

Study of rare earth encapsulated carbon nanomolecules for biomedical uses[☆]

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Received 30 July 2004; received in revised form 6 December 2004; accepted 6 December 2004

Available online 27 June 2005

Abstract

Gd@C₈₂(OH)₄₀ has been proposed to be as a new generation of the magnetic resonance imaging (MRI) contrast agent, but water-soluble fullerenols Gd@C₈₂(OH)_n with $n > 36$ can easily lead to open-caged structures of a high instability. This restricts the practical bio-uses of Gd-metallofullerenols with a large number of hydroxyl groups. To explore how the imaging efficiency varies with decreasing hydroxyl number in Gd@C₈₂(OH)_n, of a good stability in vivo, Gd@C₈₂(OH)₂₂ was prepared, characterized and its imaging efficiency in mice was studied. This work aims at searching a chemical form of water-soluble Gd-metallofullerenols that satisfy both requirements of the good stability and high imaging efficiency in vivo. The results indicate that the proton relaxivity of Gd@C₈₂(OH)₂₂ is lower than that of Gd@C₈₂(OH)₄₀, but still higher than the commercial Gd-DTPA MRI contrast agent.

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Keywords: Gd-metallofullerenol; Gd@C₈₂(OH)₂₂; Stability; MRI contrast agent; In vivo

1. Introduction

Probably, rare earth elements encapsulated metallofullerenes are the most important family in the endohedral fullerenes [1] (fullerene cage encapsulating atoms, clusters, or small molecules), because of their potential applications. So far, metallic elements that have been encapsulated by fullerene cages are shown in Table 1 (the bold element symbols). Among them, all of rare earth atoms encapsulated metallofullerenes can be produced by the conventional arc discharge method [2] similar to C₆₀ production. Applica-

tions of these metallofullerenes are of great interest, and they have been proposed for potential applications in many fields including biomedical uses. More extensive applications come from properties of a tremendous number of their derivatives that can be designed according to the practical demands and produced by chemical/physical modifications of carbon cages.

Because of the unpaired electrons in the metallic atom of the rare earth element, their application in magnetic resonance imaging (MRI) is an intriguing topic. Shinohara et al. developed the first water-soluble gadolinium-metallofullerenes, Gd@C₈₂(OH)₄₀-based MRI contrast agent [3]. The measurement of water proton relaxivity (R_1) indicated that R_1 (the effect on the longitudinal relaxation rate, $1/T_1$) was about 20 times higher than that of the commercial MRI contrast agent Gd-DTPA in vitro. The MRI study of gadolinium fullereneol in mice confirmed its significantly

[☆] A part of work was carried out in Beijing Synchrotron Radiation Facility.

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Table 1
All of the rare earth elements have been encapsulated by fullerene cages

	1																			18	
1	H																				He
2	Li	Be																			Ne
3	Na	Mg																			Ar
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr			
5	Rb	Sr	Y	Zr	Nb	Mo	To	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe			
6	Cs	Ba	Ln	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn			
7	Fr	Ra	An	Rf	Db	Sg	Bh	Hs	Mt	110	111	112				114			116		
	Lanthanoids	La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu					
	Actinoids	Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr					

In this periodic table, metallic elements marked by bold element symbols, some of their clusters, or small molecules have already been encapsulated into the fullerene cages, forming metallofullerenes. They are produced by the conventional arc discharge method similar to C₆₀ production.

high imaging efficiency in vivo. It was hence proposed as a new generation of the MRI contrast agent. Recently, Bolskar et al. developed another water-soluble gadolinium-metallofullerenes, Gd@C₆₀[C(COOH)₂]₁₀ [4]. The relaxometry measurements reveal that it possesses a relaxivity comparable to that of commercially available Gd-DTPA-based MRI contrast agent.

As all these rare earth elements encapsulated carbon nanomolecules, RE@C₈₂, RE@C₆₀, etc., are not dissolved in water, they hence need to be water-solubilized for the biomedical uses. Previously, to gain better solubility required by practical applications, it was suggested to increase the number of the hydroxyl group. Recently, a study on the influences of structural properties on the stability of water-soluble fullerenes [5] found that the stability of fullerlenols largely depends on the quantity of the attached exotic groups. In the synthesis process of fullerlenol molecules, the instantaneous formation of impure groups was observed. It was found that the water-soluble fullerlenols with hydroxyl group $n > 36$ can easily lead to open-caged structures, which are unstable and strongly influence functionalized properties mentioned above. Namely, we cannot use the water-soluble fullerlenols with too many hydroxyl groups, in particular for applications in vivo. Accordingly, it is interesting to explore how the imaging efficiency varies with the decrease of the hydroxyl number of Gd@C₈₂(OH)_{*n*}. To assure the good stability of MRI contrast agent in vivo, one may have to reduce the hydroxyl number of Gd@C₈₂(OH)_{*n*} in practical uses. To this end, we prepared water-soluble Gd-fullerenols with a less number ($n \sim 22$) of the hydroxyl groups (about half compared to Gd@C₈₂(OH)₄₀ [3]), and examined its imaging efficiency in mice. The work aims at searching an appropriate chemical form for water-soluble Gd-fullerenols that satisfies both conditions of good stability and high efficiency for magnetic resonance imaging in vivo.

2. Experimental

The metallofullerenes were synthesized using arc discharge method [2]. The soot was dissolved in DMF, and the products were extracted using a high-temperature and high-pressure method [6]. Separation and isolation of Gd@C₈₂ were performed using the high-performance liquid chromatography (HPLC, LC908-C60, Japan Analytical Industry Co.) coupling with 5PBB and then Buckyprep columns (Nacalai Co., Japan) [7]. The isolated Gd@C₈₂ species were identified by the matrix-assisted laser desorption time-of-flight mass spectrometer (MALDI-TOF-MS, AutoFlex, Bruker Co., Germany). The purity of the final Gd@C₈₂ product was about 99.5%. The synthesis method of water-soluble Gd-fullerenols was the alkaline reaction [3,8]. The Gd@C₈₂ toluene solution was first mixed with aqueous solution containing 50% NaOH, and then several drops of catalyst of 40% tetrabutylammonium hydroxide (TBAH) were added into the reaction system. The mixture of solutions was vigorously stirred at room temperature, the color of the solution in beaker was changed from the originally deep violet into colorless, meanwhile a brown sludge precipitated onto bottom of the beaker. After adding more water into the brown sludge, it was stirring over night. The brown precipitate was washed using MeOH, which was then removed by the vacuum-evaporation system. This washing manipulation was repeated several times for a complete removal of the remnant TBAH and NaOH. Finally, the brown precipitate was dissolved into deionized water with continuous stirring for 24 h until the solution color became a clear reddish brown. Then, it was purified by a Sephadex G-25 column chromatography (5 cm × 50 cm) with an eluent of neutralized water. The remained trace catalyst and Na⁺ ions were completely removed in this process. To obtain a final Gd-metallofullerenol product of a narrow region of distribution of

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