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High sensitivity microwave characterization of organic molecule solutions of nanoliter volume

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A microwave resonator composed of a sapphire cylinder and a quartz plate with a 400 nl cavity was developed for the determination of the complex permittivity of liquids at 10 GHz. This sensor was calibrated over a wide range of values for real and imaginary parts of permittivity. The measured resonator losses induced by the liquid were found to be proportional to the dipole relaxation time of the liquid molecules, as predicted by perturbation theory. Our analysis of weight concentration and temperature dependence of the measured inverse quality factor revealed a sensitivity of about 0.1% for aqueous solutions of glucose. © *2009 American Institute of Physics*. [DOI: 10.1063/1.3097015]

The precise and fast determination of the concentration of solvents in diluted aqueous solutions of organic solvents has a great application potential in medicine, biology, and food industry.[1–3] Recently, we showed that whispering gallery mode dielectric resonators can be used to detect water droplets with a volume as small as 100 pl and even determine concentrations below 5% for various aqueous solutions.[4] However, droplets of ultrasmall volume of different liquids under test are not sufficiently constant and an expensive spotting-positioning system is required. Therefore, a microfluidic system compatible approach is of interest. Kim *et al.*[5] showed that the concentration of glucose in water can be determined by a ceramic dielectric resonator with a sensitivity of 3% from frequency shifts for a liquid volume of 4 μl, but with strong temperature control requirements.

In this contribution, we report about a flip-chip approach where a simple quartz disk together with a liquid cavity (representing a simple microfluidic system) is combined with a high-Q whispering-gallery sapphire resonator at a frequency of about 10 GHz. We choose quartz as a low-loss material with micromachining capability,[6] which represents an essential requirement for a reasonable material combination comprising sufficiently high-Q. For simplicity, we employed a c-axis oriented quartz wafer of 1 mm thickness [Fig. 1(a)] with a single cavity of 1 mm diameter and 0.5 mm in height prepared by ultrasound machining. The position of the cavity was optimized with respect to the calculated field distribution (MICROWAVE STUDIO software by CST) shown in Fig. 1(b). The quartz wafer and a c-axis oriented sapphire disk of the same diameter as the quartz wafer were attached and fixed by a screw inside the central hole in both parts. The flip-chip assembly was mounted inside a semiopen copper housing.

The dielectric resonator was excited in a whispering gallery mode resonance of type $HE_{121\delta}$ at a resonant frequency of 11.62 GHz [Fig. 1(b)]. This frequency represents a reasonable trade-off between low losses of sapphire, resonator dimensions, and availability of moderate-cost microwave electronics. The selection of mode was performed with respect to high Q, high electric field strength at the position of the liquid reservoir, and electric field lines parallel to the flat surface of the cylindrically shaped liquid volume. This field geometry provides a very high electric field strength inside the liquid volume even in the case of a high-permittivity liquid such as water [Fig. 1(b)], because dielectric screening is less efficient for curved surfaces than for flat surfaces.

With this assembly we achieved a Q factor of 1.1×10^5, which was close to the maximum achievable value determined by the intrinsic dielectric losses of sapphire.[7] The cavity was filled with the test liquid of 400 nl volume by a Hamilton syringe-micropipette. Liquid induced changes of resonant frequency Δf, inverse quality factor $1/Q$, and change of transmission coefficient S_{21} were measured with an Agilent N5230A vector network analyzer. Complex permittivity measurements were performed by an Agilent coaxial probe technique on larger volumes.

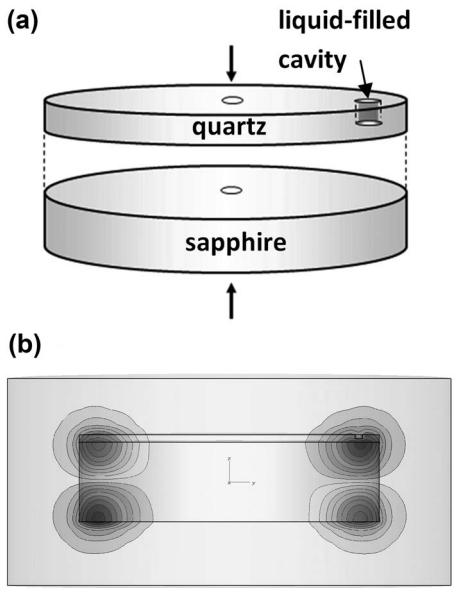

FIG. 1. (a) Flip-chip high-Q resonator: bottom part—whispering-gallery sapphire disk, upper part—a c-axis oriented quartz wafer with nanoliter cavity and; (b) simulated distribution of the electric field amplitude at resonance showing the optimum position of the cavity filled with a test liquid.

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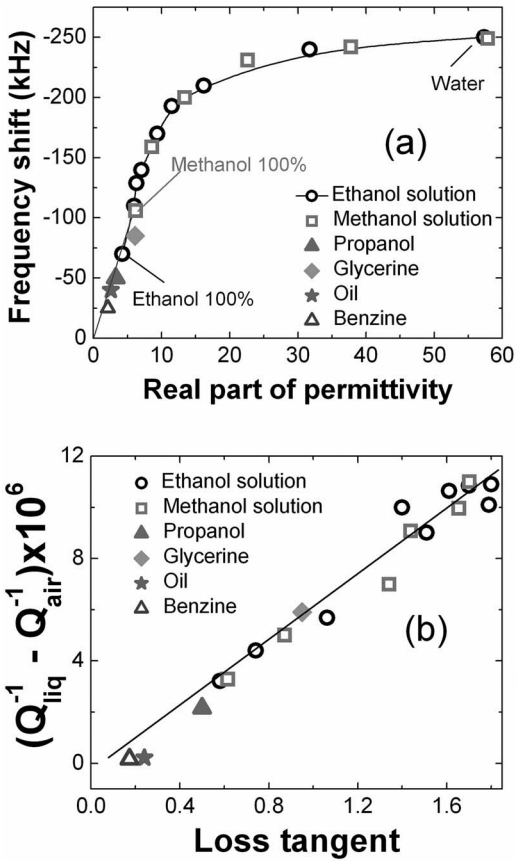

FIG. 2. Measured liquid induced changes in (a) frequency shift $\Delta f_{\text{liq-air}} = f_{\text{liq}} - f_{\text{air}}$ as a function of a real part of permittivity of liquids under test selected to cover a wide epsilon range and (b) inverse quality factor $1/Q_{\text{liq}} - 1/Q_{\text{air}}$ as a function of loss tangent (T=24 °C).

Figure 2(a) shows the measured liquid induced frequency shift value of the resonator with respect to air ($\Delta f_{\text{liq-air}} = f_{\text{liq}} - f_{\text{air}}$) as a function of the real part of permittivity ε' for aqueous solutions of ethanol and methanol, pure glycerine, oil, and benzene. Figure 2(b) shows the corresponding resonator loss values (liquid induced change in inverse quality factor) as a function of the loss tangent $\tan\delta = \varepsilon''/\varepsilon'$ (ε'' is the imaginary part of the permittivity). The results indicate that real and imaginary parts can be clearly separated. The losses are proportional to the loss tangent, but the frequency shift shows a stronger dependence on ε' for small values of permittivity. This demonstrates that for diluted aqueous solutions the losses are much more sensitive to concentration changes than the frequency shift.

Such behavior can be understood qualitatively by Slater's perturbation formula in its most general form for the case of nonmagnetic materials[8]

$$\frac{\Delta f}{f} = -\frac{1}{4W}\int_{V_L} (\vec{D}_1^*\vec{E}_0 - \vec{D}_0\vec{E}_1^*)dV$$
$$= -\frac{\frac{1}{4}\varepsilon_0}{4W}\left[\int_{V_L} (\varepsilon' E_1 E_0 - E_1 E_0)dV\right]$$
$$\approx -\frac{\varepsilon_0 V_L E_0^2}{4W}[(\varepsilon' - 1)(E_1/E_0)]. \quad (1)$$

In Eq. (1), D_1 and E_1 represent displacement current and electric field with perturbation and D_0 and E_0 without, respectively, W is the stored resonator energy, ε_0=8.85 $\times 10^{-12}$ F/m, and V_L is the volume filled with liquid. For low permittivity liquids (typically lower than permittivity of sapphire), dielectric screening is negligible ($E_1 = E_0$), corresponding to the observed linear dependence according to Fig. 2(a). For higher values of permittivity, screening becomes more significant ($E_1 < E_0$), leading to a weaker dependence of frequency shift on permittivity. In case of an electric field perpendicular to a flat air-liquid interface $E_1 = E_0/\varepsilon'$, such that the frequency shift becomes nearly independent of ε' according to Eq. (1), in qualitative agreement with the experimental results shown in Fig. 2(a).

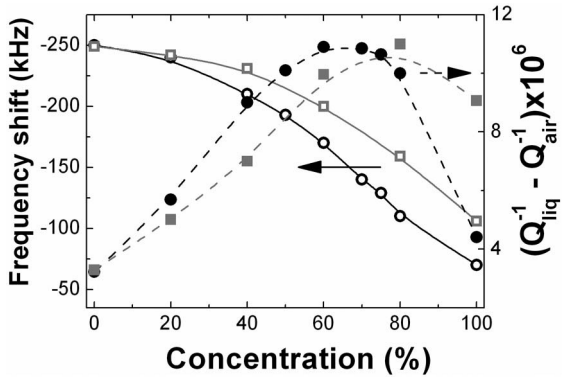

FIG. 3. Measured solution induced changes of frequency shift $\Delta f_{\text{liq-air}}$ and inverse quality factor $1/Q_{\text{liq}} - 1/Q_{\text{air}}$ as a function of ethanol and methanol solution concentration (T=24 °C): circles—ethanol solutions and squares—methanol solutions.

For the change of inverse quality factor, the incremental frequency rule applies,[9] such that

$$\Delta\left(\frac{1}{Q}\right) = \left|\frac{\Delta f}{f}\right| \tan\delta, \quad (2)$$

with $\tan\delta = \varepsilon''/\varepsilon'$ being the loss tangent. Equation (2) explains qualitatively the observed linear dependence for liquids with permittivity above 10 and the sublinear dependence observed for oil, glycerine, benzene, and highly concentrated methanol, according to Fig. 2(b).

Figure 3 shows the measured frequency shift and change of the inverse quality factor as a function of concentration for aqueous solutions of methanol and ethanol. As expected from our previous considerations, changes of the inverse Q represent a highly sensitive measure of the concentration in case of low concentration values. In order to demonstrate the high sensitivity of our technique for an aqueous solution with high relevance for biosensor applications, we have measured diluted solutions of glucose. The measured solid linear curve shown in Fig. 4(a) shows the transmission coefficient at resonance S_{21}, which apparently exhibits much less data scattering than the linear frequency shift curve [dashed line in Fig. 4(a)]. From measurements of the temperature dependence of resonant frequency and quality factor between 18 and 28 °C (not shown in the figure) we found that a change in concentration of 1% corresponds to a frequency shift caused by a temperature change of only 1 mK. This strong effect is caused by the temperature dependence of the permittivity of sapphire, which is about 100 ppm/K,[10] frequency changes due to the temperature dependence of water are very small. In strong contrast, for the temperature variation in the liquid induced change of the inverse quality factor the temperature dependence of the losses of the empty resonator can be neglected, because of the extremely low losses of sapphire and

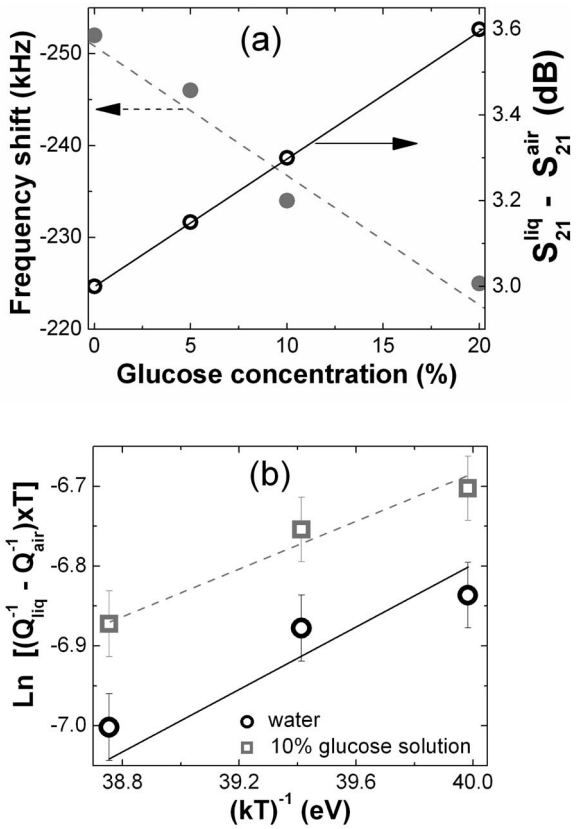

FIG. 4. (a) Measured solution induced changes of resonant frequency $\Delta f_{\text{liq-air}}$ and change of transmission coefficient $S_{21}^{\text{liq}} - S_{21}^{\text{air}}$ as a function of glucose concentration (T=24 °C); (b) Logarithm of inverse quality factor change $1/Q_{\text{liq}}$-$1/Q_{\text{air}}$ multiplied by T as a function of inverse energy kT. The solid line represents calculation results using Eq. (4) for ΔH=0.196 eV corresponding to water.

high losses of water in the range of 10 GHz. To prove this assumption, we analyzed the theoretically expected temperature dependences. The complex permittivity $\varepsilon^*(\omega)=\varepsilon'(\omega)+i\varepsilon''(\omega)$ of aqueous solutions in the microwave regime can be well described by the Debye formula

$$\varepsilon'(\omega) = \varepsilon_\infty + \frac{\varepsilon_s - \varepsilon_\infty}{1+\omega^2\tau^2} \quad \varepsilon''(\omega) = (\varepsilon_s - \varepsilon_\infty)\frac{\omega\tau}{1+\omega^2\tau^2}, \quad (3)$$

where $\varepsilon_s=\varepsilon'(\omega\to 0)$ represents the static permittivity and τ the relaxation time of the water dipole. According to broadband measurements on diluted solvents of organic molecules such as glucose and alcohol, ε_s decreases, but τ increases upon increasing the concentration.[11,12] In contrast, for nonorganic salt solutions, τ exhibits only a very weak dependence on concentration.[13] Therefore, from measurement of the relaxation time the concentration determination of organic molecules in biological liquids will not be masked by variation in the salt content.

Since the optical permittivity of water $\varepsilon_\infty \approx 4$ is rather small in comparison to real and imaginary parts of permittivity at 10 GHz (ε'=60.616 and ε''=32.789 at T=20 °C),[14] the loss tangent

$$\tan\delta(\omega,T) \approx \omega\tau(T) = \omega\tau(300\ K)\frac{300K}{T}\exp\left(\frac{\Delta H}{k}\frac{300K}{T}\right) \quad (4)$$

is proportional to the dipole relaxation time, which exhibits a temperature dependence resembling thermal activation, comprising a room temperature value of the relaxation time τ (300 K) of 8 ps and a value for the relaxation enthalpy ΔH of 0.196 eV.[15] Since the change in inverse quality factor is proportional to tan δ according to perturbation theory [see Eq. (1)], we expect that $\Delta(1/Q)$ should exhibit a temperature dependence according to Eq. (4). Figure 4(b) shows the corresponding temperature measurements for water and a 10% glucose solution, the slope for water is in very good agreement with the literature value of ΔH.[15] Notice that the data scattering apparent in Fig. 4 is caused by the uncertainty of the liquid volume in our open liquid cavity shown in Fig. 1, which would disappear completely in a closed microfluidic system.

Therefore, the maximum achievable sensitivity for concentration determination according to the Fig. 4(b) is determined by the temperature dependence of the relaxation time of the liquid. From the vertical displacement between the linear temperature curves for pure water and for the 10% glucose solution in Fig. 4(b) one can estimate that a temperature change by 6.5 K causes the same effect as a concentration change by 10%. Considering the linear characteristics indicated by Fig. 4(a), we can conclude that for a practical microfluidic glucose sensor with temperature being stabilized to 10 mK, the expected sensitivity corresponds to a glucose concentration of 0.15 ppt. For the current setup the limitation of sensitivity is determined by the resolution of amplitude measurements, which is about 0.01 dB corresponding to a weight concentration sensitivity of 0.1%.

In summary, we have studied the molecular relaxation time from microwave loss measurements of diluted aqueous solutions of organic molecules of nanoliter volume liquid using our developed flip-chip resonator technique. The slope of $\Delta(1/Q)$ as a function of temperature for water is in very good agreement with the literature data. Our analysis of concentration and temperature dependence of the resonator losses in the framework of the Debye model revealed a sensitivity of 0.1% for concentration measurements on aqueous solutions of glucose of 400 nl volume. Due to compact size, relatively low cost and short measurement time our developed high-sensitive flip-chip resonator can be used in medicine, chemistry and biology.

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