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Enhanced chemiluminescence of 6-(4-methoxyphenyl)imidazo[1,2-*a*]pyrazin-3(7*H*)-one by attachment of a cyclomaltooligosaccharide (cyclodextrin). Attachment of cyclomaltononaose (δ-cyclodextrin)

Katsunori Teranishi,[a,*] Tatsuya Nishiguchi,[a] Haruhisa Ueda[b]

[a]*Faculty of Bioresources, Mie University, 1515 Kamihama, Tsu, Mie 514-8507, Japan*
[b]*Faculty of Pharmaceutical Sciences, Hoshi University, 4-41, Ebara 2-chome, Shinagawa-ku, Tokyo 142-8501, Japan*

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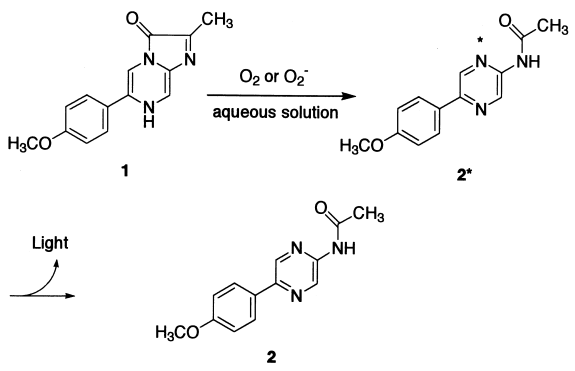
Abstract

2-Methyl-6-(4-methoxyphenyl)imidazo[1,2-*a*]pyrazin-3(7*H*)-one (MCLA) is an oxygen-induced chemiluminescent compound. It has been shown that the chemiluminescence can be enhanced by forming a cyclomaltooligosaccharide (cyclodextrin)-bound MCLA, and therefore, in continuation of the survey of the types of cyclodextrins, in this study, MCLA was attached to the secondary hydroxyl face of δ-cyclodextrin, which consists of nine D-glucose units. Although the oxygen-induced chemiluminescence efficiency of δ-cyclodextrin-bound MCLA in a pH 8.0 aqueous phosphate buffer was 12 times greater than that of MCLA, the efficiency was markedly lower than that of γ-cyclodextrin-bound MCLA, which exhibited the highest chemiluminescence efficiency in the previous investigation. Although fluorescence efficiency and light-emitter formation efficiency for δ-cyclodextrin-bound MCLA were similar to those for γ-cyclodextrin-bound MCLA, singlet-excited state formation efficiency for δ-cyclodextrin-bound MCLA was lower than that for γ-cyclodextrin-bound MCLA. This study distinctly indicated the optimum cyclodextrin for construction of greatly luminescent cyclodextrin-bound MCLA is γ-cyclodextrin.

Keywords: Cyclomaltooligosaccharide; Cyclodextrin; δ-Cyclodextrin; Chemiluminescence; MCLA

1. Introduction

It has been reported that, in the presence of *Cypridina* luciferase and triplet oxygen, aqueous solutions of *Cypridina* luciferin can generate blue light with high efficiency (0.28).[1] However, in the absence of luciferase, light was not generated.[2] *Cypridina* luciferin analogues, such as 2-methyl-6-phenylimidazo[1,2-*a*]pyrazin-3(7*H*)-one (CLA)[2] and 2-methyl-6-(4-methoxyphenyl)-imidazo[1,2-*a*]pyrazin-3(7*H*)-one (MCLA) (**1**),[3] have been prepared by Goto and co-workers as chemiluminescence substances that exhibit chemiluminescence in aqueous solutions. For these reactions, it is reasonable to assume that CLA or MCLA (**1**) reacts with triplet oxygen to form the singlet-excited amide **2*** to generate chemiluminescence, as shown in Scheme 1.[4] Although these analogues have been used in the analyses of superoxide anions[5–7] or lipid hydroperoxides[8] under aqueous conditions, their chemiluminescence efficiencies have been significantly lower than that of *Cypridina* bioluminescence.



Scheme 1. Chemiluminescence reaction of **1**.

* Corresponding author. Tel./fax: +81-59-2319615
E-mail address: teranisi@bio.mie-u.ac.jp (K. Teranishi).

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Previous investigations to improve MCLA chemiluminescence under aqueous conditions have shown that binding MCLA to the secondary hydroxyl face of cyclomaltooligosaccharides (cyclodextrins), which are cyclic α-(1→4)-linked-oligosaccharides with a hydrophobic cavity within their bucket-like structures, and hydroxyl groups consisting of primary hydroxyl groups at the C-6 and secondary hydroxyl groups at the C-2 and C-3 positions at the rim of the structures, enhanced the chemiluminescence. Among α-, β-, and γ-cyclodextrin-bound MCLA's (compounds **3**–**5**, respectively, Fig. 1) γ-cyclodextrin-bound MCLA (**5**) exhibited the highest enhancement of the luminescence properties.[9,10] In the continuation of the studies of cyclodextrin-bound MCLA compounds with enhanced luminescence, MCLA was bound to the secondary hydroxyl face of δ-cyclodextrin, which consists of nine D-glucose units, has a larger cavity with wider entrance than that of γ-cyclodextrin,[11 12] and is relatively scarce.[13] Herein, the synthesis of δ-cyclodextrin-bound MCLA (**6**) (Scheme 2) and the resulting chemiluminescence involving triplet oxygen in phosphate buffer are described.

2. Results and discussion

2.1. Chemiluminescence properties of δ-cyclodextrin-bound MCLA (6)

The synthesis of δ-cyclodextrin-bound MCLA (**6**) was carried out through the condensation of mono-3-amino-3-deoxy-(*2S*,*3S*)-δ-cyclodextrin (**7**)[14] and MCLA–COOH (**8**)[9] (Scheme 2). The chemiluminescence properties of **6**, involving triplet oxygen in phosphate buffer (0.03 M, pH 8.0), as compared with those of **1** and **3**–**5**,[10] are listed in Table 1. Although the overall chemiluminescence efficiency (Φ_{CL}) of **6** at 0.0058 based on luminol[15] was 12 times greater than that of **1**, it was markedly lower than that of **5**, which has shown the highest efficiency in the previous study.[10] However, the emitter-formation efficiency (Φ_R) of amide **10** from **6** was comparable to that of **5**. The emitter-formation efficiency in the chemiluminescence reaction was determined by comparing the luminescence-spent products against synthetic amide **10**, which was prepared by condensation of **7** and **9**[9] (Scheme 3).

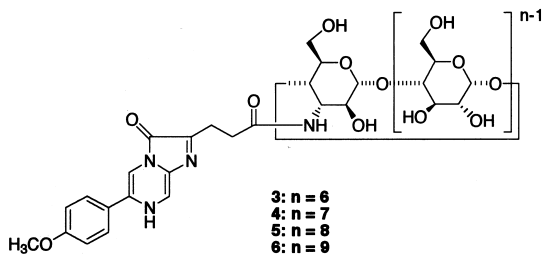
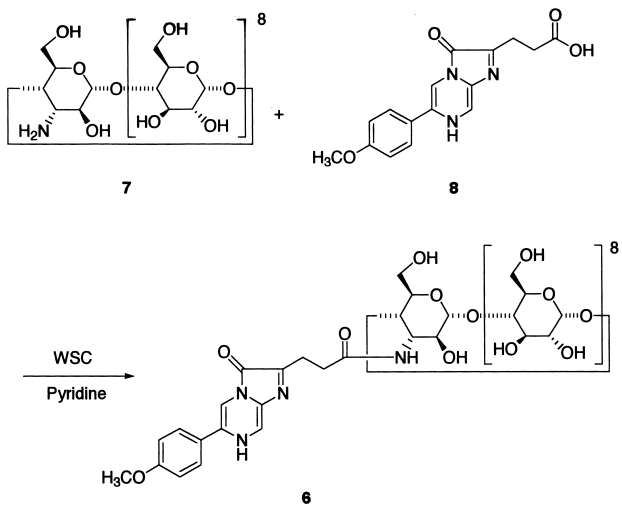


Fig. 1. Structures of cyclodextrin-bound MCLA compounds.



Scheme 2. Synthesis of **6**.

Table 1
Oxygen-induced chemiluminescence properties of cyclodextrin-bound MCLA compounds in phosphate buffer [a]

Compound	Φ_{CL} [c]	Φ_R [d]	Φ_F [e]	Φ_S [f]
1 [b]	0.00048	0.27	1.0	1.0
3 [b]	0.00062	0.22	1.2	1.3
4 [b]	0.0036	0.41	1.2	4.1
5 [b]	0.021	0.41	1.3	23
6	0.0058	0.39	1.2	7.1

[a] The chemiluminescence reactions were done in phosphate buffer (0.03 M, pH 8.0) at 30 °C. Concentrations of compounds were 0.01 mM, respectively.

[b] Data for **1**, **3**, **4**, and **5** are cited from Ref. 10.

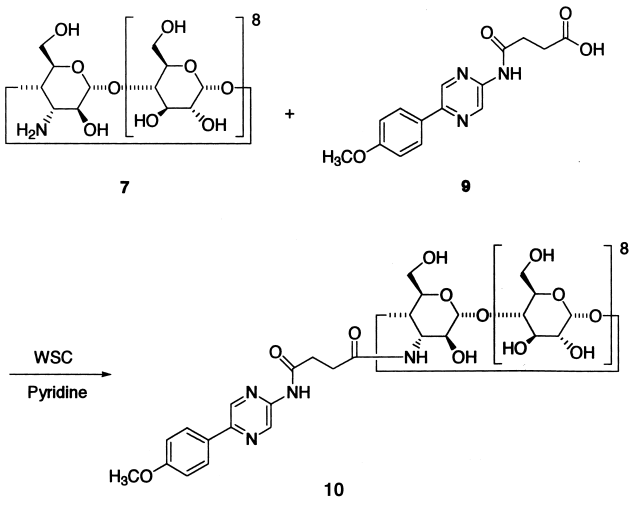
[c] Φ_{CL} = overall chemiluminescence efficiency of chemiluminescence on the basis of luminol.[15]

[d] Φ_R = formation yield of the corresponding amide.

[e] Φ_F = relative efficiency of fluorescence of the corresponding amide.

[f] Φ_S = relative efficiency of singlet-excited state formation.

The chemiluminescence reaction involves various steps, such as binding with an oxygen molecule, generation of intermediate(s) having high energy, formation of a singlet-excited state, and emission of light. The efficiencies of each reaction step determine the overall chemiluminescence efficiency (Φ_{CL}), which is defined as: $\Phi_{CL} = \Phi_R \times \Phi_F \times \Phi_S$ (Φ_R = formation efficiency of emitter; Φ_F = fluorescence efficiency of emitter; Φ_S = efficiency of singlet-excited state formation of emitter); values for Φ_{CL} and Φ_R can be readily determined experimentally. However, actual values for the efficiency of singlet-excited state formation and fluorescence efficiency of the emitter cannot always be



Scheme 3. Synthesis of **10**.

determined because the singlet-excited state molecule as the singlet-excited state intermediate that is formed in the course of the chemiluminescence reaction cannot be reproduced for fluorescence analyses. In our case, as shown in Fig. 2, the fluorescence spectrum of synthetic amide **10** as the emitter was not superimposable on the chemiluminescence spectrum of **6**, thus suggesting that the molecular state of the singlet-excited state molecule **10** that was generated in the course of the chemiluminescence reaction was slightly different than that of molecule **10** generated with light irradiation for the fluorescence measurement. The relative fluorescence efficiency of **10** at 7.1, which was measured as fluorescence efficiency of the chemiluminescence reaction of **6** for convenience, was similar to those of amides generated from **3**–**5** as shown in Table 1, and therefore, differences between the fluorescence efficiencies were insignificant. The efficiencies of singlet-excited state formation, calculated from the values of the apparent fluorescence efficiencies, are listed in Table 1. The efficiency of singlet-excited state formation of the chemiluminescence reaction of **6** was markedly lower than that of **5**. Differences among the overall chemiluminescence efficiencies of **1** and **3**–**6** were somewhat dependent on the efficiencies of singlet-excited state formation. The efficiency of singlet-excited state formation for the chemiluminescence of **6** decreased its overall chemiluminescence efficiency. In summary, the present studies

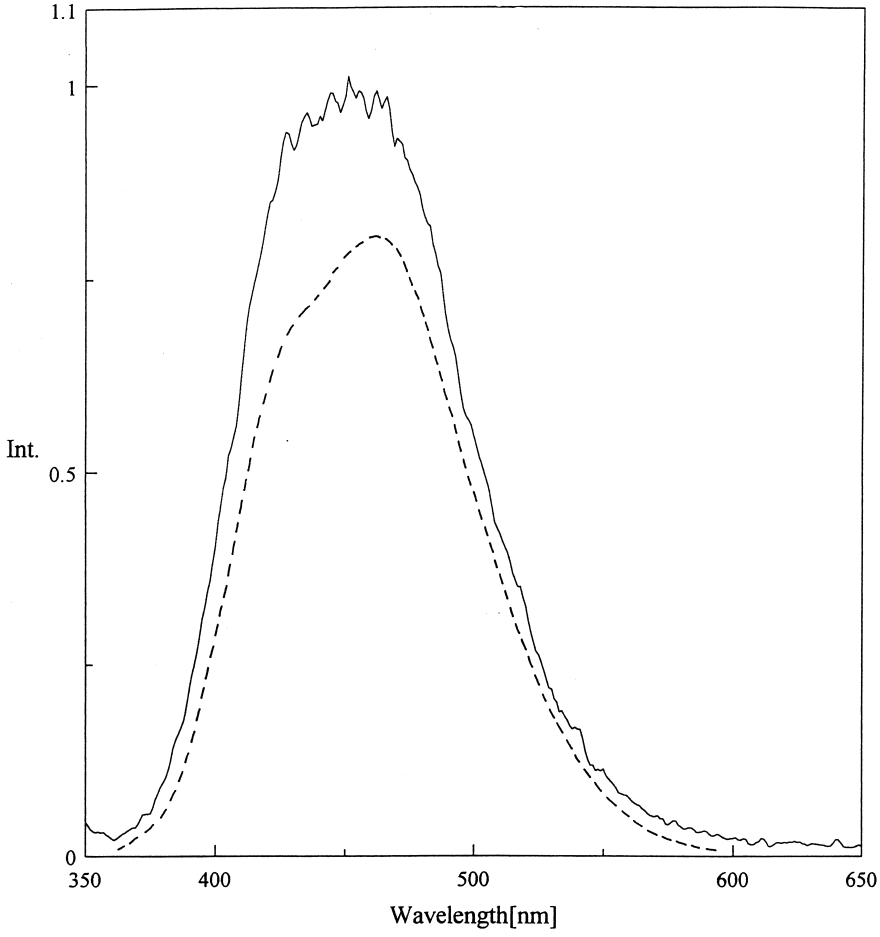


Fig. 2. Chemiluminescence spectrum of **6** (—) and fluorescence spectrum of **10** (---) in phosphate buffer (0.03 M, pH 8.0).

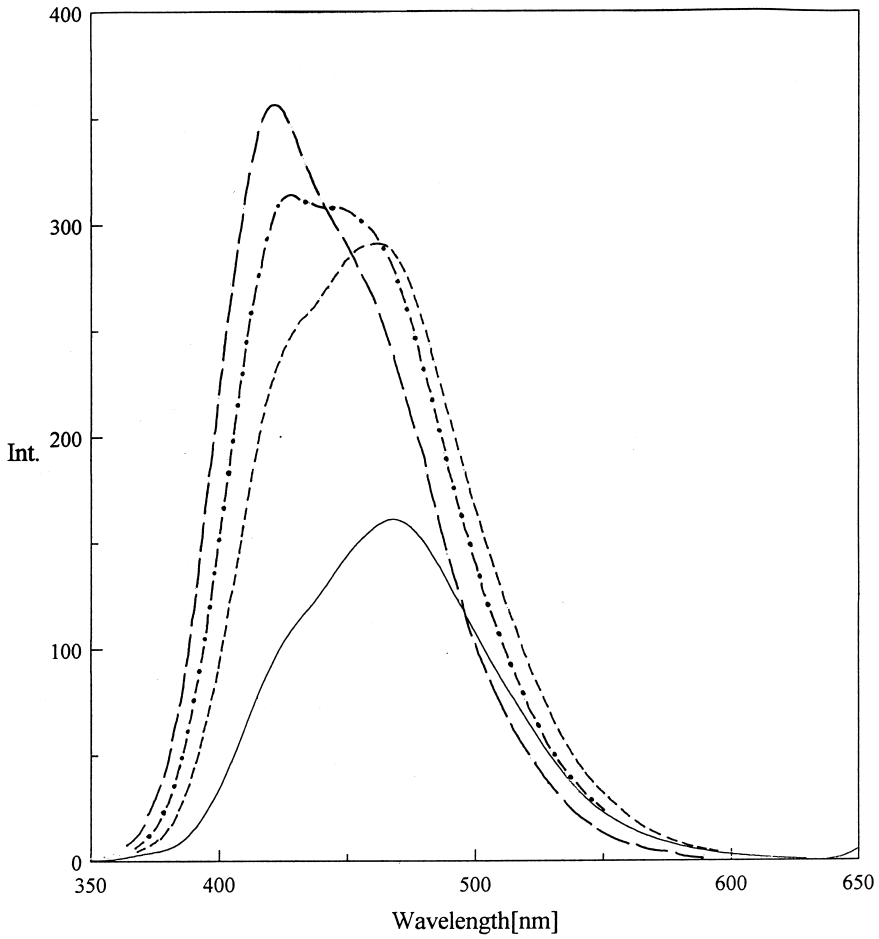


Fig. 3. Fluorescence spectra of **2** in 50% H_2O–DMF (– –), 70% H_2O–DMF (-·-), 90% H_2O–DMF (---), and phosphate buffer (0.03 M, pH 8.0) (—).

have demonstrated the importance of the type of cyclodextrin in the enhancement of chemiluminescence of MCLA; specifically γ-cyclodextrin was shown as the optimum cyclodextrin to be bound to MCLA.

2.2. Molecular state of emitter

In the previous study,[10] the chemiluminescence spectra of **1** and fluorescence spectra of **2** in 50, 70, or 90% H_2O–DMF, or phosphate buffer exhibited two emission peaks, one at 420–440 nm and another at 450–470 nm. Furthermore, the chemiluminescence spectra were superimposable on the fluorescence spectra in the corresponding solutions. It has also been shown that the ratio of the intensity levels of the two peaks was dependent on the water content of the solvents used. An increase in the water content corresponded to an increase of the intensity levels of the fluorescence and chemiluminescence peaks at 450–470 nm. Thus, the aqueous content of the environment of the emitter can be indicated by the ratio of the intensity levels of the two peaks. In the chemiluminescence reaction of **3** and **4**, the corresponding singlet-excited amides compounds existed in a roughly 100% aqueous environment, suggesting that the compounds should not be affected by the cyclodextrins.[10] In the chemiluminescence of **5**, the singlet-excited amide moiety existed in a roughly 80% aqueous environment.[10] For the chemiluminescence of **1**, the efficiency of singlet-excited state formation, which dominates the overall chemiluminescence efficiency, increased, as the water content of the chemiluminescence environmence decreased.[16] Thus, the 80% aqueous environment should be a primary factor for enhanced chemiluminescence.[10] As shown in Fig. 2, the chemiluminescence spectrum of **6** also exhibited two emission peaks (420–440 and 450–470 nm). According to the ratio of the intensity level of the two peaks, as compared to the fluorescence spectra of **2** shown in Fig. 3, the chromophore moiety of singlet-excited amide **10** should exist in a roughly 90% aqueous environment during the chemiluminescence reaction, which should result in a lower efficiency of singlet-excited state formation for the chemiluminescence of **6** than that of **5**. The chemiluminescence spectrum of **6** demonstrated

that the degree of inclusion of the singlet-excited amide moiety into the cavity of δ-cyclodextrin of emitter **10** was smaller than that of γ-cyclodextrin due to the wider entrance of the δ-cyclodextrin, whose diameter is about 10.3–11.2 Å,[12] and was somewhat greater than that for β-cyclodextrin, as illustrated in Fig. 4.

The previous study[10] of β- and γ-cyclodextrin-bound amides has demonstrated that the inclusion of the amide chromophore moieties into their corresponding cyclodextrin cavities were more prominent following the emission step rather than during the emission state, as illustrated in Fig. 4(A and B). This suggested that the time scale for the inclusion of the amide chromophore moieties of β- and γ-cyclodextrin-bound amides into the cyclodextrin cavities must be greater than the time scale of the chemiluminescence reaction and that enough time to enter into the cyclodextrin cavity can allow inclusion into the β- and γ-cyclodextrin cavities. Furthermore, it has been shown that the degree of inclusion of the amide chromophore moiety into the β-cyclodextrin cavity following the emission was greater than that of γ-cyclodextrin following the emission, indicating that β-cyclodextrin has the greater ability to strongly include the amide chromophore moiety than γ-cyclodextrin following the emission. It is suggested that after the emission the β-cyclodextrin cavity, whose diameter is about 7.0 Å,[17] should be more nearly fitted to the amide chromophore moiety than the γ-cyclodextrin cavity, whose diameter is about 8.5 Å.[17] For **10**, the fluorescence spectrum (Fig. 2) almost matched the chemiluminescence spectrum of **6**, indicating that the amide chromophore moiety of **10**, after completing the emission, should exist in a roughly 90% aqueous environment, as illustrated in Fig. 4(C). In contrast to the β- and γ-cyclodextrin-bound amides, the relatively weaker inclusion into the δ-cyclodextrin cavity following emission is attributable to the wider entrance and larger cavity of δ-cyclodextrin that could not detain the chromophore moiety in the cavity. Thus, even if there was enough time for the amide chromophore moiety to enter into the δ-cyclodextrin cavity in the chemiluminescence reaction, the singlet-excited chromophore moiety could not be strongly included in the cavity. The intermolecular inclusion ability of δ-cyclodextrin for the relatively small guest molecules like the present amide chromophore moiety has been shown to be inferior to those of β- and γ-cyclodextrins.[13,18,19] The intramolecular self-inclusion ability in the present study with δ-cyclodextrin also could not surpass that with γ-cyclodextrin both during the emission state and following the emission step.

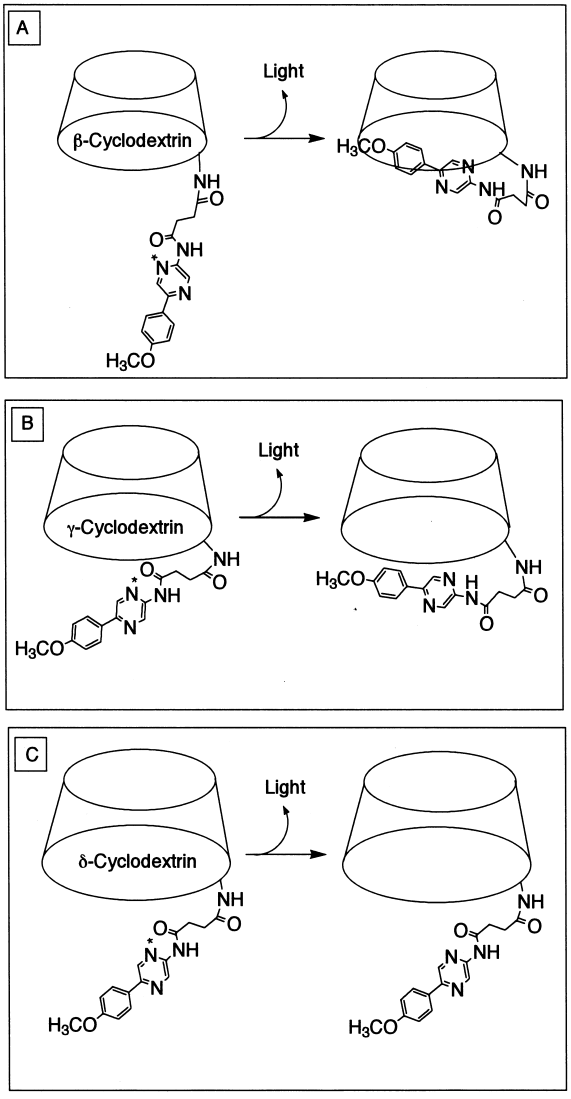


Fig. 4. Schematic structures of emitters generated from β-, γ-, δ-cyclodextrin-bound MCLA compounds (**4**, **5**, and **6**, respectively) in the chemiluminescence reactions.

3. Conclusions

The investigations herein have clearly demonstrated that γ-cyclodextrin is the optimum cyclodextrin that can be bound to MCLA for the enhancement of chemiluminescence in aqueous solution. The overall chemiluminescence efficiencies of the cyclodextrin-bound MCLA compounds were shown to depend on the efficiencies of singlet-excited state formation; the efficiency of singlet-excited state formation for **5** was the largest among all cyclodextrin-bound MCLA compounds. The entrance and cavity of δ-cyclodextrin was too large to include the singlet-excited amide moiety in the course of the chemiluminescence reaction, suggesting that light was produced in a roughly 90% aqueous environment; in contrast the entrance and cavity of β-cyclodextrin was too small.

4. Experimental

4.1. General methods

Analytical and preparative HPLCs were done using a JASCO Gulliver HPLC system with a MD-910 detector. A Cosmosil 5C18-MS column (4.6 × 150 mm) was used for the analytical HPLC. HPLC preparative chromatography was carried out with a Cosmosil 5C18-MS column (20 × 250 mm). Preparative open chromatography was conducted with a Fuji Silysia Chromatorex DM1020T ODS gel. Analytical thin-layer chromatography (TLC) was performed on E. Merck Kieselgel 60 F_{254} precoated, glass-backed plates of 0.25 mm layer thickness, and zones of compounds were visualized under a UV lamp or with a *p*-anisaldehyde–H_2SO_4–EtOH soln. Elemental analyses were measured with a Yanaco CHNCORDER MT-3 instrument. IR spectra were taken with a JASCO FTIR-410 spectrometer, and UV–Vis spectra were obtained with a JASCO V-530DS spectrometer. ^{1}H NMR spectra were measured with a JEOL JNM-A500 spectrometer operating at 500 MHz. Chemical shift values are reported in δ (ppm) relative to acetone (2.32 ppm) as an internal standard, and coupling constants (J) are in Hz. Fast atom bombardment (FAB) mass spectra were recorded on a JEOL JMS-DX303 instrument using glycerol as a matrix. The chemiluminescence intensity time curve was obtained using an Aloka Luminescence Reader BLR-301, and the chemiluminescence spectrum and fluorescence spectra were obtained using a JASCO FP-750DS spectrofluorometer.

All chemicals not otherwise mentioned were purchased from Nacalai Tesque, INC. (Kyoto, Japan) in chemically pure grade and were used as such. Cyclononakis-(1→4)-[3-amino-3-deoxy-α-D-altropyranosyl-(1→4)-α-D-*gluco*-octopyranosyl] (**7**),[14] MCLA–COOH (**8**),[9] and amide **9**[9] were prepared according to the published methods.

4.2. Synthesis

4.2.1. Cyclononakis-(1→4)-3-deoxy-3-[[3-[3,7-dihydro-6-(4-methoxyphenyl)-3-oxoimidazo[1,2-*a*]pyrazin-2-yl]-1-oxopropyl]amino]-α-D–altropyranosyl-(1→4)-α-D-*gluco*-octopyranosyl (6). To a solution of **7** (0.05 g, 0.034 mmol) in Py were added **8** (0.011 g, 0.035 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC, 0.020 g, 0.11 mmol) at rt. The reaction mixture was stirred under Ar at rt for 4 h, and then evaporated under reduced pressure to dryness. The residue was dissolved with 0.1% aq TFA and subjected to open column chromatography on a reversed-phase column (15 × 120 mm) using a gradient elution with water containing 0.1% TFA to 30% aq MeOH containing 0.1% TFA to give impure **6**, which was purified by HPLC preparative chromatography on a reversed-phase column (20 × 250 mm), eluting with 22% aq MeOH containing 0.1% TFA. The pure fractions of **6** were combined and then concentrated in vacuum to give a yellow solid (0.011 g, 18% yield): UV–Vis (0.03 M phosphate buffer, pH 8.0, without oxygen) λ_{max} nm (ε) 407 (4920), 347 (4280), and 267 (18,700); IR (KBr): ν 3389, 2933, 1783, and 1675 cm^{-1}; ^{1}H NMR (0.5% TFA–D_2O, 50 °C): δ 2.93 (2 H, t, J 6.7 Hz, CH_2CH_2), 3.32 (2 H, t, J 6.7 Hz, CH_2CH_2), 3.6–4.4 (m, H of δ-cyclodextrin), 5.01 (1 H, d, J 4.9 Hz, H-1 of glucose unit), 5.07 (1 H, d, J 4.9 Hz, H-1 of glucose unit), 5.26–5.36 (m, 7 H, H-1 of glucose units), 7.21 (2 H, d, J 8.5 Hz, ArH), 7.78 (2 H, d, J 8.5 Hz, ArH), 8.20 (1 H, s, H of pyrazine), and 8.74 (1 H, s, H of pyrazine); FABMS m/z 1753 [M + 1]. Anal. Calcd for $C_{70}H_{104}N_4O_{47}$: C, 47.95; H, 5.98; N, 3.20. Found: C, 47.55; H, 6.24; N, 2.81.

4.2.2. Cyclononakis-(1→4)-3-deoxy-3-[[4-[[5-(4-methoxyphenyl)pyrazinyl]amino]-1,4-dioxobutyl]amino]-α-D-altropyranosyl-(1→4)-α-D-*gluco*-octopyranosyl (10). To a solution of **7** (0.040 g, 0.027 mmol) in Py (1.0 mL) were added **9** (0.013 g, 0.043 mmol) and WSC (0.016 g, 0.082 mmol) at rt, and the mixture was stirred for 3 h. Pyridine was evaporated under reduced pressure to dryness. The residue was dissolved with water and subjected to an open column chromatography on a reversed-phase column using gradient elution with water to 30% aq MeOH. The fractions of the target compound were combined and then concentrated in vacuum. The residue was dissolved in water and added into acetone to give **10** (0.027 g, 56% yield) as a white solid: UV–Vis (0.03 M phosphate buffer, pH 8.0, without oxygen) λ_{max} nm (ε) 334 (13,000) and 279 (18,400); IR (KBr): ν 3376, 2930, and 1639 cm^{-1}; ^{1}H NMR (D_2O, 50 °C): δ 2.74–3.00 (4 H, m, CH_2CH_2), 3.7–4.2 (m, H of δ-cyclodextrin), 4.54 (1 H, m), 5.15 (1 H, d, J 3.7 Hz, H-1 of glucose unit), 5.17 (1 H, d, J 3.7 Hz, H-1 of glucose unit), 5.27–5.38 (7 H, m, H-1 of glucose unit), 7.18 (2 H, d, J 8.5 Hz, ArH), 7.86 (2 H, d, J 8.5 Hz, ArH), 8.65 (1 H, s, H of pyrazine), and 9.21 (1 H, s, H of pyrazine); FABMS m/z 1741 [M + 1]; Anal. Calcd for $C_{69}H_{104}N_4O_{47}$: C, 47.59; H, 6.02; N, 3.22. Found: C, 47.16; H, 6.20; N, 3.15.

4.3. Measurement of chemiluminescence

The chemiluminescence intensity time curve was obtained as follows: 40 μL of 0.25 mM compound **6** in distilled water was added to 0.96 mL of 0.03 M phosphate buffer (pH 8.0). The reaction mixture was placed in the photometer, and the chemiluminescent intensity time curve was obtained at 30 °C. The chemiluminescence efficiency was determined on the basis of luminol.[15] The chemiluminescence spectrum was obtained as

follows: the luminescence solution was placed in the spectrofluorometer and the spectrum was obtained without light irradiation.

4.4. Measurement of the yield of amide 10 generated in the chemiluminescence reaction

Yield of amide **10** generated in the chemiluminescence reaction was obtained follows: an HPLC system was employed for analyzing the luminescence-spent products, and the yield of **10** was determined to be 39% by comparison with the synthesized amide **10**. Elution conditions: solvent gradient, MeOH–water (20:80 to 40:60 over 30 min); flow rate, 0.8 mL/min.

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