Division of Multidisciplinary Chemistry
– Interdisciplinary Chemistry for Innovation –

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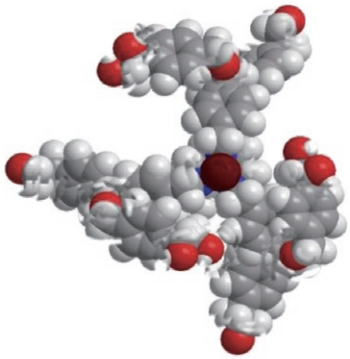
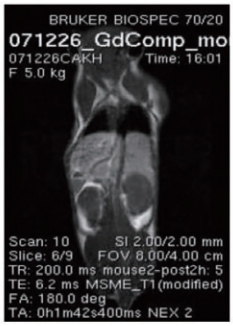
Scope of Research

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).

Kondo, T.; Kimura, Y.; Kanda, T.; Takagi, D.; Wada, K.; Toshimitsu, A., Simple and Practical Aerobic Oxidation of Alcohols Catalyzed by a (μ-Oxo)tetraruthenium Cluster, *Green Sus. Chem.*, **1,** 149-154 (2011).

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).

Synthesis and Functional Evaluation of Chiral Dendrimer-Triamine-Coordinated Gd Complexes as Highly Sensitive MRI Contrast Agents

MRI constitutes a prominent non-invasive imaging technique for disease diagnosis. Low-molecular-weight contrast agents based on Gd-DTPA (DTPA = diethylene-triaminepentaacetic acid) has been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMEA), and is widely used in the clinical diagnosis of tumors. However, the non-specificity, low contrast efficiency and rapid renal excretion of this low-molecular-weight contrast agent necessitate a high dosage (*ca*. 0.5 M), which imposes a great physical strain on the patient. The main reason for the low contrast efficiency is that, among the 9 coordination sites of Gd, up to 8 are solidly occupied with ionic chelating ligands, and thus only 1 remains for coordination with free water molecules, which is observed by MRI. In addition, the rotational motion of Gd metal in the center of existing small ligands cannot be suppressed, and as a result the image contrast is considerably reduced.

In order to overcome these difficulties, we prepared *chiral* dendrimer-triamine-coordinated Gd complexes **1-(*R*)** and **1-(*S*)** shown in Figure 1. Complexes **1-(*R*)** and **1-(*S*)** have a triamine ligand and three chloride ligands, which stably occupy 6 coordination sites of Gd. Accordingly, 3 coordination sites remain vacant for coordination with water molecules, which will be observed by MRI. In addition, large dendrimer in the periphery of Gd will suppress the molecular tumbling and rotation of Gd to result in the increase of the image contrast.

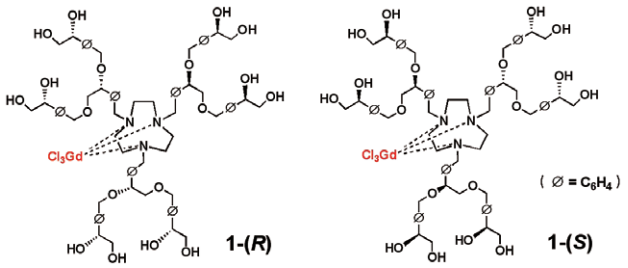


Figure 1. Structure of chiral dendrimer-triamine-coordinated Gd compleses, **1-(*R*)** and **1-(*S*)**.

The ability as the imaging agents *in vitro* was evaluated by the longitudinal relaxivities (r1) of Gd complexes (**1-(*R*)** and **1-(*S*)**), $GdCl_3 \cdot 6H_2O$, and Gd-DTPA (Figure 2). As expected, the r1 values of **1-(*R*)** and **1-(*S*)** were 11.4 and 11.1 mM^{-1} s^{-1}, respectively, which are approximately 3 times higher than that of Gd-DTPA (r1 = 4.6 mM^{-1} s^{-1}).

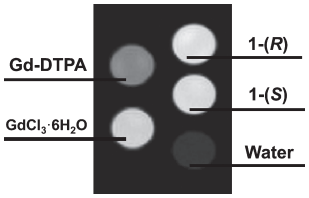


Figure 2. T1-weighted MR images of Gd-DTPA, $GdCl_36H_2O$, **1-(*R*)**, **1-(*S*)** (0.50 mM) and water.

Contrast enhancement by **1-(*R*)** and **1-(*S*)** was also evaluated *in vivo*. Figure 3 shows T1-weighted MR images of mice before and after intravenous injection of **1-(*R*)**, **1-(*S*)**, and Gd-DTPA (0.10 mmol Gd/kg). Since most of the injected Gd-DTPA was excreted through the kidney, and accumulated in the bladder within 30 min, little contrast enhancement was observed except for the kidney. In contrast, no accumulation of **1-(*R*)** or **1-(*S*)** in specific organs, such as the liver and kidney, was observed with high and prolonged contrast enhancement throughout the entire bodies of mice. They also showed improved vascular retention and a moderate renal excretion rate (completely excreted after 24 h).

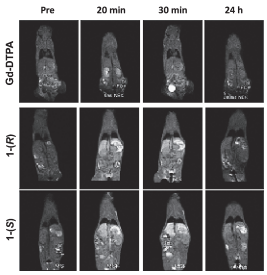


Figure 3. T1-weighted MR images before and after intravenous injection of Gd-DTPA (top), **1-(*R*)** (middle), and **1-(*S*)** (bottom).

In order to discuss the differences between optical isomers, the time-course of the signal intensities (SI) at the blood vessels in MR images was measured to indicate that the rate of clearance of **1-(*R*)** was faster than that of **1-(*S*)** (Figure 4). In addition, the concentrations of Gd^{3+} in the blood and urine, 60 minutes after the injection of **1-(*R*)** and **1-(*S*)**, were quantified by an atomic absorption spectroscopy, which showed that 30.2% of **1-(*R*)** and 20.6% of **1-(*S*)** were transferred to urine, while 22.9% of **1-(*R*)** and 27.8% of **1-(*S*)** were retained in the blood, respectively. All results obtained strongly support that **1-(*S*)** is retained in vasculature for longer than **1-(*R*)** after administration in a mouse body.

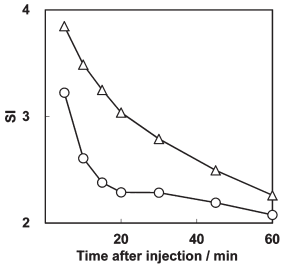


Figure 4. Time-course of the signal intensities (SI) at the blood vessels in MR images after injection of **1-(*R*)** (circular symbol) and **1-(*S*)** (triangular symbol).