

A nanoscaled contactless thermometer for biological systems

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We report on a systematic approach to exploit the potential of filled carbon nanotubes (CNT) to act as sensors that might provide non-invasive temperature control in biological systems on a cellular level. In this case the temperature is detected by measuring NMR parameters on the filling materials. The beneficial feature of a carbon nanotube is to provide protection of both (i) a human body against toxic adverse effects from the filling material and (ii) a filling material against chemical and biochemical exposure. The feasibility of this concept has been demonstrated on the example of the temperature-dependent NMR frequency and relaxation time measured on the CNT filled with the appropriate sensor materials.

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1 Introduction

There is a fastly increasing interest in applying carbon nanotubes (CNT) in biomedicine since the carbon shells provide protection of materials inside CNT and the biological environment against each other. In addition, the carbon shell enhances the possibilities for exohedral (e.g. bio-)functionalisation (cf., e.g., [1, 2]). It has been shown that CNT can penetrate a cell membrane and enter the cells [3, 4]. Being filled with tailored materials such as drugs or diagnostic agents, they can hence act as nanosized chemically and mechanically stable containers for biological applications.

In the work at hand we describe the potential application of CNT for transferring a nanothermometer into the individual cell. One application of a thermometer working on the cellular level is the temperature control during a hyperthermia treatment of cancerous tissue, which is based on the fact that tumour cells are killed when a temperature achieves 41–42 °C degree. In practice, however, it is difficult to provide uniform heating throughout the cancer tissue. Therefore, in order to avoid ineffective treatment due to insufficient heating or healthy tissue coagulation caused by overheating it is necessary to locally control the temperature. We hence propose a biocompatible thermometer as a carbon nanotube filled with a temperature sensor material where temperature is detected by a spectroscopic way, in this case, by NMR [5]. There is a quantity of such materials which might show strong temperature dependencies of NMR parameters, i.e. so-called NMR thermometers (see, e.g., [6]). This approach is of advantage because various NMR active isotopes can be probed within one substance (e.g. ¹H, ¹³C) and different NMR characteristics can be investigated (e.g. NMR shift, relaxation times, J-coupling, quadrupolar splitting or linewidth). In this work we present temperature variable NMR measurements of the filled CNT thereby

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demonstrating that the realization of such a carbon coated nanothermometer becomes feasible. Experimental evidence is provided by the temperature dependencies of NMR frequency shift and spin-lattice relaxation time measured on multi-walled CNT (MWCNT) filled with Co, Fe, CuI and single-walled CNT (SWCNT) filled with AgCl.

2 Experimental

In order to synthesize ferromagnetically filled CNT an in-situ process was applied. The CNT grow on a substrate by pyrolysis of the metal organic precursor. The detailed synthesis route is described in Ref. [7]. For this study cobalt- and iron-filled MWCNT were produced with a high filling up to 45 wt%. Metal halides (CuI and AgCl) filled CNT were produced by a wet chemistry route. For filling with CuI the MWCNT were opened using a procedure described in Ref. [8]. CuI was transported into the opened carbon nanotubes at 600 °C thanks the capillarity effect. This sublimation method yielded filling of ca. 90% of available nanotube inner space. In order to obtain AgCl-filled CNT a simple chemical replacement reaction was performed in the interior of SWCNT where a nitrate ion of silver salt was replaced by a chloride ion [9]. The resultant materials and filling yields were characterized by TEM, X-ray diffraction and EDX analysis. The transmission electron micrographs are presented in Fig. 1.

For NMR measurements CNT powder was loaded into a 2 mm o.d. quartz glass tube and tightly closed. The ferromagnetically filled CNT were measured in a zero external magnetic field in a frequency range of 205–230 MHz for ^{59}Co NMR and of 44.6–46.2 MHz for ^{57}Fe NMR. The spectra as well as spin-lattice relaxation times T_1 in CuI-CNT were measured on both ^{63}Cu and ^{127}I nuclei in an external magnetic field of 7.05 T. In AgCl-CNT both magnetic nuclei ^{35}Cl and ^{109}Ag were probed in a field of 9.2 T. The NMR spectra were obtained by a Fourier transformation of a spin echo. T_1 were measured employing an inversion recovery pulse sequence. The recovery of ^{63}Cu , ^{127}I and ^{32}Cl magnetization curves was analyzed and found in all cases to follow a simple exponential form characterized by a single

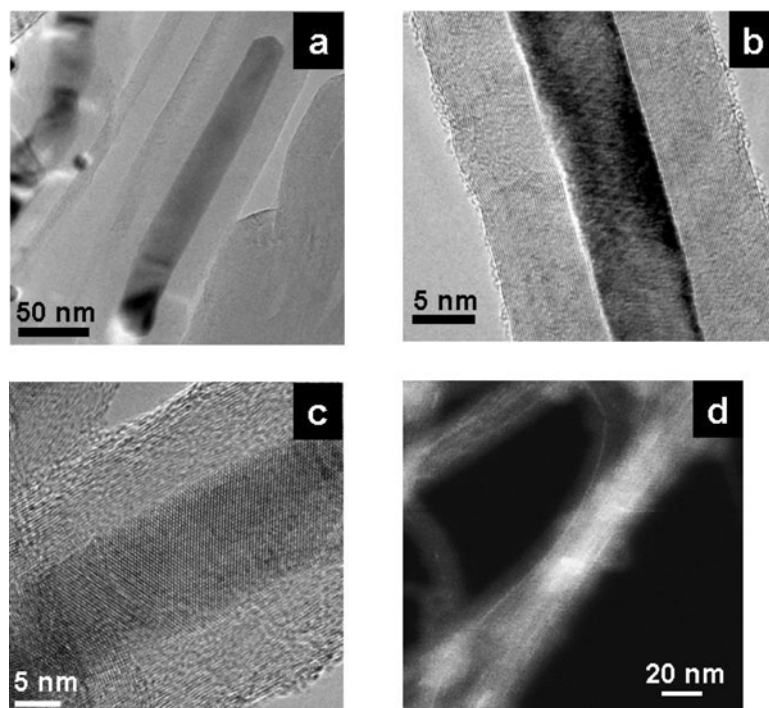


Fig. 1 TEM images of (a) cobalt-, (b) iron-, (c) CuI- and (d) AgCl-filled CNT.

spin-lattice relaxation time. All temperature variable measurements were carried out between 5.5 K and 320 K. Additionally, NMR signals from the empty quartz glass tube were tested at appropriate frequencies in order to guarantee that no signals from glass tubes or surrounding electronics do contribute to the measured NMR spectra.

3 Results and discussion

Due to very low sensitivity and low abundance in nature of a ^{57}Fe nucleus only a weak ^{57}Fe NMR signal (not shown here) was observed in iron-filled CNT after four hours of accumulation time at room temperature. The long measurement time and the low signal-to-noise ratio makes ^{57}Fe NMR spectroscopy an inefficient tool for thermometry, particularly, in the temperature range of the biological interest, i.e. $\sim 300\text{--}320\text{ K}$.

The temperature variable ^{59}Co NMR spectra of Co-filled CNT are presented in Fig. 2 together with the spectra measured on the reference metallic cobalt powder. Both samples show the remarkably intense signals resulting from 100% of natural abundance and high sensitivity of a ^{59}Co nucleus. A temperature shift of a highest peak in the ^{59}Co NMR spectrum (Fig. 2a) arising from domains in hexagonal close-packed (hcp) cobalt [10] renders a high temperature sensitivity parameter of 26 kHz/K that provides a prerequisite for the application of Co-based nanothermometers. However, the ^{59}Co NMR spectrum of Co-CNT (Fig. 2b) is broadened and unresolved due to the distribution of the resonance frequencies resulted from distribution of sizes and shapes of encapsulated cobalt. This fact depreciates accurate temperature detection by virtue of a Co-based carbon coated nanothermometer and necessitates a development of the new synthesis and purification routes, which can yield homogeneous uniform size CNT filled with cobalt.

Figure 3a shows the temperature dependence of the resonance frequencies measured on ^{63}Cu and ^{127}I nuclei in CuI-filled CNT as well as on the ^{35}Cl nucleus in AgCl-filled SWCNT. The ^{109}Ag signal from the latter was not observed due to very long relaxation time and very low receptivity of the ^{109}Ag isotope. The analysis of the ^{63}Cu frequency shift reveals insignificant changes with the temperature, while the resonance frequencies measured on ^{127}I and ^{35}Cl nuclei indicate a visible dependence on temperature caused by lattice effects which include both the lattice vibration and the lattice expansion [11]. The temperature dependencies of the ^{63}Cu , ^{127}I and ^{35}Cl spin-lattice relaxation rates T_1^{-1} are presented in Fig. 3b. This behaviour is in a very good agreement with the law $T_1^{-1} \propto T^2$ expected for a Raman two-phonon quadrupolar process [12]. It is consistent with a quadrupolar mechanism for the relaxation. The tem-

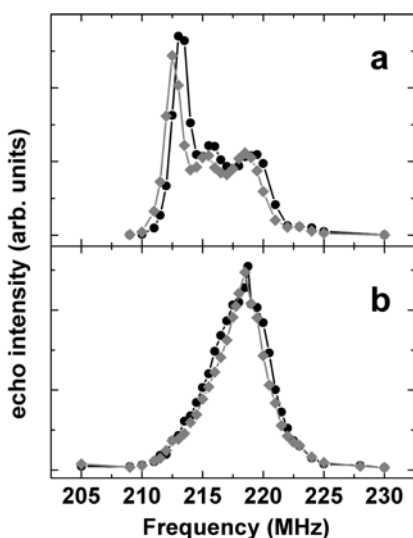


Fig. 2 ^{59}Co NMR spectra of (a) metallic Co powder and (b) Co-filled MWCNT. Dark symbols and line correspond to spectra at 295 K, light ones to spectra at 320 K.

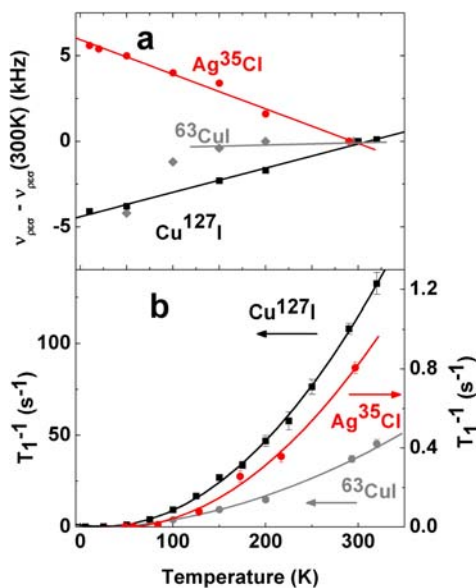


Fig. 3 (online colour at: www.pss-b.com) (a) NMR frequencies and (b) spin-lattice relaxation rates of CuI- and AgCl-filled CNT plotted versus temperature.

Table 1 Nanothermometers and temperature sensitivity parameters.

material	nucleus	T sensitivity of NMR parameter	
		dV_{res}/dT (Hz/K)	$d(T_1^{-1})/dT$ (s^{-1}/K)*
CuI-CNT	^{63}Cu	–	0.27
	^{127}I	14	0.52
AgCl-CNT	^{35}Cl	21	0.006

* Defined in the temperature range of 300–320 K.

perature sensitivity parameters which serve as a quantitative indicator for the efficacy and accuracy of a thermometer are calculated from the slope of the fitting functions and summarized in Table 1. The data show that the ^{127}I spin-lattice relaxation rate in CuI-CNT indicates the more pronounced gradient and is, consequently, more sensitive to the temperature variation providing an accuracy in temperature determination of 2 K. Further other materials have to be probed as a possible filling of CNTs in order to invent novel nanoscaled thermometers with a significantly higher accuracy.

4 Conclusion

We have shown the feasibility of filled CNT for a contactless temperature control in biological systems. Various temperature sensors were filled into CNT and experimental evidence of the carbon coated nanothermometers was provided by measuring the temperature dependencies of the NMR resonance frequency and the T_1 relaxation time. The most temperature sensitive parameter is found to be the ^{127}I spin-lattice relaxation rate in CuI-CNT which can provide the temperature detection with an accuracy of 2 K.

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