

CRITICAL REVIEW OF METHODS FOR THE DETERMINATION OF PURITY BY DIFFERENTIAL SCANNING CALORIMETRY*

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ABSTRACT

During the past few years several publications have appeared in the literature describing purity determinations by differential scanning calorimetry (DSC). Some controversies remain, however, such as the proper choice of limits for the slope determination in the plot of the sample temperature vs. the reciprocal of the fraction melted, and the applicable purity range of the DSC method. Most authors have accepted a purity of 98% as the lowest workable level. This presentation will demonstrate the possible use of DSC techniques for lower purity measurements. Four systems for obtaining the impurity content were investigated, i.e., dynamic DSC with time-sharing and on-line computer data acquisition, stepwise DSC, and the two-peak method. The applicable purity ranges were found to depend on the instrumentation and data acquisition systems used.

INTRODUCTION

One of the oldest techniques to determine purity was melting point depression¹⁻⁶. In the static (calorimetric) method heat is supplied in increments to an adiabatic calorimeter, while in the dynamic (thermometric) method it is supplied at a constant rate. But these methods require large samples, long times, and accurate temperature measurements.

More recently, differential scanning calorimetry (DSC) has been used for purity determination by analyzing the peak shape of the melting transition⁷⁻¹². As purity decreases the melting range broadens and the melting point decreases (Fig. 1). Comparison of the peak shape already provides a convenient means for purity estimation and often suffices for quality control purposes. For more precise determinations, the Van't Hoff equation is applied to the DSC scan.

$$T_s = T_0 - \frac{RT_0^2 X_2}{\Delta H_f} \cdot \frac{1}{F} \quad (1)$$

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where T_s = sample temperature (K)
 T_0 = theoretical melting point of pure component (K)
 R = gas constant ($1.987 \text{ cal mol}^{-1} \text{ K}^{-1}$)
 X_2 = mole fraction impurity
 ΔH_f = heat of fusion of pure component (cal mol^{-1})
 F = fraction of sample melted at T_s

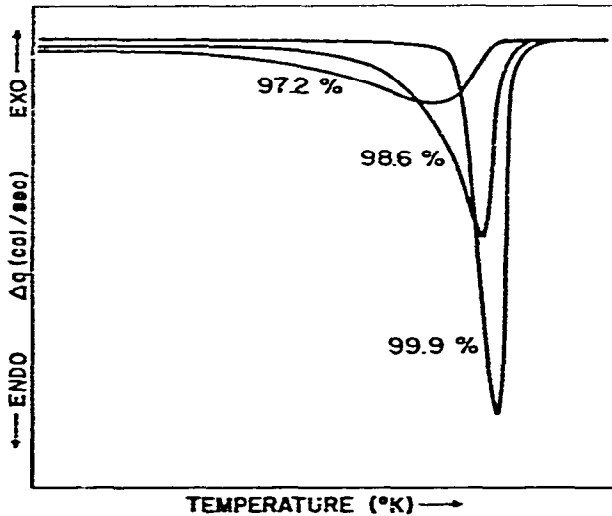


Fig. 1. Dynamic DSC scans for qualitative comparison of purity⁸.

As shown in Fig. 2, the DSC scan is sectioned into small areas of melting and the temperature of each is determined. Because of the thermal resistance of the DSC cell, the sample temperature falls behind the furnace temperature. To correct this difference the scan of a pure standard is overlaid on the sample scan to provide the sample melting temperature, T_s . If an instrument can directly monitor the sample temperature continuously, then this correction should not be required for purity calculations. A plot of T_s vs. $1/F$ should result in a straight line, as shown by the solid

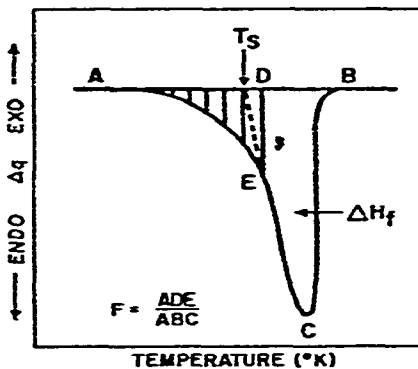


Fig. 2. Dynamic DSC scan for determination of purity¹⁰.

line in Fig. 3, with an intercept of T_0 and a slope of $-RT_0^2 X_2/\Delta H_f$ from which the mole fraction impurity may be calculated.

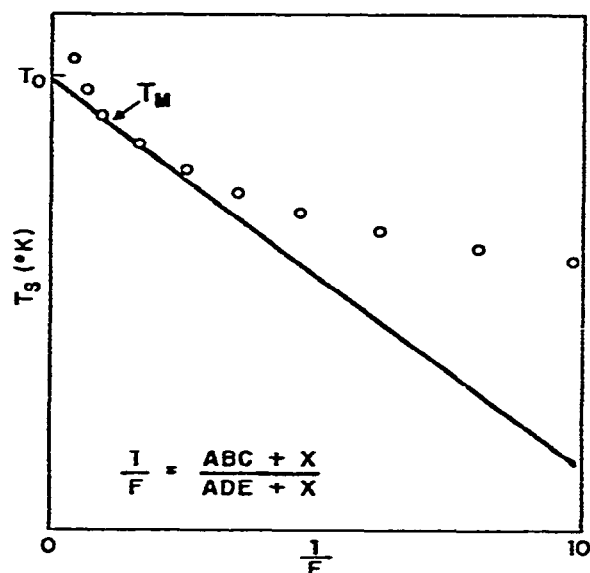


Fig. 3. Plot of sample temperature vs. reciprocal fraction melted¹⁸. O, original data; —, "x" correction linearization.

This presentation reports our studies on the applicable purity range of the DSC method by four techniques, namely dynamic DSC with time-sharing and on-line computer data acquisition, and stepwise heating with slope or two-peak calculation. The effects of sample size, heating rate, solid solution formation, $1/F$ limits, instrument sensitivity and data acquisition systems used will also be discussed.

EXPERIMENTAL

A DuPont Model 990 thermal analyser with a DSC cell attachment (DuPont Co., Wilmington, Del.) and a Perkin-Elmer differential scanning calorimeter Model DSC-2 (Perkin-Elmer Corp., Norwalk, Conn.) were used for this work. A PDP-10 computer (Digital Equipment Corp., Maynard, Mass.) was used to analyze data acquired either directly on-line or through a DuPont Model 915 computer interface connected to a time-sharing system³³. We used crimped aluminum pans for solid samples and hermetically sealed aluminum pans for liquid samples. Liquid standards, benzene-cyclohexane and benzene-thiophene, were prepared by mixing known weights of benzene and the respective dopant. Solid standards, phenacetin-benzamide and phenacetin-*p*-aminobenzoic acid, were prepared by adding known weights of phenacetin and dopant in a sealed test tube. The mixture was melted, stirred for 30 min, quenched in dry ice to maintain homogeneity, and ground with mortar and pestle. The doped phenacetin standards have been stable for over a year.

RESULTS AND DISCUSSION

Large discrepancies exist in the literature concerning the lower limit of purity determinations by DSC; for instance, 99% (refs. 13 and 14), 98.5% (ref. 15), 98% (refs. 16 and 17), 97% (ref. 18), 95% (ref. 19), 92% (ref. 20), 90% (ref. 21). Most authors agree the practical upper limit is approximately 99.9%. In this section we will discuss some of the variables that can affect the purity range, and report the ranges obtained with the DSC methods used in our laboratories.

Ideally, as shown in Fig. 3, a straight line is obtained for T_s plotted vs. $1/F$. However, this is usually not the case. Plotting the experimental data frequently results in considerable curvature, which has been variably attributed to sample size, heating rate, solid solution formation, instrument insensitivity, etc.

For best results the sample size should be kept small, 2 to 4 mg. With a sample size greater than 5 mg thermal equilibrium will not be maintained, and the T_s vs. $1/F$ plot will curve upward^{14,18,22}. Likewise, the heating rate should be low, preferably less than 1°C min^{-1} . With a faster heating rate, again thermal equilibrium will not be maintained^{14,15,22}. However, fast heating rates—up to $10^\circ\text{C min}^{-1}$ —were used for qualitative comparison²³, unstable compounds²⁴, or extremely broad melting peaks¹³.

These two variables can be controlled to reduce curvature in T_s vs. $1/F$ plots. However, a limitation which cannot be controlled is solid solution formation for impurities insoluble in the solid and soluble in the melt. The calorimetric method is prone to formation of solid solution since long times are involved. McCullough and Waddington³ have reported that about half of their melting curves showed deviation from linearity. However, the short analysis time with a small sample size aids in reducing the number of compounds that form solid solutions with the DSC technique. Modifications to the Van't Hoff equation have been suggested to correct non-linearity^{14,18}, but the DSC technique should not be used if a solid solution forms.

If thermal equilibrium is maintained and a solid solution is not formed, curvature may result from insensitivity of the instrument to detect early melting. To remove this curvature incremental areas, x , are added to the fractional and total areas until the data are linearized as in Fig. 3^{9,10,23,25,26}. This may be accomplished either manually²⁷, or with a computerized system. The most common limits for $1/F$ in the linearization procedure are 2 to 10 (10–50% melt). Other recommendations include sliding limits¹⁸, up to one half of the peak¹⁶, the entire peak¹⁹, onset of melting to vertex²², a "slope criterion" method¹⁷, and a self-data correction method²⁰. The obtained impurity actually varies with the chosen $1/F$ limits²². If too little of the curve is used the purity obtained is too high, and if too much is used the purity value is too low. Since the obtained impurity depends on the $1/F$ limits, a series of standards should be used to determine the best $1/F$ limits for a particular instrument and data acquisition system.

Results obtained using time-sharing computations with a benzene-cyclohexane series and the experimental parameters are shown in Table 1. With small sample sizes

the method is accurate up to ca. 1 mole % purity. With larger samples thermal equilibrium is not easily maintained, especially for low purity samples. Large sample size and high heating rate are known to decrease the applicable purity range.

TABLE 1

**DYNAMIC DSC METHOD WITH TIME-SHARING COMPUTATIONS—
BENZENE-CYCLOHEXANE SERIES**

Heating rate: $0.5^{\circ}\text{C min}^{-1}$; 1/F limits: 2–10 (10–50% melt); scan rate: 1 point/3 sec; N_2 flow: 15 ml min^{-1} .

<i>Sample size (mg)</i>	<i>Known mole % cyclohexane</i>	<i>Obtained mole % cyclohexane</i>
2–3	<0.10	0.05
	0.64	0.61
	1.24	1.14
	2.82	1.71
7–8	<0.10	0.07
	0.64	0.62
	0.83	0.76
	1.24	0.96

We also determined the purity of a benzene–thiophene mixture that forms a solid solution using the same parameters. Results are shown in Table 2. Obviously, the present DSC program cannot be used to calculate the impurity in this system. However, the melting point depression provides a valid measurement of the purity for this solid solution as shown in Fig. 4. This method is applicable, however, only if standards are available.

TABLE 2

**DYNAMIC DSC METHOD WITH TIME-SHARING COMPUTATIONS—
BENZENE-THIOPHENE SERIES**

<i>Known mole % thiophene</i>	<i>Obtained mole % thiophene</i>	<i>T_m (K)</i>
<0.10	0.05	278.5
0.53	0.36	278.1
1.15	0.42	277.7
1.90	0.61	277.2
2.42	0.82	276.6

To improve the applicable purity range, we used an on-line data acquisition system for dynamic DSC³³. The two main advantages of this system are time saving and fast scan rate. Parameters are typed on a teletype, analog data are digitized, acquired, and stored during the DSC scan, and the impurity is obtained within 1 min after the scan. Results for a phenacetin–benzamide series are shown in Table 3. The same parameters were used as with time-sharing data acquisition, except for a faster

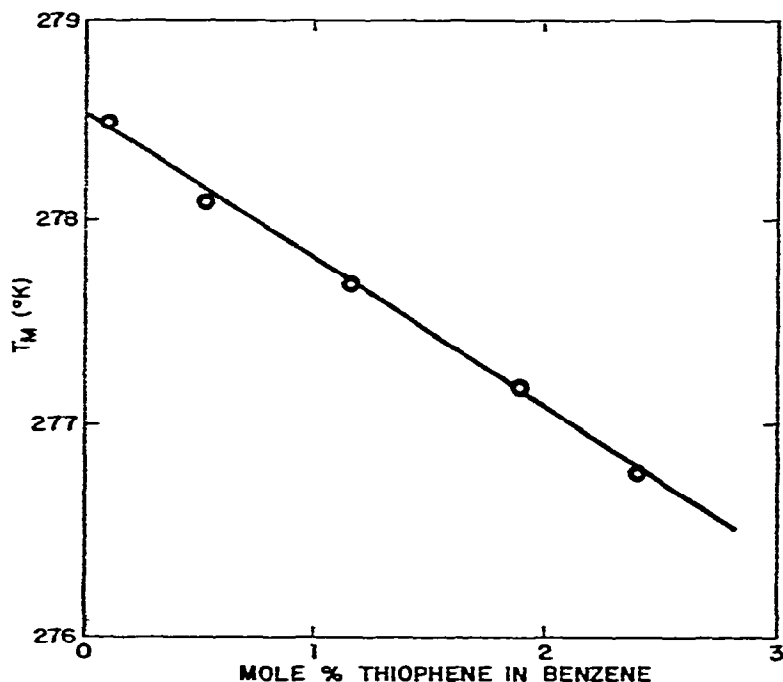


Fig. 4. Plot of melting point vs. concentration of thiophene in benzene.

TABLE 3

DYNAMIC DSC METHOD WITH ON-LINE COMPUTATIONS—
PHENACETIN-BENZAMIDE SERIES

<i>Known mole % benzamide</i>	<i>Obtained mole % benzamide</i>
<0.10	0.02
0.82	0.83
1.41	1.44
2.90	2.85
4.04	3.16

scan rate of one point per second. The purity range has now been lowered to ca. 97 mole % with this system, about the best that can be expected with dynamic DSC. Some authors have achieved lower ranges by adding the "pure" component to the mixture^{15,28}. This is feasible for an academic exercise, but in practice the pure component is not always available. To still lower the applicable purity range other methods have to be explored.

The major limitation of the dynamic method is its failure to detect early melting. This is not critical for high purity samples because melting occurs over a narrow temperature range. However, low purity samples melt over a much wider range, making dynamic DSC less accurate.

We investigated a new stepwise heating method first reported by Staub and

Perron²¹. Instead of continuously heating a sample, heat is applied in steps until melting has been completed. This is similar to the old static method, but with smaller samples and shorter times. The principle of this technique is demonstrated in Fig. 5. A temperature interval, for example 0.5 K, is selected; heat is applied until the

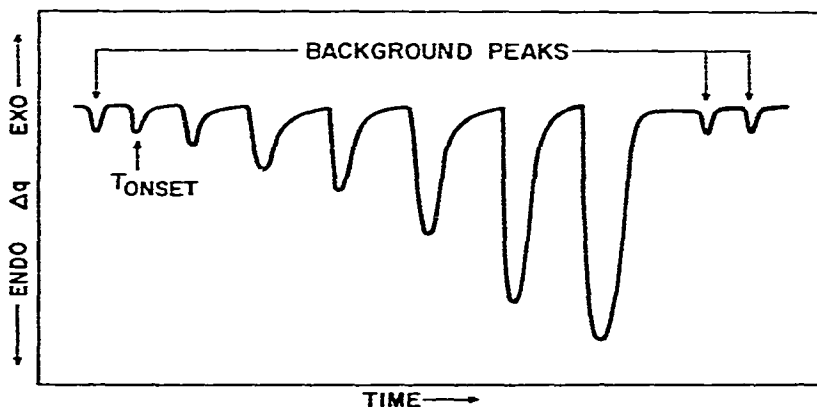


Fig. 5. Stepwise heating method. Heating rate of $5^{\circ}\text{C min}^{-1}$ for 6 sec to obtain ΔT of 0.5°C .

furnace temperature has increased by 0.5 K, then removed, and the curve is allowed to return to baseline. If no melting has occurred, an essentially constant area results from the difference in heat capacity between the reference and the sample. When a temperature is reached where melting occurs, this area increases. The temperature is increased in steps until all the sample has melted. After correcting for the background area, the isothermal step temperature, T_s , is plotted vs. $1/F$ to obtain mole % impurity. ΔH_f is calculated by summing all the areas. Usually no "x" correction is necessary to obtain linear T_s vs. $1/F$ plots. Staub and Perron²¹ claimed that non-linearity in dynamic DSC results from an absence of thermodynamic equilibrium. This should not be so for small sample sizes and low heating rates. We believe that non-linearity is mainly due to instrument insensitivity. Stepwise heating detects early melting, thus improving the linearity.

Low purity samples, as in the phenacetin-benzamide series (Fig. 6), have a broad melting range. For the 8.82%-impurity sample the melting peak is barely detected above the baseline. In most cases the onset of melting is detected 4 or 5 K below the peak melting temperature. A dramatic improvement in detectability is observed with the stepwise DSC method for these samples as shown in Table 4. The first temperature step where melting is detected for the 8.82%-sample is 25 K below the peak temperature, compared to 5 K by dynamic DSC. It should be noted that different step intervals (ΔT) were used. For high purity samples a small ΔT should be used, since melting occurs over a narrow temperature range. With a ΔT of 0.1 K, the upper limit of purity determination is 99.98 mole %. As usual the impurity is determined from the slope of the T_s vs. $1/F$ plots as shown in Fig. 7. These plots were extrapolated to obtain T_0 values within 0.1 K.

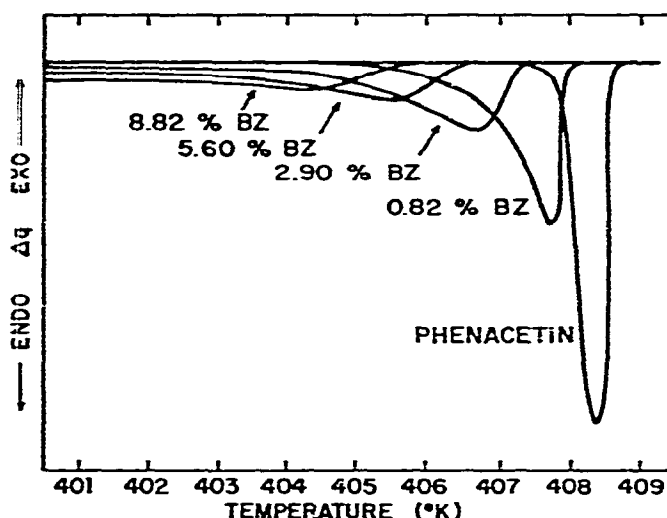


Fig. 6. Dynamic DSC scans for phenacetin-benzamide series.

As shown in Table 4 this method is probably applicable to 95 mole % purity. Some curvature in T_s vs. $1/F$ plots was observed for still lower purity samples, again because of instrument insensitivity. This slight curvature may be eliminated with an "x" correction as in the dynamic scans. Zynger²⁰ has reported an automated stepping differential calorimeter which is applicable in the 92–100% purity range. His computerized system corrects curvature for low purity samples.

TABLE 4
STEPWISE SLOPE DSC METHOD—PHENACETIN-BENZAMIDE SERIES

<i>Known mole % benzamide</i>	<i>T_{onset} (K)</i>	<i>ΔT (K)</i>	<i>Obtained mole % benzamide</i>
<0.10	406.6	0.1	0.02
0.82	400.0	0.2	0.76
2.90	391.0	0.5	2.40
5.60	386.0	1.0	5.29
8.82	380.0	2.0	6.87

We can now conclude that stepwise DSC can determine purity to 95 mole % without linearization and 92 mole % with linearization. However, the time required to step through an entire melting curve is approximately 1 or 2 h, compared to 30 min for dynamic DSC. We therefore investigated the two-peak method^{29,30}. Instead of stepping through the entire curve, only the last few peaks are used to calculate the purity as shown in Fig. 8. The background area is subtracted and T_0 is calculated from eqn (2).

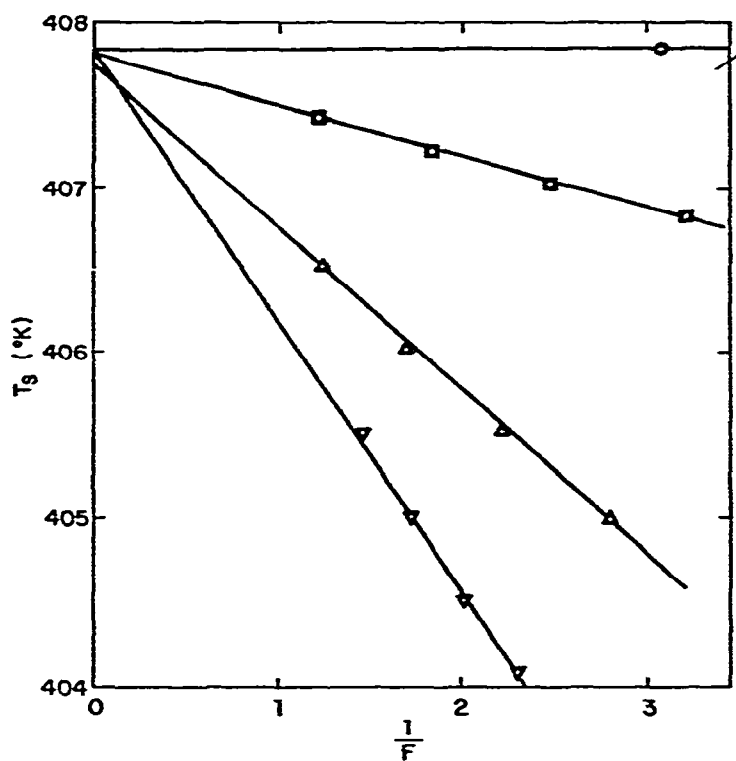


Fig. 7. Stepwise sample temperature vs. reciprocal fraction melted for phenacetin-benzamide series. ○, phenacetin (0.0% benzamide); □, 0.82 mole % benzamide; △, 2.90 mole % benzamide; ▽, 5.60 mole % benzamide.

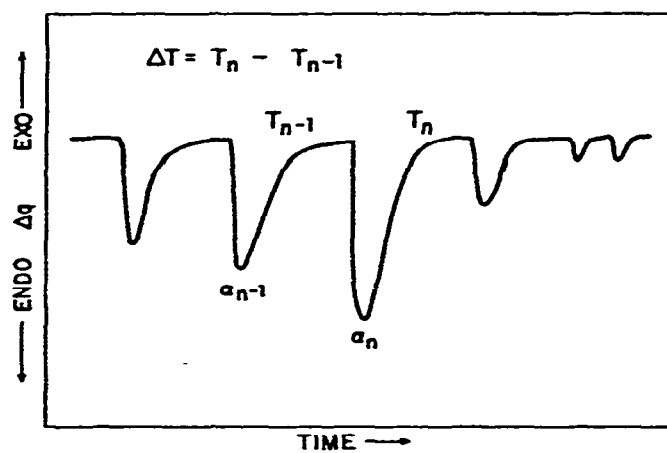


Fig. 8. Stepwise two-peak method.

$$T_0 = T_n \div \frac{2(\Delta T)(\alpha_{n-1})}{(\alpha_n - \alpha_{n-1})} \quad (2)$$

where T_n = temperature corresponding to the n th peak (K).

α_n = area of n th stepwise peak (cal g⁻¹).

α_{n-1} = area of $(n-1)$ th stepwise peak (cal g⁻¹).

The mole fraction of the impurity, X_2 , is then calculated from Eqn (3).

$$X_2 = \frac{2M\alpha_n\alpha_{n-1}\Delta T(\alpha_n + \alpha_{n-1})}{RT_0^2(\alpha_n - \alpha_{n-1})^2} \quad (3)$$

where M = molecular weight of the pure component (g mol⁻¹).

Averaged values of T_0 and X_2 from three or four consecutive pairs of peaks are normally used. However, the last pair should be avoided in this method³⁰. Results for a phenacetin-*p*-aminobenzoic acid series are in Table 5. Note again that the step interval is increased as impurity increases. With the step-wise two-peak method we are able to calculate purity down to 90 mole % with approximately 5% relative error. The method is rapid and no modification of the original data is required.

TABLE 5
STEPWISE TWO-PEAK DSC METHOD—
PHENACETIN-*p*-AMINOBENZOIC ACID (*p*-ABA) SERIES

<i>Known mole % p-ABA</i>	ΔT (K)	T_0 (calc. (K))	<i>Obtained mole % p-ABA</i>
1.41	0.2	407.9	1.47
4.04	0.5	408.0	4.00
7.79	1.0	408.2	7.33
10.12	2.0	407.5	9.51

Another attractive feature of the two-peak method is its independence of the heat of fusion. ΔH_f in eqn (1) is the heat of fusion of the pure component, supposedly constant. To determine purity the value for ΔH_f is normally calculated from the total area. As the impurity increases the calculated ΔH_f decreases as shown in Fig. 9 for a phenacetin-benzamide series. The ΔH_f calculated by dynamic DSC is lower than that by stepwise DSC because early melting is undetected^{14,18}. Now in eqn (3), ΔH_f is absent. The impurity calculation does not require a calculation of ΔH_f or detection of early melting.

Can DSC methods determine purity of less than 90 mole %? We do not believe so, because the Van't Hoff approximation becomes invalid³¹.

$$\ln X_0 = \ln (1 - X_2) = \frac{\Delta H_f}{R} \left(\frac{1}{T_0} - \frac{1}{T} \right) \quad (4)$$

where X_0 = mole fraction of major component.

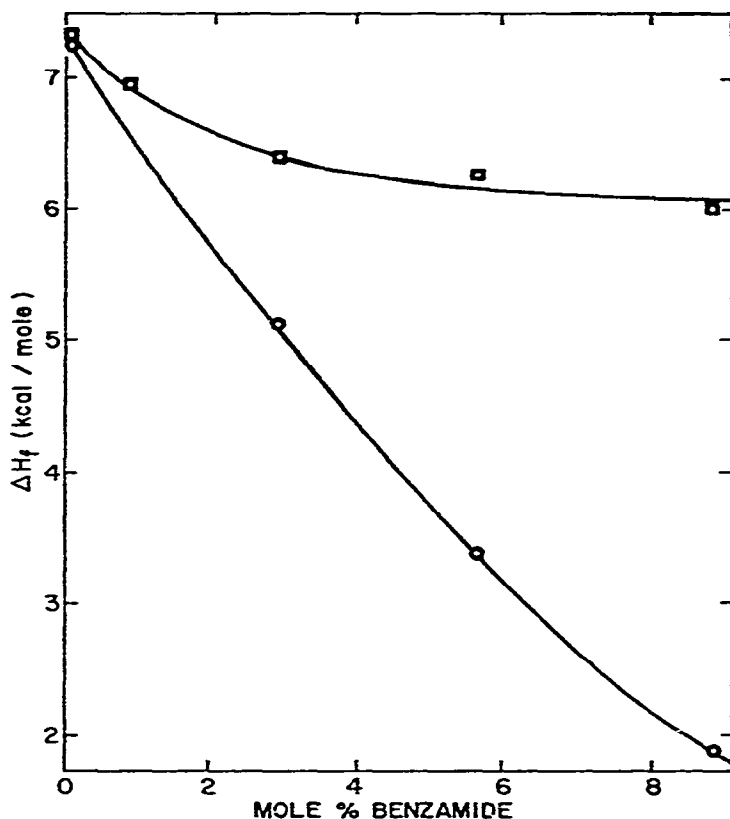


Fig. 9. Calculated heat of fusion vs. concentration of benzamide in phenacetin. □ Stepwise DSC; ○ dynamic DSC.

If X_2 is small

$$\ln(1 - X_2) \doteq -X_2 \quad (5)$$

thus,

$$X_2 = \frac{-\Delta H_f(T - T_0)}{RT_0^2} \quad (6)$$

When X_2 is 0.1, the error is 5% and increases dramatically with increasing X_2 .

In summary, we have shown that the purity range obtained with DSC methods depends on sample size, heating rate, $1/F$ limits, solid solution formation, instrument sensitivity, and the data acquisition system. The range for dynamic DSC is approximately 97–100 mole % purity, and for stepwise DSC, 90–100 mole %. Stepwise DSC with a slope calculation has the advantage that a solid solution may be detected by the curvature in the T_s vs. $1/F$ plots²¹. However, curvature may also be due to instrument insensitivity. The two-peak stepwise DSC method is independent of ΔH_f and less time-consuming. However, caution should always be exercised in purity determinations no matter which technique is used³². Other analytical methods should

always be used in conjunction with DSC methods, whenever possible. Once the applicability of the method is established, DSC may prove to be the most convenient one to use.

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