Determination of the Binary and Ternary Phase Diagrams of *R*(+)-/*S*(−)-Ketamine Using Differential Scanning Calorimetry

Rosana Emi Tamagawa,*,† Everson Alves Miranda,† Cesar Costapinto Santana,† and Marco Giulietti‡

Departamento de Processos Biotecnológicos - Faculdade de Engenharia Química, Universidade Estadual de Campinas (UNICAMP), CP6060, CEP 13083970, Campinas (SP), Brazil, and Agrupamento de Processos Químicos, Instituto de Pesquisas Tecnológicas do Estado de São Paulo (IPT), Av. Prof. Almeida Prado 532, Cidade Universitária, 05508-901, São Paulo (SP), Brazil

In this study, the binary and the ternary phase diagrams of *R*-/*S*-ketamine were determined based on differential scanning calorimetry (DSC) measurements. The binary phase diagram presented a eutectic point in the 50:50 (*R*/*S*) composition which characterizes the product as a conglomerate forming system. On the other hand, the ternary phase diagram in the presence of ethanol showed a eutectic point in the 75:25 (*R*/*S*) composition, indicating the occurrence of a racemic compound. The observed facts indicate that the solvent and the temperature may affect the eutectic point, and thus different crystal forming systems can be obtained from the melt and from the solution. The calorimetric method was demonstrated to be an excellent short-cut method for the fast construction of phase diagrams, taking only some hours and consuming only a few milligrams [(5 to 20) mg] of samples.

1. Introduction

The (*R*,*S*)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone ($C_{13}H_{16}ClNO$) known with the generic name of ketamine is a drug with sedative, analgesic, and anesthetic properties, whose molecular structure has a chiral center, thus having two enantiomers: *S*-ketamine and *R*-ketamine. Although the *R*-enantiomer is known to cause some adverse effects such as psycho reactions and illusions,[1] the commercial formulation of ketamine is very often a racemic mixture, i.e., an equimolar mixture of the two enantiomers. It is common that enantiomers present different effects in the organism; therefore, production of racemic drugs is becoming unattractive, and increasing efforts have been made in industrial and academic fields to develop efficient enantioseparation processes.

According to the literature, most of the studies aiming at the enantioseparation of ketamine have been related to chromatography[2−4] and diastereomeric resolution processes[5,6] which are the most widespread techniques in the field. In these studies, purification levels of virtually 100 % were achieved in the chromatographic laboratory scale processes; however, low productivities [(0.15 to 0.5) $g \cdot day^{-1}$] were observed, even using a simulated moving bed (SMB). As a mean for increasing the productivity of SMB processes, many authors have been pursuing the coupling of chromatography and crystallization,[7−11] resulting in a hybrid process. An optimized coupling relies, certainly, on a precise control of the combined processes based on detailed studies and improvements of the isolated processes. The design and optimization of the hybrid chromatography−crystallization processes are discussed by Fung et al.,[12] Ströhlein et al.,[13] and Amanullah and Mazzoti.[14]

In diastereomeric resolution, the process seems to be well established achieving purities of 99 % and a yield of 70 %. However, compared to direct crystallization, it has the disadvantage that additional steps are required in the diastereomeric salt conversions, which makes direct crystallization a more economically attractive process.[15] In the latter process, crystals of pure enantiomers are obtained from a solution at specific conditions according to the ternary phase diagram.

In this work, the binary and ternary phase diagrams of *S*(−)-/*R*(+)-ketamine in ethanol at different temperatures [(298.1 to 313) K] were determined based on DSC measurements. The application of DSC for determining the binary phase diagrams is a traditional procedure in the characterization of racemic drugs and thus it is widely described in the literature.[16−19] On the other hand, its use for determining ternary phase diagrams is a relatively new procedure, and it is based on recent studies suggesting its application as a short-cut method for the fast estimation of solubility curves.[18−22] Therefore, the contribution of this work was not only to provide relevant data regarding the enantioseparation of ketamine by direct crystallization but also to demonstrate the suitability of DSC as an alternative procedure for the fast determination of solubility. Certainly, the objective of the method is not the high accuracy of the traditional methods, but the fast estimation of phase diagrams.

2. Enantioseparation via Direct Crystallization from Partially Resolved Solutions

One of the most widespread processes for enantioseparation is chiral chromatography, with special focus on the simulated moving bed (SMB), which in the last decades was the breakthrough in increasing the productivity of conventional chromatographic separation processes. However, the intrinsic fall-off in productivity as the purification level increases may still be significant in some cases, especially when very high purification levels are required as happens in the enantioseparation processes. Aiming to improve the productivity in enantioseparation processes, several authors have been pursuing the coupling of chromatography to crystallization, which is a less time and cost demanding process than chromatography.[7−14] An increase in productivity is expected by lowering the purification

* Corresponding author. E-mail: rtamagawa@hotmail.com.
† Universidade Estadual de Campinas.
‡ Instituto de Pesquisas Tecnológicas do Estado de São Paulo.

10.1021/je8002207 CCC: $40.75
Published on Web 12/15/2008

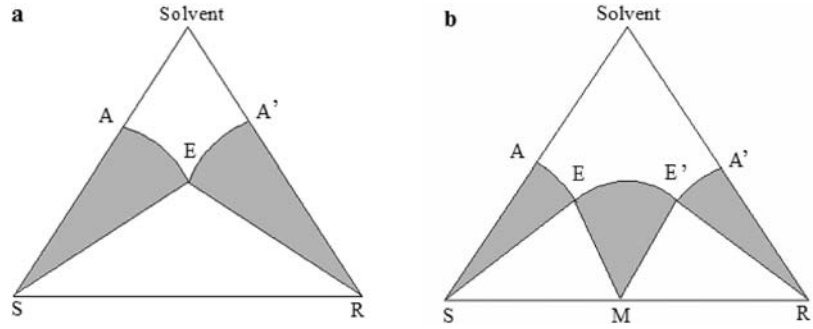

Figure 1. Illustration of typical ternary phase diagrams presented by stereoisomers *S* and *R* in a certain solvent under isothermal conditions: (a) diagram of a conglomerate forming system; (b) diagram of a racemic compound forming system.

demand from the chromatographic process and delivering the partially enriched solution to a crystallization unit.

The minimum enantiomeric enrichment required for crystallization relies on the ternary phase diagram of the enantiomers in a suitable solvent, more specifically on the eutectic points which establish the regions on the diagram wherein the pure enantiomers can crystallize. If the crystal forming system is a conglomerate (mechanical mixture of crystals composed by pure enantiomers), the phase diagram (Figure 1a) presents a eutectic point (E) at the 50:50 (*R*/*S*) composition. Then spontaneous crystallization of the pure enantiomers occurs within the regions SEA and REA′, and a conglomerate is obtained within the region SER.

On the other hand, if the crystal forming system is a racemic compound (crystal units with equal amounts of the two enantiomers), its diagram (Figure 1b) presents two eutectics (E and E′). Pure crystals of *S* and *R* enantiomers are obtained, respectively, within the regions SEA and RA'E', and a racemic compound is obtained within the region MEE′.

About (90 to 95) % of organic molecules are racemic compounds, and only (5 to 10) % are conglomerates.[23,24] Therefore, under the viewpoint of crystallization, its coupling to some other process can be a requirement, provided that in most of the cases a certain level of enantiomeric enrichment is required making it more suitable as an auxiliary than as the predominant process. As an auxiliary or as the predominant process, crystallization offers innumerous advantages, comprising a vast field of research for chiral or nonchiral systems. A recent review on direct crystallization of enantiomers, focused on conglomerates, is found in Coquerel.[25]

3. Differential Scanning Calorimetry As a Short-Cut Method for Solubility Determination

Several authors have been pursuing the use of differential scanning calorimetry (DCS) as an alternative method for solubility determination.[18−22] This alternative method allows the estimation of solubility curves in a remarkably reduced time (a few hours in some cases) demanding only a few milligrams [(5 to 20) mg] of sample. In contrast, the traditional methodology is usually carried out in stirred vessels whose volume may vary from hundreds of milliliters to a liter demanding considerable time and material even for providing simple curves. For determining an entire phase diagram, the efforts are even larger.

Some variations concerning the DSC data treatment have been presented, but all of them rely on the same fundamentals and on similar experimental procedures. The experimental procedure consists of heating the solvent−solute mixture containing an excess of solid within hermetically closed crucibles [(40 to 100) μL] until complete dissolution of the solute. The process is carried out within the calorimeter cell equipped with a set of

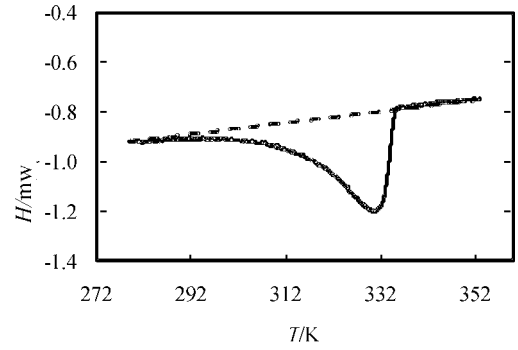

Figure 2. Typical DSC dissolution curve. *H*/mW, the measured enthalpy; *T*/K, the temperature; —, the measured curve; ---, the baseline.

thermocouples which allows the dissolution process to be monitored by recording the heat flux rate as a function of time and temperature. The measured data are presented as a peak shaped curve (Figure 2) referred to here as the DSC dissolution curve. The downward peak indicates here that the event is of endothermic nature.

A complete dissolution of the solute is indicated in the DSC curve by the end-set of the peak, which, in a simple approach, can be used to estimate the saturation temperature of a solution, as has been demonstrated by some authors.[19−22] In such an approach, the end-set temperatures of the curves collected from a sample at different heating rates are extrapolated at a heating rate of zero, resulting in the saturation temperature of the given sample. The procedure is carried out for mixtures with different solute−solvent mass ratios to get a certain range of the solubility curve.

In spite of the significant simplicity of the mentioned procedure, a more effective approach is to take not only the end-set but also the whole information provided by the curve with the advantage of estimating the solubility curve with a single calorimetric run.[26,27] Such an approach relies on the fact that the dissolution process is related to a concentration change toward the solubility limit, which makes the measured dissolution heat flow a function of solubility. Different approaches for correlating the heat flow signal with the solubility are presented in a number of studies.[26−29] A brief introduction is made on the specific method[27] used in this study. The method assumes that the heat flow (mW, $J \cdot s^{-1}$, $J \cdot °C^{-1}$) measured at the dissolution curve accounts for the suspension heat capacity for which the contribution is given by the baseline of the heat flux curve and the latent heat of dissolution, given by the peak area. Therefore, subtraction of the baseline and subsequent integration of the peak area gives the profile of the heat of dissolution ($\Delta H_{dissolution}$), which we assumed to vary proportionally to the profile of the concentration change (ΔC) along the heating interval.

$$\frac{dC}{dT} = k \cdot \frac{dH_{peak}}{dT} \quad (1)$$

with k as the proportionality factor. A disadvantage of the method is that the equilibrium concentration at the initial temperature must be known to proceed with the mass balance ending up in the solubility curve. In the procedure, relative care is required with regard to the applied heating rates which must be above the instrument sensitivity but low enough to favor the equilibrium of the process. The sensitivity relies not only on the heating rate but also mainly on the latent heat of dissolution, inherent of each particular system. A suitable heating rate can be established based on the comparison of the concentration profiles obtained at different heating rates: an optimum heating rate is the one at which the concentration profile does not change compared to those obtained at lower heating rates. As the heating rate increases, the temperature switching time may not be enough for the suspension to achieve the saturation limit (depending on the mass and heat transfer), and then, the dissolution profile does not reflect the solubility limit. An obvious drawback is the absence of stirring within the crucibles, restricting the application for systems with considerable mass and heat transfer limitations. In those systems, even at very low heating rates, the equilibrium condition may not be achieved during the process, and then a strategy would be the extrapolation of the concentration change profile to a heating rate of zero.[27] This, however, would account for the uncertainties inherent from the extrapolation.

4. Experimental Section

4.1. Instrumentation. The DSC data were collected with an 822^e DSC calorimeter from Mettler Toledo (Switzerland), and the measuring system was composed by 56 thermocouples (28 per crucible position). The allowed range of temperature was from (208.1 to 973.1) K, and the range of measurement was ± 350 mW, with a resolution of 0.04 mW at room temperature. Equipment was previously calibrated with indium (In) and zinc (Zn) standards (99.99 % pure) and checked daily for temperature and enthalpy accuracy through a test with indium standard. A continuous purge gas flow of about 40 mL·min^{-1} of nitrogen (99.9 % pure) was used. Data collection and analysis were performed with the Star^e software (Mettler Toledo). Samples were weighed with an analytical balance (Mettler Toledo XS205) with a readability of 0.1 mg.

4.2. Materials. Ketamine racemate and enantiomers with purities above 98 % were kindly supplied by Cristália Produtos Químicos Farmacêuticos (Itapira, SP, Brazil). They were provided either in the base or in the hydrochloride form. A conversion procedure was implemented to convert the hydrochlorides into their base forms. Sodium bicarbonate solution (1.0 M) was slowly added to the aqueous ketamine hydrochloride solution until the solution pH was close to 11. The resulting solution was stirred for 16 h, and then ketamine in the base form was extracted with dichloromethane. The solvent was eliminated by evaporation in a rotatory evaporator.

4.3. Determination of the Binary Phase Diagram. Ketamine samples with enantiomeric compositions ranging from 50:50 to 0:100 (*R*/*S*) were weighed (sample mass around 5 mg) inside 40 μL aluminum crucibles. The different enantiomeric compositions were achieved by weighing specific ratios of racemic ketamine and *R*-ketamine. Crucibles were hermetically sealed and submitted to sequential heating and cooling cycles (5 K·min^{-1}) at the following temperature intervals: (298.1 to 423.1) K; (423.1 to 248.1) K; and (268.1 to 423.1) K. The onset and peak temperatures observed in the second heating interval were used for building the binary phase diagram of *R*(+)- and *S*(−)-ketamine.

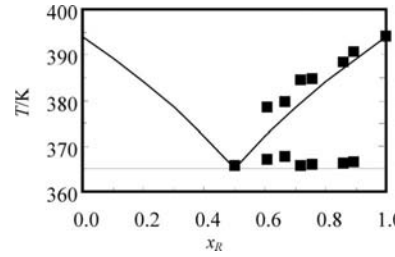

Figure 3. Binary melting phase diagram of *R*(+)-/*S*(−)-ketamine showing conglomerate formation. *T*/K is the temperature; x_R is the mole fraction of *R*-ketamine. ■, the measured melting temperature; −, the *liquidus* line predicted by the Schröder-van Laar equation.

4.4. Solubility Determination. Sample masses of (5 to 10) mg with enantiomeric compositions ranging from 50:50 to 0:100 (*R*/*S*) were weighed inside 40 μL aluminum crucibles, followed by the addition of appropriate amounts of ethanol [(5 to 10) μL]. Crucibles were hermetically sealed immediately after the solvent addition, and possible solvent loss during the heating intervals was checked by weighing the crucibles before and after each heating cycle. During data acquisition, a nonuniform distribution of the sample within the crucible can affect the heat flux disturbing the enthalpy peak signal. Intending to attenuate such an occurrence, a pre-treatment was carried out by heating the crucible until complete dissolution of the solute, followed by a slow cooling providing the sample recrystallization with a hypothetically uniform distribution of the sample mass within the crucible. Samples were then submitted to cyclic heating and cooling processes, at heating rates from (0.2 to 1.0) K·min^{-1} and a cooling rate of −2 K·min^{-1}. The heating and cooling ranges were (278.1 to 323.1) K and (323.1 to 213.1) K. The DSC dissolution peaks were then converted into the concentration profiles which at suitable heating rates provided the solubility curves. The solubility curves for mixtures containing different enantiomeric compositions allowed the determination of the ternary phase diagram at different temperatures.

5. Results and Discussion

5.1. Binary Phase Diagram. For the resolution of racemic mixtures by crystallization it is very important to know what is the crystal forming system of the mixture, which can be of basically two types: conglomerate or racemic compound. Basic characterization of the crystal forming system is by determining the binary phase diagram, also known as the melting point phase diagram. In this work, characterization of the crystal forming system of *R*-/*S*-ketamine was done by determination of its binary phase diagram (Figure 3) using DSC measurements. Only one side of the diagram was determined, considering that it is symmetrical when related to stereo isomers. Determination of only one side of the diagram is very common, avoiding unnecessary work and reducing the number of assays. The fact that the diagram was determined on R-ketamine and not on the S-form, which is the desired isomer, was due to the higher availability of the R-enantiomer. The determined melting points are presented in Table 1. The measured melting points of the pure isomers and the racemic mixture were (394.1 and 365.7) K, respectively, both obtained from the peak temperatures on the DSC curves. Except for the racemic mixture and pure enantiomers, all other samples presented two endothermic peaks, the first representing the eutectic fusion effect and the second corresponding to the complete melting of the mixture. The

Table 1. ***Solidus*** **and** ***Liquidus*** **Temperatures, T_{eu} and T_m, in the Melting Point Phase Diagram of Ketamine As a Function of the *R*-Ketamine Mole Fraction, $x_{(R\text{-ket})}$.**

$x_{(R\text{-ket})}$	T_{eu}/K	T_m/K	$x_{(R\text{-ket})}$	T_{eu}/K	T_m/K
0.50	365.70	365.70	0.76	366.02	384.60
0.61	366.98	378.30	0.86	366.30	388.40
0.67	367.62	379.70	0.90	366.39	390.50
0.72	365.72	384.50	1.00	-	394.10

temperatures T_{eu} and T_m corresponding to the eutectic fusion and the *liquidus* temperatures were obtained, respectivelly from the onset and peak temperatures on the DSC curves.

In the diagram, the calculated curve represents the *liquidus* line predicted by the classical thermodynamic expression of the van't Hoff type, the so-called Schröder-van Laar equation

$$\ln x = \frac{\Delta H_a}{R}\left(\frac{1}{T_a} - \frac{1}{T}\right) \quad (2)$$

where x is the mole fraction of the enantiomer in excess; ΔH_a and T_a are the melting enthalpy ($J \cdot mol^{-1}$) and melting temperature (K) of the pure enantiomer; T is the temperature of the mixture; and R is the universal gas constant ($J \cdot mol^{-1} \cdot K^{-1}$). The melting enthalpy, ΔH_a, determined experimentally was 120.7 $J \cdot g^{-1}$ (26600 $J \cdot mol^{-1}$). Equation 2 is a simplified expression since it does not account for the heat capacity term found to be negligible in the case of enantiomers. The relative disagreement between the measured data and the calculated lines was probably a consequence of a certain level of impurities present in the sample. The *solidus* line has been plotted on the melting temperature, T_m, of the racemic mixture, calculated from eq 2 considering that for the racemic mixture $T_m = T_{eu}$. The uncertainties of the melting temperature and enthalpy were evaluated by repeating the measurements (four replicates) of the racemic mixture melting temperature. The observed errors were within 0.5 % for both temperature and enthalpy.

According to the shape of the diagram, the ketamine crystal in the obtained form is a conglomerate forming system. Such a finding is in contradiction to the characterization given at the ternary phase diagram presented by Barros et al.[30] who found that ketamine crystals obtained from ethanol suspensions (298.1 K) were of racemic compound type, with a eutectic point of 75:25 (*R*/*S*).

Very often, the crystal forming system of a racemate indicated by the binary diagram is expected to be the same as that indicated by the ternary phase diagram, and in some cases even identical eutectics are found in both diagrams.[31] However, in some cases, the binary and ternary diagrams may provide different indications as in the work of Shiraiwa et al.,[32] who obtained a binary diagram for 2-benzoylamino-2-benzyl-3-hydroxypropanoic acid indicating that it was a racemic compound, although the ternary phase diagram in the presence of ethanol indicated that it was a conglomerate. Therefore, the expectation of having the same behavior in both diagrams is not always satisfied, which in fact is not so surprising considering that the solvent and the temperature, among other variables, can affect the melting behavior of a substance.

5.2. Solubility of Racemic Ketamine Determined by DSC. The heat flow rate measured in the dissolution process by means of a DSC calorimeter was used to estimate the solubility of racemic ketamine in ethanol. A typical DSC curve collected from the dissolution of a few microliters of suspension is presented in Figure 4. The integration profile of the dissolution peak was used for estimating the rate of concentration change along the heating interval. The procedure was carried out at

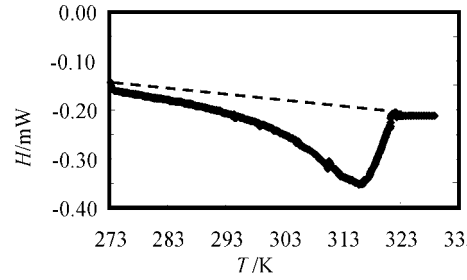

Figure 4. DSC dissolution curve of racemic ketamine in anhydrous ethanol collected at a heating rate of 0.5 $K \cdot min^{-1}$. Sample mass, 6.0 mg; solute mass fraction, $w = 0.322$. H/mW, the enthalpy; T/K, the temperature; —, the measured curve; - - -, the baseline.

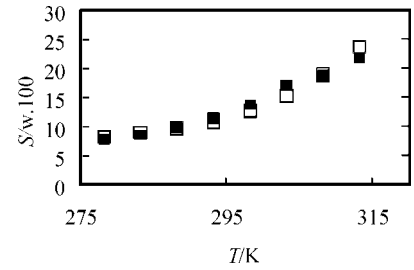

Figure 5. Solubility of racemic ketamine in anhydrous ethanol. T/K, the temperature; S, the solubility; w, the mass fraction. □, data obtained using the DSC method; ■, data obtained using the traditional isothermal method (Barros et al.[30]).

Table 2. Solubity, *S*, of Racemic Ketamine in Ethanol Determined by the DSC Method and by the Traditional Isothermal Method (Barros et al.[30])[a]

Isothermal method		DSC method	
T/K	$S/(w.100)$	$S/(w.100)$	error (%)
278.1	7.80	8.37	9.75
283.1	8.69	9.01	3.18
288.1	10.00	9.83	3.22
293.1	11.60	11.04	7.30
298.1	13.83	12.84	8.23
303.1	17.25	15.43	5.93
308.1	18.97	19.00	0.69
313.1	22.01	23.77	7.07

[a] Error, calculated from the difference between the DSC results and the data provided by a polynomial curve ($y = ax^2 + bx + c$) fitted on the literature data.

heating rates of (0.2 to 1.0) $K \cdot min^{-1}$. Through a comparison of the data obtained from these curves, it was observed that a heating rate of 0.5 $K \cdot min^{-1}$ was suitable for achieving the equilibrium condition, and therefore, the concentration profile obtained at this condition provided the solubility curve of racemic ketamine in ethanol (Figure 5). For an evaluation on the precision of the method, Figure 5 presents also the solubility curve obtained by the traditional isothermal method.[30] Data obtained from DSC were the mean values of two replicates with a standard deviation < 0.0098 $g \cdot g^{-1}$, and data from the literature were provided as the mean values of four to seven replicates with a standard deviation < 0.0070 $g \cdot g^{-1}$. The solubility data (Table 2) obtained by the two distinct methods present no significant differences, demonstrating the efficacy of the DSC-based method and its suitability for the purpose of this study.

5.3. Ternary Phase Diagram and the Eutectic Composition. Following the same procedure used for determining solubility of racemic ketamine, we determined the solubility curves of the pure isomers and of mixtures containing different enantiomeric compositions (Figure 6, Table 3). Determination was based on the concentration change profiles obtained from the

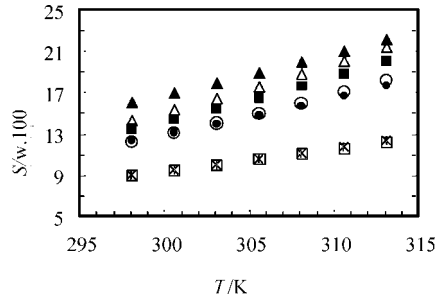

Figure 6. Solubility of ketamine mixtures containing different enantiomeric compositions in anhydrous ethanol. *T*/K, the temperature; *S*, the solubility; *w*, the mass fraction. The enantiomeric compositions: □, 0:100 *R*/*S*; ○, 50:50 *R*/*S*; ■, 60:40 *R*/*S*; Δ, 72:28 *R*/*S*; ▲,75:25 *R*/*S*; ●, 80:20 *R*/*S*; *, 100:0 *R*/*S*. Data obtained by the DSC solubility determination method.

Table 3. Solubility, *S*, of Ketamine/Ethanol As a Function of Temperature in Different Molar Fractions of *R*-Ketamine, $x_{(R\text{-ket})}$[a]

	$x_{(R\text{-ket})}$						
T/K	0.00	0.500	0.596	0.720	0.748	0.790	1.00
	$S/(w \cdot 100)$						
298.1	8.90	12.26	13.41	14.2	16.03	12.39	8.94
300.6	9.40	13.12	14.37	15.24	16.94	13.16	9.44
303.1	9.90	14.02	15.39	16.34	17.88	13.98	9.96
305.6	10.50	14.98	16.46	17.50	18.86	14.83	10.50
308.1	11.05	15.99	17.60	18.73	19.88	15.73	11.07
310.6	11.60	17.05	18.80	20.02	20.94	16.67	11.67
313.1	12.20	18.17	20.06	21.38	22.05	17.66	12.29

[a] Data obtained by the DSC solubility determination method.

DSC dissolution curves, with the initial concentrations established from the ternary diagram at 298.1 K provided in the literature.[30]

As expected, the solubility curves of the enantiopure suspensions were identical and significantly lower than the solubility of the racemic mixture. The solubility of the mixtures along the temperature interval followed the same trend presented by the diagram at 298.1 K; i.e., it increased as the enantiomeric composition increased from 50:50 (*R*/*S*) to 75:25 (*R*/*S*) and decreased as the enantiomeric composition increased from 75:25 (*R*/*S*) to 100 % *R*. Such behavior confirms the eutectic composition at the 75:25 composition. The solubility curves of mixtures containing different enantiomeric compositions allowed us to build the ternary phase diagrams of the system *R*(+)-/*S*(−)-ketamine/ethanol in different temperatures (Figure 7). To understand how the solubility data from Figure 6 and Table 3 result in the diagrams in Figure 7, notice that the mole fraction of enantiomers in Table 3 refers to the binary composition of the solute, i.e., not taking the solvent into account, whereas the sides of the diagram in Figure 7 refer to the mass fraction of each component in the ternary system. According to these diagrams, racemic ketamine crystallizes from ethanol in the form of a racemic compound, and the eutectic point at the 75:25 (*R*/*S*) enantiomeric composition implies that the pure isomers can be obtained from a suspension with an enantiomeric composition above 75 %.

6. Conclusions

In this work, a small number of experiments based on DSC measurements allowed the estimation of the ternary phase diagram of *R*/*S*-ketamine in ethanol in the temperature range of (298.1 to 313.1) K. A comparison between data obtained in the present work and data obtained from the conventional isothermal method proved the suitability of this technique, for which the advantage is the fast determination capability. The

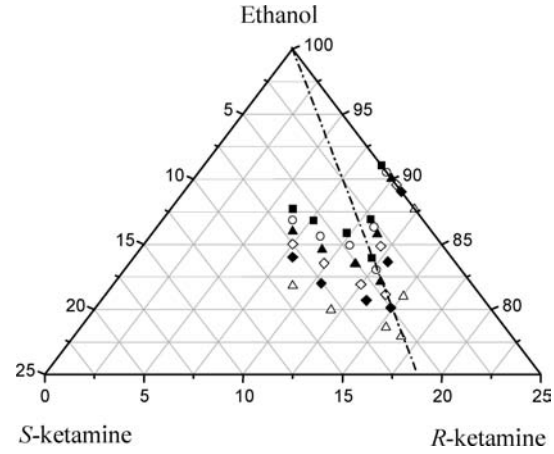

Figure 7. Ternary phase diagrams of *R*(+)-/*S*(−)-ketamine in anhydrous ethanol at different temperatures. ■, 298.1 K; ○, 300.6 K; ▲, 303.1 K; ◇, 305.6 K; ♦, 308.1 K; Δ, 313.1 K. Data obtained by the DSC solubility determination method.

determined diagrams presented a eutectic point in the enantiomeric composition of 75:25 (*R*/*S*) in the whole temperature range. These results indicated that *R*/*S*-ketamine obtained from ethanol suspension was a racemic compound, although the binary phase diagram has indicated a conglomerate formation. The different crystal forming systems observed in these conditions were probably due to effects from variables such as temperature and solvent.

Acknowledgment

We would like to thank Cristália Produtos Químicos Farmacêuticos (SP-Brazil) for the kind supply of ketamine and the Associated Laboratory of Micronal and IPT (LAMI) where the experimental work was carried out.

Literature Cited

(1) Nishizawa, N.; Nakao, S.-I.; Nagata, A.; Hirose, T.; Masuzawa, M.; Shingu, K. The effect of ketamine isomers on both mice behavioral responses and c-Fos expression in the posterior cingulated and retrosplenial cortices. *Brain Res.* **2000**, *857*, 188–192.

(2) da Silva, I. J.; dos Santos, M. A. G.; Veredas, V.; Santana, C. C. Experimental determination of chromatographic separation parameters of ketamine enantiomers on MCTA. *Sep. Sci. Technol.* **2005**, *43*, 103–110.

(3) da Silva, I. J.; dos Santos, M. A. G.; Veredas, V.; Santana, C. C. Effect of temperature on chiral separation of ketamine enantiomers by high performance liquid chromatography. *Sep. Sci. Technol.* **2005-b**, *40*, 2593–2611.

(4) Santosi, M. A. G.; Veredas, V.; Silva, I. J., Jr.; Correia, C. R. D.; Furlan, L. T.; Santana, C. C. Simulated moving-bed adsorption for separation of racemic mixtures. *Braz. J. Chem. Eng.* **2004**, *21* (01), 127–136.

(5) Steiner, K.; Gangkofner, S.; Gruenwald, J.-M. Racemic separation of ketamine. US2000/6040479, March, 21, 2000.

(6) Russo, V. F. T.; Russo, E. M. S. Process of obtainment of racemic cetamine enantiomers; process of obtainment of pharmaceutically acceptable salts from racemic cetamine enantiomers and use of pharmaceutically acceptable salts obtained by means of said mentioned process. US2003/0212143 A1, nov.13, **2003**.

(7) Lim, B.-G.; Chang, C.-B.; Tan, R. B. H.; NG, S.-C. Recovery of (−)-praziquantel from racemic mixtures by continuous chromatography and crystallization. *Chem. Eng. Sci.* **1995**, *50* (14), 2289–2298.

(8) Lorenz, H.; Sheehan, P.; Seidel-Morgenstern, A. Coupling of simulated moving bed chromatography and fractional crystallisation for efficient enantioseparation. *J. Chromatogr. A* **2001**, *908*, 201–214.

(9) Bléhaut, J.; Hombourger, O. L.; Perrin, S. R. Industrial chiral chromatography: the keys to rapid process development and successful implementation. *Chim. Oggi* **2001**.

(10) Gedicke, K. Coupling chromatography and crystallization for efficient separations of isomers. *Adsorption* **2005**, *11*, 591–596.

(11) Lorenz, H.; Polenke, D.; S-Morgenstern, A. Application of preferential crystallization to revolve racemic compounds in a hybrid process. *Chirality* **2006**, *18*, 828–840.

(12) Fung, Ka. Y.; Ng, Ka. M.; Wibowo, C. Synthesis of chromatography - crystallization hybrid separation processes. *Ind. Eng. Chem. Res.* **2005**, *44*, 910–921.

(13) Ströhlein, G.; Schulte, M.; Strube, J. Hybrid processes: Design method for optimal coupling of chromatography and crystallization units. *Sep. Sci. Technol.* **2003**, *38* (14), 3353–3383.

(14) Amanullah, M.; Mazzoti, M. Optimization of a hybrid chromatography-crystallization process for the separation of Tröger's base enantiomers. *J. Chromatogr. A* **2006**, *1107*, 36–45.

(15) Wang, X. J.; Wiehler, H.; Ching, C. B. Study of the characterization and crystallization of 4-Hydroxy-2-Pyrrolidone. *Chirality* **2004**, *16*, 220–227.

(16) Diwevedi, S. K.; Sattari, S.; Jamali, F.; Mitchell, A. G. Ibuprofen racemate and enantiomers: Phase diagram, solubility and thermodynamic studies. *Int. J. Pharm.* **1992**, *87*, 95–104.

(17) Nemák, K.; Ács, M.; Kozma, D.; Fogassy, E. Racemic compound formation-conglomerate formation. *J. Therm. Anal.* **1997**, *48*, 691–696.

(18) Lorenz, H.; Seidel-Morgenstern, A. Binary and ternary phase diagrams of two enantiomers in solvent systems. *Thermochim. Acta* **2002**, *382*, 129–142.

(19) Lorenz, H.; Sapoundjiev, D.; Seidel-Morgenstern, A. Enantiomeric mandelic acid system-melting point phase diagram and solubility in water. *J. Chem. Eng. Data* **2002**, *47*, 1280–1284.

(20) Mohan, R.; Lorenz, H.; Myerson, A. S. Solubility measurement using differential scanning calorimetry. *Ind. Chem. Eng. Res.* **2002**, *41*, 4854–4862.

(21) Park, K.; Evans, J. M. B.; Myerson, A. S. Determination of solubility of polymorphs using differential scanning calorimetry. *Cryst. Growth Des.* **2003**, *3* (6), 991–995.

(22) Young, P. H.; Schall, C. A. Cycloalkane solubility determination through differential scanning calorimetry. *Thermochim. Acta* **2001**, 387–392.

(23) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, racemates and resolutions*; Wiley-Interscience: New York, 1981.

(24) Shekunov, B. Y.; York, P. Crystallization processes in pharmaceutical technology and drug delivery design. *J. Cryst. Growth* **2000**, *211*, 122–136.

(25) Coquerel, G. Preferential Crystallization, in Novel Optical Resolution Technologies. *Topics in Current Chemistry*; Sakai, K., Hirayama, N., Tamura, R., Eds.; Springer: Berlin- Heidelberg, 2006; Vol. 269, pp 1−51.

(26) Sapoundjiev, D.; Lorenz, H.; Seidel-Morgenstern, A. Determination of solubility data by means of calorimetry. *Thermochim. Acta* **2005**, *436*, 1–9.

(27) Tamagawa, R. E.; Martins, W.; Derenzo, S.; Bernardo, A.; Rolemberg, M. P.; Carvin, P.; Giulietti, M. Short-cut method to predict the solubility of organic molecules in aqueous and non-aqueous solutions by differential scanning calorimetry. *Cryst. Growth Des.* **2006**, *6* (1), 313–320.

(28) Huang, C.-C.; Chen, Y.-P. Measurements and model prediction of the solid-liquid equilibria of organic binary mixtures. *Chem. Eng. Sci.* **2000**, *55*, 3175–3185.

(29) Coutinho, J. A. P.; Ruffier-Meray, V. A new method for measuring solid-liquid equilibrium phase diagrams using calorimetry. *Fluid Phase Equilib.* **1998**, *148*, 147–160.

(30) Barros, G. O. F.; Tamagawa, R. E.; Santana, C.; Miranda, E. A. Ternary phase diagram of ketamine ((R,S)-2-(2-chlorophenyl)-2-methylaminocyclohexanone) in ethanol and preliminary studies aiming to the enantioselective crystallization of S-ketamine. *Braz. J. Chem. Eng.,* in press.

(31) Lorenz, H.; Perlberg, A.; Sapoundjiev, D.; Elsner, M. P.; Seidel-Morgenstern, A. Crystallization of enantiomers. *Chem. Eng. Proc.* **2006**, *45* (10), 867–873.

(32) Shiraiwa, T.; Suzuki, M.; Sakai, Y.; Nagasawa, H.; Takatani, K. Optical resolution by preferential crystallization of (RS)-2-benzoylamino-2-benzyl-3-hydroxypropanoic acid and its use in synthesizing optically active 2-amino-2-methyl-3-phenylpropanoic acid. *Chem. Pharm. Bull.* **2002**, *50* (10), 1362–1366.

Received for review March 28, 2008. Accepted November 9, 2008. We would like to thank FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo) and CNPq (Conselho Nacional de apoio à Pesquisa) for the financial support to this work; Cristália Produtos Químicos Farmacêuticos (SP-Brazil) for the kind supply of ketamine; the Associated Laboratory of Micronal and IPT (LAMI) where the experimental work was carried out, and the UNICAMP program "Pesquisador Voluntário" under which this work was partially developed.

JE8002207