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Evaluation of a simple and novel fluorescent anion sensor, 4-quinolone, and modification of the emission color by substitutions based on molecular orbital calculations

Junzo Hirano, Kenji Hamase and Kiyoshi Zaitsu*

Graduate School of Pharmaceutical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

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Abstract—4-Quinolone (4-QO) was evaluated as a simple and novel fluorescent anion sensor, and the modification of its emission color was carried out. The series of 4-QO derivatives having molecular orbitals with different energy levels was designed by substitutions at the 6 and 7 positions based on the molecular orbital calculations. All derivatives showed drastic fluorescence enhancements in the presence of F^- via the intramolecular charge transfer mechanism, and the successful modification of the emission color was achieved. The anion-induced emission colors of these derivatives as well as their binding affinities for F^- could be predicted by ab initio quantum chemical calculations, indicating that the present calculations are useful in designing new anion sensors.

1. Introduction

Anion sensing has been of great interest in biological and environmental sciences for several decades, and various fluorescent sensors have been developed for sensitive and simple detections.[1–3] As signaling mechanisms, photoinduced electron transfer,[4–9] intramolecular charge transfer (ICT),[10–18] excited-state proton transfer,[19,20] metal-to-ligand charge transfer,[21] excimer/exciplex formation,[22–24] and competitive binding[25–28] are reported. Particularly, ICT based on hydrogen bond formations between anions and NH or OH groups of the sensor molecules has been widely employed because of the simplicity and capability for multipoint interactions.

ICT fluorescent anion sensors can be classified into two types; one shows fluorescence quenching when binding to anions, and the other shows a fluorescence enhancement. For sensitive detection, the latter has the best advantages, nevertheless, only a few sensors of this type have so far been reported.[11,13,15] Therefore, the discovery and/or development of new ICT sensors of this type are strongly desired to establish a variety of methods for simple and sensitive anion sensing. In a previous study, we reported that some 4-quinolone (4-QO) derivatives are useful fluorophores with high fluorescence quantum efficiency and high stability in aqueous media.[29,30] We have been focusing on the discovery of new photophysical properties of these compounds, and found that 4-QO shows a drastic fluorescence enhancement via the ICT mechanism in the presence of anions. Herein, we now report for the first time the anion-induced changes in the absorption and fluorescence of 4-QO.

In addition, we have modified the emission color of 4-QO by the substitution based on molecular orbital calculations. The emission color of a sensor is of great importance for simple and selective detection, because it is often needed to avoid potential interferences by fluorescence impurities present in environmental and biological samples. Until now, several reported studies have focused on modifying the emission color of a sensor molecule based on substituent effects.[10,14,16,18] However, the introduction of substituents was in most cases still empirical, and theoretical methods based on molecular orbital calculations have scarcely been exploited in spite of the fact that various fluorescent compounds have recently been designed using computational calculations.[31–35] To the best of our knowledge, there have been no reports demonstrating the theoretical modification of the emission color using a sensor molecule that shows a fluorescence enhancement upon binding to anions via the ICT mechanism.

In the present paper, we report a simple and novel fluorescent anion sensor, 4-QO, that shows a drastic fluorescence enhancement via the ICT mechanism. By substitutions based on molecular orbital calculations, 4-QO derivatives **1–6** (Fig. 1) were designed in order to produce different emission

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Keywords: Anion sensor; 4-Quinolone; Intramolecular charge transfer; Fluorescence; Molecular orbital calculation.

* Corresponding author. Tel.: +81 92 642 6596; fax: +81 92 642 6601; e-mail: zaitsu@phar.kyushu-u.ac.jp

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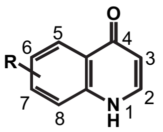

compound	R
4-QO	H
1	6-CH_3
2	6-OCH_3
3	6-$COCH_3$
4	7-CH_3
5	7-OCH_3
6	7-$COCH_3$

Figure 1. Structures of 4-QO derivatives.

colors from 4-QO. The binding affinities of these derivatives for anions were also considered using ab initio quantum chemical calculations.

2. Results and discussion

2.1. Anion response of 4-QO

The anion-induced changes in the absorption and fluorescence spectra of 4-QO were investigated using F^-, Cl^-, Br^-, HSO_4^-, AcO^-, and $H_2PO_4^-$ (as tetrabutylammonium salts). Figure 2 shows the absorption and fluorescence emission spectra in CH_3CN when titrated with F^-. The peak of the absorption spectrum was slightly red shifted from 330 to 338 nm and two isosbestic points at 332 and 299 nm were observed (Fig. 2a). In the fluorescence emission spectra, the intensity was drastically increased at 396 nm (Fig. 2b). With the titration of AcO^- and $H_2PO_4^-$ similar changes were observed, while the titrations of other anions caused no change in both spectra. This suggests that 4-QO forms complexes only with F^-, AcO^-, and $H_2PO_4^-$. This anion-selectivity is thought to be dictated by the anion basicity; F^-, AcO^-, and $H_2PO_4^-$ are stronger hydrogen acceptors than other tested anions. The Job plots for the complexation of 4-QO with anions obtained from the absorption titration experiments showed a 1:1 stoichiometry for F^- and 2:1 for AcO^-, while, more than two complex species were suggested to be present for $H_2PO_4^-$. To confirm the recognition mechanism of 4-QO for anions, a ^1H NMR titration experiment was carried out. The ^1H NMR spectrum of 4-QO in DMSO-d_6 showed a singlet signal for the NH proton at 11.70 ppm (Fig. 3a). Upon addition of 1.0 equiv F^-, the signal completely disappeared (Fig. 3b), which indicates hydrogen bond formation between the NH group of 4-QO and F^-. Ab initio quantum chemical calculations were performed, and the structure of the complex of 4-QO with F^- was optimized with B3LYP at the 6-31G(d) level. In the optimized structure, the distance between the NH proton and F^- is 1.009 Å, also indicating the presence of a hydrogen bond between these atoms. The negative charge of F^- calculated at the B3LYP/6-311+G(d,p) level using the optimized structure is −0.662; this means that a part of the negative charge is intramolecularly transferred from F^- to 4-QO. For a further confirmation, we synthesized 1-methyl-4-QO that has the CH_3 group at the recognition point, and investigated its anion response that is observed in the absorption and fluorescence emission spectra. With the addition of all anions tested, no change in both spectra was observed. These results clearly indicate that 4-QO recognizes anions via the NH group.

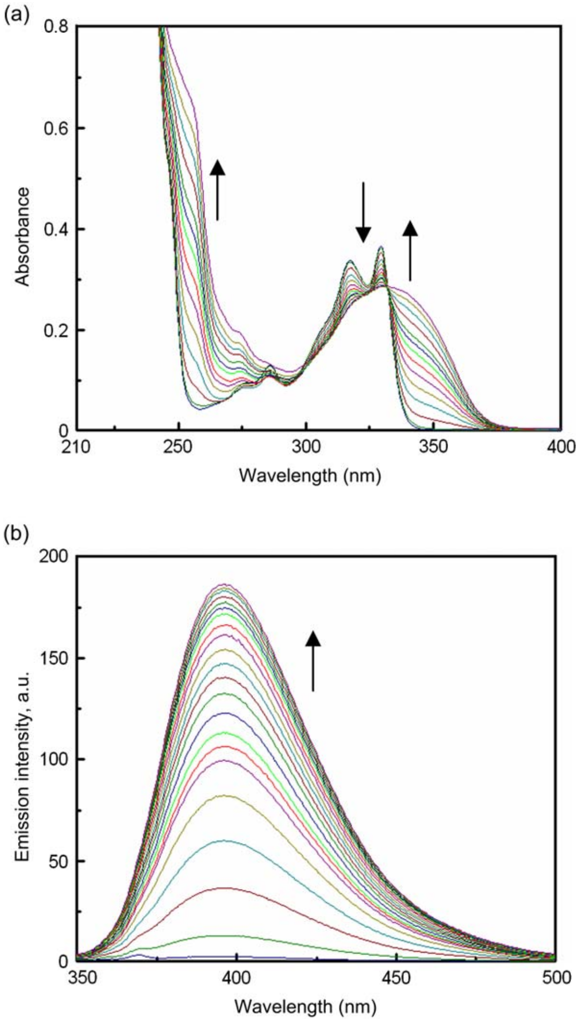

Figure 2. (a) Change in absorption spectra of 4-QO (30 μM in CH_3CN) upon the addition of F^- (0–0.3 mM); (b) change in fluorescence emission spectra of 4-QO (3 μM in CH_3CN) upon the addition of F^- (0–35 μM) with the excitation wavelength of 332 nm.

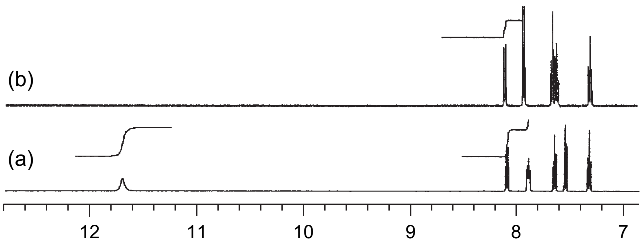

Figure 3. Partial ^1H NMR (500 MHz) spectra of 4-QO in DMSO-d_6 in (a) the absence, and (b) the presence of 1.0 equiv F^-.

2.2. Design of 4-QO derivatives as novel anion sensors using molecular orbital calculations

Adding electron-donating and/or -withdrawing groups to fluorophores is generally known to cause changes in their HOMO–LUMO gaps, and it is expected that not only a shift in the absorption wavelength, but also a shift in the emission wavelength would be induced. The complexes of 4-QO with anions emit the fluorescence at 396 nm, representing a violet-blue color. Therefore, as novel anion sensors showing distinct visible emission colors, 4-QO derivatives having smaller HOMO–LUMO gaps than that of 4-QO in the complexes with anions would be desired; these derivatives are expected to have longer emission wavelengths. Concerning the synthesis of 4-QO derivatives, Gould–Jacobs reaction[36] is generally exploited. By utilizing this reaction, the introduction of various substituents at the 6 and/or 7 positions of 4-QO could be performed. From these points of views, we designed a series of 4-QO derivatives **1–6** for this study. The HOMO levels, LUMO levels, and HOMO–LUMO gaps of the complexes of **1–6** with F^- are summarized in Table 1. In this study, we selected F^- as the target anion because of the following reasons. F^- is one of the most attractive anions for its importance in dental care[37] and treatment of osteoporosis,[38] and most anion sensors are investigated for their responses to F^-. Therefore, by investigating the emission color modification using F^-, the obtained strategy could be expanded to various fluorescent anion sensors. In the F^- complexes, the HOMO–LUMO gaps of compounds **1**, **2**, **4**, and **5**, that have the electron-donating groups at the 6 or 7 positions, show energy gaps similar to that of 4-QO, while **3** and **6** that have electron-withdrawing groups show considerably smaller energy gaps than that of 4-QO. These calculation results imply that **3** and **6** are expected to have distinct absorption and fluorescence wavelengths from those of 4-QO.

Table 1. HOMO levels, LUMO levels, and HOMO−LUMO gaps of the F^- complexes of 4-QO derivatives

Compound	HOMO (eV)	LUMO (eV)	HOMO−LUMO gap (eV)
4-QO+F^-	−1.83	2.39	4.22
1+F^-	−1.78	2.43	4.21
2+F^-	−1.74	2.40	4.14
3+F^-	−2.36	1.18	3.54
4+F^-	−1.81	2.46	4.27
5+F^-	−1.83	2.20	4.03
6+F^-	−2.16	1.05	3.21

Data were obtained at B3LYP/6-311+G(d,p)//B3LYP/6-31G(d).

2.3. Anion-induced changes in absorption and fluorescence of synthesized 4-QO derivatives

The designed 4-QO derivatives **1–6** were synthesized by Gould–Jacobs reaction, and their absorption and fluorescence properties have been investigated. All compounds showed changes in their absorption spectra upon the addition of F^-. The absorption spectra of **1**, **3**, and **6** in CH_3CN with the addition of F^- are shown in Figure 4. The results obtained for **2**, **4**, and **5** are very similar to that of **1**. These compounds (**1**, **2**, **4**, and **5**) showed the similar absorption changes to that of 4-QO (Fig. 2a); the absorption spectrum was slightly red shifted with some isosbestic points. On the other hand, compounds **3** and **6** showed the characteristic changes in absorption. In the absorption spectrum of compound **3**, the peak at 335 nm decreased, a new peak appeared at 395 nm, and three isosbestic points were observed at 351, 288, and 249 nm. In the spectrum of compound **6**, two new peaks at 389 and 337 nm and two isosbestic points at 370 and 346 nm appeared, and the absorbance at 347 nm decreased. Table 2 summarizes the wavelengths of the absorption

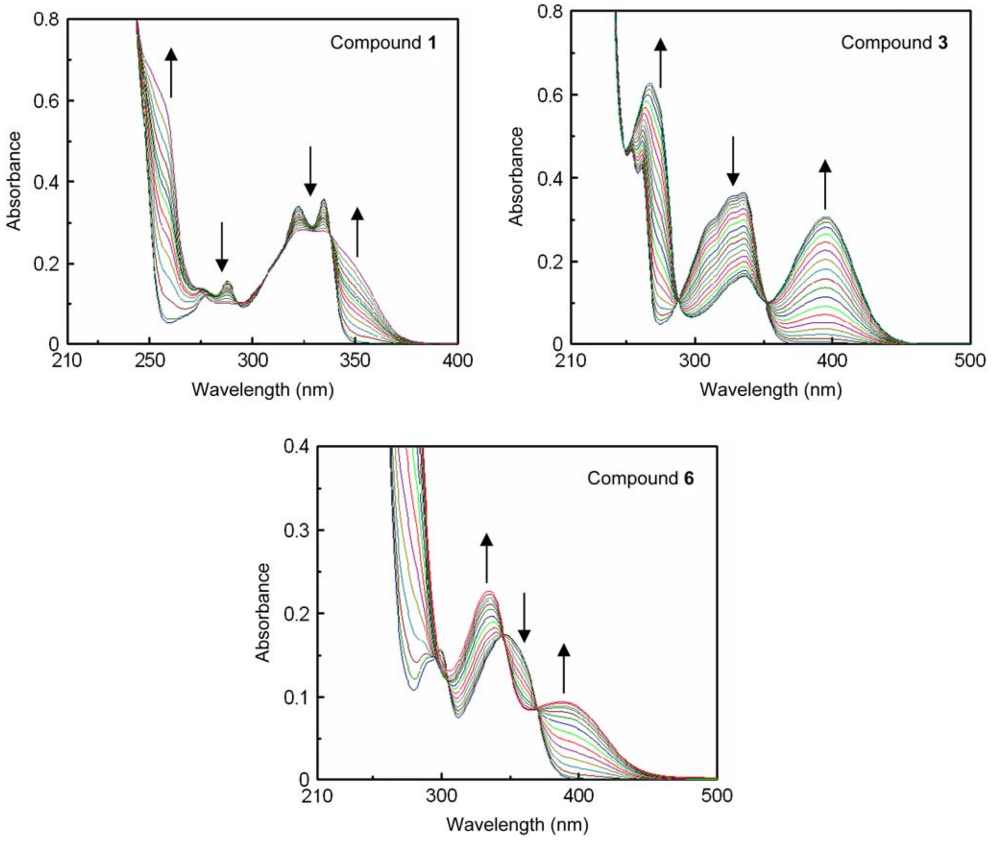

Figure 4. Changes in absorption spectra of **1**, **3**, and **6** (30 μM in CH_3CN) upon the addition of F^- (0–0.3 mM for **1**, 0–0.1 mM for **3**, and 0–0.2 mM for **6**).

Table 2. Absorption maxima of 4-QO derivatives and their F^- complexes

Compound	Absorption maximum (nm)[a]	Absorption maximum (nm)[b]
4-QO	338	330
1	336	335
2	344	345
3	395	335
4	337	328
5	340	322
6	389	347

[a] Values in the presence of F^-.

[b] Values in the absence of F^-.

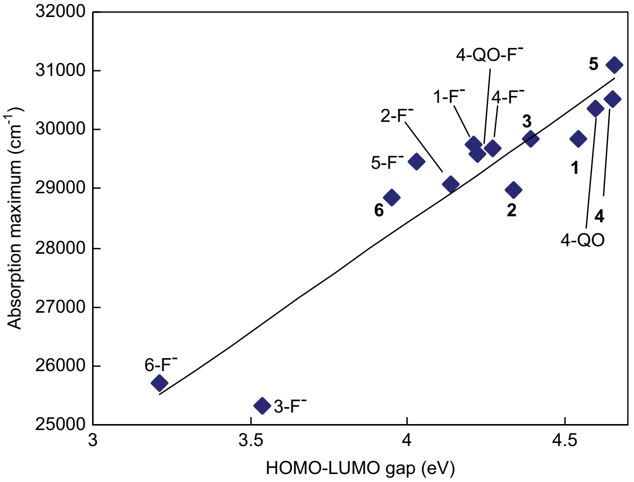

Figure 5. Correlation between the HOMO–LUMO gaps and the wavelengths of the absorption maxima of 4-QO derivatives and their F^- complexes.

maxima of the 4-QO derivatives in the F^- complexes, as well as their original absorption maxima in the absence of F^-. These values are in good agreement with the calculated HOMO–LUMO gaps (Fig. 5). This result indicates that the molecular orbital energies obtained by the quantum chemical calculations reflect the values from the experimental measurements, and the calculations performed in this study have a sufficient suitability for practical use.

Upon the addition of F^-, all compounds showed drastic fluorescence enhancements. Figure 6 shows the changes in the fluorescence emission spectra of **1**, **3**, and **6** in CH_3CN when titrated with F^-. Compounds **1**, **2**, **4**, and **5** emitted a fluorescence centered at almost the same wavelengths around 400 nm. Whereas **3** and **6**, that show considerably smaller HOMO–LUMO gaps than that of 4-QO in the F^- complexes, emitted a longer fluorescence centered at 492 and 542 nm, respectively. The emission colors of **1**, **2**, **4**, and **5** were violet-blue, being similar to that of 4-QO. On the other hand, the emission colors of **3** and **6** were green-blue and yellow-green (Fig. 7).

2.4. Association constants for 4-QO derivatives with F^-

The association constants for **1**–**6** with F^- obtained by Rose–Drago method using absorption spectroscopy[39] are summarized in Table 3. In comparison with 4-QO, compounds **1**, **2**, **4**, and **5** showed almost the same or a little lower binding affinities, while **3** and **6** showed notably higher affinities. This is empirically reasonable because the electron-withdrawing group of $COCH_3$ makes **3** and **6** strong electron acceptors by increasing the acidities of the NH protons. The structures of

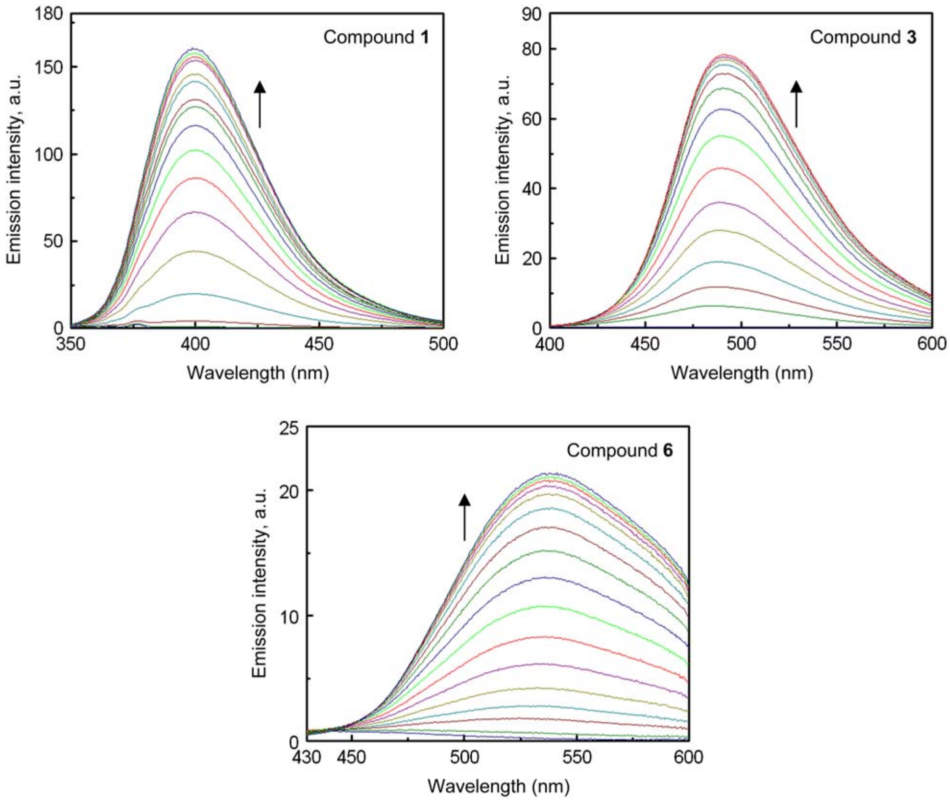

Figure 6. Changes in fluorescence emission spectra of **1**, **3**, and **6** (3 μM in CH_3CN) upon the addition of F^- (0–35 μM for **1**, 0–15 μM for **3**, and 0–18 μM for **6**) with the excitation wavelength of 338 nm for **1**, 351 nm for **3**, and 370 nm for **6**.

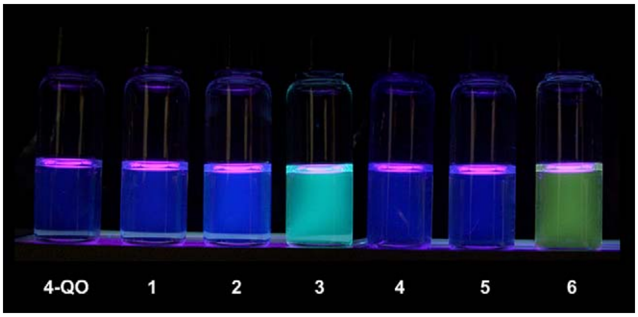

Figure 7. Emission colors of 4-QO derivatives (3 μM in CH_3CN) under UV light illumination (365 nm) in the presence of F^-.

Table 3. Association constants and binding energies for 4-QO derivatives with F^-, partial charges of F^-, and distances of $NH\cdots F^-$ in the F^- complexes

Compound	Association constant[a] (M^{-1})	Binding energy[b] (kcal/mol)	F^- charge[c]	$NH\cdots F^-$ distance (Å)
4-QO	$(6.2\pm2.3)\times10^3$	−55.8	−0.662	1.009
1	$(5.3\pm1.0)\times10^3$	−55.2	−0.663	1.009
2	$(1.9\pm0.8)\times10^3$	−55.2	−0.662	1.009
3	$(3.1\pm1.3)\times10^4$	−62.1	−0.654	1.000
4	$(5.5\pm1.1)\times10^3$	−54.6	−0.663	1.009
5	$(4.4\pm1.8)\times10^3$	−53.3	−0.661	1.008
6	$(1.3\pm0.6)\times10^4$	−59.6	−0.653	0.999

[a] Absorption titration experiments were carried out in CH_3CN at 293 K, and the errors in association constants were within 10%.

[b] Data were obtained at B3LYP/6-311+G(d,p)//B3LYP/6-31G(d).

[c] Charges were calculated with the natural population orbital analysis.

the F^- complexes of **1**–**6** optimized by ab initio quantum chemical calculations provide a detailed explanation of the magnitudes of the association constants. The calculated binding energies with F^- are −62.1 and −59.6 kcal/mol for **3** and **6**, respectively. These values indicate that the complexes are much more stable than other compounds having binding energies around −55 kcal/mol. In addition, the F^- complexes of **3** and **6** show smaller negative charges of F^- than those for other compounds by 0.007–0.010, indicating that the greater negative charge of F^- is transferred to 4-QO in the F^- complexes of **3** and **6**. The distances between the NH protons and F^- for **3** and **6** are 1 and 0.999 Å, respectively; these values are shorter than those for other compounds by 0.008–0.01 Å. These results indicate that the binding affinity for F^- could also be predicted by the binding energy calculations, negative charges of F^-, and the distances between the NH protons and F^- using the ab initio quantum chemical calculations.

3. Conclusions

We have presented a simple compound 4-QO as a valuable ICT fluorescent anion sensor. A series of 4-QO derivatives have been prepared as novel anion sensors, and revealed that not only the shift in the absorption wavelength, but also the shift in the emission color could be induced by lowering the HOMO–LUMO gap by substitutions based on molecular orbital calculations. In addition, the magnitudes of their association constants for F^- were well predicted using the ab initio quantum chemical calculations. The strategy demonstrated in the present work would be effective for the modifications of the absorption and emission properties, and the binding affinities of other ICT fluorescent anion sensors.

4. Experimental

4.1. General procedures

Commercially available materials were used without any additional purification. CH_3CN and DMSO used for the spectral studies were of spectroscopic grade, and all other solvents were of guaranteed reagent grade. 1-Methyl-4-QO was synthesized by methylation of 4-QO using CH_3I and K_2CO_3 in the general method. Compounds **1**–**6** were synthesized from aniline derivatives in four steps according to previously reported methods[40–42] with some modifications. The products were characterized by ^1H NMR, FABMS, and elemental analyses. The ^1H NMR spectra were recorded using a Varian Unity-500 spectrometer (500 MHz) in DMSO-d_6. Mass spectra were obtained using JEOL JMS 600 and JMS-SX102A mass spectrometers.

4.1.1. 1-Methyl-4-quinolone. Colorless blocks. Yield: 46.5%. Mp 152–153 °C. ^1H NMR (500 MHz, DMSO-d_6): δ ppm 3.80 (3H, s, CH_3–), 6.03 (1H, d, J=7.6 Hz, H-3), 7.39 (1H, m, H-6 or H-7), 7.64 (1H, d, J=8.5 Hz, H-5 or H-8), 7.74 (1H, m, H-6 or H-7), 7.95 (1H, d, J=7.8 Hz, H-2), 8.17 (1H, dd, J=1.4, 8.0 Hz, H-5 or H-8). HRMS (FAB): calcd for M+H, 160.0762; found, 160.0726.

4.1.2. 6-Methyl-4-quinolone (1). Colorless needles. Yield: 15.0%. Mp 240–241 °C. ^1H NMR (500 MHz, DMSO-d_6): δ ppm 2.39 (3H, s, CH_3–), 5.97 (1H, d, J=7.4 Hz, H-3), 7.27 (1H, dd, J=3.0, 8.9 Hz, H-7), 7.48–7.50 (2H, m, H-5, 8), 7.82 (1H, d, J=7.4 Hz, H-2), 11.62 (1H, br s, H-1). FABMS m/z=160.1 (M+H). Anal. Calcd for $C_{10}H_9NO\cdot H_2O$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.98; H, 6.18; N, 7.86.

4.1.3. 6-Methoxy-4-quinolone (2). Colorless needles. Yield: 15.8%. Mp 251–252 °C. ^1H NMR (500 MHz, DMSO-d_6): δ ppm 3.82 (3H, s, CH_3O–), 5.99 (1H, d, J=7.3 Hz, H-3), 7.27 (1H, dd, J=2.9, 9.0 Hz, H-7), 7.48–7.50 (2H, m, H-5, 8), 7.82 (1H, d, J=7.3 Hz, H-2), 11.70 (1H, br s, H-1). FABMS m/z=176.1 (M+H). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.16; H, 5.20; N, 8.03.

4.1.4. 6-Acetyl-4-quinolone (3). Orange plates. Yield: 25.1%. Mp>300 °C. ^1H NMR (500 MHz, DMSO-d_6): δ ppm 2.63 (3H, s, CH_3CO–), 6.11 (1H, d, J=7.4 Hz, H-3), 7.60 (1H, d, J=8.5 Hz, H-8), 7.94 (1H, d, J=7.4 Hz, H-2), 8.13 (1H, dd, J=2.2, 8.8 Hz, H-7), 8.66 (1H, d, J=2.2 Hz, H-5), 11.96 (1H, br s, H-1). FABMS m/z=188.2 (M+H). Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.46; H, 4.88; N, 7.57.

4.1.5. 7-Methyl-4-quinolone (4). Colorless needles. Yield: 4.8%. Mp 232–233 °C. ^1H NMR (500 MHz, DMSO-d_6): δ ppm 2.40 (3H, s, CH_3–), 5.96 (1H, d, J=7.3 Hz, H-3), 7.12 (1H, dd, J=1.0, 8.4 Hz, H-6), 7.28 (1H, s, H-8), 7.81 (1H, d, J=7.6 Hz, H-2), 7.95 (1H, d, J=8.2 Hz, H-5), 11.56 (1H, br s, H-1). FABMS *m*/*z*=160.1 (M+H). Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.28; H, 5.71; N, 8.84.

4.1.6. 7-Methoxy-4-quinolone (5). Colorless needles. Yield: 6.9%. Mp 219–220 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 3.84 (3H, s, CH_3O–), 5.92 (1H, d, *J*=7.3 Hz, H-3), 6.88–6.90 (2H, m, H-5, 8), 7.78 (1H, d, *J*=7.3 Hz, H-2), 7.97 (2H, dd, *J*=0.9, 8.2 Hz, H-6), 11.48 (1H, br s, H-1). FABMS *m*/*z*=176.1 (M+H). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.43; H, 5.19; N, 7.96.

4.1.7. 7-Acetyl-4-quinolone (6). Colorless prisms. Yield: 4.5%. Mp 290–291 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 2.65 (3H, s, CH_3CO–), 6.09 (1H, d, *J*=7.3 Hz, H-3), 7.81 (1H, dd, *J*=1.5, 8.4 Hz, H-6), 7.99 (1H, d, *J*=7.6 Hz, H-2), 8.11 (1H, d, *J*=0.9 Hz, H-8), 8.17 (1H, d, *J*=8.5 Hz, H-5), 11.90 (1H, br s, H-1). FABMS *m*/*z*=188.1 (M+H). Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.37; H, 4.91; N, 7.40.

4.2. Computational method

All calculations were carried out using Spartan'04(W). The geometry optimizations were performed with B3LYP at the 6-31G(d) level. The HOMO levels, LUMO levels, total energies, and atomic charges were estimated at single-point calculations (B3LYP/6-311+G(d,p)) using the geometries optimized at the B3LYP/6-31G(d) levels.

4.3. Absorption and fluorescence studies

The absorption and corrected fluorescence emission spectra were recorded using a JASCO V-530 UV–vis spectrophotometer and an F-6500 spectrofluorometer. All 4-QO derivatives were dissolved in DMSO at a 10 mM concentration. They were diluted to the appropriate concentrations with CH_3CN and used for the measurements. The titration experiments were performed by adding the anion solutions in CH_3CN to the solutions of the 4-QO derivatives. For estimation of the association constants, the absorbance data from the titration experiments were treated by Rose–Drago method.

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Supplementary data

Changes in absorption and fluorescence emission spectra of **2**, **4**, and **5** upon the addition of F^-, and Cartesian coordinates of the calculated structures are available. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.060.

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