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# Reaction Modes and Mechanism in Indolizine Photooxygenation Reactions

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Photooxygenations of 1,2-, 1,3-, and 2,3-di- and 1,2,3-trisubstituted indolizines **1a**−**1f** under different reaction conditions in methanol and acetonitrile have been investigated to establish the general reaction pattern and mechanism in indolizine photooxygenation in view of the influence of the ring substituents and substitution pattern. Photooxygenations of 1-acyl-2-phenylindolizines **1a** and **1b** and 1,3-dibenzoyl-2-phenylindolizine (**1d**) are self-sensitized, while those of 1-(*p*-nitrobenzoyl)-2-phenylindolizine (**1c**) and 2-phenyl-3-(*p*-chlorobenzoyl)indolizine (**1e**) need to be sensitized by rose bengal (RB) or methylene blue (MB). These reactions proceed via a singlet oxygen mechanism yet follow different pathways in methanol and in acetonitrile, with peroxidic zwitterion **D** (in methanol) and dioxetane **E** across the indolizine C2−C3 bond (in acetonitrile) as the intervening intermediates. Methanol trapping of the peroxidic zwitterion results in C3−N bond cleavage and pyrrole ring opening to give the corresponding (*E*)- and (*Z*)-3-(2-pyridinyl)-3-benzoylpropenoic acid methyl esters (**2** and **3**) and 4-(2-pyridinyl)-3-phenyl-5-aryl-5-hydroxyfuran-2-one (**4**) as products in methanol, while O−O bond homolysis of the dioxetane furnishes 3-(2-pyridinyl)-3-benzoyl-2-phenyloxirane-2-carboxaldehyde (**6**) and 1-(6-methyl-2-pyridinyl)-2-phenylethanedione (**5**) as products in acetonitrile. 3-Benzoyl-1-indolizinecarboxylic acid methyl ester (**1f**) is unreactive toward singlet oxygen; however, it could be photooxygenated under electron transfer conditions with 9,-10-dicyanoanthracene (DCA) as a sensitizer. This reaction takes place by the combination of the indolizine cation radical with the superoxide anion radical (or molecular oxygen) to give the pyridine ring oxidized methyl 3-benzoyl-5-methoxy-8-hydroxy-1-indolizinecarboxylate (**9f**), dimethyl 2-(2-pyridinyl)fumarate (**8f**), and dimethyl 2-(2-pyridinyl)maleate (**7f**) as products.

## Introduction

Photoinduced oxygenation reactions of many N-containing heterocycles such as pyrroles,[1−3] indoles,[1,2,4] imidazoles,[1,2,5] oxazoles,[1,2] and thiazoles[1,2] by the singlet oxygen mechanism[6] have been extensively investigated in both synthetic and mechanistic aspects.[1,2] Reaction patterns and mechanisms in view of the heterocyclic structure and ring substituents have been largely clarified. In sharp contrast, photooxygenation of the indolizines has not been widely investigated. Our recent investigation on the photooxygenation of indolizine derivatives via the selective excitation of their ground state charge transfer complex with triplet oxygen ($^3\Sigma_g$ $O_2$) is the first report on indolizine photooxygenation.[7] Indolizines and their partially and fully hydrogenated derivatives stand for a large family of naturally occurring alkaloids with

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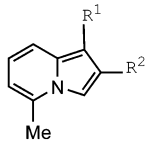
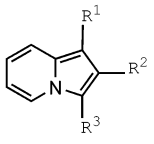
**CHART 1**



**1a** $R^1$= PhCO $R^2$= Ph

**1b** $R^1$= *p*-MeOPhCO $R^2$= Ph

**1c** $R^1$= *p*-$O_2$NPhCO $R^2$= Ph



**1d** $R^1$= COPh $R^2$= Ph $R^3$= COPh

**1e** $R^1$= H $R^2$= Ph $R^3$= *p*-ClPhCO

**1f** $R^1$= $CO_2$Me $R^2$= H $R^3$= COPh

biological activities.[8] Indolizines are also special in their electronic structure among N-containing heterocycles by having a bridgehead nitrogen atom which causes a large dipole moment in the molecule so that the pyridine and the pyrrole rings are electron deficient and electron rich, respectively.[9] This special electronic structure should be reflected in the reaction pathways in their photooxygenation reactions. Indolizines are also known to be susceptible to oxygen attack and are easily oxidized upon air and light exposure. In relation to this, it has recently been found that indolizines are highly active antioxidants that inhibit lipid peroxidation in vitro.[10] Our previous investigation on indolizine photooxygenation was based on the reactions of four 2-phenylindolizines.[7] To further establish the scope and general reaction modes and to examine the mechanisms in indolizine photooxygenation in regard to ring substituents and substitution patterns, we have investigated photoinduced oxygenation of a series of indolizines covering a wide range of substitution patterns under different conditions.

## Results and Discussion

Indolizines **1a**−**1f**, bearing 1,2-, 1,3-, 2,3-, and 1,2,3-substituents, have been synthesized, and their photooxygenations under various conditions have been investigated (Chart 1). As compared with the case of the unsubstituted indolizine, the introduction of the acyl and aryl groups in **1a**−**1f** causes drastic change in both the absorption (1) and luminescence (2) properties. (1) In the electronic spectra of **1a**−**1f**, absorptions are red shifted to show strong absorptions in the visible region so that these compounds are yellow colored. As examples, **1a** has two absorption bands at 243.4 nm ($\epsilon_{max}$ = 39200) and 378.1 nm ($\epsilon_{max}$ = 14900). Similarly, **1b** absorbs at 246.1 nm ($\epsilon_{max}$ = 35100) and 378.4 nm ($\epsilon_{max}$ = 15200). The long wavelength band at ∼378 nm tails well into the visible region. Therefore, excitation of these indolizines can be achieved by irradiation with light of $\lambda$ > 400 nm. (2) While indolizine ($\Phi_F$ = 0.84 in hexane and 0.72 in methanol) and 2-phenylindolizine ($\Phi_F$ = 0.6 in hexane and 0.67 in methanol) have high fluorescence quantum yields[11a] and are nonphosphorescent ($\Phi_P$ < 0.01), the acyl group in **1a**−**1f** serves to promote the intersystem crossing (ISC) of the singlet excited state to the triplet state, resulting in a diminished $\Phi_F$ and the occurrence of strong phosphorescence. The $\Phi_F$ values of **1b**, **1d**, and **1f** are measured to be 0.008, 0.008, and 0.005, respectively.

**TABLE 1. Photooxygenation Reactions of Compounds 1a−1f**

| substrate | solvent | irrad time (h) | conversion (%) | product (yield[a] (%)) |
|---|---|---|---|---|
| **1a**[b] | MeOH−MeCN | 9 | 100 | **2a** (22), **3a** (23), **4a** (40) |
| **1a**[b] | MeCN | 10 | 100 | **5a** (25), **6a** (64) |
| **1a**[c] | MeOH−MeCN | 9 | 100 | **2a** (25), **3a** (24), **4a** (38) |
| **1b**[b] | MeOH−MeCN | 8 | 100 | **2b** (28), **3b** (32), **4b** (9) |
| **1b**[b] | MeCN | 10 | 100 | **5b** (11), **6b** (62) |
| **1c**[d] | MeOH−MeCN | 8 | 100 | **2c** (35), **3c** (11), **4c** (44) |
| **1c**[d] | MeCN | 12 | 100 | **5c** (20), **6c** (31) |
| **1d**[b] | MeOH−MeCN | 12 | 100 | **2d** (71) |
| **1d**[b] | MeCN | 14 | 100 | **6d** (90) |
| **1e**[d] | MeOH−MeCN | 10 | 100 | **2e** (73) |
| **1e**[d] | MeCN | 11 | 100 | **6e** (81) |
| **1f**[e] | MeOH−MeCN | 20 | 64 | **7f** and **8f** (63), **9f** (27)[f] |

[a] The yield of isolated pure product. [b] Self-sensitized reactions. Irradiation with light of $\lambda$ > 400 nm. [c] Photolysis with light of $\lambda$ > 300 nm. [d] Rose bengal (RB)/methylene blue (MB) sensitized. Irradiation with light of $\lambda$ > 500 nm. [e] 9,10-Dicyanoanthracene (DCA) sensitized. Irradiation with light of $\lambda$ > 400 nm. [f] Yield based on consumed **1f**.

We have found that **1a**, **1b**, and **1d** undergo self-sensitized photooxygenation in oxygen saturated solution. Therefore, irradiation of **1a** (0.025 mol $L^{-1}$) in a methanol solution with light of $\lambda$ > 400 nm under constant oxygen purging led to the smooth consumption of **1a**, and a complete conversion was reached within 9 h. Chromatographic separation of the reaction mixture on a silica gel column gave (*E*)-2-phenyl-3-benzoyl-3-(6-methyl-2-pyridinyl)acrylic acid methyl ester (**2a**) (10%), its (*Z*)-isomer (**3a**) (58%), and 3,5-diphenyl-5-hydroxy-4-(6-methyl-2-pyridinyl)dihydrofuran-2-one (**4a**) (25%). Photooxygenation of **1a** in acetonitrile−methanol (1:1, v/v) similarly gave **2a** (22%), **3a** (23%), and **4a** (40%) (Table 1). The structures and steric configurations of these compounds are elucidated by their spectral (IR, $^1$H NMR, and MS) data and are further confirmed by X-ray crystallographic analysis. On the other hand, irradiation of **1a** in acetonitrile solution under otherwise the same conditions and silica gel chromatographic separation of the reaction mixture after photolysis gave 2-phenyl-1-(6-methyl-2-pyridinyl)ethanedione (**5a**) (25%) and oxirane product **6a** (64%). However, $^1$H NMR and TLC monitoring of the reaction course showed that **5a** is not a primary product in the photooxygenation but is derived from **6a** during the photolysis. In a control experiment, **6a** was found to decompose to give **5a** upon photolysis under photooxygenation conditions.

Similar irradiation of **1b** in methanol−acetonitrile (1:1, v/v) gave the corresponding **2b** (28%), **3b** (32%), and 2-phenyl-3-(4-methoxybenzoyl)-3-(6-methyl-2-pyridinyl)-acrylic acid (**4b**) (9%). A significant amount of *p*-methoxybenzoic acid (16%) was also obtained (Table 1). Photolysis of **1b** in acetonitrile and workup of the photolysate as before, on the other hand, gave 1-(6-methyl-2-pyridinyl)-2-(4-methoxyphenyl)ethanedione (**5b**)-(11%) and **6b** (62%) together with *p*-methoxybenzoic acid (16%). Photoinduced oxygenation of **1d** in methanol−acetonitrile (1:1, v/v) resulted in the formation of **2d** (71%)

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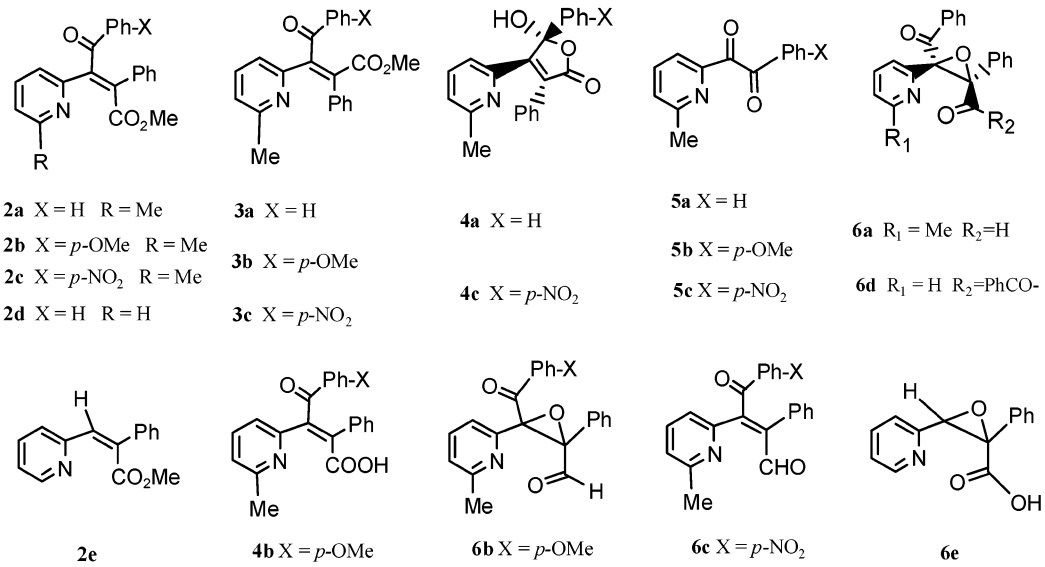
**CHART 2**




and benzoic acid (23%), while irradiation in acetonitrile gave oxirane **6d** (90%) (Chart 2).

We have measured the UV−visible absorption spectra of **1a** in oxygen saturated and oxygen free solutions in acetonitrile. The absorption curves in these two cases coincide with each other, indicating that a ground state charge transfer complex (CTC) between **1a** and $^3\Sigma_g$ $O_2$ is not formed to any detectable degree. Therefore, these photoxygenations of **1a**, **1b**, and **1d** take place via direct excitation of the substrate and are self-sensitized. The triplet energies for compounds **1b**, **1d**, and **1f** are measured from their phosphorescence spectra to be 59.0, 60.2, and 61.9 kcal mol$^{-1}$, respectively. These $E_T$ values are well above the energy of $^1\Delta_g$ $O_2$ (22.6 kcal mol$^{-1}$). ISC from $S_1$ to $T_1$ followed by energy transfer from the indolizine $T_1$ state to $^3\Sigma_g$ $O_2$ results in the generation of $^1\Delta_g$ $O_2$ as the active oxygen species. Photooxygenation of **1a** in methanol−acetonitrile with short wavelength irradiation ($\lambda$ > 300 nm) was also carried out, and this gave similar results to those in the long wavelength photolysis (Table 1). Singlet oxygen is known to be a good excited state electron acceptor, and quenching of singlet oxygen by highly nucleophilic substrates with low ionization potentials such as enamines,[12] aliphatic[13] and aromatic[14] amines, phenols,[15] sulfides,[16] and hydrazines[17] has been reported. However, since singlet oxygen is estimated to have a half-wave reduction potential ($E_{1/2}$) of ∼0.11 V (SCE, MeCN),[18] single electron transfer (SET) to $^1\Delta_g$ $O_2$ is exothermic only for those electron donors with half-wave oxidation potentials lower than ∼0.11 V.[18−20] Therefore, a large number of these singlet oxygen quenchings are of charge transfer character without ion radical pair formation taking place. Indolizine ranks among the most $\pi$-electron excessive heterocycles, and simple alkyl- and aryl-substituted indolizines have half-wave oxidation potentials ($E_{1/2}^{ox}$) in the range 0.4−0.8 V (SCE, MeCN).[21] However, with the electron withdrawing acyl in the indolizine ring, substrates **1a**, **1b**, and **1d** must have their $E_{1/2}^{ox}$ higher than 0.8 V. Therefore, SET from **1a**, **1b**, and **1d** to singlet oxygen would have $\Delta G_{ET}$ values more positive than 16 kcal/mol and would be highly endergonic, as estimated by the empirical Weller equations.[22] These photooxygenations are therefore suggested to proceed by the mechanisms shown in Scheme 1. In singlet oxygen reactions of cyclic enamines such as pyrroles, indoles, imidazoles, oxazoles, and thiazoles, dioxetane and endoperoxide formed by [2 + 2] and [2 + 4] cycloadditions of singlet oxygens to the enamine moiety are often suggested as the primary products.[1−5,23] To rationalize the results of the singlet oxygen reactions of **1a**−**1e**, we have carried out a DFT calculation of the frontier molecular orbitals and the charge density distribution in indolizines **1a**−**1e** at the B3LYP 6-31G level, and the results are given in Table 2. The calculation shows that

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(18) The half-wave reduction potential of oxygen is −0.82 V (SCE)[19a] or −0.87 V (SCE).[19b] The half-wave reduction potential of singlet oxygen ($E_s$ = 22.6 kcal/mol) is therefore −0.11 V (SCE).[20]

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**SCHEME 1**

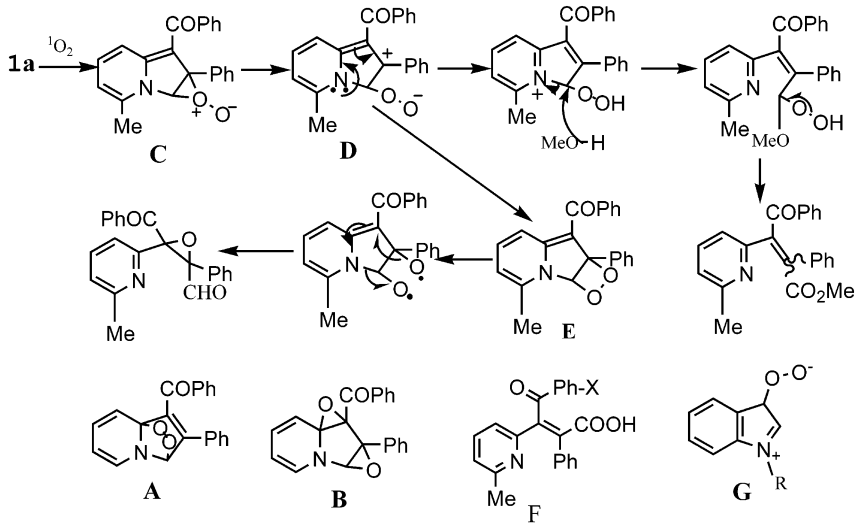



**TABLE 2. FMOs of 1a−1e**[a]

| compound | | energy (eV) | atomic coefficient |
|---|---|---|---|
| **1a** | HOMO | −5.37 | $C_1$, 0.302 27; $C_2$, −0.034 58; $C_3$, −0.034 58; $N_4$, −0.066 09; $C_5$, 0.223 64; $C_6$, 0.110 96; $C_7$, −0.202 04; $C_8$, −0.179 78; $C_9$, 0.147 608 |
| | LUMO | −1.41 | $C_1$, 0.173 39; $C_2$, −0.183 12; $C_3$, −0.065 58; $N_4$, 0.197 58; $C_5$, −0.192 28; $C_6$, −0.022 61; $C_7$, 0.248 92; $C_8$, −0.154 68; $C_9$, −0.167 42 |
| **1b** | HOMO | −4.96 | $C_1$, −0.268 07; $C_2$, 0.041 25; $C_3$, 0.273 30; $N_4$, 0.067 71; $C_5$, −0.206 10; $C_6$, −0.106 44; $C_7$, 0.178 84; $C_8$, 0.161 29; $C_9$, 0.161 29 |
| | LUMO | 1.54 | $C_1$, 0.167 61; $C_2$, −0.197 89; $C_3$, 0.041 66; $N_4$, −0.033 95; $C_5$, 0.024 30; $C_6$, 0.017 17; $C_7$, −0.038 73; $C_8$, −0.068 64; $C_9$, 0.245 69 |
| **1c** | HOMO | −5.32 | $C_1$, 0.304 15; $C_2$, 0.059 44; $C_3$, −0.190 73; $N_4$, 0.117 55; $C_5$, 0.198 66; $C_6$, 0.163 39; $C_7$, −0.145 27; $C_8$, −0.204 62; $C_9$, 0.081 25 |
| | LUMO | −3.08 | $C_1$, 0.062 18; $C_2$, −0.069 37; $C_3$, −0.013 36; $N_4$, −0.011 27; $C_5$, 0.007 98; $C_6$, 0.004 20; $C_7$, −0.015 63; $C_8$, −0.032 76; $C_9$, 0.109 00 |
| **1d** | HOMO | −5.77 | $C_1$, 0.301 70; $C_2$, −0.050 19; $C_3$, −0.283 16; $N_4$, −0.080 36; $C_5$, 0.203 85; $C_6$, 0.109 65; $C_7$, −0.182 02; $C_8$, −0,173 31; $C_9$, 0.125 50 |
| | LUMO | −1.97 | $C_1$, −0.041 85; $C_2$, −0.167 78; $C_3$, −0.165 91; $N_4$, −0.207 53; $C_5$, 0.136 72; $C_6$, −0.081 31; $C_7$, −0.161 40; $C_8$, 0.076 59; $C_9$, 0.126 29 |
| **1e** | HOMO | −5.55 | $C_1$, 0.296 75; $C_2$, 0.052 66; $C_3$, −0.293 06; $N_4$, −0.096 20; $C_5$, 0.203 83; $C_6$, 0.116 36; $C_7$, −0.186 10; $C_8$, −0.171 22; $C_9$, 0.143 72 |
| | LUMO | −1.94 | $C_1$, −0.026 33; $C_2$, −0.148 32; $C_3$, −0.158 61; $N_4$, −0.214 25; $C_5$, 0.145 26; $C_6$, −0.083 33; $C_7$, −0.172 59; $C_8$, 0.091 26; $C_9$, 0.126 61 |

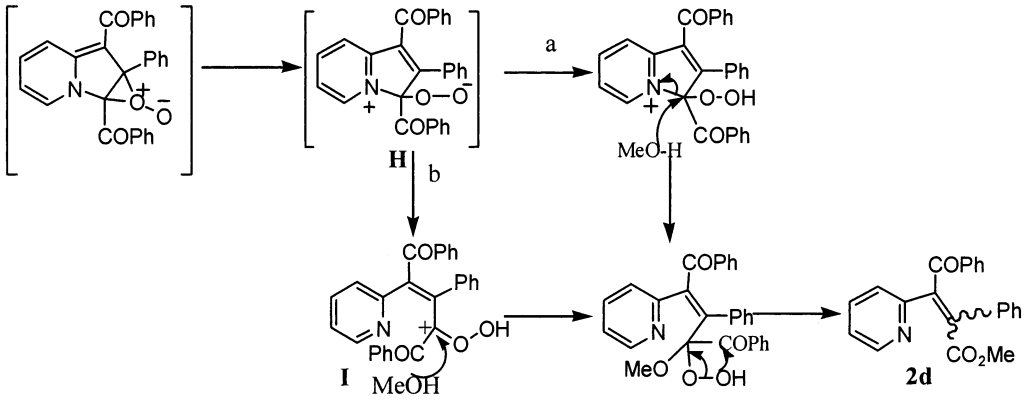
[a] Only the atomic coefficients for the atoms at the indolizine nucleus are listed.

C3 is always the carbon atom with the highest electron density and with the largest atomic coefficient in the HOMO, and it should be the preferential site of attack by an electrophile such as singlet oxygen. The photooxygenation results can be rationalized by the involvement of peroxidic zwitterion intermediate **D** (Scheme 1), which can be formed by electrophilic attack of singlet oxygen at C3 or derived from preformed perepoxide exciplex **C** (vide infra).

Nucleophilic attack at C3 by methanol and hemolytic O−O bond cleavage in zwitterion **D** resulted in the formation of **2** and **3**. Alternatively, in the aprotic solvent acetonitrile where zwitterions **D** could not be protonated, transformation of **D** into dioxetane **E** is favored, and this is followed by O−O bond homolytic scission to furnish oxirane **6**. This later pathway operates preferentially in the absence of methanol as a nucleophile when the reactions are carried out in acetonitrile. Furanones **4** are formed by cyclization via intramolecular nucleophilic attack of the carboxy group at the benzoyl carbonyl in acrylic acid **F** (Scheme 1), which in turn is formed by attack of the trace amount of water in the solvent on peroxidic zwitterions **D**. This is substantiated by a control experiment in which photolysis of a solution of **1a** in methanol−$H_2O$ (10:1, v/v) under oxygen purging gave **4a** as the sole product.

A possible pathway to zwitterionic intermediate **D** is from cyclic perepoxide **C** (Scheme 1). Figure 1 shows the FMOs of **1a** as an example. In singlet oxygen reactions with alkenes, the HOMO (alkene)−LUMO ($^1\Delta_g$ $O_2$) interaction is always predominant over the LUMO (alkene)−HOMO ($^1\Delta_g$ $O_2$) interaction because of the electrophilic character of the singlet oxygen. Figure 1 shows that, in the HOMO of the indolizine, the atomic coefficients at C9 and C3 always have opposite signs, while those at C2 and C3 are always of the same sign. Nevertheless, the absolute magnitude at C9 is larger than that at C2 in all cases. Therefore, FMO interaction consideration allows the formation of endoperoxide **A** and cyclic perepoxide **C** intermediates (Scheme 1), with the former being more favored. However, it has been known that, in singlet oxygen reactions of alkenes, solvent acidity plays an important role in deciding the [4 + 4] and [4 + 2] intermediate distribution. Protic solvents

**SCHEME 2**




such as methanol, or aprotic solvents with added acid (e.g., benzoic acid), promote the formation of the [2 + 2] intermediate derived from a cyclic perepoxide in equilibrium with the peroxidic zwitterions, at the cost of the [4 + 4] intermediate.[24] In the photooxygenation of **1a**, **1b**, and **1d**, products directly derived from endoperoxide **A** such as **B** were not found. These results may lend themselves as further evidence to show that, in the photooxygenation in methanol, the protic alcoholic solvent favors the formation of cyclic perepoxide **C** at the expense of endoperoxide **A**, while **C** is in equilibrium with zwitterions **D**. In acetonitrile, the involvement of unstable endoperoxide **A** could not be excluded, which can also transform into zwitterions **D** and dioxetane **E**.

Here, it is interesting to compare the reaction patterns in the singlet oxygen reactions of indolizine and indole, which are isoelectronic to each other and are both annulated pyrroles. The singlet oxygen reactions of these two heterocycles share the common mechanistic feature of having a peroxidic zwitterion as the intervening intermediate leading to the products. However, since, in both indolizine and indole, C3 is the carbon atom with the highest electron density, 1,4-peroxidic zwitterions **G** (Scheme 1) are formed in the indole reaction,[2,23] while 1,6-zwitterion **D** is formed in the indolizine reaction. These zwitterions result in different subsequent reaction pathways. In the case of indole, the peroxidic zwitterion is intercepted by alcohol to give 2-methoxy-3-indolinone as a trapping product when the reaction is carried out in methanol. In acetonitrile, another indole molecule serves as a nucleophile to attack the C2 atom in zwitterion **G** (Scheme 1) to lead to dimeric product.[2,23] In the case of indolizine, trapping of zwitterion **D** by methanol results in C3−N bond cleavage to give the methyl ester of 3-(2-pyridinyl)propenoate, while, in acetonitrile, the main products are formed by the thermal decomposition of the dioxetane intermediate derived from zwitterion **D** and endoperoxide **A**.

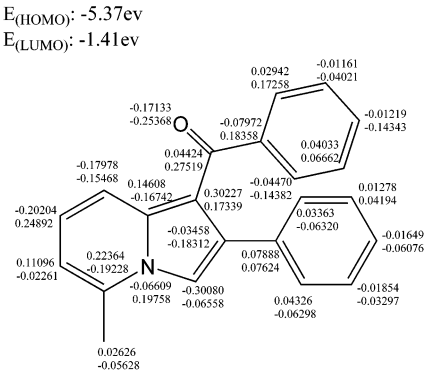



**FIGURE 1.** FMOs of **1a**. Atomic orbital coefficients in the HOMO (the upper number) and LUMO (the lower number).

In the case of **1d**, the benzoyl at C3 in the starting material is lost in product **2d**. This fact can also be accounted for by the intervention of peroxidic zwitterion **H**, which is derived from the electrophilic attack of singlet oxygen at C3 or from a perepoxide intermediate (Scheme 2). Methanol trapping of zwitterions **H** (pathway a) or cleavage of the C3−N bond followed by methanol trapping of tertiary carbocation **I** (pathway b) and subsequent O−O bond hemolytic cleavage gave **2d**.

Photooxygenations of 1-(*p*-nitrobenzoyl)-2-phenyl-5-methylindolizine (**1c**) and 2-phenyl-3-(*p*-chlorobenzoyl)-indolizine (**1e**) are extremely sluggish with direct irradiation of the indolizine in oxygen saturated solution with light of $\lambda > 400$ nm, and they need sensitization. Presumably, these more electron deficient indolizines are less reactive than **1a**, **1b**, and **1d**, and higher concentrations of singlet oxygen produced by more efficient sensitizers are needed. Photolysis of **1c** with methylene blue (MB) as a sensitizer in methanol−acetonitrile (1:1, v/v) gave (*E*)-3-(6-methyl-2-pyridinyl)-3-(*p*-nitrobenzoyl)-2-phenyl arcylate (**2c**) (35%), its (*Z*)-isomer **3c** (10%), and furan-2-one **4c** (44%) (Table 1). MB sensitized photooxygenation of **1e** in methanol−acetonitrile (1:1, v/v) furnished ester **2e** (73%) together with *p*-chlorobenzoic acid (29%). Similar MB sensitized reactions of **1e** in acetonitrile gave **6e** (81%). The singlet oxygen reactions of **1c** follow the same mechanism as those of **1a** and **1b** (Scheme 1), while the reaction of **1e** takes place by a similar pathway to that of **1d** (Scheme 2).

The participation of singlet oxygen in these reactions was further substantiated by a quenching experiment. The photooxygenation of **1** was found to be quenched by added DABCO as a $^1\Delta_g$ $O_2$ physical quencher. In the presence of $5 \times 10^{-3}$ mol $L^{-1}$ DABCO, the photooxygenation was completely quenched.

In contrast to **1a**−**1e**, 1,3-disubstituted indolizine **1f** is inert toward singlet oxygen and cannot undergo photooxygenation under either self-sensitized or RB/MB

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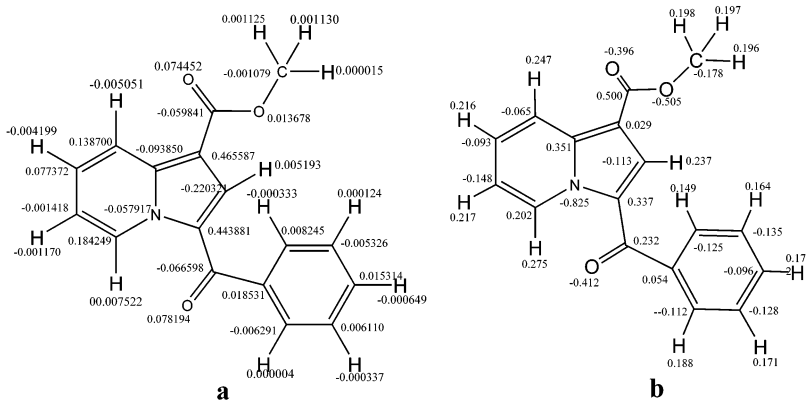
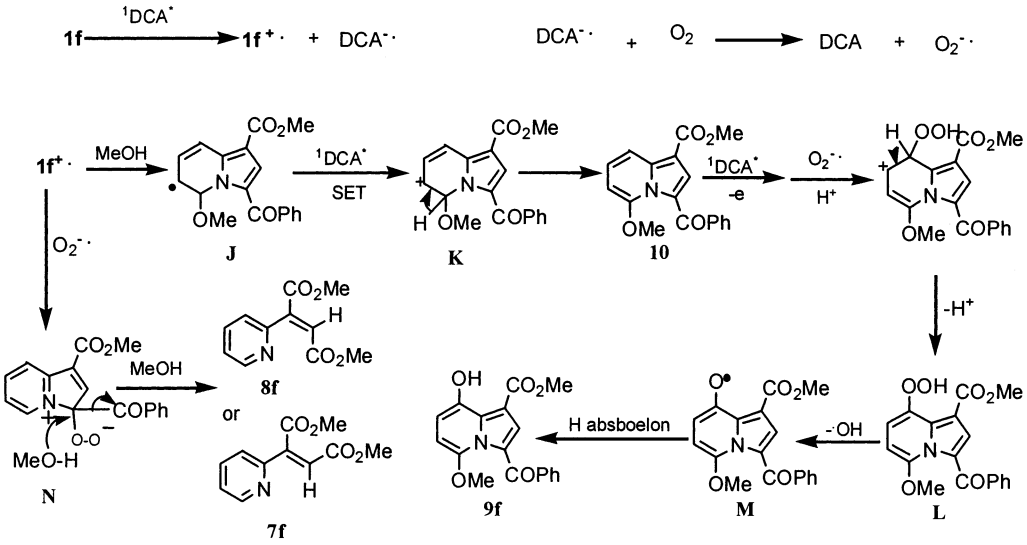



**FIGURE 2.** (a) Charge and (b) spin density distributions in the cation radical of **1f**$^{\bullet+}$.

**SCHEME 3**




sensitized conditions. However, we have found that **1f** can be smoothly photooxygenated with 9,10-dicyanoanthracene (DCA) as a sensitizer under electron transfer conditions.[25,26] Photolysis of **1f** (0.025 mol $L^{-1}$) in the presence of DCA ($10^{-4}$ mol $L^{-1}$) in methanol−acetonitrile (1:1, v/v) under oxygen atmosphere gave the nucleus oxidized methyl 3-benzoyl-8-hydroxy-5-methoxyindolizine-1-carboxylate (**9f**) (27%) and a mixture of dimethyl 2-(2-pyridinyl)maleate (**7f**) and dimethyl 2-(2-pydidinyl)-fumarate (**8f**) (total yield 63%, isomer ratio ∼ 97:3). Although in oxygen saturated solutions DCA can sensitize the formation of singlet oxygen via energy transfer from both $^1$DCA* and $^3$DCA* to triplet oxygen,[26] the active oxygen species in the DCA sensitized photooxygenation of singlet oxygen inert **1f** is the superoxide anion radical formed by electron transfer from the DCA anion radical to triplet oxygen which is exothermic for −5 kcal $mol^{-1}$.[25c]

The formation of products **7f**−**9f** could be rationalized by the electronic structure in the cation radical of **1f**. We have calculated the charge and spin densities in **1f**$^{\bullet+}$ with the DFT method at the UB3LYP 6-31G level, and the results are given in Figure 2. One can see that C3 is the carbon atom with the largest spin density and should be the preferential site for radical pair recombination with the superoxide anion radical. This leads to zwitterions **N** (Scheme 3), which upon methanol trapping and O−O bond homolysis furnish **7f** and **8f**. A possible mechanism of the formation of **9f** may involve methanol trapping of the carbocation at C5 and further oxidation of the radical center in **J** into carbocation **K** followed by proton loss to furnish methoxy-substituted indolizine **10**, which is an even better electron donor than **1f**. Further electron transfer from **10** to $^1$DCA* and subsequent **10**$^{\bullet+}$−$O_2^{\bullet-}$ recombination (or, alternatively, trapping of the radical center in **10**$^{\bullet+}$ by triplet oxygen) followed by proton loss gave hydroperoxide **L**, and O−O bond homolysis in **L** resulted in the formation of product **9f**.

In summary, singlet oxygen reactions of indolizines **2a**−**2e**, with 1,2-, 2,3-, and 1,2,3-substituents, follow the general reaction pattern by initial attack of singlet oxygen at the C3 atom in indolizine to give a 1,6-peroxidic zwitterion intermediate. However, subsequent reaction pathways and products are decided by the solvent. In

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methanol, this peroxidic zwitterion is intercepted by the alcohol at the C3 atom to lead to C3−N bond cleavage to furnish the methyl 3-(2-pyridinyl)propenoates. In acetonitrile, dioxetane in equilibrium with the peroxidic zwitterion is the intervening intermediate leading to the products. O−O bond homolysis in the dioxetane gives 3-(2-pyridinyl)-2-oxiranecarboxaldehyde as the product. Electron deficient and singlet oxygen inert **1f** can be photooxygenated under electron transfer conditions via its cation radical to give the 2-(2-pyridinyl)-2-butenedioic acid dimethyl esters and pyridine ring oxidized 8-hydroxy-5-methoxyindolizine.

## Experimental Section

**General Procedures for the Photooxygenation of 1a−1f.** The light source was a medium-pressure mercury lamp (500 W) in a cooling water jacket which was further surrounded by a filter solution (1 cm thickness, 10% aq sodium nitrite for $\lambda > 400$ nm and 10% aq potassium dichromate for $\lambda > 500$ nm). The solution of indolizines (0.025 mol $L^{-1}$) in acetonitrile or acetonitrile−methanol (1:1, v/v) was placed in glass tubes (30 mL each) and was irradiated at room temperature under continuous oxygen purging. Photooxygenation of **1a**, **1b**, and **1d** was self-sensitized, **1c** and **1e** were sensitized by RB or MB, while **lf** was sensitized by DCA. At the end of the reaction (TLC monitoring), the solvent was removed in vacuo and the residue was separated by chromatography on a silica gel column except in the case of photooxygenation of **1a** in MeCN, where the reaction mixture was separated by preparative thin-layer chromatography at a temperature below 5 °C to afford products **5a** and **6a**. The reaction scale, irradiation time, and yields of the products are given below.

**Determination of Fluorescence Quantum Yield of Compounds 1b, 1d, and 1f.** The fluorescence quantum yields of compounds **1a**, **1d**, and **1f** were determined on a fluorescence spectrophotometer in acetonitrile solution with 9,10-diphenylanthracene ($\Phi_F = 0.95$) as a standard. Phosphorescence spectra of **1a**, **1d**, and **1f** were measured on the same spectrophotometer in acetonitrile at 77 K.

**Electronic Spectra of 1a in the Presence and Absence of Oxygen.** An acetonitrile solution of **1a** (0.028 M) was divided into two parts. Through one solution was purged dry oxygen for 1 h, and through the other solution was purged dry argon for 1 h. The electronic spectra of these two solutions were then measured in the 495−600 nm region.

**Calculation Method.** FMOs of compounds **1a**−**1e** are calculated by the DFT method at the B3LYP 6-31G level, and the charge and spin densities in the cation radical of **1f** are calculated by the DFT method at the UB3LYP 6-31G level with Gaussian 98 6.0 A.[27]

**Photooxygenation of 1a. (a) In MeCN−MeOH.** Photolysis of **1a** (1.40 g, 4.5 mmol) in MeCN−MeOH (180 mL, 1:1, v/v) under oxygen purging for 9 h (100% conversion) gave **2a** (353 mg, 22%), **3a** ( 369 mg, 23%), and **4a** (617 mg, 40%).

**(b) In MeCN.** Photolysis of **1a** (0.600 g, 1.9 mmol) in MeCN (180 mL) under oxygen purging for 10 h (100% conversion) gave **5a** (112 mg, 25.3%) and **6a** (423 mg, 63.7%).

**Photooxygenation of 1a with Light of $\lambda > 300$ nm.** Photolysis of a solution of **1a** (1.00 g, 3.2 mmol) in MeOH−MeCN (130 mL, 1:1, v/v) with light of $\lambda > 300$ nm with oxygen purging for 9 h (100% conversion) and workup as before gave **2a** (286 mg, 25%), **3a** (275 mg, 24%), and **4a** (418 mg, 38%).

**Photooxygenation of 1b. (a) In MeCN−MeOH.** Photolysis of **1b** (1.53 g, 4.5 mmol) in MeCN−MeOH (180 mL, 1:1, v/v) under oxygen purging for 8 h (100% conversion) gave **2b** (488 mg, 28%), **3b** (557 mg, 32%), and **4b** (151 mg, 9%).

**(b) In MeCN.** Photolysis of **1a** (1534 mg, 4.5 mmol) in MeCN (180 mL) under oxygen purging for 10 h (100% conversion) gave **5b** (126 mg, 11%) and **6b** (1041 mg, 62%).

**Photooxygenation of 1c. (a) In MeCN−MeOH.** Irradiation of a MeCN−MeOH solution (180 mL, 1:1, v/v) of **1c** (0.800 g, 2.25 mmol) and MB (30 mg) with oxygen purging for 8 h (100% conversion) gave **2c** (317 mg, 35%), **3c** (100 mg, 11%), and **4c** (384 mg, 44%). Compound **2c** can be isomerized to **3c** on a silica gel column. Therefore, the two compounds were collected together as one fraction during the chromatographic separation. The yields given here are determined from the $^1$H NMR spectrum of the product mixture.

**(b) In MeCN.** Irradiation of a MeCN solution (120 mL) of **1c** (1.00 g, 2.81 mmol) and RB (30 mg) with oxygen purging for 12 h (100% conversion) gave **5c** (150 mg, 20%) and **6c** (320 mg, 31%).

**Photooxygenation of 1d. (a) In MeCN−MeOH.** Photolysis of **1d** (0.900 g, 2.25 mmol) in MeCN−MeOH (180 mL, 1:1, v/v) with oxygen purging for 12 h (100% conversion) gave **2d** (548 mg, 71%).

**(b) In MeCN.** Photolysis of **1d** (0.900 g, 2.25 mmol) in MeCN (180 mL) with oxygen purging for 14 h (100% conversion) gave **6d** (877 mg, 90%)

**Photooxygenation of 1e. (a) In MeCN−MeOH.** Irradiation of a MeCN−MeOH solution (180 mL, 1:1, v/v) of **1e** (0.773 g, 2.25 mmol) and MB (30 mg) with oxygen purging for 10 h (100% conversion) gave **2e** (393 mg, 73%).

**(b) In MeCN.** Irradiation of a MeCN solution (180 mL) of **1e** (773 mg, 2.25 mmol) and MB (30 mg) with oxygen purging for 11 h (100% conversion) gave **6e** (439 mg, 81%).

**Photooxygenation of 1f. In MeCN−MeOH.** Irradiation of a MeCN−MeOH solution (180 mL, 1:1, v/v) of **1f** (627 mg, 2.25 mmol) and DCA (10 mg) with oxygen purging for 20 h (64% conversion) gave **7f** and **8f** (201 mg, 63%, **7f**/**8f** = 97:3) and **9f** (126 mg, 27%).

**Crystal Structure of Compound 2a.** $C_{23}H_{19}NO_3$, $M$ = 357.39. Monoclinic, space group $C2/c$ with $\alpha = 90.00°$, $\beta = 92.2420\ (10)°$, $\gamma = 90.00°$, $a = 8.3158\ (4)$ Å, $b = 15.9641\ (7)$ Å, $c = 28.9518\ (13)$ Å, $V = 3840.5\ (3)$ Å$^3$, $Z = 8$, $D_c = 1.236$ g cm$^{-3}$, $\mu = 0.082$ mm$^{-1}$, and $F(000) = 1504$. A colorless prismatic crystal of 0.7 × 0.5 × 0.24 mm$^3$ was used. Data were collected on an area detector diffractometer with graphite monochromated Mo Kα ($\lambda = 0.710\ 73$ Å) radiation in the range $2\theta = 2.55−28.28°$. The structure was solved by the direct method (SHELXL-97) and refined on $F^2$ by the full-matrix least-squares method. A total of 4695 independent reflections [$R$(int) = 0.0159 ] were used in the refinement which converged with $R = 0.0514$ and $R_w = 0.1270$.

**Crystal Structure of Compound 4a.** $C_{22}H_{17}NO_3$, $M$ = 343.37. Monoclinic, space group $P21/c$ with $\alpha = 90.00°$, $\beta = 90.600\ (1)°$, $\gamma = 90.00°$, $a = 17.5447\ (1)$ Å, $b = 10.6953\ (1)$ Å, $c = 18.3776\ (2)$ Å, $V = 3448.29\ (5)$ Å$^3$, $Z = 8$, $D_c = 1.327$ g cm$^{-3}$, $\mu = 0.088$ mm$^{-1}$, and $F(000) = 1448$. A colorless prismatic crystal of 0.32 × 0.22 × 0.14 mm$^3$ was used. Data were collected on an area detector diffractometer with graphite monochromated Mo Kα ($\lambda = 0.710\ 73$ Å) radiation in the range $2\theta = 2.50−28.50°$. The structure was solved by the direct method (SHELXL-97) and refined on $F^2$ by the full-matrix least-squares method. A total of 5972 independent reflections [$R$(int) = 0.1201] were used in the refinement which converged with $R = 0.0721$ and $R_w = 0.1730$.

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**Supporting Information Available:** General experimental conditions, crystallographic information files of compounds **2a**, **4a**, **3b**, **3c**, and **2d**, crystallographic structure of **2a**, **3a**, **3b**, **5a**, **6d**, and **9f**, analytical and spectroscopic data for all new compounds, $^{1}$H NMR spectra of all photooxygenation products, $^{13}$C NMR of **6c**, UV spectra of compounds **1a** and **1b**, UV spectra of **1a** in the presence and absence of oxygen, and phosphorescence spectra of **1b**, **1d**, and **1f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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