MICRO-CALORIMETER WITH ENCLOSED PARYLENE CHAMBERS FOR BIO/CHEMICAL APPLICATIONS

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ABSTRACT
We have developed a novel micromachined differential scanning calorimeter (μ-DSC) with an integrated heater, thermopile, and microfluidics, which can accurately measure the temperature within liquid volumes less than 1 µL. The basic structure of the μ-DSC consists of a reaction chamber(s), temperature sensor(s), and heating element(s). The integrated thermopile has a sensitivity on the order of 55 μV/K. The time constant for the chamber to equilibrate with air and with a liquid sample is approximately 70 ms and 440 ms, respectively. The utility of the μ-DSC is demonstrated by measuring the phase transition of DNA and a hydrocarbon.

KEYWORDS: DSC, DNA melting, thermopiles, temperature sensors

INTRODUCTION
A differential scanning calorimeter (DSC) is a device that measures the amount of heat required to raise the temperature of an unknown sample with respect to a known reference. Many biological molecules exhibit endothermic and exothermic properties over a range of temperatures, such as protein denaturization or DNA melting, and can be characterized with DSC. Micromachined DSCs (μ-DSC) have advantages over macroscale DSCs because they use smaller liquid volumes resulting in smaller thermal mass and faster operation, use less sample consumption (low cost), and can be built in arrays to provide parallel operation. Existing micromachined DSCs for liquid samples either use a hybrid membrane and bulky microfluidic channels approach that severely increases the thermal mass [1,2] or are open to the atmosphere [3], making samples susceptible to evaporation. In contrast, we have fabricated an integrated μ-DSC with enclosed parylene chambers that minimizes the thermal mass of the chamber, improves the thermal isolation, and prevents liquid sample evaporation.

OPERATION PRINCIPLE AND DEVICE FABRICATION
A DSC consists of two identical reaction chambers, temperature sensors, and heaters. The temperature between a reference and sample is continuously monitored while heat is applied to the two chambers. By recording the heat required to minimize the temperature difference between the reference and sample, thermodynamic properties of the sample can be extracted. Phase changes such as DNA melting or protein denaturation can easily be detected with DSC. To create a μ-DSC, we micromachined two chambers with an integrated thermopile and heaters as shown in
Figure 1. Overview of the micromachined differential calorimeter. Shown are a perspective view of the reaction chamber (a), a cross-sectional view (b), a top view of the μ-DSC (c), and the integrated heater/thermopile on the reaction chamber (d).

Figure 1.

An anisotropic silicon wet etch was used to form and isolate the reaction chambers from the silicon substrate, improving their thermal isolation. A polyimide film was temporarily bonded to the wet anisotropic etch holes (honeycomb SiN membrane), enclosing the chambers and microfluidic channels. A parylene thin film was then deposited to coat the reaction chambers and microfluidic channels and afterwards the temporary polyimide film was removed. Thermopiles (aluminum/nickel) and heaters (aluminum) were integrated into the reaction chambers through shadow masks to complete the micromachined DSC. The integrated thermopile had a sensitivity on the order of 55 μV/K. The time constant for the chamber to equilibrate with air and with a liquid sample was approximately 70 ms and 440 ms, respectively, as shown in Figure 2. Other thermal parameters (e.g., the thermal resistance and thermal mass of the chambers) can be extracted from a step response analysis of the μ-DSC.

Figure 2. Step response measurement to extract thermal properties of the device such as time constants, thermal resistance, and thermal mass. τ1 and τ2 are estimated at 63% of the steady state temperature value. a1 and a2 in (b) are the steady state values, and b1 and b2 are 1/τ. Thermal mass can be extracted from the slope at the time the step initiated.
EXPERIMENTAL RESULTS

As an example application, Figure 3 shows measurements from a scan of 500μM 12-mer (5'-CGCGAATTCGCG-3') Dickerson sequence DNA and hydrocarbon, respectively. The measured melting temperature of the DNA from the μ-DSC (Figure 3a) is 66 °C and shows good agreement with the measured data from a commercial DSC (not shown). Figure 3b shows the phase transition of a 1 nL volume of hydrocarbon directly mounted on the integrated thermopile. These data show that the μ-DSC can be used to detect phase transitions from molecules of chemical and biological interest, ultimately in a high throughput format.

![Figure 3. Scan data from the μ-DSC for (a) 12-mer DNA and (b) hydrocarbon.](image)

CONCLUSIONS

We have demonstrated and characterized a μ-DSC with integrated closed-control system for bio/chemical applications. As shown in Figure 3, the system can detect molecular transitions within nanoliter samples. This device could be used in industrial biomolecular high throughput screening applications or as a tool for basic biomedical research.

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