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Regioselective phenyl-substitution effects on the solvatochromism of 2-phenylimidazo[1,2-*a*]pyrazin-3(7*H*)-one derivatives: expansion of the color variation range of a visible indicator for the proton donor ability of solvents

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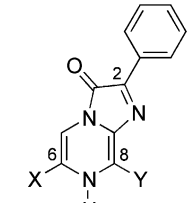
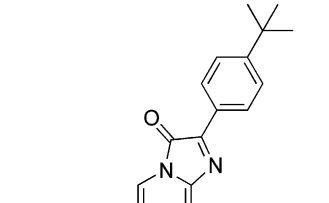
Abstract—Phenyl-substitution to the C8 position of an imidazopyrazinone ring resulted in the significant bathochromic shift of the lowest energy band, while the substitution to the C6 position does not produce such a shift. This provides evidence that a color variation range of the solvatochromism of 2-phenylimidazopyrazinone derivatives depends strongly on the position of phenyl-substitution. Results indicated that an imidazopyrazinone with the phenyl groups at the C2 and C8 positions acts as a potential indicator of the proton donor ability of solvents.

The imidazo[1,2-*a*]pyrazin-3(7*H*)-one ring is an essential core structure of the bioluminescent substrates isolated from some marine luminescent organisms.[1] During our previous studies on bio- and chemiluminescence[2] and physical properties[3] of imidazopyrazinone derivatives, it was found that 2-phenylimidazo[1,2-*a*]pyrazin-3(7*H*)-one (**1**) exhibits a significant solvatochromism.[3a] The solution color, changing from yellow to red, is controlled by the strength of the hydrogen-bonding interaction, in which the imidazopyrazinone subunits and solvent molecules act as hydrogen-bond acceptors and donors,[4] respectively. This suggests that imidazopyrazinone derivatives are applicable as an indicator of the proton donor ability of solvents. To this purpose, phenyl-substitution effects on solvatochromism of imidazopyrazinone were investigated, using 6-phenyl (**2**), 8-phenyl (**3**), and 6,8-diphenyl (**4**) derivatives of **1**, and it was found that the phenyl-substitution at the C8 position was effective in causing a bathochromic shift, but that substitution at the C6 position was not. Herein, a brief report is given on the solvatochromic properties of **2**–**5**, in addition to the crystal structure of a hydrogen-bonding complex of tri-*tert*-butylphenyl derivative (**5**) and acetic acid.



1 X = Y = H
2 X = Ph, Y = H
3 X = H, Y = Ph
4 X = Y = Ph



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Imidazopyrazinones **2**–**5** were prepared by condensation of the corresponding pyrazinamine precursors with phenylglyoxal derivatives under acidic conditions.[5,6] Figure 1 provides the UV–vis absorption spectra of **2** and **3** in dimethylsulfoxide (DMSO), acetonitrile,

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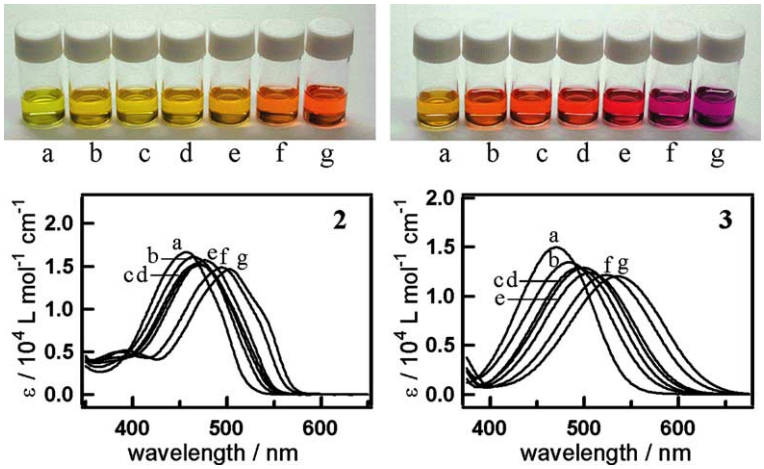

Figure 1. Solution colors and UV–vis absorption spectra of **2** and **3** in various solvents: (a) 2,2,2-trifluoroethanol, (b) acetic acid, (c) methanol, (d) ethanol, (e) 2-propanol, (f) acetonitrile, and (g) DMSO.

alcoholic solvents, and acetic acid.[7] The solution color of **2** varied from yellow to red, similarly to that of **1**, depending on the solvent, while those of **3** and **4** (not shown in Fig. 1) changed from orange to violet. The lowest energy bands of **2**–**4** are summarized in Table 1 together with those of **1**.[3a] As shown in Figure 2, the wavenumbers (ν in cm^{-1}) of the lowest energy bands of **1**–**4** are linearly correlated to Kamlet–Taft's solvatochromic parameter, the α values,[8] but not to the β and π^* values:[8] $\nu = 1370\alpha + 20{,}200$ ($r = 0.99$) for **1**, $\nu = 1400\alpha + 19{,}900$ ($r = 0.99$) for **2**, $\nu = 1690\alpha + 18{,}700$ ($r = 0.99$) for **3**, and $\nu = 1410\alpha + 19{,}200$ ($r = 0.99$) for **4**. The observed solvatochromism originates from the hydrogen-bonding interaction between **1**–**4** (hydrogen-bond acceptor) and the solvent molecules (hydrogen-bond donor).[3a] The similar slope values observed for **1**–**4** suggest that the pattern of hydrogen-bonding interaction is essentially the same among **1**–**4**; the energy levels of the frontier orbitals of **1**–**4** change similarly with dependence on the strength of hydrogen-bonding interactions.

The order of the ν values for the imidazopyrazinones is **1** ≈ **2** > **3** ≈ **4** in each solvent, indicating that the phenyl-substitution to C6 and C8 positions causes a small and large bathochromic shift of the lowest energy band, respectively. The regioselective phenyl-substitution effects on the bathochromic shift are supported by the AM1 COSMO calculation ($\varepsilon = 46.5$ for DMSO).[9,10]

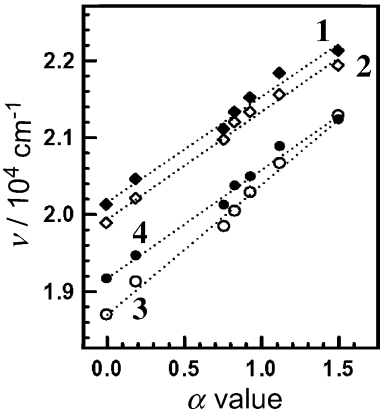

Figure 2. Plots of wavenumbers ν (in cm^{-1}) of the lowest energy bands for **1**–**4** against Kamlet–Taft's α values.

The HOMO–LUMO energy gaps, 6.74, 6.73, 6.40, and 6.40 eV, calculated for **1**, **2**, **3**, and **4**, respectively, correspond well to the ν values in the same solvent. As shown in Figure 3, π electrons in the LUMO of **4** are delocalized to the phenyl groups at C2 and C8 positions, but not at the C6 position. The phenyl groups at the C2 and C8 positions of **3** are also involved with a delocalization of π electrons in the LUMO, while only the phenyl group at the C2 position of **2** is involved. The π electron distribution in the HOMOs of **1**–**4** and the energy levels (ca. −7.9 eV) are similar to each other. By

Table 1. Absorption maxima (λ_{max}) of the lowest energy bands of **1**–**4** in various solvents

Solvent	α value	λ_{max}/nm (ε/10^4 L mol^{-1} cm^{-1})			
		1	**2**	**3**	**4**
DMSO	0.00	497 (1.67)	503 (1.46)	535 (1.18)	522[a]
Acetonitrile	0.19	489 (1.54)	495 (1.48)	523 (1.21)	514 (0.82)
2-Propanol	0.76	474 (1.62)	477 (1.57)	504 (1.23)	497 (0.81)
Ethanol	0.83	469 (1.57)	472 (1.51)	499 (1.29)	491 (0.91)
Methanol	0.93	465 (1.57)	469 (1.53)	493 (1.28)	488 (1.00)
Acetic acid	1.12	458 (1.67)	464 (1.61)	484 (1.34)	479 (0.98)
2,2,2-Trifluoroethanol	1.50	452 (1.72)	456 (1.67)	470 (1.50)	471 (1.30)

[a] An accurate molar absorptivity of **4** in DMSO was not obtained because **4** was slowly decomposed when dissolved with DMSO.

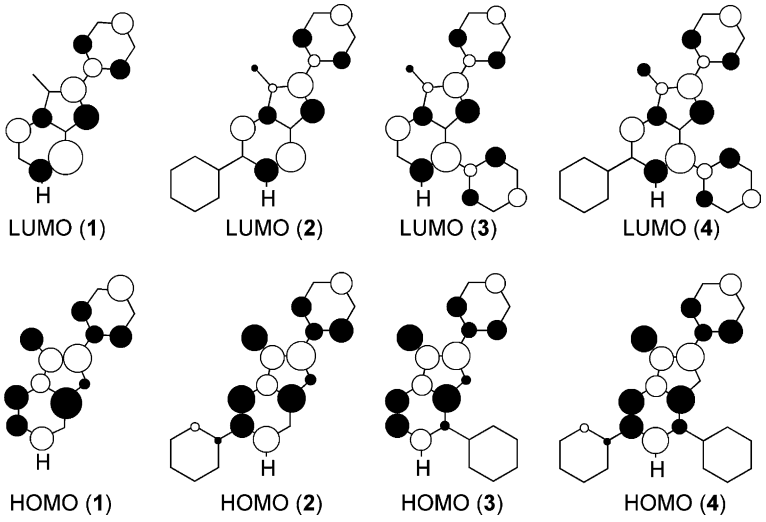

Figure 3. Schematic representation of the HOMOs and LUMOs of **1**–**4**.

contrast, the LUMO levels of **3** (−1.54 eV) and **4** (−1.57 eV) are significantly lower than those of **1** (−1.17 eV) and **2** (−1.21 eV). Consequently, the phenyl-substitution at the C8 position causes the bathochromic shift of the lowest energy band through the delocalization of π electrons in the LUMO.

Structural information of the hydrogen-bond interaction was obtained using X-ray crystallographic analysis of the hydrogen-bonding complex of **5** and acetic acid (molar ratio 1:1).[11] Figure 4 shows that a hydrogen atom of the carboxyl group is located close to the oxygen atom, O10, of **5** enabling a hydrogen bond. This observation is in accord with the AM1 COSMO calculations: the O10 atoms of **1**–**4** are suggested as being the most negatively charged (net atomic charge = ca. −0.6) among all the atoms. Consequently, the O10 of **1**–**4** must be an important and key participant for the hydrogen-bond interactions with the solvent molecules. Another characteristics of **5** in the complex is that the imidazopyrazinone ring is planar and the C=O bond length (1.263(4) Å) is comparable to that of **1** (1.259 Å),[12] indicating that the hydrogen-bond interaction in the complex causes a small perturbation to the structure of the imidazopyrazinone ring system of **5**.[3a]

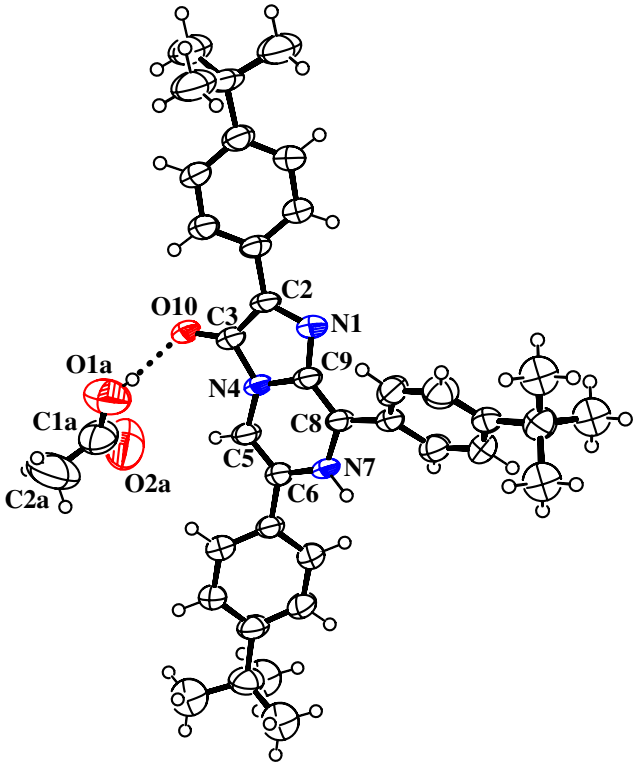

Figure 4. ORTEP drawing of the **5**–acetic acid complex.

In conclusion, it was found that phenyl-substitution at the C8 position effects a bathochromic shift, which leads to an expansion of the color variation range in the imidazopyrazinone series. These findings indicate that imidazopyrazinone derivatives with phenyl groups at C2 and C8 positions function as potential indicators of the proton donor ability of solvents. Further investigation to develop the indicators based on this molecular design is now in progress and will be published elsewhere.

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6. Compound **2**: red powder, mp 230–231 °C (dec); ^{1}H NMR (270 MHz, DMSO-d_6/CF_3COOD (6:1)) δ 9.18 (1H, s), 8.77 (1H, s), 8.30 (2H, br d, J = 8 Hz), 7.99 (2H, br d, J = 8 Hz), 7.59–7.62 (5H, m), 7.47–7.52 (1H, m); IR (KBr) 3055, 1668, 1576 cm^{-1}; EIMS *m*/*z* 287 (M^+, 93), 258 (97), 156 (100), 128 (94); HREIMS calcd for $C_{18}H_{14}N_3O$: 287.1059. Found: 287.1052. Compound **3**: red powder, mp 150–151 °C (dec); ^{1}H NMR (270 MHz, DMSO-d_6/CF_3COOD (6:1)) δ 8.31–8.40 (4H, m), 8.10 (1H, d, J = 5.7 Hz), 7.71–7.74 (3H, m), 7.50–7.55 (3H, m), 7.42 (1H, m); IR (KBr) 3026, 1616, 1560 cm^{-1}; EIMS *m*/*z* 287 (M^+, 84), 258 (100), 155 (61); HREIMS calcd for $C_{18}H_{14}N_3O$: 287.1059. Found: 287.1052. Compound **4**: red powder, mp 155–156 °C (dec); ^{1}H NMR (270 MHz, DMSO-d_6/CF_3COOD (6:1)) δ 8.71 (1H, s), 8.50 (2H, m), 8.28 (2H, br d, J = 7 Hz), 8.14 (2H, br d, J = 7 Hz), 7.70 (3H, m), 7.54–7.60 (5H, m), 7.45 (1H, m); IR (KBr) 3055, 1655, 1543 cm^{-1}; EIMS *m*/*z* 363 (M^+, 100), 334 (55); HREIMS calcd for $C_{24}H_{17}N_3O$: 363.1372. Found: 363.1363. Compound **5**: red powder, mp 193–194 °C (dec); ^{1}H NMR (270 MHz, DMSO-d_6/CF_3COOD (6:1)) δ 8.64 (1H, s), 8.32 (2H, d, 8.6 Hz), 8.18 (2H, d, 8.6 Hz), 8.01 (2H, d, 8.6 Hz), 7.73 (2H, d, 8.2 Hz), 7.63 (2H, d, 8.6 Hz), 7.60 (2H, d, 8.2 Hz), 1.42 (9H, s), 1.38 (9H, s), 1.36 (9H, s); IR (KBr) 2961, 1612, 1589 cm^{-1}; EIMS *m*/*z* 531 (M^+, 91), 446 (100); Anal. Calcd for $C_{36}H_{41}N_3O{\cdot}1/3H_2O$: C, 80.41; H, 7.81; N, 7.81. Found: C, 80.35; H, 7.72; N, 7.65.
7. Spectroscopic measurements for solutions of **1**–**4** (1.0×10^{-4} mol L^{-1}) were made in a quartz cuvette (0.5 cm path-length) at 25 ± 1 °C. Accurate UV–vis absorption spectra of **1**–**4** in water and nonpolar solvents such as *n*-hexane and chloroform were not obtained, because of low solubility in these solvents.
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10. AM1-COSMO calculations were carried out with the MOPAC package (MOPAC2000 VER. 1.0, Fujitsu Ltd, Tokyo, Japan, 1999).
11. Crystal data for the complex of **5** and acetic acid: $C_{36}H_{13}N_3O{\cdot}C_2H_4O_2$, M = 591.8, monoclinic, space group $P2_1/c$, a = 12.657(3), b = 19.763(4), c = 14.067(5) Å, β = 109.27(1)°, V = 3322(2) Å^3, Z = 4, D_x = 1.183 Mg m^{-3}, μ (synchrotron SPring-8 BL02B1 beam line; λ = 0.7085 Å)=0.075 mm^{-1}, 13,600 unique data, final R_1 = 0.114, wR_2 = 0.283 for 6875 observed data [$I>2\sigma I$]. Programs: SIR-92 [Altomare, A.; Cascarano, C.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435]; SHELXL-97 [Sheldrick, G. M. SHELXL-97. Program for crystal structure determination, University of Göttingen, Germany, 1997]. Crystallographic data has been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC 244697.
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