Division of Multidisciplinary Chemistry
– Interdisciplinary Chemistry for Innovation –

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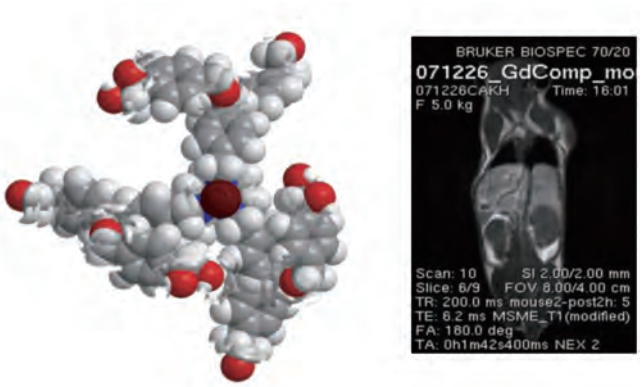
Scope of Research

Organic chemistry can contribute to the innovation through the design and synthesis of molecules those are valuable to human society. Our methodology possesses advantage in heteroatom chemistry, transition metal-catalyzed reactions, and asymmetric synthesis. As for the synthetic procedure, we take note to develop atom-economic as well as environment-benign reactions. We recognize the importance of the collaboration with various fields of technology of industry and academia. Recent examples of our projects include design, synthesis, and evaluation of aromatic compounds used in light-emitting field-effect transistors, sugar-fullerene linked compounds used in photodynamic therapy of cancers, and gadolinium complex of chiral dendrimers used in magnetic resonance imaging of cancers (shown in the figure).



KEYWORDS

Innovation
Organic Synthesis
Heteroatom Chemistry
Transition Metal Catalyst
Asymmetric Synthesis

Selected Publications

Miyake, Y.; Kimura, Y.; Ishikawa, S.; Tsujita, H.; Miura, H.; Narazaki, M.; Matsuda, T.; Tabata, Y.; Yano, T.; Toshimitsu, A.; Kondo, T., Synthesis and Functional Evaluation of Chiral Dendrimer-Triamine-Coordinated Gd Complexes as Highly Sensitive MRI Contrast Agents, *Tetrahedron Lett.*, **53,** 4580-4583(2012).

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Kondo, T.; Niimi, M.; Yoshida, Y.; Wada, K.; Mitsudo, T.; Kimira, Y.; Toshimitsu, A., Rhodium-catalyzed Linear Codimerization and Cycloaddition of Ketenes with Alkynes, *Molecules*, **15,** 4189-4200 (2010).

Sakanoue, T.; Yahiro, M.; Adachi, C.; Takimiya, K.; Toshimitsu, A., Electrical Characteristics of Single-component Ambipolar Organic Field-effect Transistors and Effects of Air Exposure of Them, *J. Appl. Phys.*, **103,** [094509-1]-[094509-6] (2008).

Sakanoue, T.; Yahiro, M.; Adachi, C.; Uchiuzou, H.; Takahashi, T.; Toshimitsu, A., Ambipolar Light-emitting Organic Field-effect Transistors Using a Wide-band-gap Blue-emitting Small Molecule, *Appl. Phys. Lett.*, **90,** [171118-1]-[171118-3] (2007).

Size-controlled and Biocompatible Gd_2O_3 Nanoparticles for Dual Photoacoustic and MR Imaging

One of the most rapidly developing and exciting applications of nanotechnology in biomedical research is the development of biocompatible nanoparticles for use in multiple, powerful and highly complementary imaging modalities. Our main goal is to synthesize and isolate new size-controlled and biocompatible Gd_2O_3 nanoparticles as an unconjugated bimodal contrast agent for use in photoacoustic tomography (PAT) and magnetic resonance (MR) imaging through the fusion of inorganic nanoparticles and organic peptide coating.

Gd_2O_3 nanoparticles used in this study were obtained by applying a previously reported protocol for the alkaline hydrolysis of $Gd(NO_3)_3$ carried out in diethylene glycol (DEG) at 180°C. To isolate the DEG-coated Gd_2O_3 nanoparticles, this reaction mixture was further added to pure acetone to give dark brown precipitates. After the precipitates were dried under vacuum and dispersed in pure water, a dynamic light scattering (DLS) measurement of the isolated Gd_2O_3-DEG nanoparticles gave a sharp and reproducible peak at 100 nm during an appropriate time-window.

However, the mean size (hydrodynamic diameter) of the isolated Gd_2O_3-DEG nanoparticles increased greatly over time in pure water, which is a sign of coarse aggregation. We found that the surface modification of Gd_2O_3-DEG nanoparticles with biocompatible gelatin could be used to maintain a constant diameter even after 45 h. In addition, the size (diameter) of the new nanoparticles could be completely controlled (20–200 nm) by timing the addition of an aqueous solution of gelatin to the suspension of Gd_2O_3-DEG nanoparticles in pure water.

A transmission electron microscopy (TEM) of the new nanoparticles of a hydrodynamic diameter of 100 nm showed that the thickness of the outer layer is 10–30 nm and Gd_2O_3-DEG nanoparticles were observed as small dots (5 nm; indicated with white circles) (Figure 1). Based on the process of synthesis, it is conceivable that the outer layer of new nanoparticles consists of gelatin (indicated with black arrowheads), and the inner small dots should be unconjugated Gd_2O_3 because of its high electron density. The remaining space in the nanoparticles was filled by DEG (indicated with white arrowheads).

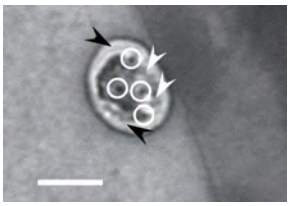

Figure 1. Transmission electron microscopy (TEM) of Gd_2O_3-DEG-gelatin nanoparticles (scale-bar; 100 nm).

Figure 2 shows a photoacoustic (PA) image of mice before and after subcutaneous injection of the new nanoparticles. After the injection, the intense signal was observed at the injected area. These signals were expected to be emitted from Gd_2O_3 nanoparticles and no PA signals for DEG or gelatin were observed.

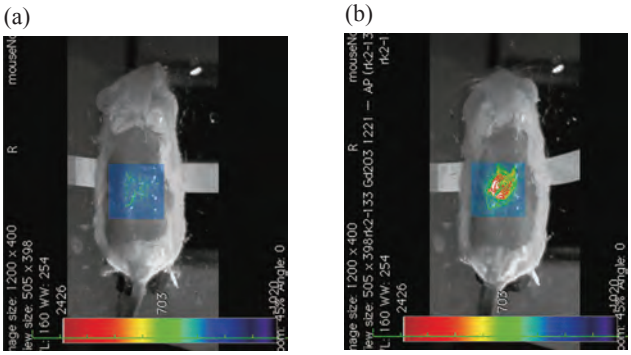

Figure 2. Photoacoustic (PA) images of mice (a) before and (b) after subcutaneous injection of Gd_2O_3-DEG-gelatin nanoparticles.

The MRI study clearly showed that the new nanoparticles are a T_1-positive MRI contrast agent, and their relaxivity r_1 is twice that of clinically available Gd-DETA. Since the relaxivity r_1 strongly depends on the rotational dynamics of molecules with a magnetic moment, the rotation of new nanoparticles could be inhibited by their gravity, which results in an increase in sensitivity as well as reduction in dose.

MR images of a whole mouse clearly showed that the new nanoparticles freely circulate in the blood vessels without undesirable accumulation in the lungs (Figure 3). We consider that these new nanoparticles could be useful as a contrast agent for angiography. In addition, signals in the liver were diminished, while signals in the colon were observed on MR imaging 24 h after injection (Figure 3b). In addition, we have confirmed that the mice 72 h after intravenous injection of the present nanoparticles were alive, and MR intensity of the liver decreased. Thus, we consider that the nanoparticles after the injection could be eliminated from the liver through the bile duct without any chemical alteration, such as generation of a free Gd^{3+} ion and the accumulation as $GdPO_4$ microcrystals in the liver.

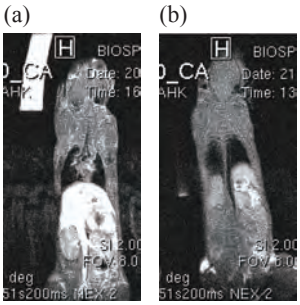

Figure 3. T1-weighted magnetic resonance (MR) images of mice (a) 5 min and (b) 24 h after intravenous injection of Gd_2O_3-DEG-gelatin nanoparticles (0.10 mmol Gd/kg).