The Gadonanotubes (GNTs) are the highest-performing T1-weighted MRI contrast agent material known with a relaxivity of ~160 mM⁻¹ s⁻¹ per Gd³⁺ ion at 1.5 T. In this work, the contribution of carbon-based free radicals at defect sites on the sidewalls of the ultra-short carbon nanotube (US-tube) component of the GNTs to the T₁ relaxation time has been investigated by Nuclear Magnetic Resonance Dispersion (NMRD) and Electron Paramagnetic Resonance (EPR) studies. The NMRD results indicate that carbon-based radicals of the US-tube structure substantially shorten water proton spin-lattice relaxation times at low frequencies (~1 MHz) and that the high water proton relaxation rate for the GNTs at these fields does not result from the Gd³⁺ ion alone. Furthermore, a computational study suggests that the defect sites of the US-tube structure increase nanotube strain and create new interband electronic states. While the presence of Gd³⁺ ions at the defect sites for the GNTs do not induce new electronic states, they do introduce a shift in the Fermi level to higher energy (0.4 eV).

Magnetic Resonance Imaging (MRI) has become a standard clinical tool to obtain human anatomical and functional information non-invasively. However, it is sometimes difficult to differentiate adjacent tissues with similar image intensities. This problem may be overcome by using chemical contrast agents (CAs) that change the local MRI signal intensities by modifying nuclear Spin-Relaxation (SR) rates, and therefore, intensities in imaging protocols run in partially-saturated modes. Paramagnetic and superparamagnetic materials are used as CA materials for magnetic resonance (MR) based techniques. The efficacy of an MRI CA is characterized by its relaxivity (r₁), which is the relaxation rate constant normalized to the concentration of the CA. These image-brightening agents shorten the water proton Spin-Lattice Relaxation (SLR) time (T₁) by the magnetic coupling of their paramagnetic centers to the surrounding water proton spin. Gadolinium ion (Gd³⁺) has been the most predominantly used paramagnetic CA owing to the presence of an S = 7/2 ground spin, a slow electronic relaxation rate for the ground state and biocompatible hydrophilic chelate compounds of Gd³⁺ that have favorable excretion rates, low toxicities, and favorable biodistributions. The use of Gd³⁺-based contrast agents (GBCAs) to enhance the sensitivity and specificity of MRI has been part of clinical practice for over 2 decades. GBCA stability is an important consideration because free Gd³⁺ ions are toxic, and they form insoluble Gd(OH)₃ at physiological pH.

Gd³⁺-ion complexes of polyaminocarboxylic acid ligands constitute the most important class of commercially-available MRI CAs. Despite the progress that has been made in CA development, some linear chelates can release toxic Gd³⁺ ions via transmetalation reactions with other metal ions in the body which can cause nephrogenic systemic fibrosis (NSF) in patients with severe kidney disease or damage. Although most current clinically-used GBCAs have excellent safety profiles, they also possess very low relaxivities of only ~4–5 at 1.5 T and 37°C. If relaxivities can be substantially increased, image quality can be improved so dose reduction and greater safety can be achieved. Therefore, more highly-performing CAs at both high and low magnetic-field strengths might provide significant advantages.

© The Author(s) 2017. Published by ECS. This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 License (CC BY, http://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse of the work in any medium, provided the original work is properly cited. [DOI: 10.1149/2.030170jss] All rights reserved.

The Gadonanotubes (GNTs) in 2005 brought light a new method for sequestering Gd³⁺ ions by encapsulating them within (or upon) ultra-short carbon nanotubes (US-tubes), as shown schematically in Figure 1a. This new carbon nanostructure with a relaxivity as high as 160 mM⁻¹ s⁻¹ per Gd³⁺ ion at 1.5 T and 37°C is the highest-performing GBCA material discovered to date. This CA has been investigated by X-ray absorption spectroscopic analysis, which demonstrated that the Gd³⁺ ions are coordinated to ~9 oxygen atoms. Thus, there is potentially a large number of water molecules coordinated to each Gd³⁺ ion, while the small size of the Gd-O₉ unit suggests an environment conducive for coordinated water protons to be simultaneously relaxed by more than one Gd³⁺ ion. The lack of Gd³⁺-ion leakage from the GNTs under physiological challenge is consistent with the known hydrolysis chemistry of lanthanide ions at pH ≥ 5 to produce μ-oxo-bridged polymeric structures similar to the crystallographically-characterized Nd³⁺-ion cluster grown from aqueous solution at pH = 7.18. Similar large μ-oxo-bridged Gd³⁺-ion clusters within (or upon) the GNTs are consistent with their ability to retain individual Gd³⁺ ions under physiological conditions (PBS, pH = 7.4). While the current trend in MRI will likely continue toward higher fields (>1.5 T), open-low-field MRI(21,22) (between 0.1 and 1 T) and ultra-low-field MRI(23,24) (<150 μT) offer advantages for some situations. Low-field MRI scanners are not only cost-effective but are advantageous when imaging in the presence of metal implants, where large and expensive magnets might be impractical and for patients who suffer from claustrophobia. The low-field penalty is a low Signal-to-Noise-Ratio (SNR), which translates to lower resolution for practical imaging times. Although the use of GBCAs is a common practice to improve SNR at high fields by reducing the SLR time (and therefore, the recycle time or TR), a higher dose of CA must be administered to patients at low fields because the intrinsic SLR rate is lower and the clinical agents have little or no magnetic-field dependence at low-field strengths, as shown in Figure 1b for the clinical agent, Magnevist. However, high doses may cause problems with toxicity and tolerability.

In a T₁-weighted image, the signal intensity of the voxel will be inversely proportional to the T₁ of the water protons contained within that voxel. The observed relaxation time is the sum of the

The Gadonanotubes (GNTs) are the highest-performing T₁-weighted MRI contrast agent material known with a relaxivity of ~160 mM⁻¹ s⁻¹ per Gd³⁺ ion at 1.5 T. In this work, the contribution of carbon-based free radicals at defect sites on the sidewalls of the ultra-short carbon nanotube (US-tube) component of the GNTs to the T₁ relaxation time has been investigated by Nuclear Magnetic Resonance Dispersion (NMRD) and Electron Paramagnetic Resonance (EPR) studies. The NMRD results indicate that carbon-based radicals of the US-tube structure substantially shorten water proton spin-lattice relaxation times at low frequencies (~1 MHz) and that the high water proton relaxation rate for the GNTs at these fields does not result from the Gd³⁺ ion alone. Furthermore, a computational study suggests that the defect sites of the US-tube structure increase nanotube strain and create new interband electronic states. While the presence of Gd³⁺ ions at the defect sites for the GNTs do not induce new electronic states, they do introduce a shift in the Fermi level to higher energy (0.4 eV).

Magnetic Resonance Imaging (MRI) has become a standard clinical tool to obtain human anatomical and functional information non-invasively. However, it is sometimes difficult to differentiate adjacent tissues with similar image intensities. This problem may be overcome by using chemical contrast agents (CAs) that change the local MRI signal intensities by modifying nuclear Spin-Relaxation (SR) rates, and therefore, intensities in imaging protocols run in partially-saturated modes. Paramagnetic and superparamagnetic materials are used as CA materials for magnetic resonance (MR) based techniques. The efficacy of an MRI CA is characterized by its relaxivity (r₁), which is the relaxation rate constant normalized to the concentration of the CA. These image-brightening agents shorten the water proton Spin-Lattice Relaxation (SLR) time (T₁) by the magnetic coupling of their paramagnetic centers to the surrounding water proton spin. Gadolinium ion (Gd³⁺) has been the most predominantly used paramagnetic CA owing to the presence of an S = 7/2 ground spin, a slow electronic relaxation rate for the ground state and biocompatible hydrophilic chelate compounds of Gd³⁺ that have favorable excretion rates, low toxicities, and favorable biodistributions. The use of Gd³⁺-based contrast agents (GBCAs) to enhance the sensitivity and specificity of MRI has been part of clinical practice for over 2 decades. GBCA stability is an important consideration because free Gd³⁺ ions are toxic, and they form insoluble Gd(OH)₃ at physiological pH.

Gd³⁺-ion complexes of polyaminocarboxylic acid ligands constitute the most important class of commercially-available MRI CAs. Despite the progress that has been made in CA development, some linear chelates can release toxic Gd³⁺ ions via transmetalation reactions with other metal ions in the body which can cause nephrogenic systemic fibrosis (NSF) in patients with severe kidney disease or damage. Although most current clinically-used GBCAs have excellent safety profiles, they also possess very low relaxivities of only ~4–5 at 1.5 T and 37°C. If relaxivities can be substantially increased, image quality can be improved so dose reduction and greater safety can be achieved. Therefore, more highly-performing CAs at both high and low magnetic-field strengths might provide significant advantages.

© The Author(s) 2017. Published by ECS. This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 License (CC BY, http://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse of the work in any medium, provided the original work is properly cited. [DOI: 10.1149/2.030170jss] All rights reserved.

The Gadonanotubes (GNTs) in 2005 brought light a new method for sequestering Gd³⁺ ions by encapsulating them within (or upon) ultra-short carbon nanotubes (US-tubes), as shown schematically in Figure 1a. This new carbon nanostructure with a relaxivity as high as 160 mM⁻¹ s⁻¹ per Gd³⁺ ion at 1.5 T and 37°C is the highest-performing GBCA material discovered to date. This CA has been investigated by X-ray absorption spectroscopic analysis, which demonstrated that the Gd³⁺ ions are coordinated to ~9 oxygen atoms. Thus, there is potentially a large number of water molecules coordinated to each Gd³⁺ ion, while the small size of the Gd-O₉ unit suggests an environment conducive for coordinated water protons to be simultaneously relaxed by more than one Gd³⁺ ion. The lack of Gd³⁺-ion leakage from the GNTs under physiological challenge is consistent with the known hydrolysis chemistry of lanthanide ions at pH ≥ 5 to produce μ-oxo-bridged polymeric structures similar to the crystallographically-characterized Nd³⁺-ion cluster grown from aqueous solution at pH = 7.18. Similar large μ-oxo-bridged Gd³⁺-ion clusters within (or upon) the GNTs are consistent with their ability to retain individual Gd³⁺ ions under physiological conditions (PBS, pH = 7.4).

While the current trend in MRI will likely continue toward higher fields (>1.5 T), open-low-field MRI(21,22) (between 0.1 and 1 T) and ultra-low-field MRI(23,24) (<150 μT) offer advantages for some situations. Low-field MRI scanners are not only cost-effective but are advantageous when imaging in the presence of metal implants, where large and expensive magnets might be impractical and for patients who suffer from claustrophobia. The low-field penalty is a low Signal-to-Noise-Ratio (SNR), which translates to lower resolution for practical imaging times. Although the use of GBCAs is a common practice to improve SNR at high fields by reducing the SLR time (and therefore, the recycle time or TR), a higher dose of CA must be administered to patients at low fields because the intrinsic SLR rate is lower and the clinical agents have little or no magnetic-field dependence at low-field strengths, as shown in Figure 1b for the clinical agent, Magnevist. However, high doses may cause problems with toxicity and tolerability.

In a T₁-weighted image, the signal intensity of the voxel will be inversely proportional to the T₁ of the water protons contained within that voxel. The observed relaxation time is the sum of the...
intrinsic relaxation time of the solvent and the contribution from the CA (Equation 1). The superscripts “OBS,” “SOL,” and “CA” are used to respectively indicate the observed, solvent and contrast agent terms. \( T_{\text{CA}}^{r} \) is modeled as the sum of three independent components (Equation 2). The superscripts “IS”, “SS” and “OS” are used to respectively indicate the inner-, second- and outer-sphere contributions to \( T_{\text{CA}}^{r} \). The relaxation time of water molecules in the inner coordination sphere (i.e., directly coordinated to the paramagnetic metal ion) is expressed as \( T_{\text{IS}}^{r} \). The relaxation time of nearby water molecules is also affected and their contribution to \( T_{\text{IS}}^{r} \) is expressed in two separate terms, \( T_{\text{SS}}^{0} \) and \( T_{\text{SS}}^{S} \).27

\[
\frac{1}{T_{\text{OBS}}^{r}} = \frac{1}{T_{\text{IS}}^{0\text{L}}} + \frac{1}{T_{\text{IS}}^{A}} \tag{1}
\]

\[
\frac{1}{T_{\text{CA}}^{r}} = \frac{1}{T_{\text{IS}}^{S}} + \frac{1}{T_{\text{SS}}^{0}} + \frac{1}{T_{\text{SS}}^{S}} \tag{2}
\]

The observed rate enhancement at high fields is related to several characteristics of the paramagnetic Gd\(^{3+}\) centers, the three most important being the proton/water accessibility and exchange rate with the Gd\(^{3+}\) ions, the relaxation rate of the Gd\(^{3+}\) electron spin, and possibly the rotational mobility of the Gd\(^{3+}\)-ion centers.27 For usual Gd\(^{3+}\) chelate compounds, this relationship is qualitatively described by the Solomon–Bloembergen–Morgan (SBM) equations29 where the first coordination sphere contribution is given approximately by

\[
\frac{1}{T_{\text{IS}}^{1}} = \frac{B^{2}}{T_{\text{IS}}^{A}} \left\{ \frac{3\tau_{\text{ex}}}{1 + \gamma_{1}^{2}\omega_{S}^{2}} + \frac{7\tau_{\text{ex}}}{1 + \gamma_{1}\omega_{S}} \right\} \tag{3}
\]

where \( r_{IS} \) is the intermomen distance, \( B = \frac{2\gamma_{1}\gamma_{S}^{2}B^{2}S}{\gamma_{I}} \) with \( \gamma_{I} \) being the magnetogyric ratio for the nuclear spin and \( \gamma_{S} \) the magnetogyric ratio for the electron spin, and \( S \) the electron spin quantum number, \( 7/2 \) for Gd\(^{3+}\); \( \omega_{S} \), \( \omega_{S} \) are the nuclear and electron Larmor frequencies. The correlation times are given by

\[
\tau_{\text{ex}} = \tau_{\text{ex}}^{1} + \tau_{\text{rotation}} + \tau_{\text{1,2e}} \tag{4}
\]

where the terms correspond to mean exchange lifetime, rotational diffusion of the complexes, and the electron spin \( T_{1} \) and \( T_{2} \). Because \( S \) is large and the electron magnetic moment is 658 times larger than the proton moment and both enter the relaxation equation as the square, the paramagnetic contribution to nuclear relaxation may be five orders of magnitude larger than the proton-proton contribution. Outer-sphere effects where the dipole-dipole coupling between the electron and the nuclear spins is modulated by the relative translational diffusion of the spins are usually not large compared to first-coordination-sphere effects; however, surface effects may amplify these comparatively weak contributions.27

Previously, the GNTs have been proposed for contrast-enhanced low-field MRI applications.30 However, the origin of the magnetic efficiency of the GNTs at lower fields was not well understood. Early studies in 2005 showed a relaxivity of ~600 mM\(^{-1}\)s\(^{-1}\) per Gd\(^{3+}\) ion for the GNTs at very low field.16 This unusually-high relaxivity, along with the steep decrease of \( r_{1} \) from 1–10 MHz in the GNT NMRD profile, suggested the presence of different magnetic-field dependent relaxation mechanisms. In this work, the GNTs and empty US-tubes have been extensively examined by Nuclear Magnetic Resonance Dispersion (NMRD) studies to better characterize the origins of their high relaxivities at both high- and low-magnetic fields. Furthermore, a computational investigation has been undertaken to better understand the possible impact of local charge distribution for different carbon nanotube (CNT) materials, including the GNTs, on their relaxation rate.

Figure 1. GNT production from US-tubes (a). Relaxivity of the GNTs (■) and Magnevist (●) at different magnetic field strengths based on [Gd\(^{3+}\)] = 0.025 mM for Magnevist and GNTs at 1.5 T/37 °C (c). b and c are reprinted by permission from Ref. 16.
Experimental

Preparation of the nanotubes samples.—HiPco SWCNTs were prepared in-house at Rice University. Arc-discharge generated SWCNTs with carbonaceous purity 60–70% were purchased from Carbon Solutions, Inc. The synthesis process utilized Ni and Y as catalysts, and to remove most of the metal catalyst particles, the SWCNTs were purified via bath sonication in HCl (conc.). Next, US-tubes (from both HiPco and Arc) were created via fluorination and pyrolysis using previously established methods.\textsuperscript{39} In solution, US-tubes exist as bundles due to the van der Waals forces between adjacent US-tubes. To produce individualized tubes or small bundles, US-tubes were reduced using Na\textsubscript{0}/THF. The end and defect sites of the reduced tubes were then mildly oxidized by refluxing them with 6 N HNO\textsubscript{3} for 5 min. This process of oxidation is called “opening” the US-tubes. The resulting opened US-tubes were then loaded with Gd\textsuperscript{3+} ions by sonication them in an aqueous solution of GdCl\textsubscript{3} at pH \textsim 3 to produce debundled and opened GNTs.\textsuperscript{10} GNTs (at pH > 5) were collected by filtration and washed multiple times with water to remove excess Gd\textsuperscript{3+} ions adhered to the outer surface. A concentration of 0.05 mg per mL of purified full-length tubes, bundled empty US-tubes, debundled empty US-tubes, and GNTs were dispersed in a biocompatible, and non-ionic pluronic polymer aqueous solution (0.17% w/v) and used for further study.

Concentration analysis.—The Gd\textsuperscript{3+} and Ni\textsuperscript{2+} ion content of the samples was determined using inductively-coupled plasma optical emission spectroscopy (ICP-OES). Briefly, the nanotube samples were treated with 500 µL of ~26% HClO\textsubscript{3} and carefully heated to dryness. The resulting precipitate was dissolved in HNO\textsubscript{3} (2% v/v) and used for ICP-OES analysis. A calibration run was made using Y\textsuperscript{3+} (5 ppm) and Ni\textsuperscript{2+} (5 ppm) as internal standards for the analysis of Gd\textsuperscript{3+} and Ni\textsuperscript{2+}, respectively.

Nuclear magnetic resonance dispersion measurements.—The NMRD data were recorded using a fast field cycling NMR spectrometer FFC-2000 (Stelar s.r.l., Mede, Italy) in the magnetic field interval corresponding to proton Larmor frequencies from 0.01 to 30 MHz. Spins were polarized at 20 MHz and the field cycled rapidly to the relaxation field at which the relaxation rate constant was measured. Following a variable relaxation delay period, the field was cycled to the resonance field with a Larmor frequency of 15.8 MHz for protons, and the free induction decay recorded following a single (5.5 ms) 90\degree excitation pulse applied at 15.8 MHz. The relaxation rate constants at the measurement field were extracted by exponential fits of the free induction decay amplitudes at 15.8 MHz vs the duration of the relaxation period in the measurement field. Samples were contained in 10 mm diameter glass tubes sealed with a rubber stopper and were not degassed; oxygen made an insignificant contribution to the total relaxation rate in these samples. Temperature was maintained at 25 °C using the Stelar VTC90 variable-temperature controller, which was calibrated using an external thermocouple inserted into a surrogate time for the Ni\textsuperscript{2+} ion concentrations found here (below 0.17 mM in all cases), the contribution to the water proton relaxation rate constant is expected to be of order 1 s\textsuperscript{-1} or less. Furthermore, the relaxation dispersion for the electron-SR time for Ni\textsuperscript{2+} is generally at magnetic-field strengths much higher than those used in these studies. Thus, the relaxation contribution from Ni\textsuperscript{2+} ion is both small and constant over the magnetic-field range studied here. Therefore, the contribution of Ni\textsuperscript{2+} to the total paramagnetic relaxation of these samples is neglected.

NMRD profiles for the full-length Arc SWCNT and US-tube samples without added Gd\textsuperscript{3+} ion are shown in Figures 2a–2c and are qualitatively similar. The low-field and high-field portions are linear in the logarithm of the Larmor frequency, and there is a transition region between Larmor frequencies of approximately 1 and 10 MHz. In all cases, the relaxation rates are high and around half of those for the GNTs at similar concentrations (NMRD profiles of different Arc GNT samples at different concentrations are shown in Figure 2S of Supporting Information). Thus, the origin of the high relaxation rates is the coupling of the water protons to the paramagnetic centers in or on the full-length SWCNTs and US-tubes (collectively referred to as nanotubes below). The observation that the low- and high-field regions are linear in the logarithm of the Larmor frequency is the signature of dimensionally-restricted diffusion of the observed water protons in the vicinity of paramagnetic centers.\textsuperscript{31–34} If we use the definition of the 2D translational correlation time as \(\tau_\parallel = \frac{\delta^2}{4D_{\parallel}}\), we can write Equation 5 in terms which are relevant to a solution where water molecules diffuse within a transient layer of some thickness at the surface,

\[
\frac{1}{T_1(\omega)} = \frac{1}{T_{1,bulk}} + \frac{\gamma_\parallel^2 \hbar}{60} S (S + 1) \frac{N_0 [S]}{1000 D_{\parallel} \lambda} x^2 \left[ 3 \ln \left( \frac{1 + \omega_\parallel^2 \tau_\parallel^2}{\omega_\parallel^2 \tau_\parallel^2} \right) + 7 \ln \left( \frac{1 + \omega_\parallel^2 \tau_\parallel^2}{\omega_\parallel^2 \tau_\parallel^2 + 1} \right) \right]
\]

where \(N_0\) is the Avogadro constant and \([S]\) is the molar spin concentration. Here, \(x\) is a parameter which takes into account a variable distance of minimal approach between spins \(S\) and \(\omega\) compared to the molecular size and \(\tau_\parallel\) is the surface or interface residence time. From this, the logarithmic dependence on Larmor frequency becomes clear. Figure 2a includes two parallel straight lines in the highlighted areas as a reference for the eye. Such effects are often observed in high surface area systems where there are usually adventitious paramagnetic centers in the µM concentration range or higher. In the case that is observed here, where water protons may exchange with the bulk water pool, there may be a low-frequency plateau caused by the exchange of water from the restricted diffusion environment into the isotropic bulk environment. The plateau onset provides a measure of the lifetime in the diffusionally-restricted environment. However, in the samples shown here, a low-field plateau is not apparent; therefore, there is no exchange rate limitation on environmental mixing. Furthermore, the persistence of the linear dependence on magnetic field to the lowest-field values indicates that the paramagnetic centers that cause this contribution must have electron SR times that are longer than the effective correlation time for the electron-nuclear coupling, which apparently derives from translational diffusion. If these
Figure 2. The water proton SLR rate constant as a function of the magnetic-field strength shown as the $^1H$ Larmor frequency for purified full-length Arc SWCNTs (a), empty bundled US-tubes (b), empty debundled US-tubes (c), debundled GNTs (d). All concentrations are 0.05 mg of solid dispersed in 1 mL of 0.17 w/v% pluronic aqueous solution. Concentration of Gd$^{3+}$ ions in the GNTs solution is 0.11 mM. Longitudinal axes are different for the purpose of showing clear NMRD profiles for each sample. For an NMRD plot of different CNT-based materials with the same longitudinal axis, see Figure 1S in Supporting Information.

electron spins relaxed rapidly, the electron-spin flips would interrupt the electron-nuclear correlation, and a flat low-field plateau would result below the Larmor frequency of the electron flip rate, which is not observed. The origin of the water entrapment may be of three kinds: inside the nanotubes, on the surface of the nanotubes, or in between the nanotubes in aggregated nanotube clusters or bundles. It is important to note that even though the main concentration of the nanotubes may not be aggregated, a relatively low concentration of aggregated species may dominate the low-field SR dispersion profile.

One attractive hypothesis is that water fills the nanotubes, relaxes by restricted diffusion inside the tubes, and then exchanges with the bulk water pool outside. If paramagnetic centers are inside the tubes, then the effects of restricted diffusion are amplified by the large magnetic moments of the electrons, even if outer-sphere effects dominate. However, the signature of diffusion inside a nanotube, i.e., 1-dimensional diffusion, is a power law in the Larmor frequency and not the observed dependence on the logarithm of the Larmor frequency. Thus, we must conclude that the effect of 1-dimensional water diffusion inside the nanotubes does not make a dominant contribution to the observed water proton SLR profile. For the GNTs, if the Gd$^{3+}$ ions were well inside the nanotubes, one would expect to see the effects of 1-dimensional diffusion reflected strongly in the relaxation dispersion profile. However, this is not the case, which suggests that the Gd$^{3+}$ ions of the GNTs are at the surface defect sites of the nanotube. In fact, hydroxyl or carboxylate group of US-tubes defect sites may well chelate the Gd$^{3+}$ ion clusters and provide many first-coordination-sphere sites for water exchange.

The middle or transition region of the relaxation-dispersion profiles for purified Arc full-length tubes, empty bundled US-tubes and empty debundled US-tubes may reflect the effects of 3-dimensional diffusion of water in the vicinity of the paramagnetic centers which may become important if the paramagnetic centers are not all strongly surface bound. The characteristics of relaxation dispersion profiles for 3-dimensional diffusion are low- and high-field plateaus with a broad dispersion as seen, for example, in Figure 2a. However, it is also possible to achieve this dispersion shape if there are two different classes of entrapped environment for restricted or 2-dimensional diffusion, that is, one on the outside surface and the other one either inside the nanotubes or between aggregated bundles. The present experiments do not permit an easy distinction between these alternatives.

The GNT sample (Figure 2d) has a Gd$^{3+}$-ion concentration of 0.11 mM and the highest water proton SR rate constants of the data shown. This relaxation profile is characteristic of Gd$^{3+}$ ion coordinated to a slowly tumbling environment, and therefore, the contribution from unbound or free aqueous Gd$^{3+}$ ion is negligible. The large SR rate constants and the profile shape are characteristic of first-coordination-sphere interactions of water with the Gd$^{3+}$ ion. The low-field decrease in water proton SR rate with a midpoint close to a Larmor frequency of 1 MHz is diagnostic of the electron SR rate constant limiting the correlation time for the first-coordination-sphere electron-nuclear dipolar coupling. This observation is common for slowly tumbling Gd$^{3+}$ coordination compounds. The increase in relaxation rate above 10 MHz signals that the electron SR time disperses or increases with
increasing magnetic field strength. The effect of this electron SR time increase is to increase the effective correlation time for the electron-nuclear coupling and thereby increase the water proton-relaxation rate constant. At higher fields, the water-proton-SLR rate constant will peak and fall rapidly to small values. The transverse relaxation rate constant will remain fairly high at high fields.43 We note that the low-field portion of the relaxation profile appears to increase slowly with decreasing field. The changes are small, but based on the other samples studied, the approximately linear dependence on the logarithm of field strength is consistent with the restricted diffusion effects discussed above.

For purposes of comparison with our previously reported \( r_1 \) value of \( \sim 600 \text{ mM}^{-1} \text{s}^{-1} \) at 0.01 MHz for the GNTs, we have plotted \( r_1 \) vs magnetic field for the present GNT data shown in Figure 2d, and this plot is displayed in Figure 3S with an \( r_1 \) value \( \sim 200 \text{ mM}^{-1} \text{s}^{-1} \) at 0.01 MHz. This value at 0.01 MHz is still unusually high, but not as high as previous reported for a different GNT sample.46 However, at 1.5 T (30 MHz) the two different GNT samples gave comparable values of \( r_1 \sim 160 \text{ mM}^{-1} \text{s}^{-1} \).

Since different kinds of carbon nanotubes (CNTs) are synthesized by different methods, we also examined the NMRD profiles of HiPco SWCNTs and the HiPco GNTs. While Arc SWCNTs are a product of the ultrasonication of HiPco SWCNTs, Arc GNTs are a product of an Arc discharge plasma. HiPco SWCNTs are formed under a high pressure carbon monoxide condition. Other key differences between these two types of SWCNTs are the somewhat larger diameter at the Arc tubes (1.4 nm vs 1.0 nm) and far fewer (and possibly zero) sidewall defects for pristine HiPco tubes.42–44 Figure 2 presents the NMRD profiles of full-length Arc SWCNTs and HiPco SWCNTs and the GNTs made from them at comparable concentrations of solid samples in a 0.17 w/v% pluronic aqueous solution. Since HiPco SWCNTs are known to have far fewer defect sites compared to Arc tubes,45–48 not unexpectedly they also showed low relaxation rates at all low Larmor frequencies. This result is likely due to a lower density of defect sites and thus, fewer radical centers on HiPco SWCNTs compared to Arc SWCNTs. This suggests that at fields lower than 10 MHz, the low SR rates for HiPco GNTs is also probably due to a relatively low concentration of carbon-based radical centers. While HiPco GNTs should have comparable SR rates to Arc GNTs at high fields, their lower relaxation rate at these fields, as shown in Figure 3, is likely due in this case, to much lower Gd\(^{15+}\) ion concentration in the HiPco GNT sample which was at least 50% lower (estimated) than that for the Arc GNTs.

**EPR study.**—The NMRD profiles discussed above indicate the presence of a significant electron spin concentration characterized by relatively long electron relaxation times. Free radical polynuclear aromatic systems are common and may be expected in cases where the conditions of synthesis and modification are chemically vigorous such as when the US-tubes are prepared from SWCNTs using the F\(_2\)/pyrolysis procedure.39,50 EPR is expected to be sensitive to paramagnetic metal impurities and also to carbon-based radical centers at defect sites on samples of full-length Arc SWCNTs.51,52 Previous EPR studies on CNTs have shown that the EPR spectra of purified nanotubes at room temperature consist of up to three overlapping lines that can be attributed to the conduction electrons (an asymmetric or Dysonian line), to defect sites and/or to the magnetic metal particles used as catalysts during the synthesis.53 The magnetic particles used as catalysts during SWCNT synthesis are seen as a very wide resonance line which prevents observation of the expected conduction electron line.51 The simultaneous presence of both broad and narrow resonances is considered to be indicative of the heterogeneous nature of CNT samples of any nature.54 EPR spectra at room temperature for purified full-length Arc SWCNTs and Arc GNTs are shown in Figures 4a and 4b, respectively. Similar spectra have been reported for other CNT preparations and all demonstrate the presence of magnetically-active electron spins.51,55 However, the observed EPR spectra are a function of the synthesis method, chemical treatment, catalyst metals remaining, oxygen, thermal history and temperature, as well as other added paramagnetic materials.56,57 We simply note here that the EPR spectra in Figure 4 are consistent with the high SR rates found in the NMRD studies of the purified full-length Arc SWCNTs and Arc GNTs, as discussed above.

**Computational study of pristine CNTs, US-tubes and GNTs.**—Electronic properties of pristine and defect-site CNTs and GNTs were determined using the SIESTA software package, based on self-consistent density functional theory (DFT) calculations,38 that uses localized basis sets and a periodic supercell method. It also uses pseudopotentials that reproduce all-electron eigenvalues and excitation energies of multiple atomic configurations. The calculations were performed within the generalized gradient approximation (GGA) in conjunction with double-zeta polarized orbitals for the basis sets of carbon, hydrogen and gadolinium. We used a norm-conserving Troullier-Martins type pseudopotential for carbon, hydrogen and gadolinium atoms. The sampling of the Brillouin zone included a fine 18 × 18 × 1 Monkhorst-Pack k-points grid for all adsorption sites studied. A similar fine grid was used to produce an accurate band structure. The geometry optimization was pursued until the convergence criterion was less than 10\(^{-5}\) eV for total energy and less than 0.01 eV/Å for forces. Using ab initio calculations, a number of possible physical models were considered to understand the role of local electronic states and electron-hole excitations from the CNT chemical cutting process used to produce US-tubes. Figure 5a shows a pristine CNT (6,6) and Figures 5b, 5c show a 6% vacancy defect-site CNT and a 13.3% vacancy defect-site CNT, which are two of the possible consequences of cutting of full-length CNTs into US-tubes. We acquired structural relaxation and electronic properties of a pristine CNT, a defect-site CNT and a GNT in the ab initio framework based on density functional theory (DFT).

To gain deeper insight into the electronic properties of the CNTs, Figure 5d shows the total density of states (DOS) of a pristine CNT and CNTs with defect sites. The DOS of a pristine CNT is constant near the Fermi energy (E\(_F\)), while at higher energies, sharp peaks (van Hove singularities) can be observed. We found that CNTs with defect sites which form double pentagon-heptagon defects (Figure 5b) tend to increase nanotube strain. Eventually, as the defect site increases in size, electronic states appear near the Fermi-level from the response
Figure 4. The room temperature EPR spectra of 1 scan, modulation amplitude 4 G, microwave attenuation 18 db, receiver gain 105; purified full-length Arc SWCNTs, sweep width 3600 g (a); Arc GNTs, sweep width 2900 g (b). The low-field sharp feature (∗) is an artifact of the resonator employed and not of the CNT sample.

Figure 5. Pristine CNT (6,6) (a), 6% defect-site CNT (b) and 13.3% defect-site CNT (c). Total density of states (DOS) for pristine CNT and 6% and 13.3% defect-site CNTs (6,6) (d).

Figure 6. Schematic model of doping Gd\(^{3+}\) ions (●) into defect sites of a CNT to produce GNTs (a). Total density of states (DOS) for spin-up and spin-down of Gd\(^{3+}\) ions doped into a defect-site CNT (b).

of mechanical instability. The small curvature of carbon bonds due to the vacancy defect sites induces \(\sigma - \pi/\sigma^* - \pi^*\) hybridization and creates new interband electronic states as clearly shown in Figure 5d.

From Figure 5d, we conclude that CNTs with defect sites create electronic states in the DOS of the system near the Fermi energy, which is related to induced strain in the nanotube structure due to vacancy defects. This increase in electronic states near the Fermi level (within the gap of pristine CNTs) enhances the number of transitions between localized electron-hole excitations similar to that which can take place for semiconductors. CNTs with defect-sites induce states within the gap, which allows localized electron-hole excitons to take place with increasing vacancy defect-site concentration from 6% to 13.3%.

Figure 6 indicates the electronic states for spin-up and spin-down of Gd\(^{3+}\) ions doped into a defect site of a CNT, as obtained by a spin-polarized calculation. The electronic states for spin-up and spin-down are separated which results in a magnetic moment of the system of \(\approx 7 \mu_B\) per Gd\(^{3+}\) ion. As can be seen from Figure 6b, doping of Gd\(^{3+}\) ions into defect sites of a CNT does not induce new CNT electronic
states, but rather it slightly shifts the Fermi level to a higher energy (0.4 eV) as a result of charge transfer between Gd$^{3+}$ and the CNT.

Finally, a series of simulated Scanning Tunneling Microscopy (STM) images were obtained for a pristine CNT and a vacancy defect-site CNT by using a numerical STM tool for probing electronic states and the states mixing in our case of study. Figure 7 gives two perspectives of the influence of a vacancy defect site on an STM image. The lower panels show the topographic simulated STM images calculated for a pristine CNT and a vacancy 6% defect-site CNT. Obviously, comparing computed STM images of pristine and defect-site CNTs reveal subtle information about the variation of electronic properties and extra electronic states present for the defect-site CNT as shown in Figure 7b (green, yellow and red protrusions).

**Conclusions**

This work reveals the reason behind the extraordinary high relaxivities for the GNTs at low magnetic fields, as previously reported. The NMRD profiles reported here indicate that at low magnetic fields, the relaxation efficiency of commercially-available Arc SWCNTs and their US-tube product are derived from the presence of carbon-based radical centers that are supported by the polyaromatic structure of the CNT. While 1-dimensional water or proton diffusion inside the nanotubes is not apparent, the magnetic-field dependency of the radical contributions to the relaxation rates is dominated by the effects of 2-dimensional diffusion either on the surface of the CNTs or entrapped in aggregates of nanotubes. This observation proposes that the predominant contribution from the Gd$^{3+}$ ions at higher magnetic fields is also from 2-dimensional diffusion of water on the surface or at the edges of the nanotubes where carboxylic acid groups (created by the mild oxidation of the US-tubes with HNO$_3$ prior to metatation with Gd$^{3+}$ to prepare the GNTs; see the Experimental section) are likely bound to the Gd$^{3+}$ ion clusters as ligands. Furthermore, the present computational study of CNT and GNT materials demonstrates that CNT defect sites introduce new interband electronic states into the system. However, the Gd$^{3+}$ ions of the GNTs do not change the interband state number, but they do shift the Fermi level to higher energy by 0.4 eV. In conclusion, this work reveals that our previously reported extremely large relaxivities for the GNTs ($\geq 600$ mM$^{-1}$s$^{-1}$ based on [Gd$^{3+}$]) at very low fields must be reconsidered since the important role of carbon-based radical centers of the US-tube component of the GNTs was not previously appreciated. However, at a clinical-field strength of 1.5 T, Gd$^{3+}$ ions appear to dominate the proton relaxation rate, as expected, and as previously reported.

**Acknowledgments**

At Rice University, this work was supported by the Welch Foundation (grant C-0627, LJW).

**References**

1. P. Caravan, J. J. Ellison, T. J. McMurry, and R. B. Lauffer, *Chemical Reviews*, 99(9), 2293 (1999).
2. A. J. M. Lubig, L. M. De Leon-Rodriguez, S. C. Burgess, and A. D. Sherry, *Proceedings of the National Academy of Sciences of the United States of America*, 108(45), 18400 (2011).
3. T. Inoue, E. Kozawa, H. Okada, K. Inukai, S. Watanabe, T. Kikuta, Y. Watanabe, T. Takenaka, S. Katayama, J. Tanaka, and H. Suzuki, *Journal of the American Society of Nephrology : JASN*, 22(8), 1420 (2011).
4. C. Barsanti, F. Lenzarini, and C. Kusmic, *World Journal of Diabetes*, 6(6), 792 (2015).
5. C. Zhang, S. S. Moonshi, H. Peng, S. Puttack, J. Reid, S. Bernardi, D. J. Sealeys, and A. K. Whittaker, *ACS Sensors*, 1(6), 737 (2016).
6. E. M. Gale, I. P. Atanasova, F. Blasi, I. Ay, and P. Caravan, *Journal of the American Chemical Society*, 137(49), 15548 (2015).
7. D. V. Hingorani, A. S. Bernstein, and M. D. Pagel, *Contrast Media & Molecular Imaging*, 10(4), 245 (2014).
8. P. Caravan, J. J. Ellison, T. J. McMurry, and R. B. Lauffer, *Chemical Reviews*, 99(9), 2293 (1999).
9. J. S. Gustav, J. M. M. Willem, A. F. v., T. Geralda, and N. Klaas, *Anti-Cancer Agents in Medicinal Chemistry*, 7(3), 291 (2007).
10. D. Pan, A. H. Schmieder, S. A. Wickline, and G. M. Lanza, *Tetrahedron*, 67(44), 8431 (2011).
11. C. F. G. C. Gerales and S. Laurent, *Contrast Media & Molecular Imaging*, 4(1), 1 (2009).
12. D. T. Puerta, M. Botts, C. J. Jocher, E. J. Werner, S. Avedano, K. N. Raymond, and S. M. Cohen, *Journal of the American Chemical Society*, 128(7), 2222 (2006).
13. E. Brucher, in *Contrast Agents I: Magnetic Resonance Imaging*, W. Krause, ed., p. 103, Springer Berlin Heidelberg, Berlin, Heidelberg, (2002).
14. K. D. G. Chan and W.-T. Wong, *Coordination Chemistry Reviews*, 251(17), 2428 (2007).
15. P. Markcs, L. Skov, K. Rossen, A. DuPont, M. B. Damholt, J. G. Heaf, and H. S. Thomsen, *Journal of the American Society of Nephrology*, 17(9), 2359 (2006).
16. B. Sutharam, K. R. Kissell, K. B. Hartman, L. A. Tran, A. Baikalov, I. Russakova, Y. Sun, H. A. Khan, S. J. Ludwek, W. Chiu, S. Laus, T. Toth, L. Helm, A. E. Merbach, and L. J. Wilson, *Chemical Communications*, (31), 3915 (2005).
17. Q. Ma, M. Jabb, M. F. Tweelde, and L. J. Wilson, *Journal of Materials Chemistry B*, 1(42), 5791 (2013).
18. R. Wang, H. D. Selby, H. Liu, M. D. Carducci, T. Jin, Z. Zheng, J. W. Anthis, and R. J. Staples, *Inorganic Chemistry*, 41(2), 278 (2002).
19. R. Sethi, Y. Mackeyev, and L. J. Wilson, *Inorganica Chimica Acta*, 393, 165 (2012).
20. K. B. Hartman, S. Laus, R. D. Bolskar, R. Muthupillai, L. Helm, E. Toth, A. E. Merbach, and L. J. Wilson, *Nanos Letters*, 8(2), 415 (2008).
