Cesium Cation Complexation by a Flavin Receptor via Self-Assembly and Deprotonation

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ABSTRACT: This study focuses on the self-assembly of a new flavin compound and its scaffolding function for a Cs⁺ ion. 7,8-Dimethyl-10-[4′-(methoxycarbonyl)phenyl]-isoalloxazine (FIH-MB) displays self-assembly in a DMSO solution and has strong dependence on the solvent. In the DMSO solution, both the resulting scaffold and the deprotonation of FIH-MB were demonstrated to induce complex formation with a Cs⁺ ion, which was investigated by UV-vis, 1H NMR, and fluorescence titrations. This complex formation involves both Coulombic and cation-π interactions through the FI⁻ site in an FI⁻—MB dimer.

1. INTRODUCTION
Supramolecular chemistry is of great current interest because of the intriguing structural diversity of supramolecular compounds and their potential applications. Various macrocyclic compounds such as crown ethers, calixarenes, cyclophanes, and naphthalenes have been investigated as cavities for various ions. In this regard, studying the design and synthesis of receptors capable of sensing environmentally and chemically important ions is a topic of interest. The leakage of radioactive Cs-137, related to the Fukushima disaster, remains a grave problem because microparticulate aerosols have resulted in long-term soil and water contamination. To address this issue, a supramolecular fluorescent probe with a cavity suitable for sequestering a Cs⁺ ion has been reported, which holds promise for the detection of Cs-137.

Flavooquinone, the oxidized form of a flavin moiety and a well-known fluorescent dye, has been widely investigated because of its biochemical importance. Several researchers have proposed that the flavin dimer is involved in biological reactions. Crystal structure analysis revealed that some flavin derivatives, such as 10-arylfлавins, form π-stacking structures. Previous investigations into flavin complexes reported that these complexes contain 3d transition metal cations and soft metal cations such as Ag⁺ and Cu⁺. The latter metal cations form chelates by bonding to O(4) and N(5) of the isoalloxazine ring in flavonone and can coordinate the flavonone anion at basic pH conditions.

To my knowledge, flavin clathrate compounds that involve cation-π interactions have not been reported to date. I have focused on the self-assembly of flavin derivatives via π-π interactions and characterization of the resulting scaffolds. It is anticipated that this approach will provide new supramolecular probes and modulating methods for flavin reactions. In this work, the synthesis, crystal structure, and optical properties (particularly related to self-assembly exhibiting a strong solvent effect) of 7,8-dimethyl-10-[4′-(methoxycarbonyl)phenyl]-isoalloxazine (FIH-MB) and its resulting scaffold for a Cs⁺ ion are reported. These structures were probed using UV-vis spectroscopy, 1H NMR spectroscopy, and fluorescence titration with Cs₂CO₃. The results indicated that the unique scaffold of FIH-MB acts strictly as FI⁻—MB after deprotonation and sequesters the Cs⁺ ion. A schematic illustration of this key function is shown in Scheme 1.

2. RESULTS AND DISCUSSION
The crystal structure of FIH-MB revealed a π-stacking structure as shown in Figure 1. The shortest intermolecular separation between the isoalloxazine rings through π-π interactions was 3.57 Å, which is similar to the separation in 10-aryl-3-methylisoalloxazine (3.5 Å) and 10-alkylisoalloxazine derivatives (3.2–3.6 Å; these derivatives usually contain two independent moieties forming shorter and longer separations). Furthermore, hydrogen bonding between N(3)–H and C=O(2) and their inversion in the pyrimidinoid of the isoalloxazine rings resulted in the formation of a 3D network (Figure S3). Assessment of the planarity of the isoalloxazine rings allowed the oxidized form to be distinguished. The isoalloxazine moieties of FIH-MB is approximately planar but slightly more distorted compared to 10-methylisoalloxazine, perhaps due to the MB substituent (Figure S4 and Table S2). The phenyl ring of MB orients approximately perpendicular to the isoalloxazine ring (dihedral angles of 78.5 and 80.9°),
Scheme 1. Schematic Illustration of Receptor 7,8-dimethyl-10-[4’-(methoxycarbonyl)phenyl]-isoalloxazine (FIH−MB) for Cs+ Ion

Figure 1. π-Stacking structure of an FIH−MB crystal with distances (in Å) between neighboring isoalloxazine rings. H atoms were removed for clarity. Gray, blue, and red ellipsoids represent C, N, and O atoms, respectively, at the 50% probability level.

which corresponds well with the reported 10-arylfлавins.15 In FIH−MB π-stacking, the MB substituents exhibit elongated alternating arrangements with each other with little interaction. The crystal structure suggests that the FIH−MB scaffold may be suitable for a Cs+ ion, as the ionic radius of Cs+ is 1.7–1.8 Å.

The absorption maxima for FIH−MB in a DMSO solution at 298 K occurred at 447 nm (S0−S1, ε = 10,900 M−1 cm−1) and 344 nm (S0−S2, ε = 6,900 M−1 cm−1), consistent with the values for the oxidized forms of common flavin compounds.11,12 Excitation of FIH−MB at 450 nm resulted in a fluorescence emission at 515 nm, which also corresponds well with the reported 10-aryl flavin moieties, spectral blue shifts have been reported for FIH−avin have been described: the absorbance decreases with a little peak shift of the S0−S1 band as the pH is changed from neutral to basic conditions due to generation of a flavoquinone anion.21 In addition, in organic solvents such as DMF, an alkylation reaction at the N(3) position of isoalloxazine proceeds with high yield through deprotonation using alkali metal carbonates and alkyl halide agents.22 Moreover, although not regarded as flavin moieties, spectral blue shifts have been reported for metal ion-induced H-aggregation.23 Therefore, the above-described nonselective process at the first step for FIH−MB is likely associated with the deprotonation of FIH−MB by CO3−. The subsequent step resulting in a significant blue shift appears to result from complex formation with the Cs+ ion, which may induce tighter H-dimeric formation between Fl−MB and FIH−MB, and/or Fl−MB and Fl−MB. Given an

Figure 2. Absorption spectra of FIH−MB titrated with Cs2CO3, K2CO3, and Na2CO3. To a 50 μM DMSO solution of FIH−MB, up to 500 μM Cs2CO3 aq., 1 mM K2CO3 aq., or 1 mM Na2CO3 aq. were added.

of the titration was the addition of a solution with a concentration of ≤2 molar equivalents of Cs2CO3 ([Cs2CO3] ≤ 100 μM), which resulted in decreased absorbance without any shifts in the peak maxima of the S0−S1 and S0−S2 bands. The second step was the addition of a solution with a concentration of ≥4 molar equivalents of Cs2CO3 ([Cs2CO3] ≥ 200 μM), which resulted in blue shifts of both bands, a decrease in absorbance, and broadening of the S0−S1 band to around 550 nm. These outcomes of the second step were distinct from titrations with Na2CO3 and K2CO3, even when these carbonates were added in concentrations of up to 1 mM (Figure 2). Thus, these distinct features are due to the selective interaction of FIH−MB and the Cs+ ion. The pH-induced spectral changes of water-soluble riboflavin have been described: the absorbance decreases with a little peak shift of the S0−S1 band as the pH is changed from neutral to basic conditions due to generation of a flavoquinone anion.21 In addition, in organic solvents such as DMF, an alkylation reaction at the N(3) position of isoalloxazine proceeds with high yield through deprotonation using alkali metal carbonates and alkyl halide agents.22 Moreover, although not regarded as flavin moieties, spectral blue shifts have been reported for metal ion-induced H-aggregation.23 Therefore, the above-described nonselective process at the first step for FIH−MB is likely associated with the deprotonation of FIH−MB by CO3−. The subsequent step resulting in a significant blue shift appears to result from complex formation with the Cs+ ion, which may induce tighter H-dimeric formation between Fl−MB and FIH−MB, and/or Fl−MB and Fl−MB. Given an
expected pKa value of 10.3 for the reported oxidized flavin mononucleotide\(^2\) and the requirement of at least 100 \(\mu\)M \(\text{CO}_3^{2-}\) as the limit for the first step, the anion dimer of FII−MB (i.e., the FII−MB/FF−MB species) may be the dominant reactant at the second step.

As a control experiment, titrations of FII−MB in an acetonitrile solution with \(\text{Cs}_2\text{CO}_3\) aq. resulted in a little peak shift (Figure S8), supporting that FII−MB self-aggregates in solution to complex with the Cs\(^+\) ion, probably through both Coulombic and cation−π interactions. Furthermore, titrations of riboflavin in the DMSO solution with \(\text{Cs}_2\text{CO}_3\) aq. resulted in a blue shift but a lower degree of spectral change compared to FII−MB (Figure S9), confirming that the FII− site aggregates and sequesters the Cs\(^+\) ion. On the other hand, the Cs\(^+\) ion, usually adopting coordination numbers greater than 6, enhances π-stacking interactions of the FII− sites possibly via binding to O(4), N(5), C＝C(η\(^2\)) and/or N(1), the former two of which are more reliable according to the reports for flavin complexes comprising of soft metal cations.\(^{17,18}\) Additionally, the MB site seems to assist FII− aggregation due to rigidity and may have a perpendicular orientation to the FII− site, as well as in FII−MB.

\(^1\)H NMR titrations were performed to gain insight into the reaction mechanism. \(^1\)H NMR spectra of a 9:1 DMSO-d\(_6\)/D\(_2\)O solution of FII−MB titrated with \(\text{Cs}_2\text{CO}_3\) aq. are shown in Figure S10, and they indicate that the Cs\(^+\) ion-binding dynamics displays fast exchange on the NMR time scale. Additionally, upfield shifts of aromatic protons and two series of signals were observed as \(\text{Cs}_2\text{CO}_3\) was titrated. The resulting chemical shift differences (\(\Delta\delta\)) are shown in Figure 3, together with the molecular structure of FII−MB and its signal assignments. Upon the addition of 0.5 molar equivalents (or slightly larger amounts) of \(\text{Cs}_2\text{CO}_3\), there is little change in \(\Delta\delta\), indicating that the deprotonation reaction of FII−MB initially proceeds exclusively due to \(\text{CO}_3^{2-}\), based on a comparison with the limit of \(\Delta\delta\) with an excess of \(\text{Na}_2\text{CO}_3\) or \(\text{K}_2\text{CO}_3\) (Figure S11 and Figure 3). In the absence of a base, little change in \(\Delta\delta\) was confirmed using CsCl (Figure S12).

Considering that \([(\text{FII−MB})\_2 + \text{Cs}^+\)]\(^+\) was observed by ESI−MS, the neutral dimer has low ability to form a complex with the Cs\(^+\) ion, not enough to be detected by \(^1\)H NMR. In the region with more than 1 molar equivalent of \(\text{Cs}_2\text{CO}_3\), the increase in \(\Delta\delta\) suggests that FII−MB forms a complex with the Cs\(^+\) ion, complex 1, through the FII− site since the FII− protons (b′ and d′ shown in Figure 3) are more strongly affected than the MB protons (α′, c′, and e′ shown in Figure 3). Given the distinctive \(\Delta\delta\) change induced by the Cs\(^+\) ion and the crystal structure, the FII−MB/FF−MB dimer scaffold, in which both MB substituents and FII− moieties may assume alternating orientations to each other to avoid steric and Coulombic repulsions, respectively (as shown in Scheme 1), is suitable for sequestering the Cs\(^+\) ion through Coulombic and cation−π interactions. This result from \(^1\)H NMR titrations is consistent with that from UV−vis titrations.

Further addition of \(\geq 1.5\) molar equivalents of \(\text{Cs}_2\text{CO}_3\) resulted in the appearance of new signals (α′−γ′ shown in Figure S10). Integral analysis showed that the relative ratio of the new species to complex 1 increased as \(\text{Cs}_2\text{CO}_3\) was titrated (see Table S4 of Supporting Information). The \(\text{Cs}_2\text{CO}_3\)-induced \(\Delta\delta\) for the new species showed that a methoxy proton in MB (α′ shown in Figure S10) is most strongly affected. For evaluating the feasibility of MB hydrolysis, NaOD was added to the FII−MB solution, and the resulting spectrum (shown in Figure S13) was compared to that in the presence of a high concentration of \(\text{Cs}_2\text{CO}_3\), indicating that the hydrolysis product is the origin for the new species under strongly basic conditions. The plausible reaction pathways of FII−MB when titrated with \(\text{Cs}_2\text{CO}_3\) are illustrated in Figure S10.

Moreover, the ability of FII−MB to complex with Cs\(^+\) ions under NMR titration conditions was roughly estimated using the Benesi−Hildebrand equation\(^5,7\) which provided a complex formation constant \(K(\text{complex 1})\) of \(38 \pm 4\ M^{-1}\) at 297 K (Figure S14). This value seems to be somewhat smaller than that assumed for metal-coordinated N and O atoms.

Fluorescence titrations with \(\text{Cs}_2\text{CO}_3\) were performed to investigate whether FII−MB can act as a scaffold for the Cs\(^+\) ion. The fluorescence of 10 \(\mu\)M FII−MB in the DMSO solution showed significant quenching by \(\text{Cs}_2\text{CO}_3\), as shown in Figure S15. The fluorescence intensity (I) relative to that in the absence of \(\text{Cs}_2\text{CO}_3\) (I\(_0\)) is plotted in Figure 4. These data together with the results of \(^1\)H NMR titrations can explain that the FII−MB/FF−MB dimer is completely quenched via two main steps: (1) deprotonation (in the region of \(\leq 40\ \mu\)M

![Figure 3](https://example.com/figure3.png)

**Figure 3.** \(^1\)H NMR titration curves for FII−MB with \(\text{Cs}_2\text{CO}_3\) corresponding to complex 1. To a 1.8 mM solution (DMSO-d\(_6\)/D\(_2\)O = 9:1) of FII−MB, 0−5 molar equivalents of \(\text{Cs}_2\text{CO}_3\) were added and the spectra were measured at 297 K. The average of the control experiments using \(\text{Na}_2\text{CO}_3\) and \(\text{K}_2\text{CO}_3\) (20 mM, saturated solution) for each proton is also plotted (×).

![Figure 4](https://example.com/figure4.png)

**Figure 4.** Relative fluorescence intensities of FII−MB (10 \(\mu\)M, DMSO solution) titrated with \(\text{Cs}_2\text{CO}_3\) aq. The intensity in the absence of \(\text{Cs}_2\text{CO}_3\) is defined as I\(_0\). Excitation: 450 nm and emission: 515 nm.
Cs$_2$CO$_3$) and (2) complex formation (in the region of $\geq$60 $\mu$M Cs$_2$CO$_3$). On the basis of much lower concentrations of the base during the fluorescence titrations than those in the $^1$H NMR titrations described above, a hydrolysis reaction is unlikely to occur and complex 1 is most likely the fluorescence quenching form.

3. CONCLUSIONS
In summary, a new flavin compound FlH−MB was synthesized and characterized, the latter focusing on its self-assembly and the acquired scaffolding function for a Cs$^+$. According to the crystal structure, FlH−MB formed dimeric assemblies via $\pi$−$\pi$ interactions between the isoalloxazine rings, consistent with the observed [(FlH−MB)$_2$ + Cs$^+$] species by ESI−MS and fluorescence quenching by self-assembly in a DMSO solution. Additionally, a dramatic solvent effect on self-aggregation of FlH−MB was found due to the rigidity of the MB side chain. Titration experiments revealed complex formation between FlH−MB and a Cs$^+$ ion, where self-assembly leading to scaffold functioning and deprotonation of FlH−MB played essential roles, that is, the Fl−MB dimer worked as a receptor for the Cs$^+$ ion. For this mechanism, the concrete evidence was as follows: the absorption spectrum of FlH−MB in DMSO exhibited a significant blue shift induced by the Cs$^+$ ion following deprotonation of FlH by a CO$_3^{2−}$ ion, distinctive from that observed with K$^+$ and Na$^+$ ions. The results can be interpreted as the H-dimeric Fl−MB form having a tighter structure due to complexation with the Cs$^+$ ion than that in the absence of a Cs$^+$ ion. $^1$H NMR titrations with Cs$_2$CO$_3$ revealed that the Fl−MB dimer has a detectable site for the Cs$^+$ ion, that is, the Fl$^-$ site, and the Cs$^+$ ion is bound through both Coulombic and cation−$\pi$ interactions. The fluorescence of FlH−MB in the DMSO solution (present only as Fl$^-$−MB after deprotonation) is turned off by the Cs$^+$ ion, with complex 1 (shown in Scheme 1) likely playing a key role.

4. EXPERIMENTAL SECTION
FlH−MB was synthesized through a three-step reaction, as shown in Scheme S1 of Supporting Information. The reaction scheme involves cross-coupling between 4,5-dimethyl-2-nitroaniline and methyl 4-iodobenzoate, reduction of a nitro group by LiAlH$_4$, and condensation reactions. The overall reaction yield of FlH−MB was 61%. FlH−MB was crystallized from a DMSO solution at room temperature, and orange crystals suitable for X-ray crystal structure analysis were obtained (see Supporting Information).

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c03006..

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Notes
The author declares no competing financial interest.

ACKNOWLEDGMENTS
The author would like to thank Prof. K. Tsuge for his help in crystal structure measurement and analysis at the Instrument and Research Technology Center, University of Toyama. The author is grateful to Mr. T. Tanaka at the Evaluation Center of Materials Properties and Function, Institute for Materials Chemistry and Engineering, Kyusyu University for the ESI−MS measurements. The fluorescence measurements were performed at the Instrument Center, Institute for Molecular Science. This work was supported by the Sekisui Chemical Grant Program for Research on Manufacturing Based on Innovations Inspired by Nature, Iketani Science and Technology Foundation, Research Funding Granted by Oita University President, and Nanotechnology Platform Program <Molecule and Material Synthesis> of the Ministry of Education, Sports, Science, and Technology (MEXT), Japan.

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