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Controlled Release of the Guest Molecule via Borate Formation of Fluorinated Boronic Ester Cage

Hisatsugu Takata, Kosuke Ono and Nobuharu Iwasawa*

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

A boronic ester cage, which exhibits stimuli-responsive guest-release behavior, was constructed utilizing self-assembly of the tetrol with indacene backbone and a fluorine-substituted benzenetriboronic acid derivative. The presence of fluorine substituents made it possible to control the guest release rate using simple amines by forming tetrahedral borates.

Controlled release of guest molecules is a desirable feature of host-guest complexes for the applications such as drug delivery, fragrance or pesticide release, separations, purifications or self-healing materials.[1] Many kinds of functional polymer-based supramolecular assemblies such as micelles, reverse micelles, vesicles and gel have been studied as guest carriers.[1] Discrete self-assembled cage molecules are another candidate of carriers which can release a precise amount of guest molecules due to their ability to bind a strict number of guest molecules.[2-6] Stimuli-responsive coordination cages[7] can release guest molecules in response to external stimuli such as addition of extra ligand[2] or guest molecules,[3] redox[4] or pH[2a,5] control, and light irradiation.[6] In most of these cases, partial or complete disassembly of cage framework triggered the immediate and quantitative guest release (Fig. 1a)[2-5] and the study to control the rate of guest release is limited.[3c] Furthermore, compared to the coordination cages, stimuli-responsive self-assembled covalent organic cages with the ability of guest release have rarely been explored due to the stability of the covalent structure,[8,9] although covalent organic cages have advantage over coordination cages which often contain toxic heavy metals when considering the application to the drug delivery system.

We previously reported construction of a boronic ester cage (*homo*-**[3+2]-H$_6$**) composed of three molecules of the same enantiomer of tetrol **1**[10] and two molecules of 1,3,5-benzentriboronic acid,[11] simply by mixing these two components in methanol.[12] When the same reaction was run in the presence of aromatic co-solvents such as benzene or toluene, *homo*-**[3+2]-H$_6$** including one molecule of the aromatic guests precipitated out in high yield, while a diastereomeric boronic ester cage *hetero*-**[3+2]-H$_6$** composed of different enantiomers of **1** formed selectively with one molecule of *o*-xylene inside the cage by mixing in a methanol-*o*-xylene mixed solvent. However, once these host-guest complexes were dissolved in chloroform, the guest molecule was released from *homo*- or *hetero*-**[3+2]-H$_6$** rapidly through apertures of the cage, and only the guest molecule outside of the cage was observed by ^{1}H NMR spectra. During these works, we happened to find that the guest-release process could be observed by ^{1}H NMR when *o*-xylene@*homo*-**[3+2]-H$_6$**, which was prepared by recrystallization of apohost *homo*-**[3+2]-H$_6$** from *o*-xylene, was dissolved in $CDCl_3$. In this paper, we describe stronger encapsulation of the guest molecule by using a fluorine-substituted boronic ester cage and its application to a stimuli-

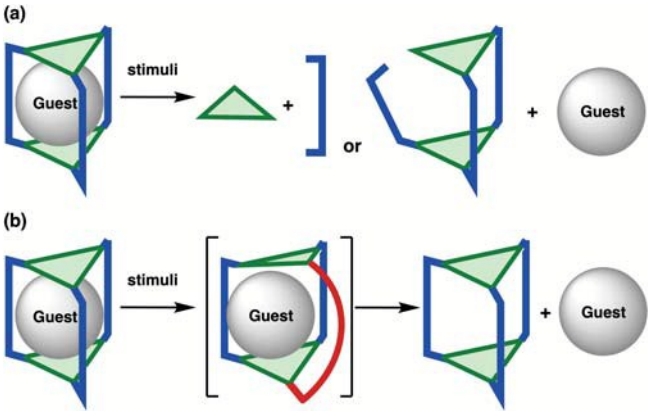


Fig. 1 Schematic representation of release of guest molecules from stimuli-responsive self-assembled cages (a) by complete or partial disassembly of cage framework or (b) via conformational change of cage framework.

Department of Chemistry, Tokyo Institute of Technology
O-okayama, Meguro-ku, Tokyo 152-8551 (Japan)
E-mail: niwasawa@chem.titech.ac.jp

† Electronic Supplementary Information (ESI) available: For materials, instrumentation, synthetic procedures, kinetic studies and X-ray crystallographic studies. CCDC 1908938. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

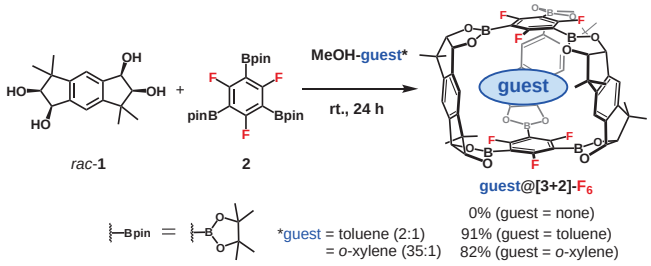
responsive, controlled guest-release system by utilizing coordination of a Lewis base to the boron atom, which induces conformational change of the covalent cage framework for guest release (Fig. 1b).[13]

Just after the dissolution of *o*-xylene@*homo*-**[3+2]-H$_6$** in $CDCl_3$, the chemical shift of *o*-xylene included in the cage was observed in higher field (5.4 and 3.2 ppm for aromatic protons, -0.1 ppm for methyl protons) than that of outside of the cage (7.1 ppm for aromatic protons, 2.2 ppm for methyl protons, Fig. S1a). Intensity of these encapsulated peaks decreased gradually and disappeared completely within 2 hours. In order to make the guest-release much slower, we thought of constructing a similar cage which contained fluorine atoms in benzenetriboronic acid moieties with the expectation that electron-deficient nature of the fluorinated benzene ring would increase the π-π interaction with the guest molecule[14] and that the fluorine atoms would become a steric hindrance to the release of the guest molecule.[15] We further expected that fluorinated boronic ester would have higher Lewis acidity, which might make the borate formation easier, resulting in the change of the structure of the host molecule.[16]

The boronic ester cage containing six fluorine atoms (**[3+2]-F$_6$**) was prepared by using the tetrol **1** and 2,4,6-trifluoro-1,3,5-benzenetriboronic acid tris(pinacol) ester **2**. As in the case of **[3+2]-H$_6$**,[12] **[3+2]-F$_6$** containing an aromatic guest precipitated out simply by mixing **1** and **2** in a methanol-guest mixed solvent (Scheme 1), and X-ray analysis of the complex confirmed the structure to be *homo*-**[3+2]-F$_6$** composed of three molecules of the same enantiomer of **1** (Fig. 2) (see the ESI†).[17] There were some differences between **[3+2]-H$_6$** and **[3+2]-F$_6$** in the self-assembling behavior. When using this fluorinated boronic acid, no formation of any cage was observed in the absence of an appropriate guest in contrast to **[3+2]-H$_6$** which was formed even without any aromatic guest molecule in methanol. Furthermore, *o*-xylene@*homo*-**[3+2]-F$_6$** was obtained by mixing the components in methanol-*o*-xylene mixed solvent, while *o*-xylene@*hetero*-**[3+2]-H$_6$** was formed by the similar procedure and recrystallization of the apohost from *o*-xylene was required for formation of *o*-xylene@*homo*-**[3+2]-H$_6$**.

Next, we compared the guest-release rate of **[3+2]-F$_6$** with that of **[3+2]-H$_6$** in solution. It was found that in contrast to the case of *o*-xylene@*homo*-**[3+2]-H$_6$** which released *o*-xylene in 2 hours, it took more than 2 days for *o*-xylene@*homo*-**[3+2]-F$_6$** to release the guest molecule completely (Fig. 3). Then we calculated the rate constants of the *o*-xylene-release from time-dependent change in the ratio of the concentration of *o*-xylene inside and outside of the cage. The rate of guest-release from *homo*-**[3+2]-F$_6$** turned out to be 6.52×10^{-6} s^{-1} which was only one-sixtieth of that of *homo*-**[3+2]-H$_6$** (3.82×10^{-4} s^{-1}, Scheme 2). In other words, introduction of fluorine atoms expectedly made the release of *o*-xylene sixty times slower.

We first thought that this suppression of *o*-xylene-release was simply due to the relatively strong π–π interaction between



Scheme 1 Self-assembly of fluorinated cage employing the template effect.

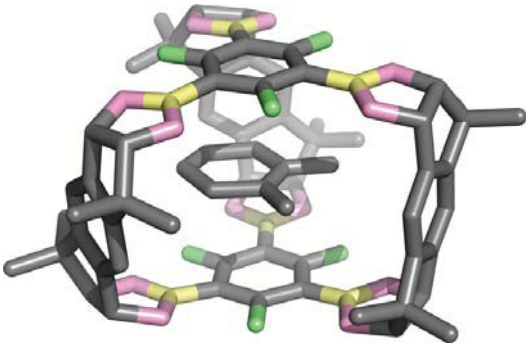


Fig. 2 X-ray crystal structure of *o*-xylene@*homo*-**[3+2]-F$_6$**.

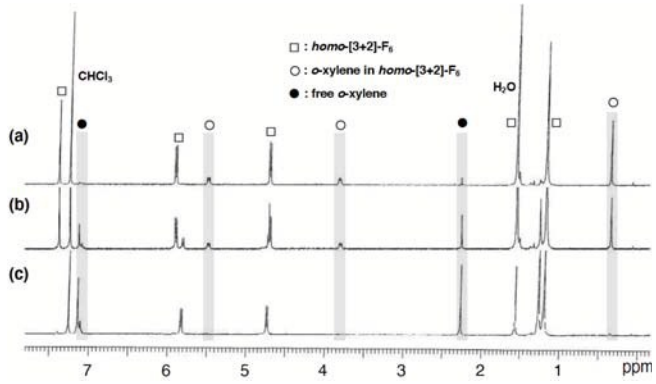
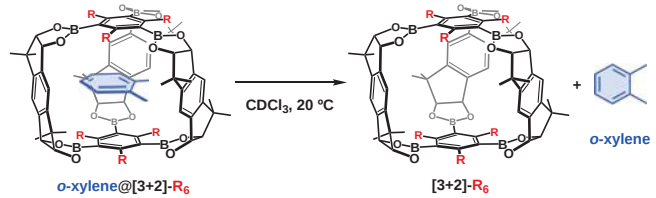


Fig. 3 Time-dependent change of ^{1}H NMR spectra after dissolution of *o*-xylene@*homo*-**[3+2]-F$_6$** in $CDCl_3$. (a) 5 minutes, (b) 8 hours and (c) 2 days.



R	k / s^{-1}
H	3.82×10^{-4}
F	6.52×10^{-6}

Scheme 2 Substitution effect of fluorine atoms on guest-release rate.

Table 1 Activation parameters of the guest-release of *homo*-**[3+2]-R$_6$** at 293 K.[a]

	ΔG‡ / kcal mol^{-1}	ΔH‡ / kcal mol^{-1}	ΔS‡ / cal mol^{-1} K^{-1}
R = H	**21.9**	**21.1**	**−2.6**
R = F	**24.1**	**17.0**	**−24.2**

[a] See the Supporting Information.

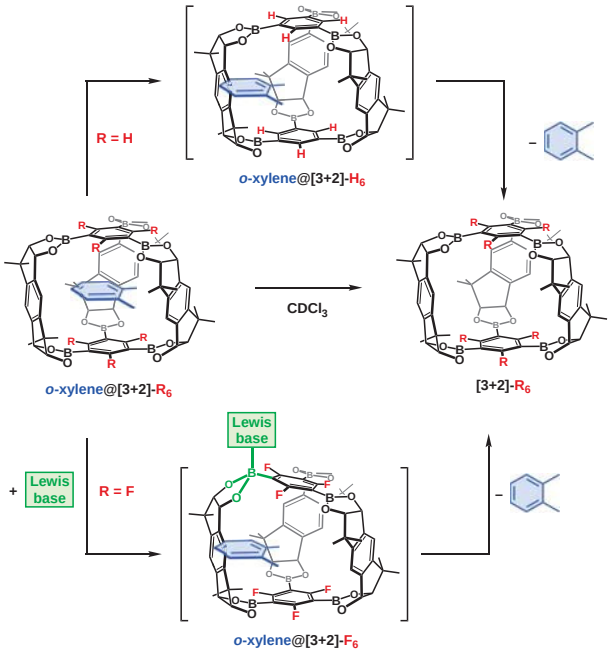
Table 2 Rate constants of the guest-release of *o*-xylene@*homo*-**[3+2]-R$_6$** in the presence of amines in $CDCl_3$.[a]

amine	none	DABCO	DMAP	piperidine
R = H	3.82×10^{-4} (1.0)	1.39×10^{-3} (3.6)	9.84×10^{-4} (2.6)	1.01×10^{-3} (2.6)
R = F	6.52×10^{-6} (1.0)	4.76×10^{-4} (73)	2.09×10^{-3} (320)	5 min complete (>1840)

[a] Measured at 293 K with 10 equivalents of amines.

benzenetriboronic acid moiety of **[3+2]-F$_6$** and *o*-xylene, and therefore activation enthalpy of the *o*-xylene-release of **[3+2]-F$_6$** would be higher than that of **[3+2]-H$_6$**. Unexpectedly, however, according to the Arrhenius plot created on the rate constants measured at various temperatures, the value of activation enthalpy of **[3+2]-F$_6$** was found to be considerably lower than that of **[3+2]-H$_6$** (Table 1). Furthermore, the activation entropy of the guest-release from **[3+2]-F$_6$** was much more negative than that from **[3+2]-H$_6$** (−24.2 cal mol^{-1} K^{-1} vs. −2.6 cal mol^{-1} K^{-1}).

These differences in activation parameters suggested that *o*-xylene was released from the two hosts by different mechanisms. In the case of **[3+2]-H$_6$**, *o*-xylene included inside is thought to be released from the aperture slightly-expanded by simple conformational change of the cage (Scheme 3, top). In the case of **[3+2]-F$_6$**, however, the guest-release is thought hardly to proceed by the same mechanism as with **[3+2]-H$_6$** probably because of stabilization for the host-guest complex due to enhancement of π–π interaction, and/or steric hindrance of fluorine atoms which are somewhat larger than hydrogen atoms.[14,15] Instead, the guest molecule was thought to be released via borate-formation between the boron atom in **[3+2]-F$_6$** and a Lewis base such as water present in a trace amount in chloroform-*d*, resulting in expansion of the cavity (Scheme 3, bottom).[16]



Scheme 3 Proposed mechanism of *o*-xylene-release from *homo*-**[3+2]-R$_6$** (R = H or F).

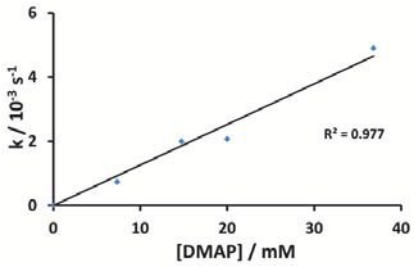


Fig. 4 Relation between the rate constant of *o*-xylene-release and concentration of DMAP.

To support this assumption, addition of a more effective Lewis base in the guest-release reaction was examined. It was found that the release of *o*-xylene was really accelerated in the presence of an amine (Table 2). It is noteworthy that the accelerating effect was much larger in the case of **[3+2]-F$_6$** compared to **[3+2]-H$_6$**. For example, the release rate of *o*-xylene from *o*-xylene@**[3+2]-F$_6$** was about 300 times higher in the presence of 10 equivalents of *N,N'*-dimethylaminopyridine (DMAP) while the rate from o-xylene@**[3+2]-H$_6$** became only 2.6 times higher. Furthermore, the acceleration effect is dependent on the kind of amine base, and piperidine drastically shortened the time required for complete release of *o*-xylene in **[3+2]-F$_6$** from 2 days to less than 5 minutes suggesting that the acceleration effect is >1840. Thus, control of the guest-release rate could be achieved by the choice of base.

Additional experiments using various amounts of DMAP showed that the reaction rate constant increased in the first-order proportion to concentration of DMAP (Fig. 4). Thus *o*-xylene was released from **[3+2]-F$_6$** via borate formation in which one DMAP molecule coordinates to one of boron atoms in **[3+2]-F$_6$** (Scheme 3). Borate formation was clarified by several measurements. Upon the addition of DMAP to the solution of **[3+2]-F$_6$**, up-field shift (Δδ = –8 ppm) of the peak in ^{11}B NMR was observed (Fig. S11).[13] The adduct formation of **[3+2]-F$_6$** and DMAP was also examined by ITC measurement (Fig S12). It was found that **[3+2]-F$_6$** formed an adduct with one DMAP molecule with the association constant ca. 716 M^{-1}. Based on the

association constant about 88% **[3+2]-F_6** formed 1:1 adduct with DMAP in the guest-release experiment.

In conclusion, we constructed boronic ester cage which can keep *o*-xylene inside its cavity for prolonged periods of time even in solution by employing fluorine-substituted skeleton. Furthermore, its application as a stimuli-responsive guest-release system was also achieved.[18] This guest-release does not require any competitive guest molecules or partial or complete collapse of the cage structure, and proceeds by the addition of simple amines. Furthermore, the guest release rate could be controlled by the kind of amines employed. This boronic ester cage provides a new possibility of boron-containing supramolecular hosts for functional materials.

We thank Drs. Hidehiro Uekusa and Kotaro Fujii for performing X-ray analysis. This work was supported by a CREST (Core Research for Evolution Science and Technology) project from the Japan Science and Technology Agency (JST) and JSPS KAKENHI Grant Number 15H05800.

Conflicts of interest

There are no conflicts to declare.

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18 Stimuli-responsive guest-release was also observed by using 2-methylanisole@**[3+2]-F_6** and DMAP as additive; see Table S2 for details.

