Journal of Thermal Analysis and Calorimetry, Vol. 90 (2007) 2, 359–365

STUDY OF THE QUATERNARY SYSTEM(+) AND (–)5-PHENYL-5-TRIFLUOROMETHYL-IMIDAZOLIDINE-2,4-DIONE/(–)1-PHENYL-ETHYLAMINE/ETHANOL AT 20°C UNDER ATMOSPHERIC PRESSURE

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The resolution of (±)-5-phenyl-5-trifluoromethyl-imidazolidine-2,4-dione ((±)-$CF_3$61H hereafter) using 1-phenyl-ethylamine (αMBA hereafter) in ethanol was investigated. At 20°C, the evolution of the resolution efficiency *vs.* the excess of αMBA was studied by establishing a part of the quaternary system: (+) and (–)-$CF_3$61H/(–)-αMBA/ethanol.

Competition between two equilibria has been highlighted:

- Metastable equilibria between diastereomeric salts ((±)-$CF_3$61H and enantiopure (–)-αMBA).
- Stable equilibria involving a double salt Q which exhibits a non-congruent solubility.

The presence of this double salt leads to the resolution of diastereomeric salts but can drastically drop the yield if nothing could act as inhibitor of its nucleation and growth.

Keywords: *double salt, hydantoins, pasteurian resolution, phase equilibria*

Introduction

The pasteurian resolution is a well-known method [1, 2] applicable at the laboratory and industrial scales for enantioseparation of chiral acids and bases. Basically, it consists in the formation of diastereomeric salts between a racemic acid (or base) ((+) or (–) hereafter) and an enantiomerically pure base (or acid), called resolving agent ((–)R hereafter). It follows the reaction:

$$(+)+(-)+2(-)R \rightarrow (-)R.(+)+(-)R.(-) \qquad (1)$$

where (–)R.(+) and (–)R.(–) are diastereomeric salts and unlike the enantiomers to be resolved have not the same physical properties, such as solubilities. To improve efficiency of the enantioseparation, several parameters can be optimized: nature and quantity of the resolving agent [3], temperature, and solvent. This work aims at finding the influence of an excess of resolving agent on the resolution of the title compound: (±)-5-phenyl-5-trifluoromethyl-imidazolidine-2,4-dione ((±)-$CF_3$61H hereafter) by using (–)-1-phenyl-ethylamine (also called α-methylbenzylamine (–)-αMBA hereafter) in ethanol at 20°C and under atmospheric pressure.

Experimental

Materials

The description of all initial products is presented in Table 1.

(±)-$CF_3$61H, which belongs to the wide family of hydantoins, was synthesized in the laboratory using Bucherer–Bergs reaction [4, 5] starting from trifluoromethylacetophenone (yield=85%). The crude product has been purified by means of recrystallization as salts of racemic (±)-αMBA in diethyl ether.

(–)-αMBA (Acros organics, assay: 99+%, 99% e.e) is a chiral base often used as resolving agent [6]. As it is a liquid base it can undergo carbonation at free air (pKa=9.83 for $\alpha MBAH^+/\alpha MBA$).

The diastereomeric salts between (±)-$CF_3$61H and αMBA (following Eq. (1), with (+) and (–) as (+) and (–)-$CF_3$61H and (–)R as (–)-αMBA) are called by convention salt 'P' if $CF_3$61H and αMBA have the same rotatory power sign (– –) and salt 'N' if they have different rotatory power signs (–+). P and N have both a molecular mass of 365.35 g mol^{-1}.

Solvent used is absolute ethanol (Carlo Erba, purity: 99.7±0.2%). Molar hydrochloric acid used for salting out was obtained from dilution of hydrochloric acid 37% (VWR Prolabo assay 37.7%).

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1388–6150/$20.00

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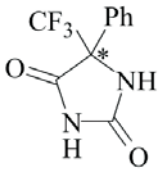
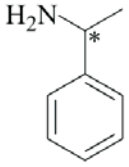
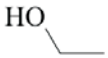
Table 1 Description of products used in this study

Nouns	$CF_3$61H	αMBA	Ethanol
representation *=asymmetry centre			
supplier	Synthesized in the laboratory	Acros Organics	Carlo Erba
molar mass/ g mol^{-1}	244.17	121.18	46.07

Remark: to avoid confusion with enantiomeric excess, the diastereomeric excess d.e. was used to characterise mixture of diastereomeric salts (Eq. (2)).

$$\text{d.e.}=\frac{m_P - m_N}{m_P + m_N} \quad (2)$$

Methods

The determination of phase boundaries in the quaternary diagram was pursued by using discontinuous isoperibolic thermal analysis (DITA hereafter). This experimental technique is thoroughly described in [7].

Several suspensions were prepared in order to determine the nature and composition of phases in equilibrium in each domain detected by DITA. The saturated solutions were analyzed and the remaining slurries submitted to filtration.

- Solid phases were analyzed by X-ray powder diffraction (Bruker D5000 start 2θ: 3° final 2θ: 30° step: 0.04° step time: 4 s).
- Saturated solutions with no excess of αMBA were studied by simple gravimetric method (for ethanol content determination) and the d.e. of the dry residues obtained was measured.
- The gravimetric method could not be used for saturated solutions with an excess of αMBA (non reproducible carbonation/evaporation of αMBA in excess). Instead, $CF_3$61H and αMBA contents in the samples were determined by pH-metric titrations (Radiometer Analytical PHM210 pH-meter with glass electrode and non-aqueous reference electrode). The weighed sample was diluted in absolute ethanol, titrated by decimolar aqueous sodium hydroxide (determination of $CF_3$61H content) and then titrated in return by decimolar aqueous hydrochloric acid (determination of αMBA content). Ethanol content of the solution was then deduced. After every titration, the liquid mixture was evaporated and the d.e. of the remaining solid was measured.

In view to access to the quantity of each diastereomeric salt (d.e. determination), solid mixture of salts were salted out by molar hydrochloric acid to give a solid mixture of (+) and (–) $CF_3$61H enantiomers after filtration. The deviation from the racemic composition of hydantoin was determined by:

- polarimetry (Perkin Elmer 341, about 10 mg of sample in 2 mL absolute ethanol, enantiopure $CF_3$61H has the following specific rotatory powers: $\alpha^{\circ\,25℃}_{365\,nm} \approx 133°$, $\alpha^{\circ\,25℃}_{436\,nm} \approx 76°$, $\alpha^{\circ\,25℃}_{546\,nm} \approx 43°$, $\alpha^{\circ\,25℃}_{578\,nm} \approx 37°$)
- chiral HPLC (Varian 9010/9050, UV 235 nm, chiralpak AD, 20°C, elution by absolute ethanol, flow 1.0 mL min^{-1}, 20 μL loop loaded with a solution of about 2 mg of sample in 1 mL of absolute ethanol, retention times: (–)=3.4 min (+)=5.5 min).

Results and discussion

Description of the system and methodology

The quaternary system (+)-$CF_3$61H, (–)-$CF_3$61H, (–)-αMBA, ethanol is represented in Fig. 1. For different excesses in (–)-αMBA, ternary working sections (N/P/(solvent+resolving agent) mixture) have the same global phase distribution (Fig. 1). Each ternary section contains several characteristic points [8]:

- When an equimolar mixture of the two salts N and P is suspended in ethanol, points K and L delimit the domain in which a single crystallized phase only (the less soluble salt; here salt N) is present in the suspension (needed condition for the resolution).
- The productivity and the efficiency of the resolution can be determined from the polysaturated solution composition, represented by the point I.

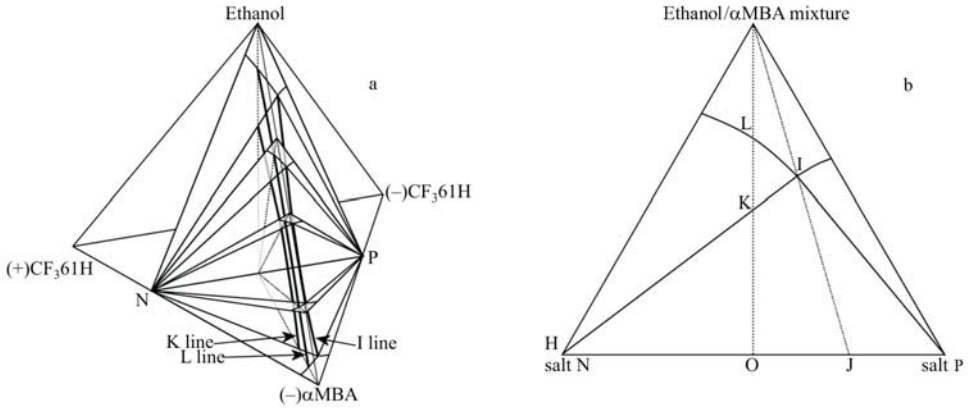


Fig. 1 a – Schematic representation of the quaternary diagram showing several ternary working sections as well as K, L and I lines; b – detail of a ternary working section showing characteristic points: K, L and I

In addition, we can define K, L and I lines that are the loci of K, L and I points along the working sections in the quaternary phase diagram.

The location of the characteristic points can be used to gather important information relevant to the resolution process:

- The maximum theoretical productivity of the resolution

$$P = \frac{IK}{IH} = \frac{m_{\text{collected}}}{m_{\text{total}}}$$

It corresponds to the mass of salt N that can be collected, divided by the mass of the suspension.

- The maximum theoretical efficiency of the resolution,

$$E = 2\frac{OJ}{HJ} = \frac{2|\text{d.e.}_\text{I}|}{1+|\text{d.e.}_\text{I}|}$$

with d.e._I the d.e. of the solution at point I. It corresponds to the mass of salt N that can be collected, divided by the mass of salt N present in the suspension.

In this study we wish to assess the evolution of these two parameters *vs.* the (–)-αMBA excess. In each working section, productivity and efficiency can be determined following this two-step procedure:

- Location of points K and L as function of (–)-αMBA excess by DITA measurements.
- Determination of the composition of the *bis*-saturated solution in the three-phase domain (point I) as function of (–)-αMBA excess. Suitable 3-phase suspensions were prepared after determining the location of point K.

Resolution of $CF_3$61H with (–)-αMBA in a 1:1 ratio

The location of points K, L and I were determined experimentally for the 1 equivalent (–)-αMBA working section. The results are collected in Table 2 and represented in Fig. 2.

To complete the ternary section (Fig. 2), the solubilities of pure salt N (2.4% in mass) and pure salt P (5.1% in mass) have been determined in ethanol at 20°C by gravimetric method.

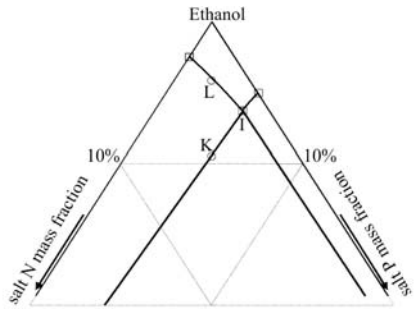


Fig. 2 Zoom on the experimental isobaric isothermal phase diagram between N, P and ethanol (1 eq ternary working section). Circles: points K and L (determined by DITA), squares: solubility determined by saturated solution analyses

Table 2 Location of characteristic points of the 1 eq working section

Points	K	L	I
ethanol mass fraction	90.9%	95.8%	93.7%
d.e.	0%	0%	+54%

Thus, the theoretical resolution conditions for (±)-$CF_3$61H by using one equivalent of (–)-αMBA in ethanol at 20°C are:

- (90.9±0.2)% in mass of ethanol
- theoretical efficiency: 70.1%
- theoretical productivity: 3.1%

The resolution was tested with a security margin based on the data collected in Table 2: the ethanol content was 92 instead of 90.9%. The resolution procedure can be described as follow. (±)-$CF_3$61H has been dissolved in absolute ethanol. After total dissolution, 1 eq of (–)-αMBA was added in the solution under constant magnetic stirring at 20°C. Crystallization occurred after few minutes and three suspensions were kept under stirring for 90–180 and 240 min respectively. The solids collected by

Table 3 Experimental data of the resolution attempts with one equivalent of (–)-αMBA

Attempt	1	2	3
Mass of racemic $CF_3$61H/g	1.918	2.031	2.001
Mass of ethanol/g	33.134	35.021	35.004
Mass of (-)αMBA/g	0.955	1.025	1.016
Equilibration time/s	90	180	240
Washing	no washing	20 mL of ether	20 mL of ether
Mass of salt collected/g	0.759	0.83	0.802
d.e.	–85%	–96%	–99%
Productivity	1.8%	2.1%	2.1%
Efficiency	44.9%	52.1%	52.6%

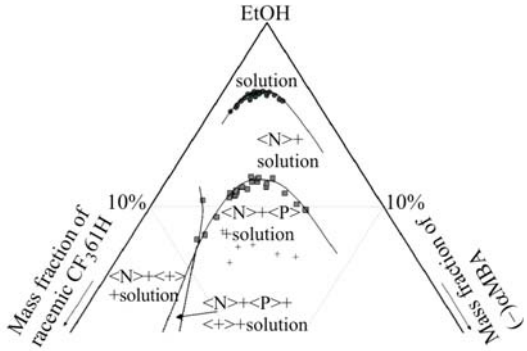


Fig. 3 Experimental racemic section investigated by DITA. Circles are on the L line, squares are on the K line. 3-phase suspensions prepared for *bis*-saturated solution analyses are represented by crosses

filtration (which were supposed to be almost pure salt N), were salted out to give almost enantiomerically pure (+)-$CF_3$61H.

The experimental data and results of the resolving attempts are summarized in Table 3.

The resolution has been successful after an easy optimization of the so-called 'equilibration time' and by implementing a washing of the filtration cake. Under those conditions, the resolution is satisfying and can be proposed as a preparative route. Productivity and efficiency are lower than the theoretical values due the security margin taken, and the small scale of the experiments which induced an extra loss of mass, and some uncertainties in the final composition of the system.

Influence of the resolving agent excess

A series of DITA experiments have permitted to establish K and L lines (Fig. 3) and then five 3-phase suspensions have been prepared with different excesses of (–)-αMBA in order to describe the I line. They will be named '*x*' eq where *x* stands for the number of equivalents of (–)-αMBA. After an equilibration and settle time (several days to several weeks) solutions were sampled and analyzed to locate the corresponding point I. In parallel, the solid phases were characterized by XRPD (Fig. 4). The results are summarized in the Table 4.

The results can be divided into two groups. The first group (1 and 1.23 eq) contains only the expected solid phases, namely salts N and P. The productivity and efficiency are stable for a small excess of resolving agent. For the second group (1.34 to 3.01 eq), the suspensions contain an unexpected crystallized phase, labelled: Q. Productivity and efficiency both decrease with excess of (–)-αMBA.

It is worth noting that Q is not present in suspensions before two weeks of isothermal continuous stirring. For instance, when suspensions containing 1.34 and 1.66 eq of (–)-αMBA were prepared again

Table 4 Compositions of the bis-saturated solutions and nature of the crystallized phases in equilibrium as function of the (-)-αMBA excess

αMBA/$CF_3$61H molar ratio (number of equivalents)	1	1.23	1.34	1.66	2.34	3.01
Composition of saturated solution						
mass fraction of (–)-$CF_3$61H	0.0313	0.0312	0.0274	0.0238	0.0193	0.0171
mass fraction of (+)-$CF_3$61H	0.0096	0.0094	0.0088	0.0073	0.0065	0.0062
mass fraction of (–)-αMBA	0.0203	0.0289	0.0299	0.0379	0.0505	0.0639
mass fraction of EtOH	0.9388	0.9305	0.9339	0.931	0.9237	0.9128
d.e. of the solution	54%	54%	51%	53%	49%	47%
Maximum theoretical efficiency	70%	70%	68%	69%	66%	64%
Maximum theoretical productivity	3.1%	3.1%	2.7%	2.4%	1.9%	1.6%
Nature of the solid phases	P and N	P and N	Q and N	P, Q and N	Q and N	Q and N
Equilibration time	6 days	8 days	37 days	15 days	16 days	16 days

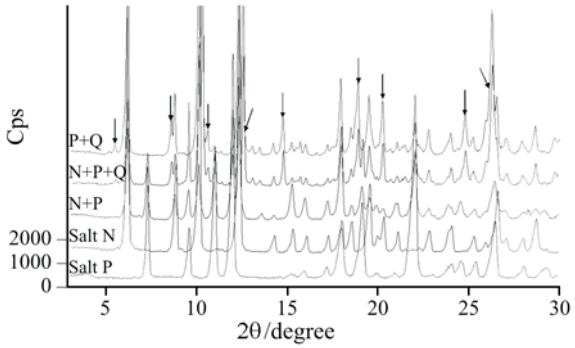


Fig. 4 XRPD patterns of the solid phases in equilibrium with analyzed polysaturated solutions. From the bottom to the top: salt P, salt N, N+P (1 and 1.23eq), N+P+Q (1.66eq), P+Q (1.34, 2.34 and 3.01 eq). Peaks attributed to the phase Q are highlighted with arrows

with a shorter equilibration time (4 days), they did not contain phase Q. This leads to the conclusion that Q has a slow crystallization kinetics. Moreover, the equilibrium between N, P and the saturated solution of the first group could also be metastable.

Nature of phase Q

Regarding the nature of phase Q, one shall bear in mind that the XRPD pattern of salt P seems to be replaced by the XRPD pattern of phase Q with long equilibration time. Therefore, the following hypotheses can be emitted:

- Q can be an ethanol solvate of P
- Q can be a compound between P and (–)-αMBA (co-crystal)
- Q can be a mix of two previous assumptions
- Q can be a polymorph of P
- Q can be a compound between P and N: a double salt.

Some of these hypotheses can be discarded by geometric considerations in the quaternary system (see supplementary materials).

So, among assumptions considered above, the two last ones can still be considered:

Several 3-phase suspensions at different d.e. and 85% of ethanol were prepared and seeded with a N+Q mixture. After equilibration (about a week), solids were analyzed by XRPD (Fig. 5). At d.e.=20%, the solid in equilibrium was almost pure phase Q and has a d.e. of almost 0%. These complementary experimental results let to consider that phase Q is a double salt whose formula is: (+)-$CF_3$61H(–)-$CF_3$61H·2(–)-αMBA.

Moreover, it can be deduced that the phase Q presents a non-congruent solubility in ethanol. Indeed, a suspension in ethanol of this double salt will give pure N or N+Q mixture depending on the concentration.

With regard to the information collected on the nature of phase Q, a new theoretical working section

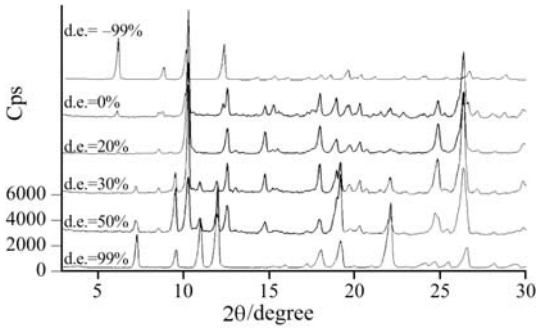


Fig. 5 XRPD pattern of solid phases in equilibrium with the liquid in suspension that contains 85% of ethanol. From bottom to top: pure salt P d.e.=99%, d.e.=50%, d.e.=30%, almost pure Q d.e.=20%, d.e.=0%, pure salt N d.e.= –99%

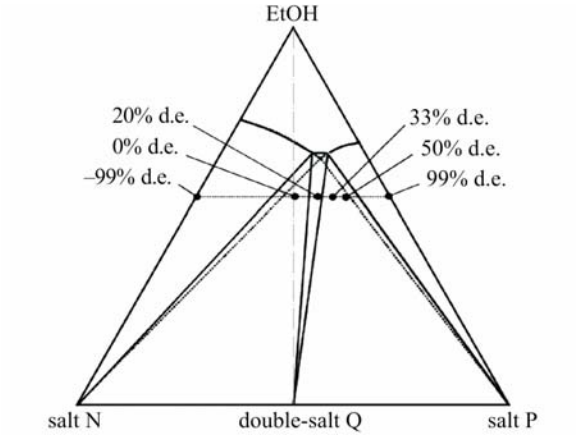


Fig. 6 Theoretical isothermal isobaric section of the ternary phase diagram between salt N, salt P and ethanol exhibiting the double-salt Q. Black circles show the position of suspensions analyzed in Fig. 5

can be drawn (Fig. 6). This case of double salt with non-congruent solubility has already been observed with racemic αMBA when resolved by mandelic acid [9]. More investigations are needed to fully characterize Q, such as its solubilities and its crystalline structure.

Conclusions

(±)-$CF_3$61H has been successfully resolved with one equivalent of (–)-αMBA. Excess of (–)-αMBA associated with long equilibration time, did not give any benefit, but appearance of an original phase Q. With the help of dedicated experiments and a geometrical method the new phase was partially characterized as a double-salt with a non-congruent solubility.

Therefore the optimization of this resolving process needs a complete description of both metastable and stable equilibria. The evolution of resolution parameters will be described *vs.* the excess of resolving agent with or without phase Q. Because efficiency and productivity of the resolution can decrease drastically if

the double salt is present, the resolution process should avoid the crystallization of phase Q whether by adjusting the temperature and composition parameters (thermodynamic equilibrium will therefore govern this process) or, if possible, by inhibiting the crystallization of phase Q by means of a fine tuning of thermodynamic and kinetic parameters (metastable equilibria only will govern the process).

Supplementary appendix: Geometric considerations

In every sample submitted to a long equilibration time, three phases are in equilibrium: phase Q, salt N and a *bis*-saturated solution. This situation is represented by a triangular flat domain in the phase diagram. This domain contains every mixture which

Table 5 Coefficients of plane equations calculated from coordinates of N, suspensions and solutions

αMBA/$CF_3$61H molar ratio (number of equivalents)	1.23	1.34	1.66	2.34	3.01
Solution					
Mass fraction of (–)-$CF_3$61H	0.0312	0.0274	0.0238	0.0193	0.0171
Mass fraction of (+)-$CF_3$61H	0.0094	0.0088	0.0073	0.0065	0.0062
Mass fraction of (–)-αMBA	0.0289	0.0299	0.0379	0.0505	0.0639
Mass fraction of ethanol	0.9305	0.9339	0.931	0.9237	0.9128
Suspension					
Mass of racemic $CF_3$61H/g	1.243	1.15	1.038	0.926	0.807
Mass of (–)-αMBA/g	0.757	0.764	0.857	1.075	1.204
Mass of ethanol/g	13.371	13.816	13.832	13.923	13.787
Coefficient					
a	–1.483	–1.478	–1.461	–1.439	–1.416
b	–1.512	–1.515	–1.480	–1.563	–1.455
c	0.991	0.988	0.977	0.962	0.946
intersection with Y axis ((–)-$CF_3$61H mass fraction)	0.655	0.652	0.660	0.615	0.650

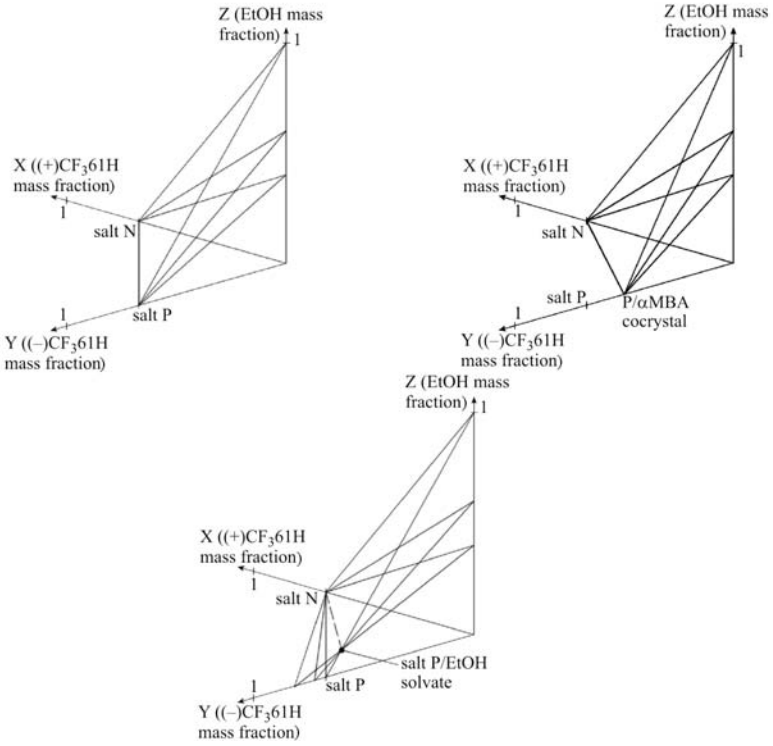


Fig. 7 Behaviour of planes defined by N, a solution and a suspension with excess of αMBA. N and the solution are in equilibrium with a – a phase located between P and N; b – a cocrystal between P and αMBA; c – a solvate between P and ethanol

has the same three phases in equilibrium. So, the knowledge of the composition of two phases and the composition of the mixture, defines a geometric plane where phase Q is present.

Here, compositions of the initial mixture and of two phases in equilibrium (polysaturated solution and N) are known. So, the equation of the plane can be calculated.

Considering the composition space (X, Y, Z) with:

- X=mass fraction of (+)-$CF_3$61H
- Y=mass fraction of (–)-$CF_3$61H
- Z=mass fraction of ethanol (the mass fraction of (–)-αMBA is 1–X–Y–Z))

A plane will be defined by the Eq. (3)

$$Z=aX+bY+c \quad (3)$$

The three coefficients a, b and c have been calculated from the coordinates of the three known points that define the plane (Table 5). It is remarkable that intersections of the planes with the Y axis are always close from the salt P (0.668 on the Y axis). For 1.23 eq it is obvious since salt P is indeed the phase in equilibrium (the slight difference results from the loss of ethanol by evaporation during the preparation prior the analysis), but for the other suspensions it constitutes useful information: P belongs to plane define by the suspension, the solution and N in each case. If not we should have a different intersection with Y axis, that can even evolves with αMBA excess (Fig. 7).

As a consequence, the third phase Q (in equilibrium with N and a polysaturated solution) belongs to planes defined by N, P and the solution. The only way that Q can belong simultaneously to all these planes (Fig. 1) is that it belongs to the intersection of these planes: the NP segment.

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DOI: 10.1007/s10973-007-8394-z