

Development of metallofullerene separation by chemical reduction

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Endohedral metallofullerene (EMF) is promising material for the nuclear medicines. For such application, rapid and efficient separation method of EMFs from empty fullerenes is required. Recently, we developed a new separation method combining the reduction of EMFs using an electron donor and the difference between reduced EMFs and empty fullerenes in the solubility to a polar solvent, such as methanol (MeOH), acetonitrile (MeCN) and ethanol (EtOH). We quantitatively investigated the separation efficiency of whole EMFs by the radio-tracer method using ¹³⁹Ce and also the recovery rate focused on M@C₈₂ by high performance liquid chromatography (HPLC) analysis. The determined separation rate of whole EMFs using MeOH, MeCN, and EtOH as a polar solvent were found to be 41±1%, 58.1±0.6%, and 53±1%, respectively. The recovery rate of M@C₈₂ using MeOH was found to be 65%, while those using MeCN and EtOH could not be determined because of insufficient separation for higher fullerenes.

I. INTRODUCTION

EMF is a molecule encapsulating metal atoms or metal clusters such as tri-metal nitride clusters and di-metal carbide clusters in a fullerene cage [1]. In addition to this unique structure, the electronic properties of EMFs are also interesting. For example, EMFs are easily reduced and oxidized compare to empty fullerenes because of their small electrochemical bandgap. By the use of these unique properties, it is considered that EMF is promising material for a radiopharmaceutical to deliver encapsulated radioisotopes safely. In general, it is required high specific radioactivity and chemical purity for such application.

It is well known that the large amount of empty fullerenes, such as C₆₀ and C₇₀, are produced as a by-product during the EMF production by the arc-discharge method which is typically used for the fullerene synthesis [2]. Considering about radiopharmaceutical application, it is necessary to remove such large amount of by-products. To remove these empty fullerenes, HPLC method have been conventionally used. But this method is time and solvent consuming process. Therefore, to obtain the radioactive EMFs (REMFs) with high specific radioactivity and chemical purity, it is required to develop the efficient separation method for trace amount of REMFs from by-products instead of HPLC separation method.

Various separation methods of EMF have been reported, so far. One of the most efficient method is the electrochemical separation using the difference in the redox potential between EMF and empty fullerenes [3-5]. In 2012, we reported the separation method of EMFs from large amount of empty fullerenes using chemical oxidation by the strong oxidant of TiCl₄ [6]. In this method, EMFs in empty fullerenes are selectively oxidized with TiCl₄, and efficiently separated as the precipitate. So the formation of precipitate composed of EMF-TiCl₄ aggregate and their particle size is the most important parameters, this separation method could be effectively applied for the separation of the “Cold” EMFs. However, this method is not suitable for the separation of trace amount of REMF, because the formation of aggregate and their size are expected to be insufficient.

Recently, we developed a new separation method without aggregation of EMFs combining the reduction of EMFs using an electron donor and the difference of solubility in a polar solvent between reduced EMFs and empty fullerenes. In this session, we will report the quantitative results of this separation method using radiotracer technique.

II. EXPERIMENTAL

The radioisotope ¹³⁹Ce ($T_{1/2} = 137.6$ d) was produced in the ^{nat}La(d, 2n) reactions at the RIKEN AVF cyclotron. Irradiated La oxide including ¹³⁹Ce was employed for the EMF production. Fullerene crude with EMFs was prepared by arc-discharge method using porous carbon rod containing irradiated La. Produced fullerene crude were dissolved to CS₂. Triethylamine (TEA) was added to these solutions for the reduction of EMFs and then polar solvent of MeOH, MeCN and EtOH was added to remove empty fullerenes as precipitate, respectively. After stirring, these suspended solutions were filtered. The filtrates were treated with dichloroacetic acid (DCA) to neutralize reduced EMFs. After shaking, DCA was

removed by decantation with distilled water. The residue on the filters were recovered by CS₂. Gamma-ray measurement was performed for each filtrate and residue.

HPLC (column: 5PYE, eluent: chlorobenzene) analysis for each sample was also performed to investigate recovery rate of individual EMFs and empty fullerenes.

III. RESULTS AND DISCUSSION

The separation rate $S\%$ is defined as the following:

$$S\% = \frac{\text{EMF amount after separation}}{\text{EMF amount before separation}} \times 100 \quad (\text{eq. 1})$$

EMF amount in the equation 1 is determined by γ -ray measurement of the samples. In the case of using MeOH as a polar solvent, $S\%$ for filtrate and residue were found to be $41 \pm 1\%$ and $51 \pm 1\%$, respectively. Remained radioactivity was found in filter. About half of EMFs found in residue is considered due to insufficient reduction by TEA or low solubility of reduced EMFs to MeOH. In the case of MeCN, $S\%$ for filtrate, residue and in filter were found to be $58 \pm 1\%$, $30 \pm 1\%$, and $12 \pm 0.2\%$, respectively. The $S\%$ for filtrate in this case was little bit increased compare to that in the case of MeOH. However, $S\%$ in filter was also increased. These results indicate that MeCN is suitable for extraction of reduced EMFs but not stabilize the reduced EMFs. In the case of EtOH, $S\%$ for filtrate, residue and in filter were found to be $43 \pm 1\%$, $53 \pm 1\%$, and $4 \pm 1\%$, respectively. These results were almost same as those for MeOH.

Figure 1 shows HPLC chromatograms of (a) fullerene crude extract, (b) residue, and (c) filtrate separated by MeOH. The recovery rate $R\%$ of M@C₈₂ was defined as following:

$$R\% = \frac{\text{HPLC peak area after separation}}{\text{HPLC peak area before separation}} \times 100 \quad (\text{eq. 2})$$

Evaluated $R\%$ for M@C₈₂ in filtrate and residue was found to be 65% and 0%, respectively. Remained 35% of M@C₈₂ was not able to recover. $R\%$ of C₆₀ and C₇₀ in filtrate was found to be 1.3% and 0.43%, respectively. These results show successful removal of C₆₀ and C₇₀ as the main by-products of EMF production. The $R\%$ for C₈₄ as a major higher fullerene is found to be only 1.0%. Although this result is not sufficient, it can be said to be relatively good result. On the other hand, $R\%$ for C₈₄ in the case of MeCN and EtOH were both extremely large compare to that of MeOH case. From these results, MeOH is found to be the best polar solvent among the studied solvent.

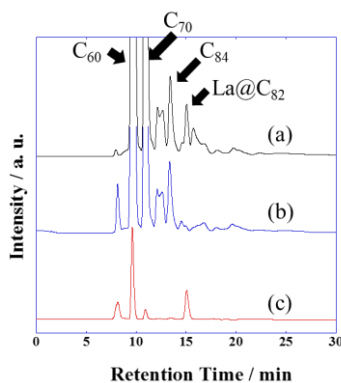


Fig.1. HPLC chromatograms of (a) fullerene crude extract, (b) residue and (c) filtrate by the separation with MeOH.

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