

Scanning calorimeter for nanoliter-scale liquid samples

E. A. Olson, M. Yu. Efremov, A. T. Kwan, S. Lai,^{a)} V. Petrova, F. Schiettekatte, J. T. Warren, M. Zhang, and L. H. Allen^{b)}

Department of Materials Science and Engineering and Coordinated Science Laboratory, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801

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We introduce a scanning calorimeter for use with a single solid or liquid sample with a volume down to a few nanoliters. Its use is demonstrated with the melting of 52 nL of indium, using heating rates from 100 to 1000 K/s. The heat of fusion was measured to within 5% of the bulk value, and the sensitivity of the measurement was $\pm 7 \mu\text{W}$. The heat of vaporization of water was measured in the scanning mode to be within $\pm 23\%$ of the bulk value by actively vaporizing water droplets from 2 to 100 nL in volume. Results within 25% were obtained for the heat of vaporization by using the calorimeter in a heat-conductive mode and measuring the passive evaporation of water. Temperature measurements over a period of 10 h had a standard deviation of 3 mK. © 2000 American Institute of Physics. [S0003-6951(00)01243-2]

Calorimetry is a universal technique for studying the thermodynamic properties and kinetic processes of materials and biological systems.¹ It is especially useful for energetic studies of exothermic and endothermic reactions and phase transformations. The conventional differential scanning calorimeter (DSC) is a well-established analytic tool, but is limited to a macroscopic sample no smaller than a fraction of a milliliter.^{2,3} Macroscale DSC can be used on small-scale systems by increasing the sample size or by studying a population,⁴⁻⁶ but conventional methods and apparatus do not work well for sample sizes on the order of nanoliters. Alternating current microcalorimeters have been designed for samples as small as 1 μL ,^{7,8} but this technique is not generally used for energetics studies.⁹

Calorimetry has potential in both pure and applied science for the investigation of material on the nanoliter scale. For example, it might be possible to nonintrusively study the basic biological processes of individual cells. In the microelectronics industry, it would also be possible to study individual flip-chip solder bumps. In addition, with the use of silicon micromachining technology, an array of calorimeters could be designed on a single wafer for rapid analysis of materials for combinatorial experiments.

Advances have been made in the development of calorimeters for the analysis of ultrathin films. These nanojoule calorimeters have been used to study the melting phenomena of nanometer-sized metal particles,¹⁰ thin films,¹¹ and individual superconductor crystals.^{12,13} Other developments in membrane materials¹⁴ may lead to improvements in nanocalorimeter design and construction, and increased sensitivity. For nanoliter bulk samples, however, and especially for liquid samples, little progress has been made in the development of calorimeters for energetic studies.

In this letter, we report a calorimetric technique for the study of a single solid or liquid sample with a volume in the nanoliter range. This technique is demonstrated by examining simple liquid-solid and liquid-vapor transformations at small scales and near room temperature. Ultimately, we in-

tend to use this calorimeter¹⁵ in the study of polymer single crystals, biological macromolecules, and the energy uptake of individual or small clusters of cells.

The calorimeters described in this work were fabricated similarly to those previously reported.¹⁰ A silicon-nitride membrane, 0.3 μm thick, held by a silicon frame, is constructed by etching a silicon-nitride-coated silicon wafer in aqueous potassium hydroxide. As a container for liquid samples, a small "box" remains unetched and has a volume of ~ 35 nL. On the opposite face of the membrane, a 50 nm nickel strip is patterned and deposited, using 3 nm of titanium as an adhesion layer. A cross section of the device as well as an electron micrograph of the box is shown in Fig. 1.

Calorimetric measurements are taken by resistively heat-

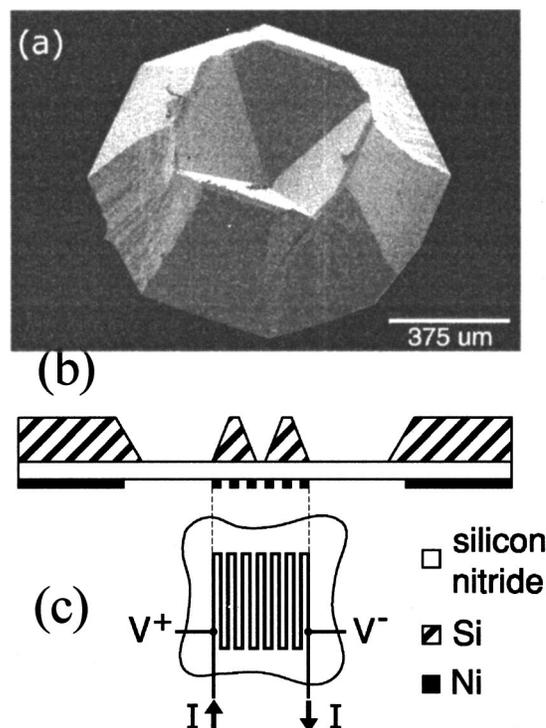


FIG. 1. Electron micrograph of the silicon box (a), a cut-away schematic of the calorimeter (b), and a top view of the heater (c). Relative dimensions in (b) and (c) have been exaggerated for clarity.

^{a)}Present address: CTS Wireless Components Inc., Albuquerque, NM 87113.

^{b)}Electronic mail: L-ALLEN9@uiuc.edu

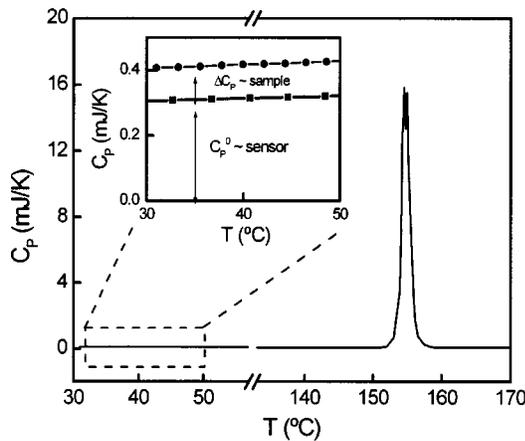


FIG. 2. Melting of a 52 nL particle of indium at 150 K/s (average of six scans). The inset graph shows the base-line heat capacity of just the calorimeter (■) and the calorimeter plus the sample (●). The midpoint of the peak is at 155 °C, with a FWHM of 1.3 K. Measured H_m is 27.2 J/g. Bulk values for T_m and H_m of indium are 156.6 °C and 28.6 J/g, respectively. Sensitivity in this experiment was $\pm 7 \mu\text{W}$.

ing the calorimeter by applying a dc voltage across the nickel strip. The current through the heater, as well as its resistance, is measured in real time. The temperature of the calorimeter is determined from the electrical resistance of the nickel strip.

The heat capacity of the calorimeter is then determined using

$$C_P = \frac{dQ}{dT} = \frac{P(t)}{dT/dt}, \quad (1)$$

where Q is the amount of heat absorbed; T the temperature; and P the power dissipated in the heater strip as a function of time. Latent heats are calculated by integrating the power dissipated by the heater from the beginning to end of a transformation. Corrections for heat lost to the environment are made where necessary. Additionally, the calorimeter is used as a microbalance by comparing the heat capacity of the calorimeter with and without a sample at 30 °C.

We evaluate the performance of the calorimeter in the scanning mode by measuring the melting and vaporization of standard materials. The heat of fusion and the melting point of indium at heating rates from 100 to 1100 K/s are measured, as well as the heat of vaporization of individual droplets of water of various volumes. To evaluate the calorimeter in a heatconductive mode, the vaporization energy of single droplets of water without active heating is measured.

The first sample used in this work is a small section of indium wire (Alfa Aesar, 99.9985%), and is transferred into the box of the calorimeter with a glass pipette drawn to a fine, flexible end. Indium exhibits bulk characteristics at this size, unlike the size-dependent properties of metal nanostructures.¹⁶ Figure 2 shows heat capacity measurements on a 52 nL indium sample, scanned at a heating rate of 150 K/s. The curve shown in Fig. 2 is an average of six calorimetric scans. As determined by the midpoint of the peak, the melting point T_m was 155 °C and compares well with the bulk value²⁰ $T_m = 156.6$ °C. The precision of the technique is high; the standard deviation of T_m was less than 0.1 K for these six measurements and the full width at half maximum (FWHM) of the melting peak is less than 1.3 K. The power sensitivity of this measurement was $\pm 7 \mu\text{W}$.

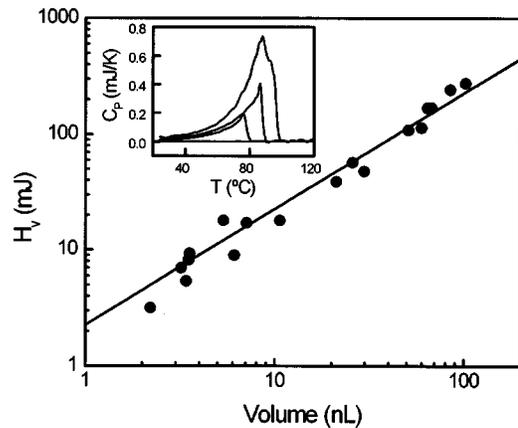


FIG. 3. Nineteen water droplets and the heat it took to vaporize each one. The initial volume of the droplets ranged from 2 to 100 nL. (1 nL = 1 μg). The inset graph shows the heat capacity of three droplets, 2, 3, and 7 nL in size, and of the calorimeter with no sample. The measured H_v was 2250 ± 500 J/g (solid line), compared with the bulk value of H_v of 2260 J/g.

The size of the indium sample is comparable to solder bumps (diam = 200 μm) used in flip-chip microelectronic interconnects. Two independent methods were used to obtain the mass of the sample: a change in the heat capacity base line and a conventional analytical microbalance. Since the mass of the sample is comparable to the mass of the calorimeter, there is a large ($\sim 30\%$) increase in the total heat capacity of the system after transferring the indium sample to the calorimeter, as can be seen in the inset of Fig. 2. Assuming the bulk value of specific heat for indium, 0.23 J/g K at 30 °C,¹⁷ we obtain a value of 390 μg for the mass of the In sample using the C_p base-line method, compared to the 373 μg value from the microbalance (Mettler UMT2).

The latent heat of melting is calculated by integrating the area under the heat capacity peak. In this case, the total heat involved is 11 mJ. Using the previously determined mass, we obtain a value of 27.2 J/g for the latent heat of fusion H_m , compared to the bulk value²⁰ of 28.6 J/g. Measured values for H_m were within $\pm 6\%$ over a range of heating rates from 100 to 1100 K/s. Corrections were made to account for the heat lost to the ambient at the slower heating rates.

Most biological studies involve aqueous solutions, and therefore require the study of liquids between 20 and 100 °C. To evaluate the use of this calorimetric device for liquid samples, we measure the vaporization of single, nanoliter-sized water droplets using the calorimeter in both scanning and heat-conductive modes. To obtain a quantitative value for the volume of water for each droplet used for this letter, the droplet was placed on the heater side of the device. This gives an optical microscope a view of the droplet unobstructed by the Si box.

Figure 3 shows the results of a vaporization study of water droplets heated at ~ 100 K/s. Each water droplet was placed on the calorimeter using a syringe coupled to a capillary tube drawn to a $\sim 100 \mu\text{m}$ point. In future designs, microfluidic channels^{18,19} may be incorporated into the device as a sample delivery system. The size of the droplet is determined immediately prior to heating by measuring the diameter of the droplet using a conventional 40 \times optical microscope. The height-to-diameter ratio for water on silicon nitride was previously determined by simultaneously mea-

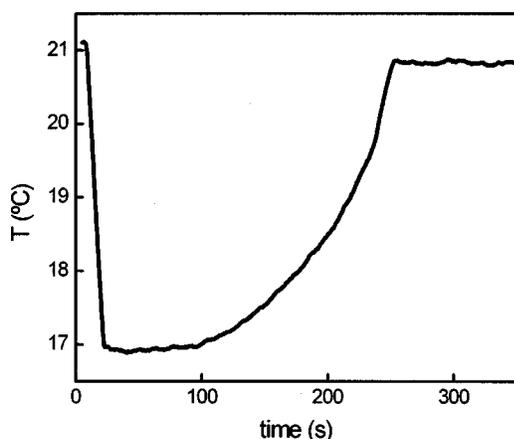


FIG. 4. Passive temperature monitoring of water evaporation. At about $t = 10$ s, a small droplet of water was placed on the calorimeter, and the temperature measured throughout its evaporation. The data are smoothed with a 1.4 s moving average. We find H_v is within 25% of the expected value. Temperature sensitivity in this experiment is ± 13 mK.

asuring the height and diameter of a series of drops using the microscope and a 3 mm \times 3 mm, 45°, Al₂O₃ mirror. Using the measured diameter of the droplet and the height-to-diameter ratio, the volume of the (truncated sphere) droplet is then calculated.

The inset for Fig. 3 shows the C_p vs. T curves for 2, 3 and 7 nL water droplets. Note the increased heat required for vaporization as the size of the droplet increases. Shown in the main figure is the heat of vaporization H_v (area under the C_p peak) for variously sized droplets ranging from 2 to 100 nL. Excellent agreement is obtained for the average value of H_v , 2250 ± 500 J/g (solid line), as compared with the bulk value for water²⁰ $H_v = 2260$ J/g at 100 °C.

The final investigation presented in this letter demonstrates the device operated in the heat-conductive mode, which is especially useful in the study of biological processes occurring near room temperature. For this experiment, a small (~ 60 nL) droplet of water is transferred to the calorimeter, then the temperature of the system is monitored as the droplet evaporates. In this mode, the current used to measure the resistance/temperature of the calorimeter is small, so that the resultant Joule heating is negligible. A typical result is shown in Fig. 4. As the droplet evaporates, heat is consumed, which cools ($\Delta T \approx 5$ K) the calorimeter in proportion to the rate of evaporation. As the size of the droplet decreases, the evaporation rate and cooling rate also decrease, until finally ($t = 240$ s) the temperature of the calorimeter reaches the original ambient conditions.

The value of H_v for the droplet is determined by heating the bare sensor the same amount that the evaporation of the droplet had cooled it. The heat consumed during evaporation is found to be within 25% of the expected amount. Using the heat-conductive mode of the calorimeter, we find the sensitivity of the system can be as high as ± 13 mK or ± 3 μ W. Further improvement of the technique can be gained by using an additional reference calorimeter and measuring the difference in temperature. In this case, the temperature sensitivity is increased to ± 3 mK when measured over 36 000 s (10 h). This would correspond to a power sensitivity of ± 0.7 μ W. Additional gains in sensitivity can also be realized by developing a true differential calorimetric system.²¹

The calorimeter described in this letter can also be used in an enclosed configuration where the entire sensor or just the sample cavity is sealed to prevent undesired evaporation of material during the calorimetric measurements. In preliminary enclosure designs, a single water droplet was stable in size for approximately an hour.

In summary, we have developed a calorimeter that allows us to study systems at sample sizes much smaller than normally accessible to a calorimeter. Intended for use with either liquid or solid samples, this calorimeter is able to measure the latent heat of transformations or simply act as a temperature sensor. Its use has been demonstrated with the melting of indium, by actively vaporizing water droplets, and by passively monitoring temperature during the evaporation of water. The calorimeter can reach sensitivity up to ± 13 mK and ± 3 μ W in a heat-conductive mode and ± 0.1 K and ± 7 μ W in scanning mode. By measuring two calorimeters, the temperature sensitivity in the heat-conductive mode can be increased to ± 3 mK.

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