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ABSTRACT

Magnetic resonance imaging is a non-invasive imaging method that offers high-resolution, high quality in vivo visualization for medical diagnostics. Magnetic nanoparticles (NPs) containing Mn$^{2+}$ offer an attractive alternative to Gd-based molecular contrast agents for $T_1$ MRI. In this work, we show that highly anisotropic MnO NPs can be generated from a single precursor using simple synthetic protocols. These anisotropic morphologies offer better contrast augmentation when compared to spherical MnO NPs of similar sizes.

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I. INTRODUCTION

As magnetic resonance imaging (MRI) continues to be a leading non-invasive diagnostic protocol in medicine, the importance of contrast agents (CAs) - magnetic species administered to the patient prior to MRI for augmented imaging - can not be stressed enough. Among these, $T_1$-MRI CAs, which preferentially shorten the longitudinal relaxation times ($T_1$) of water protons in their close proximity, leading to brighter signals, are preferred by radiologists for easier diagnosis of abnormal anatomical features. Irrespective of the relaxation mechanism, the figure of merit for such a CA is its relaxivity $r_i$ (in units of mM$^{-1}$ s$^{-1}$). Experimentally, $r_i$ is determined by measuring the relaxation rate $R_i$ or relaxation time $T_i$ ($R_i = T_i^{-1}$) as a function of CA concentration ($[CA]$) [$R_i = \frac{1}{T_i} = r_i \cdot [CA]$] where $i$ = 1,2 and $T_{i0}$ is the relaxation time of water molecules in the medium in the absence of CA. In general, for a $T_1$-MRI CA, a high $r_1$ and a $r_2/r_1$ ratio as close as possible to unity are desired.

With its d$^5$ and S = $\frac{5}{2}$ electron configuration, Mn$^{2+}$ has emerged as the d-block paramagnetic ion of choice for building $T_1$-MRI CAs.$^{4,5}$ Surface-capped MnO nanoparticles (NPs) with enhanced biocompatibility and stability in biological media have been examined as both standalone MRI CAs$^{6,7}$ as well as multimodal bionanoprobes combining MRI with other bio-imaging regimes.$^{8-10}$

Shape-control is an extensively studied approach to enhance the relaxivities of NP MRI CAs. Novel morphologies (e.g., cubes, stars, dog-bones, flowers, octapods, hexapods, crosses, and threads) have been synthesized, with the expectation that these might show improved contrast enhancement when compared to spherical NPs.$^{11-16}$ While the relation between morphology and $r_2$ relaxivity is well-established,$^{17}$ the impact of NP shape on $r_1$ values is somewhat unclear, partly owing to strong covalent contributions in Mn–O bonds in MnO, as well as the diversity of its crystal packing structures.$^{18}$ Empirical studies have been conducted to improve our understanding of this relationship. For example, Murrie et al. synthesized MnO nano-spheres and -octapods, showing the much larger octapods had similar $r_1$ to the smaller spheres, which was attributed to the higher surface-to-volume ratio of the octapod particles.$^{3}$ Lei et al. synthesized rod-like, polyhedral, cube-like, and...
spherical MnO NPs, however, only the cubes and spheres were evaluated for MRI at $B_0 = 0.5$ T. The nanocubes’ $r_1$ was 2-3 times higher than their spherical counterparts of comparable dimensions, again ascribed to a higher surface-to-volume ratio. Various MnO nanomorphologies were also examined recently as potential $T_2$-MRI CAs, correlating their evaluated for MRI at $B_0 = 1.5$ T. Spherical MnO NPs, with a greater surface concentration of Mn$^{2+}$ ions, manifest stronger enhancement of $T_2$-relaxation times of protons in their vicinity. A self-assembled aggregate of whisker-like MnO nanostructures showed higher-than-expected $r_1$ values due to geometrical confinement effects.

As part of our ongoing examination of simple first-row transition metal oxide NPs for use as high-field MRI CAs, in this study we present the synthesis of a variety of MnO NP morphology and their MRI capabilities at $B_0 = 9.4$ T. It is found that the structural variations with greater anisotropy, higher surface areas, negative surface curvature, and geometrical confinement demonstrate superior $T_1$ contrast enhancement. In particular, a cactus-like morphology displays a high $r_1$ and a small $r_2/r_1$, potentially owing to the presence of diffusion-restricted water molecules confined to the fork-like inter-branch geometrical zones unique to the MnO nanocacti.

II. RESULTS AND DISCUSSION

MnO NPs were synthesized by decomposition of manganese diolate in octadecene under anoxic conditions. In order to transfer the hydrophobic MnO NPs from organic phase to water, we used $\alpha$-cyclodextrin to form an inclusion complex with the surface-bound oleate groups, thereby transferring the NPs from hexanes to water. The synthesis of the NPs and other physical characterization details are in the supplementary material.

The observed reflections in the x-ray diffractogram (PXRD, Fig. 1) are indexed to cubic MnO ($Fm\bar{3}m$, JCPDS: 07-0230).

The presence of a strong capping agent (oleic acid) likely prevents oxidation of Mn to higher oxidation states. Crystallite sizes were determined using the Scherrer equation (Fig. S1 and Table S1).

Here, we briefly comment on the MnO NPs morphologies observed by transmission electron microscopy (TEM, see Fig. 2 and Table S2). It is not our intention to rationalize the mechanisms behind the formation of each shape; interested readers are referred to the cited literature for further explanations. Details about the measurements for all these morphologies, formulae used in the calculation of their surface areas ($S$) and volumes ($V$), and other relevant information are in the supplementary material.

Nanospheres (spheres). The as-synthesized spheres (Fig. 2) are similar to the ones synthesized in the past by, e.g., Tremel and colleagues. These NPs are capped with the free oleic acid that is generated upon decomposition of the manganese diolate precursor. An analysis of their TEM images reveals an average diameter of 5.6±3.0 nm.

Nanocubes (cubes). The cubes are cube-shaped, with slightly rounded edges and corners, and an average edge length of 27±3 nm. They are generated by step-wise heating in the presence of sodium oleate. Literature precedents indicate that these cubes originate from small spherical clusters via poly-face intermediates, when the [100] facets stop growing. Sodium oleate has been used extensively to form Fe$_2$O$_3$ nanocubes. It is postulated its structure-tuning effect comes from its facile dissociation and the ability of the dissociated surfactants to either suppress or accelerate the surface growth rates of specific crystal facets.

Nanorhombohedra (rhombohedra). It was recently demonstrated that highly anisotropic morphologies of metal oxide NPs might be obtained by the injection of a large portion of metal oleate precursor after an initial stunted nucleation, while carrying out the thermal decomposition of metal oleates in inert solvents. This technique was found to be favorable for the formation of metastable nucleation seeds, and their subsequent growth into anisotropic NPs. In their case-study, Xu et al. obtained thin triangular magnetite nanoplates using iron oleate. Adapting this protocol to manganese diolate, we obtained rhombohedral MnO NPs. Fig. S2 shows a single rhombohedral MnO NP, with an edge length of $\sim 20$ nm, and an acute rhombic angle of $\sim 85^\circ$. We expect the formation mechanism of rhombohedra is similar to the one described in the aforementioned account: the flat top and bottom surfaces of a nascent MnO nucleus are likely passivated by oleate initially formed from the decomposition of manganese diolate in the reaction mixture, while the crystal facets on the side surfaces remain less protected. Upon the addition of excess precursor immediately after nucleation starts, it is possible that some crystal planes get preferentially passivated, leading to the formation of rhombohedral geometries. In line with Xu et al.’s observation, we noticed that additional manganese diolate precursor compensated for the depletion of monomer during the nucleation stage, thereby forming uniformly sized kite-like nanostructures with a narrow size distribution.

Nanooctapods (octapods). Octapods with multiple high-index surface facets are a coveted anisotropic nano-architecture for the purposes of catalysis and imaging. We generated this morphology by adapting Zhao et al.’s protocol for the synthesis of Fe$_3$O$_4$.
octapods with unparalleled $r_2$ values. The procedure calls for the addition of oleic acid and NaCl to the reaction mixture, along with small amounts of H$_2$O. Several publications delve deep into the role of each additive in the formation of octapods.\cite{11,13} Our octapods resemble those commonly seen in the literature\cite{11,13,26} – eight protrusions arising from a roughly cubic core with an average tip angle of $\sim$36°. This shape was seen to be more prone to polydispersity than the others, with octapods of a variety of sizes being formed. A single MnO octapod is shown in Fig. S3. The volume and surface area of the octapods may be calculated from a metric ($\alpha$), such that the edge-to-edge diagonal of the top view of an octapod equals $4\alpha$. The average values of this $\alpha$ quantity was found to be 30.6±6.3 nm.

Nanocacti (cacti). The cacti are structurally related to some of the 3D structural variations of MnO NPs reported by Cheng et al.\cite{16} They are unique in the sense that they are more ‘assembled’ than the other morphologies described so far, with several short branches coming out of a single ‘fleshy stem’, much like Noto-cactus warasii plants, which inspired the name. We suggest this morphology is created by oriented attachment of rounded MnO nanorods that are known to form upon step-wise heating of manganese dioleate in the presence of minute quantities of NaCl.\cite{15} A simplified geometrical model of this morphology assumes cacti to be aggregated cylindrical capsule-like entities, with the non-conjoined end of each cylindrical arm being capped by a hemisphere (see Fig. S4). The average cylinder height was found to be 20±4 nm and the average diameter of the hemisphere was determined to be 9.6±1.8 nm.

Infrared vibrational spectra of the as-synthesized, oleate-capped MnO spheres as well as that of the cyclodextrinated MnO octapods are shown in Fig. S5. The appearance of new peaks corresponding to $\nu$(C-O-C) and $\nu$(C-C/C-O) of $\alpha$-cyclodextrin in the MnO octapods after ligand exchange confirm the presence of $\alpha$-cyclodextrin on the NP surfaces.

Bulk MnO demonstrates antiferromagnetic behaviour, with a $T_{\text{Neff}}$ of ~122 K owing to the superexchange interactions between adjacent Mn$^{2+}$ ions.\cite{27} At 1.9 K, our MnO nanostructures produce $M(H)$ reversal loops with slight hysteresis (Fig. S6a), characteristic of ferromagnetic behavior and previously observed in MnO NPs.\cite{8,28} The hysteresis may be due to uncompensated spins on the NP surfaces.\cite{28} At 300 K, a linear $M(H)$ characteristic of a paramagnetic material is observed (Fig. S6b). The $M(T)$ was examined under field-cooled and zero-field-cooled conditions (Fig. S6c). All the MnO nanomorphologies show transition from a low-$T$, ordered magnetic phase to a paramagnetic phase at higher temperatures.

The $r_1$ and $r_2$ (Fig. 3 and Table S2) were determined from $^1$H relaxation times measured at $B_0 = 9.4$ T as a function of CA concentration (Fig. S7). On a per-Mn$^{2+}$ basis, the $r_1$ values increase in the following order: cubes $< $ spheres $< $ rhombohedra $< $ octapods $< $ cacti. However, the morphologies differ greatly from one another in terms of volumes, surface-to-volume ratios, and potential sites for geometric confinement of H$_2$O molecules.
In general, our $r_1$ tally well with those of previously reported similar MnO nanostructures, such as 2.5-nm MnO nanospheres ($r_1 = 1.4$ mM$^{-1}$ s$^{-1}$; $r_2/r_1 = 2.6$) and 21-nm MnO nanocubes ($r_1 = 1.08$ mM$^{-1}$ s$^{-1}$). The octapods show reduced $r_1$-values compared to literature examples, potentially due to the slightly larger sizes and greater polydispersity of our octapods. The $r_1$ show a general improvement when more complex shapes (beyond spherical) are used. This clearly highlights the benefit of controlling shape for improving both $r_1$ and $r_2$ for high-field MRI when using MnO NPs. It is hard to ascribe this trend to surface-to-volume ratios alone, given the NPs have very different volumes. However, two pairs of samples have similar $S/V$ ratios (spheres and cacti; and rhombohedra and octapods). In both pairwise comparisons, the sample with the larger volume boasts the higher $r_1$. This trend could be explained by differing rotational dynamics, where the large NPs would presumably tumble slower than the smaller NPs with lower moments of inertia. We are currently carrying out NMR dispersion experiments to test this hypothesis.

Amongst all the morphologies examined here, the MnO cacti possess the most desirable $r_1$ and $r_2/r_1$ values, making them particularly suited for high-field $T_1$-MRI. While other factors beyond morphology may be responsible for the results obtained here (e.g., different exchange times due to different binding strengths on various facets), an explanation behind the enhanced $r_1$ values of cacti and octapods, compared to the other compact shapes (such as cubes and rhombohedra) may be gleaned from studies on the dependence of $r_1$ on surface curvatures of nano-sized CAs.

For Gd$^{3+}$-DNA functionalized many-armed Au nanostars – containing Gd$^{3+}$ in regions of positive, negative, and neutral curvature, it was hypothesized that the $^1$H relaxation enhancement originated from hydrophilic environment found in highly concave regions. In these regions, the residency time of outer-sphere H$_2$O molecules near Gd$^{3+}$ increased by an order of magnitude compared to diffusion, leading to enhanced $r_1$ values. The octapods present a similar, concave morphology; they also show a five-fold increase in $r_1$ values compared to the cubes, despite the increase in average volume. These observations support the hypothesis that negative curvature between the branches of MnO cacti and octapods facilitates a long-lived second hydration sphere surrounding the Mn(II)-α-cyclodextrin, leading to enhanced $r_1$ values. The Solomon-Bloembergen-Morgan equations indicate that the outer-shell $r_1$ contribution depends on certain properties associated with the CA, including the diffusion times, $D_T$. A longer $D_T$ enhances the dipolar and Curie relaxation, leading to better $T_1$ shortening. In comparison to the other, compact morphologies described here, the MnO cacti (and, to a smaller extent, the octapods), have zones between the “branches” of the cacti or prongs of the octapods that restrict diffusion of H$_2$O molecules, confining them to those spaces, thereby increasing $r_1$.

### III. CONCLUSIONS

This study focuses on a simple synthetic route to obtain a variety of MnO nanostructures, ranging from spheres to convoluted shapes (octapods, cacti), with a view to using these shaped-tuned NPs as $T_1$-MRI CAs at high field (9.4 T). The cacti, and to a smaller extent, the octapods, have superior $r_1$ owing to a combination of factors such as unique surface curvatures and geometric confinement effects. While certain trends in the recorded $r_1$-values could be explained empirically from geometric and other considerations, more experimentation (including NMR dispersion studies) is required to develop a quantitative model that relates MnO NP shapes to their relaxivity parameters. These experiments and model development are currently ongoing.

### SUPPLEMENTARY MATERIAL

See supplementary material for synthetic details, experimental details, and supporting data (XRD, TEM, ATR-IR spectroscopy, SQUID magnetometry, and $r_1$ measurements).

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