

Luminescent double-decker type guanine octets with trivalent lanthanide cations: in situ self-assembling and stability evaluation in homogeneous organic media

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Abstract Silylated guanine formed luminescent double-decker type octet complexes with trivalent lanthanide cations (lanthanide cation : guanine = 1:8) in organic media, while a deaminated guanine derivative gave only 1:2 complexes. The octet formation was evidenced by characteristic UV/Vis absorption changes, CSI-TOF MS and ^1H NMR spectra. The octet with Tb^{3+} showed intense green luminescence with a long lifetime by photo-excitation of the guanine chromophore. The trivalent lanthanide cations stabilized the octets more effectively than common mono- and divalent metal cations.

Keywords Lanthanides · G-Quadruplexes · Self-assembly · Luminescence · Cold-Spray Ionization Mass Spectrometry

Introduction

Guanosine and its derivatives are a family of the most programmed molecules to form structure-defined self-assemblies [1, 2]. In particular, metal-templated quartets, octets and higher assemblies have received wide attention, not only because they are found in nature [3, 4] but because they can provide useful scaffolds to develop self-assembled nanomaterials [5]. Some alkali and alkaline earth metal cations worked as effective templates in self-assembly processes of 5'-GMP and its analogs. Pinnavaia et al. [6] determined the crystal structure of a Na^+ - or K^+ -templated quartet (1:4 complexation), in which one metal cation was coordinated by four carbonyl oxygen atoms from the guanines. The double-decker type of guanine octets (1:8 complexes) is another self-assembly mode. These complexes are usually prepared by solid (metal salt)–liquid (guanine solution) extraction, and their self-assembling profiles have been characterized after extraction procedures [7, 8]. Lanthanide cations have large coordination numbers and high coordination flexibility, and Wu et al. [9] reported that some of them promoted octet formation in a similar fashion to the alkali and alkaline earth cations. Since some nucleotides are known to enhance the emission of Eu^{3+} and Tb^{3+} cations in solution [10, 11], proper combinations of lanthanide cations and designed guanines can provide a new series of functional assembled materials.

We report here that silylated guanine **1** forms double-decker type octet complexes upon mixing with lanthanide triflates in homogeneous CHCl_3 solution. Compound **1** and its deaminated derivative **2** were prepared in order to examine in situ formation of the metal-templated octets (Fig. 1). Previously reported guanines mostly had complex lipophilic substituents and chiral sugar moieties to be examined in the extraction processes, which often provided additional interacting sites and diastereomerism in the metal

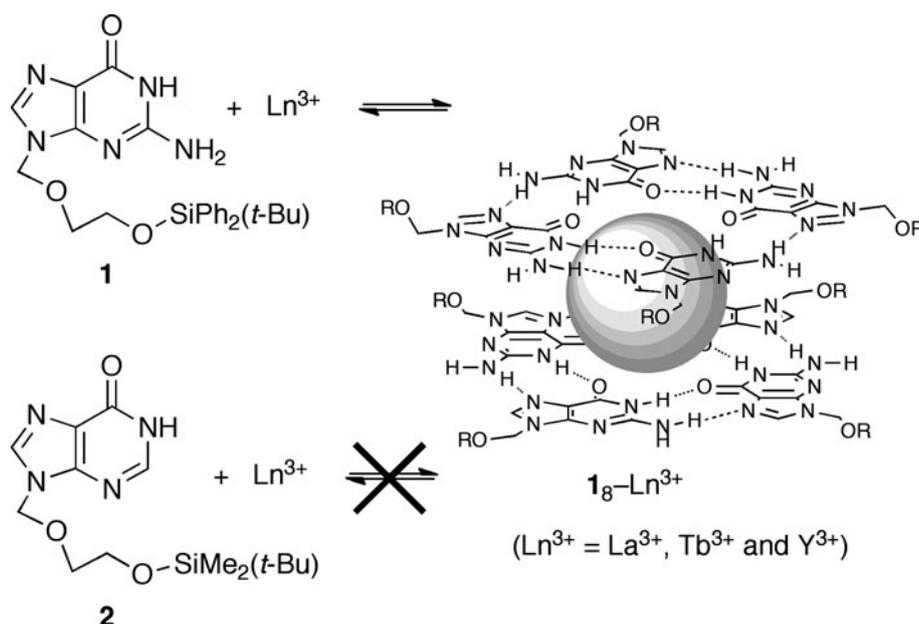
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Fig. 1 Guanine derivatives and double-decker type guanine octet



complexation. We demonstrate here that simply silylated guanine **1** forms more stable octets with trivalent lanthanide cations than those with common alkali and alkaline earth cations. Thus, the present results provide various possibilities that new synthetic strategies toward self-assembled materials can be developed for coordination, material, biochemical and related applications.

Results and discussion

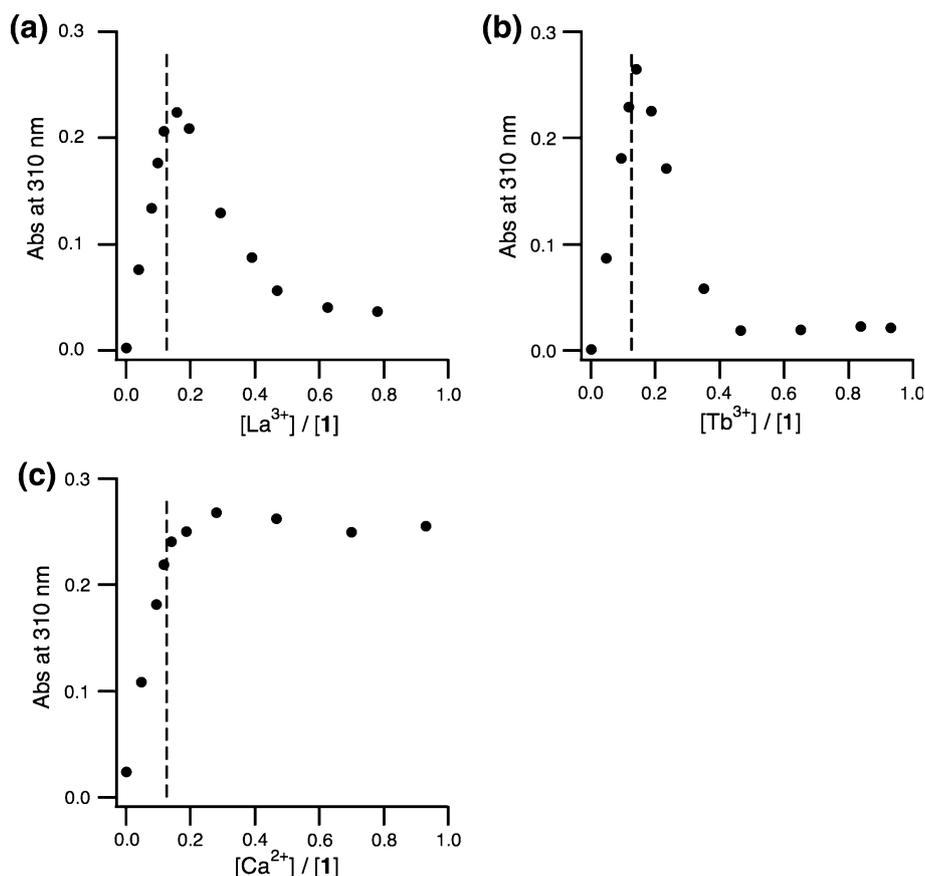
We prepared guanine derivatives **1** and **2** by silylation of acyclovir and 4-[(2-hydroxyethoxy)methyl]-1,9-dihydroxy-6H-purine-6-one in 64 and 86% yields, respectively. UV spectral changes of guanine **1** upon stepwise addition of La^{3+} , Tb^{3+} and Ca^{2+} cations are shown in Fig. 2. When $\text{La}(\text{OTf})_3$ was added to a CHCl_3 solution of guanine **1**, a new peak appeared around 310 nm. Its intensity increased at $\text{La}^{3+}/\text{guanine } \mathbf{1} < 1/8$, and then decreased at $\text{La}^{3+}/\text{guanine } \mathbf{1} > 1/8$. The plots clearly showed that La^{3+} and Tb^{3+} cations predominantly formed the octets with guanine **1** at low ratios of metal cation/guanine, while Ca^{2+} cation gave the octet under wider conditions. Since guanine **2** formed 1:2 complexes, the N^2 -amino-hydrogen atoms of guanine **1** formed strong intermolecular hydrogen bonds. Guanine **1** exhibited characteristic fluorescence spectral changes upon addition of metal triflates. These spectral changes indicated that La^{3+} cation formed both 1:8 and 1:2 complexes but Ca^{2+} cation gave only the 1:8 complex (see Fig. S1 in Supplementary material). ^1H NMR spectra also demonstrated that guanine **1** gave a 1:8 complex in the presence of 1/8 equivalent of La^{3+} cation (see Fig. S2 in Supplementary material). As observed with the Ca^{2+} complex, two amino

protons of guanine **1** exhibited separate signals at 8.9 and 5.4 ppm. One of them, H_A , shifted dramatically upon formation of an intermolecular hydrogen bond and the other, H_B , shifted only slightly. Since the amide proton also appeared at two distinct positions, it was concluded that the resulting octet was composed of two diastereomers. The La^{3+} octet exhibited NOE cross peaks between N^8 and the amide protons, indicating that four guanines self-assembled in the metal complex (Fig. S3 in Supplementary material).

The cold spray ionization (CSI) TOF-MS method, well recognized as an effective method of non-covalent complexes [12], was applied in detection of the guanine-metal cation assemblies. When 1/8 equivalent of metal triflate (K^+ , Ca^{2+} , Ba^{2+} , Y^{3+} , La^{3+} or Tb^{3+}) was added to the solution of guanine **1** ($\text{CHCl}_3/\text{CH}_3\text{CN} = 4:1$), intense mass signals from the double-decker type octets were observed (Fig. 3 and Fig. S4 in Supplementary material): $m/z = 3748$ for $[\mathbf{1}_8\text{-K}]^+$; 1874 for $[\mathbf{1}_8\text{-Ca}]^{2+}$; 1923 for $[\mathbf{1}_8\text{-Ba}]^{2+}$; 1266 for $[\mathbf{1}_8\text{-Y}]^{3+}$; 1283 for $[\mathbf{1}_8\text{-La}]^{3+}$; and 1289 for $[\mathbf{1}_8\text{-Tb}]^{3+}$.

The octet with Tb^{3+} cation exhibited intense green luminescence signals upon excitation of the guanine chromophore via efficient energy transfer. Its luminescence lifetime was estimated to be 1.6 ms, indicating that the Tb^{3+} ion was effectively protected from solvation in the octet (Fig. S5 in Supplementary material). The luminescence was monitored not only by spectrometry but also by the naked eye (Fig. 4). Competitive luminescence experiments were carried out with combinations of equimolar Tb^{3+} and other metal cations to estimate the relative stability of the octets. Addition of other metal ions gave only small enhancements of the absorbance at the excitation wavelength (285 nm). When $\text{Ca}(\text{OTf})_2$ was added to the CHCl_3 solution of guanine **1** and $\text{Tb}(\text{OTf})_3$ ($\text{Ca}^{2+}:\text{Tb}^{3+}:\text{guanine } \mathbf{1} = 1:1:8$), the

Fig. 2 Absorbance changes of guanine **1** upon stepwise addition of $\text{La}(\text{OTf})_3$, $\text{Tb}(\text{OTf})_3$ and $\text{Ca}(\text{OTf})_2$ in CHCl_3 . $[\mathbf{1}] = 1.0 \times 10^{-4} \text{ M}$



luminescence intensity of the resulting solution slightly decreased compared to the guanine **1**– Tb^{3+} complex (91%). Although Ca^{2+} cation formed an octet, its stability was confirmed to be much lower than that of the Tb^{3+} complex. In contrast, addition of La^{3+} and Y^{3+} cations significantly decreased the Tb^{3+} luminescence intensities (33% for La^{3+} and 47% for Y^{3+}), indicating that their 1:8 complexes had comparable stability to that of the Tb^{3+} complex. Thus, our luminescence studies confirmed the following stability order of the octets in a semi-quantitative sense: $\mathbf{1}_8\text{-La}^{3+} > \mathbf{1}_8\text{-Tb}^{3+}$ and $\mathbf{1}_8\text{-Y}^{3+} > \mathbf{1}_8\text{-Ca}^{2+} > \mathbf{1}_8\text{-K}^+$ and $\mathbf{1}_8\text{-Ba}^{2+}$. Since the employed metal cations have similar ionic radii [13], this order emphasizes the significant effect of highly charged lanthanide centers on octet stability.

Conclusions

We have developed an in situ preparation method of double-decker type octets in organic media, in which the trivalent lanthanide cations effectively organized a coordination mode and hydrogen bonding pattern to promote self-assembly of the silylated guanine **1**. Competitive luminescence experiments with Tb^{3+} and other metal cations revealed that trivalent lanthanide cations such as La^{3+} , Tb^{3+} and Y^{3+} formed stable

double-decker type octets. Since these lanthanide cations have multiple functionalities, double-decker type octets can have wide applications.

Experimental section

Acyclovir and its deamino derivative were purchased from Maybridge. Chloroform was a spectroscopic grade of Wako Pure Chemical Industries, Ltd. and used after passing through alumina column.

Guanine **1:** Acyclovir (111 mg), imidazole (91.5 mg), and *t*-butyldiphenylsilyl chloride (244 mg) were dissolved in dry DMF (2 ml) and stirred for 8 h at room temperature. Water (5 ml) was added and all the solvent was removed by evaporation. The product was separated by chromatography (silica gel, $\text{CHCl}_3\text{-MeOH}$, 10:1) and purified by washing with hexane, and then water. After drying in vacuo, **1** was obtained as white solids (141 mg, 64%). m.p. 248–250 °C; $^1\text{H NMR}$ ($\text{DMSO-}d_6$, 400 MHz): $\delta = 0.94$ (s, 9H), 3.60 (t, 2H), 3.70 (t, 2H), 5.36 (s, 2H), 6.48 (s, 2H), 7.39–7.58 (s, 10H), 7.80 (s, 1H) and 10.6 (s, 1H); $^{13}\text{C NMR}$ ($\text{DMSO-}d_6$, 100 MHz): $\delta = 18.7, 26.5, 62.7, 69.8, 72.0, 116.5, 127.8, 129.8, 133.0, 135.0, 137.6, 151.4, 153.8$ and 156.8; FAB-MS m/z 464.2 (M^+) and 486.2 ($\text{M}+\text{Na}^+$);

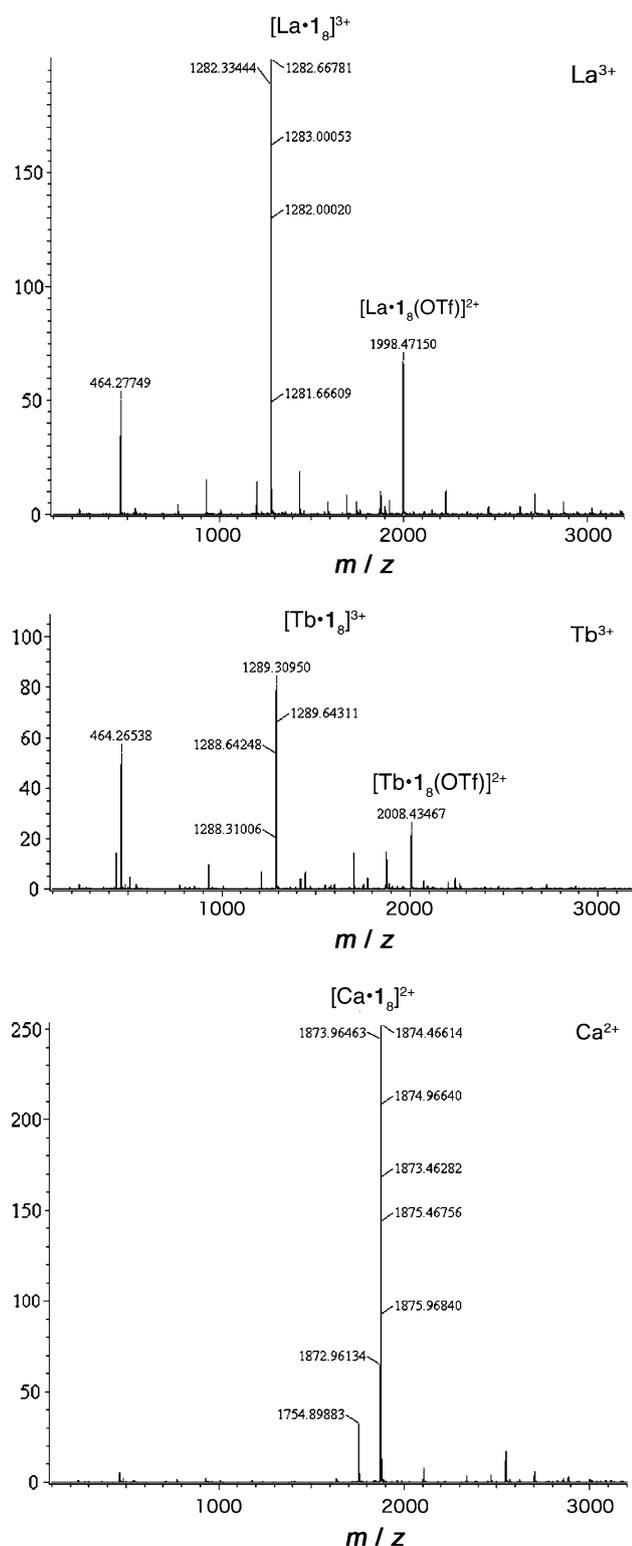


Fig. 3 CSI TOF-Mass spectra of guanine octets with La^{3+} , Tb^{3+} and Ca^{2+} in $\text{CHCl}_3\text{-CH}_3\text{CN}$ (4:1, v/v). $[\mathbf{1}] = 7.6 \times 10^{-4}$ M, [metal triflate] = 9.5×10^{-5} M

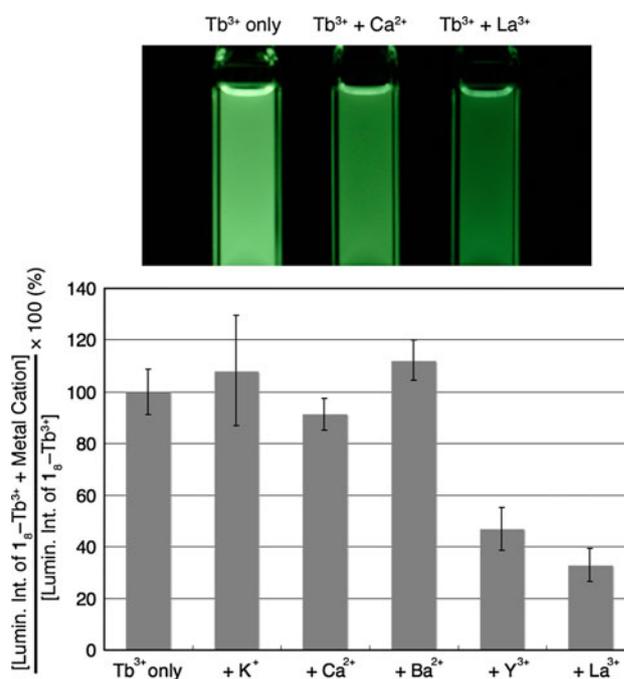


Fig. 4 Pictures of green luminescence from Tb^{3+} -guanine octet photo-excited by UV illuminator (8 W, 302 nm) and spectral changes upon addition of other metal cations in CHCl_3 . $[\mathbf{1}] = 1.0 \times 10^{-4}$ M, $[\text{Tb}(\text{OTf})_3] = 1.3 \times 10^{-5}$ M, [metal triflate] = 0 or 1.3×10^{-5} M, $\lambda_{\text{ex}} = 285$ nm, slit widths: 5.0 (ex) and 2.5 nm (em)

Anal. calcd for $\text{C}_{23}\text{H}_{27}\text{N}_5\text{O}_3\text{Si}$: C, 62.18; H, 6.30; N, 15.11, found: C, 62.40; H, 6.33; N, 15.15.

Guanine **2** was obtained (133 mg, 86%) from deaminoacyclovir (100 mg), imidazole (97 mg), and *t*-butyldimethylsilyl chloride (108 mg) in a similar way. m.p. 238–239 °C; ^1H NMR (300 MHz, $\text{DMSO-}d_6$): $\delta = -0.04$ (s, 6H), 0.79 (s, 9H), 3.55 (t, 2H), 3.62 (t, 2H), 5.54 (s, 2H), 8.07 (s, 1H), 8.20 (s, 1H) and 12.36 (s, 1H); ^{13}C NMR ($\text{DMSO-}d_6$, 100 MHz): $\delta = -5.4$, 17.9, 25.7, 61.8, 70.5, 72.7, 124.0, 140.6, 146.0, 148.5 and 156.6; FAB-MS m/z 324.2 (M^+); Anal. calcd for $\text{C}_{14}\text{H}_{24}\text{N}_4\text{O}_3\text{Si}$: C, 51.83; H, 7.46; N, 17.27, found: C, 51.64; H, 7.46; N, 17.23.

Since these rarely extracted lanthanide triflates, the guanine octets were not synthesized under common extraction conditions.

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