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Effect of addition of trifluoroacetic acid on the photophysical properties and photoreactions of aromatic imides

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ABSTRACT

The UV and IR spectra of *N*-methyl-1,8-naphthalimide in benzene showed a two-step consecutive complexation (hydrogen bond formation) with trifluoroacetic acid (TFA). The equilibrium constant K_1 for the first complexation in benzene was determined from the UV spectrum to be 48 M^{-1}. The fluorescence intensities of the imide in benzene were found to be remarkably enhanced by the addition of TFA. Furthermore, photochemical cyclobutane formation of the imide with styrene in benzene was enhanced by the addition of TFA. Enhancement of the fluorescence intensity and the photoreaction of the imide by complexation with TFA was explained by a decrease of the efficiency of the intersystem crossing from $^1(\pi\pi^*)$ to $^3(n\pi^*)$, that results from an increase in the energy of the $^3(n\pi^*)$ level due to the complexation.

1. Introduction

Naphthalimides are known to be promising anticancer agents, showing broad-spectrum activity against a variety of human solid tumor cells.[1] Some naphthalimides have reached the phase of clinical trials.[2] Their DNA binding or enzyme inhibitory activity is believed to be pivotal in exerting antitumor effects. 1,8-Naphthalimide derivatives with intramolecular dialkylammonium moieties exhibit much stronger association to oligodeoxynucleotides than the corresponding neutral molecules due to electrostatic interactions with the phosphate groups.[3]

Photoinduced processes of naphthalimides are also of particular interest because of their broad-ranging applications in fundamental studies and advanced technology as well as in biological and medical areas. Naphthalimides are capable of initiating the photocleavage of DNA[4] and photochemical crosslinking of proteins.[5]

Additionally, investigations on the photophysical behavior of naphthalimides have contributed to the development of new fluorescent probes[6] and optical sensors.[7] Dual fluorescence has been reported for several substituted *N*-phenylnaphthalimides[8] and the relative intensity of the two fluorescence bands has been shown to be sensitive to solvent polarity, temperature,[9] viscosity,[10] and pressure.[11] Some substituted *N*-phenyl-1,8-naphthalimides have been reported to show remarkable sensitivity and selectivity for saccharides.[12]

The photoreactions of naphthalimides have been investigated for the past decade in our laboratory.[13] We have recently shown that the fluorescence intensity and photoreactivity of *N*-methyl-1,8-naphthalimide (**2**) are remarkably increased by intermolecular hydrogen bonding with 2,2,2-trifluoroethanol (TFE), possibly through a decrease in the efficiency of intersystem crossing from $^1(\pi\pi^*)$ to $^3(n\pi^*)$, because the energy of the $^3(n\pi^*)$ level increases as a result of the hydrogen bonding.[14] In this paper, we report the effect of the addition of trifluoroacetic acid (TFA) on the photophysical properties and photoreactions of aromatic imide compounds in expectation of a more pronounced effect than that which arose from hydrogen bond formation with TFE.

2. Results and discussion

Five aromatic imide compounds, *N*-methylphthalimide (**1**), *N*-methyl-1,8-, -2,3-, and -1,2-naphthalimides (**2**–**4**), and *N*-methyl-9,10-phenanthrenedicarboximide (**5**), were chosen in this investigation, because of differing energies of their $\pi\pi^*$ and $n\pi^*$ excited states (Scheme 1). The lowest singlet excited state of phthalimide **1** has been reported to be an $n\pi^*$ state.[15] On the other hand, the lowest singlet excited states of naphthalimides **2**–**4** and phenanthrenedicarboximide **5** have been reported to be $\pi\pi^*$ states, though the energy of the singlet states vary, namely, 80.6 kcal mol^{-1} for **2**, 79.4 kcal mol^{-1} for **3**, 72.7 kcal mol^{-1} for **4**, and 68.6 kcal mol^{-1} for **5**.[15] The second excited singlet states of naphthalimides **2**–**4** and phenanthrenedicarboximide **5** may have $n\pi^*$ characters with similar energies, since the $n\pi^*$ excitation is localized mainly on the carbonyl group.

Since hydrogen bond formation has been known to affect the energy levels of $n\pi^*$ states compared to those of $\pi\pi^*$ states,

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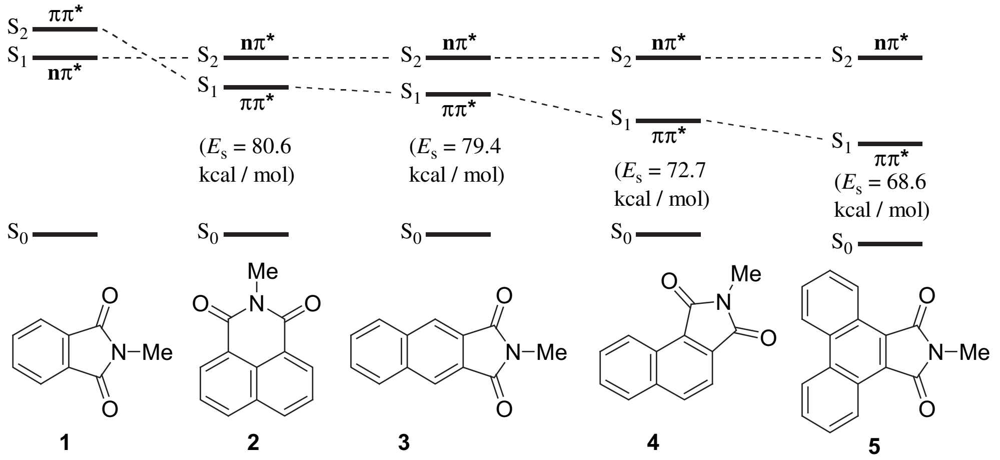


Scheme 1.

hydrogen bond formation is predicted to have a different effect on the photophysical properties and photoreactions of aromatic imides **1**–**5**. Thus, we examined the photophysical properties and the photoreactions of **1**–**5** in the presence of TFA in expectation of a more pronounced effect. Indeed, we found that the photophysical properties and the photoreactions of **2**, in which the ππ* and nπ* levels were close together in energy, were remarkably affected by hydrogen bond formation with TFA.

2.1. UV spectra

To clarify the effect of the addition of TFA in the ground state, UV spectra of **2** in the absence and presence of various concentrations of TFA were measured in benzene (Fig. 1). Fig. 1 shows a two-step consecutive complexation (hydrogen bond formation) of **2** and TFA shown in Eqs. 1 and 2, while there is no evidence for the stepwise complexation of **2** and alcohols in the UV spectra.[14] In the low concentration range (0–30 mM) of TFA, an isosbestic point is observed around 336 nm. On the other hand, in the high concentration range (30–150 mM) of TFA, there is another isosbestic point around 339 nm.

In the low concentration range of TFA, the presence of the isosbestic point suggests that the first complexation step shown in Eq. 1 is dominant and the equilibrium constant K_1 for the first complexation in benzene is determined to be 48 M^{-1} from a linear Benesi–Hildebrand plot using the absorbance at 360 nm (Fig. 2 and Eq. 3).

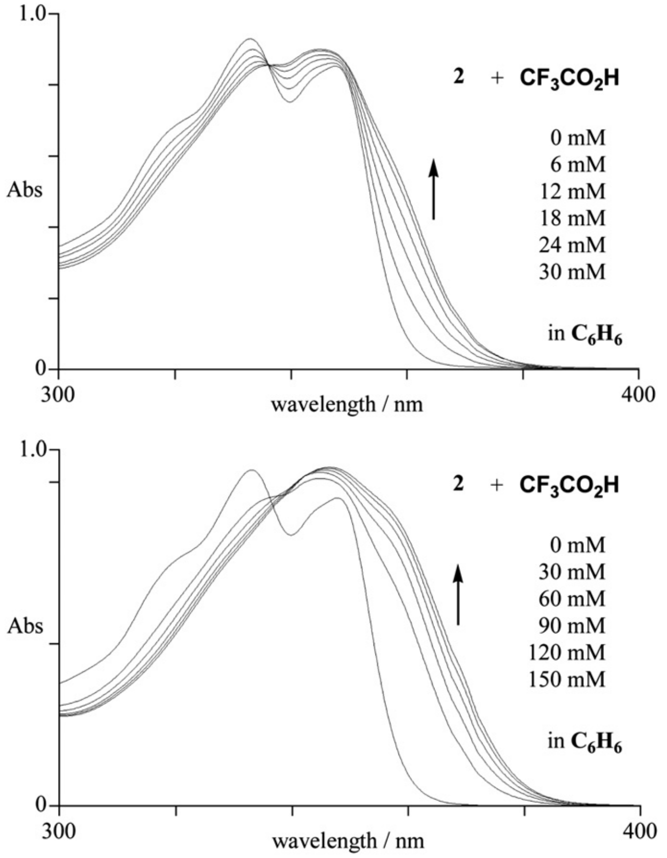


Fig. 1. Absorption spectra of **2** (0.075 mM) with various concentrations of TFA in benzene.

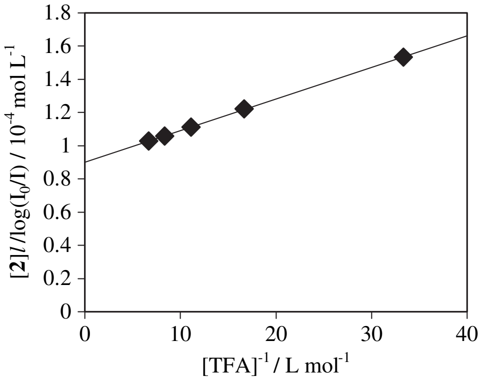
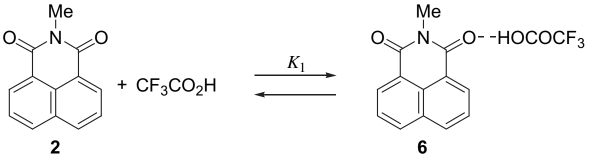
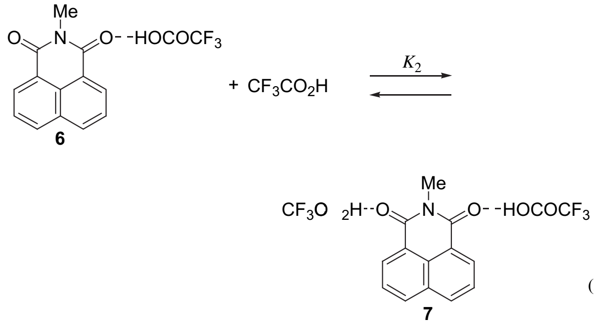


Fig. 2. Benesi–Hildebrand plot for the protonation of **2** by TFA in benzene.



(1)



(2)

$$[\mathrm{Im}]l/\mathrm{Abs} + 1/K_1\epsilon(1/[\mathrm{TFA}]) + 1/\epsilon \tag{3}$$

Here, [Im] and [TFA] are the concentrations of imide **2** and TFA, respectively, l is optical path length, ϵ is molar extinction coefficient of the 1:1 complex **6**, and K_1 is the equilibrium constant for the first complexation. The value of K_1 is considerably larger compared to that of 1.5 M^{-1} for the corresponding complexation of **2** and TFE.[14]

Similar spectral changes were observed in dichloromethane. In nonpolar hexane, well-defined spectral changes for the two-step consecutive complexation were observed (Fig. 3). A new absorption maximum appeared around 355 nm in the low concentration range (0–6 mM) of TFA and a new absorption around 362 nm developed in the high concentration range (30–150 mM). On the other hand, no clear evidence for the complexation was observed in polar acetonitrile (Fig. 4).

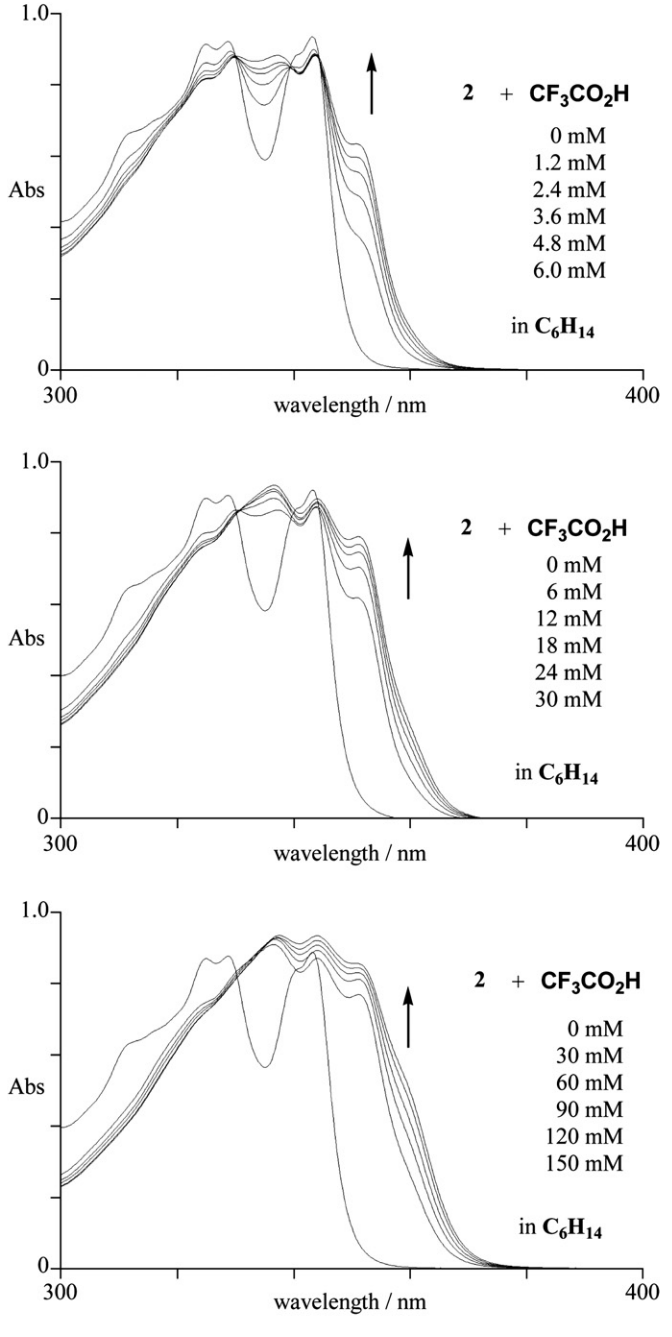


Fig. 3. Absorption spectra of **2** (0.075 mM) with various concentrations of TFA in hexane.

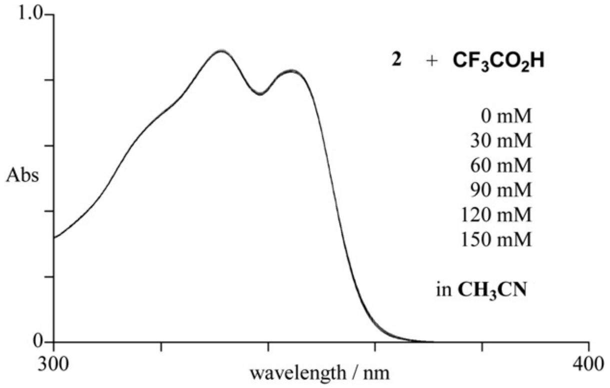


Fig. 4. Absorption spectra of **2** (0.075 mM) with various concentrations of TFA in acetonitrile.

2.2. IR spectra

IR spectra of **2** in the absence and presence of various concentrations of TFA were measured in benzene (Fig. 5). Fig. 5 shows the decrease of the intensity of the 1669 cm^{-1} band attributed to ν C=O of **2** and the simultaneous increase of new 1642 and 1617 cm^{-1} bands of the complexed species of **2** by the addition of TFA. These results indicate that the complexation with TFA occurs at the carbonyl group of **2**.

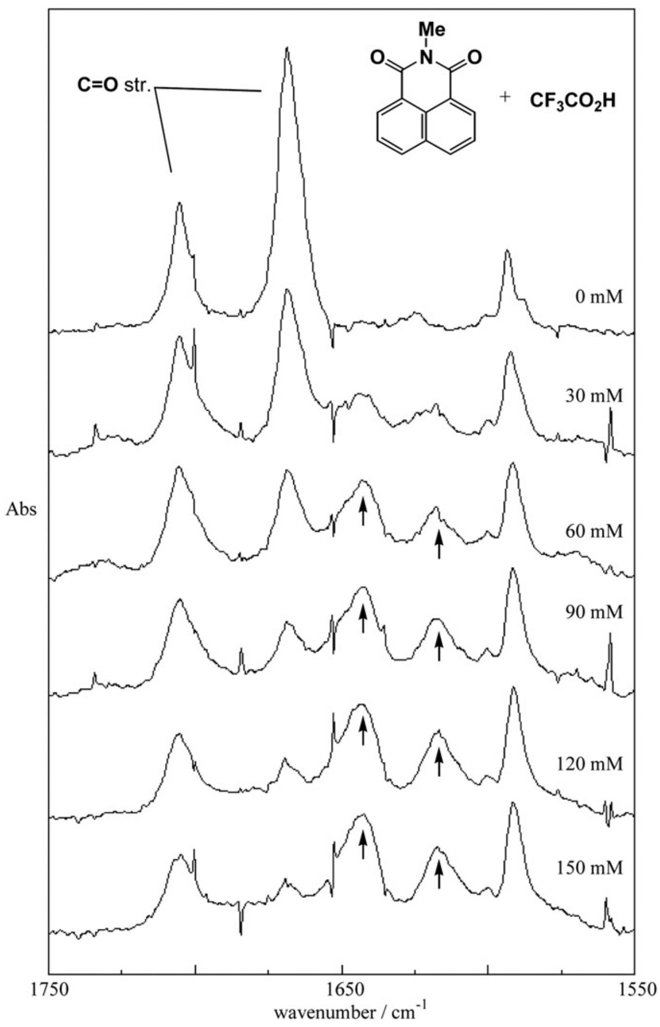


Fig. 5. IR spectra of the ν C=O region of **2** (20 mM) with various concentrations of TFA in benzene.

2.3. Fluorescence spectra

To clarify the effect of the addition of TFA in the excited singlet state, fluorescence spectra of **2** in the absence and presence of various concentrations of TFA were measured in benzene (Fig. 6). The fluorescence intensity of **2** was enhanced in the low concentration range (0–30 mM) of TFA, in which the first complexation shown in Eq. 1 was dominant, and then markedly decreased in the high concentration range (30–150 mM) of TFA, in which the second complexation shown in Eq. 2 was dominant.

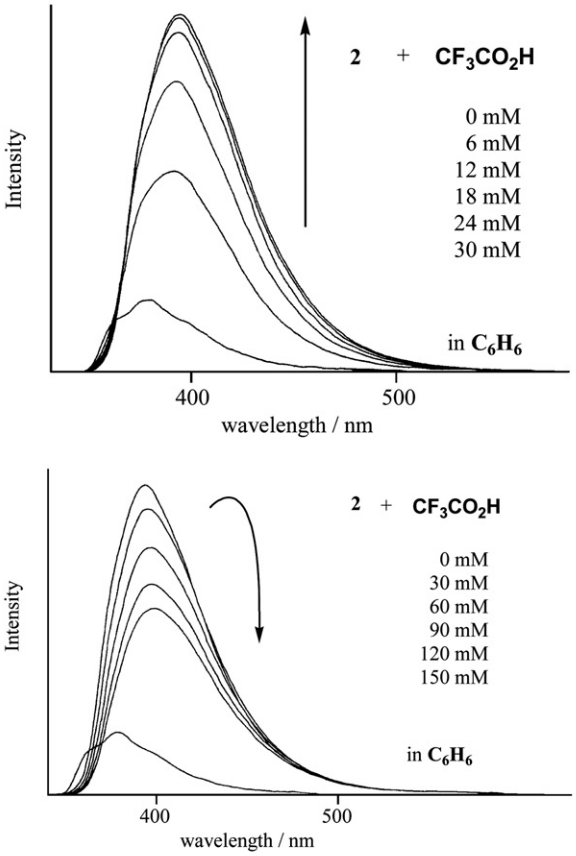


Fig. 6. Fluorescence spectra of **2** (0.075 mM) with various concentrations of TFA in benzene.

Fig. 7 shows the effect of the addition of TFA on the fluorescence quantum yield Φ_{flu} of **2** in various solvents. In polar acetonitrile, the fluorescence of **2** was little enhanced by the addition of TFA. In less polar dichloromethane and in nonpolar hexane, the fluorescence of **2** was remarkably enhanced in the low concentration range of TFA, and then increased more gradually in the high concentration range of TFA. In contrast, in benzene, the fluorescence of **2** was enhanced in the low concentration range (0–30 mM) of TFA and then decreased in the high concentration range (30–150 mM) of TFA. These results indicate that the fluorescence intensity of the doubly complexed species **7** (Eq. 2) in benzene is small compared with those in dichloromethane and hexane.

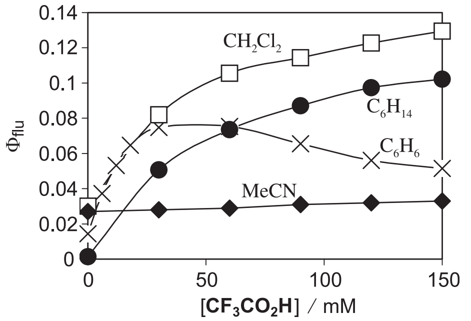


Fig. 7. Fluorescence quantum yield Φ_{flu} of **2** with various concentration of TFA in various solvents.

Furthermore, the effect of the addition of benzene on the fluorescence of **2** in dichloromethane was examined. While the fluorescence of **2** was only slightly affected by the addition of benzene in the presence of 30 mM of TFA (Fig. 8), in the presence of 150 mM of TFA, the fluorescence intensity of **2** was remarkably decreased by the addition of benzene and a weak emission appeared around 500 nm (Fig. 9). These results indicate that the fluorescence intensity of the doubly complexed species **7** is markedly decreased by the addition of a small amount of benzene, possibly through the formation of an exciplex of **7** and benzene as indicated by the weak emission.

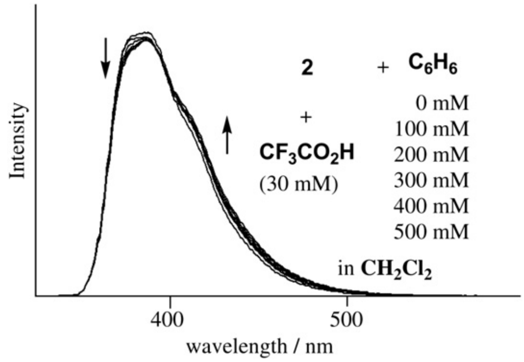


Fig. 8. Fluorescence spectra of **2** in the presence of 30 mM of TFA and various concentrations of benzene in dichloromethane.

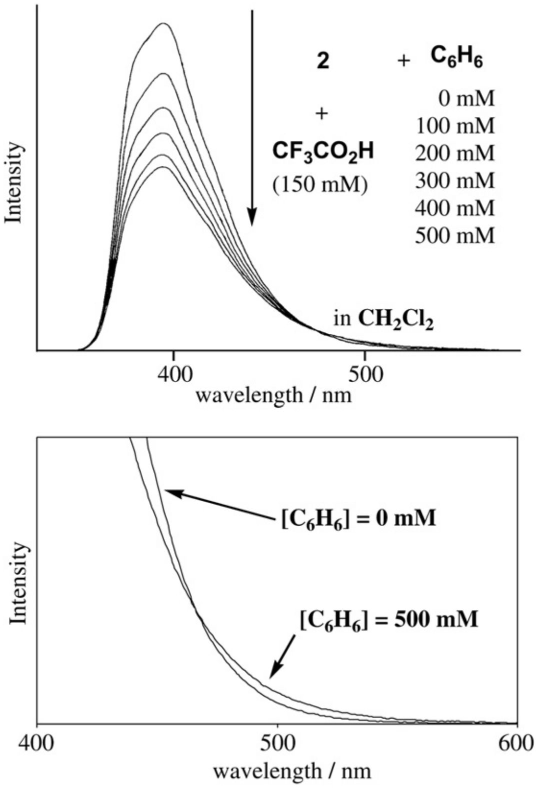


Fig. 9. Fluorescence spectra of **2** in the presence of 150 mM of TFA and various concentrations of benzene in dichloromethane.

2.4. UV and fluorescence spectra of other aromatic imides

The effect of the addition of TFA on the absorption spectra of aromatic imides **1**, **3**, **4**, and **5**, in benzene are shown in Figs. S1, S3, S5, and S7, respectively, in the Supplementary data. The equilibrium constants K_1 for the first complexation of **1**, **3**, **4**, and **5** with TFA were determined to be 21, 43, 15, and 9.6 M^{-1}, respectively.

The effect of the addition of TFA on the fluorescence spectra of **1**, **3**, **4**, and **5** in benzene are shown in Figs. S2, S4, S6, and S8, respectively, in the Supplementary data. These results indicate that the fluorescence of **1** is enhanced by the addition of TFA in benzene, while the fluorescence of **3**–**5** is little enhanced by the addition of TFA. Fig. 10 shows the effect of addition of TFA on the relative fluorescence intensity of **1**–**5** in benzene. Moderate and remarkable enhancement effects were observed for **1** and **2**, respectively, in which the $\pi\pi*$ and $n\pi*$ levels were close together in energy. The fluorescence of **2** in the presence of 30 mM of TFA was thus most remarkably enhanced by a factor of more than 5 compared with that in the absence of TFA.

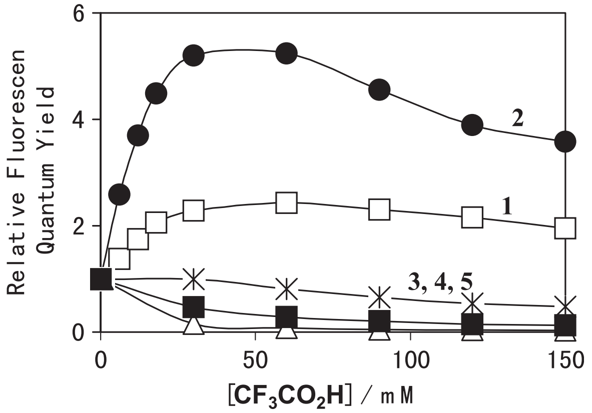


Fig. 10. Relative fluorescence quantum yield of **1**–**5** with various concentrations of TFA in benzene.

2.5. Effect of complexation on the photoreaction of 2 with styrene

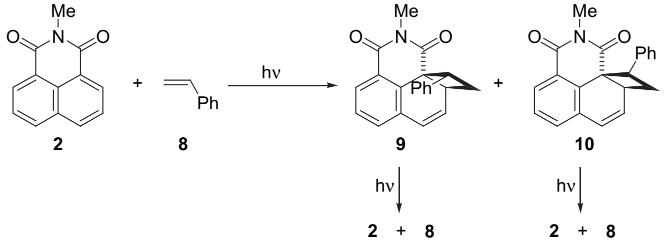
To clarify the effect of the addition of TFA on the photoreactions of aromatic imides, photoreactions of **2** and styrene (**8**) in benzene were examined in the absence of TFA and in the presence of 30 mM of TFA, and the results are shown in Table 1. In the photoreactions of **2** and **8**, two regioisomers of cyclobutanes **9** and **10** were formed from the reaction of ^{1}**2**$*$ with **8**, **9**, and **10** were decomposed to starting materials **2** and **8** upon prolonged irradiation (Scheme 2).[13]

Table 1
Yield of adducts **9** and **10** in the photoreactions of **2** and **8** in the absence and the presence of TFA[a]

Additive	Irradiation time (min)	Conversion (%)	Yield[b] (%)	
			9	10
None	1	7	27	19
	2	9	42	35
	3	14	35	30
	4	16	35	29
	5	18	35	31
TFA (CF_3CO_2H, 30 mM)	1	13	42	12
	2	26	30	9
	3	34	36	9
	4	38	38	10
	5	45	35	9

[a] Irradiation was carried out at room temperature under N_2 in benzene. [**2**]=2.0 mM. [**8**]=100 mM.

[b] Yield was based on consumed **2**.



Scheme 2.

Table 1 shows that the addition of TFA accelerates the photoreaction of **2** and **8** in a similar way as the fluorescence quantum yield. Fig. 11 shows the effect of the concentration of TFA on the relative fluorescence quantum yield and the relative reactivity. These results show that the complexation with TFA increases both the photoreactivity of **2** and the fluorescence quantum yield in a similar way.

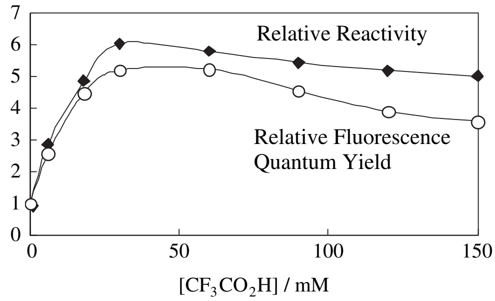
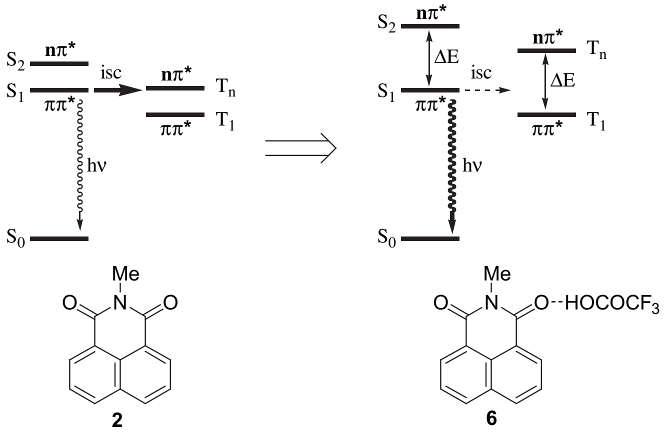


Fig. 11. Effect of addition of TFA on relative fluorescence quantum yield and relative reactivity of **2** in benzene.

2.6. Mechanism to account for the effect of the complexation

Wintgens et al. have reported that the rate of the intersystem crossing from ^{1}**2**$*$ to ^{3}**2**$*$ is faster than those of other naphthalimides **3** and **4**, and the intersystem crossing of **2** accounts for more than 90% of the deactivation processes of ^{1}**2**$*$.[15] This suggests that the $^1(\pi\pi*)$ and $^3(n\pi*)$ levels of **2** are close together in energy.

As mentioned above, the fluorescence quantum yield Φ_{flu} and photoreactivity of **2** toward **8** in benzene was remarkably enhanced by the addition of TFA. As the $^1(\pi\pi*)$ and $^3(n\pi*)$ levels of **2** are close together in energy and the complexation (hydrogen bond formation) is known to increase the energy of $n\pi*$ states compared with those of $\pi\pi*$ states, the complexation with TFA may increase the energy of the $^3(n\pi*)$ compared with that of $^1(\pi\pi*)$, and decrease the rate of the intersystem crossing from the $^1(\pi\pi*)$ to the $^3(n\pi*)$, thus increasing the fluorescence quantum yield Φ_{flu} and photoreactivity of the singlet excited state (Scheme 3).



Scheme 3.

3. Conclusion

To our knowledge, there have been few systematic investigations on the effect of the addition of TFA on the photophysical properties of aromatic imides, even though TFA has frequently been used as a chemical switch of the fluorescence intensity of aromatic imides with an intramolecular amino group, which can quench the fluorescence of the imides by electron transfer in the neutral state.[16] Our results show that the complexation of **1** and **2** with TFA in the ground state decreases the rate of the intersystem crossing from the $^1(\pi\pi^*)$ to the $^3(n\pi^*)$ levels, whose energy is selectively increased by the complexation, and thus increases the fluorescence quantum yield Φ_{flu} and photoreactivity of the singlet excited state of **2**. The effect of the complexation of **2** and TFA on the photophysical properties and photoreactivity is more remarkable than those with complexation of TFE.[14] It is interesting that the simple addition of a small amount of acid can markedly control the photophysical properties and photoreactivity of aromatic imides widely used in numerous applications.

4. Experimental section

4.1. General

UV spectra were measured by use of a JASCO UVIDEC-650 spectrometer. Fluorescence spectra were obtained on a Hitachi 850 spectrophotometer. NMR spectra were recorded on a JEOL JNM-AL-400 (400 MHz) instrument.

Fluorescence spectra were measured under aerated conditions. Fluorescence quantum yields were determined relative to that of *N*-methyl-1,8-naphthalimide (**2**) in MeCN (Φ_f=0.027).[15] The fluorescence quantum yields in benzene were determined to be 0.00026, 0.014, 0.22, 0.82, and 0.48 for imides **1**, **2**, **3**, **4**, and **5**, respectively.

The preparation, purification, and characterization of imides **1**,[17] **2**,[18] **3**,[19] **4**,[15] and **5**[20] have been described elsewhere. Solvents, TFA, and styrene (**8**) were commercially available.

Photoreactions of **2** and **8** were carried out under N_2 by using an Eikosha EHB-W-300 high-pressure Hg-lamp through an aq $CuSO_4$ filter (λ>320 nm).

Supplementary data

UV and fluorescence spectra of **1**, **3**, **4**, and **5** in the presence of various concentrations of TFA in benzene. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.09.022. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. (a) Bailly, C.; Carrasco, C.; Joubert, A.; Bal, C.; Wattez, N.; Hildebrand, M.-P.; Lansiaux, A.; Colson, P.; Houssier, C.; Cacho, M.; Ramos, A.; Brana, M. F. *Biochemistry* **2003**, *42*, 4136; (b) Brana, M. F.; Ramos, A. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 237.
2. Malvyiya, V. K.; Liu, P. Y.; Alberts, D. S.; Surwitt, E. A.; Craig, J. B.; Hanningan, E. V. *Am. J. Clin. Oncol.* **1992**, *15*, 41.
3. Takada, T.; Kawai, K.; Tojo, S.; Majima, T. *J. Phys. Chem. B* **2004**, *108*, 761.
4. (a) Rogers, J. E.; Rostkowski, B. A.; Kelly, L. A. *Photochem. Photobiol.* **2001**, *74*, 521; (b) Rogers, J. E.; Weiss, S. J.; Kelly, L. A. *J. Am. Chem. Soc.* **2000**, *122*, 427; (c) Aveline, B. M.; Matsugo, S.; Redmond, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 11785; (d) Saito, I.; Takayama, M.; Sugiyama, H.; Nakatani, K. *J. Am. Chem. Soc.* **1995**, *117*, 6406; (e) Saito, I.; Takayama, M.; Kawanishi, S. *J. Am. Chem. Soc.* **1995**, *117*, 5590.
5. (a) Zhang, J.; Woods, J.; Brown, P. B.; Lee, K. D.; Kane, R. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 853; (b) Brana, M. F.; Castellano, J. M.; Moran, M.; Perez de Vega, M. J.; Qian, X. D.; Romerdahl, C. A.; Kelhauer, G. *Eur. J. Med. Chem.* **1995**, *30*, 235; (c) Abraham, B.; Kelly, L. A. *J. Phys. Chem. B* **2003**, *107*, 12534.
6. Cosnard, F.; Wintgens, V. *Tetrahedron Lett.* **1998**, *39*, 2751.
7. Niu, C. G.; Li, Z. Z.; Zhang, X. B.; Lin, W. Q.; Shen, G. L.; Yu, R. Q. *Anal. Bioanal. Chem.* **2002**, *372*, 519.
8. (a) Nandhikonda, P.; Begaye, M. P.; Cao, Z.; Heagy, M. D. *Chem. Commun.* **2009**, 4941; (b) Paudel, S.; Nandhikonda, P.; Heagy, M. D. *J. Fluoresc.* **2009**, *19*, 681; (c) Cao, H.; Chang, V.; Hernandez, R.; Heagy, M. D. *J. Org. Chem.* **2005**, *70*, 4929; (d) Demeter, A.; Bérces, T.; Biczók, L.; Wintgens, V.; Valat, P.; Kossanyi, J. *J. Phys. Chem.* **1996**, *100*, 2001; (e) Wintgens, V.; Valat, P.; Kossanyi, J.; Demeter, A.; Biczók, L.; Berces, T. *J. Photochem. Photobiol., A* **1996**, *93*, 109; (f) Demerter, A.; Berces, T.; Biczók, L.; Wintgens, V.; Valat, P.; Kossanyi, J. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 2635.
9. Valat, P.; Wintgens, V.; Kossanyi, J.; Biczók, L.; Demeter, A.; Bérces, T. *Helv. Chim. Acta* **2001**, *84*, 2813.
10. Valat, P.; Wintgens, V.; Kossanyi, J.; Biczók, L.; Demeter, A.; Bérces, T. *J. Am. Chem. Soc.* **1992**, *114*, 946.
11. Bon Hoa, G. H.; Kossanyi, J.; Demeter, A.; Biczók, L.; Bérces, T. *Photochem. Photobiol. Sci.* **2004**, *3*, 473.
12. Cao, H.; McGill, T.; Heagy, M. D. *J. Org. Chem.* **2004**, *69*, 2959.
13. Kubo, Y.; Suto, M.; Tojo, S.; Araki, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 771.
14. Matsubayashi, K.; Kubo, Y. *J. Org. Chem.* **2008**, *73*, 4915.
15. Wintgens, V.; Valat, P.; Kossanyi, J.; Biczók, L.; Demerter, A.; Bérces, T. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 411.
16. Abad, S.; Kluciar, M.; Miranda, M. A.; Pischel, U. *J. Org. Chem.* **2005**, *52*, 3614.
17. Sachs, F. *Chem. Ber.* **1898**, *31*, 1228.
18. Somich, C.; Mazzocchi, P. H.; Ammon, H. L. *J. Org. Chem.* **1987**, *70*, 10565.
19. Kubo, Y.; Suto, M.; Araki, T. *J. Org. Chem.* **1986**, *51*, 4404.
20. Kubo, Y.; Asai, N.; Araki, T. *J. Org. Chem.* **1985**, *50*, 5484.