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Photooxidation of Alkaloids: Considerable Quantum Yield Enhancement by Rose Bengal-sensitized Singlet Molecular Oxygen Generation

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ABSTRACT

The photooxidation of sanguinarine, coralyne and berberine was studied in oxygenated alkaline methanol solutions. Rose bengal as photosensitizer significantly accelerates the process, indicating the importance of singlet molecular oxygen in the reaction mechanism. The quantum yield of sensitized oxidation was found to increase significantly with pH and reaches 0.4 for berberine at pH 13.8. The direct oxidation of alkaloids is less efficient, the quantum yield does not exceed 0.01 even in oxygen-saturated solutions. The photoinduced electron ejection does not play a role in the oxidation. The uncharged pseudobase forms, which are present in alkaline medium, are oxidized much more easily than the alkaloid cations.

INTRODUCTION

Despite the large biological and pharmaceutical importance of alkaloids, the mechanistic details of their photoinitiated processes are still largely unknown. Alkaloids, such as berberine, coralyne (1–17) and sanguinarine (18–24), are sensitive to light and can induce adverse phototoxic reactions. The solvent and molecular structure variations markedly affect the quantum yield of singlet molecular oxygen, $O_2(^1\Delta_g)$ generation (5–7,16). The quantum yields of triplet and $O_2(^1\Delta_g)$ formation strongly diminish with increasing polarity of the environment in the cases of berberine, palmitine and sanguinarine, but are barely changed for coralyne (16). Binding to DNA significantly enhanced the efficiency of the berberine-sensitized formation of $O_2(^1\Delta_g)$ (11,12) and coralyne initiates easily the photochemical DNA damage (9). The photoinduced processes of berberine have been examined most intensively (5–7). The transients produced upon exposure to UV light were identified by laser flash photolysis (13,14,16), whereas the short-lived intermediates of the reaction between berberine and strongly oxidizing or reducing species were examined by pulse radiolysis (17).

The photoirradiation of various alkaloids in the presence of triethylamine results in dihydroalkaloids, which were back-converted on admission of oxygen (16). The rate of photoreduction is significantly accelerated by the combined utilization of a ketone with triethylamine or alcohol as photoinitiators and a quantum yield of close to unity was achieved for dihydroalkaloid formation (16).

Knowledge of the oxidation processes of natural isoquinoline alkaloids is scarce. 8-Oxoberberine was synthesized by oxidation of berberine (25). For sanguinarine in alkaline media, a conversion of the alkanolamine form to oxysanguinarine was performed photochemically and the fluorescence signal of sanguinarine in water at pH 11 is unstable due to an oxidative photoreaction (21,24). The photooxidation followed second-order kinetics and inclusion complex formation of sanguinarine with cucurbit[7]uril significantly inhibits any reaction (24). It was demonstrated that electron transfer to $O_2(^1\Delta_g)$ plays an important role in the oxidation of indol alkaloids (26). The reactions of $O_2(^1\Delta_g)$ with biologically active heteroaromatics such as dihydropterins (27), purine nucleotides (28), folic acid (29,30) and other oxidized pterins (31) have also attracted considerable attention.

The main goal of the present work was to reveal the reaction mechanism of the photooxidation of sanguinarine, berberine and coralyne in alkaline media. To examine whether $O_2(^1\Delta_g)$ plays an important role in the oxidation, rose bengal was used as a sensitizer.

MATERIALS AND METHODS

Berberine (Sigma), coralyne (Acros) and sanguinarine (Fluka) as chloride salts were used as received. The solvents (Merck) were of the purest spectroscopic quality. The absorption spectra were monitored on a spectrophotometer (HP, 8453). The molar absorption coefficients of coralyne and sanguinarine in (m)ethanol were taken as $\varepsilon_{420} = 1.5 \times 10^5$ and $\varepsilon_{327} = 3.1 \times 10^4$ M^{-1} cm^{-1}, respectively. The initial rate of photoreactions was determined from the changes in absorbance. The number of absorbed photons was measured using the aberchrome 540 actinometer as reference (32). The quantum yield Φ_{ox} of photooxidation was calculated as a ratio of these quantities. For the sensitized cases, 0.1, 0.2 or 1 cm cells and the tail of the Hg-lamp spectrum above 500 nm were used (33). At constant rose bengal concentration and the same irradiation conditions, the initial rates of the alkaloid photooxidation were compared to that of a reference reaction having a known quantum yield. For this, the rose bengal-sensitized oxidation of 0.2 mM 5-hydroxy-1-naphthol in air-saturated methanol was used, whose quantum yield is $\varphi_{sen} = 0.003$ (34). Alternatively, the rose bengal-sensitized oxidation of 1 mM 1-naphthol to 1,4-naphthoquinone in a methanol and water 1:30 mixture at pH 10 was also used as a reference with $\varphi_{sen} = 0.25$ (33). On the basis of many experiments with the same method for various compounds, a conservative

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*Corresponding author email: biczok@chemres.hu (László Biczók) estimate of the experimental error of the quantum yield determinations is ±30%. For photoinduced oxygen consumption measurements a Clark cell was used (33). An excimer laser (Lambda Physik, EMG 200, pulse width of 20 ns and energy of < 30 mJ) was used for excitation at 308 nm (33).

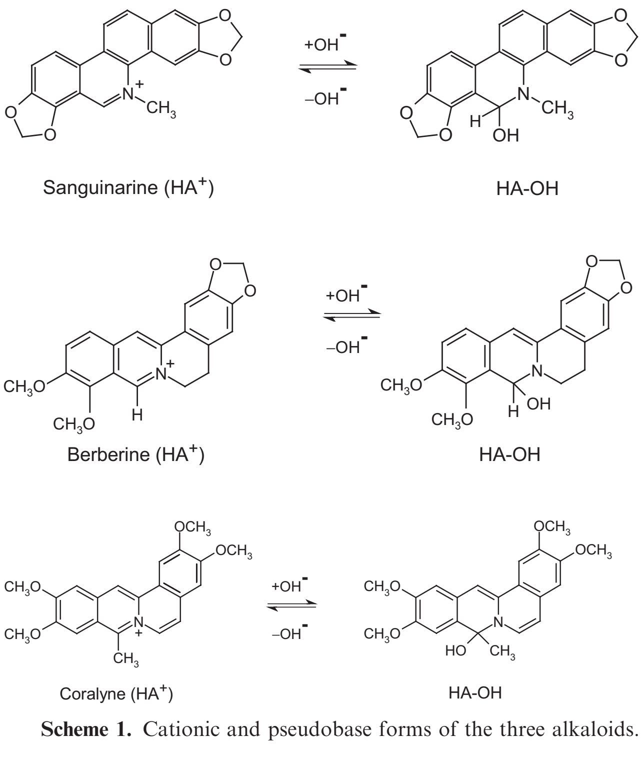
RESULTS AND DISCUSSION

Ground state of alkaloids

The absorption spectra of sanguinarine in a 9:1 mixture of methanol and water change with pH in a manner that the orange color disappears on going to higher pH and the maximum is shifted from 320 to 290 nm. The equilibrium between the iminium and alkanolamine forms is due to the introduction of the OH^- group at position 6, where HA-OH is the pseudobase with the $pK_a = 7.14$ value in water (24), see Scheme 1.

$$HA^+ + OH^- \rightleftharpoons HA\text{-}OH \tag{1}$$

Addition of saturated NaOH aqueous solution to berberine in water leads to the corresponding pseudobase (35). For the analogous methoxide adduct formation of berberine in methanol, $pK_a = 15.4$ has been reported (36). For the addition of OH^- to berberine in methanol–water mixtures, the pK_a is probably smaller. Note that the alkaloids are not stable in aqueous solution at pH > 12, but coralyne and berberine are stable in NaOH plus methanol for several minutes, a timeframe during which our spectrophotometric and quantum yield measurements were completed. The water-induced decomposition at pH > 12 may be a ring opening. Reversible addition of OH^- followed by ring opening has been reported for coralyne (37).



Scheme 1. Cationic and pseudobase forms of the three alkaloids.

Photoirradiation of sanguinarine

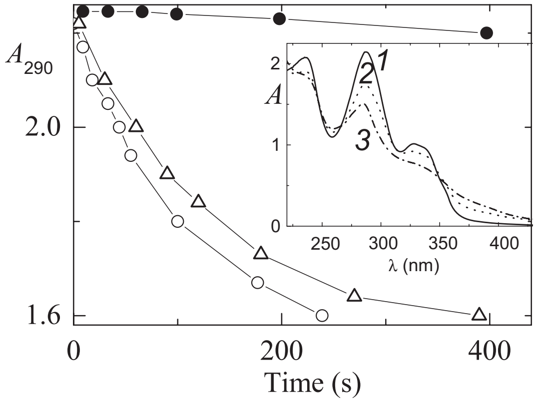


Figure 1. Plots of A_{290} as a function of the time of 313 nm irradiation of sanguinarine in argon- (●), air- (Δ) and oxygen-saturated (○) methanol–water (9:1, vol) at pH 8. Inset: absorption spectra in oxygen-saturated solution at 0, 60 and 180 s irradiation at 313 nm, *1–3*, respectively.

The inset to Fig. 1 shows the alteration of the absorption spectra of sanguinarine upon irradiation at 313 nm in methanol–water (9:1, vol) mixtures at pH 8. A gradual absorbance diminution around 290 nm is accompanied by the concomitant rise of the absorption in the 355–400 nm range. Several isosbestic points indicate that secondary photolysis does not occur. The main photoproduct has been identified as 6-oxysanguinarine (21) (Scheme 2). A very slow reaction takes place in argon-saturated solution, but a significant rate enhancement was found in the presence of air and especially under oxygen saturation. Table 1 summarizes the quantum yields of photooxidation (Φ_{ox}) derived from the initial slope of the absorbance changes at 290 nm (A_{290}) during photolysis. It is seen that Φ_{ox} remains below 0.01 under all conditions. The primary step of photooxidation can be the formation of singlet oxygen, $O_2(^1\Delta_g)$ or the solvated electron (e_{solv}^-). The former is analogous to the sensitized oxidation of different related types of heteroaromatics, *e.g.* dihydropterins (27), folic acid (30) and alkaloid tertiary amines (26). In fact, photoinduced radical cation and e_{solv}^- formation initiates the oxidation of phenols (33). In the ionization reaction sequence 2–4, e_{solv}^- is converted into the superoxide radical, $O_2^{\bullet-}$, which then reacts with the HA-O• radical produced in the primary photoprocess.

$$HA\text{-}OH\ +\ h\nu \rightarrow HA\text{-}OH^{\bullet+} \rightarrow +e_{solv}^- \rightarrow HA\text{-}O^\bullet + H^+ + e_{solv}^- \tag{2}$$

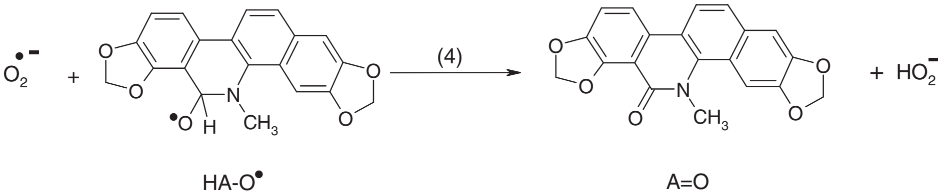
$$e_{solv}^- + O_2 \rightarrow O_2^{\bullet-} \tag{3}$$

$$HA\text{-}O^\bullet + O_2^{\bullet-} \rightarrow A{=}O\ +\ HO_2^- \tag{4}$$

Table 1. Quantum yield Φ_{ox} of direct photooxidation of alkaloids*

		Φ_{ox}		
Alkaloid	pH	Argon	Air	O_2
Sanguinarine	5	< 0.0001	0.003	0.0005
	8			0.005
	12			0.004
Berberine	12	< 0.0001		0.004
Coralyne	8	< 0.0001	0.008	< 0.001
	12			0.010

*In MeOH–H_2O, 9:1, $\lambda_{irr} = 313$ nm.



Scheme 2. Reaction 4 of sanguinarine.

This reaction mechanism may be valid for the alkanolamine form of sanguinarine (HA-OH), Scheme 2.

An alternative reaction mechanism is the $O_2(^1\Delta_g)$-mediated oxidation, as shown in Scheme 3. Here, $O_2(^1\Delta_g)$ is produced by energy transfer from triplet sanguinarine and reacts with the sanguinarine pseudobase (HA-OH in step 5), resulting in a radical cation and $O_2^{\bullet-}$. The rate constant of this process (k_5) is unknown, but for related cases k_5 is $(0.01–1) \times 10^9$ M^{-1} s^{-1} (33,34).

$$O_2(^1\Delta_g) + \text{HA-OH} \rightarrow O_2^{\bullet-} + \text{HA-OH}^{\bullet+} \qquad (5)$$

$$\text{HA-OH}^{\bullet+} \rightarrow +\text{HA-O}^{\bullet} + H^+ \qquad (6)$$

$$\text{HA-O}^{\bullet} + O_2(^1\Delta_g) \rightarrow \text{A=O} + O_2^{\bullet-} + H^+ \qquad (7)$$

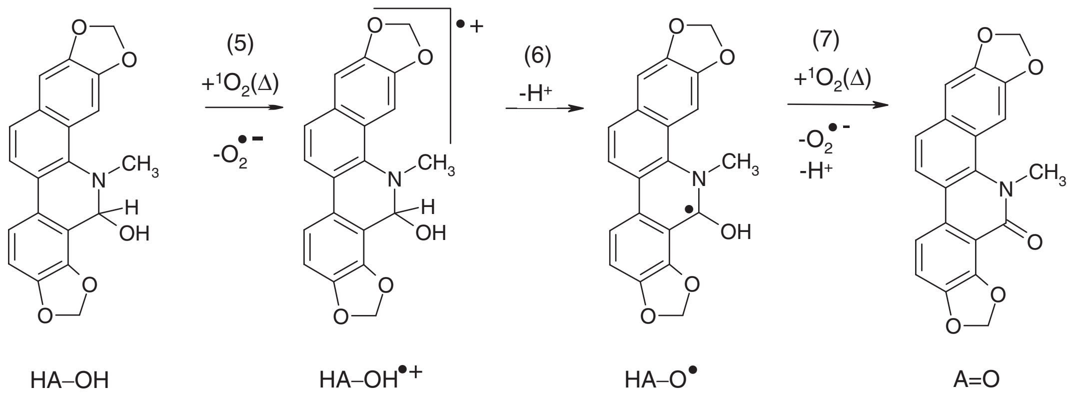
$$2O_2^{\bullet-} + 2H_2O \rightarrow H_2O_2 + O_2 + 2OH^- \qquad (8)$$

After deprotonation of the radical cation ($\text{HA-OH}^{\bullet+}$, step 6), a second electron transfer (step 7) can occur from the HA-O• radical to $O_2(^1\Delta_g)$, which, after deprotonation, leads eventually to the stable A=O keto-product. The formed superoxide radicals ($O_2^{\bullet-}$) undergo disproportionation in the presence of water resulting in hydrogen peroxide (step 8). Since no evidence was found for e_{solv}^- formation by laser flash photolysis and the sensitized $O_2(^1\Delta_g)$ production promotes the photooxidation (*vide infra*), the reaction mechanism displayed in Scheme 3 seems to be the correct one.

Irradiation of coralyne and berberine

Irradiation of coralyne at 313 nm in oxygen-saturated methanol–water (9:1, vol) leads to significant absorption diminution in oxygen-saturated solution above pH 10 (Fig. 2), but the quantum yield of this photoreaction in the absence of oxygen is very small at pH 6–10 (Table 1). The most efficient photooxidation is achieved at pH 12 ($\Phi_{ox} = 0.01$). Coralyne is unstable above pH 12 due to the conversion to 6′-acetylpapaverine in a reversible process (37). The first step of this reaction is addition of OH^- at the 8th position (Scheme 1). The more than one order of magnitude increase of Φ_{ox} when pH is changed from 8 to 12 implies the important role of the OH^- adduct in the photooxidation. At pH 8, coralyne is present in the cationic form that is difficult to oxidize. The extent of conversion from the cationic form to the adduct increases with the OH^- concentration. As the uncharged species (coralyne-OH) is more prone to oxidation, a substantial rise of Φ_{ox} is expected and indeed found at pH 12. Transient absorption could not be detected by laser flash photolysis in the 1–2 μs range because of the strong fluorescence of coralyne. No solvated electron absorption was found after disappearance of this strong fluorescence signal (*ca* 1 μs). Therefore, the first reaction step cannot be photoionization.

Berberine was also photooxidized upon exposure to 313 nm light at pH 12 in oxygen-saturated 9:1 MeOH–H_2O mixtures and $\Phi_{ox} = 0.004$ was found (Table 1). To test the possibility of photoionization, laser flash photolysis with 308 nm pulses was carried out. Despite the large molar absorption coefficient of the solvated electron ($\varepsilon_{700} = 1.5 \times 10^4$ M^{-1} cm^{-1}), no significant absorption was detected at 700 nm, indicating a negligible yield of electron photoejection. For the structurally similar palmatine, photoinduced $O_2^{\bullet-}$ formation has been suggested (6). The quantum yield of singlet molecular oxygen production is in the 0.39–0.42 range, irrespective of the solvent polarity for coralyne, but low (< 0.05) for berberine in polar solvents (16). The low Φ_{ox} values at pH 8–12 (Table 1) indicate a too low reactivity (*i.e.* k_5 is small) rather than a correlation with the quantum yield of intersystem crossing (Φ_{isc}). If Φ_{isc} controlled the yield of oxidation, Φ_{ox} of coralyne would be much larger than that of berberine, which is not the case (Table 1).



Scheme 3. Reactions 5–7 of singlet molecular oxygen with sanguinarine.

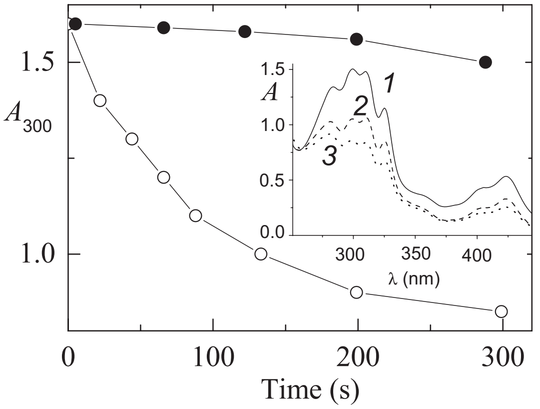


Figure 2. Plots of A_{300} as a function of the time of 313 nm irradiation of coralyne in argon- (●) and oxygen-saturated (○) methanol–water (9:1, vol) at pH 11. Inset: spectra in oxygen-saturated solution at 0, 90 and 300 s irradiation at 313 nm, *1–3*, respectively.

Sensitized irradiation of sanguinarine

To confirm the essential role of $O_2(^1\Delta_g)$ in the photooxidation of alkaloids, rose bengal was chosen as a sensitizer. Lambert and Kochevar provided evidence for the very inefficient formation of $O_2^{\bullet-}$ *via* electron transfer from triplet rose bengal to O_2 and concluded that this process has a negligible rate compared to the energy transfer from triplet rose bengal to O_2 producing $O_2(^1\Delta_g)$ (38). When rose bengal was irradiated at 500–560 nm in the presence of both oxygen and 0.1 mM sanguinarine in 99:1 methanol–water mixtures at pH 8–10, the spectral change increased with the oxygen concentration, but the quantum yields of the sensitized oxidation (φ_{sen}) even in air- and oxygen-saturated solutions remained small (Table 2). Figure 3 displays the spectra together with the absorbance change at 280 and 380 nm as a function of the time of irradiation (inset). We propose that the sensitized oxidation of the sanguinarine alkanolamine form follows the mechanism shown in Scheme 4. The reaction sequence involves the radical cation HA-OH$^{\bullet+}$, the radical HA-O$^{\bullet}$ and two molecules of $O_2(^1\Delta_g)$.

Table 2. Quantum yield φ_{sen} of rose-bengal-sensitized oxidation of alkaloids*

Alkaloid	pH	[Alkaloid] (mM)	φ_{sen} Air	φ_{sen} O_2
Sanguinarine	8–10	0.2	0.005†	0.007
Berberine	12.0	0.8	0.015	0.02
	13.0			0.2
	13.8		0.3†	0.4
Coralyne	12.0	0.5		0.012
	13.0		0.07†	0.1

*In MeOH–H_2O, 99:1, using λ_{irr} = 500–550 nm. †Under argon: φ_{sen} < 0.002.

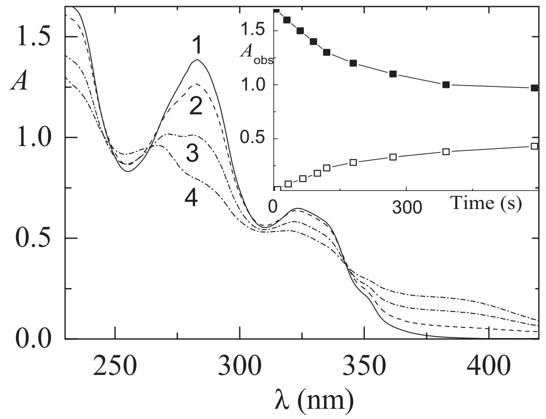
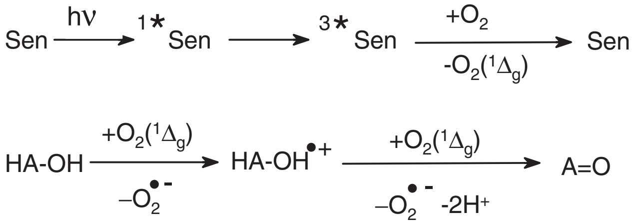


Figure 3. Absorption spectra of 0.2 mM sanguinarine in oxygen-saturated methanol–water (99:1, vol) at pH 9 after 0, 30, 90 and 180 s irradiation of rose bengal at 500–560 nm, *1–4*, respectively. Inset: plots of A_{280} (■) and A_{380} (□) as a function of the irradiation time.



Scheme 4. Formation of singlet molecular oxygen and reaction with the pseudobase forms of the three alkaloids.

Sensitized irradiation of berberine and coralyne

When rose bengal is irradiated at 500–560 nm in oxygen-saturated methanol–water (99:1, vol) at pH 11, A_{270}, A_{345} and A_{430} of berberine decrease strongly and isosbestics points at 290 and 310 nm appear. The latter indicates sensitized conversion to 8-oxyberberine (A = O) without significant formation of byproducts. Examples for spectral alteration are shown in the insets of Figs. 4 and 5. The substantial difference in the time dependences in the absence and presence of O_2 (Fig. 4) is convincing evidence for an oxygen-mediated photoreaction. The spectral changes for relatively small (0.1 mM) and large (0.8 mM) berberine concentrations are the same. The φ_{sen} values in oxygen-saturated solution are slightly larger than under air at the same OH^- concentration (Table 2), but a marked difference is not to be expected. When the pH was raised from 12 to 13.8, a considerable increase of φ_{sen} was observed reaching a value of 0.4. This effect probably indicates that the uncharged pseudobase (Scheme 1), which is produced in strongly alkaline medium in the ground state (35), can be oxidized more efficiently by $O_2(^1\Delta_g)$ than the cationic berberine. The latter form dominates at pH 12. Therefore, φ_{sen} is only 0.02 even in oxygen-saturated solution at pH 12. The amount of the easier oxidizable pseudobase grows with increasing OH^- concentration. This effect accelerates the reaction with $O_2(^1\Delta_g)$, resulting in a substantial rise of φ_{sen} with pH (Fig. 5). The decrease of φ_{sen} above pH 13.8 probably arises from the instability of the berberine pseudobase under this condition. At pH 13.8, most berberine molecules are converted to the pseudobase. Therefore, φ_{sen} reaches a maximum value of 0.4. As it can be seen in Fig. 5, φ_{sen} is very small below pH 11.5, when the solution contains negligible amounts of the pseudobase. This indicates that electron transfer to $O_2(^1\Delta_g)$ is necessary to induce sensitized

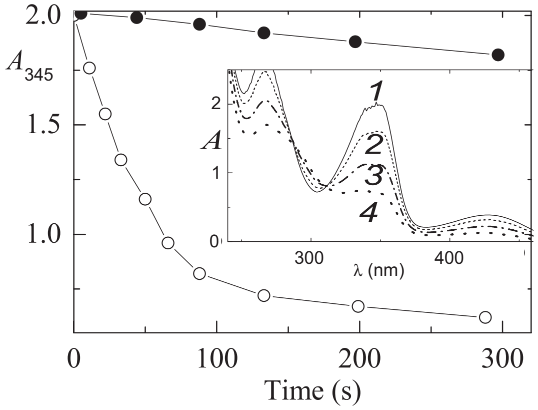


Figure 4. Plots of A_{345} as a function of the time of irradiation of rose bengal at 500–560 nm in the presence of 0.8 mM berberine in argon- (●) and oxygen-saturated (○) methanol–water (99:1 vol) at pH 11. Inset: absorption spectra at 0, 30, 60 and 180 s, *1–4*, respectively.

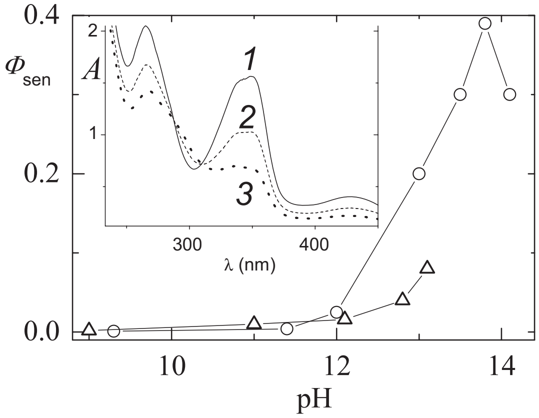


Figure 5. Plots of φ_{sen} with rose bengal as a function of the pH for berberine (○) and coralyne (Δ) in oxygen-saturated methanol–water (99:1, vol). Inset: absorption spectra of berberine at pH 13.8 and at 0, 3 and 6 s, *1–3*, respectively.

berberine oxidation. The higher oxidation potential of the berberine cation precludes electron donation to $O_2(^1\Delta_g)$. It is worth noting that φ_{sen} does not change significantly when methanol is replaced by acetonitrile in the solvent mixture as the electron transfer from the pseudobase form to $O_2(^1\Delta_g)$ remains sufficiently exothermic. The reaction of singlet oxygen with the berberine pseudobase is supported by photoinduced oxygen consumption measurements in a Clark cell. The decrease of the oxygen concentration in the pH range 11–13 in methanol containing 1–2% water corresponds to the pseudobase absorbance diminution.

The sensitized photooxidation of coralyne shows a similar behavior to that found for berberine. Fig. 5 shows that φ_{sen} values grow above pH 12 due to the increase in concentration of the pseudobase, the species that can be oxidized more readily. Because of the instability of coralyne, measurements could not be performed above pH 13. The photoreaction is efficient as long as the water content does not exceed 1%. The addition of more water reduces φ_{sen} in the case of coralyne and berberine alike. The water content probably modifies the equilibrium constant of OH^- addition to the alkaloid cation, thereby lessening the concentration of the pseudobase form.

CONCLUSIONS

The studied alkaloids are photochemically stable in neutral aqueous solution in argon atmosphere, but undergo photooxidation in the presence of oxygen. Relatively efficient oxidation occurs *via* the pseudobase form of the alkaloids. The suggested primary photochemical reaction in the oxidation process is not the electron ejection but the formation of $O_2(^1\Delta_g)$. The sensitized $O_2(^1\Delta_g)$ generation using rose bengal significantly accelerates the oxidation of coralyne and berberine. The suggested reaction mechanism involves two electron transfer steps to $O_2(^1\Delta_g)$. The substantial increase of the quantum yield of photooxidation with pH is due to formation of the pseudobase, which more readily accepts an electron from $O_2(^1\Delta_g)$ than the cationic alkaloid.

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