環境分析化学分野　Environmental Analytical Chemistry

環境系・生体系物質計測への展開を目指した新しい化学分析モチーフの開発

Development of Chemical Motifs for Environmental and Biomedicinal Analysis

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当研究室では、環境や医療分野における課題を解決することを目指し、分子認識に基づく新しい分析手法の開発を行っている。分子認識化学に基づき新しい化学モチーフを開発し、実際の分析手法に応用していくことは、分析技術の飛躍的な発展につながると考えている。今年度得た主な成果の中から1) 異核４核 Ca-Tb-TCAS 錯体の合成、および2) がん細胞へ送達可能な Pt(II)-ジラジカル錯体の開発について述べる。

The aim and goal of this division is to develop analytical methods based on molecular recognition, which provides solutions for environmental problems and tasks in medicine. We believe that breakthroughs in analytical technology will be facilitated through the development and application of chemical motifs capable of recognizing materials and through the establishment of methodology for separation/preconcentration and detection/determination methods for materials of environmental and biological importance. Among such chemical motifs that we studied this year, two examples will be described: (1) synthesis of heterotetranuclear Ca-Tb-TCAS complex and (2) active delivery of Pt(II)-diradical complex to cancer cells.

異核４核 Ca-Tb-TCAS 錯体の選択的合成と発光特性

一分子中に異なる金属イオンを有する異核錯体の合成には、同核錯体などの副生成物の生成を抑制するため、配位子の精密な設計や複雑な合成方法が必要であった。我々はチアカリックスアレーン（TCAS）が水溶液中で３種類の異核４核錯体（$Ca_{4-x}Tb_xTCAS_2$, x = 1-3）を自己組織的に形成することを見出した。混合比（Ca:Tb:TCAS）と pH を制御することで、$Ca_1Tb_3TCAS_2$ 錯体（Ca:Tb:TCAS = 1:3:2, pH 6.0）、$Ca_2Tb_2TCAS_2$ 錯体（Ca:Tb:TCAS = 2:2:2, pH 10）、$Ca_3Tb_1TCAS_2$ 錯体（Ca:Tb:TCAS = 3:1:2, pH 11）がそれぞれ選択的に合成可能であった（Fig.1）。また、既報の Tb_3TCAS_2 錯体を合成後、一当量の Ca イオンと混合することで、$Ca_1Tb_3TCAS_2$ 錯体を選択的に合成できた。以上より、構成要素（Ca, Tb, TCAS）を任意の割合で混合し、pH を調整するだけで３種類の異核４核錯体を選択的に合成する方法を確立した。さらに、これらの異核４核錯体は TCAS から Tb へのエネルギー移動発光を示し（Fig.2）、高い量子収率と長寿命発光を持つことを明らかにした。以上より、高い発光機能を持つ異核４核 Ca-Tb-TCAS 錯体の選択的合成法の確立に成功した。

がん細胞への能動的送達を可能とする Pt(II)- ジラジカル錯体の開発

がんの新たな治療法として光熱治療が注目されている。これは生体透過性の高い近赤外（NIR）光を吸収する光熱変換体をがんに送達し、外部から NIR 光を照射することで発生した熱でがん細胞を殺傷することに基づく。課題はがんへの選択的送達である。がん細胞表面に過剰発現しているレセプターをターゲットとするリガンドを光熱変換体に導入できれば、がん細胞に能動的に輸送できる。我々は既に細胞内で NIR 吸収能を示す Pt(II)- ジラジカル錯体を見いだしている。今回モデルとして葉酸（FA）を Pt(II)- ジラジカル錯体へ修飾した。本錯体のがん細胞への送達量を調べたところ非修飾錯体に比べ 10 倍以上であり、FA 修飾の有用性を示すことが出来た。リンカー導入錯体は他のリガンド修飾も可能であり、特定の腫瘍細胞への送達に応用可能である（*Chem. Lett.*, 2022, 51, 1157）。

Selective synthesis and luminescence properties of heterotetranuclear Ca-Tb-TCAS complexes

The synthesis of heteronuclear complex comprising different metal ions required a precise design of ligands or a convoluted synthesis method to circumvent the formation of by-products such as homonuclear complexes. We have found that thiacalixarene (TCAS) self-assembled into three types of heterotetranuclear complexes ($Ca_{4-x}Tb_xTCAS_2$, x= 1-3) in aqueous solution. In the optimum conditions of the mixing ratio (Ca:Tb:TCAS) and pH value, the selective formation of $Ca_1Tb_3TCAS_2$ complex (Ca:Tb:TCAS = 1:3:2, pH 6.0), $Ca_2Tb_2TCAS_2$ complex (Ca:Tb:TCAS = 2:2:2, pH 10), and $Ca_3Tb_1TCAS_2$ complex (Ca:Tb:TCAS = 3:1:2, pH 11) was achieved (Fig.1). In addition, the $Ca_1Tb_3TCAS_2$ complex was selectively synthesized by mixing the previously reported Tb_3TCAS_2 complex with one equivalent amount of Ca ion. As a result of these findings, selective synthesis methods for three types of heterotetranuclear complexes have been developed through the optimization of the Ca:Tb:TCAS ratio and pH condition. Furthermore, these heterotetranuclear complexes exhibited energy-transfer luminescence from TCAS to Tb, with high quantum yield and long luminescence lifetime (Fig.2). In conclusion, we have succeeded in the development of a selective synthesis method of heterotetranuclear Ca-Tb-TCAS complexes possessing high luminescence properties.

Development of Pt(II)-diradical-complex-enabling active targeting of cancer cells

Photothermal therapy, whereby materials capable of a photothermal effect are delivered to cancer and then highly transmitting near infrared (NIR) light is irradiated to produce heat to kill the cancer, has attracted much attention. Selective delivery of the materials to cancer is of key importance. Active targeting is one promising strategy to modify the materials with a ligand that binds to a receptor excessively expressing at the surface of cancer cells. We have already reported Pt(II)-diradical complexes having high photothermal conversion efficiency. Herein, we attached folic acid (FA) to the complex as one of the ligand materials for cancer. As a result, the amount of Pt(II) complex introduced into cancer cells increased 10 times more than that of unmodified Pt(II) complex. The strategy can be applicable to other ligands (*Chem. Lett.*, 2022, 51, 1157).

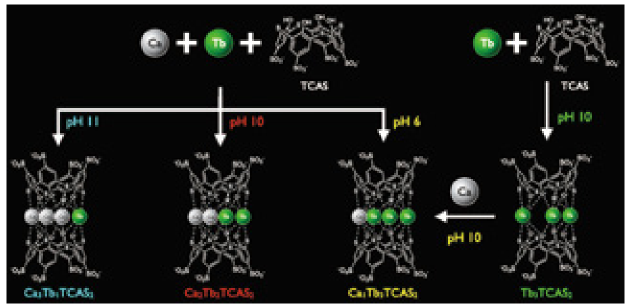

Fig.1 The formation of three types of heterotetranuclear Ca-Tb-TCAS complexes.

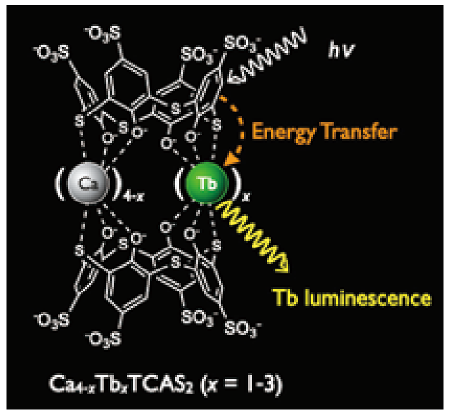

Fig.2 The schematic representation of energy-transfer luminescence in heterotetranuclear Ca-Tb-TCAS complexes.

その他の活動

〔Handbook of Physics and Chemistry of Rare Earth 62の出版〕Naoya Morohashi, Nobuhiko Iki, Lanthanide-calixarene complexes and their applications, HPCRE, Volume 62, 2022, Pages 1-280, Elsevier.

本ハンドブックは希土類の物理と化学の関係する研究領域を網羅する。第 62 巻では Calixarene- 希土類の化学について 531 の文献を渉猟し、配位子設計、錯体の安定性、構造、光物性、機能、材料応用の観点から解説し、445 種類の Calixarene 配位子を取りあげた。

〔基調講演〕Nobuhiko Iki, "Capillary electrophoresis as a tool for kinetics and thermodynamics of biomolecular and metal complex systems" APCE-CECE-ITP-IUPAC 2022, Cambodia.

〔出張講義・見学受入〕宮城県仙台第一高等学校（45 名 , 12 月 7 日）, 北海道北見北斗高校（11 名 , 12 月 15 日）。

〔受賞〕

- 東北分析化学奨励賞「異核複核ランタニド錯体の高機能化と分離分析法の開発」唐島田龍之介、日本分析化学会東北支部、12 月 17 日
- フロンティア・ラボ賞「分光イメージングを用いた近赤外吸収ジラジカル白金錯体の細胞導入の観察」D3 澤村瞭太、みちのく分析科学シンポジウム、7 月 23 日

Other Activities

[Publication of Handbook of Physics and Chemistry of Rare Earth 62]
Naoya Morohashi, Nobuhiko Iki, Lanthanide-calixarene complexes and their applications, HPCRE, Volume 62, 2022, Pages 1-280, Elsevier.
The handbook deals with a research area related to physics and chemistry of rare earth. In Volume 62, we cited 531 studies to describe chemistry of a rare-earth–calixarene complex in terms of ligand design, stability, structure, photophysical properties, functions, and application to materials. The number of calixarene ligands described is up to 445.

[Keynote Lecture]
Nobuhiko Iki, "Capillary electrophoresis as a tool for kinetics and thermodynamics of biomolecular and metal complex systems," APCE-CECE-ITP-IUPAC 2022, Cambodia.

[Visiting lectures and acceptance of lab tours]
Sendai Daiichi High School, Miyagi Prefecture (45 students, December 7) and Kitami Hokuto High School, Hokkaido (11 students, December 15).

[Awards]
- Tohoku Encouragement Award for Analytical Chemistry for "Functionalization of Heteronuclear Dinuclear Lanthanide Complexes and Development of their Separation and Analysis Methods," by Ryunosuke Karashimada, Tohoku Branch, the Japan Society for Analytical Chemistry, December 17.
- Poster Award, Michinoku Symposium of Analytical Sciences, for "Development of near-infrared-absorbing Pt^{II} complexes toward cancer photothermal therapy agents," Ryota Sawamura (D2), October 2.

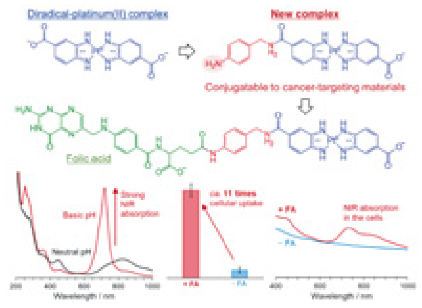

Fig.3 Modification of the Pt(II)-diradical complex with folic acid and enhancement of the delivery to the cells.

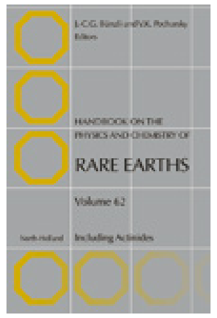

Fig.4 Handbook on the Physics and Chemistry of Rare Earths, vol. 62.

Fig.5 Snapshot of the lab-tour.

Fig.6 Certificate of Tohoku Encouragement Award for Analytical Chemistry.