

PRECISION OF PURITY DETERMINATIONS BY DIFFERENTIAL SCANNING CALORIMETRY*

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ABSTRACT

Differential scanning calorimetry (DSC) produces thermograms which should be satisfactory for purity analyses using the van't Hoff equation. Using mixtures characterized by accepted alternate methods the precision and accuracy of the DSC method have been explored. The single most important variable has been found to be the thermal resistance of the cell sample-encapsulation package. Sample size and heating rate are also important in the accuracy of the determination. This is due to a combination of thermal resistance and response rate of the DSC instrument. When all variables are properly controlled a precision of $\pm 3\%$ of the component in lowest concentration can easily be obtained. Eutectic formation was found to cause serious errors only when the eutectic melted near the principal component peak.

INTRODUCTION

The determination of the absolute purity of organic and inorganic materials by freezing-point depression is an historically old and well established method. Broad application of the method has not been feasible in the past since it was necessary to: (1) measure temperatures very accurately ($\pm 0.005^\circ\text{C}$) using platinum resistance thermometers; (2) determine the melting-point depression constant, and (3) control closely the equilibrium in relatively large samples by very slow cooling. Classically, cooling techniques have been the most frequently employed. These techniques required good stirring and frequent seeding of the melt with microcrystals to avoid supercooling near the freezing point. Operation of classical temperature measuring equipment in the heating mode is difficult due to the thermal gradients established in the relatively large samples employed in the measurements.

Recently, Watson *et al.*^{1,2} announced a method for purity determination using the heat uptake-temperature curve obtained in the heating mode using a Perkin-Elmer DSC-1B. Given the proper conditions, the melting curve has all of the information necessary to calculate the mole fraction of impurity using the van't Hoff equation, *i.e.*, molar heat of fusion and fractional melting as a function of temperature. Driscoll,

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Duling, and Magnotta³ have presented a study using this technique on several well made synthetic mixtures. DeAngelis and Papariello^{3a} have examined the DSC method using known samples of certain pharmaceutical materials. Their results indicated that the method is satisfactory within certain limitations. Plato and Glasgow⁴ have applied the method to over 90 materials. However, no attempt was made to determine the actual impurity content by independent methods. Barrall, Johnson, Porter, Vogel, Mignosa, and Ennulat⁵⁻⁹ have applied the method to obtain rough purities on liquid crystal forming materials.

The purpose of this study was to review all major systematic variables connected with DSC traces and to develop a purity method which would take advantage of optimum conditions.

DESCRIPTION OF THE METHOD

The van't Hoff method has been described elsewhere in detail^{2,3}. However, for the purpose of completeness a brief outline will be given here.

Given the van't Hoff equation the following melting-point depression-impurity content relationship can be developed:

$$T_s = T_0 - \frac{RT_0^2 X}{\Delta H} \cdot \frac{1}{F}$$

where T_s is the instantaneous temperature of the sample ($^{\circ}\text{K}$); T_0 is the melting point of the infinitely pure sample (solvent, $^{\circ}\text{K}$); R is the gas constant (1.987 cal/mole, $^{\circ}\text{K}$); ΔH is the heat of fusion of the sample (solvent, cal/mole); X is the mole fraction of impurity; F is the fraction of the total sample melted at T_s . Thus, a plot of T_s versus $1/F$ should give a straight line of slope $-RT_0^2 X/\Delta H$ with an intercept of T_0 . ΔH is obtainable from the DSC curve; T_s is measurable from the curve as is $1/F$ (the reciprocal of the partial area of the DSC curve up to T_s , divided by the total area).

Assumptions of the van't Hoff equation

The equation as given previously assumes:

- (1) the impurity is *insoluble* in the predominant solid phase;
- (2) the impurity is completely soluble, *i.e.*, ideal solution, in the molten or liquid phase.

These assumptions make the equation inapplicable as given for (a) co-crystals — the impurity can crystallize in the host lattice, (b) cases where the impurity forms a non-ideal solution in the melt by association or chemical reaction, and (c) total insolubility in the liquid phase. A simple case of item c is sand in water. Essentially, the van't Hoff equation describes the molar entropy of mixing and solution of the impurity in the melt. The latter is the total melt, not just a small fraction.

Unfortunately, for this simple application two corrections are required to account for instrumental variables^{2,3}: (1) thermal resistance of the instrument and (2) undetected melting.

Thermal resistance

Between the heater/sensor platform and the bottom of the sample pan there exists a thermal resistance. This problem has been recognized in the past^{2,10}, and corrections suggested. To a first approximation it is necessary only to melt a material of very high purity (>99.99%) and record the melting curve. The leading edge slope is directly proportional to the thermal resistance. To correct any temperature in a recorded transition it is necessary to superimpose this slope on the curve and extrapolate to the isothermal base line (Fig. 1). High purity indium is normally employed. For

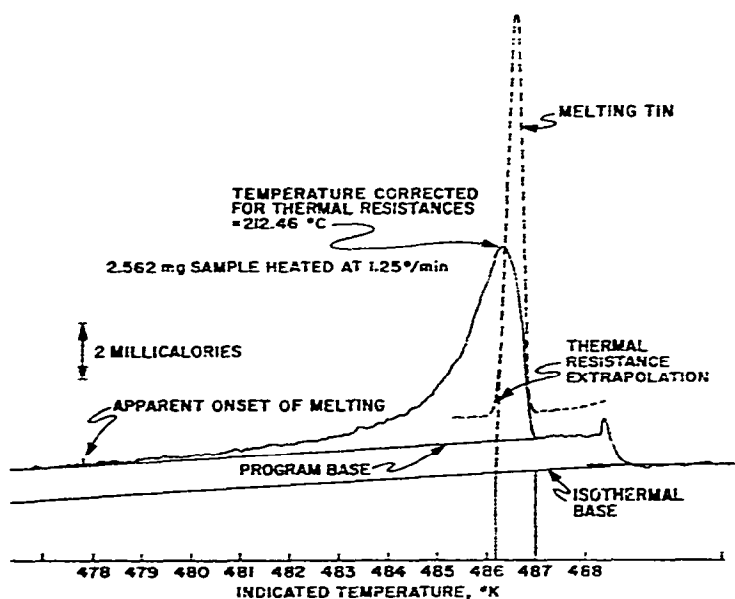


Fig. 1. Correction of a DSC curve for thermal resistance 9,10-dichloro anthracene containing 1.10 mole % anthracene (2.562 mg sample heated at 1.25°/min).

maximum precision, the pure material must melt in or near the range for which it is being used as a correction. This is logical since as total temperature increases the thermal resistance must change in fact, become larger. This is demonstrated for the melting of high purity indium, tin, and lead in Fig. 2. To make the correction the standard curve must be obtained at the same chart speed, sensitivity and heating rate as the sample.

Undetected melting

If the DSC is set at a sensitivity low enough to keep the complete record on the chart, then the low temperature melting will not be adequately detected by the recorder. That is, area will be lost and the initial small fraction melted, F , will be too small. An analysis of the circuit indicates that this small amount of heat is detected by the DSC and compensated for in the differential circuit, but is not detected by the recorder. This small amount of heat can be recovered by linearizing the T_s vs. $1/F$ plot.

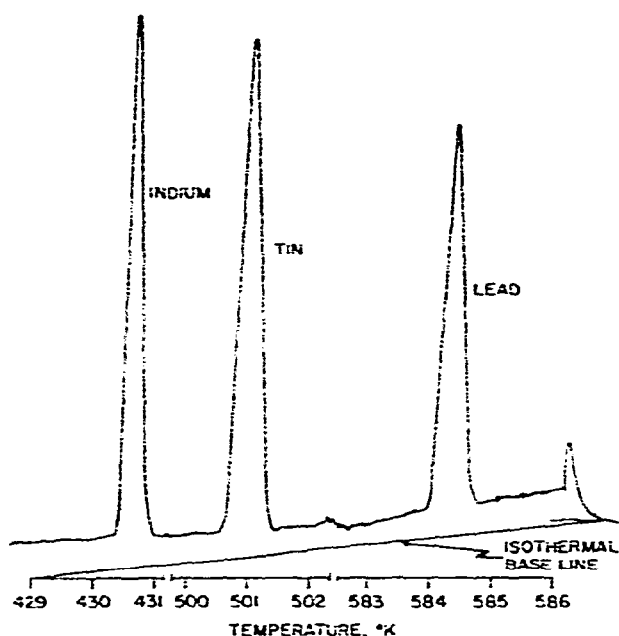


Fig. 2. Variation of a sharp-melting peak slope with transition temperature. All samples 99.99999 mole% pure 1.25°/min at 2.00 mcal/inch.

This is done by trial and error using progressively larger area increments to be added and determining the effect on the plot. The formula for compensation is:

$$\text{true } F_1 = \frac{a_1 + x}{A + x}, \text{ true } F_2 = \frac{a_1 + a_2 + x}{A + x}, \text{ etc.}$$

where a_1 and a_2 are the partial areas; x is the small area missed in integration at low temperatures; A is the total area under the curve. The x has a large effect at small fractions melted. Overcompensation results in a curve which bows downward. The method is not arbitrary since only one value of x will result in a linear plot. The assumptions of the van't Hoff equation require that the plot of T , vs. $1/F$ be linear.

Although the above restrictions may appear severe, a large number of organic and inorganic systems should be satisfactory if the instrument is capable of giving a satisfactory curve under the operating conditions.

EXPERIMENTAL

Instrumentation

A Perkin-Elmer differential scanning calorimeter Model DSC-1B was used in this study. The records were obtained on a 1 mV/inch Servoriter recorder. The calorimeter cell was operated in a continuous, 1 ml/min, stream of nitrogen. The samples were weighed on a Cahn microbalance set on the 5-mg range. An empty sample pan was used as a counter balance. With this particular DSC-1B the best system balance was obtained with no reference pan on the calorimeter platform. Aluminum domes

were used to cover both sample and reference platforms. The room-temperature cover was used over the calorimeter cell. Data were reduced with a polar planimeter and the results calculated with a computer program developed at IBM. All runs consisted of an isothermal base line, a program base line and ending temperature isothermal base line.

Preparation of samples

The preparation of samples containing a small known amount of impurity is extremely difficult to carry out on an absolute basis. Uniform mixing of a few micrograms in several grams of material at elevated temperatures and inert conditions is the principal stumbling block. To circumvent this problem, samples were chosen which could be analysed by alternate methods for the specific impurity. The actual sample scanned in the DSC was subjected to analysis — not a portion of the bulk sample. The metal mixtures, lead-tin, indium-lead, and tin-indium were analysed by atomic absorption spectrometry. The organic mixtures were analysed by UV-absorption spectrophotometry, fluorescence photometry and thin-layer chromatography as required.

The organic materials were all zone refined to a very high degree of purity. The pure forms all gave DSC peaks equivalent to, and in some cases better than, the semiconductor grade metals. The metals were all 99.9999% or better. The indium sample was 99.99999%. These materials were obtained from Research Organic/Inorganic Chemical Corp., 11686 Sheldon St., Sun Valley, Calif. 91352. U. S. A.

The samples were prepared by weighing in the appropriate amount of each material, sealing under nitrogen and melting with agitation. It is interesting to note that a sample of lead in tin made to be 0.54 mole% lead was found to contain 0.41 mole% lead by atomic-absorption analysis in the chip chosen for DSC. Another sample made to contain 1.197 mole% lead was found to contain 1.16 mole% lead. This serves to illustrate the difficulties encountered when making low concentration standards. The same kind of variation was noted with the organic materials.

Mounting samples for DSC

Most organic materials have a finite vapor pressure near the melting point. Therefore, it is desirable to use the cold welded volatile sample sealers at all times. The sample must be sealed in these containers under nitrogen if oxidative decomposition is to be avoided. To accomplish this end, the sealing press was placed with the sample in a nitrogen filled dry box. About 15 min or more is required for most organic materials to equilibrate with the dry box atmosphere.

The volatile sample sealers have one disadvantage; the sample is not pressed into intimate contact with the encapsulation metal. This permits the sample to relocate in the cell during fusion and freezing and alters the thermal resistance between the sample and heater. This is a very serious problem since alteration of the thermal resistance changes the shape of the DSC curve independent of purity. The problem of sample relocation is particularly serious with tin metal. On melting, the

tin sample forms a small bead having a point contact with the pan. The initial heating of a flat chip of 99.9999% tin results in a very sharp endotherm. A second heating of the sample produces a very broad endotherm moved to a *higher* temperature on the DSC curve. To overcome this problem small disks of aluminum which fitted snugly into the bottom of the volatile sample sealer were made. These were forced into the pan after the sample was weighed in and equilibrated with nitrogen. The pans were then sealed as usual with the volatile sample sealer lid. The sandwich configuration maintained the sample in contact with the pan throughout repeated heatings and coolings.

The above precautions are absolutely necessary if reliable information on purity is to be obtained. It is also necessary to position the pan in the same location in the calorimeter for each run. The thermal resistance is not the same when the pan is in the center of the furnace platform as when it is in contact with the edge of the platform. The act of locking down the cover jars and relocates the pan irrespective of how carefully the pan has been placed in the calorimeter cell. To overcome this problem, we eliminated the locking down procedure and gently placed the outside cover over the cell. The rings of the outer cover were coated with silicone grease and a lead weight was placed atop the cell to obtain a good nitrogen seal around the calorimeter elements. After repeated trials it was found that placing the encapsulated sample directly in the center of the cell platform gave the most reproducible results. Aluminum dome lids were used over the individual heater platforms. The tabs on these lids must be oriented in the same direction for each run to eliminate thermal emission variations.

Maintenance of the calorimeter cell

It is impossible to obtain reproducible values from a DSC cell which has been poorly handled. For the work discussed here a new calorimeter cell was chosen and used only for purity determinations. This cell was maintained in a flowing nitrogen atmosphere at all times during operation. Between runs, the cell was held at 100°C in flowing nitrogen while mounted in the DSC-1B.

Calibration of the temperature axis

Since the temperature of the sample is not a direct but a relative measurement in the DSC-1B, it is necessary to calibrate the temperature axis. In the range studied this is conveniently done with pure samples of indium, tin, and lead. Zone-refined benzoic acid, stearic acid, and semiconductor-grade gallium are convenient for the lower range. The method of reading temperatures is shown in Fig. 1. A calibration plot is shown in Fig. 3. The complete curve looks like a parabola, since the error begins to decrease towards zero below the melting point of indium. The calibration is different for each heating range due to the thermal resistance term.

It is very important not to adjust the average temperature control on the DSC-1B after calibration. The resistance control is so coarse that it is extremely difficult to reset the reading exactly to the previous reading. If the control is readjusted a new calibration is required.

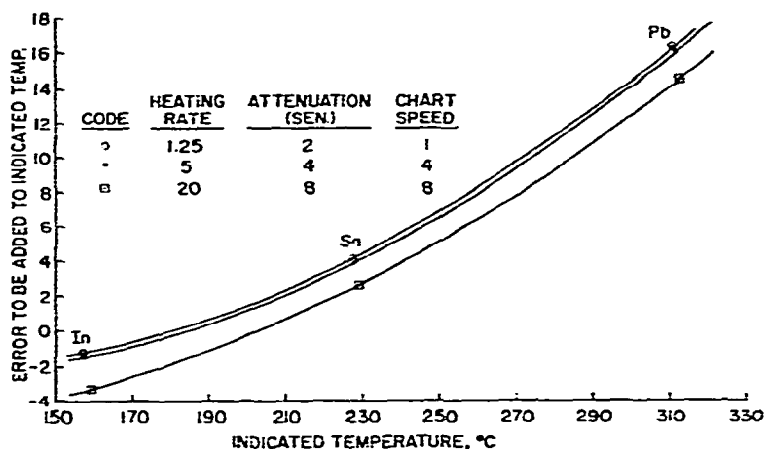


Fig. 3. Temperature axis calibration curve for the Perkin-Elmer differential scanning calorimeter.

Calibration of the calorie/area response

There is a small dependence between response and temperature in the DSC-1B. The function appears to be linear from 30–320°C. The sensitivity in terms of cal/unit area of the chart decreases (becomes a larger number) with increasing temperature. This is logical from heat-capacity considerations. Within the heating-rate range 0.625 to 5°/min no variation in the response factor was noted when the chart speed was adjusted to give equally spaced temperature plips at all heating rates.

RESULTS

Effect of heating rate

Since the van't Hoff equation describes an equilibrium condition, the sample must be in equilibrium both physically and thermally at all times during the melting process. Physical equilibrium is promoted by using very small samples, 3 mg or less, distributed in a thin compact layer. The heating rate should be very important, since the calorimeter is probably not at equilibrium at large rates of heating. An interaction should occur between sample size (total heat uptake) and heating rate. This is demonstrated in Table I.

With sample sizes of 3 mg or less and a heating rate of 1.25°/min, very good purity results can be obtained. The error is ~1.4%. An increase in the sample size of ~30% at the same heating-rate results in a lead analysis ~23% too low. Doubling the sample size, 6 mg, results in a 23% error even at a very slow, 0.625°/min, heating rate. The total area, in integrated fractions, from the onset of melting to the indicated vertex was used in constructing the T_s vs. $1/F$ plot in all cases. This was done because this system appeared less arbitrary than others which have been suggested. In addition, the van't Hoff equation operates on the total entropy of solution *and mixing* of the impurity in the *total* molten phase. To neglect any fractional area from the first detectable melting to the conversion of the last solid to melt would violate the

TABLE I

EFFECT OF SAMPLE SIZE AND HEATING RATE ON CALCULATED PURITY

Mixture	Sample size (mg)	Heating rate ($^{\circ}$ /min)	Purity(mole%)	
			Found ^a	Known ^b
Lead in tin	3.084	1.25	0.425	0.419
Lead in tin	3.084	5.0	0.185	0.419
Lead in tin	3.084	20.0	0.0828	0.419
Lead in tin	4.300	1.25	0.321	0.419
Lead in tin	6.284	5.0	0.857	1.16
Lead in tin	6.284	1.25	0.871	1.16
Lead in tin	6.284	0.625	0.890	1.16

^aCalculated with partial areas considered to the vertex of the endotherm. ^bDetermined by atomic absorption of lead with a Perkin-Elmer Model 503 Spectrophotometer. Nitrous oxide used as oxidizing agent to dissociate the tin compounds.

thermodynamics of the equation. The vertex of the melting endotherm is probably very near the temperature of final melting at *low heating* rates. At heating rates above 1.25 $^{\circ}$ /min or samples with a mass greater than ~ 3 mg the sample is not at equilibrium during the entire melting process. That is to say, once melting exceeds a certain rate, the calorimeter is not capable of responding rapidly enough to record accurately the process. As a result of this response rate effect, errors become more serious (see Table I) at high degrees of purity for both mass and heating rate.

Very pure samples melt at a more rapid rate, F/t (t = time in min), than less pure samples which have a broader melting range, $\Delta T/t$. This observation is completely congruent with the observations of Driscoll, Duling, and Magnotta³ and DeAngelis and Papariello^{3a}. They chose not to consider $1/F$ values in plotting the T_g vs. $1/F$ curve which lay beyond a certain arbitrary rate of melting, the rate at $1/2$ peak height for a pure sample (standard). Beyond this rate the error was observed to increase. However, if the melting of the compound did not exceed this rate at any temperature, the whole curve up to the vertex could be used. Area beyond the vertex is a function of the calorimeter response time. Only the curve for the 1.25 $^{\circ}$ /min, 3.084 mg sample lay below this point in Table I. The effect is obvious. The areas considered in the $1/F$ calculation should consist of not fewer than 6 segments; ten or more are preferable.

Effect of area choice

The use of the linearization operation on the T_g vs. $1/F$ curve imposes severe constraints on the choice of area considered in the calculation. If too little of the total curve is used to obtain $1/F$, then the purity calculated will be too high. If too much of the total area is used, the purity will be calculated too low. The terms too much and too little are far from quantitative. In Table II the effect of the total area considered is explored. The samples were run so that the calorimeter should have been in balance according to previous evidence.

It is apparent from Table II that the "correct" area to consider is the required area of the van't Hoff equation, *i.e.*, the area covering the melting process from onset to the conversion of the last portion of the solid to the liquid. It is also interesting to note that T_0 , the temperature of the equilibrium melting point for 100% tin, is very near the generally accepted value for the white tin allotrope¹¹ only when the area up to the vertex is considered. The precision and accuracy of the analysis are very good when the above criteria are considered: $\pm 3.5\%$, 2.4% , and 1% . On an average of 30 determinations the precision was $\pm 5\%$ for organic samples.

TABLE II

EFFECT OF TOTAL AREA CONSIDERED ON THE CALCULATED PURITY

	% Area considered ^b	Calculated mole% lead	Extrapolated T_0
1.16 Mole % lead-tin mixture ^a	43.6	0.512	229.60
	70.2	0.871	230.96
	88.3	0.874	230.98
	96.4	1.11	231.60
	98.1 ^c	1.12	231.61
	100.0 ^d	1.44	232.43
0.419 Mole % lead-tin mixture ^a	27.5	0.221	230.60
	28.6	0.313	231.12
	59.8	0.321	231.30
	61.5 ^e	0.421	231.61
	100.0	0.450	232.40
1.10 Mole% anthracene in 9,10-dichloroanthracene ^a		Calculated mole% anthracene	
	35.3	0.836	213.10
	55.2	1.084	213.32
	77.2	1.093	213.46
	88.0 ^c	1.110	213.50
	100.0	2.147	214.45

^aSee Table I for analysis, all samples run at 1.25°/min, 2.500 mg sample. ^bCalculated from the onset of melting; the base is the area of the complete endotherm. ^cArea to the endothermal vertex. ^dTotal area of curve, *i.e.*, complete endotherm. All of the above calculations were done with at least 10 well-spaced points of integration within the allotted area. ^eAnthracene determined by fluorescence analysis.

Effect of eutectic formation on accuracy

Although lead and tin form a well known eutectic, the eutectic point is well removed from the melting points of either lead or tin. Thus, interference at low mole percentages should be minimal. The effect of a close eutectic may be very different, especially if the eutectic melts within the low-melting tail of the impure principal component. The formation of the eutectic should "use up" all of the impurity at low mole percentages. However, by definition the eutectic melt is insoluble (phase excluded) in the solid phase of the principal component. The eutectic melt should be soluble in the melt of the principal component. Thus, the eutectic melt should approximate an impurity as described by the van't Hoff equation. This assumption was tested using stilbene as an impurity in triphenylmethane.

At a known impurity of 0.71 mole% stilbene (from thin layer chromatography, extraction and UV analyses), a 0.640 mole% impurity was found. This is ~10% error; much greater than noted previously but acceptable for most analyses. At high mole percentages the eutectic interferes seriously with the initial melting (see Fig. 4) and 1.71 mole% was found for a sample containing 3.06 mole%. It appears that eutectic formation in impure samples can cause serious errors in the DSC method. However, eutectics are easily detected in most cases. A widely separated eutectic should offer no serious problem.

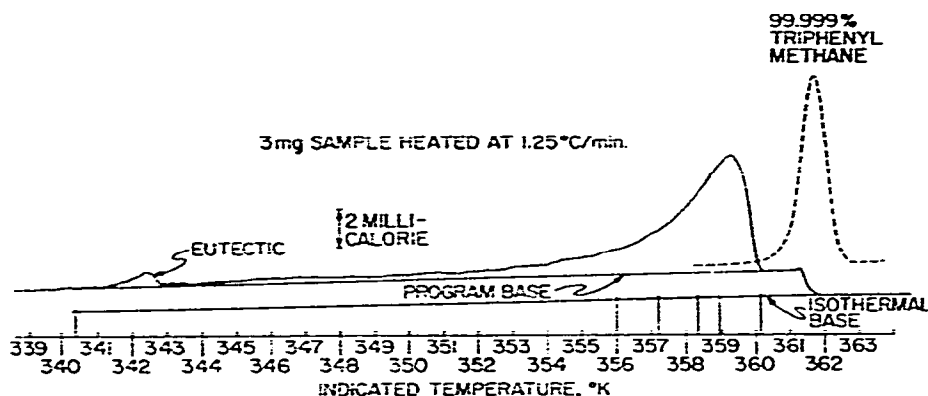


Fig. 4. The eutectic forming system *trans*-stilbene–triphenyl methane (3.06 mole% *trans*-stilbene).

Effect of co-crystallization

The formation of solid solutions or co-crystals removes the melting curve from the range where the sample van't Hoff equation is applicable. Driscoll *et al.*³ used a modified form of the van't Hoff equation:

$$T_s = T_0 - \frac{RT_0^2 X_2}{\Delta H_f} \cdot \frac{1}{\frac{K}{1-K} + F}$$

where $K = k/k'$, the distribution ratio of the impurity between the solid and liquid phases. The value of K is a difficult quantity to measure. However, if many samples of the same material are to be studied, it may be worthwhile to evaluate this constant.

As an alternative to an evaluation of K and application of the van't Hoff equation, the treatment of thermal data by Block's method¹² is attractive. He studied the fusion of mixed silver chloride–bromide precipitates. These mixed salts are true lattice substitution co-crystals. The bromide substitutes very well for the chloride ion in the solid crystal structure. Block found that the total area under the fusion endotherm of the mixed salt was an almost linear function of the concentration of the two ions. In repeating this work the present authors found that the temperature of the endothermal minimum was an even more sensitive measure of the ion in lower concentration at low impurity levels. The relationship between temperature and true ion content is non-linear.

In addition to the above, it was found that lead-indium form a co-crystal. The area and temperature vary in the same fashion as the mixed silver chloride-bromide salts. Endotherms for co-crystals behave in an anomalous manner. For lead-indium mixtures at indium concentrations <5 mole%, the lead endotherm moves to lower temperatures without broadening — some *increase* in sharpness was noted. A sample containing <1% indium translated the lead endotherm some 10°C to lower temperatures and *decreased* the apparent melting range by 2 out of 5°C. With proper calibration it should be possible to measure as little as 0.005 mole% indium in lead by this method.

CONCLUSIONS

This study has indicated that the DSC purity determination as previously described^{2,3,4} can yield very accurate and precise purity information on materials which melt in an ideal fashion. To obtain usable data it is necessary to observe the following guidelines:

- (1) Sample size less than 3 mg.
- (2) Heating rate $\leq 1.25^\circ/\text{min}$.
- (3) Encapsulation in a volatile sample sealer modified to maintain good thermal contact.
- (4) Precise calibration of the temperature axis.
- (5) The area considered for $1/F$ calculation must start at the first detectable melting and finish with a point at the endothermal minimum and contain at least six points.
- (6) Heating rate and sample size must be adjusted so that the slope of the endotherm never exceeds the slope of the pure standard at $1/2$ peak height of the standard.
- (7) The thermal lag must be measured with a standard which melts near the sample.

These seven steps are all due to the inherent thermal lag and response time of the calorimeter and the requirements of a close approach to thermal equilibrium.

The formation of an eutectic mixture melting near the principal component will decrease the accuracy of the method. However, at low concentrations sufficient accuracy is maintained to make the method relatively satisfactory.

Materials which form co-crystals can be studied by DSC in some cases, but the van't Hoff method cannot be applied satisfactorily to these materials. A calibration curve constructed on the basis of endothermal minimum as a function of the minor component concentration is very sensitive to purity at concentrations of <5 mole% of impurity.

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