPLC system equipped with a Phenomenex Chirex 3126 column was used. System 1: The material was dissolved in distilled water (1 wt%) and analyzed under the following conditions: eluent – 5 mM $CuSO_4$ at pH 3.2 (acetic acid), flow

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rate – 0.5 mL min^{-1}, injection volume – 2 μL, temperature – 25 °C, wavelength – 254 nm.[29] System 2: The material was dissolved in distilled water (up to 0.2 wt%) and analyzed using the following conditions: eluent – 2 mM aqueous $CuSO_4$ solution/MeOH 85/15 (v/v), flow rate – 0.5 mL min^{-1}, injection volume – 5 μL, temperature – 25 °C, wavelength – 280 nm.[34]

Differential scanning calorimetry (DSC). System 1: For the melting temperature measurement, a SETARAM DSC 131 unit (France) was employed. Helium purge gas flow was 20 mL min^{-1}. About 10 mg of the substance were studied in closed aluminum crucibles at a heating rate of 1 K min^{-1} in the range of 30–150 °C.[29] Melting temperatures were taken from the extrapolated onset temperatures of the melting peaks.

Powder X-ray diffractometry (PXRD). System 1: Measurements were performed using a Bruker D2 Phaser diffractometer (Germany) applying $Cu_{K\alpha}$ radiation and collecting data in 2θ range of 5–45° with a step of 0.02°.[29] System 2: Measurements were carried out at an X'Pert Pro diffractometer (PANalytical GmbH, Germany) using $Cu_{K\alpha}$ radiation and an X'Celerator detector in a 2θ range of 3–40° with a step size of 0.017°.[34] The diffraction patterns obtained for both systems were processed using a STOE WinXPOW software package.

Temperature-resolved powder X-ray diffractometry (TRPXRD). System 1: A STOE diffractometer (Germany) ($Cu_{K\alpha}$ radiation) provided with high-temperature equipment was used in an air atmosphere. The temperature variation was from room temperature to the substance decomposition point with a temperature step of 2–10 °C.[27, This work]

Single crystal X-ray diffractometry (SCXRD). Systems 1[This work] and 2:[34] A diffractometer, Agilent Technologies SuperNova (USA), with $Cu_{K\alpha}$ radiation was used at a temperature of 100 K. The structure was solved by direct methods and refined by means of the SHELX program incorporated in the OLEX2 program package.

Infrared spectroscopy (IR). System 1: A Bruker ALPHA FT-IR-spectrometer (Germany) equipped with a Platinum-ATR-sampling module was used for the analysis of solid samples.[This work]

Hot stage microscopy (HSM). System 1: A Linkam LTS 420 hot stage (UK) combined with a Zeiss Axioskop microscope (Germany) was applied. Samples prepared on a microscope glass slide were continuously heated from room temperature to the substance melting point at 2 K min^{-1} heating rate. The temperature was held constant at certain temperatures to observe the changes in the sample behaviour.

3. Systems of enantiomers of the same compound containing non-equimolar discrete phases

3.1 Overview

A list of enantiomeric systems, which are found to contain equimolar, as well as non-equimolar discrete compounds («anomalous racemates»), is presented in Table 2. Published data on the formation of non-equimolar discrete compounds in chiral systems is not always reliable, in particular, when the study is only based on melting point/DSC analyses, and the crystal structure of the compounds is not deciphered. A brief description of some systems is presented below.

β-hydro-di-γ-benzoylamino-butyric acid. M. Bergmann and M. Lissitzin[51] were the first (in 1930) to introduce the concept of so-called "anomalous racemate". In the research,[51] they tried to separate enantiomers of β-hydro-di-γ-benzoylamino-

Table 2 Non-equimolar discrete compounds in binary systems of enantiomers

Ratio *S*:*R*	Compounds	Crystal structure; methods of research	Ref.
1:3	2,4-Dimethylglutaric acid	Not determined; melt phase diagram	36, 37
1:3	Tetramisole (6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*][1,3]thiazole)	Not determined; DSC, PXRD	38
1:3	3-Hydroxy-4-(2,4,5-trifluorophenyl)butanoic acid	Not determined; DSC, PXRD, HPLC	21
1:4	Carvone (2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one)	Not determined; DSC	39
1:5	4-Methyl-7-methylenetricyclo[7.2.1.$0^{1,5}$]dodecan-12-one oxime	Determined	40
1:2	Bicyclic bis-lactam derivative BBL7	Determined	41
1:2	Exo-*trans*-exo-(13R,24R)-14,23-dioxaoctacyclo (25.3.0.$0^{2,5}$.$0^{3,29}$.$0^{4,8}$.$0^{6,10}$.$0^{9,13}$.$0^{24,28}$) triacontane-15,22-dione	Determined	42
1:2	1-(Hydroxymethyl)-4,10-dimethyl-3-oxatricyclo[5.2.1.$0^{2,4}$]decan-10-ol	Determined	43
1:2	2-Diisopropylcarbamoyl-3-methylpentane-3,4-diol	Determined	44
1:2	rac-2,2′-di(Ethoxycarbonyl)-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline	Determined	45
1:2	(*E*)-3,4-Di-*t*-butyl-1,1,2,2-tetrakis(trimethylsilyl)-1,2-disilacyclobutane	Determined	46
1:2	*trans*-(1*RS*,3*RS*)-2-*N*,*N*′-Dimethylaminomethyl-1,3-dithiolane-1,3-dioxide	Determined	47
1:2	3-Propyl-4-(*p*-toluenesulfonylamino)-1,2-diselenolane	Determined	48
1:3	3-(2-*tert*-Butylphenoxy)-propane-1,2-diol	Determined	49
1:3	6-(Dimethoxymethylene)-dibenzo(*d*,*k*)tricyclo(5.2.2.$0^{3,7}$)undeca-4,10-dien-8-one	Determined	50
1:3	Malic acid	Determined;[a] PXRD, DSC, SCXRD, TRPXRD, IR, HSM	29, 37, and[a]

[a] This work.

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butyric acid *via* rapid crystallization from a highly supersaturated aqueous solution containing both enantiomers in the ratio of about 1 : 2. They found that the homogeneous precipitate obtained *via* such crystallization has a unique optical activity value. Its angle of optical rotation $[\alpha]_D$ was +/−7.2°, while the same parameter for the enantiomers was +/−22°. On this basis, they stated that the compound in question could crystallize in the racemic form and two additional compounds 1 : 2 and 2 : 1. Quite recently (2015), A. A. Bredikhin *et al.*[52] proved in a reinvestigation *via* IR spectra, SCXRD and PXRD analysis, and solubility data that no additional compounds exist in the system. Taking this into account, we did not include the system in Table 2.

Naringenin. Furthermore, Table 2 does not include the system of naringenin enantiomers, which was studied by P. J. Cox *et al.*[53] The authors synthesized racemic naringenin *via* recrystallization of the precursor substance from an ethanol solution. They detected the micro-inhomogeneity of a crystal of racemic composition. Despite the fact that its crystal structure corresponds to that of the racemate, the crystal is a combination of two types of unit cells; those of the 1st type are populated with *R*- and *S*-molecules in proportions of 77.5% and 22.5%, while the proportions in the 2nd type unit cells are 22.5% and 77.5%, respectively. These proportions roughly correspond to compositions of $S:R$ = 3 : 1 and 1 : 3. The authors[53] assumed that the matter analyzed was a solid solution. Later, J. E. Tabora *et al.*[21] mentioned that the existence of unit cells with 1 : 3 and 3 : 1 populations in the crystal structure of racemic naringenin can be indirect evidence of the presence of 1 : 3 phases in the system. In our opinion, this crystal structure can be regarded as a partially disordered racemate since the authors[21] showed it to be centrosymmetric (present authors' note: pseudo-centrosymmetric).

As a result, Table 2 contains 16 systems with non-equimolar discrete compounds of which we have knowledge. It should be mentioned that crystal structures of four of the listed compounds have not yet been clarified.[21,36–39] For example, paper[21] reports the results of the crystallization of different mixtures of the *3-hydroxy-4-(2,4,5-trifluorophenyl) butanoic acid* enantiomers from toluene solutions. In the ternary phase diagram, two additional eutonics and a maximum in-between were detected. The composition $S:R$ = 1 : 3, corresponding to the maximum, showed both a unique melting point and X-ray powder pattern, leading to the conclusion that it is a discrete compound.

Thus, the compounds found in the systems discussed must be further investigated since a final conclusion can be drawn only after depicting their crystal structures. For this reason, the detection of such compounds can be considered completely valid only for 12 (ref. 29, 40–50) of the systems shown in Table 2. Among them, 1 : 2 and 1 : 3 compounds are reported for eight and three cases, respectively; for one system, a 1 : 5 compound is described. Beside our research on the *malic acid* system in section 3.2, two examples shall be briefly mentioned.

R. G. Kostyanovsky *et al.*[41] determined crystal structures for two chiral compounds belonging to the group of *bicyclic bis-lactam* (*BBL*). There, compound BBL7 is composed of three different, independent homochiral chains: two of them comprising molecules of the same chirality, *–R–R–R–*, while the third contains molecules of chirality *–S–S–S–*. Therefore, it could be classified as a compound of an $S:R$ = 1 : 2 type. A. A. Bredikhin *et al.*[49] studied the *3-(2-tert-butylphenoxy)-propane-1,2-diol* system and found an additional peak in the DSC curve for the composition with an $S:R$ ratio close to 1 : 3. SCXRD analysis of that sample allowed identification of a discrete phase and its crystal structure.

3.2 The system (*S*)-malic acid–(*R*)-malic acid

3.2.1 History. The system of malic acid enantiomers has been investigated over decades. One of the four carbon atoms forming the malic acid $C_4H_6O_5$ molecule includes a chiral center. As already mentioned, it is a representative of the chiral systems containing a racemic compound,[54] and it is also remarkable for being an example of the combination of a few complications discussed in the work.[6] For example, the *RS* compound can crystallize in various polymorphic modifications. The data on the crystal structure and diffraction spectra of the two monoclinic modifications of *RS*-malic acid (designated as *RS*I and *RS*II in the following), as well as the malic acid enantiomers, are available from the Cambridge Structural Database (CSD)[55] and the International Centre for Diffraction Data (ICDD).[56] In the crystal structures of the *S*-enantiomer and racemic compounds *RS*I and *RS*II, malic acid molecules form chains with neighbour molecules in the chains being linked by hydrogen bonds.[57–60] This is a common arrangement for dicarboxylic acids, such as terephthalic,[61] succinic[62] and adipic[62] acids.

In addition to the racemic compound, the presence of "anomalous racemates" in the malic acid system was firstly reported in paper.[37] The authors studied some enantiomeric compositions using HSM and plotted the phase diagram. Besides the maximum corresponding to the racemic compound (*RS*I, the only modification known at that time), they found additional inflexion points of the liquidus line at compositions $S:R$ = 3 : 1 and 3 : 1. They also found that the sample crystallized from aqueous solution with the composition $S:R$ = 1 : 3 was characterized by a unique diffraction pattern. Later, the authors of other work[63] discovered a second monoclinic polymorph of the racemic compound (*RS*II). They assumed that the inflexions of the liquidus line discovered by previous authors resulted from the intersections of two liquidus lines belonging to the different polymorphs of the racemic compound, which, consequently, could not be proof of the anomalous racemates existence. For many years, this point of view has prevailed. Later, H. Kaemmerer *et al.*[26] carried out experiments to verify that the racemic forms *RS*I and *RS*II are monotropically related. They showed that the lower melting form *RS*II undergoes a polymorphic phase transition to *RS*I by storage at room temperature. The DSC data also

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proved monotropy in accordance with the heat-of-fusion rule.[64] DSC and DTA studies on *S*- and *RS*-malic acid have been also reported by other authors.[65]

3.2.2 Phase relations in the system based on PXRD, TRPXRD, IR-spectroscopy, DSC and HSM investigations

Phase diversity in the (S)-malic acid–(R)-malic acid system. The system of malic acid enantiomers appeared to be more complex than it seemed before. Firstly, along with the known monoclinic modifications *RS*I and *RS*II, a third modification of the racemic compound *RS*III can be formed. Secondly, in addition to the equimolar compound *RS*, non-equimolar discrete phases with the ratio $S:R$ = 3 : 1 and 1 : 3 occur that thirdly, can crystallize as stable S_3R (SR_3) and metastable 3*S*1*R* (1*S*3*R*) modifications. Moreover, the discovery of additional discrete phases necessitated further adjusting the limits of solid solutions in this system.

Equimolar discrete compounds. PXRD studies of samples of the racemic compounds crystallized from various solvents showed[27] that the polymorphic diversity of the *RS* compound depends, first of all, upon the crystallization medium and the crystallization rate (ESI:† Table 1). The influence of some other crystallization conditions is discussed in details in the paper.[27] Phase distribution of the crystallization products according to the crystallization time (ESI:† Table 1) correlates with estimation of the stability of the various phases based on DSC data.

Non-equimolar discrete compounds. A PXRD study of samples with an enantiomer ratio of $S:R$ = 3 : 1 (1 : 3) allowed the determination of stable S_3R (SR_3) and metastable modifications 3*S*1*R* (1*S*3*R*) of 3 : 1 and 1 : 3 discrete compounds in the system.[66] As for the racemic compound, the diversity of the polymorphic modifications of these compounds depends upon the crystallization medium and the crystallization rate (ESI:† Table 1). The presence of the non-equimolar discrete phases in the system was also confirmed by IR-spectroscopy, DSC and HSM studies. We obtained IR spectra of the malic acid equimolar and non-equimolar compounds in the area of 4000–400 cm^{-1}. Fig. 2a and b show the IR spectra of *S*-enantiomer, racemic compounds *RS*I and *RS*II and non-equimolar S_3R and 3*S*1*R* discrete phases in the diagnostic ranges of 3600–3300 cm^{-1} and 1740–1630 cm^{-1}. It can be seen that each of the phases *S*, *RS*I, *RS*II, SR_3, and 3*S*1*R*, of malic acid has its own spectrum that allows for the use of IR-spectroscopy for their identification. The results for the known racemic and enantiomer phases agree with data reported in the works[26,63] and do not contradict other literature findings.[67]

Phase relationships in the (S)-malic acid–(R)-malic acid system. The TRPXRD method showed that the racemic phases *RS*I and *RS*III do not undergo polymorph transformations until the substances reached their melting points at 124 °C and 123 °C, respectively. However, heating a sample of an *RS*I + *RS*III mixture resulted in a homogenization at 110–123 °C to form *RS*I and the subsequent melting of the latter at 124 °C. In addition, a slurry experiment where a *RS*I + *RS*III mixture was slurried in an acetonitrile solution for 1 month

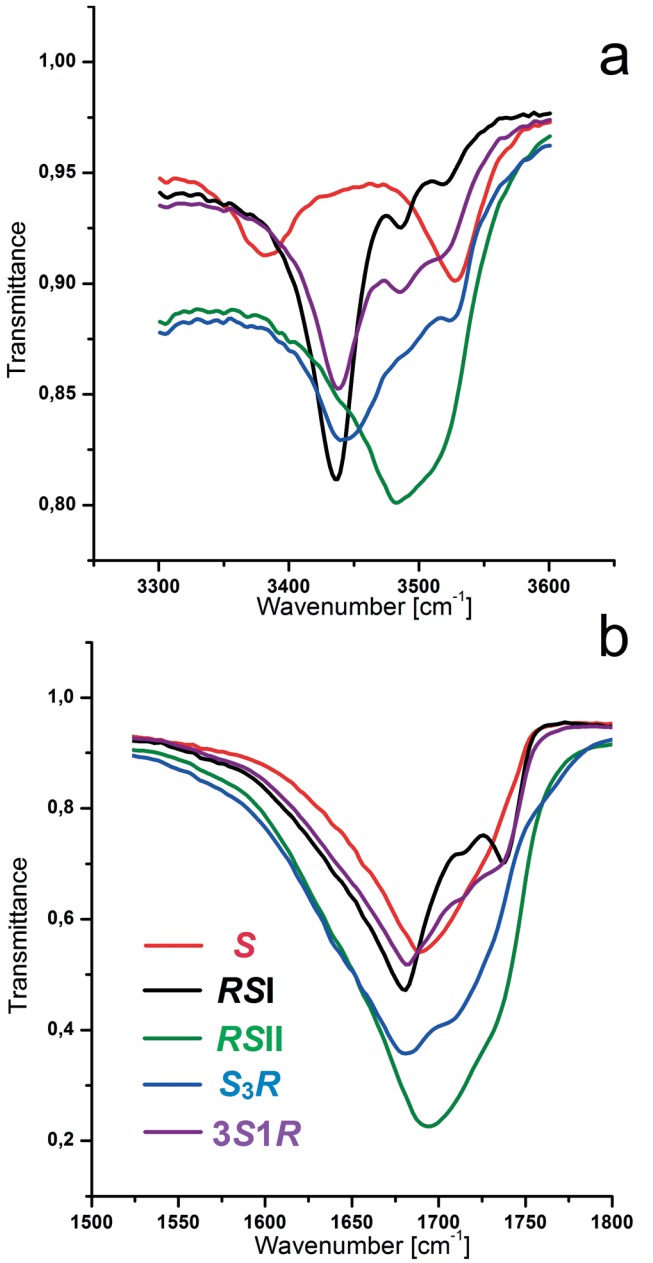

Fig. 2 IR spectra in the ranges 3600–3300 cm^{-1} (a) and 1800–1500 cm^{-1} (b) of *S*-enantiomer (red line), racemic compounds *RS*I and *RS*II (black and green lines), stable S_3R and metastable 3*S*1*R* compounds (blue and purple lines) of malic acid.

also showed *RS*I to be stable and *RS*III to be metastable. Upon heating, the *RS*II phase transforms into *RS*I at a temperature of 106–108 °C. The experiments confirmed stability of the *RS*I phase, the obvious metastability of *RS*II, and the less obvious metastability of *RS*III at ambient temperature.

Fig. 3 shows the DSC melting curves for the three racemic phases and the non-equimolar $S:R$ = 3 : 1 modifications of malic acid. The melting temperatures increased in the order 3*S*1*R*, S_3R, *RS*II, *RS*III, *RS*I. Based on the heat-of-fusion rule,[64] the monotropic relationships between the polymorphs *RS*I,

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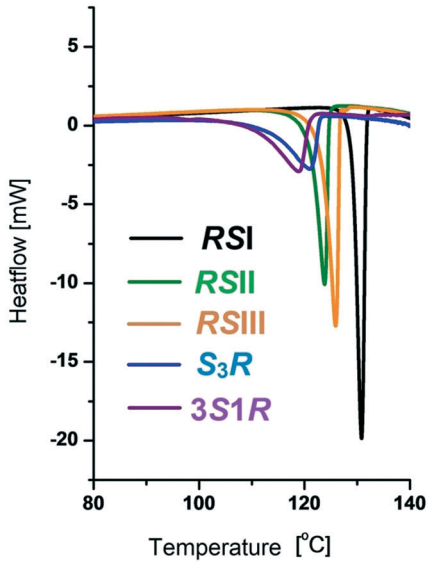

	RSI	RSIII	RSII	S_3R	3S1R
Melting point [°C]	129.0	123.3	121.1	112.0	111.2
Heat of fusion [J/g]	238	208	187	169	163

Fig. 3 DSC curves and derived melting data of the racemic compounds *RS*I, *RS*II, and *RS*III and the S_3R and 3*S*1*R* compounds of malic acid.

*RS*II and *RS*III of the racemic compound as well as the polymorphs S_3R and 3*S*1*R* of the non-equimolar discrete compounds could be proven (Fig. 3).

Thermomicroscopic (HSM) investigations of the *S*-enantiomer, racemic compounds *RS*I and *RS*II, physical mixtures of enantiomers *S* + *R* with the proportions of 1 : 1 and 1 : 3 for the components, and the non-equimolar discrete compounds S_3R and 3*S*1*R* were performed (ESI:† Fig. 1). Close to the DSC results, the heating of the enantiomer and racemates *RS*I and *RS*II did not lead to any noticeable changes until melting of the substances. Instead of powders, in experiments with a 1 : 1 physical mixture of enantiomers *S* + *R*, we used two homochiral crystallites obtained by quenching the melt of the corresponding enantiomers (ESI:† Fig. 1a). The interaction between the enantiomers starts at the contact area of the two grains and leads to the formation of racemic compound. This correlates with the fact that the crystallization of a melt containing two enantiomers provides the compound *RS*II (ESI:† Table 1). Experiments with the 3 : 1 physical mixture (*S* + *R*) were run with powders (ESI:† Fig. 1b). They resulted in the formation of the discrete compound that finally melts. After recrystallization, a crystallite was taken, which was the metastable discrete phase 3*S*1*R*, and analyzed (ESI:† Fig. 1c). A visible transformation of the metastable into the stable phase, 3*S*1*R* → S_3R, was not observed. The substance melted and recrystallized after removal of the heat.

The thorough study of the malic acid system resulting in identification of various modifications of the equimolar and non-equimolar discrete phases as well as the limits of solid solutions in two of the systems[28] facilitates compiling a schematic representation of the phase diagram (Fig. 4). It is based on the data obtained by the PXRD, TRPXRD, DSC, HSM, IR, and SCXRD methods mentioned. The given melting points originate from both the DSC and TRPXRD results. The limits of solid solutions were allocated using the results of a PXRD study of molten mixtures (ESI:† Fig. 2). When compared with the known diagrams of the second type[5,21] (see Fig. 1), the diagram of the malic acid system is very complex with the following characteristics. 1) The racemic compound can form three polymorphic modifications, with two of them already known[26,58–60,63,65] (*RS*I and *RS*II), and the third one (*RS*III) discovered by the present authors.[27] 2) Non-equimolar discrete compounds with the ratio *S* : *R* = 3 : 1 and 1 : 3 (ref. 29) are formed in the system. 3) The non-equimolar discrete compounds can crystallize in stable (S_3R and SR_3) and metastable (3*S*1*R* and 1*S*3*R*) modifications. 4) Studies of the detected discrete phases allow determination of the areas of solid solutions in this system, which are found in the vicinity of all the discrete phases.[28]

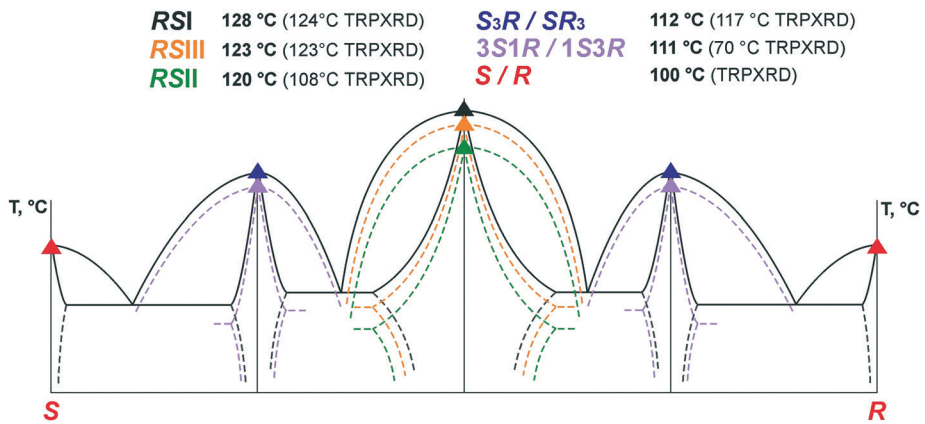

Fig. 4 Schematic representation of the phase diagram of the malic acid enantiomers (not scaled) with melting temperatures added. Explanations are provided in the discussion.

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3.2.3 Crystal structure of compound S_3R. Definitive confirmation of the existence of non-equimolar discrete compounds in the system became possible after determining the crystal structure of the stable compound S_3R. A single crystal with the $S:R$ ratio of 75 : 25% obtained from an acetonitrile solution *via* an isothermal evaporation method was studied by means of SCXRD. The crystal structure data and structure refinement of the compound are presented in ESI:† Table 2. The powder X-ray diffraction pattern calculated using the structural data (ESI:† Fig. 3a) is consistent with the experimental diffractogram of the stable compound S_3R (ESI:† Fig. 3b) and differs from the pattern of the metastable compound 3*S*1*R* (ESI:† Fig. 3c). ESI:† Table 3 shows the triclinic cell parameters of the compound S_3R in comparison to the other discrete phases in the system.

Fig. 5 presents the crystal structure of the compound S_3R in projections on the planes *ab* (a), *bc* (b), and *ac* (c). It might be described as an arrangement of molecular chains of two types. Chains of the first "enantiomeric" type are composed of molecules of the same chirality –*S*–*S*–*S*–*S*–, while chains of the second "racemic" type include alternating molecules of both chiralities –*S*–*R*–*S*–*R*–.

ESI:† Fig. 4 shows projections of the crystal structures of racemate *RS*I, racemate *RS*II, *S*-enantiomer, and compound S_3R onto the *ab* and *bc* planes. The most interesting for analysis of these crystal structures are their projections on the *ac* plane depicted in Fig. 6. It can be seen that the neighbor molecules within the chains are interlinked *via* hydrogen bonds in all the crystal structures of *RS*I (Fig. 6a), *RS*II (Fig. 6b), *S* (Fig. 6c), and S_3R (Fig. 6d). For a convenient description, two opposite edges of the molecules will be designated here as a "head" and a "tail", where the head is the end of the molecule, which is closer to the side OH group, while the opposite end is, correspondingly, the tail.

In the crystal structures of racemate *RS*I, *S*-enantiomer and compound S_3R, the neighbor molecules have "head-to-head, tail-to-tail" connections. Molecules of different chiralities are characterized by the same conformation in the case of *RS*I chains and "racemic" chains of S_3R. Alternatively, molecules of the same chirality in the case of enantiomer chains and "enantiomeric" chains of S_3R are characterized by two conformations; this allows interlinking of such molecules. The crystal structure of *RS*II contains "head-to-tail" arrangements of molecules. As for *RS*I, the molecules are also characterized by different chiralities and by the same conformation.

In the crystal structures of all the malic acid compounds, the hydrogen bonds between neighbor molecules are conducted by the edge COOH groups. Two COOH groups belonging to neighbor molecules form carboxylic dimers (dimer ring). The differences in H-bond topography between various compounds (*RS*I, *RS*II, *S*, and S_3R) are due to the number of such contacts linking the molecules of the neighbor chains. In the case of *RS*I (Fig. 6a), there is an alternating number of H-bonds that connect the carboxylic rings corresponding to the neighbor chains. Carboxylic rings forming four contacts alternate with those forming six contacts. In Fig. 6, the contacts connecting the carboxylic dimers, as well as the contacts forming the dimers, are shown by the blue dashed lines. In

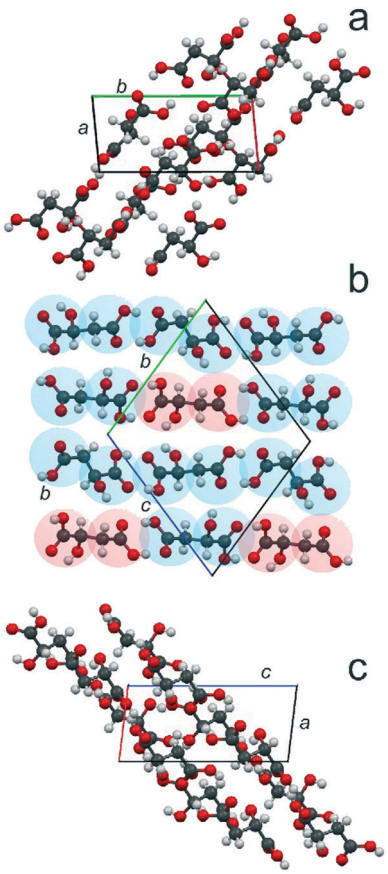

Fig. 5 Crystal structure of malic acid compound S_3R in projections upon the *ab* (a), *bc* (b), and *ac* (c) planes. On the *bc* projection (b), the *S*- and *R*-molecules are denoted by blue and red shadows, respectively.

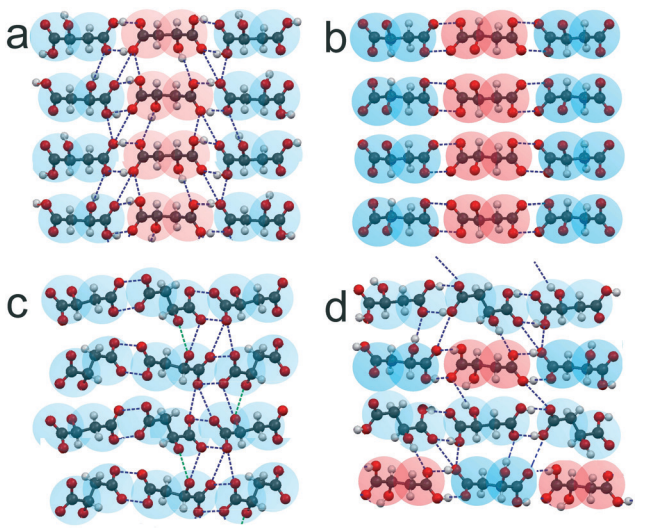

Fig. 6 Crystal structures of the racemic compounds *RS*I (a) and *RS*II (b), enantiomer *S* (c), and compound S_3R (d) of malic acid in projections upon the *ac* plane. The color designations of the *S*- and *R*-molecules are the same as in Fig. 5.

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Table 3 Equimolar discrete compounds in binary systems of enantiomers of different organic compounds

Systems	Methods of research	Crystal structure	Ref.
(+)-Chlorosuccinic acid–(−)-bromosuccinic acid	Melt phase diagram	Not determined	68
(+)-Mercaptosuccinic acid–(−)-methylsuccinic acid	Melt phase diagram	Not determined	69
(−)-Dilactic acid–(+)-2,4-dimethylglutaric acid	Melt phase diagram	Not determined	70
(−)-Thiodilactic acid–(+)-2,4-dimethylglutaric acid	Melt phase diagram	Not determined	70
(+)-2-Methylglutaric acid–(−)-2,4-dimethylglutaric acid	Melt phase diagram	Not determined	36
(+)-*m*-Methoxyphenoxypropionic acid–(−)-*m*-bromophenoxypropionic acid	SCXRD	Determined	71
(*S*)-2-(3-Bromophenoxy)propionic acid–(*R*)-2-(3-methoxyphenoxy)propionic acid	SCXRD	Determined	72
(*R*)-2-(2,4-Dichlorophenyl)propanoic acid–(*S*)-2-(2-chloro-4-nitrophenyl)propanoic acid	SCXRD	Determined	73
(*R*)-*N*-(4-Methylbenzoyl)-*R*-methylbenzylamine–(*S*)-*N*-(4-nitrobenzoyl)-*R*-methylbenzylamine	SCXRD	Determined	74
(*S*)-2-(2,4,5-Trichloroanilino)propanoic acid–(*R*)-2-(2,4,5-trichlorophenoxy)propanoic acid	SCXRD	Determined	75
(*R*)-*N*-(2-Chlorobenzoyl)methylbenzylamine–(*S*)-*N*-(2-bromobenzoyl)methylbenzylamine	SCXRD	Determined	76
(*S*,*S*)-2,8-Dichloro-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine–(*R*,*R*)-2,8-dibromo-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine	SCXRD	Determined	77
L-Malic–L-tartaric acid	SCXRD	Determined	78
L-Malic–D-tartaric acid	SCXRD	Determined	79
D-Valine–L-isoleucine	SCXRD	Determined	80

the case of *RS*II (Fig. 6b), there are no hydrogen bonds between the neighbor chains. In the case of the *S*-enantiomer (Fig. 6c), only half of the carboxylic rings are connected to those of a neighbor chain. There are five H-bonds per one ring. Moreover, there are two H-bonds on both sides from the ring that connect the pendant OH groups of the molecules corresponding to the neighbor chains. The contacts are shown by green dashed lines. In the case of S_3R (Fig. 6d), there are rings of four types. This is due to molecular chains of two types alternating in the crystal structure – enantiomeric and racemic. In the enantiomeric chains, there are alternating dimers with three and two contacts with the neighbor chains. In the racemic chains, there are alternating dimers forming two and four such contacts.

For convenience, the crystal structures described are schematically shown in Fig. 7(a–d). The use of different colors enables distinguishing *S*- and *R*-enantiomer molecules, and the OH groups are indicated to recognize the "tails" and the "heads" of the molecules. The molecule shape reflects its conformation – a straight shape corresponds to the "racemic" conformation, while the slanted shape corresponds to the "enantiomeric" conformation. This representation shows the principle packing of molecular chains of two types in the crystal structure of the compound S_3R. The crystal structure is a combination of the racemate *RS*I chains and *S*-enantiomer chains.

4. Systems of enantiomers of different compounds containing equimolar and non-equimolar discrete phases

4.1 Systems of enantiomers of different compounds containing equimolar discrete phases

In the available literature, there are a considerable number of publications reporting systems composed of enantiomers of different compounds. Some of these systems belong to the type two (see Fig. 1) since their equimolar compositions are discrete compounds. Fifteen examples of such systems are presented in Table 3,[36,68–80] and for ten of the related compounds, the crystal structures were determined using SCXRD. Almost all the represented enantiomeric molecules have only one chiral center, the exceptions being (−)-dilactic acid, (+)-2,4-dimethylglutaric acid and tartaric acid molecules with two equal chiral centers, *i.e.*, the carbon atoms with the chiral centers have the same substituents.[70]

The most interesting for our discussion are three systems: L-malic acid–L-tartaric acid,[78] L-malic acid–D-tartaric acid[79] and D-valine–L-isoleucine,[80] while malic acid and L-valine–L-isoleucine are, in turn, the subjects of our studies (see Table 1).

The first two systems differ from each other only in the type of chirality of tartaric acid as the second component. It should be noted that malic and tartaric acids have non-coinciding directions of rotation for the polarized light plane, which are L(−) and D(+) for malic acid and L(+) and D(−) for tartaric acid. The configuration difference of the tartaric acid molecule is reflected in the structure of the resulting binary compounds. The compound formed in the L-malic acid–D-tartaric acid system has the space group $P2_1$, while the one in the L-malic acid–L-tartaric acid system is characterized by the space group $P1$. The schematic representations of the molecular packing in the equimolar compounds of the above systems and selected discrete phases in the system of malic acid enantiomers are shown in Fig. 7(e and f) and (a–d), respectively. The third system, D-valine–L-isoleucine, differs from the one we studied only in having a different chirality in valine. This discrepancy determines the differences in the molecular compositions of the discrete compounds formed in the corresponding systems. A comparative analysis of their crystal structures is given in section 4.2.

L-Malic acid–D-tartaric acid system (Fig. 7e) is denoted L–D′. In the molecular chains of the LD′ binary compound of this system, the malic acid molecules only have the "racemic" conformation. In contrast to the chain arrangements in malic acid *RS*I and *RS*II (Fig. 7a and b), the neighbor chains are shifted relative to each other by one molecule in the direction

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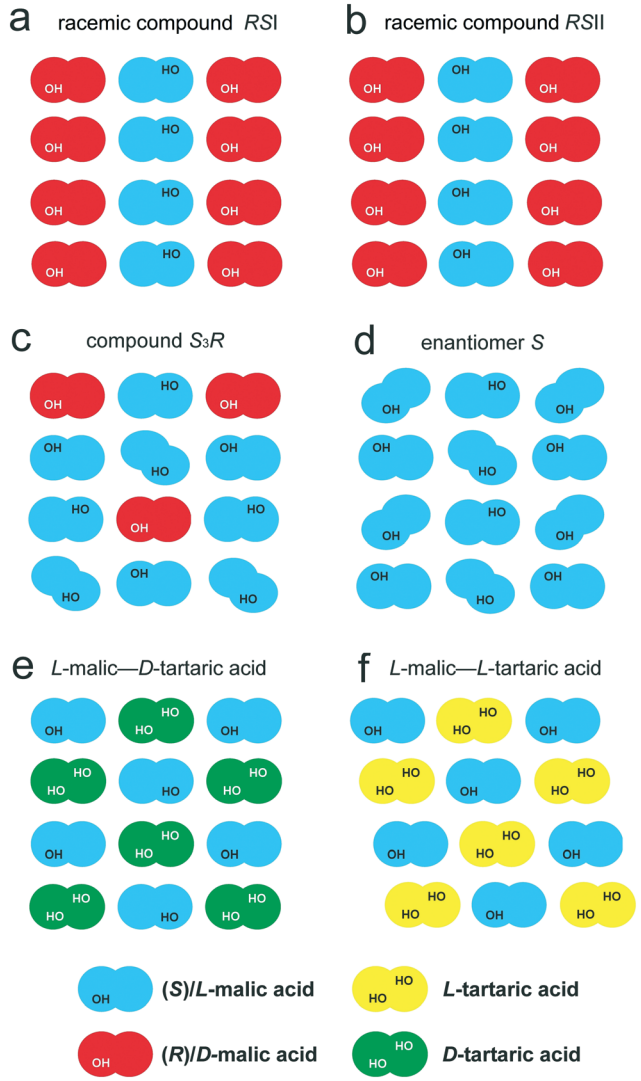

Fig. 7 Schematic representations of molecular packing in the crystal structures of racemic compounds *RS*I (a) and *RS*II (b), non-equimolar compound S_3R (c), and *S*-enantiomer (d) in the system formed by enantiomers of the same compound, *i.e.*, (*S*)-malic acid–(*R*)-malic acid, and in the crystal structures of equimolar compounds LD′ (e) and LL′ (f), in the systems formed by enantiomers of different substances, *i.e.*, L-malic acid–D-tartaric acid and L-malic acid–L-tartaric acid, correspondingly. Explanations are provided in the discussion.

of their elongation. This shift results in the molecules having a staggered arrangement (Fig. 7e). The tartaric acid molecule contains two side OH groups, while malic acid only has one. Hence, the neighbor molecular chains in the crystal structure of tartaric acid form more hydrogen bonds than the chains in the crystal structure of the malic acid racemate *RS*I.

L-Malic acid–L-tartaric acid system (Fig. 7f) is denoted L–L′. Similar to the LD′ compound, in the molecular chains of the LL′ discrete compound, the malic acid molecules only have the "racemic" conformation, and the neighbor chains are shifted, forming a staggered arrangement. The difference is that the "heads" of the malic acid molecules in the neighbor chains of the binary compound LL′ are directed to the same direction (Fig. 7f), while in the LD′ compound, they face the opposite sides (Fig. 7e).

4.2 Systems of enantiomers of different compounds containing non-equimolar discrete phases: the example of L-Val–L-Ile

We are aware of the existence of only three such systems containing non-equimolar discrete phases (Table 4). Two of them have been studied by means of melting point measurements,[36,70] and both are cited in Table 3 since they also include equimolar compounds. According to work,[5] these systems tend to form non-equimolar discrete compounds because they involve 2,4-dimethylglutaric acid as a component. The crystal structures of the 1 : 3 discrete compounds have not been determined; their presence was indicated by additional inflexion points in the liquidus lines. Molecules constituting both systems have different chiralities. Each of the molecular components of the system (−)-dilactic acid–(+)-2,4-dimethylglutaric acid has two equal chiral centers, while the molecules of the system (+)-2-methylglutaric acid–(−)-2,4-dimethylglutaric acid possess (with one and two) different numbers of chiral centers.

The principal feature distinguishing the L-valine–L-isoleucine system from those discussed above is the same – the L-chirality (configuration) of its components. The valine molecule has one chiral center; isoleucine contains two unequal chiral centers that differ from the (−)-dilactic and (+)-2,4-dimethylglutaric acid molecules, which have equal chiral centers (Table 4).

At least since 1933,[81] studies of solubility of Ile and Val in combination, and of individual solubilities of Val[82,83] and Ile[84,85] have been performed. The equilibria between the solid and liquid phases in the ternary system L-Val–L-Ile–water were studied by I. Kurosawa *et al.*[86] (HPLC and PXRD) and by D. Binev *et al.*[87] (HPLC). H. Koolman and R. Rousseau[88] investigated (SCXRD) the effect of small amounts of Val admixture on the growth and morphology of Ile crystals. The detailed correlation to our findings is discussed in work,[34] where most of our results for the L-Val–L-Ile system using HPLC (11 samples), PXRD (13 compositions), and SCXRD methods are published. First data obtained by TRPXRD was recently reported.[35]

According to the PXRD data, the limits of solid solutions in the system L-Val–L-Ile are rather limited. The system has been found to contain a non-equimolar discrete compound V_2I with the ratio Val : Ile = 2 : 1 (~66 mol% Val). According to this, three areas of solid solutions (ss) originating from valine ssV (>70 mol% Val), isoleucine ssI (<10 mol% Val), and discrete compound ssV_2I (60–68 mol% Val) were distinguished; also, two-phase regions were identified consisting of solid solutions ssI + ssV_2I (10–60 mol% Val) and ssV_2I + ssV (68–70 mol% Val). The results agree well with that obtained by independent HPLC studies. As shown in Fig. 8, the ternary phase diagram of the system L-Val–L-Ile–water contains a local solubility minimum that corresponds to the composition of ~66

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Table 4 Non-equimolar discrete compounds in binary systems of enantiomers of different organic compounds

Systems	Ratio	Methods of research	Crystal structure	Ref.
(+)-2,4-Dimethylglutaric acid–(−)-dilactic acid	3 : 1	Melt phase diagram	Not determined	70
(−)-2,4-Dimethylglutaric acid–(+)-2-methylglutaric acid	3 : 1	Melt phase diagram	Not determined	36
L-Valine–L-isoleucine	2 : 1	SCXRD, PXRD, TRPXRD	Determined	34, 35

mol% Val and is positioned in-between two eutonics laying asymmetrically left and right from it. Such behavior of the solubility curve is characteristic for systems containing a binary discrete compound.[22,89] Although the absolute solubility data (obtained by different methods) differ slightly from each other, they clearly indicate the local solubility minimum close to the 2 : 1 Val : Ile composition and verify the presence of the related V_2I compound in the system.

Crystal structure of compound V_2I. Crystal structures of the system components, valine and isoleucine, are known.[90–94] The newly discovered non-equimolar discrete compound V_2I has been studied by means of SCXRD.

The monoclinic cells of Val and Ile (space group $P2_1$) (Fig. 9a and b) are characterized by two crystallographically independent positions of the molecules.[90–94] Molecules occupying both positions have the same conformation. The monoclinic cell of V_2I (space group $C2$) (Fig. 9c) is characterized by four independent positions of the molecules, each of which have mixed populations, *i.e.*, can be occupied by either a Val or Ile molecule. The parameter a of the V_2I monoclinic cell is doubled in comparison to the corresponding parameters c of Val and Ile monoclinic cells (due to different unit cell orientations). The empirical formula of compound V_2I calculated on the basis of structural data corresponds to the Val : Ile ratio of ~60 : 40 and is practically confirmed by the composition of the sample studied (66 mol% Val). The calculated powder X-ray diffraction pattern shows good agreement with the experimentally obtained one.[34]

Similar to the crystal structures of Val[90,92,94] and Ile,[91,93,94] the crystal structure of the discrete compound V_2I is layered. Molecules in the three crystal structures are combined in H-bonded dimer molecules, and dimers form molecular layers also *via* H-bonds. The layers interact with each other by van der Waals forces. The Val and Ile dimers are elongated along the c axis, and the layers are connected by axes 2_1. However, the dimers in the crystal structure of V_2I are elongated along the a axis, and the layers are connected by axes 2_1 and 2. The difference in the azimuthal arrangement of the molecular layers can be seen easily if the doubled unit cell of Ile and the unit cell of V_2I are compared (see ESI:† Fig. 5 and work[34]).

Components of the system D-Val–L-Ile are known in the literature[80] and were mentioned before (Table 3). They differ from those of the system L-Val–L-Ile only by the configuration of the valine molecules. These systems exemplify the effect of the different chiralities of the molecules forming a binary system. In the first system,[80] an equimolar discrete compound VI (Val : Ile = 1 : 1) is formed, while in the second system, a non-equimolar discrete compound V_2I (Val : Ile = 2 : 1) is formed. The crystal structures of both compounds are characterized by alternating azimuthally non-equivalent molecular

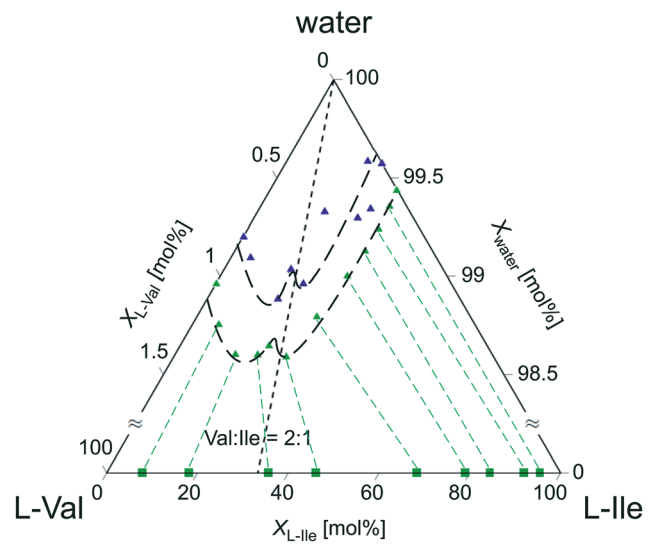

Fig. 8 Ternary phase diagram (50 °C) of the system L-Val–L-Ile–water. Green and blue triangles denote solubility data obtained by evaporation and cooling methods, respectively. Note that the solubilities occupy only the upper 1.5 mol% of the diagram. Green squares denote the compositions of the corresponding solids obtained from HPLC compositional analyses. Isotherm line is just to guide the eye (part of the data was published in former work[34]).

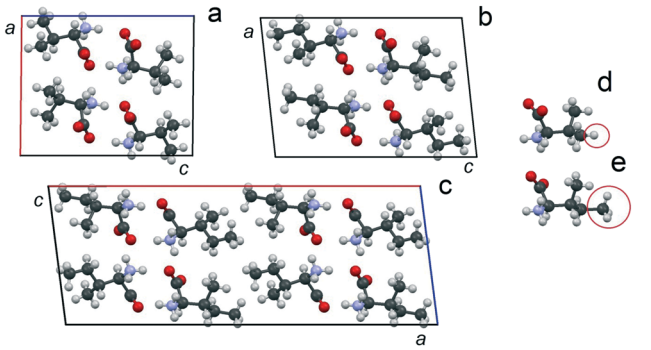

Fig. 9 Projections of the monoclinic cells of Val (a), Ile (b) and the discrete compound V_2I (c) on the *ac* plane[34] as well as levorotatory molecules of Val (d) and Ile (e). Atoms C, O, N, and H are colored in black, red, blue, and gray, respectively. The H atom of Val and CH_3 group of Ile are circled. The projections of the monoclinic cells of Val and Ile are plotted using structural data from CSD (identifiers LVALIN01 and LISLEU02, respectively).[94]

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layers and by doubled unit cells including two layers in corresponding translation. Wherein, the compound VI crystallizes in the space group $P2_1$, and the compound V_2I in the space group $C2$.

Schematic representations of the molecular packing in the crystal structures of Val, Ile, V_2I, and VI are shown in Fig. 10 for comparison. Molecules with L-configuration and the coordinates y and $y + 1/2$ at the b axis of the unit cell are shown in blue and light blue colors, respectively; molecules with D-configuration are in green. Different shapes of the Val and Ile molecules reflect the fact that in comparison to Val, the edge H atom is replaced by a CH_3 group in Ile. The group is shown by an additional rear circle. Partial coloring of the circle in the case of V_2I symbolizes the partial (33%) occupation of the site by a rear CH_3 group.

5. Systematization of discrete compounds formed in binary chiral systems of organic substances

The term "racemate" or "racemic modification" was introduced as early as the 2nd half of the 19th century after L. Pasteur's well-known experiments to describe an enantiomer mixture containing equimolar amounts of the components. However, this definition does not reveal the nature of the mixture itself. In the published literature, there are plenty of terms used for *discrete* phases in related systems, *e.g.*, true racemates, false conglomerates, quasiracemates, anomalous racemates, anomalous quasiracemates, anomalous conglomerates, cocrystals, 1 : 1 complexes, and others. The importance of knowledge about the variety of solid phases in chiral systems (*e.g.*, for pharmaceutical and food industries) as well as the great scope of acquired data made the following questions emerge: Which particular type of compound is implied when one of the above definitions is used? How do they relate to each other?

We have attempted to systematize the data on discrete compounds in such systems, and the results are compiled in Table 5. The systematization is not aimed at changing the terminology but clarifying what is exactly meant under the terms mentioned. To make the systematics viable, it is necessary to define the border lines covering the types of compounds that can be included.

First, it is applicable only to chiral compounds that are "true" organic substances (known to contain a selected number of chemical elements[95]) and, therefore, excludes organometallic compounds. Second, the systematization is proposed only for compounds formed in true binary systems, *i.e.*, substances composed of only two molecular species. That is why it does not encompass compounds containing solvent molecules. For example, E. Wachter *et al.*[96] recently described the crystal structure of a PF_6^- salt of [Ru(2,9-dimethyl-1,10-phenanthroline)$_2$(dipyrido[3,2-*d*:2′,3′-*f*]quinoxaline)]$^{2+}$ with the enantiomer ratio of 5 : 4. However, the crystal structure of this

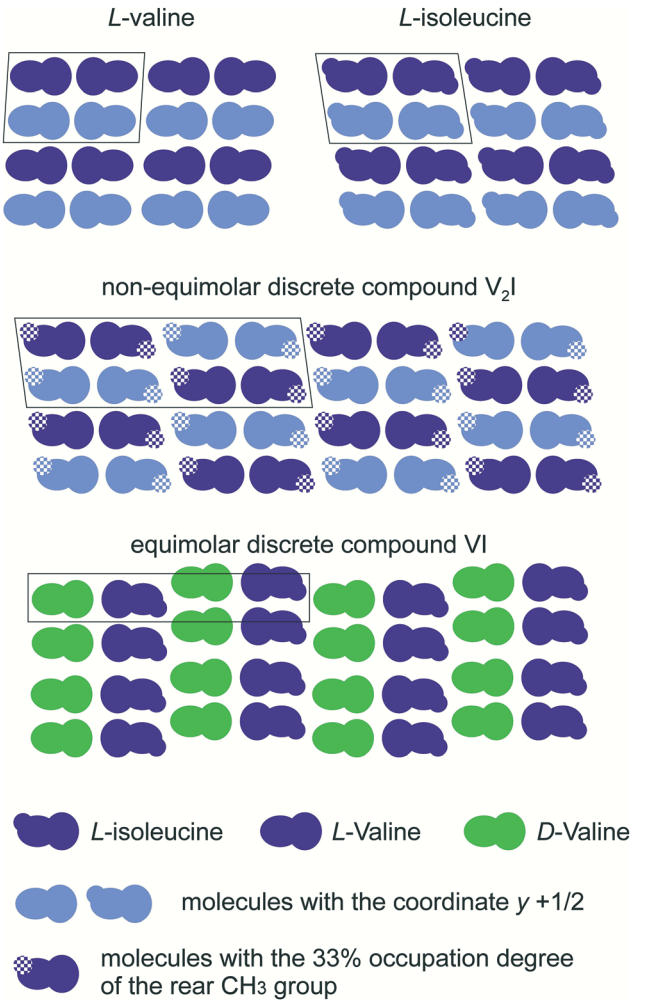

Fig. 10 Schematic representations of molecular packing in crystal structures of Val, Ile, and non-equimolar compound V_2I in the L-Val–L-Ile system and the equimolar compound VI in the D-Val–L-Ile system.

compound incorporates molecules of the solvents (acetone, diethyl ether, and water) in addition to the organometallic component. Third, we only consider hydrogen and van der Waals-bonded crystals where the molecular components are related to each other as enantiomers or quasi-enantiomers (including diastereomers).[97] Furthermore, attention should be paid to the term "cocrystals," which is frequently used in relation to pharmaceuticals with the potential to improve their physicochemical properties.[98] A broadly accepted definition of the term comprises substances composed of two or more neutral molecular components at definite stoichiometric amounts, which are characterized by structural homogeneity and the absence of solvate molecules in their crystal structure.[99,100] Therefore, related compounds include binary donor–acceptor complexes and crystals with hydrogen bonds.[99] Consequently, the term cocrystal has a rather broad definition, especially considering chiral and achiral compounds. Accordingly, only cocrystals containing chiral components and only two of them find proper positions in our systematization.

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Table 5 Discrete compounds in binary systems of organic substances with chiral molecules

Equimolar discrete compounds 1 : 1

Homomolecular (racemic) compounds				**Heteromolecular compounds**		
Centrosymmetric	Non-centrosymmetric *S* and *R* molecules are connected *via* other symmetry elements	Independent *S* and *R* molecules	1 : 1 Complexes[104]	Pseudo-centrosymmetric Quasiracemates[105]	Non-centrosymmetric Cocrystals[79]	1 : 1 complexes[106,108]
Racemic compounds (true racemates)[5]	Racemic compounds (true racemates)[5]	Kryptoracemates[101] (= false conglomerates[102])				
Enantiomers *S* : *R*	Enantiomers *S* : *R*	Enantiomers *S* : *R*	Diastereomers *S* : *Sa* (*R* : *Ra*) and *S* : *Ra* (*R* : *Sa*)	Enantiomers of different substances *S* : *R*′ (*S*′ : *R*)	Enantiomers of different substances *S* : *R*′ (*S*′ : *R*) and *S* : *S*′ (*R*′ : *R*)	Diastereomers of different substances
e.g.: Malic acid *RS*I[29]	*e.g.*: Malic acid *RS*II[29]	*e.g.*: *SR*-Allylglycine[103]	*e.g.* (*S* : *Sa*): L-Isoleucine–L-*allo*-isoleucine[104] *e.g.* (*S* : *Ra*): L-Isoleucine–D-*allo*-isoleucine[104]	*e.g.*: L-Isoleucine–D-valine[80]	*e.g.* (L : L′): L-Malic acid–L-tartaric acid[78] *e.g.* (L : D′): L-Malic acid–D-tartaric acid[79]	*e.g.* (*R*′ : *Sa*): D-Norleucine–L-*allo*-isoleucine[106] *e.g.* (*S* : *Ra*′): L-Phenylalanine–D–*allo*-isoleucine[108]

Non-equimolar discrete compounds 1 : N

Homomolecular compounds		**Heteromolecular compounds**		
Anomalous racemates[51] (= anomalous conglomerates[52,107])	Diastereomers *S* : *Sa* (*R* : *Ra*) and *S* : *Ra* (*R* : *Sa*) = 1 : N and N : 1	Anomalous quasiracemates[37]	Enantiomers of different substances *S* : *S*′ (*R* : *R*′) = 1 : N or N : 1	Diastereomers of different substances *S*′ : *Ra* (*R*′ : *Sa*) and *S* : *Ra*′ (*R* : *Sa*′) = 1 : N or N : 1
Enantiomers *S* : *R* = 1 : N and N : 1		Enantiomers of different substances *S* : *R*′ (*S*′ : *R*) = 1 : N or N : 1		
e.g.: Malic acid *S* : *R* = 1 : 3 and 3 : 1 (ref. 29)	No examples found	*e.g.* (*S* : *R*′): Dilactic acid–dimethylglutaric acid = 1 : 3 (ref. 70)	*e.g.* (*S* : *S*′): L-Valine–L-isoleucine = 2 : 1 (ref. 34)	No examples found

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The systematization in Table 5 is based on the following two principles. **Principle 1**: Classification according to the composition of the compound: 1) division into two major groups, *viz.*: equimolar and non-equimolar discrete compounds (at top and bottom of Table 5), and 2) further division into two subgroups, *viz.*: homomolecular and heteromolecular compounds, *i.e.*, compounds composed of molecules of the same or different substances. **Principle 2**: Classification within each one of the four resulting subgroups according to 1) compound stereochemistry (enantiomers or diastereomers) and 2) crystallographic features. Each subsection in the table provides particular examples. The references given there correspond to the original publications with the authors' definitions.

Homomolecular (racemic) compounds

Homomolecular (racemic) compounds can be divided into centrosymmetric and non-centrosymmetric compounds.

Centrosymmetric compounds of this group are represented only by racemic compounds or *true racemates.*[5] They form the most abundant and most frequently studied group. In the compounds, molecules form dimers, wherein a dextrorotatory molecule is connected to a levorotatory one *via* an inversion center. One of the feasible examples is racemic malic acid of the *RS*I modification.[27–29]

Non-centrosymmetric compounds of this group are much less frequently occurring and can be divided into three subgroups. The first one is also represented by racemic compounds. *S* and *R* molecules do not form dimers here; they are combined *via* other symmetry elements instead of an inversion center. It includes the *RS*II modification of racemic malic acid discussed before.[27–29] The second subgroup consists of *kryptoracemates*,[101] also known as *false conglomerates*.[102] In compounds of this type, *S* and *R* molecules occupy independent crystallographic positions, *i.e.*, they are not connected *via* symmetry elements. According to the authors,[101] about 180 substances form compounds of this type. The third subgroup is comprised of compounds named 1 : 1 *complexes*,[104] where the components are diastereomers of the same substance and can have either the same chirality (*S* : *Sa* and *R* : *Ra*) or different chiralities (*S* : *Ra* and *R* : *Sa*). Diastereomeric molecules forming such pairs cannot be related *via* symmetry elements.

Heteromolecular compounds 1 : 1

Heteromolecular compounds 1 : 1 cannot be centrosymmetric by definition. However, they can also be classified into two subgroups: pseudo-centrosymmetric and non-centrosymmetric ones.

Pseudo-centrosymmetric compounds of this type are known to be reported as *quasiracemates*.[105] They contain enantiomer molecules of different substances (see Table 3). However, structural differences between the molecules are rather insignificant, and, usually, they differ only by one atom or a small group of atoms. In some works,[97] the term "quasienantiomers" is used for such molecules. In a crystal structure, a pair of such molecules usually forms a dimer, wherein the molecules are connected to each other *via* a pseudo-inversion center.

Non-centrosymmetric compounds of this group can be subdivided into two subgroups. One of them would include *cocrystals*,[79] *i.e.*, the system components are enantiomers of different substances. The other one contains 1 : 1 *complexes*,[97,106] wherein the system components are diastereomers of different compounds.

Homomolecular compounds 1 : N

Homomolecular compounds 1 : N (Table 5, bottom part) can formally be classified into two subgroups. One of them contains *anomalous racemates*[51] or *anomalous conglomerates*.[52,107] Both terms were introduced to define non-equimolar compounds formed by enantiomers. Compounds of this type have not been found yet among diastereomeric pairs. Systems containing anomalous racemates are rather rare and scarcely studied, and most publications, with a couple of minor exceptions, are devoted to compounds of enantiomer pairs with the enantiomer ratio of 1 : 3 (see Table 2). Examples include the stable S_3R and metastable 3*S*1*R* modifications of malic acid described above.

Heteromolecular compounds 1 : N

Heteromolecular compounds 1 : N (Table 5, bottom part) form the rarest group, and the number of reported studies of such compounds is very limited. Technically, three subgroups can be distinguished. The first one was named *anomalous quasiracemates*[50] and contains compounds of enantiomer molecules of different substances. The term has been introduced to denote 1 : N compounds formed in addition to quasiracemates in systems of components of different chiralities. The second subgroup (no name yet) includes compounds occurring in systems of components of the same chirality; such systems do not produce quasiracemates. A representative of this subgroup, compound V_2I, has been depicted above. The third subgroup (also no name yet) is comprised of compounds formed by diastereomers of different substances. We know only three systems forming 1 : N heteromolecular compounds (see Table 4), and they belong to the first and second subgroups.

According to statistical data,[96] the occurrence of non-equimolar discrete compounds among substances with chiral molecules is negligible, being 1 : 100 000. If so, is their study practical? We think that it is. Their physicochemical properties (beneficial, harmful, or neutral) have not been sufficiently investigated yet. We suppose that this may change in the future provided the examinations of chiral systems (enantiomers and diastereomers) are performed using a combination of precision methods. Both systems that we investigated can serve as good examples.

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6. Summary

Information on non-equimolar discrete compounds in binary systems of chiral organic substances, which is available in the literature, has been reviewed and systematized, including the rate of occurrence of such systems and the current state of knowledge in the field.

For the systems (*S*)-malic acid–(*R*)-malic acid and L-valine–L-isoleucine, as examples representing different types of binary systems, the crystal structures of the non-equimolar discrete compounds were analyzed on the basis of comprehensive experimental studies. The results obtained were compared with the data reported in the literature for these two and other similar systems.

The **(*S*)-malic acid–(*R*)-malic acid system** was shown to form 1) an equimolar compound, which could occur in three modifications; two of these, the *RS*I and *RS*II modifications, have been known for some time, while the third form, *RS*III, was discovered and described by the present authors, and 2) the non-equimolar stable (S_3R and SR_3) and metastable (3*S*1*R* and 1*S*3*R*) compounds with ratios $S:R$ equal to 3 : 1 and 1 : 3, correspondingly. Crystallization conditions resulting in the formation of a particular modification of both equimolar and non-equimolar compounds have been ascertained, and the polymorphic transformations between the discrete phases have been studied. The data obtained were used to plot a schematic representation of the system phase diagram. The (triclinic) crystal structure of the non-equimolar discrete compound S_3R has been identified and compared to those of the *S*-enantiomer and the racemic compounds *RS*I and *RS*II. At present, information on the crystal structures of non-equimolar discrete compounds is available only for a dozen systems of enantiomers of the same compound of which we have knowledge (including our data).

For the **L-valine–L-isoleucine system**, the occurrence of a non-equimolar compound V_2I with the Val : Ile ratio of 2 : 1 could be proven. The solubility diagram plotted for the ternary L-valine–L-isoleucine–water system exhibits two eutonics located on both sides from the local solubility minimum, which corresponds to the composition of compound V_2I. The (monoclinic) crystal structure of the V_2I compound has been determined and compared to those of the system components L-Val, L-Ile and the equimolar compound formed in the D-Val–L-Ile system. To the best of our knowledge, this is the only available information on the crystal structure of a non-equimolar compound in a system of enantiomers of different substances and, at the same time, the only example of a binary compound where these enantiomers are of the same chirality.

Based on the results of the study, a systematization of discrete compounds occurring in binary chiral systems of organic substances was proposed. This was motivated by the great scope of the acquired knowledge and the variety of terms used in the literature. The presented systematics define chemical and crystallographic characteristics of the discrete compounds that can be ascertained when using a particular term. To increase its applicability, the types of compounds covered with the systematization were defined. Of course, we do not consider this systematization as complete and all-encompassing. New materials are steadily appearing that might fill the still empty places in the systematization table and support a deeper understanding of the structure–property relationships within the systems studied.

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