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Metal-ion complexation of imidazo[1,2-*a*]pyrazin-3(7*H*)-ones: continuous changes in absorption spectra of complexes depending on the Lewis acidity of the metal ion

Takashi Sekiguchi,[a] Shojiro Maki,[a] Haruki Niwa,[a] Hiroshi Ikeda[b] and Takashi Hirano[a,*]

[a] *Department of Applied Physics and Chemistry, The University of Electro-Communications, Chofu, Tokyo 182-8585, Japan*
[b] *Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan*

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This paper is dedicated to Professor Tsutomu Miyashi on the occasion of his retirement from Tohoku University

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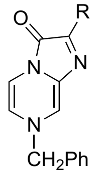
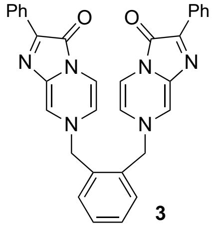
Abstract—The spectroscopic properties of metal-ion complexes of several imidazopyrazinone derivatives with Li^+, Mg^{2+}, Ca^{2+}, Ba^{2+}, Sc^{3+}, and La^{3+} ions were studied. The spectral characteristics and the formation constants of the complexes changed continuously depending on the Lewis acidity of the metal ion, suggesting that the imidazopyrazinones can find application as indicators of Lewis acidity. In the case of bis-imidazopyrazinone derivatives, the complexation abilities were enhanced by chelate effects.

The imidazo[1,2-*a*]pyrazin-3(7*H*)-one (imidazopyrazinone) ring system is an important core structure for the bioluminescent substrates isolated from marine luminescent organisms, such as the crustacea *Vargula*,[1] the jellyfish *Aequorea*,[2] and the squid *Symplectoteuthis*.[3] These bioluminescent substrates construct supramolecules with luciferins or apophotoproteins, and then their luminescent reactions proceed under air. Thus, imidazopyrazinone derivatives have potential not only for bio- and chemiluminescence[4] but also as building blocks for supramolecules that involve large polypeptide molecules.[5] In this connection, we have previously studied the luminescent reactivity[6] as well as the fundamental physical properties[5,7] of a systematic series of imidazopyrazinone derivatives. In addition to the characteristic luminescent property, we found a remarkable feature: the color of the imidazopyrazinone derivatives can be varied by an external factor such as the hydrogen-bonding interaction with solvent molecules.[5] From the viewpoint of developing colored probe molecules for external factors,[8] it is intriguing to control the color of an imidazopyrazinone derivative by means of a metal-ion complexation. For this purpose, we studied the spectroscopic properties of metal-ion complexation of mono- (**1** and **2**) and bis- (**3** and **4**) imidazopyrazinone derivatives. We now report a new complexation system, which can be used as an indicator of the Lewis acidity of a metal ion.



1 R = CH_3
2 R = Ph



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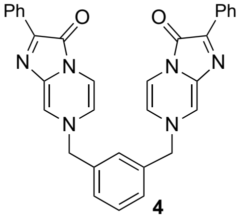

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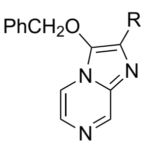

5 R = CH_3
6 R = Ph

Keywords: Bioluminescence; Metal-ion complexation; Lewis acidity; Absorption spectra.

* Corresponding author. Tel./fax: +81-424-86-1966; e-mail: hirano@pc.uec.ac.jp

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Imidazopyrazinone derivatives **1**–**4** were prepared by arylmethylation of the corresponding N–H imidazopyrazinone derivatives with benzyl halides.[5,9] During the preparations of **1** and **2**, benzyloxyimidazopyrazine derivatives **5** and **6** were also isolated and used as reference compounds with a different π electronic character.[5] The complexation of **1** and **2** with various metal ions (Li^+, Mg^{2+}, Ca^{2+}, Ba^{2+}, Sc^{3+}, and La^{3+}) was confirmed by UV/visible absorption spectral measurements in acetonitrile, as shown in Figure 1. Perchlorate salts of Li^+, Mg^{2+}, Ca^{2+}, and Ba^{2+} and trifluoromethanesulfonate salts of Sc^{3+} and La^{3+} were used for the experiments.[10] In the order listed in Table 1, the solution color of **1** changed from deep to pale yellow, while that of **2** turned from red to yellow. The spectral changes of **1** and **2** in the presence of Li^+, Mg^{2+}, Ca^{2+}, and Ba^{2+} were analyzed satisfactorily on the assumption of a 1:1 equilibrium (Scheme 1),[11] as exemplified by the combination of **1** and Mg^{2+} in Figure 2. To estimate the formation constants (K) of the complexes, the spectral changes were analyzed by nonlinear least squares curve fitting for the 1:1 equilibrium,[12] as shown in Figure 2B for **1** and Mg^{2+}. In contrast, however, the complexation of **1** and **2** with Sc^{3+} and La^{3+} showed a complicated stoichiometry, although these complexes were formed efficiently.

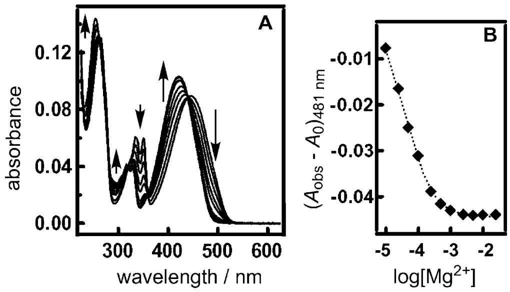


Figure 2. UV/visible absorption spectra of **1** (9.7×10^{-6} mol dm^{-3}) in CH_3CN containing various amounts of Mg^{2+} (1.0×10^{-5}–2.5×10^{-2} mol dm^{-3}) at 25 °C (**A**) and plot of $(A_{obs} - A_0)$ at 481 nm versus log[Mg^{2+}] for complexation (**B**). The dotted line in **B** is the fitted curve corresponding to 1:1 complexation.

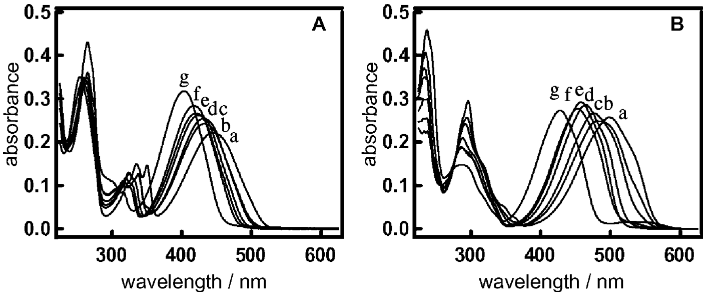


Figure 1. UV/visible absorption spectra of **1** (2.4×10^{-5} mol dm^{-3}) (**A**) and **2** (1.4×10^{-5} mol dm^{-3}) (**B**) in CH_3CN containing various metal ions at 25 °C; free (a), Li^+ (b), Ba^{2+} (c), Ca^{2+} (d), Mg^{2+} (e), La^{3+} (f), and Sc^{3+} (g) (**A**: $[Li^+] = [Ba^{2+}] = [Ca^{2+}] = [Mg^{2+}] = 0.025$ mol dm^{-3}, $[La^{3+}] = [Sc^{3+}] = 2.5\times10^{-4}$ mol dm^{-3}; **B**: $[Li^+] = [Ba^{2+}] = [Ca^{2+}] = [Mg^{2+}] = 0.010$ mol dm^{-3}, $[La^{3+}] = [Sc^{3+}] = 1.0\times10^{-4}$ mol dm^{-3}).

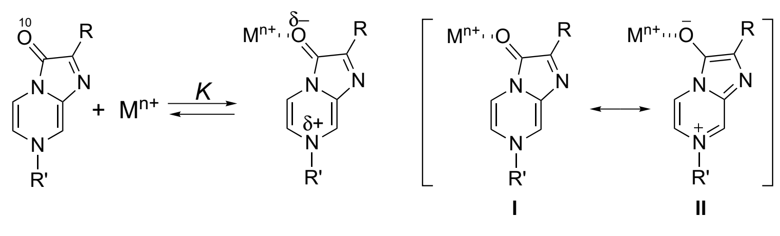
Table 1. Absorption maxima (λ_{max}) and formation constants (K)[a] for **1** and **2** and their metal-ion complexes in acetonitrile at 25 °C

Metal ion (ΔE/eV)[b]	**1**		**2**	
	λ_{max}/nm	K/mol^{-1} dm^3	λ_{max}/nm	K/mol^{-1} dm^3
Free	447	—	500	—
Ba^{2+} (0.49)	431	1.1×10^3	476	5.6×10^2
Li^+ (0.53)	430	2.5×10^2	475	1.2×10^2
Ca^{2+} (0.58)	424	1.5×10^4	464	6.2×10^3
Mg^{2+} (0.65)	422	2.8×10^4	457	8.0×10^3
La^{3+} (0.82)	418	[c]	452	[c]
Sc^{3+} (1.00)	403	[c]	428	[c]

[a] The errors are within 8%.

[b] The Fukuzumi parameter for the Lewis acidity quoted from Ref. 13.

[c] Complexation occurred with a complicated stoichiometry.



Scheme 1.

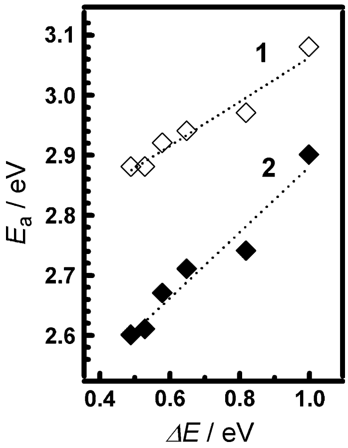
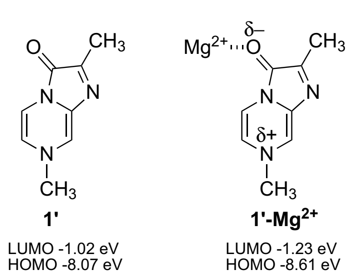


Figure 3. Plot of the energies E_a of the metal-ion complexes of **1** and **2** versus the Fukuzumi parameter ΔE for the Lewis acidity.

The absorption maxima (λ_{max}) of the lowest energy bands and K values of the complexes of **1** and **2** are summarized in Table 1. To gain insight into the spectroscopic properties of the metal-ion complexes, we examined the relationships between the energies [E_a (eV)] of the lowest absorption energy bands and the Fukuzumi parameters [ΔE (eV)] for the Lewis acidity of the metal ions.[13] The resulting plot (Fig. 3) shows that the E_a values for the complexes of **1** and **2** are nicely correlated with the ΔE parameters. The linear relationships for the complexes of **1** and **2** are represented as $E_a = 0.37\Delta E + 2.69$ ($r = 0.98$) and $E_a = 0.54\Delta E + 2.33$ ($r = 0.97$), respectively. With increasing Lewis acidity of the metal ion, the λ_{max} values exhibited a blue shift. Based on these results, it is clear that **1** and **2** act as Lewis bases toward metal ions, and that an enhancement of the Lewis acid/base interaction causes changes in the π-electronic character of **1** and **2** in their respective metal-ion complexes, resulting in the blue shift of the lowest energy bands. The enhancement of the Lewis acid/base interaction also reflects on an increase of the K values, although the order of the K values between Li^+ and Ba^{2+} was inverted.

Since the imidazopyrazinone derivative has a zwitterionic structure, in which the largest negative partial charge is localized on the oxygen atom (O-10) at the 10 position,[5,14] the O-10 must be the actual center of the Lewis base. According to previous studies,[5,16] it is known that the O-10 acts as a Brønsted base site, and the protonation of O-10 gives rise to the blue shift of the lowest energy band. Thus, the O-10 atoms of **1** and **2** are proposed to coordinate to the metal ion (M^{n+}). The π electronic character of the resulting metal-ion complex is described by resonance structures **I** and **II** (Scheme 1). In the structure **II**, the 7-imidazopyrazinium portion possesses the character originating in the imidazopyrazine ring system analogous to **5** and **6**. The lowest energy bands of **5** and **6** were observed at 324 (ε 4500 cm^{-1} mol^{-1} dm^3) and 342 nm (ε 7500 cm^{-1} mol^{-1} dm^3) in acetonitrile, respectively, suggesting that an increase in the **II** character resulted in the blue shift of the lowest energy band. To confirm this explanation, we performed semi-empirical MO calculations (AM1–COSMO, dielectric constant = 35.9 for acetonitrile)[15] for the Mg^{2+} complex of **1′**, a structurally related model compound (Scheme 2). The calculated HOMO–LUMO energy gap for the **1′**–Mg^{2+} complex (7.39 eV) is larger than that for the free **1′** (7.05 eV), supporting the blue shift induced by complexation.



Scheme 2.

Metal-ion complexations of **3** and **4** were also observed by UV/visible absorption spectral measurements in acetonitrile in the presence of Li^+, Mg^{2+}, Ca^{2+}, and Ba^{2+} (Fig. 4). While **3** and **4** themselves showed absorption spectra similar to that of the mono-derivative **2**, absorption spectra of their metal-ion complexes were different from those of the corresponding complexes of **2**. In particular, the metal-ion complexes of **3** showed the lowest energy bands with some structures, suggesting that two imidazopyrazinone rings are brought close together, giving rise to a π–π interaction of two rings. These results indicate that **3** and **4** formed complexes with the metal ion: both of the imidazopyrazinone moieties of **3**, as well as both of those of **4**, coordinate to the same metal ion in a bidentate fashion. The absorption spectral changes for **3** and **4** were examined in the

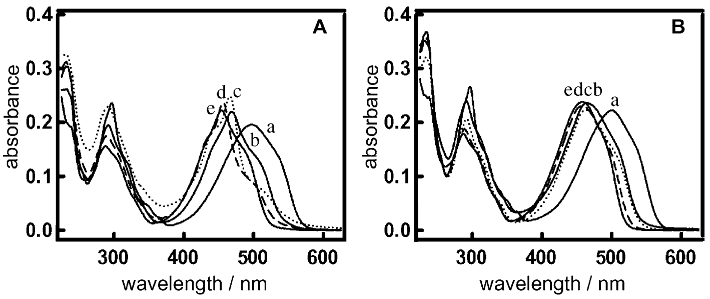


Figure 4. UV/visible absorption spectra of **3** (5.3×10^{-6} mol dm^{-3}) (**A**) and **4** (7.1×10^{-6} mol dm^{-3}) (**B**) in CH_3CN containing various metal ions at 25 °C; free (a), Li^+ (b), Ba^{2+} (c), Ca^{2+} (d), and Mg^{2+} (e) (**A** and **B**: $[Li^+] = 0.10$ mol dm^{-3}, $[Ba^{2+}] = [Ca^{2+}] = [Mg^{2+}] = 0.010$ mol dm^{-3}).

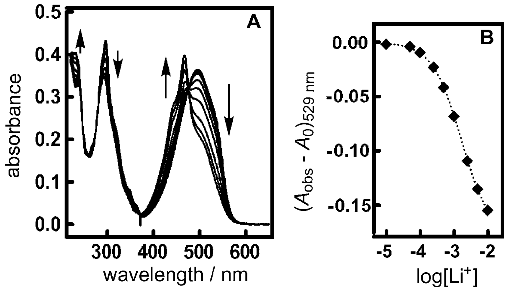


Figure 5. UV/visible absorption spectra of **3** (9.7×10^{-6} mol dm^{-3}) in CH_3CN containing various amounts of Li^+ (1.0×10^{-5}–1.0×10^{-2} mol dm^{-3}) at 25 °C (**A**) and plot of ($A_{obs} - A_0$) at 529 nm versus log[Li^+] for complexation (**B**). The dotted line in **B** is the fitted curve corresponding to 1:1 complexation.

presence of various concentrations of Li^+ and Mg^{2+} as representative metal ions. These spectral changes, which had clear isosbestic points, were analyzed satisfactorily under the assumption that there was an equilibrium forming a 1:1 complex (Fig. 5). The K values estimated for the Li^+ complexes of **3** and **4** are 610 and 1600 mol^{-1} dm^3, respectively, and those for the Mg^{2+}–complexes of **3** and **4** are over 10^5 mol^{-1} dm^3. These K values for **3** and **4** are remarkably larger than those for the corresponding Li^+ and Mg^{2+} complexes of **2**, indicating that efficient chelate effects operate in the bis-imidazopyrazinone systems.

In conclusion, we found a new complexation system, the mono- and bis-imidazopyrazinone derivatives (**1**–**4**), the former being potentially applicable as indicators of the Lewis acidity of metal ions. In the complex structure, the O-10 of the imidazopyrazinone derivative probably coordinates to the metal ion. The continuous blue shift of the lowest energy band and the increase in K value were caused by an enhancement of the Lewis acid/base interaction between **1** (or **2**) and the metal ion. The design of the bisimidazopyrazinone derivatives **3** and **4** demonstrated that complexation with the metal ion is enhanced by chelate effects. Further studies to reveal the molecular and electronic structures of the metal-ion complexes are now in progress.

Acknowledgements

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9. Preparation of **1** as a typical procedure: To a solution of 2-methylimidazo[1,2-*a*]pyrazin-3(7*H*)-one hydrochloride (306 mg, 1.65 mmol) in DMF (2 mL) were added benzyl chloride (0.35 mL, 3.1 mmol) and K_2CO_3 (822 mg, 6.1 mmol) at room temperature under Ar. After stirring overnight, water was added to the reaction mixture and the products were extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography, to give **1** (106 mg, 27%) as yellow powder and **5** (51 mg, 13%) as colorless crystals; **1**: mp 198 °C (dec); ^1H NMR (270 MHz, CD_3OD) δ 7.99 (1H, s), 7.3–7.5 (6H, m), 6.98 (1H, dd, $J = 1.3$, 5.9 Hz), 5.11 (2H, s), 2.42 (3H, s); IR (KBr) 3093, 3076, 2925, 2360, 1684, 1599, 1558, 1498 cm^{-1}; EIMS m/z 239 (M^+, 78), 120 (26), 91 (100); HREIMS calcd for $C_{14}H_{13}N_3O$: 239.1059. Found: 239.1053. Anal. Calcd for $C_{14}H_{13}N_3O\cdot1/5H_2O$: C, 69.23; H, 5.56; N, 17.30. Found: C, 69.49; H, 5.65; N, 16.99. **5**: mp 76–77 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 8.82 (1H, d, $J = 1.6$ Hz), 7.68 (1H, d, $J = 4.3$ Hz), 7.56 (1H, dd, $J = 1.3$, 4.6 Hz), 7.3–7.4 (5H, m), 5.13 (2H, s), 2.38 (3H, s); IR (KBr) 3035, 2941, 2360, 1616, 1552, 1496 cm^{-1}; EIMS m/z 239 (M^+, 70), 120 (40), 91 (100); HREIMS calcd for $C_{14}H_{13}N_3O$: 239.1059. Found: 239.1052.
   Compounds **2**–**4** and **6** were prepared by procedures analogous to that used for **1** and **5**. **2**: red powder, mp 192 °C (dec); ^1H NMR (270 MHz, CD_3OD) δ 8.44 (2H, m), 8.12 (1H, d, $J = 1.3$ Hz), 7.58 (1H, d, $J = 5.9$ Hz), 7.3–7.5 (8H, m), 7.01 (1H, dd, $J = 1.6$, 5.9 Hz), 5.17 (2H, s); IR (KBr) 3093, 3060, 2920, 1668, 1591, 1496 cm^{-1}; EIMS m/z 301 (M^+, 100), 182 (87), 91 (92); HREIMS calcd for $C_{19}H_{15}N_3O$: 301.1215. Found: 301.1209. Anal. Calcd for $C_{19}H_{15}N_3O\cdot1/3H_2O$: C, 74.25; H, 5.14; N, 13.67. Found: C, 74.45; H, 5.11; N, 13.46. **3**: red powder, mp 231 °C (dec); ^1H NMR (270 MHz, CD_3OD) δ 8.30 (4H, m), 7.76 (2H, d, $J = 1.6$ Hz), 7.3–7.6 (12H, m), 6.85 (2H, dd, $J = 1.6$, 5.9 Hz), 5.31 (4H, s); IR (KBr) 3059, 1670, 1591, 1498 cm^{-1}; FABMS (glycerol) m/z 547 ($[M+Na]^+$). Anal. Calcd for $C_{32}H_{24}N_6O_2\cdot5/3H_2O$: C, 69.30; H, 4.97; N, 15.15. Found: C, 69.23; H, 5.17; N, 14.90. **4**: red powder, mp 223 °C (dec); ^1H NMR (270 MHz, CD_3OD) δ 8.40 (4H, m), 8.09 (2H, d, $J = 1.3$ Hz), 7.3–7.6 (12H, m), 6.99 (2H, dd, $J = 1.6$, 5.9 Hz), 5.19 (4H, s); IR (KBr) 3064, 1670, 1603, 1589, 1498 cm^{-1}; FABMS (glycerol) m/z 525 ($[M+H]^+$). Anal. Calcd for $C_{32}H_{24}N_6O_2\cdot5/4H_2O$: C, 70.06; H, 4.90; N, 15.32. Found: C, 70.01; H, 5.15; N, 15.08. **6**:

colorless powder, mp 105–106 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.94 (1H, d, $J = 1.6$ Hz), 8.15 (2H, m), 7.67 (1H, d, $J = 4.6$ Hz), 7.2–7.5 (9H, m), 5.11 (2H, s); IR (KBr) 3030, 2360, 1549, 1489 cm^{-1}; EIMS m/z 301 (M^+, 70), 210 (25), 182 (100), 91 (39); HREIMS calcd for $C_{19}H_{15}N_3O$: 301.1215. Found: 301.1211.

10. No spectral change of **1** and **2** was observed on adding $NaClO_4$ and $KClO_4$.
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12. The difference in absorbance of an imidazopyrazinone substrate ([sub.]) at a chosen wavelength comparing solutions before (A_0) and after (A_{obs}) adding a metal ion ($[M^{n+}]$) is given by the following nonlinear equation, which includes the K value:[11]

$$A_{\mathrm{obs}} - A_0 = 0.5\Delta\varepsilon([\mathrm{sub.}]_{\mathrm{i}} + [\mathrm{M}^{n+}]_{\mathrm{i}} + 1/K - \{([\mathrm{sub.}]_{\mathrm{i}} + [\mathrm{M}^{n+}]_{\mathrm{i}} + 1/K)^2 - [\mathrm{sub.}]_{\mathrm{i}}[\mathrm{M}^{n+}]_{\mathrm{i}}\}^{1/2}),$$

where $[\mathrm{sub.}]_{\mathrm{i}}$ and $[\mathrm{M}^{n+}]_{\mathrm{i}}$ are the initial concentrations and $\Delta\varepsilon$ is the difference in the molar absorptivity between the imidazopyrazinone substrate and its metal-ion complex.

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