Solubility and Metastable Zone Width of 1-Keto-1,2,3,4-tetrahydro-6-methylcarbazole in Acetone

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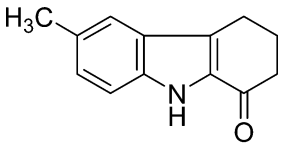
The solubility of 1-keto-1,2,3,4-tetrahydro-6-methylcarbazole (KTMC) in acetone in the temperature range from 18 to 55 °C was determined by the residue solid technique and the polythermal method using a heat flow calorimeter with turbidity measurement capacities. The results were correlated using a polynomial equation. Utilizing the polythermal method, the metastable zone has also been determined. The broadening of the metastable zone with increasing cooling was observed from 0.05 to 2.0 °C·min^{-1}.

Introduction

Carbazole derivatives have gained considerable importance in recent years due to their diverse biological activity and synthetic applications.[1] Namely, the compound 1-keto-1,2,3,4-tetrahydro-6-methylcarbazole (KTMC) (**1**)



(**1**)

has been shown to be a useful starting material for the synthesis of antibacterial and antifungal agents[2] and as an intermediate in the synthesis of pirlindole hydrochloride (2,3,3a,4,5,6-hexahydro-8-methyl-1*H*-pyrasino-[3,2,1-*j*,*k*]carbazole hydrochloride), which is the active pharmaceutical ingredient of an antidepressant drug.[3−9] KTMC is not currently on the market and has been synthesized during a study of this drug.

KTMC can be purified by crystallization, and preliminary tests carried out in our laboratory showed that acetone was an adequate solvent for scale-up studies. Essential to the optimization and control of this process is the knowledge of the solubility and supersaturation curves, which define the boundaries of the metastable zone of the KTMC/acetone system.[10,11] On the basis of these data, it is possible to design a crystallization protocol where a constant supersaturation is approximately maintained throughout the cooling. This allows control of the nucleation rate and hence of the optimum crystal size and size distribution in the obtained product, which may be critical for further use or processing.

In this work we report the determination of solubility and of the metastable zone in the system KTMC/acetone as a function of cooling/heating rates. The solubility determinations were compared against those obtained using the residue solid technique.

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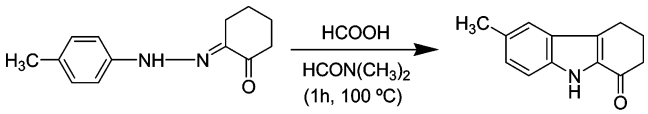
Scheme 1



(**2**) (**1**)

Experimental Section

Materials. The KTMC sample used in this work was prepared by cyclization of cyclohexane-1,2-dione-mono-*p*-tolylhydrazone (**2**) as shown in Scheme 1.[7] The crude material was treated with activated charcoal, recrystallized several times from acetone, and dried in an oven at 50 °C for 36 h. Elemental analysis led to the following results for the mass percentage of C, H, and N in $C_{13}H_{13}ON$: calcd. C, 78.36; H, 6.58; N 6.89; found: C, 77.91 ± 0.42; H, 6.87 ± 0.43; N 6.97 ± 0.05 (average of two determinations). The GC−MS analysis indicated that the purity of the sample was > 99.9 %. The ^{1}H NMR chemical shifts relative to TMS were as follows: δ = 2.19 (m, C**H**, 2H), 2.38 (s, C**H**, 3H), 2.58 (t, C**H**, 1H), 2.91 (t, C**H**, 1H), 7.13 (dd, C**H**, 1H), 7.23 (d, C**H**, 1H), 7.36 (d, C**H**, 1H), and 8.69 (s, N**H**, 1H). The X-ray powder diffraction pattern showed the following main reflections (*d* spacing in Å; normalized intensity): (10.7689, 7.3 %), (8.5922, 100 %), (5.4494, 3.4 %), (4.3395, 42.7 %), (4.3114, 50.1 %), (3.8103, 5.6 %), (3.3942, 6.7 %). The fusion enthalpy and melting temperature obtained by differential scanning calorimetry (DSC) were $\Delta_{fus}H = 26.9 \pm 0.07$ kJ·mol^{-1} and T_m = 195.3 ± 0.4 °C, respectively (mean of three determinations).

Acetone was from Riedel-deHaën (purity > 99.5 %) and was used without further purification. Norit PN2 and Sigma C-4386 activated charcoals were used in the purification of KTMC.

Apparatus and Procedure. Elemental analyses were carried out on a Fisons Instruments EA1108 apparatus. GC−MS experiments were performed on an Agilent 6890 gas chromatograph coupled to an Agilent 5973N mass detector. The transfer line, ion source, and quadrupole analyzer were maintained at 280, 230, and 150 °C, respectively. A HP-5MS capillary column from Agilent (5 % diphenyl/95 % dimethylpolysiloxane; 30 m × 0.25 mm i.d., 0.25 μm d_f) was used. The carrier gas was helium maintained at a constant pressure of 17.30 psi. The

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Table 1. KTMC Solubility in Acetone Obtained by the Residue Solid Technique and by the Polythermal Method Using the RC1*e* Reactor[a]

residue solid technique		polythermal method						
			t_s					
t_s	c_s	c_s	$\beta = 0.05$	$\beta = 0.1$	$\beta = 0.2$	$\beta = 0.5$	$\beta = 1.0$	$\beta = 2.0$
50.0	5.69 ± 0.01	5.94	51.1 ± 0.05	51.2 ± 0.05	51.4 ± 0.05	52.3 ± 0.14	53.6 ± 0.07	54.2 ± 0.07
42.0	4.57 ± 0.01	5.06	45.6 ± 0.08	45.8 ± 0.10	46.0 ± 0.12	47.0 ± 0.14	48.4 ± 0.19	50.2 ± 0.24
40.0	4.32 ± 0.02	4.26	40.1 ± 0.11	40.2 ± 0.15	40.4 ± 0.11	41.4 ± 0.21	42.9 ± 0.12	44.9 ± 0.23
33.0	3.55 ± 0.02	3.39	32.1 ± 0.15	32.1 ± 0.18	32.3 ± 0.24	33.3 ± 0.17	34.9 ± 0.11	37.5 ± 0.29
18.3	2.35 ± 0.01	2.65	23.3 ± 0.10	23.2 ± 0.30	23.2 ± 0.49	24.1 ± 0.68	25.9 ± 0.57	28.9 ± 0.51

[a] c_s in g of KTMC/100 g of acetone; t_s in °C; β in °C·min^{-1}.

temperature of the injector was set at 250 °C, and the oven temperature was programmed as follows: 100 °C (3 min), ramp at 10 °C·min^{-1}, 210 °C (3 min), ramp at 10 °C·min^{-1}, 290 °C (15 min). The ^{1}H NMR spectra were obtained at ambient temperature, in $CDCl_3$, on a Bruker Ultrashield 400 MHz spectrometer. X-ray powder diffractometry (XRD) was carried out over the range $5° \leq 2\theta \leq 35°$, on a Philips diffractometer employing Cu Kα radiation ($\lambda = 1.54178$ Å). DSC measurements were made with a Perkin-Elmer DSC 7 apparatus using indium and zinc for calibration. All solutions were prepared by weighing using a Mettler AG 204 balance with an accuracy of ± 0.0001 g.

Measurement of Solubility. Solubility measurements by the residue solid technique[10] were performed in the temperature range between 18 and 50 °C. Acetone and solid KTMC were weighed and placed in a 100 mL jacketed glass reactor equipped with a reflux condenser and a Teflon-coated magnetic stirring bar. The temperature of the solution was monitored with a calibrated mercury thermometer (resolution ± 0.05 °C). The calibration was made against the melting and normal boiling point of distilled water. A constant temperature of the solution was maintained by circulating oil through the reactor jacket. The temperature of the oil in the jacket was controlled to ± 0.1 °C by a Lauda RCS 20 unit. The mixture was equilibrated at constant temperature and with agitation for 3 h. The agitation was then stopped, and the solid particles in suspension were allowed to settle for 2 h. Samples of the supernatant liquid (approximately 3 cm^3) were withdrawn using a preheated syringe adapted with a microfilter (0.20 μm) and transferred to a vial, and the solution was taken to dryness. The concentration of the saturated solution was computed from the masses of the empty vial, vial + solution, and vial + residue. Each experiment was conducted in triplicate, and the standard deviation of the measurements was ± 0.01 g of KTMC/100 g of acetone.

Measurement of Metastable Zone Width. Solubility and supersaturation measurements for the determination of the metastable zone width for the crystallization of KTMC from acetone were carried out in the temperature range between 23 and 55 °C, using an automated method through a computer-controlled RC1*e* calorimeter from Mettler-Toledo. The crystallization process was followed by turbidity (FSC402 optical controller). This technique has been shown to be suitable for online monitoring of the onset of solubilization or nucleation during scale-up studies using an apparatus such as the RC1*e* calorimeter.[12−17] The programmed method was based on the conventional polythermal technique[18] and involved the following protocol: (i) a weighed KTMC sample was dissolved in acetone above the saturation temperature to obtain a homogeneous solution; (ii) cooling at constant rate until the onset of crystallization was detected (the corresponding temperature defined a point on the supersaturation curve); (iii) heating at the same constant rate until dissolution of all solid material (the corresponding temperature defined a point on the saturation curve); (iv) automatic addition of a pre-defined mass of acetone to change the concentration of the solution. Steps (ii) through (iv) were repeated until the saturation and supersaturation curves were conveniently defined. Heating/cooling rates of 0.05, 0.1, 0.2, 0.5, 1.0, and 2.0 °C·min^{-1} and a stirring rate of 300 rpm were used. Agitation was maintained with a glass impeller with five agitation stages, each one with a three pitched-blade turbine.

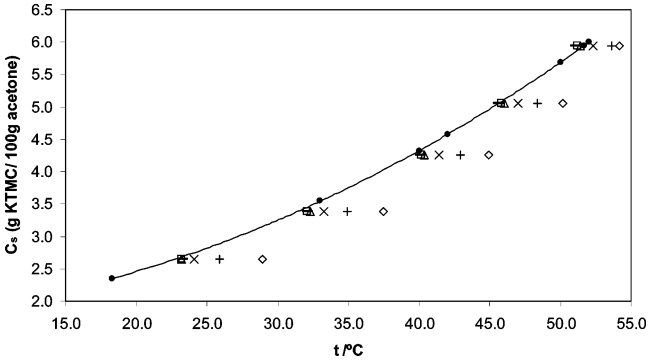

Figure 1. Solubility of KTMC in acetone obtained by the residue solid method (−●−) and by the polythermal method (RC1*e* reactor) using a stirring rate of 300 rpm and heating rates of −, 0.05 °C·min^{-1}; □, 0.1 °C·min^{-1}; △, 0.2 °C·min^{-1}; ×, 0.5 °C·min^{-1}; +, 1.0 °C·min^{-1}; and ◇, 2.0 °C·min^{-1}.

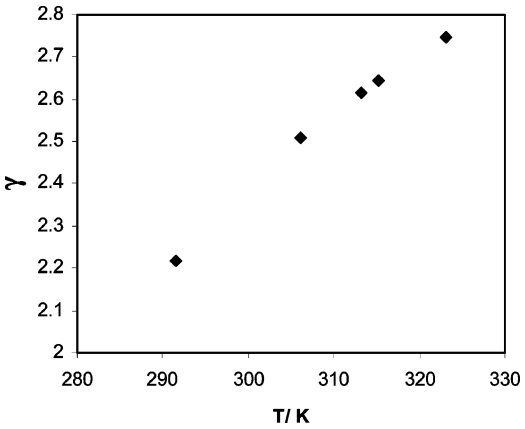

Figure 2. KTMC activity coefficient, γ, vs temperature.

Results and Discussion

Solubility. The saturation concentrations (c_s/(g of solute/100 g of solvent)) of KTMC in acetone obtained by the residue solid technique at five different temperatures (t_s/°C) are shown in Table 1. A polynomial fit to these results led to

$$c_s = 0.001425t_s^2 + 0.00785t_s + 1.7305 \qquad (1)$$

The root-mean-square deviation (RMSD) between the measured solubility data and the data calculated from eq 1 is 0.008 g of

Table 2. Width of the Metastable Zone (Δt_{max}) for the Crystallization of KTMC from Acetone as a Function of the Cooling Rate (β) and Ordinate (a) and Slope (b) of the Linear Relations Obtained by Using the Modified Regression Method[18,20] [a]

	Δt_{max}						
c_s	$\beta = 0.1$	$\beta = 0.2$	$\beta = 0.5$	$\beta = 1.0$	$\beta = 2.0$	a	b
5.94	4.7 ± 0.18	5.5 ± 0.15	7.7 ± 0.57	11.3 ± 0.49	14.1 ± 0.14	1.0417	0.4163
5.06	5.2 ± 0.10	5.9 ± 0.08	7.9 ± 0.07	12.7 ± 0.14	17.0 ± 0.21	1.0852	0.4163
4.26	5.3 ± 0.21	6.0 ± 0.23	8.2 ± 0.43	12.4 ± 0.28	16.6 ± 0.19	1.0874	0.4163
3.39	5.4 ± 0.25	6.4 ± 0.30	9.0 ± 0.37	12.8 ± 0.56	21.1 ± 0.50	1.1263	0.4163
2.65	6.4 ± 0.38	9.9 ± 0.51	13.8 ± 0.70	18.2 ± 0.39	22.7 ± 0.88	1.2530	0.4163

[a] c_s in g of KTMC/100 g of acetone; Δt_{max} in °C; β in °C·min^{-1}.

solute/100 g of solvent and is defined by

$$\mathrm{RMSD} = \left[\frac{\sum (c_s(\mathrm{calc}) - c_s)_i^2}{N - p}\right]^{1/2} \quad (2)$$

where N and p are the number of data points and the number of empirical coefficients, respectively.

Equation 1 is plotted as the solid line in Figure 1 along with the experimental values of the residue solid technique and the ones presented in Table 1 measured by the polythermal technique with the RC1*e* apparatus, using the stirring rate of 300 rpm and heating rates (β) of 0.05, 0.1, 0.2, 0.5, 1.0, and 2.0 °C·min^{-1}.

Observing the solubility values obtained by the two different methods, it can be concluded that only the values obtained at the lower heating rate, 0.05 °C·min^{-1}, compare well with the values of the residue solid technique. These results confirm the statement[13] that, in solubility determinations by the polythermal method, the heating process must be done very slowly, where the heating rate has to be lower than the dissolution rate.

From the theory of solid−liquid equilibrium, the solubility of solids in liquids can be estimated by the following expression:[19]

$$\ln x\gamma = \frac{-\Delta_{fus}H}{RT}\left(1 - \frac{T}{T_m}\right) \quad (3)$$

where x is the solute mole fraction in the liquid phase, $\Delta_{fus}H$ is the enthalpy of fusion at the melting point T_m, T is the equilibrium temperature, and γ the solute activity coefficient. Assuming an ideal solution, $\gamma = 1$, the equilibrium concentration c_s (g of KTMC/100 g of acetone) can be evaluated by

$$c_s = M\frac{100}{58.08}\left(\frac{x}{1 - x}\right) \quad (4)$$

where M is the molecular weight of the solute and the value of x is calculated from eq 3 ($\gamma = 1$) through the experimental values of the fusion enthalpy and the melting temperature obtained in this work. The experimental solubility values are lower than those assuming ideality. The comparison of those values allows estimating the activity coefficients of the solute in the saturated solutions at various temperatures. These values are given in Figure 2, and it can be observed that the activity coefficient increases with increasing temperature.

Metastable Zone Width. The difference between the saturation (T_s) and nucleation (T_{ss}) temperatures—which corresponds to the metastable zone width—represents the maximum allowable undercooling, ΔT_{max}, corresponding to a particular set of experimental conditions:

$$\Delta T_{max} = T_s - T_{ss} \quad (5)$$

The value of ΔT_{max} is influenced by the cooling rates, and this effect was studied in this work for the KTMC/acetone system using the polythermal method. It is also important to specify the agitation rate. Usually, when the stirring rate increases a decrease of the metastable zone is observed.

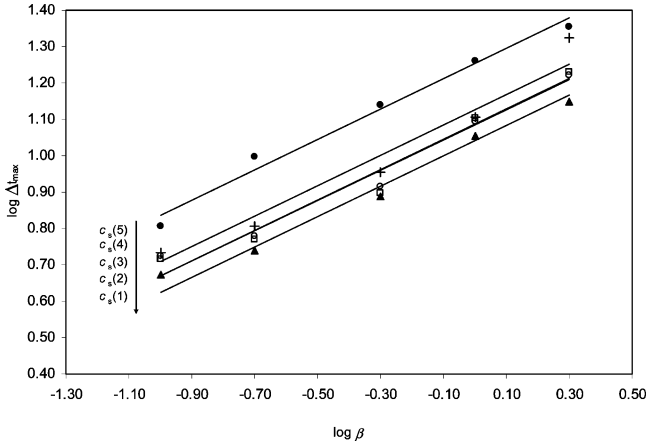

Figure 3. Plots of log Δt_{max} against log β for the crystallization of KTMC in acetone. Experimental c_s data in g of KTMC/100 g of acetone: ●, $c_s(1) = 5.94$; +, $c_s(2) = 5.06$; ○, $c_s(3) = 4.26$; □, $c_s(4) = 3.39$; ▲, $c_s(5) = 2.65$.

For nucleation from a solution cooled at a constant rate and with a constant stirring rate, the relationship between the metastable zone width and the cooling rate can be given by[18]

$$\log \Delta T_{max} = \frac{1 - n}{n}\log\left(\frac{dc_s}{dT}\right) - \frac{1}{n}\log k_n + \frac{1}{n}\log \beta \quad (6)$$

where k_n is a constant related to the nucleation rate and n is the apparent nucleation order.[10,18,20] According to eq 6, a plot of log ΔT_{max} against log β at constant c_s should lead to a straight line with ordinate $a = [(1 - n)\log(dc_s/dT) - \log k_n]/n$ and slope $b = 1/n$. Since this slope is the inverse of the apparent nucleation order, the lines corresponding to the various saturation concentrations should be exactly parallel. Hence, the experimental data in Table 2 were fitted to eq 6 by using the modified regression method recommended by Nývlt et al.[18] The obtained log ΔT_{max} against log β plots are shown in Figure 3, and the corresponding values of the coefficients a and b are listed in Table 2. These results lead to an apparent nucleation order of KTMC in acetone of 2.4. It also shows that the metastable zone width broadens with increasing cooling rate.

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