Structural Features for Fluorescing Present in Methoxycoumarin Derivatives

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Structural features of fluorescent methoxycoumarins were examined from the viewpoint of substituent effect and ring structure in connection with intramolecular charge-transfer (ICT). The fluorescence of methoxycoumarins depended primarily upon the ICT from a C_6-electron-donating group to the substituents at the C_3-position of the coumarin ring. Furthermore, the presence of a lactone ring itself, including a carbonyl group, cyclic ether oxygen and ethylenic bond as partial ring structures, was found to be essential for fluorescing in methoxycoumarins according to the fluorescent behaviors of chemically deformed model compounds.

Key words methoxycoumarin; fluorophore; fluorescence emission mechanism; intramolecular charge-transfer

Fluorometric analysis is one of the most sensitive methods for detecting organic and/or inorganic compounds, and therefore it has been widely used in many scientific fields with improving analytical instruments such as high-performance liquid chromatography (HPLC), capillary electrophoresis (CE), and the like. However, as most compounds in nature are not fluorescent, it is necessary to give them fluorescence by reacting them chemically with fluorescent or fluorogenic molecules. For this purpose, a great deal of effort has gone into the development of fluorescence derivatization reagents using various fluorophores. At the stage of molecular design, having sufficient information on the relationship between the chemical structures and fluorescence characteristics of fluorophores should facilitate the development of the reagents.

Recently, Imai and co-workers established a method of predicting the fluorescent behaviour of benzofurazane compounds, some of which are commonly purchased as fluorescence derivatization reagents, from a standpoint of the Hammett's substituent effects[1] and by semi-empirical molecular orbital calculations.[2]

In a previous paper,[3] we have also reported the fluorescence characteristics of methoxycoumarins, some of which have been utilized as the fluorophores of the analytical reagents,[4] as well as benzofurazanes. Next, the structural features of strongly fluorescing methoxycoumarins were discussed in connection with their spectroscopic properties based on intramolecular charge-transfer (ICT) from the substituents to a coumarin ring.

Now, this paper describes the fluorescence characteristics of methoxycoumarins in further detail by means of additional substituent effects, and the conclusive and reductive chemical conversion of coumarins, because an adequate understanding of fluorophores is essential for the development of excellent fluorescence reagents, as described above.

Experimental

Materials All chemicals were of reagent grade, unless noted otherwise. The solvents (Luminasol) used for the fluorescence measurement were purchased from Dojindo Laboratories (Kumamoto, Japan). Compounds **1a**—**k** were prepared by means of Knovenagel condensation of 4,5-dimethoxysalicylaldehyde with the corresponding active methylene compounds, according to the methods described in the literature.[5—10]

Typical synthetic procedures, as well as physical and spectral data of unknown compounds, were as follows:

1f: Yield 45%, mp 216—217 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.93, 3.96 (3H, s, C_6-, C_7-OCH_3), 6.88 (1H, s, C_5-H), 6.98 (1H, s, C_8-H), 8.37 (1H, s, C_4-H), 10.22 (1H, s, C_3-CHO). MS *m/z*: 234 (M^+).

1h: Yield 26%, mp 167—168 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.94, 3.98 (3H, s, C_6-, C_7-OCH_3), 6.89 (1H, s, C_5-H), 6.90 (1H, s, C_8-H), 7.68 (1H, s, C_4-H). MS *m/z*: 354 (M^+).

1j: Yield 69%, mp 293—294 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.97, 4.01 (3H, s, C_6-, C_7-OCH_3), 6.87 (1H, s, C_5-H), 6.89 (1H, s, C_8-H), 8.15 (1H, s, C_4-H). MS *m/z*: 231 (M^+).

2a: A mixture of 2,5-dihydroxy-4-methoxybenzaldehyde[11] (10 mmol) and ethyl acetoacetate (10 mmol) in absolute ethanol was refluxed in the presence of a few drops of piperidine for 10 min. After cooling, the resulting precipitates were recrystallized from ethanol to give 3-acetyl-6-hydroxy-7-methoxycoumarin as yellow needles [mp 215—216 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.71 (3H, s, C_3-$COCH_3$), 4.02 (3H, s, C_7-OCH_3), 5.63 (1H, s, C_6-OH), 6.86 (1H, s, C_5-H), 7.11 (1H, s, C_8-H), 8.46 (1H, s, C_4-H). MS *m/z*: 234 (M^+)]. Acetylation of this compound with acetic anhydride in pyridine by the usual method gave **2a** as pale yellow needles. Yield 75%, mp 178—179 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s, C_6-$OCOCH_3$), 2.71 (3H, s, C_3-$COCH_3$), 3.94 (3H, s, C_7-OCH_3), 6.91 (1H, s, C_5-H), 7.31 (1H, s, C_8-H), 8.45 (1H, s, C_4-H), 8.45 (1H, s, C_4-H). MS *m/z*: 276 (M^+).

Compound **2b** was obtained in the same manner as that of **2a**, other than employing 3-acetyl-7-hydroxy-6-methoxycoumarin [mp 237—238 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.71 (3H, s, C_3-$COCH_3$), 3.98 (3H, s, C_6-OCH_3), 6.42 (1H, s, C_7-OH), 6.94 (1H, s, C_8-H), 6.97 (1H, s, C_5-H), 8.48 (1H, s, C_4-H). MS *m/z*: 234 (M^+)] derived from 2,4-dihydroxy-5-methoxybenzaldehyde.[12] Yield 83%, mp 213—215 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (3H, s, C_7-$OCOCH_3$), 2.73 (3H, s, C_3-$COCH_3$), 3.90 (3H, s, C_6-OCH_3), 6.91 (1H, s, C_5-H), 7.31 (1H, s, C_8-H), 8.45 (1H, s, C_4-H). MS *m/z*: 276 (M^+).

2c: A mixture of 2,5-dihydroxy-4-methoxybenzaldehyde (5 mmol) and 2-(tosyloxymethyl)-15-crown-5-ether[13] (5 mmol) in anhydrous acetone (50 ml) was refluxed in the presence of K_2CO_3 (5 mmol) for 72 h, filtered and evaporated to dryness under reduced pressure. The residue was extracted with dichloromethane and then washed successively with water and saturated sodium chloride solution. Evaporation of the solvent left an oil, 2-hydroxy-4-methoxy-5-[2′-(15-crown-5)-methyleneoxy]benzaldehyde, which was refluxed with ethyl acetoacetate (5 mmol) and a catalytic amount of piperidine in absolute ethanol (20 ml) for 10 min without purification. The resulting precipitates were recrystallized from ethanol to give yellow-green needles of **2c**. Yield 35%, mp 148—150 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.71 (3H, s, C_3-$COCH_3$), 3.64—4.20 (21H, m, C_6-OCH_2-15-crown-5), 3.95 (3H, s, C_7-OCH_3), 6.83 (1H, s, C_5-H), 7.06 (1H, s, C_8-H), 8.46 (1H, s, C_4-H). MS *m/z*: 466 (M^+).

Compound **2d** was prepared in the same manner as that of **2c**, other than employing 2,4-dihydroxy-5-methoxybenzaldehyde. Yield 26%, mp 138—140 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.71 (3H, s, C_3-$COCH_3$), 3.64—4.20 (21H, m, C_6-OCH_2-15-crown-5), 3.89 (3H, s, C_6-OCH_3), 6.91 (1H, s, C_5-H), 6.94 (1H, s, C_8-H), 8.48 (1H, s, C_4-H). MS *m/z*: 466 (M^+).

Compound **3** was obtained by cyclic condensation of 4,5-dimethoxy-salicylaldehyde with methylvinylketone in the presence of K_2CO_3 in dioxane, according to the methods of Rene and Vincenzo.[14] Yield 15%, mp 115—116 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s, C_3-$COCH_3$), 3.86, 3.88 (3H, s, C_6, C_7-OCH_3), 4.97 (2H, s, C_2-H_2), 6.47 (1H, s, C_8-H), 6.68 (1H, s, C_5-H), 6.84

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(1H, s, C_4-H). MS *m/z*: 234 (M^+).

Compound **4** was prepared by acetylation of 1,2-dihyro-6,7-dimethoxynaphthalene[15] with acetic anhydride in the presence of aluminum chloride. Yield 56%, mp 131—133 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s, $COCH_3$), 2.57 (2H, t, C_1-CH_2), 2.78 (2H, t, C_2-CH_2), 3.90 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 6.73 (1H, s, C_5-H), 6.78 (1H, s, C_8-H). MS *m/z*: 232 (M^+).

Compound **5** was prepared by the reaction of commercially available 3,4-dimethoxybenzaldehyde with acetone according to the text.[16] Yield 65%, mp 71—74 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (3H, s, $COCH_3$), 3.94 (6H, s, OCH_3), 6.56 (1H, d, olefinic-H), 6.88 (1H, d, C_5-H), 7.08 (1H, s, C_2-H), 7.11 (1H, d, C_6-H), 7.46 (1H, d, olefinic-H). MS *m/z*: 206 (M^+).

Apparatus and Measurements The melting points were measured on a Yanagimoto micro-melting point apparatus, and are uncorrected. ^{1}H-NMR were obtained with a JEOL JNM-GSX 500FT-NMR spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: s, singlet; d, doublet; t, triplet; and m, multiplet. The mass spectra (MS) were taken with a JEOL JMS-DX303 spectrometer, using the electron impact ionization (EI) mode at 70 eV. The fluorescence spectra were taken with a Hitachi F-4000 fluorescence spectrophotometer. Fluorescence quantum yields were determined according to the method of Parker and Rees,[17] and the value (0.55) for quinine sulfate in 0.5 M H_2SO_4 was used as the standard.

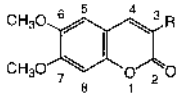
Fluorescence Quenching Efficiences (FQE): These values were calculated by means of the following equation: FQE (%)=$(I_0-I_M)/I_0\times100$, where I_0 and I_M are the fluorescence intensities (*E*x 387 nm, *E*m 477 nm) of **2c** or **2d** (5.0×10^{-6} M) in the absence and the presence of sodium acetate (5.0×10^{-4} M), respectively, in methanol solution.

Stability Constants[18]: Measurements for the stability constants (*Ks*) were made on a methanol solution of **2c** or **2d** (5.0×10^{-6} M) and sodium acetate (5.0×10^{-6}—5.0×10^{-3} M). The *Ks* were estimated by the usual treatment of Benesi–Hildebrand plots obtained from the changes in fluorescence intensities (*E*x 387 nm, *E*m 477 nm).

Results and Discussion

Effects of Substituents at the C_3-Position In a recent publication,[3] we described that i) the arrangements of an electron-donating group at the C_6-position and an electron-withdrawing group at the C_3-position on the coumarin ring contribute predominantly to the fluorescence enhancement of methoxycoumarins, ii) this enhancement can be appreciated by approximating the relationship of two substituents at the C_6- and the C_3-positions to the *para*-position in the disubstituted benzene model, and also iii) additional structural features of coumarins required for intense fluorescence include diether bonds at both the C_6- and C_7-positions, and an electron-withdrawing group at the C_3-position, as shown in 3-acetyl-6,7-dimethoxycoumarin with a quantum yield of 0.52. On the basis of these structural requirements, 3-substituted-6,7-dimethoxycoumarins, **1a**—**k**, with two fixed methoxy groups at the C_6- and C_7-positions were prepared to examine the effects of the substituents at C_3-position in this study. In order to understand the contribution of these substituent groups to the fluorescence characteristics, a suitable, easily available parameter was searched for. As is distinct from the condensed-ring compounds, such as pyrene and anthracene, fluorescence characteristics of the heterocyclic compounds such as coumarin and benzofurazane were attributed to the electronic effects of substituents in the molecule. The Hammett substituent constants (σ_p or σ_m)[19] are practical parameters used to estimate the electronic effect in the chemical reactions. Although these constants represent gross values, including the polar effect, the resonance effect, and the solvent effect, they seemed suitable for representing total electronic effects. Thus, we tried to understand the fluorescence characteristics of 3-substituted-6,7-dimethoxycoumarins using Hammett σ_p-values as suitable parameters. Fluorescence spectral data of **1a**—**k**, together with Hammett σ_p-values[19] are summarized in Table 1, where the relative fluorescence intensities (RFI) are relative values against the fluorescence intensity (100) of the standard compound, **1d**. As shown in Table 1, an increase in fluorescence intensities was observed for **1e**—**j**, substituted with electron-withdrawing groups (σ_p=0.31—0.66), compared with that of **1d**. However, non-fluorescence was observed for **1k**, with the stronger electron-withdrawing nitro group (σ_p=0.78). On the other hand, compounds **1a** and **b**, which were introduced electron-donating groups such as hydroxy- and methoxy groups at the C_3-position, showed a tendency to decrease in fluorescence intensity. The fluorescence wavelengths of these compounds were also shifted to longer wavelength regions, with increases in the electron-withdrawing ability of substituents, except for **1a**. It was suggested from these results that the fluorescence of such coumarins are subject to the ICT effect through a push–pull system between C_6- and C_7-electron-donating groups and electron-withdrawing groups on the lactone ring. As can be seen in Hammett's plots (Fig. 1) obtained from the data in Table 1, the fluorescence intensities in general increased with an increase in the electron-withdrawing ability of substituents, but a nonlinear relationship was observed. The fluorescence intensity of **1k** was particularly low. This drastic fall-off in fluorescence intensity may be ascribed to the conversion of the planar ICT state to a conformer displaying full charge separation, a twisted ICT state,[20] which is non-emissive in a polar solvent such as methanol, and by the acceleration of ICT between the electron-donating methoxy groups and the stronger electron-withdrawing C_3-nitro group. This is also supported by the fact that the fluorescence of **1k** is restored in less polar solvents such as benzene and chloroform. Furthermore, ^{1}H-NMR spectroscopic study[21] gave additional information on the substituent effect from the standpoint of the polarization of molecules in the ground state. The plot of ^{1}H-NMR chemical shifts of C_4-H on the coumarin ring in deuterated chloroform, and σ_p-values, gave a positive correlation similar to that in Fig. 1, namely, the δ values of C_4-H increased with an increase in the electron-withdrawing ability of substituents at the C_3-position (Fig. 2).

Table 1. Fluorescence Properties of 6,7-Dimethoxy-3-substituted Coumarins in Methanol



Compound No.	R	Fλ_{max}/nm (*E*x λ/nm)	RFI	σ_p [b]
1a	OH	487 (389)	91	−0.37
1b	OCH_3	437 (338)	32	−0.27
1c	CH_3	423 (339)	176	−0.17
1d	H[a]	432 (344)	100	0
1e	$OCOCH_3$	435 (344)	317	0.31
1f	CHO	433 (345)	175	0.44
1g	$COOC_2H_5$	458 (374)	458	0.45
1h	OSO_2CF_3	448 (355)	219	0.47
1i	$COCH_3$[a]	482 (382)	295	0.50
1j	CN	465 (377)	530	0.66
1k	NO_2	443 (390)	6	0.78

a) Ref. 3. *b*) Ref. 19.

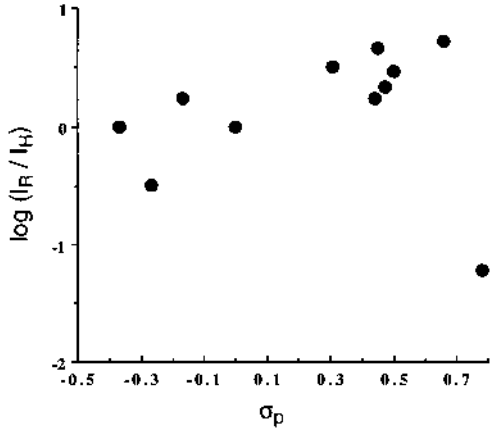


Fig. 1. Plot of RFI and Hammett Constants

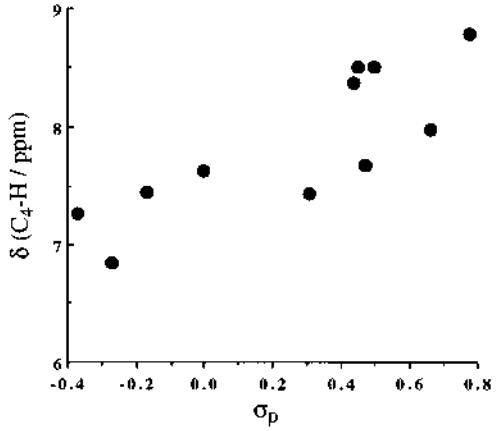


Fig. 2. Plot of C_4-H Chemical Shift and Hammett Constants

Such downfield shifts apparently suggest an electron deficiency at the C_4-position caused by electron-withdrawing substituents at the adjoined C_3-position in the ground state. From these results, the fluorescence of such coumarins was found to be strongly dependent upon ICT between the electron-donating methoxy groups and the C_3-substituents. However, the virtual fluorescence mechanism is apparently not so simple.

Effects of Substituents at C_6- or C_7-position To specify the contribution of the position of the C_6- or C_7-electron-donating groups to the fluorescence, 3-acetylcoumarin derivatives, **2a**—**d**, were prepared. Figure 3 shows the fluorescence spectra of **2a**,**b**, together with **1i** for comparison. The fluorescence of **2a**, a derivative of **1i** whose C_6-methoxy group was replaced with an electron-withdrawing acetoxy group, was quenched, and its blue-shifted spectrum resembled that of 7-methoxy-3-acetylcoumarin (Fλ_{max} 428 nm).[3] In contrast with **2a**, a 7-acetoxy-compound, **2b**, still held about 20% of the fluorescence of **1i**. This fact suggests that the strong fluorescence of **1i** is predominantly attributable to the ICT from the C_6-methoxy group to the C_3-acetyl group on the lactone ring. This estimate was examined in further detail by employing the newly prepared crowned-coumarins, **2c**, **d**. The 15-crown-5 ether moieties introduced into C_6- or C_7-positions of **2c**, **d** have been well known to form complexes with Na^+ or K^+ by the electrostatic interaction of their electron-donating oxygens with metal cations.[22] Therefore, this complexation event may prove the contribution of both electron-donating groups at the C_6- and C_7-positions in the fluorescence of **1i**, the same as the above substituent effect. In a recent study concerning fluorescent sensors for metal ions, photoinduced electron transfer (PET) has attracted attention as a novel operating principle.[23] A number of excellent fluorescence signaling systems based on the PET mechanism have been proposed. Among them, de Silva's group has reported a unique PET sensory system[24] in which the benzocrown unit can act not only as a receptor for metal ions but also as an efficient fluorescence quencher for fluorophores such as anthracene. More recently, Nishizawa *et al*. reported a similar fluorescent PET sensor for metal ions using pyrene as a fluorophore and benzo-15-crown-5 as a receptor for metal ions and an electron donor (a fluorescence quencher of pyrene monomer) for exciplex formation at the same time.[25] However, aliphatic crown ether, the 15-crown-5 ether moieties introduced into the C_6- or C_7-positions of **2c**, **d** scarcely quenched their fluorescence, suggesting no PET interaction between the 15-crown-5 ether moieties and the coumarin fluorophore, as shown in Table 2. Thus, the effect of metal ions on the fluorescence spectra of **2c**, **d** was examined in methanol. The fluorescence intensities of **2c**, **d** in methanol were, in fact, decreased with the addition of sodium or potassium acetates. On the other hand, a corresponding derivative **1i**, without a 15-crown-5 ether moiety, showed no change in the fluorescence spectrum by adding these metal ions. This indicates the formation of complexes of **2c** and **2d** with metal ions. The fluorescence quenching of **2c**, **d** is considered to lower the electron-donating ability of C_6- or C_7-substituents because of the electrostatic interaction[22] of electron-donating oxygens on the crown ether with metal ions. FQE and stability constants (log *Ks*) for **2c**, **d** are shown in Table 2. It was noteworthy from the results that the stability constants of **2c**, **d** were almost comparable; nevertheless, a remarkable difference in FQEs of **2c** (16.9%) and **2d** (10.3%) was observed. This supports the foregoing estimate, that is, the fluorescence in methoxycoumarins depends predominantly on ICT from the C_6-electron-donating group to C_3-electron-withdrawing substituents on the lactone ring.

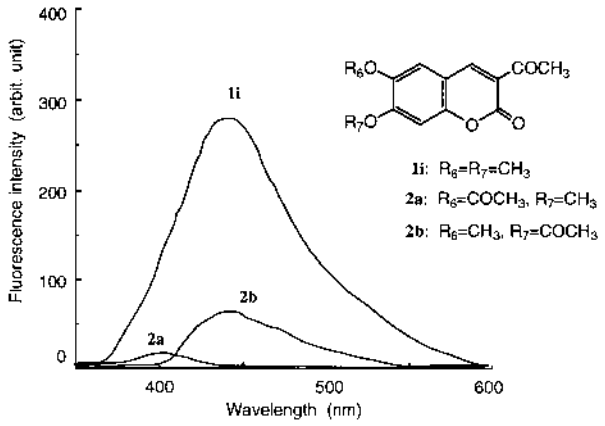
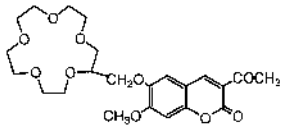


Fig. 3. Fluorescence Spectra of **1i** and **2a, b** in Methanol at 25 °C

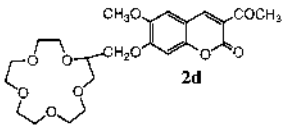
The concentration of coumarins; 1.0×10^{-6} M. Excitation wavelength: 382 nm for **1i**, 375 nm for **2a**, and 447 nm for **2b**.

Effects of Lactone Ring Structure In addition to the above substituents effects, the contribution of ring structures to the fluorescence of this type of coumarin was examined

Table 2. Fluorescence Spectral Properties of **1i**, **2c**, and **2d** in Methanol at 25 °C in the Absence and Presence of Na^+



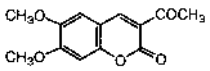
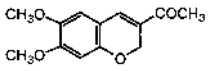
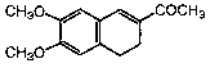
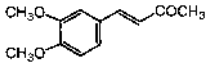
2c



2d

Compound No.	Fλ_{max}/nm (*Ex* λ/nm)	Φ_F (rel)	FQE (%)	log *Ks* (Na^+)
1i	479 (383)	100	—	—
2c	480 (383)	99	16.9	3.03
2d	479 (385)	103	10.3	3.11

Table 3. Fluorescence Spectral Data of **1i**, **3**, **4**, and **5** in Methanol

Compound No.	Structural formula	Fλ_{max}/nm (*Ex* λ/nm)	Φ_F
1i		482 (385)	0.52
3		543 (375)	0.02
4		491 (369)	0.01
5		n.d.	n.d.

n.d.: not detected.

from the viewpoint of the necessity of a carbonyl group and ether oxygen on the lactone ring, and also on the ring itself. For this purpose, compounds **3** (chromene type), **4** (dihydronaphthalene type) and **5** (styrene type) were prepared. Their fluorescence spectral data are listed in Table 3.

First, the contribution of a lactone carbonyl group to the strong fluorescence of **1i** was estimated from the fluorescence behaviors of **3** lacking a carbonyl group. As shown in Table 3, the fluorescence quantum yield of **3** (ϕ_F=0.02) was remarkably low in comparison with that of **1i** (ϕ_F=0.52).[3] However, the Fλ_{max} (543 nm) of **3** shifted to a much longer wavelength region than that (482 nm) of **1i**, and also, the emission color in the solution was distinct yellow in contrast to the whitish blue of **1i**. Thus, the presence of a lactone carbonyl group on **1i** from these results is suggested to contribute primarily to the fluorescence intensity. The remarkable red shift in Fλ_{max} of **3** may be attributed to the enhanced ICT effect from the C_6-methoxy group to the C_3-acetyl group, due to the lack of a carbonyl group. This is also supported by the difference in Fλ_{max}s[3] of 6-methoxy-3-acetylcoumarin (506 nm) and 7-methoxy-3-acetyl-coumarin (428 nm). The strong fluorescence of **1i**, therefore, is presumed to result from two different ICT routes, from the C_6- and C_7-electron-donating groups to either a lactone carbonyl or a C_3-electron-withdrawing group. The former route may contribute to the fluorescence intensity and the later to the fluorescence wavelength. Further investigation, however, is required to elucidate these mechanisms.

Subsequently, compound **4**, which converted a lactone moiety into a cyclic ethylene structure, showed a lowered quantum yield and slight red shift in Fλ_{max} compared with **1i**, and an additional lowering in quantum yield together with a blue shift compared with the cases of **3**. The fluorescence behaviors of **4** are considered to be due to the effect of a slightly distorted cyclohexene ring. The fluorescence of **5** in the absence of a lactone ring structure was no longer detectable under the same conditions as the other compounds. These results indicate the requirement of at least a ring structure, as can be seen in **3**, as a part of the coumarin ring for fluorescing. This chromene-type compound, **3**, may also be promising for use as a novel fluorophore for fluorescent imaging because of emitting a distinct yellow.

Thus, such an approach to determing fluorescence characteristics by chemical tools was found to be practically effective for establishing reagent design structural requirements for various purposes.

References

1) Uchiyama S., Santa T., Fukushima T., Homma H., Imai K., *J. Chem. Soc., Perkin Trans. 2*, **1998**, 2165—2173.
2) Uchiyama S., Santa T., Imai K., *J. Chem. Soc., Perkin Trans. 2*, **1999**, 569—576.
3) Takadate A., Masuda T., Murata C., Tanaka T., Irikura M., Goya S., *Anal. Sci*., **11**, 97—101 (1995).
4) Takadate A., Masuda T., Murata C., Tanaka T., Irikura M., Goya S., *Anal. Sci*., **8**, 663—668 (1992); Takadate A., Masuda T., Murata C., Haratake C., Isobe A., Irikura M., Goya S., *ibid*., **8**, 695—697 (1992); Takadate A., Masuda T., Murata C., Tanaka T., Miyahara H., Goya S., *Chem. Lett*., **1993**, 811—814; Takadate A., Masuda T., Murata C., Tanaka T., Goya S., *Bull. Chem. Soc. Jpn*., **68**, 3105—3110 (1995).
5) Jackson Y. A., *Heterocycles*, **41**, 1979—1986 (1995).
6) Shaw K. N., McMillan A., Armstrong M. D., *J. Org. Chem*., **21**, 601—604 (1956).
7) Horning E. C., Horning M. G., *J. Am. Chem. Soc*., **69**, 968—969 (1947).
8) Jackson A. H., Martin J. A., *J. Chem. Soc.* (*C*), **1966**, 2222—2229.
9) Mali R. S., Yeola S. N., Kulkarmi B. K., *Indian J. Chem*., **22B**, 352—354 (1983).
10) Ito K., Nakajima K., *J. Heterocyclic Chem*., **25**, 511—515 (1988).
11) Head F. S. H., Robertson A., *J. Chem. Soc*., **1930**, 2434.
12) Mali R. S., Yadav V. J., Zaware R. N., *Indian J. Chem*., **21B**, 759—760 (1982).
13) Dishong D. M., Diamond C. J., Cinoman M. I., Gokel G. W., *J. Am. Chem. Soc*., **105**, 586—593 (1983).
14) Rene L., Royer R., *Eur. J. Med. Chem.-Chimica. Therapeutica*, **10**, 72—78 (1975). Fulvio L., Antonio L., Pasquale B., Vincenzo T., *Tetrahedron: Asymmetry*, **6**, 1001—1011 (1995).
15) Craig J. C., Torkelson S. M., Findel P. R., Weiner R. I., *J. Med. Chem*., **32**, 961—968 (1989).
16) Drake N. L., Allen P., Jr., "Organic Syntheses," Coll. Vol. I, ed. by Gilman H., John Wiley and Sons, Inc., New York, 1950, p. 77.
17) Parker C. A., Rees W. T., *Analyst* (London), **85**, 587—600 (1960).
18) Fery-Forgues S., LeBris M. T., Guett J. P., Valeur B., *J. Chem. Soc. Chem. Commun*., **1988**, 384—385; *idem*, *J. Phys. Chem*., **92**, 6233—6237 (1988); Bourson J., Valeur B., *ibid*., **93**, 3871—3876 (1989).
19) Wells P. R., "Linear Free Energy Relationships," Academic Press, London, 1968; Lowry T. H., Richardson K. S., "Mechanism and Theory in Organic Chemistry," 2nd ed., Harper & Row, Publishers, New York, 1981, pp. 130—134; Corwin H., Leo A., Taft R. W., *Chem. Rev*., **91**, 165 (1991).
20) Jones II G., Jackson W. R., Halpern A. M., *Chem. Phys. Lett*., **72**, 391—395 (1980); Jones II G., Jackson W. R., Kanoktanaporn S., Bergmark W. R., *Photochem. Photobiol*., **42**, 477—483 (1985); Rettig

W., Klock A., *Can. J. Chem*., **63**, 1649—1653 (1985).
21) Gottlieb H. E., de Lima R. A., delle Monache F., *J. Chem. Soc. Perkin Trans. 2*, **1979**, 435—437.
22) Hiraoka E., "Crown Compounds—their characteristics and applications—," Elsvier, Tokyo, 1982; Vogtle F., (ed.), "Topics in Current Chemistry 98—Host Guest Complex Chemistry I—," Springer-Verlag, Berlin, 1981; Izatt R. M., Bradshow J., Nielsen S. A., Lamb J. D., Christensen J., *Chem. Rev*., **85**, 271—339 (1985).
23) de Silva A. P., Gunaratne H. Q. N., Huxley A. J. M., McCoy C. P., Rademacher J. T., Rice T. E., *Chem. Rev*., **97**, 1515—1566 (1997).
24) de Silva A. P., Sandarayake K. R. A. S., *J. Chem. Soc., Chem. Commum*., **1989**, 1183—1185.
25) Nishizawa S., Watanabe M., Uchida T., Teramae N., *J. Chem. Soc., Perkin Trans. 2*, **1999**, 141—143.