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DYNAMIC DSC PURITY ANALYSIS STUDIES OF TWO COMPONENT DOPED SYSTEMS *

J.P. ELDER

Mettler Instrument Corporation, Hightstown, NJ 08520 (U.S.A.)

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ABSTRACT

Up to the present time, the accuracy and precision of dynamic DSC purity analysis measurements have been tested by using simple binary systems as models. For the most part, pure organic substances have served as host and eutectic-forming low level dopant. As a first step in considering whether the DSC method can be applied to multicomponent impure substances, the simple ternary model system, phenacetin doped with benzamide and *p*-aminobenzoic acid, has been studied. Separately, the two dopants form well defined eutectics with the host melting at 370 K (benzamide dopant) and 385 K (*p*-aminobenzoic acid dopant). When the two dopants are combined, a third eutectic melting at 353 K is produced. Evidence is presented confirming the fact that in the range 100—98.5 mole % purity, the total DSC measured impurity is the sum of the two individual dopant levels, and is independent of their relative proportions.

INTRODUCTION

The determination of the purity of crystalline materials by measurement of melting point depression is a well established calorimetric method. Concurrent with the advances in the design of heat flow and power compensated differential scanning calorimeters has been the increasing interest in the utilization of DSC for purity analyses. This culminated in the extensive review by Marti [1], in which he discussed the dynamic scan technique in detail. More recently, Palermo and Jen Chiu [2] compared the dynamic method with the isothermal step method [3], and its offshoot, the two peak ratio method [4]. Detailed references pertaining to theoretical precepts and experimental procedures are given in these reviews [1,2].

In studying the many factors which can affect the accuracy and precision of measurement, extensive use has been made of well defined binary systems; a host vehicle with a single eutectic forming dopant. Phenacetin with either benzamide, acetanilide or *p*-aminobenzoic acid has been widely used. Realistically, in analysing intermediate or final products in, for example, the pharmaceutical industry, one must recognize that several components may contribute to the total impurity. Are such multiple impurity systems

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capable of being measured quantitatively? Hitherto, a positive answer has been assumed. As a first step in answering this question, purity analysis measurements have been made on the ternary system, phenacetin doped with mixtures of benzamide and *p*-aminobenzoic acid. In this study, both the total impurity level and the mole ratio of dopants were varied.

EXPERIMENTAL

All heat flow DSC measurements were made using the Mettler TA2000B system. The resulting data were monitored and analysed in two ways. First, using the Mettler CT data transfer system, the data were digitized and recorded on tape at selected intervals for off-line analysis on an NCR-151 computer with the appropriate FORTRAN programs. Secondly, using the TA2000Z system, the data were digitized and transferred directly to a Hewlett-Packard HP9815A programmable calculator for on-line analysis [5]. Simultaneous TG/DTA measurements made with the Mettler TA1 thermoanalyzer, were used to assess component weight loss during fusion.

High purity materials were used throughout. Phenacetin and benzamide (B.D.H.) were dried to constant weight at 50°C. The *p*-aminobenzoic acid, specially prepared for purity analysis studies, was used as received. When not in use, the materials were stored over a desiccant. The DSC samples were prepared in situ by direct weighing into aluminum crucibles, using the Mettler ME22 microbalance. Following the advice of Barrall and Diller [6], great care was taken in sample preparation. A standard size of 3 mg was employed. Prior to component addition, the crucible cup and lid were ultrasonically cleaned in ethylene dichloride and dried. The dopants were added first, followed by the main component. The cup and lid were then crimp sealed. Three ways of closure have been used: (i) hermetic sealing, (ii) sealing with a lid with a pierced pinhole to obviate pressure effects, (iii) flattening the pinhole-pierced lid to simulate the volatile pan with inside cover, suggested by Gray [7] to minimize volatilization. The characteristic DSC fusion endotherm is the same for all three methods, and with the pierced lids, no detectable weight loss is observed. A pierced lid is necessary for *p*-aminobenzoic acid alone, since a high vapor pressure is exhibited during its fusion. For the doped samples, hermetically sealed crucibles were used, thereby ensuring completely against loss of material and possible introduction of unknown material.

All DSC scans were performed in a flowing nitrogen atmosphere, the normal mode of operation of the instrument for which it is calibrated. Initially, all samples were heated over their melting range at 2.5 K min^{-1}. Following recrystallization, the purity analysis scan was performed at 0.5 K min^{-1}. Digital DSC data was recorded at regular intervals starting, in the case of the doped samples, at the conclusion of the eutectic fusion endotherm. For the off-line analysis, the data acquisition interval was chosen to correspond with a temperature interval of <0.1 K, and such that the data collected did not exceed the size of the data storage capability of the computer program. In this series of experiments, a 10 sec interval was suitable, 400—500 data

points were collected in each dynamic scan. For the on-line analysis, since data is integrated as received, and no large scale storage is required, a standard acquisition rate of 1 sec is used.

RESULTS AND DISCUSSION

Purity analyses were first performed on the individual components. The pertinent thermodynamic properties are listed in Table 1. Following fusion of *p*-aminobenzoic acid in the DSC cell, a 10% weight loss was observed. Simultaneous TG/DTA measurements showed that the major weight loss occurs after melt completion, at and following the endotherm peak. Weight losses occurring after this point will have little effect on the calculated molar enthalpy of fusion, and hence on the resulting purity level. At the end of a transition, the heat flow to a sample is dependent only on the time constant governing the exponential decay of the DSC signal to the dynamic baseline. This parameter is independent of the nature of the sample undergoing the transition [8,9]. This is confirmed by the good agreement between the experimental heat of fusion and the literature value.

The equilibrium melt temperature, T_F and the melt fraction, F are related by eqn. (1), which results from Raoult's law applied to dilute solutions [10].

$$T_F = T_0 - x_2^2 \frac{RT_0^2}{\Delta H_f} \frac{1}{F} \tag{1}$$

where T_0 and ΔH_f are the melting point and molar enthalpy of fusion, respectively, of the pure main component, and x_2^2 is the mole fraction of the impurity. The melt fraction, F is given by the ratio of the partial to the total heat of fusion.

$$F = \frac{H_F}{H_1} \tag{2}$$

Figure 1 shows a plot of the melt temperature versus the reciprocal melt fraction for a number of phenacetin samples doped singly with benzamide,

TABLE 1

Thermodynamic properties of model system components

Substance	Purity (mole %)	T_0 (K)	Heat of fusion, ΔH_f (kJ mole^{-1})		Weight loss during fusion (simult. TG/DTA)
			Expt.	Lit. value	
Phenacetin	99.96_6	407.8	31.14	32.98 [a]	< 0.01%
Benzamide	99.90_7	400.4	22.22	20.51 [a]	0.35%
p-Aminobenzoic acid	99.98_8	460.9	19.76	20.93 [b]	1.7% [c]

[a] Quoted by Marti [1].

[b] Handbook of Chemistry and Physics, CRC Press, Cleveland, Ohio, 57th edn., 1976–1977

[c] At end of transition (DSC peak).

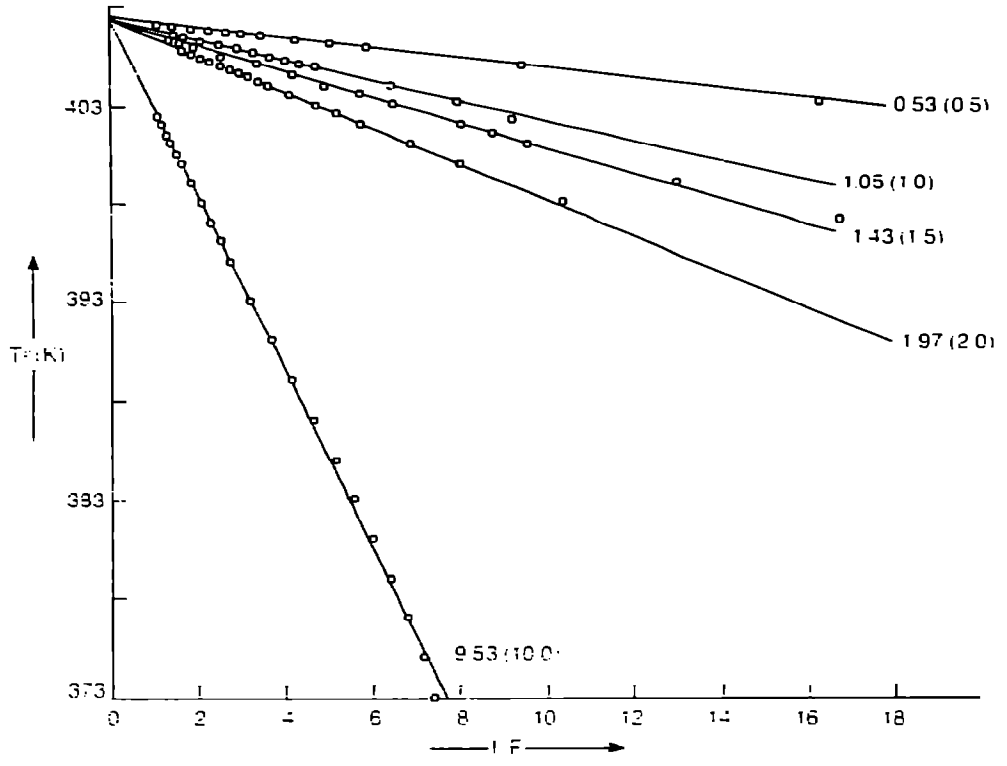

Fig. 1. Phenacetin doped with benzamide. Isothermal step method with 3 mg sample.

obtained under true equilibrium conditions by the isothermal step method. In preparing 3 mg samples with a 0—1.5 mole % dopant level, by weighing in situ, a ±0.05 mole % error will result from a ±1 μg weighing en or. As is seen, the DSC impurity values are in excellent agreement with the weight calculated values, given in parentheses in Fig. 1. T_F—$1/F$ plots obtained from dynamic scan experiments show curvature, even when small samples (<5 mg) are heated at low rates (<1 K min^{-1}). Linearization results from the use of a corrected melt fraction, given by eqn. (3).

$$F_{corr} = \frac{H_F + k_s}{H_1 + k_s} \tag{3}$$

Various procedures have been proposed for computing the "hidden" heat term, k_s [1,2]. Although use of the computer is conducive to the use of least-squares iterative techniques [11], such procedures are not without their problems. Although Cooksey and Hill [12] have proposed an analytical method which eliminates the need for a prior knowledge of k_s, the three point empirical procedure due to Sondack [13], when used in the range 20—50% melt, has proved highly successful with the TA2000 DSC system [10]. In calculating the molar fusion enthalpy, ΔH_f from the measured heat, H_1, in addition to the k_s correction, allowance is also made for the sample purity. This small adjustment is carried out iteratively, and usually three iterations are sufficient.

To show clearly the temperatures at which the various eutectics melt, and

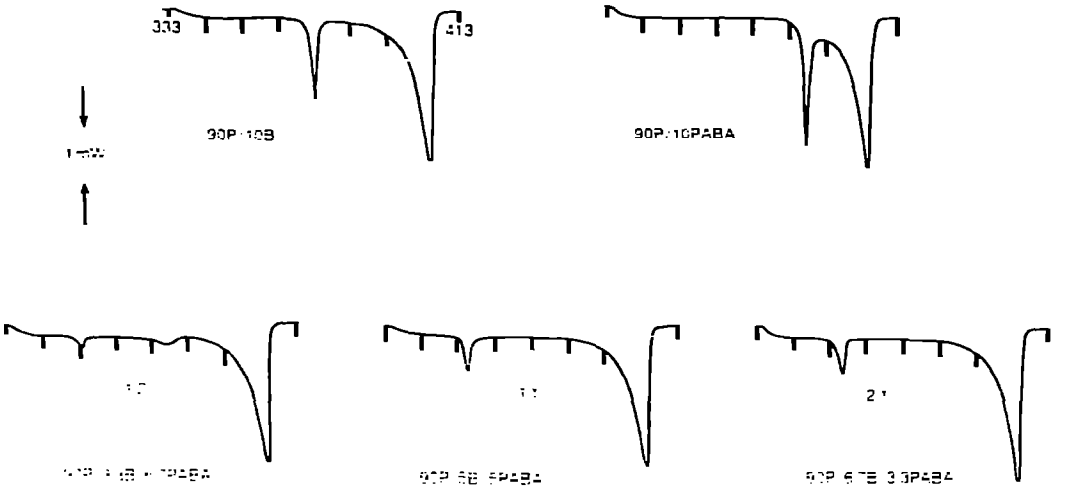

Fig. 2. Phenacetin doped with benzamide and *p*-aminobenzoic acid. Sample, 3 mg; heating rate, 2.5 K min^{-1}; total impurity, 10 mole %.

the proximity of the eutectic endotherms to the fusion endotherm of the main component, samples with a total impurity level of 10 mole % were prepared. In the case of the ternary system, the mole ratio of benzamide to *p*-aminobenzoic acid was varied from 1 : 2 to 1 : 1 and 2 : 1. Figure 2 shows the characteristic analog DSC fusion data. The small vertical lines superimposed on the curves indicate the programmed furnace temperature at 10 K intervals from 333 K to 413 K, (60—140°C). Benzamide and *p*-aminobenzoic acid separately form well defined eutectics with phenacetin, melting at 370 K and 385 K, respectively. When a 1 : 2 benzamide/*p*-aminobenzoic acid mixture is used as the model impurity, a ternary eutectic results, melting at 353 K. There is, however, sufficient residual *p*-aminobenzoic acid to produce the 385 K binary eutectic. This compound's characteristic sharp endotherm is broadened by the presence of the ternary, acting as impurity, just as it, in a similar manner, affects the phenacetin fusion endotherm. When a 1 : 1 benzamide/*p*-aminobenzoic acid mixture is used, the relative proportions of the ternary and binary compounds are such that the fusion endotherm of the binary can only be seen as a shoulder on the trailing edge of the ternary melt endotherm. In the 2 : 1 mixture, 90 mole % phenacetin—6.7 mole % benzamide—3.3 mole % *p*-aminobenzoic acid, only the ternary eutectic melt endotherm can be seen. The fusion enthalpy of the ternary eutectic is considerably less than that of either binary compound. Thus, at much lower total impurity levels, the eutectic endotherms will be insignificant in comparison with that describing the phenacetin fusion. This is exemplified in Fig. 3, which shows the DSC fusion curve for the 99.97 mole % pure phenacetin in comparison with that for the ternary model at the 1 mole % total impurity level. Irrespective of the relative proportions of the individual dopants, the DSC signal data falls on the dashed line.

For the detailed purity analysis studies at the lower heating rate, digital data acquisition was initiated at a programmed furnace temperature cor-

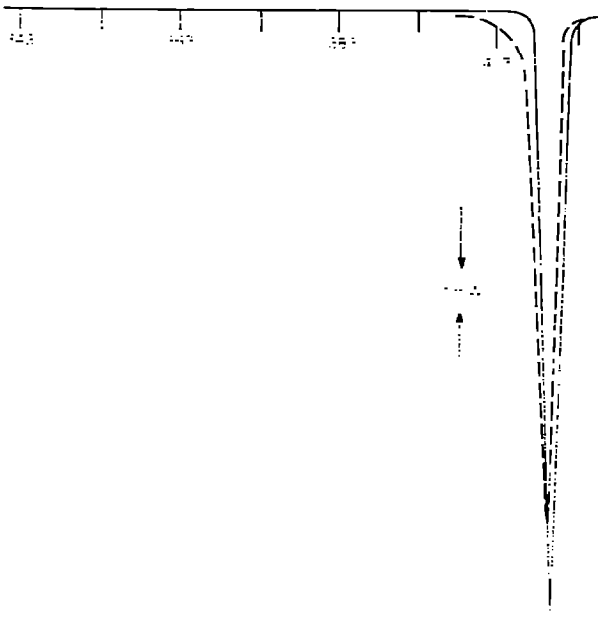

Fig. 3. Phenacetin doped with benzamide and *p*-aminobenzoic acid. Sample, 3 mg; heating rate, 2.5 K min^{-1}. ———, Phenacetin; - - - - - -, phenacetin + 1 mole % dopant.

responding to the conclusion of the various eutectic melts. For the benzamide dopant binary system, 373 K was selected. For all the other model systems, the data acquisition start temperature was 388 K.

In Table 2 the pertinent thermal information resulting from the analysis of several samples in the range 98.5—99.97 mole % purity are summarized. In two cases, the 2 : 1 and 1 : 2 doped systems, 10 mg as well as 3 mg

TABLE 2

Dynamic DSC purity analyses of doped phenacetin

Dopant 1 benzamide (mole %)	Dopant 2 *p*-aminobenzoic acid (mole %)	Sondack correction k_s (%)	ΔH_f (kJ $mole^{-1}$)	T_0 (K)	ΔT (K)	Total impurity x_2^* (mole %)
0.5		4.9	31.83_1	407.3	0.23	0.53_6
1.0		8.4	30.73_6	407.3	0.45	0.99_8
1.5		9.3	30.51_6	407.4	0.68	1.49_5
	0.5	3.6	30.50_8	407.4	0.22	0.48_8
	1.0	11.8	31.16_7	407.4	0.45	1.01_2
	1.5	8.9	31.14_6	407.5	0.67	1.51_4
0.25	0.25	14.6	29.92_6	407.4	0.22	0.48_2
0.50	0.50	13.0	32.00_7	407.4	0.43	1.00_7
0.75	0.75	13.2	30.38_1	407.5	0.67	1.47_7
0.67	0.33	5.3	31.83_4	407.5	0.44	1.02_4
0.33	0.67	9.9	32.34_5	407.4	0.47	1.09_7
0.67 [a]	0 33	11.4	30.90_7	407.5	0.46	1.03_4
0.33 [a]	0.67	30.4	30.31_7	407.6	0.49	1.09_0

[a] 10 mg sample.

samples were studied. In this tabulation the Sondack calculated heat correction factor, k_s, is expressed as a percentage of the measured heat of fusion, H_1. This tends to increase with increase in both impurity level and sample size. A consistent value for the molar enthalpy of fusion of phenacetin is obtained, namely 31.09 kJ mole^{-1} (σ = 0.72 kJ mole^{-1}). In this range of impurity levels, Marti [1] reported a value of 30.97 kJ mole^{-1}, using the "correction to the weight of main component" evaluation procedure. The cryoscopic constant for phenacetin is thus 44 K. The DSC determined impurity levels are in excellent agreement with the weight calculated values. For a constant impurity level, the DSC values are independent of the model system type, be it a single or double dopant system. Thus, at the 1 mole % impurity level, a mean DSC value of 1.03_7 mole % ($\sigma = 0.04_0$ mole %) is obtained.

Although studies on other model systems should be made as a further verification, the results obtained do confirm what has hitherto been assumed. Irrespective of the number of impurities, in the absence of solid solution formation, dynamic DSC is an accurate and fairly rapid means of measuring purity levels in the 98.5—100 mole % range.

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