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Atmosphere Dependent Photoreaction of 4-Pyridinecarboxylic Ester in Acidic Methanolic Solutions

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The UV-irradiation of methyl 4-pyridinecarboxylate (**1**) in methanol under oxygen in the presence of sulfuric acid brings about methoxylation at the 3-position of the pyridine ring, while under nitrogen methoxylation and hydroxymethylation occur at the 2-position. The change of photoreactions of **1** caused by oxygen can not be explained either by the promotion of intersystem crossing by O_2 or by the charge transfer interactions between **1** and O_2.

The UV-irradiation of pyridinecarboxylic acid derivatives in acidic alcoholic solutions generally leads to alkylation, hydroxyalkylation, and alkoxylation at the α-and γ-positions of the pyridine ring.[1–5] In the course of our studies on the photoreactions of pyridinecarboxylic acid derivatives, we have observed a remarkable effect of oxygen in the photoreaction of 4-pyridinecarboxylic ester in alcohols in the presence of sulfuric acid.[6]

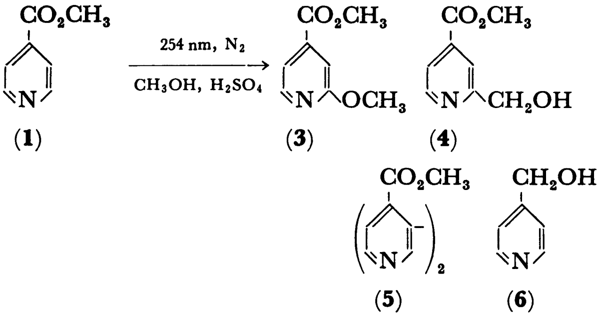
Although the photoreactions in the presence of oxygen have been extensively investigated, the roles of oxygen in the photoreactions have not yet been fully clarified. Besides the well-investigated reactions *via* singlet oxygen, the interest in the effects of oxygen *via* electron transfer interactions is increasing.[7] Pac *et al.* reported a marked increase in the quantum yields by oxygen on the sensitized retro-cycloaddition of dimethylthymine dimers.[8] Mizuno *et al.* have recently reported that the photoisomerization of 1,2-diarylcyclopropanes in the presence of 9,10-dicyanoanthracene is promoted by the addition of air.[9] The acceleration by oxygen in these photoreactions has been ascribed to the electron transfer interactions between the excited substrates and oxygen.

There remain, however, several interesting effects of oxygen, the roles of which have not yet been elucidated. Among them is promotion of the photochemical alcoholysis of organic halides by oxygen.[10]

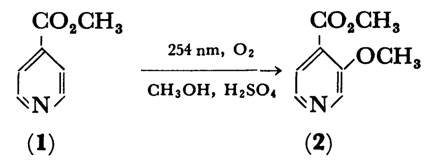
In this paper we report the analysis of the effects of oxygen in the photoreactions of methyl 4-pyridinecarboxylate in acidic methanolic solutions.

Results and Discussion

Types of Photoreactions under N_2 and O_2 Atmosphere. The UV-irradiation of methyl 4-pyridinecarboxylate(**1**) in methanol under nitrogen atmosphere in the presence of sulfuric acid brings about methoxylation and hydroxymethylation at the 2-position of the pyridine ring accompanied by the formation of trace amounts of dimethyl 3,3′-bipyridine-4,4′-dicarboxylate and 4-pyridylmethanol (Table 1).



Under oxygen atmosphere, these reactions are inhibited and **1** gives the methoxylation product at the 3-position selectively (Table 1).



The photoreaction of **1** is characterized by the fact that the presence of oxygen causes a dramatic change in the position of the methoxylation Such a remarkable oxygen effect was not observed in the photoreactions of 2- and 3-pyridinecarboxylic esters.

Photoreactions under N_2. The photoreactions of methyl 4-pyridinecarboxylate (**1**) in an acidic methanolic solution under nitrogen are essentially similar to those of 2- and 3-pyridinecarboxylic esters:[3,4] ionic methoxylation and hydroxymethylation in radical reaction occur in parallel. The difference of the photo-

TABLE 1. PHOTOREACTIONS OF METHYL 4-PYRIDINECARBOXYLATE (**1**) IN METHANOL IN THE PRESENCE OF H_2SO_4.[a)]

Atmosphere	Conversion of **1**	(Yield of product)[b)]/%				
	%	**2**	**3**	**4**	**5**	**6**
N_2	47.5	Trace	14	5.5	Trace	Trace
O_2	14	88	Trace	0.0	0.0	0.0

a) [**1**] = 0.02 mol dm^{-3}; [H_2SO_4] = 0.25 mol dm^{-3}; Irradiation time, 25 min; Temp., 30 °C. b) Yields were determined by means of GLC and/or HPLC, and were calculated on the basis of **1** consumed.

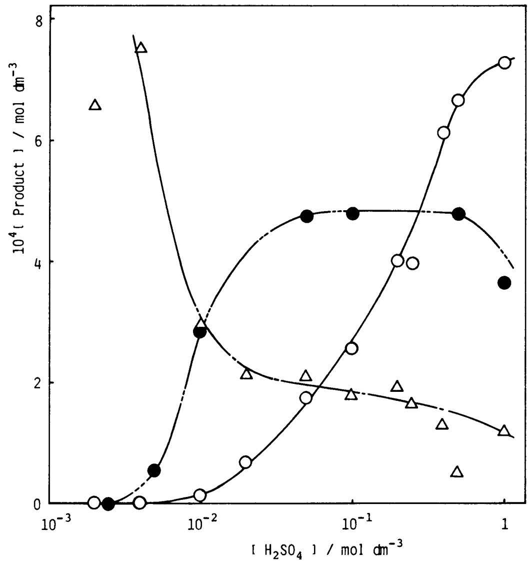


Fig. 1. Dependence of photo-methoxylation and -hydroxymethylation at the 2-position under N_2 and photo-methoxylation at the 3-position under O_2 on the concentration of sulfuric acid.
[**1**]=0.01 mol dm^{-3}, —○—: **3**, —△– – –: **4** (under N_2), —●– – –: **2** (under O_2).

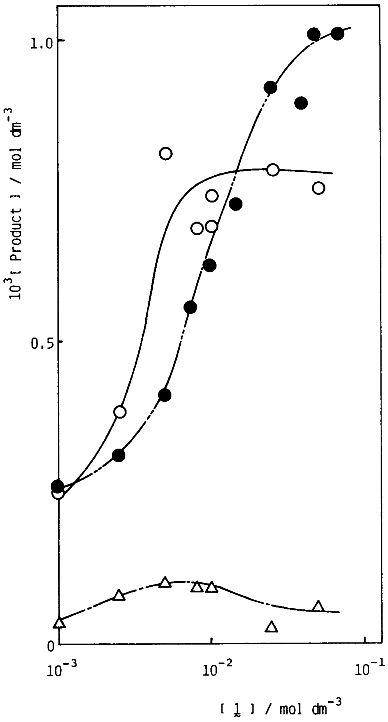


Fig. 2. Dependence of yields of **3** and **4** under N_2 and **2** under O_2 on the concentration of **1**.
[H_2SO_4]=1.0 mol dm^{-3}, —○—: **3**, —△– – –: **4** (under N_2), —●– – –: **2** (under O_2).

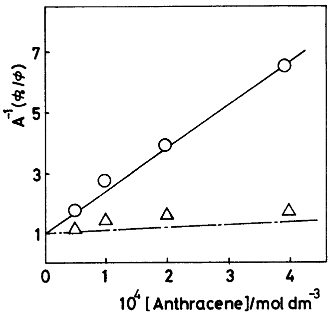


Fig. 3. Effects of anthracene on the photo-methoxylation and -hydroxymethylation at the 2-position of **1**.
[**1**]=0.01 mol dm^{-3}, [H_2SO_4]=0.05 mol dm^{-3}, —○—: **3**, —△– – –: **4**.

reactions of 4-pyridinecarboxylic ester from those of 2- and 3-isomers are: 1) the occurrence of hydroxymethylation in place of methylation which occurs in 2- and 3-pyridinecarboxylic esters and 2) the formation of dimethyl 3,3′-bipyridine-4,4′-dicarboxylate (dimerization) and 4-pyridylmethanol (reduction).

The photoreaction of **1** is dependent on the concentration of added sulfuric acid and on the concentration of the substrate itself.

Figure 1 shows the effect of the concentration of sulfuric acid on the photoreaction. In the lower concentrations of sulfuric acid, hydroxymethylation occurs exclusively. As the concentration of sulfuric acid increases, hydroxymethylation is suppressed and methoxylation becomes dominant. This shows that non-protonated **1** undergoes only hydroxymethylation and protonated **1** undergoes methoxylation and hydroxymethylation.

The photo-methoxylation of **1** shows a remarkable concentration dependence of the substrate (Fig. 2). A similar concentration dependence was observed in the photo-methoxylation of methyl 2-pyridinecarboxylate and a kinetic analysis revealed that the photo-methoxylation of 2-pyridinecarboxylic ester proceeds *via* an excimer of the substrate.[3] The similarity of the concentration dependences in the photo-methoxylations of 2- and 4-pyridinecarboxylic esters suggests the participation of an excited dimer in the formation of **3**.

The inhibition of photo-methoxylation of **1** by aromatic hydrocarbons is very similar to that of 2-pyridinecarboxylic ester.[3] Photo-methoxylation at the 2-position under nitrogen atmosphere is inhibited by anthracene effectively as is shown in a Stern-Volmer plot in Fig. 3.[11] Similar inhibitions are observed for *trans*-1,3-pentadiene, naphthalene, triphenylene, azulene, and even for benzene which is considered as a triplet sensitizer. The efficiencies for the quenching of the formation of **3** by the additives correlate very well with the ionization potentials of the additives (Fig. 4). These facts can be explained by the quenching of an excimer *via* an electron transfer (from aromatic hydrocarbons to **1**) mechanism proposed by Caldwell *et al.*[12]

Hydroxymethylation should originate from an excited monomer in the singlet excited state, because it is not inhibited by anthracene as is shown in Fig. 3.

Photo-hydroxymethylation should be initiated by the hydrogen abstraction by an excited **1** from methanol. The radical pair thus formed combines to give an addition product which is converted to 4-pyridylmethanol either *via* disproportionation or *via* a kind of oxidation.

Mechanism for the photo-methoxylation and the hydroxymethylation of **1** is summarized in Scheme 1.

Although the bipyridine formation (a kind of dimerization) and the reduction of the ester carbonyl to alcohol are characteristic for the photoreaction of **1**, the detailed analyses of the mechanism for the formation of these products could not be done, because their yields are very low.

Photo-methoxylation at the 3-Position under O_2. The UV-irradiation of **1** in methanol in the presence of sulfuric acid under O_2 gives methyl 3-methoxy-4-pyridinecarboxylate (**2**) selectively. The results summarized in Table 2 indicate that the yields of the products are changed by the addition of oxygen. When the solution is deoxyganated by bubbling nitrogen, the methoxylation at the 2-position becomes dominant. As the partial pressure of oxygen becomes higher, the methoxylation at the 3-position remarkably increases, while the methoxylation and the hydroxymethylation at the 2-position as well as the rate of decomposition of **1** are suppressed.

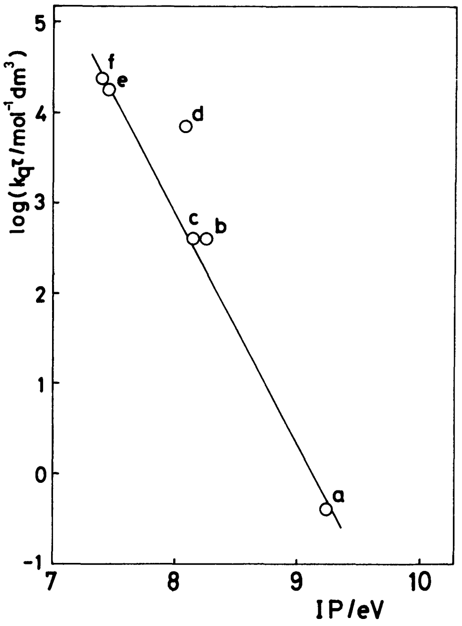


Fig. 4. Relation between $k_q\tau$ for the quenching of photo-methoxylation at the 2-position and ionization potentials of quenchers. a) benzene, b) *trans*-1,3-pentadiene, c) naphthalene, d) triphenylene, e) anthracene, f) azulene.

Oxygen does not serve as an oxidizing agent of a precursor of **2**, because the addition of $K_3[Fe(CN)_6]$ as an oxidizing agent after the irradiation of **1** under N_2 does not increase the yield of **2** (Table 2). The bubbling of oxygen through the solution which has been irradiated under N_2 causes no increase in the yield of **2**.

Such a dramatic change of photoreactions by oxygen has not been observed in the cases of 2- and 3-pyridinecarboxylic esters for which oxygen only inhibits the photoreactions.[3,4]

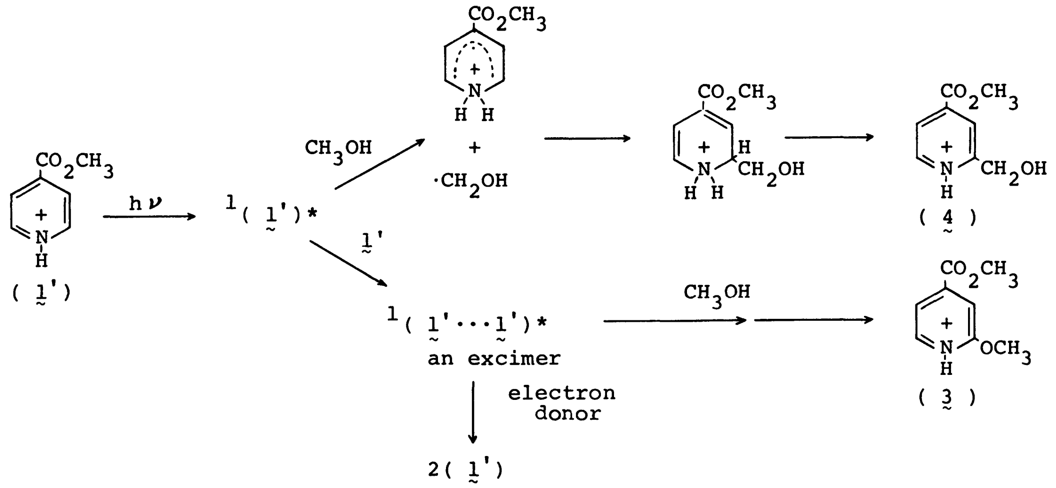
As is shown on Figs. 1 and 2 the methoxylation at the 3-position under O_2 shows dependence on the concentrations of sulfuric acid and **1**. These facts are somewhat similar to the methoxylation at the 2-position under N_2 described in the preceeding section.

However, the effects of additives on the methoxylation at the 3-position are different from those of the methoxylation at the 2-position under N_2. Methoxylation under O_2 is not inhibited by anthracene and by *trans*-1,3-pentadiene, while that under N_2 are inhibited by aromatic hydrocarbons. This fact indicates that the excited states responsible for the two kinds of methoxylation are different in character.

Role of Oxygen in the Photo-methoxylation at the 3-Position. In order to explore the role of oxygen in the promotion of the photo-methoxylation at the 3-position, we have tested the following possibilities for the role of oxygen: 1) the acceleration of intersystem crossing and 2) charge transfer interaction between **1** and oxygen resulting in the electron transfer.

Unexpectedly, no evidence in support of the role of oxygen is observed as described in the following sections.

Possibility of Acceleration of Intersystem Crossing. Oxygen could accelerate intersystem crossing of an excited singlet state of **1** to a triplet state and the triplet would give the methoxylation product at the



Scheme 1. Mechanism of photoreactions of **1** under N_2.

TABLE 2. PHOTOREACTIONS OF **1** IN METHANOL IN THE PRESENCE OF H_2SO_4[a)]

Atmosphere[b)]	Additive	Conversion of **1**	10^4[Product]/mol dm^{-3}		
		%	**2**	**3**	**4**
N_2	—	24	0.35	4.12	2.31
Air	—	17	6.25	1.82	0.90
O_2	—	10	5.69	0.00	0.00
NO	—	0	0.00	0.00	0.00
N_2	O_2[c)]	22	0.27	4.01	1.69
N_2	$[Fe(CN)_6]^{3-}$[d)]	21	0.25	2.67	3.20
N_2	Ph_2CO[e)]	0	0.00	0.00	0.00
O_2	Ph_2CO[e)]	0	0.00	0.00	0.00

a) [**1**]=0.01 mol dm^{-3}; [H_2SO_4]=0.25 mol dm^{-3}; Irradiation time, 1 h; Temp., 20 °C. b) The solution was purged with gas for 50 min before irradiation. c) O_2 was bubbled after irradiation. d) $K_3[Fe(CN)_6]$ was added after irradiation. e) [**1**]=5×10^{-3} mol dm^{-3}; [H_2SO_4]=1×10^{-1} mol dm^{-3}; Irradiation time, 48 h; Temp., 25.5 °C; Irradiated with monochromatic light of 365 nm.

3-position (**2**). This possibility can be tested by examining the contribution of a triplet state of **2** for the formation of **2**.

Triplet quenchers such as anthracene and *trans*-1,3-pentadiene have little effect on the formation of **2**, as mentioned before. When the irradiation is carried out in the presence of benzophenone, no reaction occurs under either O_2 or N_2. The irradiation is carried out under NO, a paramagnetic gas, but no reaction occurs, as is shown in Table 2.

Possibility of Effect via Charge Transfer Interaction between Substrate and Oxygen. Oxygen is an efficient electron acceptor and can affect the photoreactions *via* charge transfer interaction either in the ground[13–16)] or in the excited state. Oxygen could abstract an electron from the substrate and the irradiation of **1** under O_2 may give an electron-deficient intermediate (the postulated intermediate formed in the above process should easily undergo the necleophilic methoxylation). If this process actually occurs, electron acceptors other than oxygen could show the same effect as oxygen. To test this possibility, the irradiation in the presence of several typical electron acceptors in place of oxygen (reduction potential, $E_{1/2}=-0.94$ V *vs.* SCE in CH_3CN)[7)] are carried out under N_2 atmosphere. *p*-Dicyanobenzene ($E_{1/2}=-1.97$ V *vs.* Ag/AgClO$_4$ (0.1 mol dm^{-3}) in DMF)[17)] and 1,2,4,5-tetracyanobenzene ($E_{1/2}=-1.02$ V *vs.* Ag/AgClO$_4$ (0.1 mol dm^{-3}) in DMF)[17)] have almost no effect on the photoreaction of **1**: the electron acceptors neither promote the methoxylation at the 3-position nor inhibit the methoxylation at the 2-position (Table 3).[11)]

The above results indicate that the remarkable change of the photoreactivity of **1** by oxygen is not due to the charge transfer interactions between the substrate and oxygen.

Since the concentration dependence curves of the methoxylations under N_2 and O_2 are somewhat different as shown in Fig. 2, it seems that the excimer leading to the methoxylation at the 3-position under O_2 is different in character from that leading to the methoxylation at the 2-position under N_2.

The present study revealed that the oxygen effect observed in the photoreaction of **1** in acidic methanolic solutions can not be categorized as types of oxygen effect which have been generally accepted. The processes of the photo-methoxylation of 4-pyridinecarboxylic ester at the 3-position should contain a novel type of the interaction between oxygen and the excited molecule.

TABLE 3. EFFECTS OF ELECTRON ACCEPTORS ON THE PHOTO-METHOXYLATIONS OF **1** UNDER N_2[a)]

Acceptor	[Acceptor] / mol dm^{-3}	Relative yield[b)]	
		2	**3**
None	—	0.12	1.00
DCNB[c)]	8.0×10^{-4}	0.05	0.99
TCNB[d)]	1.6×10^{-4}	0.08	0.99
TCNB[d)]	3.2×10^{-4}	0.11	1.01

a) [**1**]=0.01 mol dm^{-3}; [H_2SO_4]=0.05 mol dm^{-3}; Irradiation time, 1 h; Temp., 20 °C. b) Relative yields based on the A value of **3**.[11)] c) *p*-Dicyanobenzene. d) 1,2,4,5-Tetracyanobenzene.

Experimental

Materials. Commercial methly 4-pyridinecarboxylate (GR grade reagent of Tokyo Kasei Co) was purified by vacuum distillation; bp, 94—95 °C/16.5 mmHg (1 mmHg≈133.322 Pa). Anthracene (standard reagent for elemental analysis made by E. Merck Co.), triphenylene (GR grade reagent of Tokyo Kasei Co.), *trans*-1,3-pentadiene (GR grade reagent of Wako Junyaku Co.), and azulene (GR grade reagent of Tokyo Kasei Co.) were used without further purification. Commercial *p*-dicyanobenzene was purified by recrystallization; mp, 228—229 °C. 1,2,4,5-tetracyanobenzene was kindly supplied by Mr. Haruhiko Tomoda of Shibaura Institute of Technology.

UV-Irradiation for Preparation of Products. Through the solutions of **1** (0.02 mol dm^{-3}, 50 cm^3) containing sulfuric acaid (0.25 mol dm^{-3}) oxygen or nitrogen were bubbled for 50 min before irradiation. The solutions were irradiated with a 17 W low pressure mercury lamp for 25 min at 30 °C.

UV-Irradiation for Study of Mechanism. The solutions of **1** (20 cm^3) containing sulfuric acid and the additives, if necessary, were purged with a gas (O_2, air, or N_2) for 50 min before irradiation. The solutions were irradiated with a 17 W low pressure mercury lamp in a merry-go-round type apparatus at 20°C.

For wavelength effect experiments the irradiation was carried out by using a Shimadzu-Bausch-Lomb Co. monochrometer equipped with a 200 W super high pressure mercury lamp.

Isolation and Identification of Photo-products. After the irradiation the solution was concentrated with a rotary evaporator and neutralized with sodium carbonate solution. The neutralized solution was extracted with ethyl acetate. The products were separated by means of TLC (Plate, GF_{254} Type 60 of E. Merck Co.; developing solvent, ethyl acetate-dichloromethane 3:7 v/v).

Methyl 3-methoxy-4-pyridinecarboxylate (**2**): Mp 55—56.5 °C; IR (KBr disk) 1720 (ester C=O) and 1220 cm^{-1} (C-O-C); ^{1}H NMR ($CDCl_3$) δ=8.44 (1 H, s), 8.29 (1 H, d, *J*=4 Hz), 7.55 (1 H, d, *J*=4 Hz), 4.02 (3H,s), and 3.91 (3H,s); MS (70 ev), *m/z* (rel intensity) 167 (M$^+$; 77), 152 (14), 138 (18), 137 (9), 136 (100), 135 (18), 134 (79), 106 (31), 93 (36), and 78 (74), Found: *m/z* 167.0585. Calcd for $C_8H_9NO_3$: M, 167.0583.

Methyl 2-methoxy-4-pyridinecarboxylate (**3**) was identified by the accordance of its ^{1}H NMR spectra with those obtained by Deady *et al.*[18]

Methyl 2-hydroxymethyl-4-pyridinecarboxylate(**4**) (mp 67.5—68 °C; lit,[19] 68—69 °C) was identified by means of spectral analyses.

Dimethyl 3,3′-bipyridine-4,4′-dicarboxylate(**5**): Mp 184—187 °C(sub); IR (KBr disk), 1720 cm^{-1} (ester C=O); ^{1}H NMR ($CDCl_3$) δ=8.95 (1 H, d. *J*=1.6 Hz), 8.85 (1 H, d, *J*=5 Hz), 7.87 (1 H, dd, *J*=1.6 and 5 Hz), and 4.00 (3H, s); Found: C, 61.7; H, 4.7; N, 10.2% M$^+$, 272. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29%; M, 272.

4-Pyridylmethanol (**6**) was identified by the accordance of gas-chromatographic and spectral properties with those of authentic sample.

Quantitative Analyses of Photo-products. The yields of the products were determined by means of GLC (1.5 m column of 10% PEG 20M on 60—80 mesh Celite 545) with a Shimadzu gas chromatograph model GC 6A and/or by means of HPLC with Shimadzu liquid chromatograph model LC 1 and LC 3A (4.6 mm×25 cm column of Zorbax ODS; eluent, H_2O-MeOH 4:6 v/v).

Spectral Measurments. IR spectra were measured on a Hitachi 215 spectrometer, and ^{1}H NMR spectra were determined with Hitachi R 22 NMR spectrometer (90M Hz) with tetramethylsilane as an internal standard. MS spectra were recorded on a JEOL D-300 spectrometer.

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11) In this case, the effects of additives were analyzed by means of an index A, the relative quantum yield calculated on the basis of the light absorbed by **1**, because the additives absorb the 254 nm light competitively with **1**. A^{-1} corresponds ϕ_0/ϕ in the Stern-Volmer plots for the quenching experiments. A=Y/L, Y=(Yield in the presence of additive (**Q**))/(Yield in the absence of additive (**Q**)), $L=\varepsilon_1[\mathbf{1}]/(\varepsilon_1[\mathbf{1}]+\varepsilon_Q[\mathbf{Q}])$, where ε_1 and ε_Q are the molar absorption coefficients of **1** and **Q** at 254 nm, respectively.

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