Development of Functional Imidazole Derivatives: A Potential Chemiluminescent Chemosensor

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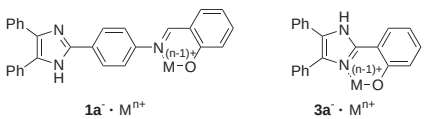
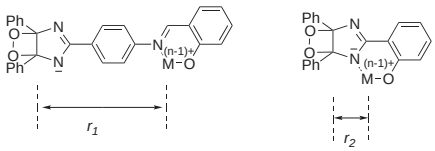
A potential functional chemiluminescent (CL) bidentate chemosensor, 2-[4-(*N*-salicylidene)aminophenyl]-4,5-diphenylimidazole (**1a**), was prepared. The chemiluminescence (CL) efficiency of the corresponding bidentate peroxide **2a** was independent of bridge length between the CL and acceptor centers. The peroxide was 10 times as efficient as the monodentate peroxide **2b**. Ionic Zn^{II} worked as a CL enhancer of **2a**, whereas transition metals Co^{II}, Fe^{III}, and Cu^{II} worked as quenchers.

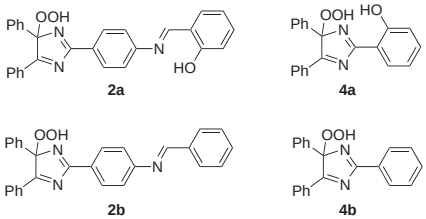
Recently, many investigations have been focused on chemosensors based on chelation-enhanced fluorescence.[1,2] Furthermore, a number of analytical applications of the lophine chemiluminescence (CL) reaction to inorganic compounds have been developed in recent years.[3] Development of sensitive and selective sensors is an interesting application in CL metal ion analysis.[4] This trend prompted us to investigate the possibility of using lophine CL in a similar manner to, and in place of, fluorescence. The advantage of CL systems over fluorophores is that the excitation of a chromophore can be achieved without irradiation. Despite the potential value of a variety of metal ion controlled photoresponsive behavior, there have been no basic studies other than a few investigations by Kimura et al.[5] We observed that enhanced CL of lophine peroxides by Zn^{II} is attributable to fixation of the conformation.[5] In order to develop a new type of CL chemosensors, we prepared two functional bidentate imidazoles, **1a** and **3a**, in which a CL system is linked directly, to or through a benzene bridge with, a bidentate receptor hosting a metal ion, as shown in Scheme 1. A pair of CL sensors **2a** and **4a** are prepared to estimate the chain length dependence of the efficiency as a sensor. The



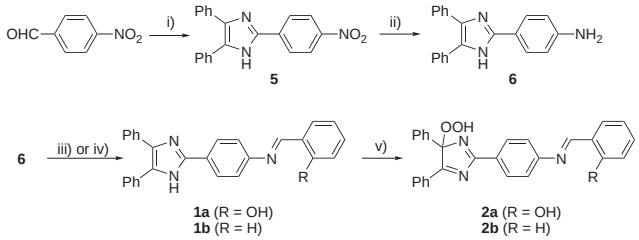
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4. Condition: i) benzil, $AcONH_4$, AcOH, reflux, 91%, ii) $NH_2NH_2 \cdot H_2O$, $FeCl_3$, active carbon, MeOH, reflux, 90%, iii) salicylaldehyde, EtOH, rt, 90% (**1a**), iv) benzaldehyde, EtOH, rt, 77% (**1b**), v) $h\nu$, O_2, methylene blue, CH_2Cl_2/MeOH, 99% (**2a**), 30% (**2b**).

distances (r_1, r_2) between a CL center and a metal center are defined as shown in Scheme 2. Measurements of quenching or enhancing efficiencies were performed for the bidentates **2a** and **4a** and corresponding monodentates **2b** and **4b**, shown in Scheme 3, in the absence and presence of metal ions.

Schiff bases **1a** and **1b** possessing an imidazole ring were prepared as follows (Scheme 4). The 2-(4-nitrophenyl)-4,5-diphenylimidazole (**5**) was prepared according to the method of Cook et al. in 91% yield.[6] The reduction of the nitro-compound **5** with $FeCl_3$ and hydrazine hydrate gave 2-(4-aminophenyl)-4,5-diphenylimidazole (**6**) in 90% yield using the similar method of Hirashima.[7] The condensation reaction of **6** with salicylaldehyde or benzaldehyde gave 2-[4-(*N*-salicylideneamino)phenyl]-4,5-diphenylimidazole (**1a**) in 90% yield or 2-[4-(*N*-benzylideneamino)phenyl]-4,5-diphenylimidazole (**1b**) in 77% yield, respectively. The oxidation of compounds **1a** and **1b** with singlet oxygen (generated by methylene blue photosensitization at -78 °C)[8] gave the corresponding hydroperoxides **2a** and **2b** in 99% and 30% yields, respectively. Hydroperoxides **4a** and **4b** were prepared by the method of Kimura et al.[5]

Chemiluminescence was measured by means of a photodiode array (PMA, Hamamatsu Photonics) which recorded integrated light yield in terms of the number of photons. A methanol solution of 1 mol L^{-1} $[Bu_4N]OH$ (0.2 mL) was added to 1.2 mL of 4.2 mM MeCN/MeOH = 5/1 (v/v) solution of hydroperoxides in the presence of metal cations or in their absence. These results are summarized in Table 1, Table 2, and

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Table 1. Relative CL Intensity of Hydroperoxides (**2a** and **2b**)

Compd	Metal chloride	$[M^{n+}]$ /mM	Φ_{cl}/Φ_0
2a[a)]	None	—	6.73
2a[a)]	$ZnCl_2$	2.1	7.48
2a[a)]	$EuCl_3$	2.1	6.49
2a[a)]	$CuCl_2$	0.42	3.47
2a[a)]	$FeCl_3$	0.42	4.55
2a[a)]	$CoCl_2$	0.42	0.48
2b[a)]	None	—	0.64
2b[a)]	$ZnCl_2$	2.1	0.57
2b[a)]	$CuCl_2$	0.42	0.38
2a[b)]	None	—	1.56
2b[b)]	None	—	0.87

a) Solvent: MeCN/MeOH = 5/1 (v/v), Base: 1 mol L^{-1} $[Bu_4N]OH$ in MeOH. b) Solvent: CH_2Cl_2, Base: 0.5 mol L^{-1} KOH in MeOH. c) Φ_0 is the chemiluminescence quantum yield of 1 mL of 5 mM CH_2Cl_2 solution of lophine hydroperoxide (**4b**) as the standard substance using 0.2 mL of 0.5 mol L^{-1} KOH in MeOH as the base.

Table 2. Relative CL Intensity of Hydroperoxides (**4a** and **4b**)

Compd	Metal chloride	$[M^{n+}]$ /mM	Φ_{cl}/Φ_0
4a[a)]	None	—	2.50
4a[a)]	$ZnCl_2$	2.1	3.13
4a[a)]	$EuCl_3$	2.1	0.63
4a[a)]	$CuCl_2$	0.42	0.98
4a[a)]	$FeCl_3$	0.42	0.20
4a[a)]	$CoCl_2$	0.42	0.89
4b[a)]	None	—	0.82
4b[a)]	$ZnCl_2$	2.1	0.73
4b[a)]	$CuCl_2$	0.42	0.50
4a[b)]	None	—	0.28
4b[b)]	None	—	1

a) Solvent: MeCN/MeOH = 5/1 (v/v), Base: 1 mol L^{-1} $[Bu_4N]OH$ in MeOH. b) Solvent: CH_2Cl_2, Base: 0.5 mol L^{-1} KOH in MeOH. c) Φ_0 is the chemiluminescence quantum yield of 1 mL of 5 mM CH_2Cl_2 solution of lophine hydroperoxide (**4b**) as the standard substance using 0.2 mL of 0.5 mol L^{-1} KOH in MeOH as the base.

Fig. 1. The CL efficiency of bidentate **2a** increased to about 10 times that of monodentate **2b** in MeCN/MeOH = 5/1 (v/v). The CL efficiency of **2a** was two times as much as that of **2b** in CH_2Cl_2. In the case of bidentate **4a**, the efficiency was 3 times as much as that of monodentate **4b**. In the absence of metal cations, the CL efficiencies of these bidentates in MeCN/MeOH = 5/1 (v/v) were increased compare to the corresponding efficiencies in CH_2Cl_2.

Addition of transition metals Cu^{II}, Fe^{III}, and Co^{II} to the solutions of the hydroperoxides resulted in significant quenching of chemiluminescence for all hydroperoxides tested. However, Zn^{II} worked as an enhancer in the cases of bidentates **2a** and **4a**. Eu^{III} also worked as an enhancer for bidentate **2a**, but not for **4a**. In the presence of Zn^{II}, CL emission maxima were blue shifted by 17 nm for **2a** and by a few nm for **4a**, respectively. Judging from the degree of the blue shift, the chelating ability of **2a** should be higher than that of **4a**. The extent of CL efficiency of **2a** in the presence of Zn^{II} is higher than that of **4a**, probably reflecting the chelating ability. CL spectra of **2a** in the presence of Eu^{II} were slightly red shifted (Fig. 1). In the presence of a quenching ion, the bidentates were more efficiently quenched than the corresponding monodentates **2b** and **4b**. Higher quenching caused by transition metal ions for the bidentates should be ascribable to their binding ability because orbital overlap between a chelating center and a metal ion may be enhanced. These observations resemble those reported for energy transfer of riboflavin fluorescence by Wehry et al., who inferred that electronic energy transfer might be an important quenching mechanism.[9] They observed quenching of riboflavin fluorescence (λ_{max} 520 nm), which is slightly higher energy region than that of lophine hydroperoxide CL (λ_{max} ~540 nm), by metal ions due to the energy transfer.[9] The ionic Zn^{II} exhibits no electronically excited states lower in energy than the first riboflavin singlet and energy transfer would therefore be extremely endothermic.[9] It is inferred that transition metal ions act as energy-transfer acceptors in the presence of excited singlet riboflavin by collisional energy transfer. These results are consistent with the findings of bidentates and the change of CL efficiency is rationalized by intramolecular energy transfer. The monodentate imino derivative **2b** is well known as undergoing syn–anti photoisomerization, which may be related to decreasing the CL efficiency. In the bidentate **2a**, this isomerization may be blocked by metal chelation due to fixation of the conformation, which may lead to enhancement of the CL efficiency. The CL efficiency enhancement of bidentates is ascribable to the fixation of conformation in the presence of Zn^{II}.[10] The quenching efficiency is not straightforwardly dependent on the distances r_1 and r_2 be-

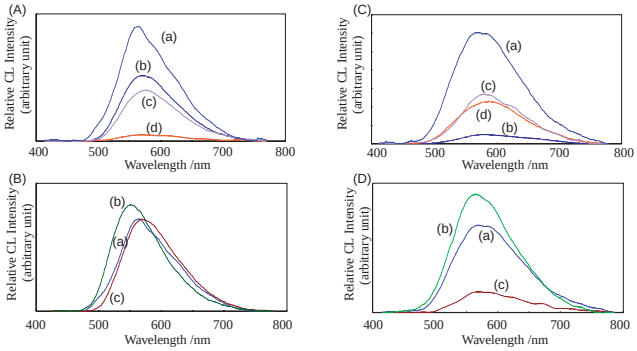

Fig. 1. Chemiluminescence spectra of **2a** and **4a**. (A) (a), (b), (c), and (d) are chemiluminescence spectra of **2a** in the absence of metal cation, in the presence of Fe^{III}, Cu^{II}, and Co^{II}, respectively. (B) (a), (b), and (c) are chemiluminescence spectra of **2a** in the absence of metal cation, in the presence of Zn^{II} and Eu^{III}, respectively. (C) (a), (b), (c), and (d) are chemiluminescence spectra of **4a** in the absence of metal cation, in the presence of Fe^{III}, Cu^{II}, and Co^{II}, respectively. (D) (a), (b), and (c) are chemiluminescence spectra of **4a** in the absence of metal cation, in the presence of Zn^{II} and Eu^{III}, respectively.

tween chromophores. The extents of CL quenching of **2a** and **4a** by metal ions are similar, suggesting that the distance was not a crucial factor to determine the quenching efficiencies in this case. It seems that there are energy transfers assisted by π conjugation through the benzene bridge in **4a**.

As shown above, these bidentates **2a** and **4a** appeared to be a potential CL chemosensors responsive to metal cations. The transition metals Co^{II}, Fe^{III}, and Cu^{II} worked as quenchers, whereas the ionic Zn^{II} worked as an enhancer in the case of the functional imidazole.

Experimental

CL Measurement. Chemiluminescent emission was measured using a photodiode array (Hamamatsu Photonics Model C-2491 Phonic Multichannel Analyzer) to record integrated illumination in photons. Relative chemiluminescence efficiency Φ_{cl}/Φ_0 is defined as the relative amount of chemiluminescence of hydroperoxides **2** and **4** compared to that of lophine peroxide **4b** as the standard. In typical chemiluminescence measurement, metal chloride in methanol (2.5 mol L^{-1}, 0.2 mL) was added to a MeCN solution consisting of 1.0 mL of a hydroperoxide derivative (5 mM), and then 0.2 mL of 1 mol L^{-1} $[Bu_4N]OH$ in methanol was added to the resulting mixed solution immediately.

2-[4-(*N*-Salicylideneamino)phenyl]-4,5-diphenylimidazole (1a). Yellow needles, mp 257–258 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.2 (s, 1H), 9.64 (brs, 1H), 8.66 (s, 1H), 7.96 (d, J = 8.5 Hz, 2H), 7.56 (brs, 4H), 7.44–7.22 (m, J = 8.5, 8.0, 7.2, 1 Hz, 10H), 7.01 (d, J = 8.0 Hz, 1H), 6.95 (td, J = 7.2, 1 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.4 (d), 160.5 (s), 149.5 (s), 147.7 (s), 147.0 (s), 145.2 (s), 133.5 (d), 132.8 (d), 129.1 (s), 128.6 (d), 126.4 (d), 122.1 (d), 119.6 (s), 119.4 (d), 116.8 (d). IR (KBr) 3400 (OH, NH), 2926 (CH), 1624, 1603 (CN), 1572, 1489, 1282 cm^{-1}. MS (EI^+) m/z 415 (M^+, 69%), 281 (82), 207 (100), 104 (52). HRMS (FAB) Calcd for $C_{28}H_{21}N_3O$: 416.1763, Found: 416.1764. UV (EtOH) λ_{max} (log ε) 236 (sh, 4.37), 280 (4.38), 370 nm (4.49). Anal. Calcd for $C_{28}H_{21}N_3O$: C, 80.94; H, 5.09; N, 10.11%. Found: C, 80.71; H, 5.00; N, 10.06%.

2-[4-(*N*-Benzylideneamino)phenyl]-4,5-diphenylimidazole (1b). Yellow needles, mp 169–170 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.95 (d, J = 8.6 Hz, 2H), 7.98–7.44 (m, 7H), 7.40–7.24 (m, J = 8.6 Hz, 8H), NH was not observed. IR (KBr) 3030 (NH), 1605 (CN), 1566, 1315 cm^{-1}. HRMS (FAB) Calcd for $C_{28}H_{22}N_3$: 400.1814, Found: 400.1808. UV (EtOH) λ_{max} (log ε) 278 (4.42), 357 nm (4.40). Anal. Calcd for $C_{28}H_{21}N_3$: C, 84.18; H, 5.30; N, 10.52%. Found: C, 84.38; H, 5.07; N, 10.42%.

4-Hydroperoxy-2-[4-(*N*-salicylideneamino)phenyl]-4,5-diphenyl-4*H*-imidazole (2a). Yellow crystals, mp 120.5–122 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.6 (brs, 1H), 13.0 (s, 1H), 8.55 (s, 1H), 8.39 (d, J = 7.5 Hz, 2H), 8.05 (d, J = 8.0 Hz, 2H), 7.66–7.24 (m, 10H), 7.09 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 7.6 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H). IR (KBr) 3400 (OH), 2926 (CH), 1601 (CN), 1566, 1278 cm^{-1}. UV (EtOH) λ_{max} (log ε) 313 (2.01), 373 nm (1.95). Anal. Calcd for $C_{28}H_{21}N_3O_3$: C, 75.15; H, 4.73; N, 9.39%. Found: C, 74.90; H, 4.68; N, 9.34%.

2-[4-(*N*-Benzylideneamino)phenyl]-4-hydroperoxy-4,5-diphenyl-4*H*-imidazole (2b). Yellow crystals, mp 124–125 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.5 (s, 1H), 8.38 (dd, J = 8.4, 1.8 Hz, 1H), 8.34 (s, 1H), 8.05 (d, J = 8.5 Hz, 2H), 7.93–7.90 (m, 2H), 7.56–7.26 (m, 11H), 7.03 (d, J = 8.5 Hz, 2H). IR (KBr) 2926 (CH), 1609 (CN), 1562 (CN), 1278 cm^{-1}. UV (EtOH) λ_{max} (log ε) 240 (4.42), 277 (4.50), 354 nm (4.34). HRMS (FAB) Calcd for $C_{28}H_{21}N_3O_2$: 432.1712, Found: 432.1762.

We thank the SC-NMR Laboratory of Okayama University for NMR spectral measurements.

Supporting Information

General procedure, and synthesis and spectra data of 2-(4-nitrophenyl)-4,5-diphenylimidazole (**5**), 2-(4-aminophenyl)-4,5-diphenylimidazole (**6**), 2-[4-(*N*-salicylideneamino)phenyl]-4,5-diphenylimidazole (**1a**), 2-[4-(*N*-benzylideneamino)phenyl]-4,5-diphenylimidazole (**1b**), 4-hydroperoxy-2-[4-(*N*-salicylideneamino)phenyl]-4,5-diphenyl-4*H*-imidazole (**2a**), and 2-[4-(*N*-benzylideneamino)phenyl]-4-hydroperoxy-4,5-diphenyl-4*H*-imidazole (**2b**). These material is available free of charge on Web at: http//www.csj.jp/journal/bcsj/.

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10 Probable emitters should be final products, but the resulted solutions of **2** and **4** were all not fluorescent. From the resulted solution, we failed to isolate an emitters related to the CL of **2** and **4**. In the chemiluminescent reaction of lophineperoxides, confirmation of emitter is an important work but acylated amidines are occasionally hard to be isolated. An emitter of the case of the standard lophine peroxide **4b** also has not been known.

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