ウェブサイト公開用

（様式 10）
（海外特別研究員事業）
令和　1年　6月　23日

海外特別研究員最終報告書

独立行政法人 日本学術振興会 理事長　殿

採用年度　平成30年度
受付番号　201860537
氏　　名　三原のぞみ
（氏名は必ず自署すること）

海外特別研究員としての派遣期間を終了しましたので、下記のとおり報告いたします。
なお、下記及び別紙記載の内容については相違ありません。

記

1. 用務地（派遣先国名）用務地：　ケンブリッジ　（国名：　イギリス　）

2. 研究課題名（和文）※研究課題名は申請時のものと違わないように記載すること。
外部刺激応答性超分子ケージのダイナミックな構造変化を利用した分子認識・放出

3. 派遣期間：平成　30　年　4　月　1　日　～　令和　1　年　6　月　25　日

4. 受入機関名及び部局名
Department of Chemistry, University of Cambridge,

5. 所期の目的の遂行状況及び成果…書式任意 **書式任意（A4 判相当 3 ページ以上、英語で記入も可）**

（研究・調査実施状況及びその成果の発表・関係学会への参加状況等）

（注）「6. 研究発表」以降については様式 10－別紙 1～4 に記入の上、併せて提出すること。

Progress of the research

As I planned in the original research proposal, I successfully synthesized a stimuli-responsive coordination cage. Although the stimuli-responsive uptake and release of guest molecules was not observed, even more interesting phenomenon involving circulatory motion of the cage was achieved as described below. This result has been accepted to the journal "*Angew. Chem. Int. Ed.*". I presented this result on "14th International Symposium on Macrocyclic and Supramolecular Chemistry", "The 9th Joint CSJ RSC Symposium", and "The BP Sustainable Lecture of Department of Chemistry, University of Cambridge" where I got "The Best Poster Award".

(1) Abstract

Controlled directional transport of molecules is essential to complex natural systems, exemplified by cellular transport up to organismal circulatory systems. In contrast to these natural systems, synthetic systems that enable transport of molecules between several spatial locations on the macroscopic scale, when external stimuli are applied, remain to be explored. Here we report the transfer of a supramolecular cage with controlled directionality between three phases, based on the cage that responds reversibly in two distinct ways to different anions. Notably, circulatory phase transfer of the cage was demonstrated based on a system where the three layers of solvent are arranged within a circular track. The direction of circulation between solvent phases depended upon the order of addition of anions.

(2) Introduction

Transport of molecules between several spatial locations is essential to the functioning of complex natural systems. On a macroscopic scale, a circulatory system allows blood to transport nutrients throughout an organism. Scaled down to cellular transport, molecules are continuously transported between organelles, and in and out of the cell. Taking inspiration from these natural systems, it would be desirable to construct artificial systems where components are controllably transported between locations on a macroscopic scale, based on synthetic molecules that can interact with chemical signals, which induce different transport processes. In the present study we demonstrate phase transfer of a stimuli-responsive cage within a system consisting of three mutually immiscible solvent phases, in which the direction of transfer is controlled by the order of application of distinct chemical signals. Notably, the cage showed circulatory phase transfer with controlled directionality when the three solvent phases were arranged in a circuit. This circulation could enable the development of new chemical purification systems involving the selective uptake and release of cargoes in specific spatial locations.

Supramolecular cages and macrocycles are a versatile platform for the construction of stimuli-responsive materials, since a wide variety of stimuli-responsive subcomponents may be incorporated into them. The structure and electronic state of these assemblies can be altered by the application of stimuli that include electrons, light, pH, ions, and small molecules. This stimuli-responsive behavior has been utilized to control their functions that have included molecular recognition and catalysis. A remaining important challenge in this field is the construction of supramolecular cages which respond to more than two stimuli in reversible and distinct ways, resulting in different outputs. Such cages could serve as building blocks for complex and functional supramolecular systems, where the output of one part serves as the input for another.

Herein we report the circulatory phase transfer of a newly synthesized $Fe^{II}_4L_4$ tetrahedral cage containing tricoordinated boron atoms at the center of each face (Figure 1a), in response to the addition of three different anions. Each such boron center shows selective and reversible binding of F^- to form a four-coordinate fluoroborate, thus diminishing the total charge of the cage from 8+ to 4+. Since the cationic character of the cage also drives interaction with a variety of non-coordinating anions, the phase preference of the cage can be controlled by the addition of different anions to induce transfer between specific pairs of phases. An anion grafted with perfluoroalkyl groups was found to solubilize the cage selectively in a fluorous phase, which made it possible to construct a triphasic system of immiscible solvent phases. Notably, the direction of the circulatory phase transfer of the cage can be controlled by changing the order of stimulus addition. Although phase transfer of molecules within conventional biphasic systems is well-known, to the best of our knowledge this is the first example of a molecule which can be transferred within a triphasic solvent system in response to chemical stimuli.

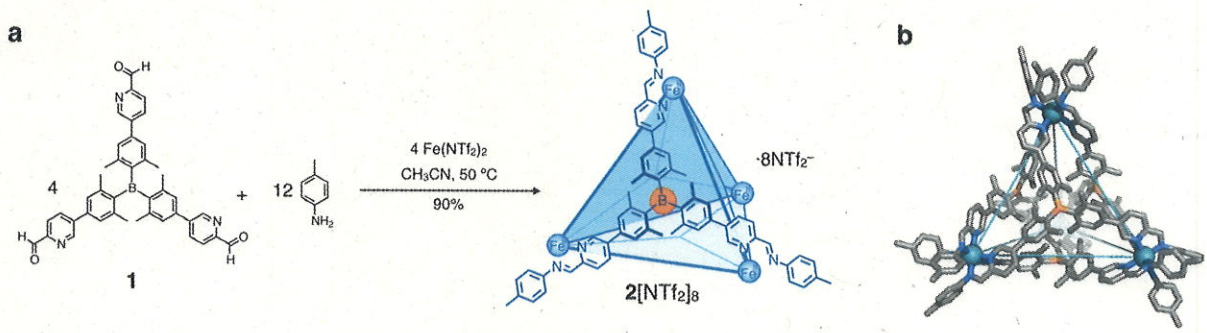

Figure 1. (a) Cage **2** was prepared from tritopic aldehyde **1**, p-toluidine, and iron(II) triflimide. (b) the crystal structure of **2** (Fe, light blue; N, blue; B, orange; C, grey). Hydrogen atoms, counteranions and disorder are omitted for clarity.

(3) Results and Discussion

Borane-containing tris(formylpyridine) **1** was prepared in 3 steps from 5-bromo-2-iodo-1,3-xylene. The reaction of **1** (4.0 equiv), p-toluidine (12 equiv), and iron(II) bis(trifluoromethanesulfonyl)imide (iron(II) triflimide or $Fe^{II}(NTf_2)_2$, 4.0 equiv) yielded $Fe^{II}_4L_4$ assembly **2**$[NTf_2]_8$ (Figure 1a), as confirmed by NMR spectroscopy and ESI-MS (Figure 2a). Vapor diffusion of benzene into an acetonitrile solution of **2**$[NTf_2]_8$ gave crystals suitable for structure determination by X-ray diffraction. A representation of the X-ray structure of **2** is shown in Figure 1b.[12] Four octahedral Fe(II) centers are bridged by four ligands, each of which caps a face of the tetrahedron. All of the boron atoms have a planar sp^2 configuration. The ligands on all faces of **2** have the same C_3-symmetric propeller-like configuration, in which the handedness of the propeller is the same as that of the Fe^{II} centers due to the conformational rigidity of the cage framework.

To investigate the binding of F^- by **2**$[NTf_2]_8$, F^- was titrated into a solution of **2**$[NTf_2]_8$ (Figure 2a-b). During the progressive addition of 4 equivalents of tetrabutylammonium fluoride (TBAF) to **2**$[NTf_2]_8$ in CD_3CN, the color of the solution changed from violet to green and new sets of ^1H NMR peaks corresponding to adducts incorporating 1 - 4 equivalents of F^- were observed. This observation indicates that the binding of F^- to the boron centers is slow on the ^1H NMR time scale. A single set of ligand signals was obtained after the addition of 4 equivalents of TBAF (Figure 2b), consistent with the tetrafluoride adduct **2**$\cdot F_4[NTf_2]_4$ having a symmetric structure. In the ^{19}F NMR spectra, a broad signal corresponding to F^- bound to boron was observed at −169 ppm during titration, consistent with the formation of a B-F^- adduct. Since the methyl groups nearest the borane centers were observed as two distinct ^1H NMR peaks, corresponding to inward- and outward-facing methyls, a ^1H-^{19}F HOESY experiment was undertaken to elucidate the geometry of the F^- group. A NOE correlation was only observed between the externally-oriented methyl resonance and the F^- signal, allowing us to conclude that all four F^- ions faced outward. ESI-MS and UV-Vis titration also confirmed the binding of F^- to **2**.

Treatment with 4 equivalents of $BF_3\cdot Et_2O$ was observed to immediately remove F^- from the boron atoms of **2**, resulting in a color change from green back to violet. Peaks corresponding to the original cage **2** were observed in the ^1H NMR spectrum after the reaction (Figure 2b-c), as were ^{19}F NMR signals corresponding to the co-product BF_4^-. F^- binding can thus be used as a stimulus to reversibly change the structure and charge of **2**, which is the key feature allowing the circulatory phase transfer of **2**.

To construct a system composed of three mutually immiscible solvents, fluorous solvents were investigated as one of the solvent phases, since they are known to be immiscible with both water and many organic solvents. Although most nonfluorinated organic molecules are known not to dissolve in fluorous solvents, we found that a substituted tetraphenylborate bearing C_6F_{13} chains (BAr_{f6}^-, Figure 3a) imparted enough fluorous character (59% fluorine content by weight) to render **2** preferentially soluble in fluorous solvents, even though the cage cation contains no fluorine. Counterion exchange of **2** from NTf_2^- to

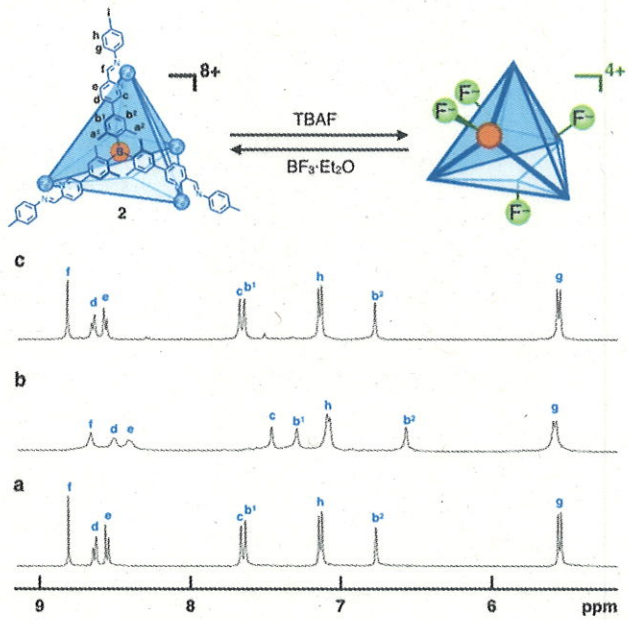

Figure 2. F^- binding of **2** in CD_3CN. ^1H NMR of (a) **2**$[NTf_2]_8$, (b) **2**$[NTf_2]_8$ after the addition of 4 equivalents of TBAF to generate **2**$\cdot F_4[NTf_2]_4$, and (c) the reaction mixture of **2**$\cdot F_4[NTf_2]_4$ with 4 equivalents of $BF_3\cdot Et_2O$.

BAr_{f6}^- thus solubilized **2** in fluorous solvents such as perfluoromethylcyclohexane (PFMC), perfluoro-1,3-dimethylcyclohexane, and perfluorohexane. Notably, this is the first example of a coordination cage that is soluble in fluorous solvents; we anticipate that the use of BAr_{f6}^- could provide a general strategy to solubilize other cationic cages in fluorous phases.

Thus, a triphasic solvent system composed of PFMC, 2,2-dichloropropane (DCP), and water containing 25% acetonitrile was constructed, as shown in Figure 3. When both F^- and BAr_{f6}^- were added, **2** was no longer soluble in the fluorous phase and became soluble in DCP (Figure 3b). It was also found that SO_4^{2-} could solubilize **2** in water containing 25% acetonitrile, consistent with prior reports (Figure 3c).

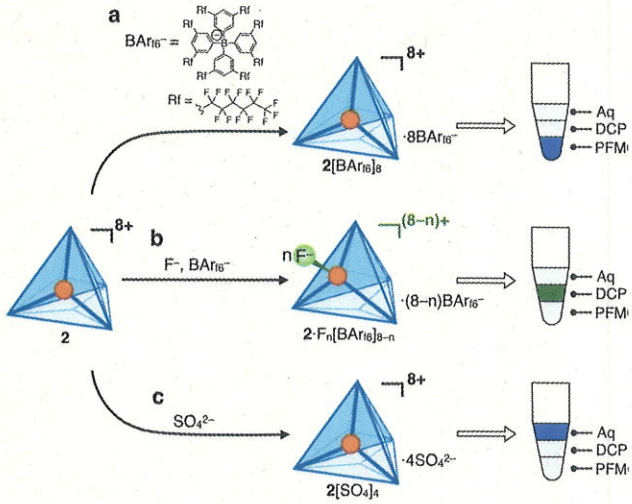

Figure 3. Stimuli-responsive phase preferences of **2**. A triphasic solvent system composed of perfluoromethylcyclohexane (PFMC, densest), 2,2-dichloropropane (DCP, middle), 25% acetonitrile in water (Aq, least dense) was used to investigate the phase preference of **2** under the influence of different anionic stimuli. a) Highly fluorinated BAr_{f6}^- brings **2** into fluorous PFMC. b) The presence of both F^- and BAr_{f6}^- brings **2** into organic DCP. c) Hydrophilic SO_4^{2-} solubilizes **2** in the aqueous phase.

Stimuli could bring cage **2** from any of the phases of Figure 3 into any other phase. Starting with **2**[BAr_{f6}]$_8$ in fluorous PFMC, addition of TBAF (4.0 equiv) to the triphasic system resulted in **2** transferring to organic DCP (Figure 4a). During this process, the color of **2** changed from violet to green, consistent with the formation of the F^- adduct of **2** as described above. The selective binding of F^- to **2** results in a reduced degree of ion pairing with fluorous BAr_{f6}^-. We infer that the resulting fluoride adduct no longer has sufficient fluorous character to be soluble in PFMC. The addition of tetrabutylammonium sulfate (TBA_2SO_4, 3.0 equiv), and $MgSO_4$ (2.0 equiv) resulted in transfer of **2** to the aqueous phase, with the color changing back to violet (Figure 4b). F^- was removed from the system by precipitating as MgF_2 in this step. This phase-transfer cycle could be repeated a second time by the sequential addition of $NaBAr_{f6}$, then TBAF, and finally TBA_2SO_4, and $MgSO_4$ (Figure 4c–e).

Conversely, when TBA_2SO_4 (4.0 equiv) was added to the initial state of the triphasic system, cage **2** transferred to the aqueous phase, then to DCP following the addition of TBAF (8.0 equiv) and $NaBAr_{f6}$ (8.9 equiv). This cycle could also be repeated following the successive additions of the different salts. These results demonstrate that cage **2** underwent directional and reversible transport within the triphasic system depending on the order of addition of anions.

Based upon these results, we designed a platform for circulatory phase transfer by arranging the three solvent layers within a circular glass tube with three injection points, as shown in Figure 5. The transport experiment was performed in a similar manner to the experiments in microtubes. To the initial state, with **2**[BAr_{f6}]$_8$ in fluorous PFMC, TBAF (4.0 equiv) was added (Figure 5a). Gentle agitation resulted in the

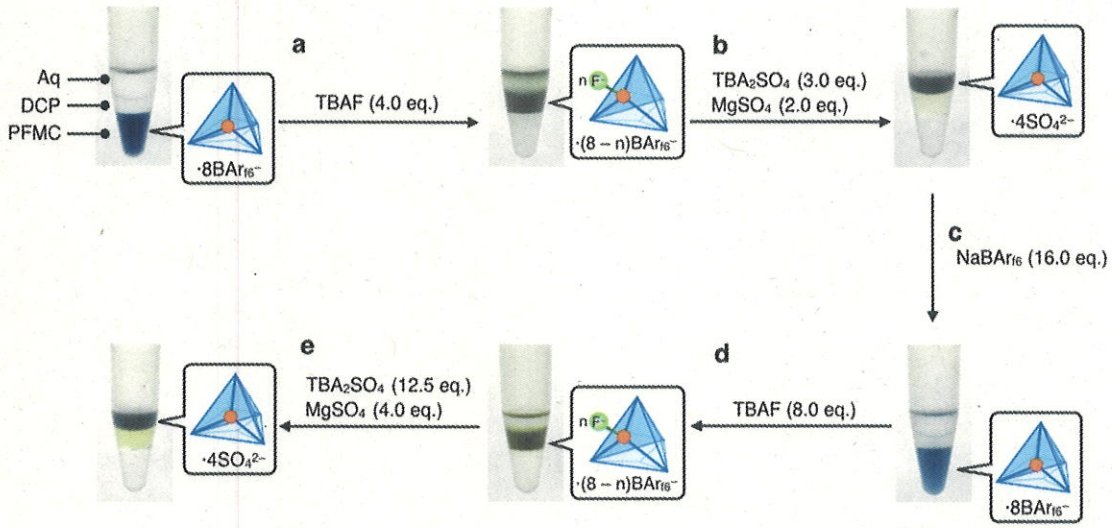

Figure 4. Transport experiment of **2** within the triphasic solvent system. a) Addition of TBAF to **2**[BAr_{f6}]$_8$ in PFMC resulted in cage transfer to DCP. b) Subsequent addition of TBA_2SO_4 and $MgSO_4$ led to the transport of **2** to the aqueous phase. c-e), Progressive addition of $NaBAr_{f6}$, then TBAF, and finally TBA_2SO_4, and $MgSO_4$ led to a second cycle of transport.

transportation of **2** from PFMC to DCP. Subsequent addition of TBA_2SO_4 (3.0 equiv) and $MgSO_4$ (2.0 equiv) resulted in the transfer of **2** to the aqueous phase (Figure 5b). Cage **2** thus moved in a clockwise direction through the circuit. On the other hand, when TBA_2SO_4 (4.0 equiv) was first added, followed by TBAF (8.0 equiv) with $NaBAr_{f6}$ (8.9 equiv), **2** circulated in an anticlockwise direction (first to the aqueous phase and then to DCP, (Figure 5c,d)). The order of applied stimuli thus enabled control over the direction of circulatory phase transfer.

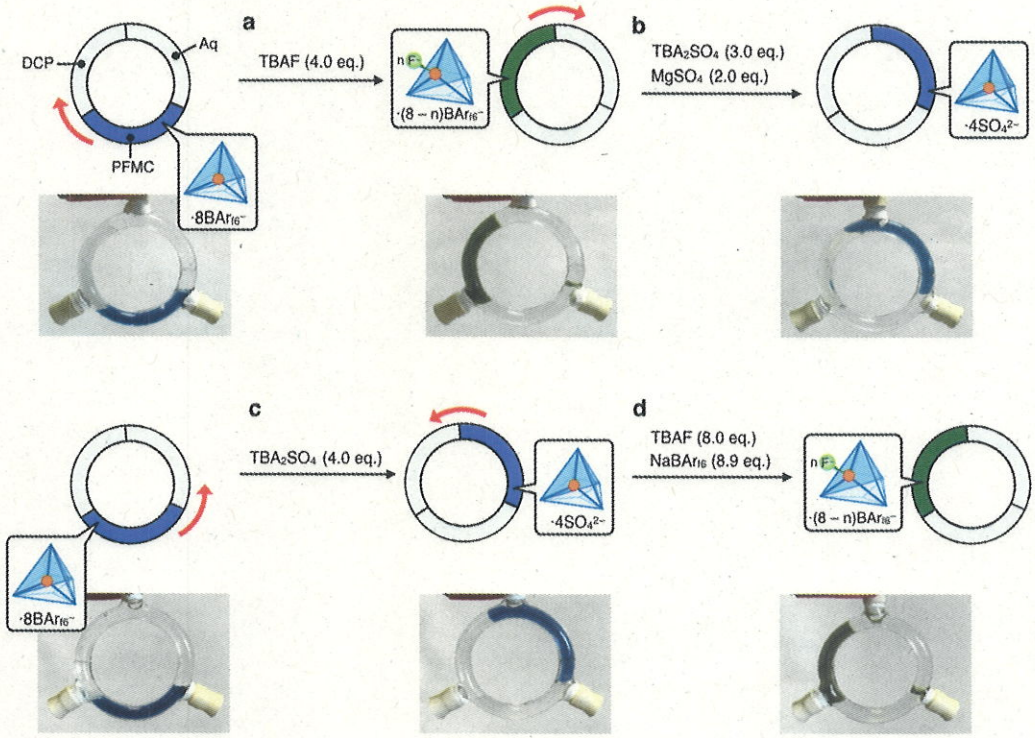

Figure 5. Phase transfer of **2** within a circuit. a-b) When TBAF was first added and TBA_2SO_4 and $MgSO_4$ were added subsequently, **2** was first transported to DCP and then to the aqueous phase, in a clockwise direction. c-d), When TBA_2SO_4 was added first and TBAF and $NaBAr_{f6}$ were added subsequently, **2** moved to the aqueous phase first and then DCP, showing anticlockwise transfer.

(4) Conclusion

This study thus establishes the circulatory phase transfer of stimuli-responsive coordination cage **2**. Directional control over circulatory phase transfer depends upon the responsiveness of **2** to three stimuli: fluoride, the highly fluorinated anion BAr_{f6}^-, and sulfate. The selective fluoride binding to the borane centers is the key feature enabling the phase preference of **2** to be switched. Notably, we present the first example of a coordination cage solubilized in fluorous solvents by utilizing BAr_{f6}^-, which could form the basis of a general strategy for other polycationic cages, which may enable the exploration of new guest recognition phenomena in fluorous solvents. Larger cages than **2**, which would show the ability to bind a range of guest molecules, could be constructed by incorporating the central borane motif of **1** into larger ligand panels. Such larger cages could be built into more sophisticated circulatory guest transport systems. The ability to transit reversibly between three different phases could allow **2** and its analogues to be directed along complex pathways within a fluid network of linked rings, or circulatory phase transfer could be used to pick up a guest in one phase, then move it to another where the cage might open to release its cargo. Such circulatory guest transport could be useful as a new mode of chemical purification.