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Diastereomeric resolution rationalized by phase diagrams under the actual conditions of the experimental process

Pierric Marchand,[a] Loïc Lefèbvre,[a] Florian Querniard,[a] Pascal Cardinaël,[b] Guy Perez,[b] Jean-Jacques Counioux[c] and Gérard Coquerel[a,b,*]

[a]*Thermodynamique des Systèmes Hétérogènes Organiques, ERT 27, IRCOF, University of Rouen, 76821 Mont-Saint-Aignan Cedex, France*
[b]*Sciences et Méthodes Séparatives, UPRES EA 3233, IRCOF, University of Rouen, 76821 Mont-Saint-Aignan Cedex, France*
[c]*Hydrazines et Procédés, UMR 5179, University of Lyon I, 43 boulevard du 11 novembre 1918, 69622 Villeurbanne Cedex, France*

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Abstract—A brief survey on phase diagrams involved in Pasteurian resolutions in solution is proposed. Various heterogeneous equilibria (limited to ternary systems involving two diastereomers with a nonchiral solvent as a third component) are depicted including stoichiometric intermediate compounds and solid solutions. Polymorphism is not considered in this study. A collection of adapted investigations on these heterogeneous systems are presented; they aim at defining the optimum process under the actual experimental conditions prevailing during the resolution. A new technique (discontinuous isoperibolic thermal analysis: DITA) designed to access to these relevant data is presented. Two typical examples of Pasteurian resolution are given as illustrations: (±)-mandelic acid resolved by (−)-ephedrine in ethanol at 24.7 °C and (±)-mandelic acid resolved by quinine in methanol at 20 °C.

1. Introduction

Sources of enantiomerically pure compounds are of great importance for chemistry in general and the pharmaceutical industry in particular. They are often obtained from the resolution of racemic mixtures[1] whose organic syntheses are generally much easier and cheaper to carry out than that of pure enantiomers.

Among the other methods of resolution of racemic mixtures, such as preparative chromatography[2] or preferential crystallization,[3] the most popular one is still the crystallization of diastereomers (Pasteurian resolution).[4] Typically, this method consists of forming diastereomeric salts: to a racemic acid (resp. base) is added a resolving agent, which is an enantiomerically pure base (resp. acid). Diastereomers do not exhibit the symmetry, which exists between the enantiomers[5] and under appropriate conditions (in a solvent or solvent mixture) it is possible to crystallize at equilibrium a single solid phase (supposed to be a pure salt) and then obtain a pure enantiomer (after having removed the resolving agent, usually by a simple salting out). Variations of the Pasteurian resolution method are already known such as the Marckwald's method:[6] only one half equivalent of the resolving agent is added to one equivalent of the racemic mixture; or the Pope and Peachey's method:[7] one half equivalent of resolving agent plus one half equivalent of a nonchiral agent are added on one equivalent of a racemic mixture. In both cases, the aim is to form preferentially only one diastereomer (enhanced yield), to lower the quantity of the resolving agent, to decrease the viscosity of the slurry... Research on diastereomeric resolution methods are still active, as proven by the recent development of the so-called 'Dutch resolution':[8] a mixture of structurally related resolving agents is added to the racemic mixture. An enhanced efficiency is often observed (in comparison to cases where any of those resolving agents is used individually). Interestingly, the resolving agents can be present in a nonstoichiometric ratio in the solid phase.

Even if the Pasteurian resolution is not quantitative (the yield is never 100%), this method is robust and offers convenient access to enantiomerically pure compounds at laboratory as well as at industrial scales. In the latter case, the control and the optimization of such a resolution process is of great importance. However the

* Corresponding author. Tel./fax: +33(0)-2-35522927; e-mail: gerard.coquerel@univ-rouen.fr

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theoretical background is generally poorly understood. Investigations on the systems to be resolved often rely on the 'trial and error' method and when a rational method is proposed, several assumptions are needed. Such a method, carried out by means of DSC analysis,[9] has been proposed; nevertheless severe limitative conditions are implicitly supposed:

1. No chemical decomposition of the sample occurs on heating.
2. Each diastereomer crystallizes as a pure solid phase, there is no miscibility at the solid state (no solid solution).
3. No intermediate compound crystallizes (no double salt in the binary system of the two diastereomers, nor any solvate in the ternary system with a solvent as a third component).
4. Liquidus curves in the binary system of the two diastereomers can be calculated by Schröder–van Laar equation[10] from DSC data (ideality assumption in the binary system).
5. The polysaturated solution exhibits the same composition (in the two diastereomers) as the binary eutectic whatever the temperature (ideality assumption in the ternary system).

This set of conditions limits the applicability of the 'DSC method' as in many cases the system is far from ideal and the DSC measurements provide experimental data often at high temperature (usually above 100 °C) compared to that of the actual resolution experiment (usually room temperature). Moreover even if by chance the system fulfills the conditions listed above, the practical resolution process is still not established (overall composition of the sample, including the quantity of solvent, at a given temperature).

The aim herein is to provide the minimum theoretical knowledge and to propose adapted experimental investigations needed to carry out Pasteurian resolution under optimal conditions. First a collection of phase diagrams corresponding to the main types of heterogeneous equilibria between diastereomers in ternary systems are presented (with a nonchiral solvent as the third component). In order to simplify this presentation, no polymorphism and no intermediate compound of unusual stoichiometry are considered. The first part of the investigation will be focused on how to determine the favorable conditions for an optimum resolution process while the second part will detail a new analytical technique (discontinuous isoperibolic thermal analysis: DITA)[11] designed to access to the pertinent information for an optimized process. Two experimental examples are also depicted.

2. Phase diagrams[12]

2.1. 'Classical' case

The first type of heterogeneous system contemplated, corresponds to the most simple case: no miscibility at the solid state and no intermediate compound. Other assumptions (ideality for calculation of the liquidus curves, ideality for the composition of the polysaturated solution, no decomposition at high temperature) are not needed to draw the general shape of the corresponding phase diagram. The components forming the ternary system are

1. salt A (hereafter, it corresponds to the less soluble salt),
2. salt B (the more soluble salt),
3. the solvent.

An isothermal section (temperature T^* of the resolution process) of the ternary phase diagram, salt A/salt B/solvent, is represented (Fig. 1) with the three constitutive binary phase diagrams (composition vs temperature):

1. salt A/salt B,
2. salt A/solvent,
3. salt B/solvent.

The difference between the composition of the polysaturated solution and the binary eutectic is visible if the system deviates from ideality on cooling (Fig. 2).

The information needed to run an efficient resolution process is directly readable on the isothermal ternary phase diagram (Fig. 3). Starting from the equimolar mixture of the two diastereomers (point O in Fig. 3), various quantities of solvent can be added. The overall composition of such a system evolves along the equimolar isoplethal segment: point O/solvent. In order to isolate by filtration solely salt A as a pure solid phase, the overall composition of the system must be located within the composition range [KL] (at temperature T^*). If the process is performed with an insufficient quantity of solvent (overall composition located below point K in Fig. 3), the purification is not efficient as a mix of salts A and B will be collected by filtration. If the process is performed with an excessive quantity of solvent (overall composition above point L in Fig. 3), the purification is senseless as there is no solid phase to filter. In the composition range [KL], pure salt A is the only solid phase in equilibrium with its saturated solution whose composition evolves from points I to L on increasing amount of solvent. The solid phase collected (pure salt A) corresponds to point H in Figure 3.

The optimum process is reached when the overall composition of the system is represented by point K. Thus the quality of the resolution (applied to an equimolar mixture of the two salts) can be assessed by two quantitative criteria: productivity and efficiency.

Productivity (P), that is, the mass of salt A collected by filtration compared to the total mass of the system (including the solvent), can be expressed (according the lever rule) as $P = KI/HI$; where KI and HI are the lengths of the corresponding segments on the phase diagram (Fig. 3). By considering the densities of the different phases in equilibrium, the productivity P is related to

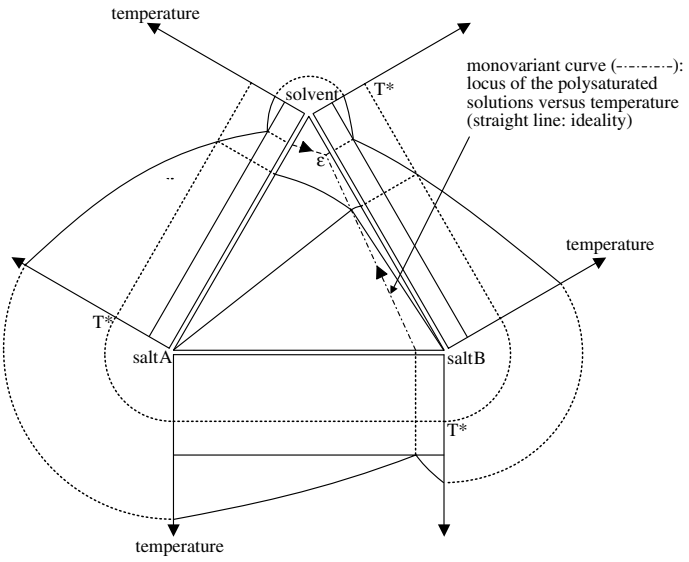

Figure 1. Ternary isotherm at temperature T^* exhibiting ideal behavior and the relations between the three binary systems (monovariant curves, intended toward low temperature, meet at the ternary eutectic: ε).

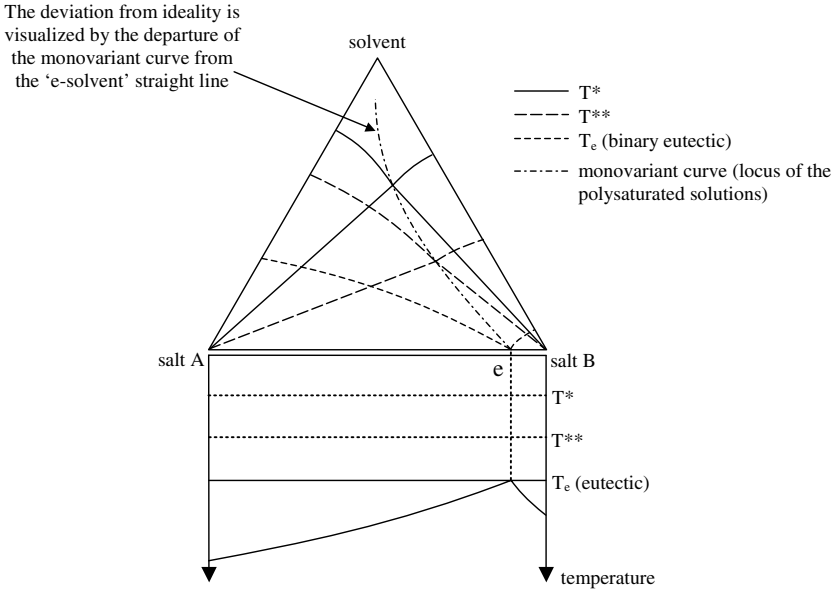

Figure 2. Ternary system exhibiting deviation from ideality; this deviation makes the resolution process less efficient as temperature is lowered.

the volumic yield. The productivity value evolved from 0 to 0.5.

Efficiency (E), that is, the mass of salt A collected by filtration compared to the total mass of salt A in the system (without considering salt B and the solvent), can be expressed (according to the lever rule) as $E = 2\cdot(OJ/HJ)$ where OJ and HJ are the lengths of the corresponding segments on the phase diagram (Fig. 3). The efficiency can also be expressed as $E = (1-2x_J)/(1-x_J)$; where x_J stands for the composition in salt A of the dry residue of the polysaturated solution (point J; Fig. 3). This point, corresponding to solvent evaporation of the polysaturated solution, is determined on the diagram by the isoplethal projection of the polysaturated solution from the pure solvent toward the solvent-free side of the diagram (salt A/salt B binary system); the reader should pay special attention not to confuse the monovariant curve (gathering the set of points I at different temperatures, cf. Fig. 2) and the isoplethal projection of the polysaturated solution at a given temperature T^*. As a consequence the only criterion having an impact on the efficiency of the resolution is the composition of the dry residue of the polysaturated solution (point J). A high efficiency E can be reached for a low value of x_J. The efficiency value evolved from 0 to 1.

2.2. Solid solutions

Partial or total miscibility at the solid state can be encountered. This leads to a diminution of the quality

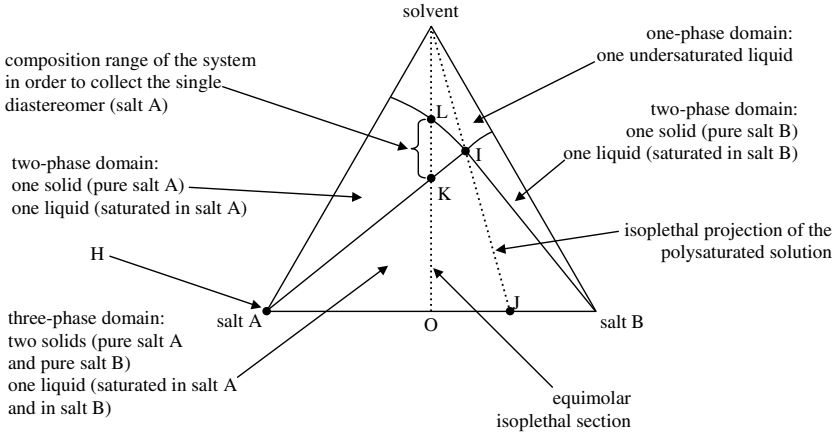

Figure 3. Information needed for an efficient resolution process.

of the resolution. The first case envisaged is a partial miscibility of salt B in the salt A solid phase (Fig. 4).

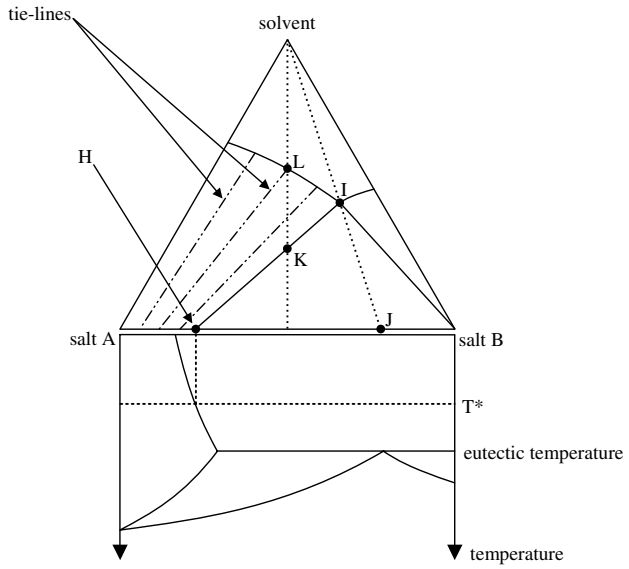

Figure 4. Partial solid solution of salt B in the pure salt A solid phase.

If the process is performed at point K, the solid collected by filtration will contain a single solid phase, which is a homogeneous mixture of the two diastereomers whose composition is given by the extremity of the tie-line IK (in Fig. 4, point H corresponds to the solid solution saturated in salt B at temperature T^*).

The tie-lines connect the representative composition points of the phases in equilibrium: the solid phase and its saturated solution. From composition K to composition L, the quantity of solid to filtrate tends to zero. In order to increase the purity of the solid phase, several recrystallizations are needed. Unfortunately in this case, as the excess in salt A tends to 100%, the yield tends to 0%.

A total solid solution between the two salts can also be encountered (Fig. 5). This type of crystallization behavior leads to a poorly efficient resolution. There is no polysaturated solution and all along the equimolar section, the composition of the solid phase in equilibrium never corresponds to a pure component. Several recrystallizations may increase the excess of the solid phase in salt A but, as for the partial solid solution, as the excess in salt A tends to 100%, the yield tends to 0%.

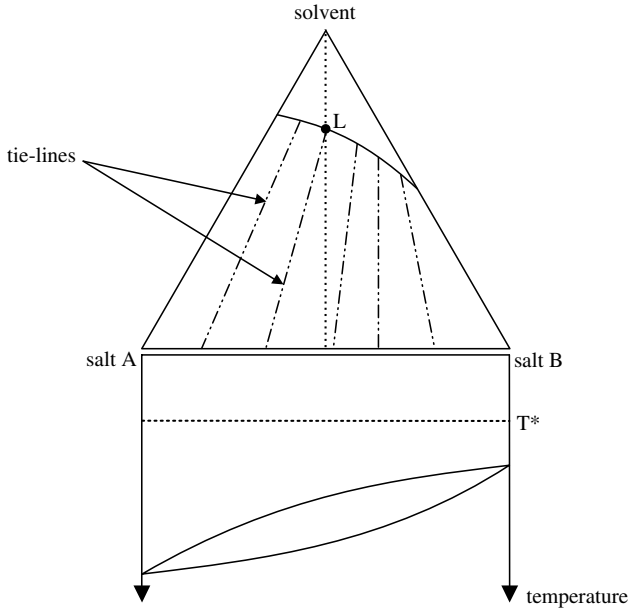

Figure 5. Total solid solution between the two salts.

2.3. Intermediate stoichiometric compound crystallization (double salts and solvates)

From the mix of the three independent components, one (or more) stoichiometric intermediate compound(s) can crystallize at equilibrium. The first case depicted here is the crystallization of a (1–1) double salt in the binary system of the two diastereomers. The main thermal behaviors of such a compound are a congruent melting (Fig. 6a), a noncongruent melting (peritectic, Fig. 6b) or reversible decompositions at the solid state: a eutectoid (Fig. 6c) or a peritectoid (Fig. 6d).

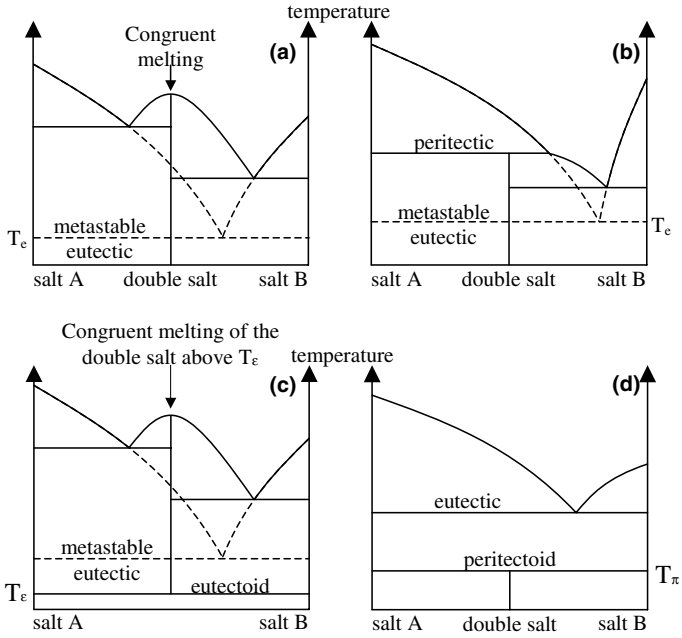

Figure 6. Possible thermal behaviors of the double salt (stoichiometric intermediate compound); T_e: temperature of the eutectic; T_p: temperature of the peritectic; T_ε: temperature of the eutectoid; T_π: temperature of the peritectoid (dashed line: metastable equilibria).

In the case of congruent melting (Fig. 6a) or peritectic (Fig. 6b), a DSC analysis should reveal the typical thermal signals associated with these equilibria. However if the equimolar mixture of the diastereomers is not crystallized according to the stable equilibrium (because of the poor diffusion rate at the solid state), it should be possible to detect the metastable equilibria by means of DSC (the typical thermal signal corresponding to the eutectic at temperature T_e). Several European pharmaceutical industries have undergone the spontaneous appearance of the double salt, ruining a resolution process, which has been operated for months or even years before the detection of the intermediate compound. This type of phenomenon is comparable to that of 'appearing/disappearing' polymorphs.[13]

In the case of a eutectoid (Fig. 6c), a DSC experiment can detect the existence of the double salt at 'high' temperatures (with a congruent melting in the example) and miss an exploitable situation at 'low' temperatures (below the eutectoid temperature: T_ε); in the case of a peritectoid (Fig. 6d), a DSC experiment can show up the stable eutectic at 'high' temperatures (above the peritectoid temperature: T_π) and miss the double salt at 'low' temperatures because of the weak thermal effect and the poor diffusion rate at the solid state associated with this invariant.

In the actual conditions of the resolution (room temperature, presence of solvent) a double salt can crystallize (even if it has not been detected by DSC) and exhibit a congruent solubility (Fig. 7). In this case, the resolution relies only on metastable equilibria and without avoiding the nucleation of the double salt, the process cannot be run at equilibrium. This makes the process difficult or even impossible to handle. In equilibrium

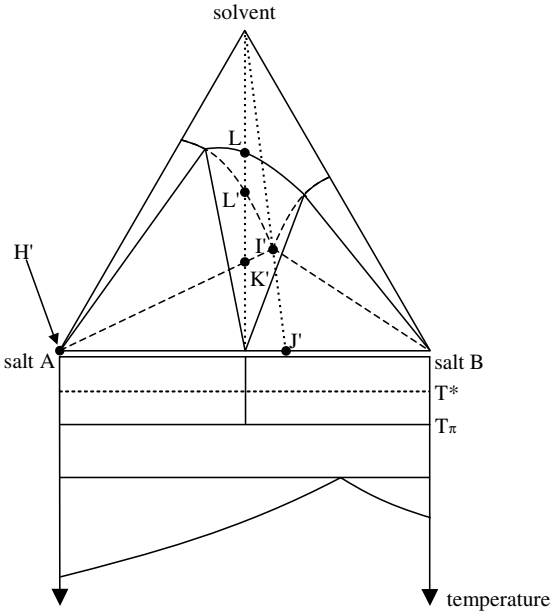

Figure 7. Congruent solubility of the double salt (with a peritectoid at temperature T_π in the binary system salt A/salt B as example).

conditions, the only solid phase to be collected is the double salt. The metastable situation (absence of the double salt) is associated with points H', I', J', K', and L' in Figure 7; this corresponds to the 'classical' case (Fig. 3). By increasing the temperature above T_π (Fig. 7), the behavior is back to the classical' case (i.e., there is no crystallization of the double salt anymore).

In the case of crystallization of a double salt exhibiting a noncongruent solubility[14] (Fig. 8; the saturated solution formed by the addition of a small amount of pure

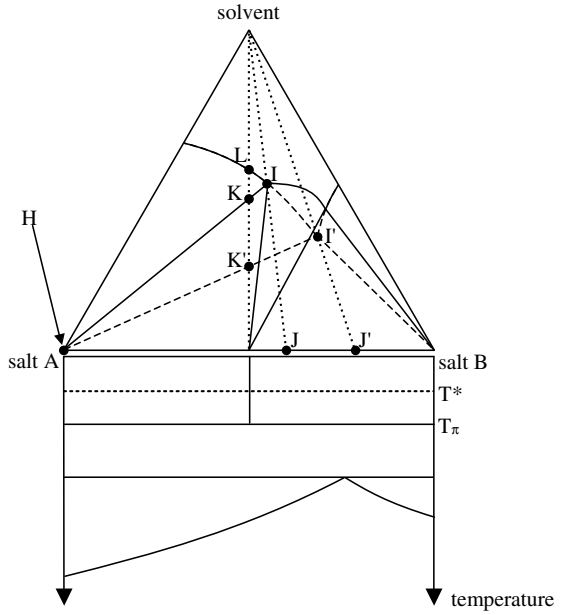

Figure 8. Noncongruent solubility of the double salt (with a peritectoid at temperature T_π in the binary system salt A/salt B as example).

solvent on the double salt does not have the same composition as the double salt itself), the resolution process can be run. There exists a composition range [KL] compatible with the resolution. This situation, associated with points H, I, J, K, and L in Figure 8, can be compared to the 'classical' case (Fig. 3). If the filtration is performed at point K, the solid collected (point H) corresponds to the pure salt A. The metastable situation (absence of the double salt) is to be associated with points H, I', J', K', and L in Figure 8; this corresponds to the 'classical' case (Fig. 3). The crystallization of a double salt with a noncongruent solubility allows the resolution process to be run but decreases its efficiency when compared to the absence of this salt (the comparison between the location of points J and J' in Fig. 8). By increasing the temperature above T_π (Fig. 8), the behavior goes back to the 'classical' case (i.e., there is no crystallization of the double salt anymore).

Another type of intermediate compound crystallization in the binary system salt A/solvent is a solvate of salt A (the same can apply to salt B). It is obvious that the crystallization of such a compound cannot be detected by DSC analysis on a mixture of the two salts (the solvate does not belong to the salt A–salt B binary phase diagram). This situation, associated with points H, I, J, K, and L in Figure 9, can be compared to the 'classical' case (Fig. 3). In such a case there exists a composition range (points K and L in Fig. 9) allowing the resolution process. The purification is efficient as salt B is not included in the composition of the solvate, which is only a cocrystal of salt A and solvent. A desolvation process is needed to recover pure salt A; this can be concomitant to the salting out operation. The metastable equilibria (absence of solvate) are represented in dashed lines associated with points H', I', J', K', and L' in Figure 9; this metastable situation corresponds to the 'classical' case (Fig. 3). A change of solvent allows us to return to the 'classical' case. Nevertheless, a solvate crystallization might be beneficial to the process (comparison between the location of points J and J' in Fig. 9).

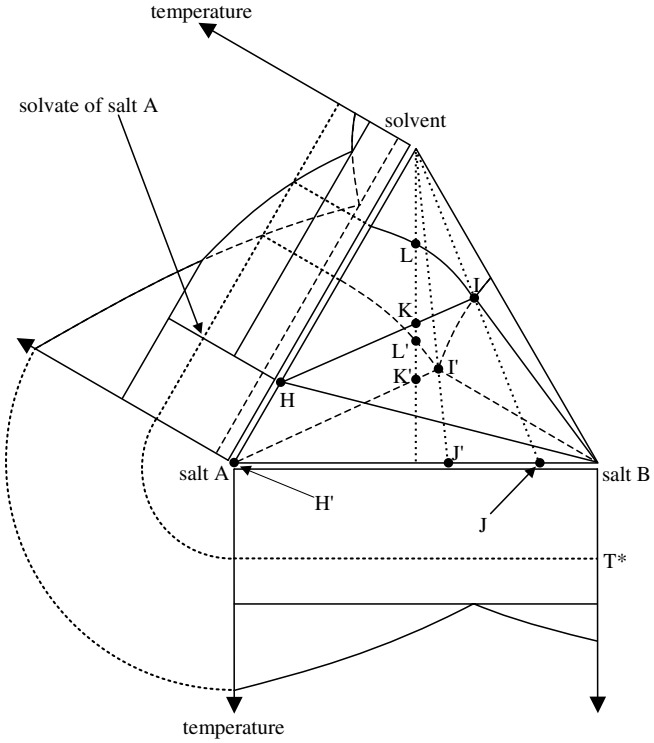

Figure 9. Solvate of salt A.

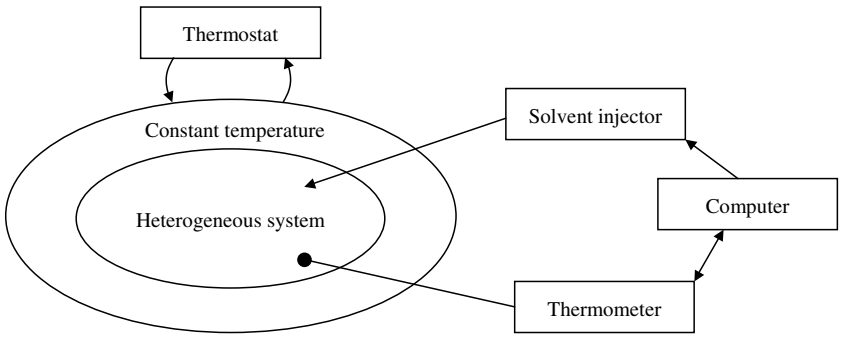

Figure 10. Principle of the DITA setup.

2.4. Stoichiometry of the resolving agent

Until now, the diastereomeric salts were considered as independent components. The standard preparation of the diastereomeric salts consisted of the addition of one equivalent of resolving agent (RA) per equivalent of racemic mixture (+ and −). However it is possible to consider the diastereomeric salts as intermediate compounds obtained from the enantiomers and the resolving agent. The ternary system salt A/salt B/solvent is then a section of the quaternary system (+)/(−)/RA/solvent. In the cases of Marckwald's method,[6] Pope and Peachey's method[7] or the so called 'Dutch resolution',[8] the stoichiometry or even the number of resolving agents are no longer 'classical'. Moreover, a mixture of solvents can be used for the process. The systems to be investigated can no longer be contemplated as ternary systems but of a higher order: that is, quaternary, quinary, etc. The representations of the corresponding phase diagrams are out of the scope of this paper (they are no longer triangles but tetrahedrons or even polyhedrons of higher dimensions) but the principle of the resolution is not affected as the location of the appropriate composition range [KL] corresponding to the isothermal section of the biphasic domain ('last' domain before homogenization on successive additions of solvent) is still the relevant information.

These heterogeneous equilibrium considerations are of great help in understanding the phenomena controlling the resolution process and its optimization. The key step is thus the experimental determination of the location of the composition range [KL]. Moreover this determination must be carried out in the actual conditions prevailing during the resolution process (same temperature, same solvent). The experimental determinations of phase diagrams are generally presented as time and sample consuming and the need for pure components leads often to the impossibility of carrying out the experiments (as the pure enantiomers are not already available). By using a new experimental technique, it is possible to determine the composition range [KL] as shown below.

3. Experimental

A complete description of the DITA technique, modeling of the signal, and data treatment have already been presented.[11] A schematic description is proposed here (Fig. 10).

The heterogeneous system to be investigated is set under isoperibolic conditions. The system is neither isothermal nor adiabatic but its direct environment is considered as remaining perfectly isothermal. Starting from a system in thermal equilibrium, a fast injection of a small amount of pure solvent conditioned exactly at the same temperature as that of the system is performed. Physical phenomena (mainly dissolution and/or dilution but it can also be crystallization, demixion, etc.), corresponding to the spontaneous evolution of the system after this small composition shift, occur. These phenomena lead to heat exchanges (corresponding to enthalpy changes as pressure is constant) involving temperature variations. The recording of such variations is performed by an accurate thermometer with a resolution down to $\pm 10^{-4}$ K. The temperature variations are then plotted versus time. A typical 'temperature variations-versus-time' relaxation curve is presented in Figure 11.

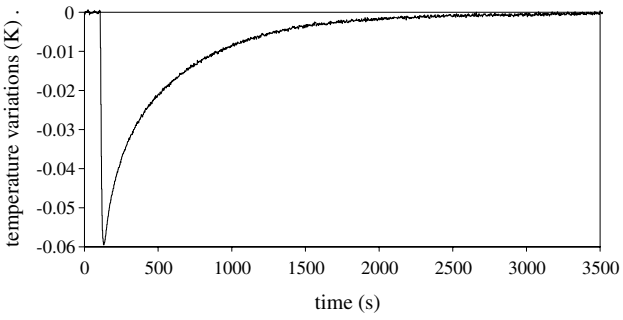

Figure 11. DITA signal of temperature variations versus time.

The integration value of such a curve is proportional to the enthalpy change (the unit of integration values is K s). A whole experiment is composed of several injections (typically 20–40) and therefore as many 'temperature-variations-versus-time' relaxation curves are obtained. The cumulated integration values versus the cumulated injection volumes lead to the exploitation plot. On such a plot, slope disruptions are detected and related to the intersections between

1. The working section (from the equimolar mixture of the two salts to solvent).

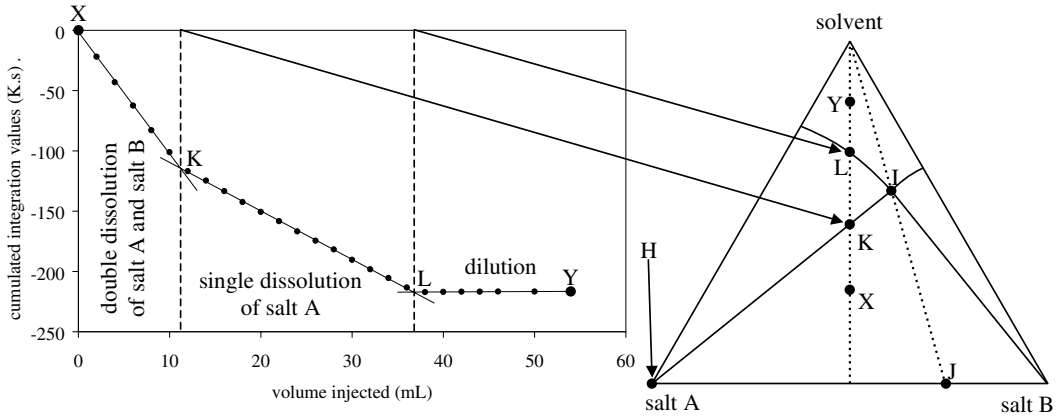

Figure 12. Experimental determination of [KL] range.

2. The limits on the corresponding phase diagram (Fig. 12).

The starting composition of the analysis corresponds to point X (at least one liquid phase is needed for accurate temperature measurements) while the end corresponds to point Y. The two slope disruptions are directly related to points K and L (the same interpretation applies for situations presented in Figs. 3, 4, 8, and 9).

In the case of a single slope disruption, a visual inspection, or turbidimetry is needed:

- If a homogeneous solution is observed, the disruption corresponds to a point L and the analysis should be started with a lower solvent composition in order to reach point K; if such a point cannot be reached, the situation corresponds to Figures 5 or 7.
- If a suspension is observed, the disruption corresponds to a point K and more additions of solvent should be performed to reach point L.

A typical analysis requires a few grams of the samples and lasts 10–20 h. The process is completely automated and the only sample needed is the equimolar mixture of the two diastereomers (available from the racemic mixture and the resolving agent). When points K and L have been detected, they are located on a phase diagram. In order to collect good quality data, two conditions of great importance have to be fulfilled:

1. The starting solid phases should have reached the stable equilibrium state.
2. The chemical purity of the samples must be high enough as low purity samples imply less visible slope disruptions.

A complementary experiment is also needed: a mixture corresponding to point K composition must be prepared (kept thermostated and under stirring for several hours to ensure that the system is in stable equilibrium). The liquid phase (corresponding to point I) and the solid phase (corresponding to point H) are separated by filtration and analyzed (composition in solvent, in salt A and in salt B).

In the phase diagram, the three points, H, K, and I, must be located on the same straight line. If not, a solvate of salt A can be suspected. Indeed if the analysis of the solid phase is only dedicated to the relative composition between the two salts, no information is gathered about the composition in solvent of the solid phase. In this case, the solid sample composition can be erroneously located as point H' in Figure 9 (H', K, and I are not located on the same straight line).

This presentation is limited to general cases but more complicated cases (such as polymorphism, nonstoichiometric solvates, etc.) can be encountered and additional specific analyses might be needed to construct the necessary part of the phase diagram.

4. Examples

Two examples of resolution are presented; the resolution of (±)-mandelic acid by (−)-ephedrine in ethanol at 24.7 °C and the resolution of (±)-mandelic acid by quinine in methanol at 20 °C.

In order to determine the enantiomeric excess of mandelic acid, the analysis was performed by means of chiral HPLC: Chirobiotic T 4.6 mm × 15 cm × 5 μm; triethyl ammonium acetate (pH = 4.1) 80% and methanol 20%; 1 mL/min; λ = 230 nm. Two peaks were detected:

- 3.7 min: (*R*)-(−)-mandelic acid,
- 6.2 min: (*S*)-(+)-mandelic acid.

4.1. Resolution of (±)-mandelic acid by (−)-ephedrine in ethanol at 24.7 °C

An equimolar mixture of the two salts (+)- and (−)-mandelic acid/(−)-ephedrine was prepared by mixing

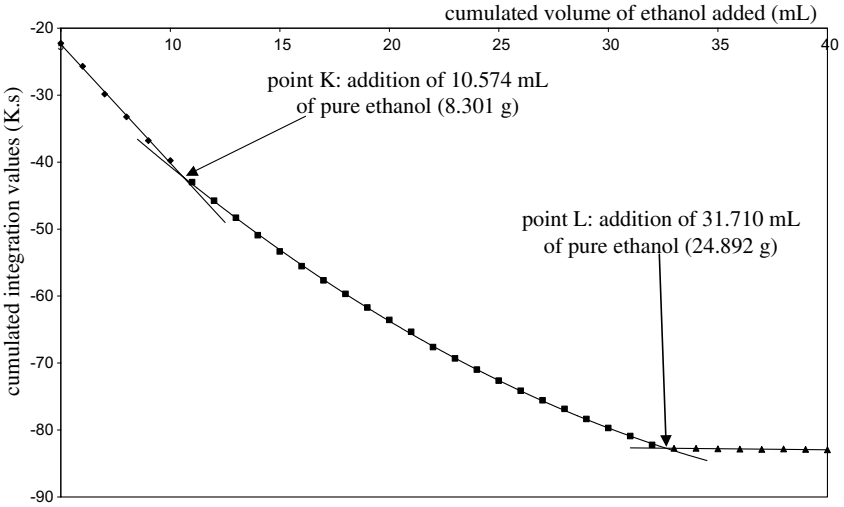

Figure 13. Result of the DITA experiment for the system (±)-mandelic acid/(−)-ephedrine/ethanol at 24.7 °C.

1.046 g of (−)-ephedrine (6.331 mmol) dissolved in ethanol with 0.964 g of (±)-mandelic acid (6.336 mmol) dissolved in ethanol. After complete evaporation, an oil was obtained and a recrystallization performed in diethyl ether. After complete evaporation of diethyl ether about 1.6 g of a white powder were collected, XRPD measurements were performed to confirm the good crystallinity of the sample.

A DITA experiment was then carried out. Equimolar mixture (1.189 g) of the two salts and 6.399 g of ethanol were mixed in the DITA measuring vessel. Automated additions of pure ethanol were performed (density at the temperature of the experiment: 0.785 g/mL) and slope disruptions detected after mathematical treatment (Fig. 13). The first slope disruption occurred at 10.574 mL of ethanol added (or 8.301 g) while the second disruption occurred at 31.710 mL of ethanol added (or 24.892 g). The compositions of the system at these disruptions are expressed in solvent mass fraction:

- first disruption: 92.52% (point K),
- second disruption: 96.34% (point L).

A sample whose composition corresponded to the first disruption (point K) was prepared. Equimolar mixture (1.295 g) of the two salts were mixed with 16.018 g of ethanol in a closed tube at 24.7 °C under stirring for 24 h. Stirring was then stopped and after sedimentation of the suspension, three weighted samplings of the liquid phase were performed. The samples were submitted to evaporation and the dry residues weighed. The composition of the liquid phase expressed in solvent mass fraction is reported in Table 1. The dry residues were analyzed by means of chiral HPLC and the rest of the suspension filtrated. The solid phase was analyzed by means of chiral HPLC. These results are shown in Table 2 (the less soluble salt is noted as salt A, the more soluble salt is noted as salt B). The compositions of all relevant mixtures: solid phase (point H), polysaturated solution (point I), first DITA disruption (point K), and second DITA disruption (point L) expressed in mass fractions of salt A, salt B, and solvent are shown in Table 3. From these data, the part of the corresponding isothermal phase diagram necessary to describe and

Table 1. Calculation of the solvent mass fraction of the polysaturated solution for the system (±)-mandelic acid/(−)-ephedrine/ethanol at 24.7 °C

Sample number	Mass of the sampling (g)	Mass of the dry residue (g)	Composition of the liquid phase (in solvent mass fraction), %
1	1.425	0.084	94.11
2	1.425	0.083	94.18
3	1.459	0.087	94.04
Mean			94.11

Table 2. Composition in salt A [with (*R*)-(−)-mandelic acid] and salt B [with (*S*)-(+)-mandelic acid] of the solid phase and the dry residue of the polysaturated solution for the system (±)-mandelic acid/(−)-ephedrine/ethanol at 24.7 °C

Sample	Salt A	Salt B
Dry residue	35.5%	64.5%
Solid phase	99.1%	0.9%

Table 3. Composition of every relevant mixtures for the system (±)-mandelic acid/(−)-ephedrine/ethanol at 24.7 °C

Mixture	Salt A mass fraction (%)	Salt B mass fraction (%)	Solvent mass fraction (%)
Solid phase (point H)	99.1	0.9	0
Polysaturated solution (point I)	2.09	3.80	94.11
First disruption (point K)	3.74	3.74	92.52
Second disruption (point L)	1.83	1.83	96.34

optimize the process can be built. Points H, K, and I are located on the same straight line. This situation corresponds to the 'classical' case (Fig. 3) and an optimized resolution process can be operated by preparing a sample whose composition corresponds to point K. The optimum efficiency of this resolution process can then be calculated ($x_J = 0.355$ according to Table 2): $E = 45\%$.

4.2. Resolution of (±)-mandelic acid by quinine as the resolving agent in methanol at 20 °C

An equimolar mixture of the salts (+)- and (−)-mandelic acid/quinine was prepared by mixing 4.121 g of quinine (12.703 mmol) dissolved in methanol with 1.933 g of (±)-mandelic acid (12.705 mmol) dissolved in methanol. After complete evaporation, an oil was obtained and recrystallization then performed in diethyl ether. After complete evaporation of diethyl ether about 5.9 g of a white powder was collected. XRPD measurements were performed to confirm the good crystallinity of the sample.

A DITA experiment was then carried out. Equimolar mixture (2.522 g) of the two salts and 3.441 g of methanol were mixed in the DITA measuring vessel. Automated additions of pure methanol were performed (density at the temperature of the experiment: 0.79 g/mL) and the slope disruptions detected after mathematical treatment (Fig. 14). The first slope disruption occurred at 5.602 mL of methanol added (or 4.426 g) while the second disruption occurred at 34.713 mL of methanol added (or 27.423 g). The compositions of the system at these disruptions is expressed in solvent mass fraction:

- first disruption: 75.72% (point K),
- second disruption: 92.45% (point L).

A sample whose composition corresponded to the first disruption (point K) was prepared. Equimolar mixture (3.356 g) of the two salts were mixed with 10.460 g of methanol in a closed tube at 20 °C under stirring for 24 h. Stirring was then stopped and after sedimentation of the suspension, three weighted samplings of the liquid phase were performed. The samples were submitted to evaporation and the dry residues weighed. The composition of the liquid phase expressed in mass fraction of the two salts is reported in Table 4. The dry residues were analyzed by means of chiral HPLC and the rest of the suspension filtrated. The solid phase was analyzed by means of chiral HPLC. These results are shown in Table 5. The composition of all relevant mixtures: solid phase (point H), polysaturated solution (point I), first DITA disruption (point K), and second DITA disruption (point L) expressed in mass fractions of salt A, salt B, and solvent are shown in Table 6. From these data, the part of the corresponding isothermal phase diagram necessary to describe and optimize the process can be built. Points H, K, and I are located on the same straight line. This situation corresponds to the solid solution case (Fig. 4): a poorly efficient resolution process can be run with this system. The mass composition in salt A of the solid phase corresponding to point H was only 67%.

Table 4. Calculation of the solvent mass fraction of the polysaturated solution for the system (±)-mandelic acid/quinine/methanol at 20 °C

Sample number	Mass of the sampling (g)	Mass of the dry residue (g)	Composition of the liquid phase (in solvent mass fraction), %
1	1.318	0.142	89.23
2	1.290	0.139	89.22
3	1.230	0.132	89.27
Mean			89.24

5. Conclusion

A rational approach to Pasteurian resolutions is provided by the description of heterogeneous equilibria involving the solvent(s) as an active component. At a

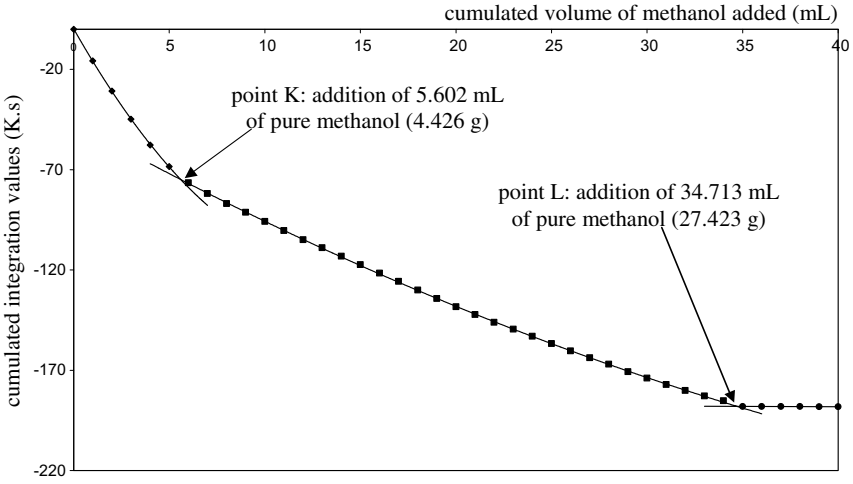

Figure 14. Result of the DITA experiment for the system (±)-mandelic acid/quinine/methanol at 20 °C.

Table 5. Composition in salt A [with (*R*)-(−)-mandelic acid] and salt B [with (*S*)-(+)-mandelic acid] of the solid phase and the dry residue of the polysaturated solution for the system (±)-mandelic acid/quinine/methanol at 20 °C

Sample	Salt A	Salt B
Dry residue	26.0%	74.0%
Solid phase	67.0%	33.0%

Table 6. Composition of every relevant mixtures for the system (±)-mandelic acid/quinine/methanol at 20 °C

Mixture	Salt A mass fraction (%)	Salt B mass fraction (%)	Solvent mass fraction (%)
Solid phase (point H)	67.0	33.0	0
Polysaturated solution (point I)	2.80	7.96	89.24
First disruption (point K)	12.14	12.14	75.72
Second disruption (point L)	3.77_5	3.77_5	92.45

given temperature and starting from equimolar quantities of solutes to resolve, the main issues are the determinations of

- The composition of the system with the minimum quantity of solvent(s) so that the system is biphasic at thermodynamic equilibrium.
- The nature of the solid phase in equilibrium with its saturated solution.

In a broader context of variants of the Pasteurian method, the relevant data for an optimum process are still the limits of the last domain before homogenization. An efficient experimental technique (DITA) specifically dedicated to collecting this information has been developed. Applications of this technique do not rely on any extrapolation (by contrast to methods, which take into account binary data between diastereomeric salts only) or any special assumptions such as ideality, no existence of any solid solution, no intermediate compound, no polymorphism, and no solvate. The system can be directly investigated under the actual conditions prevailing during the experimental process.

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