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DIFFERENTIAL SCANNING CALORIMETRIC ASSESSMENT OF HIGH PURITY*

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ABSTRACT

The value and limitations of differential scanning calorimetry in the assessment of high-purity substances has been examined. In favorable cases, good agreement has been secured for polycyclic hydrocarbons between DSC purity values and GC assay values. For some halogenated benzoic acids, used as microanalytical reference standards, good agreement has been obtained between DSC purity values and acid–base titration results. DSC studies on cholesterol and urea, which have limited thermal stability, are presented. With the available instrument and technique, the *practical* upper limit of absolute DSC purity values may be 99.95 mole%, although higher numerical values can be obtained. Because the DSC technique is "blind" to equilibrium solid solution formation, DSC values should not be used as a sole criterion of purity; this recommendation is of special importance for compounds purified by fractional solidification processes.

INTRODUCTION

The practical analysis of high-purity chemicals has been studied in depth in our laboratories during the past few years. By high-purity chemicals is intended those having about 500 parts per million or less of total impurity; such chemicals are sometimes termed "ultrapure". Our studies have been pursued in the framework of an extensive program for the development of a viable line of high-purity chemicals, both inorganic and organic, distinguished by broad analytical definition and by advanced protective packaging. The analytical portion of this program differs from earlier studies of high-purity materials by the need to keep analytical costs at a sufficiently low level that the products are not priced out of salient markets in analytical chemistry, research and development, and materials science. An overview of this analytical effort has been given[1,2] and the methods developed and perfected for the analytical characterization of high-purity EDTA have been published[1].

For the broad characterization of a high-purity chemical, the major constituent should be determined or some overall expression of purity be sought. Additionally

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*Paper III in the series "Practical analysis of high-purity chemicals".

key impurities should be determined. Also various general tests can be performed and physical properties can be measured. For the assessment of purity, thermal methods based on melting of freezing phenomena are valuable and the calorimetric measurements of Wichers and coworkers[3] for certain standards have showed the power of the approach in the high-purity range. However, the method requires large samples, extended equilibration times, and high-precision thermometry.

With the automation of thermal methods, differential thermal analysis (DTA) was used by various workers to assess purity, but largely in a qualitative way. Attempts were made to quantify the approach by calculations based on the shape of the melting curve as compared to that of one or more standard samples of known purity. Differential scanning calorimetry[4] (DSC) became available in terms of a practical instrument sometime after 1964. It was early recognized that the DSC technique was applicable to the assessment of purity. Comparisons with standards of known purity have been used[4–6]. Gray recognized that a single DSC curve could be analyzed in terms of the Van't Hoff equation without the need for standards[7]. The manual calculations are somewhat tedious and computer processing of the data was introduced by Driscoll and coworkers[8]. Additional computer programs have been developed by Scott and Gray[9] and by Barrall II and Diller[10]. The calculations, however performed, provide the molar *impurity* content, which is usually expressed in mole%. This value can be substracted from 100 to yield a value for the mole% *purity*. This practice has been followed in this work; however, in the discussion of the precision or accuracy of the DSC technique reference to the mole% impurity found is sometimes preferable.

The DSC approach to the assessment of purity during the past few years has been applied to a variety of organic compounds, including aliphatic hydrocarbons[8], amides, amines and carbamates[11,12], benzene derivatives[7,11–13], halogenated compounds[8,12], heterocyclic compounds[11,12], malic acid[13], organophosphates[12], pesticidal chemicals[12], pharmaceuticals[11,13], polycyclic hydrocarbons and quinones[8,11], and steroids[7,13]. The conclusions to be drawn from reported studies is that this DSC technique is most useful above 98.0 mole%. One paper, however, has reported extension to the 95% purity level by means of the addition of a high-purity form of the major component, thereby bringing the composition within the favorable 99.0–99.5 mole% region[13].

Some attempts have been made[10,11,13] to relate the purity values found by the DSC technique with those established by other methods. Reubke and Mollica[11] compared the DSC value found for anthraquinone with that by GC assay; the values found were 99.69 mole% and >99.5%, respectively. These workers also compared DSC and phase solubility measurements for diallylbarbituric acid. The values for the two techniques were 99.80 mole% (average of duplicate) and 100.0% by weight. For methyl reserpate, they also related the DSC value with the purity estimated by the temperature solubility technique and indicated that the DSC technique might serve as a rapid control method. DeAngelis and Papariello[13] for various samples of a steroid with a purity above 99.0% found good agreement for DSC measurements, phase solubility analysis, and thin-layer chromatography (t.l.c.) with densitometric evaluation. For an investigational carbamate, at a purity less than 98.0% poor agreement was found for DSC assessment, n.m.r. and t.l.c; at a purity greater than 98.0% better agreement was secured.

Additional attempts have been made[8,10,12-14] to confirm the accuracy of DSC purity measurements by the study of known mixtures, ranging in purity from about 97 to 99.9%. The analytical recovery of the minor component in most studies has been within ±20% relative. Driscoll and coworkers[8] suggested that where the recovery was poorer, as with a thiophene–benzene mixture, equilibrium solid solution formation is involved.

Barrall II and Diller[10] have reported that for binary mixtures of metals the DSC purity values were in excellent agreement, ±3% relative, with the impurity content established by atomic absorption photometry. For mixtures of organic compounds, comparison of the u.v. absorbance, fluorescence photometry and t.l.c. was reported to give good agreement. They emphasized that favorable agreement was secured when the DSC instrumental parameters were properly controlled and the calculations were based on use of the energy–temperature curve up to the maximum.

The accuracy achieved for DSC purity measurements in published studies is shown graphically in Fig. 1. In this log–log plot the impurity content found by DSC measurements is correlated with the impurity content either established by another method or calculated from the composition of a known mixture. Some workers have emphasized that the agreement is within ±20% relative. This view is supported by the many points that fall within the +20 and −20% lines also drawn on the graph. It should be added, however, that this plot does not include runs for which the original workers suspected solid solution formation or other disturbance, including incomplete solubility in the melt.

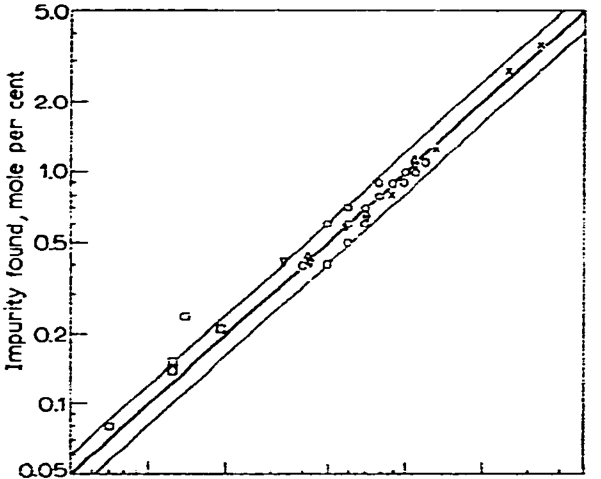

Fig. 1. For published studies, correlation of content of impurity found by DSC measurements and impurity taken. Heavy line corresponds to exact correlation. Upper and lower light lines correspond to +20% and −20% relative departure; ○, Ref. 13; □, Ref. 8; ▽, Ref. 12; ×, Ref. 14; ◇, Ref. 10.

Our studies of the DSC assessment of purity were initiated in December 1967 and have been concurrent with most of the reports mentioned above. Our objective has been the application of this DSC technique to the practical characterization of high-purity substances where the mole impurity is less than 0.10% and often less than 0.05%. Much of the work was necessarily directed to establishing the validity of the technique. Our experiences reported in this paper throw light on both the value and limitations of DSC purity assessments for high-purity substances.

DSC technique

All of the DSC measurements reported in this paper were obtained with the Perkin–Elmer DSC-1B instrument. Unless otherwise noted, the temperature scanning rate was 0.625°C/min and with maximum sensitivity (range 1). All high-purity samples ranged from 0.5 to 2 mg in size and were weighed on a Cahn gram electrobalance. All samples were run on an "as is" basis (that is without drying) and in a nitrogen atmosphere. All materials in the program were routinely protected after their final purification by storage under an atmosphere of either argon or nitrogen.

With a variety of high-purity volatile and non-volatile compounds, our experience has been that better agreement is secured in the purity values for replicates when so-called "volatile" cells are used. Following the manufacturer's recommendations, a close fitting aluminum disc is inserted over the sample before sealing of the cell. All DSC purity values in this paper, unless otherwise stated, were obtained using volatile cells. In all cases a similar cell with the aluminum disc insert was used on the reference side of the instrument.

Calculations of DSC purity values

In this study although a few DSC purity values were obtained by planimeter measurements of the curve and desk calculations following the recommendations of Perkin–Elmer[7,15], most were secured by application of the computer program developed by Driscoll, Duling and Magnotta[8]. The original Fortran program was rewritten into a basic program operable on a time-shared computer terminal.

The calculation of impurity (or purity) content by the DSC technique is based on the Van't Hoff equation, which relates the melting-point depression to the impurity content. On the basis of this equation a plot of T_s, the instantaneous temperature of the sample, *vs.* $1/F$, where F is the fraction melted at T_s, should give a straight line with an intercept of T_0, the melting point of the infinitely pure compound, and a slope $-RT_0^2X_2/\Delta H_f$, where R is the gas constant, X_2 the mole fraction of impurity, and ΔH_f the heat of fusion of the compound. However, the plot of T_s *vs.* $1/F$ immediately derived from the DSC data does not afford a straight line. The cause of this departure is the failure to measure some area under the DSC energy *vs.* time (temperature) output curve due to the inherent sensitivity limitations of the instrument. A straight line relation is achieved by the trial and error addition of small increments to both the partial areas and total area. Details of this area correction and linearization process have been given by various workers [7,8,12,15].

Driscoll and coworkers[8] with computer-based calculations recommended that the largest $1/F$ value used should be 50. This value has been used in computations of all DSC values recorded in this paper. In our experience, use of a higher $1/F$ limit results in a smaller area correction and an unreasonably low impurity content. These findings are to be associated with the fact that too much weight is placed on the initial, poorly defined premelting region. Additionally the plot of T *vs.* $1/F$ is actually S shaped and with higher 1/F values the straight line fitted has a smaller slope, which corresponds to lower impurity content. The lower limit for $1/F$ in the computer program of Driscoll and coworkers[8] is taken as the point corresponding to one-half of the peak height in the energy–temperature curve. A similar limit has been taken by earlier workers following the recommendations of Perkin–Elmer[7].

Driscoll and coworkers[8] introduced an empirical correction for *nonequilibrium* solid solution formation based on a previously developed formula employed in static calorimetry[16]. By this correction of the impurity content better agreement was achieved by those workers in the assessment of the molar composition of mixtures. The limited study of mixtures in our laboratories confirms this finding (see below). All DSC values reported in this paper include this correction unless otherwise stated. This correction results in an increase in the impurity content assigned, that is, a decrease in the purity content, and, if nothing more, affords a more conservative assessment of the purity of a high-purity chemical. The size of the correction increases with the extent of the area correction involved in the linearization of the T_s *vs.* $1/F$ plot. At 99.90 mole% purity, a 5% area correction leads to an absolute decrease in the mole purity of only 0.016% when the nonequilibrium solid solution correction is applied.

Scott and Gray[9] with their recent computer program have recommended, as an alternative, use of a "slope criterion", that is, the lower $1/F$ limit is taken as the point at which the slope of the sample curve exceeds one-sixth of the slope of the tangent line to the calibration (indium) curve. These workers also recommended a "partial area start criterion", that is, the upper $1/F$ limit is taken at the point, proceeding from the starting point, as the next point after "5 ordinate values [have remained]... above the initial base line by one encoder unit". In other words, the upper $1/F$ limit is taken as the first point at which the signal is significantly above the noise. However, the program of Scott and Gray[9] permits the user options to use either of these criteria or to select his own $1/F$ limits.

Barrall II and Diller[10] have recently recommended a lower $1/F$ value corresponding to the vertex of the energy curve and provide data to support this selection by their study of mixtures. It was their view that selection of this limit was less arbitrary than others that have been suggested.

DSC study of a zone-refined bar

Differential scanning calorimetry is an attractive approach in following the purification of an organic compound by zone melting. Where the operation has a favorable separation factor, pronounced change in impurity content can be measured along the length of the bar. Additionally, small differences in impurity content can often be detected radially. For example, in our laboratories, the impurity distribution of zone refined bars of benzil and benzoic acid has been explored.

The study of one benzoic acid bar is noteworthy. At the less pure end a center hollow was present and the radial impurity content varied quite irregularly. In contrast at the purer end, with no center hollow present, the radial change in composition was no greater than the reproducibility of the DSC measurement of a single sample.

By multipass zone refining, benzil, which was previously purified by crystallization to a DSC purity of 99.913 mole%, yielded a bar ranging from 99.996 mole% at the purer end to 99.6 mole% toward the other end. The distribution of impurity along the bar could be measured and showed regular progression.

Study of binary mixtures

In the introduction to this paper, some investigations were reviewed that had the goal of confirming the accuracy of DSC purity measurements by the study of known binary mixtures. In this earlier work the range of the minor component was from 0.1 to 3 mole%. With our interest in the use of DSC techniques with high-purity substances, the study of binary mixtures of compositions having 0.1 mole% or less of the minor component was undertaken. The fact that various substances were being purified in our programs by multipass zone refining made this study attractive. Three binary systems were selected for examination, namely, naphthalene–biphenyl, benzil–benzoic acid, and benzil–biphenyl. In all cases the first-named component was the major one. A cursory study of literature failed to reveal any references to possible equilibrium solid solution formation in these systems. Using zone refined compounds, attempts were made to prepare the required mixtures. The difficulties in preparing homogeneous mixtures of the expected composition were recognized. It was also appreciated that the problem was magnified because a sample of about 1 mg is appropriate in the DSC run of a high-purity compound. Mixtures for the naphthalene–biphenyl system were prepared by evaporation of solutions (using bulk crystallization and flash evaporation) and also by dry grinding using a mortar and pestle.

For the two benzil systems, fusion alone and fusion followed by crushing and mixing were employed. Only with some samples of the naphthalene–biphenyl system, prepared by grinding, could recoveries of the minor component as great as 75 to 80% relative be obtained in the DSC purity measurements, and only with inclusion of the correction for nonequilibrium solid solution formation[8]. Since all results were in the direction of low recoveries and sometimes with the values for duplicates scattered, further attempts were abandoned to prepare and to study binary mixtures with less than 0.1 mole% of the minor component.

Comparison of DSC purity values and GC assay values

For a number of polycyclic hydrocarbons purified by multipass zone refining followed by simple sublimation, the purity was established by DSC measurements of duplicate samples. Additionally these compounds were assayed by gas chromatography. The results obtained by the two methods are compared in Table I, with a statement of the instrumental conditions. Gas chromatography of such high-melting hydrocarbons has been placed on a firm footing by the work of Sawicki[17] and others.

TABLE I

COMPARISON OF GC ASSAY AND DSC PURITY VALUES FOR SOME ZONE-REFINED HYDROCARBONS

Compound	*J. T. Baker ULTREX Lot No.*	*GC assay*[a] *(area %)*	*DSC purity*[b] *(mole %)*
Acenaphthene	UHC 322	99.99 (170)	99.99; 99.99
Anthracene	UHC 323	99.99 (220[c])	99.95; 99.96
Bibenzyl	[d]	98.24 (125)	99.97; 99.96
Biphenyl	UHC 324	99.99 (170)	99.99; 99.96 99.99[e]; 99.99[e]
Durene	UHC 325	99.99 (75[f])	99.96; 99.98
Naphthalene	UHC 326	99.99 (140)	99.96; 99.93
	UHC 327	99.99 (140)	99.99; 99.97
Phenanthrene	[g]	99.99 (210)	99.75; 99.77
	[h]	99.99 (210)	99.73; 99.92
Pyrene	UHC 328	99.97 (250)	99.94; 99.94
	UHC 329	99.99 (250)	99.97; 99.98
trans-Stilbene	[i]	99.77 (200)	99.97; 99.94
p-Terphenyl	UHC 330	99.99 (240[c])	99.97[e]; 99.96[e]

[a] All GC assays using F & M model 500 with flame ionization detection; silicone gum rubber SE-30 on Chromosorb W column (6-ft length, 0.25-in outside diameter); sample dissolved in benzene for injection. Column temp. used (in °C) between parentheses. [b] All DSC values corrected for non-equilibrium solid solution formation (see text) and obtained with use of volatile cell, nitrogen flow, and a scanning rate of 0.625 °C/min. [c] Solid sample injection. [d] Sample 829-55-2; lot rejected, see text for explanation. [e] Values for nonvolatile cell. [f] 2-ft Column, rather than 6-ft. [g] Sample 829-54-5; lot rejected on basis of DSC values below 99.95%. [h] Sample 829-63-5; lot rejected on basis of DSC values below 99.95%. [i] Sample 829-54-4; lot rejected on basis of low GC assay value.

As can be seen, in most cases, the agreement between the two methods is good considering the quite different underlying phenomena. It should be noted that a value of 99.99 area % was assigned for the GC assay whenever no impurity peak was detected.

The study of the sample of bibenzyl delineated some of the limitations of differential scanning calorimetry. The values for the purity content obtained by DSC measurements were 99.97 and 99.96 mole%. These values suggested that a high-purity product had indeed been secured. Assay by gas chromatography was then attempted. The first GC assay value of 97.63 area % was obtained on a 6-ft 1/4-in diameter silicone SE-30 column at 190 °C with the inlet port at 300 °C and with flame ionization detection. Since this high port temperature might have caused thermal decomposition of the sample and thereby a low GC assay value, the work was repeated under milder thermal conditions, namely, with a similar 2-ft column, a temperature of 125°C and a port temperature of 190°C. In this way a somewhat higher GC assay value of 98.24 area% was secured. The chromatogram in each case showed only a single significant impurity peak and under the milder conditions this peak corresponded to 1.76 area%. To study this pronounced discrepancy between the GC and DSC purity values, the impurity was isolated in milligram amounts by gas chromatography employing an 8-ft 3/8-in diameter silicone SE-30 column. Then 1.89 parts by weight of this isolated impurity was added to 100 parts by weight of the original bibenzyl. Assuming that the GC area% found for the impurity approximates a weight percent, the total content of the impurity in the resulting mixture was about 3.58% by weight. This mixture was then subjected to DSC measurements and the purity value found was 99.95 mole%, which is only slightly less than the DSC value found for the original bibenzyl! These findings clearly show that the differential scanning calorimetric technique was virtually blind to the impurity (solid solution formation).

With *trans*-stilbene the disagreement between the DSC and GC assay values was less marked than for the bibenzyl situation (see Table I), and solid solution formation was suspected.

Thin-layer chromatography using flexible sheets is widely used in our laboratories in the characterization of high-purity compounds. The hydrocarbons listed in Table I were examined by this technique using both aluminum oxide IB-F (with carbon tetrachloride for development) and silica gel IB-F (with carbon tetrachloride and hexane separately for development). Spots were located by examination under both long and short wave u.v. illumination. Even at the heavy sample loadings employed, no impurity spot was seen for most of the hydrocarbons. In the few cases that an extraneous spot was detected, the relative intensities indicated that the impurity was present only in trace amounts.

Comparison of DSC purity values and titrimetric assay values

Organic elemental analysis requires a variety of reference standards that serve to assure that the combustion or other technique affords satisfactory results. In our programs a number of halogenated benzoic acids have been purified for consideration as microanalytical reference standards. Since such acids appeared to melt without decomposition and were being assayed by acid–base titrimetry, it was also of interest to establish their purity by DSC measurements. These compounds were also analyzed for carbon and hydrogen in duplicate and for the halogen substituent five or more times. The results of the DSC and titrimetric evaluation of these compounds are summarized in Table II. The agreement of averages in all cases was within 0.1% absolute. It is noteworthy that the titrimetric assay as well as the determination of the halogen content would be blind to isomeric impurities; in contrast, DSC measurements might be expected to respond to such impurities. The combination of the DSC assessment, the acidimetric assay, and the determination of halogen content taken together affords good evidence that the purification processes employed do indeed yield high-quality microanalytical reference standards.

TABLE II

COMPARISON OF TITRIMETRIC ASSAY AND DSC PURITY VALUES FOR SOME MICROANALYTICAL REFERENCE STANDARDS

Compound	*J. T. Baker ULTREX Lot No.*	*Titrimetric assay*[a] *(%)*	*DSC purity (mole %)*
m-Bromobenzoic acid	[b]	99.78, 99.73	99.71, 99.54
m-Chlorobenzoic acid	UHC 318	99.81, 99.81	99.87, 99.89
p-Fluorobenzoic acid	UHC 314	99.93, 99.94	99.86, 99.95
o-Iodobenzoic acid	UHC 319	99.97, 100.00	99.88

[a] Via volume-based acid–base titrations, except *m*-chlorobenzoic acid by precision weight titrimetry. [b] Sample No. 816-95b; lot rejected for low assay and DSC purity; bromine content by oxygen-filled flask combustion: Theory 39.75%; found 39.83±0.018% (mean of 5 values and standard deviation of the mean).

DSC study of urea

Urea presents an interesting challenge in its specification as a reference material for the clinical laboratory. The staff of the National Bureau of Standards explored the DSC technique with high-purity urea and for the NBS reference material[18] "an apparent purity of 99.82±0.003 mole%" was listed. The calculation of the purity did not include any correction for nonequilibrium solid solution formation. An "apparent" purity value by phase-solubility analysis of 99.82% by weight was also given. The modifier "apparent" was used "because neither method accounted for the moisture content of the urea". A satisfactory method for drying was stated not to have been found.

In our laboratories, DSC assessment ofhigh-purity urea was also undertaken concurrently with the work of the National Bureau of Standards, but somewhat lower DSC values were secured with a variety of purified samples and at scanning rates varying from 0.625 to 2.5°C/min. At that time these low results were attributed to insufficient thermal stability for the compound at and near its melting point. Phase solubility analysis was undertaken for one lot of high-purity urea when the success of the National Bureau of Standards was communicated and a value of 99.87% by weight was asssigned for the "as is" material on the basis of eight points[19]. Subsequent study of the same lot by the DSC technique was then undertaken. Both the "as is" material and a portion dried for 3 h in a pistol at 108°C over phosphorus pentoxide were run at scanning rates of 0.625 and 1.25°C/min. The DSC mole purity values found can be summarized:

Urea ULTREX Lot No. UCS 209	*Mole % purity found*	
	0.625°C/min	*1.25°C/min*
"as is"	99.66 (av. of 3)	99.66
	99.76*	99.76*
dried	99.65 (av. of 3)	99.71
	99.74*	99.78*

The starred values are for the same DSC runs with the correction for nonequilibrium solid solution omitted from the calculations. Even these values are numerically lower than the phase solubility value by about 0.12% absolute. However, for an unknown impurity the comparison of mole- and weight-% values has limited validity.

The DSC technique for the absolute assessment of purity fails for a compound of low thermal stability in its melting range. Our experience with urea suggests that it shows "borderline" thermal stability with this technique and the analytical information secured is of limited usefulness.

DSC study of cholesterol

In studies of the purification of cholesterol for use as a clinical laboratory standard, DSC purity measurements were early applied in our laboratory. At a scanning rate of 0.625°C/min reasonable purity values could be obtained and the agreement of replicates was within ±0.1 mole%. The National Bureau of Standards subsequently undertook DSC evaluation of high-purity cholesterol and secured good agreement between DSC values and those obtained by gas chromatography using glass columns and by phase solubility analysis[20]. Using similar gas chromatography, Goldstein[21] has analyzed both the J. T. Baker high-purity cholesterol and that certified by the National Bureau of Standards. The impurities found are consistent with the DSC purity values assigned in our laboratory.

Our experience with cholesterol offers one intriguing application for the DSC technique. Flame-sealing of ampoules of high-purity cholesterol and the use of an inert atmosphere was considered as a means of reducing moisture pickup and of maintaining the quality of the product. Cholesterol was experimentally ampouled, the ampoules opened, and the DSC purity of the contained product was compared with that of the original material. Significantly lower DSC values were found for the ampouled material, presumably due to the presence of small amounts of decomposed product. It should be added that the properties of cholesterol make it difficult to fill this compound into an ampoule under drybox conditions without leaving a few small particles clinging high on the walls of the ampoule. As a result of this study, the ampouling of cholesterol was abandoned and containment of the product in a screw cap vial was adopted. The DSC study of ampouled products has been extended to other high-purity compounds. Additionally the technique can be useful in storage and container studies for pharmaceuticals and laboratory chemicals.

Remarks

In view of its rapidity, use of milligram samples, and its application to the purity region from 98.0 to 99.95 mole%, differential scanning calorimetry is a most valuable tool in the characterization of organic compounds. The DSC technique can effectively compliment such established approaches as elemental analysis, titrimetric and gravimetric assay, and gas chromatography.

For a thermally stable compound, a *low* DSC purity value, based on a satisfactory run of the instrument, is clear evidence that a compound is not of high-purity!

In contrast, a *high* DSC purity value cannot be taken as conclusive evidence that the compound is indeed of high purity. In the latter case, confirmatory evidence should be secured by techniques not dependent on melting or freezing phenomena, since the DSC technique is blind to equilibrium solid solution formation. This confirmation is especially important where the compound has been purified by zone refining or other solidification processes where solid solutions can persist.

In the application of the differential scanning calorimetric assessment of purity to the high-purity region, the operating conditions selected should approach equilibrium melting as closely as a kinetic process allows. In brief, small samples and the lowest scanning rate practical should be used. These factors require that the commercial instrument be operated at maximum sensitivity. Additionally thermal contact should be optimized.

Above 99.90 mole% purity, the premelting behavior on which the DSC calculation is based, becomes progressively smaller and the purity value assigned becomes strongly dependent on the assumptions made in the calculation ($1/F$ limits). The *practical* upper limit for *absolute* DSC measurements may therefore be about 99.95 mole% with the presently available instrument and technique. This should not be confused with the ability to detect differences in impurity content as little as 0.005 mole %. Indeed the *relative* purity of two lots of a single compound can be assessed up to 99.99 mole%, especially if replicates are run.

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