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Nicolas Estime, Richard Pena, Sébastien Teychené, Jean Marie Autret, Béatrice Biscans. Characterization of the conglomerate form of acetyl-dl-leucine by thermal analysis and solubility measurements. Journal of Crystal Growth, 2012, vol. 342 (n° 1), pp. 28-33. 10.1016/J.JCRYSGRO.2011.03.023 . hal-03536619

HAL Id: hal-03536619

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To link to this article: DOI:10.1016/J.JCRYSGRO.2011.03.023
URL: http://dx.doi.org/10.1016/J.JCRYSGRO.2011.03.023

To cite this version: Estime, Nicolas and Pena, Richard and Teychené, Sébastien and Autret, Jean Marie and Biscans, Béatrice (2011) Characterization of the conglomerate form of acetyl-dl-leucine by thermal analysis and solubility measurements. *Journal of Crystal Growth*, vol. 342 (n°1). pp. 28-33. ISSN 0022-0248

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Characterization of the conglomerate form of acetyl-DL-leucine by thermal analysis and solubility measurements

N. Estime [a,*], R. Pena [b], S. Teychené [a], J.M. Autret [c], B. Biscans [a]

[a] Université de Toulouse, CNRS Laboratoire de Génie Chimique UMR 5503, 4 allée Émile Monso, BP 84234, 31432 Toulouse Cedex 4, France
[b] Centre de Recherche Pierre Fabre, Département Chimie, 17, avenue Jean Moulin, 81106 Castres Cedex 06, France
[c] Institut de Recherche Pierre Fabre, 16 rue Jean Rostand, BP 92, 81603 Gaillac Cedex, France

A B S T R A C T

Starting from a mixture of enantiomers in solution, crystallization can generate different types of crystals. In order to determine which type of crystal is obtained in the case of acetyl leucine, an active pharmaceutical ingredient (API), analytical methods have been used to partially elucidate the binary and ternary phase diagrams of the system composed of the two enantiomers and water.

The melting temperature phase diagram of this compound has been obtained by using differential scanning calorimetry (DSC) analyzes. The results show that it is characteristic of a conglomerate. This mode of crystallization has also been confirmed by X-ray powder diffraction analysis.

Solubility measurements of enantiomerical mixtures in water enabled the determination of the ternary diagram of solubility. The empiric Meyerhoffer double solubility rule has been modified, due to the characterization of interactions between enantiomers.

1. Introduction

Life is essentially constructed using L-amino acids as building blocks, which are enantiomers, that is to say chiral compounds that are non-superimposable mirror images at each other. In many cases, only one enantiomer provides the desired physiological effect whereas the other enantiomer has no effect. Thus, there is an important interest in the pharmaceutical, food and agrochemical industries to produce pure enantiomers or to separate them from a racemic mixture. An economical way to obtain pure enantiomer is the separation by crystallization as Pasteur did with sodium ammonium tartrate enantiomers [1]. As opposite enantiomers can crystallize in the same crystal or separately, the feasibility of a selective crystallization is then strongly dependent on the mode of crystallization of the compound. The design and the optimization of a crystallization process thus rely on the knowledge of the type of the enantiomerical crystallization [2].

Three different types of crystallization, corresponding to the three different kinds of racemates [3,4], are usually identified (see Fig. 1) :

- The conglomerate (or racemic conglomerate) consists of a physical mixture of pure crystals of one enantiomer and its counterpart. In the crystal structure, molecules have a greater affinity for the same enantiomer than for the counterpart and the two enantiomers crystallize separately. Only 5–10% of the racemic mixtures belong to the conglomerate-forming group [5].
- The true racemate (or racemic compound) is formed by a single crystalline phase in which the two enantiomers are ordered in a 1:1 ratio. In this case, molecules have a greater affinity for the counterpart than for the same enantiomer. The racemic compound behaves as a pure compound and has its own physical properties.
- The racemic solid solution (or pseudoracemate) is a crystal composed of both enantiomers, in equal proportions, but coexisting in an unordered manner in the crystal lattice, because there is no significant difference in affinity between the same and opposite enantiomers.

Each mode has its own physical properties [3]: melting temperature [6], solubility in a given solvent [7], structure [4] or density [8,9]. These differences enable the determination of the mode of crystallization of a compound by building phase diagrams (see [10] for the propanolol hydrochloride case), which are useful for the control of the crystallization process.

The molecule studied in this paper is acetyl leucine. Its pharmaceutical activity is detailed by Neuzil et al. [11]. This API is found in the final drug as acetyl-DL-leucine, an equimolar mixture of acetyl-D-leucine and acetyl-L-leucine. The chemical way of preparation of this API is well known and studied [12]. Previous works have also been carried out on enantiomers separation of acetyl-DL-leucine by solvent extraction [13] or by preferential crystallization method [14]. However, to our knowledge, no thermodynamic data are available in the

* Corresponding author. Tel.: +33 5 34 32 36 42; fax: +33 5 34 32 37 00.
E-mail address: nicolas.estime@ensiacet.fr (N. Estime).

literature for this compound and for the building of its phase diagrams. This is usually the case for enantiomerical systems [2,15]. The goal of this paper is then to determine the type of crystallization of this compound and to explain the possible separation of its enantiomers, by determining the binary phase diagram of melting temperature and the ternary diagram of solubility of this compound in water.

2. Materials and method

2.1. Materials

Three different forms of acetyl leucine were used in this work: the two enantiomerical forms, named D and L, and the racemic form, named acetyl-DL-leucine. All these products were provided by Pierre Fabre laboratories with a HPLC purity of 99.9%, evaluated by HPLC. The solvent used was bidistilled water.

2.2. Methods

2.2.1. Enantiomer mixture preparation

Two different kinds of mixture were used in this study:

- *Physical mixtures* which are prepared by mixing dry crystals in different ratios of acetyl-L-leucine and acetyl-D-leucine (ranging from 10% to 90%). Two kinds of physical mixtures were prepared: either by mixing both enantiomers [16,17], or by mixing the racemate (acetyl-DL-leucine) with one of the pure enantiomers.
- *Recrystallized samples* obtained from under-saturated aqueous solutions of enantiomers slowly heated in an oven at 50 °C in order to generate crystallization by solvent evaporation [18].

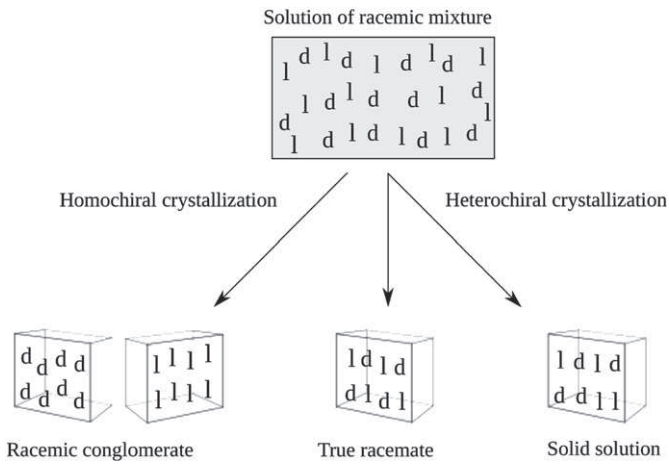

Fig. 1. Crystallization modes of racemic mixtures.

2.2.2. Thermal characterization

Classical and modulated differential scanning calorimetry (DSC) profiles were obtained with a TA Instruments Q2000. The apparatus was calibrated using the melting enthalpy of indium (28.5 J/g) used as a reference [19].

For DSC analyzes, the samples (4–6 mg) were introduced into a 20 μL aluminum crucible. Sealed crucibles were heated at a temperature rate of 1 or 5 °C/min, from 0 to 200 °C, under a stream of nitrogen (50 mL/min). The melting temperature corresponds to the extrapolated onset temperature.

2.2.3. X-ray powder diffraction (XRPD)

X-ray powder diffraction pattern was recorded in transmission mode on a D8 Advance diffractometer q/q (Bruker AXS) operating with copper radiation (Ka = 1.54060 Å) and fitting with the Vantec detector. The parallel beam geometry (Göbel mirror) was used, with a divergence slit of 0.2 mm. The powder samples were sealed in 1 mm quartz capillary tube. Data were recorded at 22 °C with a step size of 0.007° and a counting time of 2 s/step from 2° to 60°.

2.2.4. Solubility measurements

Solubility measurements were carried out in water with physical mixtures of enantiomers by the analytical shake-flask method, using constant-temperature jacketed glass cells. A constant temperature of 25 °C (± 0.1 °C) was maintained with circulating water bath. The way of preparing the saturated solutions was slightly modified compared to the classical method. Here, solubility was determined by adding weighed quantities of powder mixture to a known volume of distilled water, until crystals cannot be dissolved anymore. Small amounts of solid (about 20 mg) were added each time and no addition was performed before the solution was clear. When the equilibrium was reached, solutions were stirred for 24 h. The pH of the saturated solutions was then measured, using a pH meter pHM210 from Radiometer Analytical with a pHC3001 electrode and the mass of solid added was calculated in order to get the solubility.

The uncertainty of solubility determination ΔS is lower than 5%.

3. Results and discussion

3.1. Binary phase diagram

3.1.1. DSC analysis

In a mixture of enantiomers, some physical properties are modified according to the composition of enantiomers [3,20]. The evolution of these properties, reported in a phase diagram, is characteristic of the type of crystallization of the compound. Fig. 2 shows the evolution of the typical melting phase diagrams, for the three modes of crystallization [4].

If crystals form a racemic conglomerate (part a) of Fig. 2, there is only one eutectic point obtained for equimolar composition,

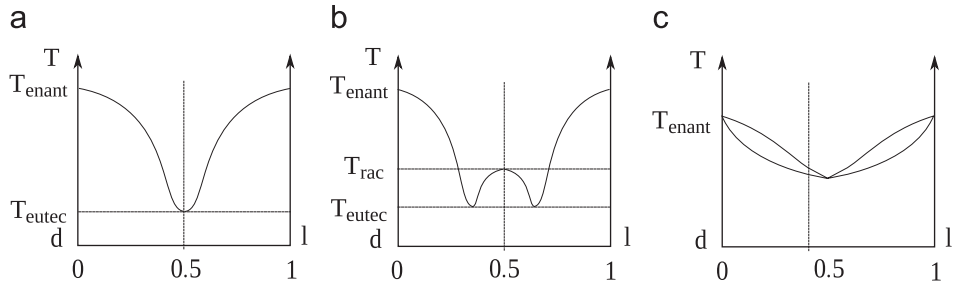

Fig. 2. Different types of melting temperature binary diagrams: (a) racemic conglomerate; (b) true racemate and (c) solid solution.

and its melting temperature is always lower than the pure enantiomer one. The addition of a small amount of one enantiomer to the conglomerate increases the melting temperature.

If crystals form a true racemate (Fig. 2b), there are two eutectic points, symmetrical in relation to the equimolar composition, with lower melting temperatures than the racemic compound one. In that case, the addition of a small amount of one enantiomer to the racemic compound decreases the melting temperature. However, the pure enantiomer may have a higher or lower melting temperature than the true racemate.

Finally, in the case of a solid solution, the evolution of the melting temperature is difficult to predict and there is no eutectic point. Part (c) of Fig. 2 gives the example of one kind of solid solution [21] but other solid solution phase diagrams can be found [22].

DSC thermograms of physical mixtures of enantiomers (acetyl-L-leucine and acetyl-D-leucine) and of racemate (acetyl-DL-leucine) with one enantiomer are, respectively, reported in Figs. 3 and 4.

First, in the case of pure enantiomer, only one endothermic peak corresponding to the melting of the crystals is obtained whereas when mixtures were analyzed by DSC, two distinct peaks appear. The thermograms given in Fig. 3 clearly show that the temperature corresponding to the first peak is constant (158 °C) for all the mixtures studied. This temperature corresponds to the melting temperature of the eutectic. The second peak depends on the enantiomer composition. It defines the liquidus curve in the liquid–solid diagram. When the composition of the mixture becomes close to the racemic composition, the second peak is close to the eutectic one. For example, in the cases of the mixtures (30% L–70% D) and (60% L–40% D) shown in Fig. 3, the two peaks overlap each other and it is not possible to separate the two peaks.

Physical mixtures of pure enantiomers can be representative of conglomerates, in which each enantiomer crystallizes separately, with their own crystal structure. This kind of mixtures cannot represent true racemate or solid solution, in which both enantiomers are present inside the crystal structure. In order to determine the type of crystallization of the acetyl leucine racemate, physical mixtures of the racemate and of a pure enantiomer were also analyzed by DSC and compared. The onset difference with the previous mixtures is low (about 1°) which indicates a similar behavior for the two mixtures. The onset of acetyl-DL-leucine is lower than the racemic mixture of acetyl-L-leucine and acetyl-D-leucine. This result cannot happen in the case of a true racemate. Indeed, the melting temperature of a true racemate is always higher than the melting temperature of its eutectics. So, the racemic conglomerate is the mode of crystallization of acetyl leucine.

Similar results were obtained for recrystallized solid samples obtained from aqueous solutions of acetyl leucine (Fig. 5). For a racemic composition, the melting temperature of the recrystallized sample corresponds to the eutectic melting temperature obtained for the other enantiomerical composition. As the results are similar to the physical mixtures ones, the formation of a conglomerate has been demonstrated.

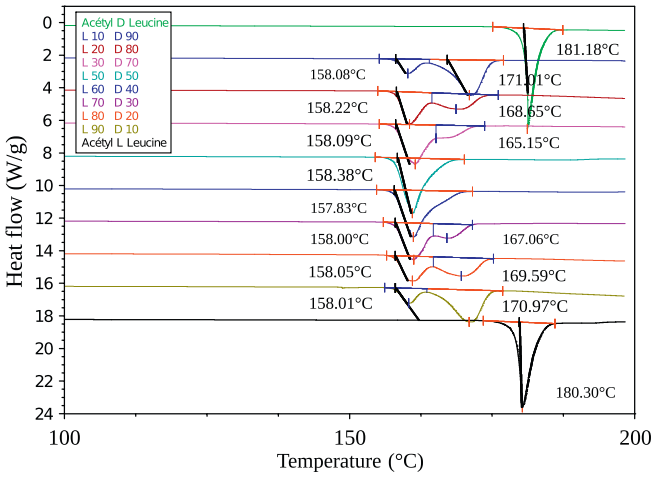

Fig. 3. DSC analyzes as a function of the proportion of acetyl-L-leucine, for physical mixtures of acetyl-L-leucine and acetyl-D-leucine.

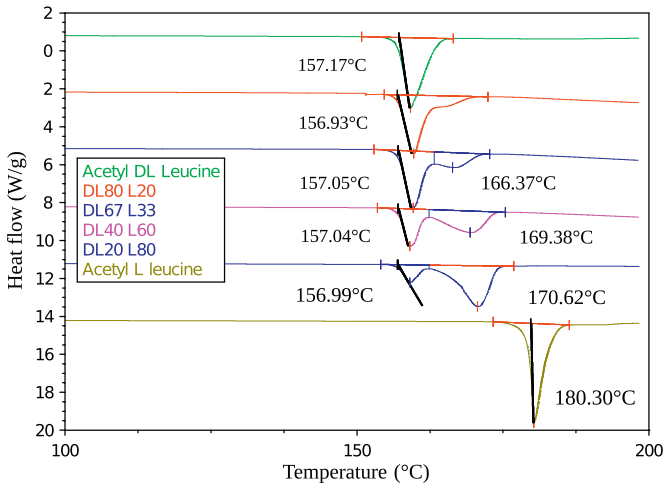

Fig. 4. DSC analyzes as a function of the proportion of acetyl-L-leucine, for physical mixtures of acetyl-DL-leucine and acetyl-L-leucine.

3.1.2. Characterization by X-ray analyzes

X-ray diffraction has been used in two main areas, for the fingerprint characterization of crystalline materials and for the determination of their structure. Each crystalline solid has its unique characteristic X-ray powder pattern which may be used as a "fingerprint" for its identification. The crystal structure of acetyl-L-leucine has already been solved [23]. The crystals are orthorhombic, and the space group is $P2_12_12_1$. Each unit cell contains four molecules and has the dimensions: $a = 10.184$ Å, $b = 17.249$ Å and $c = 5.779$ Å. Same results are obtained from analyzes of the crystals of acetyl-L-leucine produced industrially. The crystallinity of the product is then well controlled.

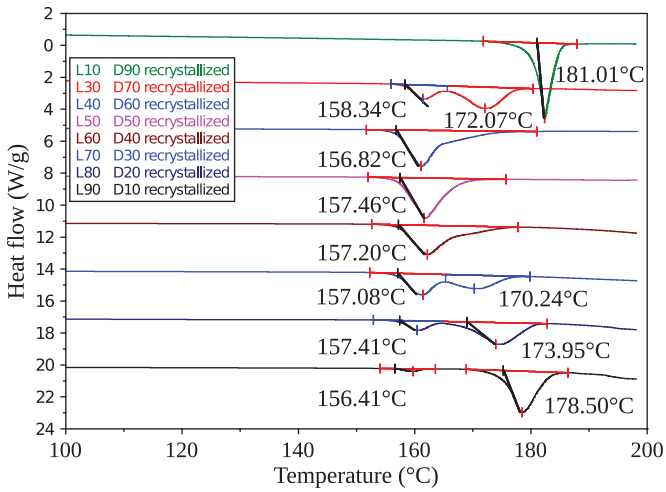

Fig. 5. DSC analyzes as a function of the proportion of acetyl-L-leucine, for recrystallized samples.

Analysis also shows that the two enantiomers, acetyl-L-leucine and acetyl-D-leucine, have the same X-ray diffractogram, so have the same crystal structure. In that case, X-ray powder diffraction does not enable to distinguish pure enantiomers from each other in a physical mixture. On the contrary, a true racemate has its own crystal structure, leading to different X-ray powder patterns from the pure enantiomer one.

The distinction between conglomerate and true racemate can then simply be obtained by analyzing a sample of the racemate by X-ray diffraction. This analysis, reported in Fig. 6, shows that the racemic form diffractogram has exactly the same peaks as the enantiomers. It corresponds to a physical mixture of enantiomers, thus to a conglomerate.

3.1.3. *Determination of the binary diagram composed of the two enantiomers of acetyl leucine*

The DSC measurements performed in the previous section enable to draw a part of the phase diagram of the binary D and L acetyl leucine compounds system (see Fig. 7). This diagram clearly shows a horizontal straight line defining the eutectic melting temperature.

Assuming that acetyl leucine forms a conglomerate, this binary phase diagram can also be calculated from the Schröder Van Laar equation (Eq. (1)). This equation gives the liquidus curve as a function of the enantiomerical composition:

$$\ln(x_s) = -\frac{\Delta H_{mel}}{R}\left(\frac{1}{T} - \frac{1}{T_{mel}}\right) + \frac{\Delta C_p}{R}\left[\frac{T_{mel}}{T} - \ln\left(\frac{T_{mel}}{T}\right) - 1\right] - \ln(\gamma_s) \quad (1)$$

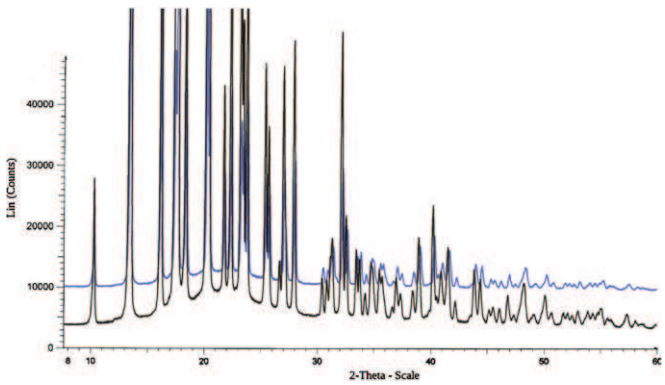

Fig. 6. X-ray analyzes of acetyl-D-leucine and acetyl-DL-leucine.

where

- x_s is the enantiomerical molar fraction;
- ΔH_{mel} is the melting enthalpy;
- ΔC_p is the difference of specific heat capacities between the solid and the liquid phases;
- R is the gas constant (8.314 J/K mol);
- T is the melting temperature of the mixture of enantiomers;
- T_{mel} is the melting temperature of pure enantiomer;
- γ_s is the activity coefficient of the product.

Several assumptions can be made to simplify this equation. The first hypothesis is that the difference of specific heat capacities is negligible. The second one supposes the ideal model, with the activity coefficient equal to unity [15]. The simplified equation (Eq. (2)) can then be rewritten as follows :

$$\ln(x_s) = -\frac{\Delta H_{mel}}{R}\left(\frac{1}{T} - \frac{1}{T_{mel}}\right) \quad (2)$$

On the basis of this simplified model and from the data obtained by DSC analyzes ($\Delta H_{mel} = 31.5$ kJ/mol and $T_{mel} = 180.5$ °C), a theoretical diagram is plotted and compared with experimental data (Fig. 7).

There are great differences between experimental data points and the model.

By applying Eq. (2), the melting temperature of the eutectic should be 145.8 °C instead of 158.3 °C. In order to have a model that fits experimental data points, the melting enthalpy should be equal to 71 kJ/mol and the melting temperature of enantiomer should be 174 °C. Results of this model are reported in Fig. 8.

Events, like degradation [24] or chemical reactions, may occur during the melting of a compound and modify the enthalpy determined by DSC analyzes. Additional investigation are needed to go further to this explanation and to determine if a simultaneous reaction occurs during the melting of the compound. It is not developed in this work.

3.2. *Ternary diagram of the two enantiomers of acetyl leucine and water*

3.2.1. *Experimental ternary diagram*

In a non-chiral solvent, opposite pure enantiomers have always the same solubility because changes of asymmetric carbon configuration do not modify interactions with other species in solution. However, mixtures of enantiomers have their own solubility. The knowledge of the solubility of a racemic mixture

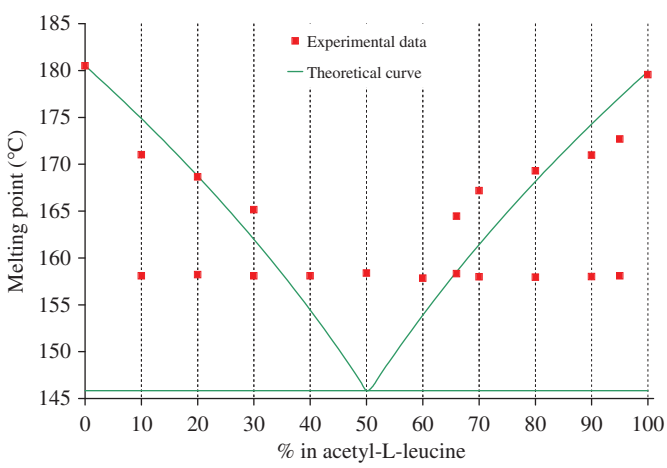

Fig. 7. Experimental data and predicted melting temperature phase diagram.

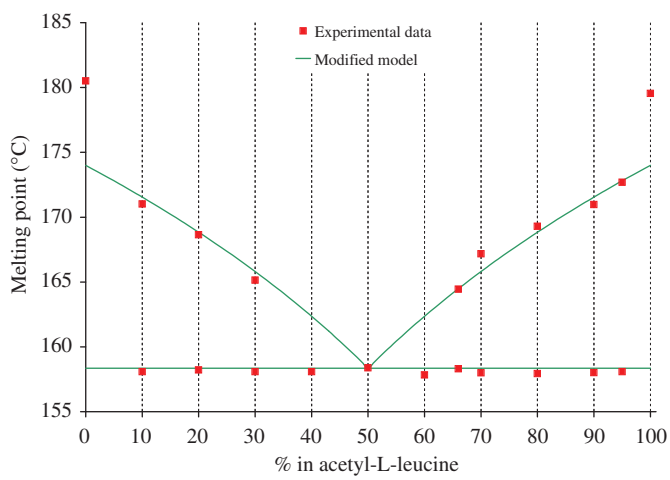

Fig. 8. Experimental data and modelised melting temperature phase diagram.

in a selected solvent represents an industrial interest when crystallization control is necessary. Furthermore, the solubility of an API impacts its bioavailability and its therapeutic activity.

Isothermal ternary diagrams have been used by several authors, giving the composition of each enantiomer and of the solvent [25]. These diagrams are always symmetrical, so only one part of them can be experimentally studied.

In the case of a conglomerate, the racemic composition has the higher solubility and the solubility evolution from pure enantiomer to racemic mixture is linear. On the contrary, in the case of true racemate, the higher solubility is obtained for the eutectic points and a solubility decrease is observed around the racemic composition.

Solubility measurements in water have then been carried out for several compositions of acetyl-L-leucine and acetyl-D-leucine in order to determine the solubility ternary diagram. The evolution of the pH of the saturated solutions during the solubility measurements was found to be no significant and has no influence on the measured solubility.

Mixtures of acetyl-L-leucine and acetyl-D-leucine were prepared with a ratio of acetyl-L-leucine ranging from 10% to 90%. Table 1 reports the measured solubility at a constant temperature of 25 °C, for the considered molar ratios of L and D species. The solubility ratio C*, calculated for each mixture, is the ratio between the solubility of this mixture and the solubility of acetyl-L-leucine. Molar fractions of each species in solution are also given in Table 1.

The measured solubility is low and the obtained experimental phase diagram is given in Fig. 9.

This ternary diagram shows linear increase of solubility toward the racemic composition. The highest solubility is obtained for a ratio of 50% of acetyl-L-leucine, so for the racemic composition. This diagram is characteristic of a conglomerate.

3.2.2. The Meyerhoffer double solubility rule

Conglomerates are a physical mixture of D and L crystals. In the ideal case, no interaction between species should be observed. So the solubility of the racemic form should be equal to the sum of the two solubilities of each enantiomer [26] given below:

$$S_{\text{mixture}} = S_L + S_D \tag{3}$$

As each enantiomer has the same solubility, the solubility of the racemic conglomerate is then doubled. This is the empirical Meyerhoffer double solubility rule. This rule can only be applied on conglomerates because a true racemate constitutes a single phase with its own solubility.

However, the acetyl leucine is partially dissociated in water. Indeed, this molecule behaves as a weak acid ($pK_A = 3.7$) because

Table 1
Experimental solubility data of mixtures of enantiomers.

Proportion of L (%)	Solubility at 25 °C (mol/L)	C*	Molar fraction of D (%)	Molar fraction of L (%)	Molar fraction of S (%)
0	0.0499	1.05	0.090	0.000	99.910
10	0.0546	1.15	0.088	0.010	99.902
20	0.0617	1.30	0.089	0.022	99.889
30	0.0700	1.47	0.088	0.038	99.874
40	0.0785	1.65	0.085	0.056	99.859
50	0.0920	1.93	0.083	0.083	99.835
60	0.0803	1.68	0.058	0.087	99.856
70	0.0686	1.44	0.037	0.086	99.877
80	0.0633	1.33	0.023	0.091	99.886
90	0.0564	1.18	0.010	0.091	99.899
100	0.0477	1.00	0.000	0.086	99.914

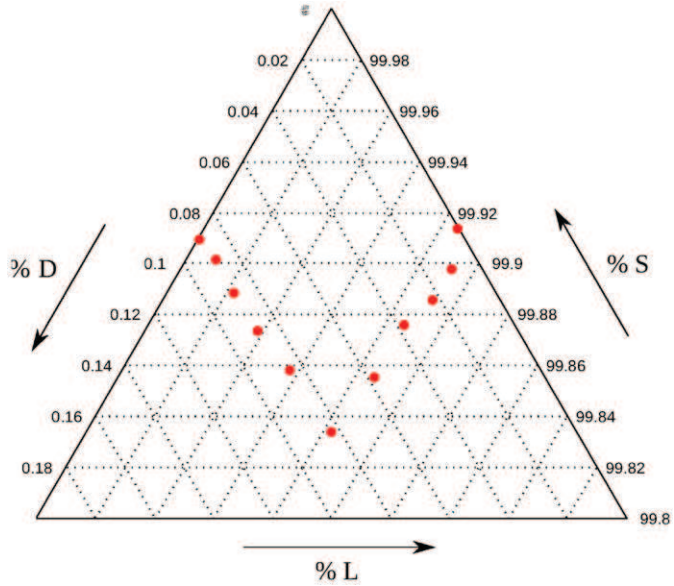

Fig. 9. Ternary phase diagram of solubility of acetyl leucine at a constant temperature of 25 °C.

of the presence of a carboxylic acid group. Its solubility depends on the pH. For pure acetyl-L-leucine, a model was proposed in a previous work [27] in order to predict the evolution of the solubility as a function of pH and S_0, the solubility of the non-dissociated molecule, noted ALH. S_0 has been experimentally determined to be equal to 0.045 mol/L. The solubility of a pure enantiomer predicted by this model was noted S' and detailed in Eq. (4). It enabled the determination of the acidity constant K_A in the case of a saturated solution of pure enantiomer given in the following equation:

$$S_{\text{enantiomer}} = S' = [\text{ALH}] + [\text{AL}^-] = S_0 \cdot (1 + 10^{\text{pH} - \text{p}K_A}) \tag{4}$$

$$K_A = \frac{[\text{AL}^-][H^+]}{[\text{ALH}]} = \frac{(S' - S_0)^2}{S_0} \tag{5}$$

In the case of a racemic mixture for which S_R is its solubility, $S_R/2$ is the solubility of one of the enantiomer in solution (Eq. (6)) and the concentration of hydron $[H^+]$ is equal to the sum of the concentrations of the dissociated species (Eq. (7)).

$$\begin{aligned} S_{\text{enantiomer}} = \frac{S_R}{2} &= [\text{ALH}_{\text{enantiomer}}] + [\text{AL}^-_{\text{enantiomer}}] \\ &= S_0 + [\text{AL}^-_{\text{enantiomer}}] \end{aligned} \tag{6}$$

$$[H^+] = 2[\text{AL}^-_{\text{enantiomer}}] \tag{7}$$

The expression of the acidity constant for the racemate is then given in the following equation:

$$K_A = \frac{[\text{AL}^-_{\text{enantiomer}}][H^+]}{[\text{ALH}_{\text{enantiomer}}]} = \frac{2\left(\frac{S_R}{2} - S_0\right)^2}{S_0} \tag{8}$$

By combining Eqs. (5) and (8), the solubility of the racemate S_R can be expressed in Eq. (9), considering the partial dissociation of the product [7]:

$$\frac{S_R}{2} - S_0 = \frac{S' - S_0}{\sqrt{2}},$$

$$\text{so } S_R = S_0 \cdot (2 + 10^{\text{pH} - \text{p}K_A}\sqrt{2}) \tag{9}$$

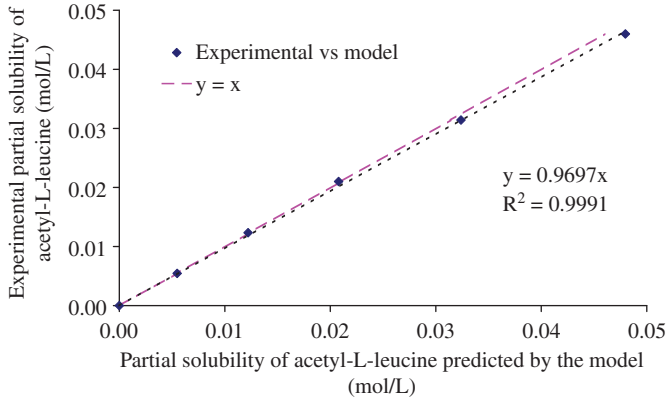

Fig. 10. Comparison of experimental and calculated solubilities.

As the pH in saturated solutions is equal to 2.6, the theoretical solubility ratio C^* calculated by Eq. (10) is equal to 1.96:

$$\frac{S_{\text{racemic}}}{S_{\text{enantiomer}}} = \frac{2+10^{\text{pH}-\text{p}K_A}\sqrt{2}}{1+10^{\text{pH}-\text{p}K_A}} \tag{10}$$

Experimentally, the racemate solubility ratio is equal to 1.93 (Table 1). The model which considers the partial dissociation of the product gives better results than the empirical Meyerhoffer rule. The slight difference with the experimental results could be attributed to the non-ideality of the system and to the interaction between the enantiomers.

The next step is then to develop a model which predicts the solubility, not only for the racemic composition, but as a function of the enantiomerical composition.

3.2.3. *Solubility model for conglomerates*

The proportion of acetyl-L-leucine is noted x. When acetyl-D-leucine is the main compound ($x \leq 50\%$), the solubility of acetyl-D-leucine S_D is equal to the solubility of the pure enantiomer S'. By molar balance and using Eq. (3), S_L is equal to $(x/(1-x))S'$ The case is symmetrical when acetyl-L-leucine is the main compound. This simple model gives two cases summarized in the following equation:

$$\text{For } x \leq 50\%, S_D = S' \quad \text{and} \quad S_L = \frac{x}{1-x}S',$$
$$\text{so } S_{\text{mixture}} = S'\left(1+\frac{x}{1-x}\right) = \frac{S'}{1-x} \tag{11}$$

$$\text{For } x \geq 50\%, S_L = S' \quad \text{and} \quad S_D = \frac{1-x}{x}S',$$
$$\text{so } S_{\text{mixture}} = S'\left(1+\frac{1-x}{x}\right) = \frac{S'}{x} \tag{12}$$

To check the validity of the model, the calculated solubilities were compared to the experimental ones, in the case of acetyl-L-leucine (the example is symmetrical with the enantiomerical counterpart). Fig. 10 shows the evolution of the experimental partial solubility as a function of the partial solubility predicted by the model. The evolution clearly shows a straight line which confirms that the model is correct. However, the slope is not exactly equal to unity. This could be due to slight interactions between enantiomers that decrease the solubility of the mixture.

4. Conclusion

This paper shows that acetyl-DL-leucine crystallizes as a conglomerate. A model has then been developed to describe the solubility profile as a function of pH and enantiomerical compositions.

Melting points measured by thermal analyzes showed differences with the values predicted by the Schröder Van Laar equation. That could be explained by the existence of a concomitant phenomenon during the melting. Further work will be done to explain this.

Acknowledgments

The authors want to acknowledge CNRS (French National Scientific Research Centre) and Pierre Fabre laboratories for their financial support.

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