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Solvent effects on reactions of singlet molecular oxygen, $O_2(^1\Delta_g)$, with antimalarial drugs

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Abstract

Detection of $O_2(^1\Delta_g)$ emission, $\lambda_{max} = 1270$ nm, following laser excitation and steady-state methods were employed to measure total reaction rate constants, k_T, for the reaction between singlet oxygen and the antimalarial drugs quinine (QU), quinacrine (QC), chloroquine (CQ) and amodiaquine (AQ) in several solvents. Values for k_T range from $0.45 \pm 0.03 \times 10^7$ M^{-1} s^{-1} for AQ in benzene to $25.1 \pm 0.88 \times 10^7$ M^{-1} s^{-1} for CQ in *N*,*N*-dimethylformamide. Analysis of solvent effect on k_T for QU, QC, and CQ by using the LSER formalism indicates that singlet oxygen deactivation by these drugs is accelerated by solvents with large π^* values and hydrogen bond acceptor (HBA) properties and is inhibited by hydrogen bond donors (HBD) solvents. This result support the formation of an exciplex intermediate of charge transfer character, as proposed for reactions of tertiary amines with singlet oxygen, process largely governed by physical quenching. AQ behaves in a different manner. The LSER equation for this drug shows that k_T increases in solvents with large π^* values and diminishes in HBD solvents. In this case, reaction mechanism probably involves a partially concerted cycloaddition of singlet oxygen to the aminophenolic ring in position 4.

Keywords: Antimalarial drugs; Singlet oxygen; Solvent effect; LSER; Time-resolved kinetics

1. Introduction

Many quinoline-based antimalarials posses other pharmaceutical activities as well. Some have been used successfully to treat other medical conditions such as lupus erythematosus, polymorphous light eruption, cutaneous lymphoma, and rheumatoid arthritis [1]. The majority of synthetic antimalarials derived from quinoline possess undesirable photosensitizing properties that produce phototoxic side effects in both the skin and the eye [2–4]. Cutaneous and ocular effects that may be caused by light include changes in skin pigmentation, corneal opacity, cataract formation, and other visual disturbances such as irreversible retinal damage (retinopathy), which leads to blindness [1]. The precise mechanisms for these reactions in humans remains unknown, although singlet molecular oxygen, $O_2(^1\Delta_g)$, and free radicals including superoxide/hydroperoxyl or peroxyl adduct, carbon-centered and nitrogen-centered radicals have been invoked as responsible for these phototoxic effects [5–9].

It has also been demonstrated that irradiation in aqueous media of several antimalarial drugs containing the quinoline ring, produces in general, a relatively complex mixture of degradation products, including both photooxidation and photocleavage derivatives. For example, irradiation of hydroxychloroquine [10], chloroquine [11], and primaquine [12] in an oxygenated medium causes cleavage of the side chain substituents in the aromatic ring without cyclization. The quinoline structure remains intact, giving rise to photochemically active degradation products. Also, it has been shown that competitive reactions gives photooxidation products in which oxidation can occur either in the quinoline ring [12,13] or in the side chain. It is evident that different photoproducts will be formed depending upon the experimental conditions, such as the formation of photooxidation derived products involving singlet oxygen, $O_2(^1\Delta_g)$, as previously proposed [8].

Singlet oxygen reactions are important in biological systems, where it can play deleterious (damaging valuable biomolecules) and/or beneficial roles [14,15]. Consequently, the relevance of the singlet oxygen-mediated photosensitizing effects of antimalarials can be related to the efficiency which the drug produces $O_2(^1\Delta_g)$ and/or to the antimalarial reactivity towards this active species of oxygen.

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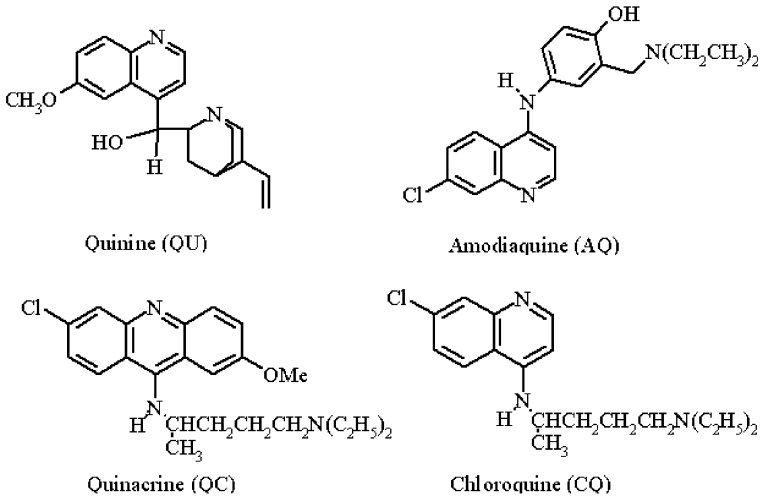


Fig. 1. Molecular structures of antimalarial drugs.

Bimolecular rate constants for quenching of singlet oxygen by antimalarial drugs have been determined by Motten et al. [9] in D_2O at pD = 7.4. They found that primaquine quenches efficiently $O_2(^1\Delta_g)$ with a rate constant of $2.6 \times 10^8\ M^{-1}\ s^{-1}$. Quinine, hydroxychloroquine, amodiaquine, and quinacrine, also quench singlet oxygen with bimolecular rate constants from 1.4×10^7 to $4.6 \times 10^7\ M^{-1}\ s^{-1}$. The less efficient quenchers were chloroquine and mefloquine. No other data regarding reactivity of quinoline-derived antimalarial drugs towards singlet molecular oxygen have been published and studies on the reaction mechanism have not been done. In view of the current interest in antimalarial drug photoreactions, because of their photosensitizing properties and the possible role of singlet molecular oxygen to generate photooxidation products of the drugs that also can be photochemically active, we want to evaluate the reactivity of these compounds with singlet oxygen.

Structurally, antimalarial drugs (Fig. 1) have several potentially reactive centres, which can interact with $O_2(^1\Delta_g)$: the quinoline ring, the tertiary and secondary amine groups, and the phenol ring in AQ. In a previous work [16], we show that the linear solvation energy relationship formalism, LSER, allows a quantitative evaluation of the solvent effect in singlet oxygen reactions, being a useful tool in interpreting the reaction mechanism. Furthermore, LSER analysis can be used to determine the main reaction centre in polyfunctional compounds. In this paper, we report on the kinetic results obtained in the study of the sensitized photooxidation of four antimalarial drugs in several media.

2. Experimental

Quinacrine hydrochloride and quinine (Sigma), primaquine diphosphate, chloroquine diphosphate, perinaphtenone, 5,10,15,20-tetraphenyl-21H,23H-porphine (TPP), 9,10-dimethylanthracene (DMA), benzophenone (BPH), and 1,3-diphenylisobenzofurane (DPBF) (Aldrich) were used without further purification. Quinine (Aldrich) was vacuum-distilled before use. Rose Bengal (Fluka) was recrystallized from ethanol prior to use. All solvents (Merck) were of spectroscopic or HPLC grade.

The free bases of quinacrine (QC), amodiaquine (AQ), and chloroquine (CQ) were obtained by dissolving the corresponding salt in water, followed by addition of 10% NaOH up to pH = 12 and several extractions with chloroform or diethylether. The organic phase was dried over anhydrous sodium sulphate and the solvent was removed. Chloroquine was purified by successive recrystallization from ethanol giving a pale yellow powder, m.p. 85–86 °C. Recrystallization of amodiaquine from chloroform:petroleum ether (5:1) yield a pale yellow powder, m.p. 205.5–207.5 °C. Quinacrine was purified by column chromatography. Purity of the free bases was assessed by their melting points, ^1H NMR spectra and GC-NPD chromatograms.

Time-resolved experiments were carried out by measuring $O_2(^1\Delta_g)$ phosphorescence emission at 1270 nm. The measurements of the total quenching rate constant were carried out in fluorescence cells (1 cm optical path) following the decrease in singlet oxygen lifetime by the addition of the antimalarial drug. TPP or Rose Bengal, in appropriate amount to give absorbance <0.2 at the excitation wavelength, were employed as sensitizers. All measurements were performed in air-equilibrated solutions. TPP was irradiated by 500-ps light pulse of a PTI model PL-202 dye laser (414 nm, ca. 200 μJ per pulse). A PTI model PL-2300 nitrogen laser was employed to pump the dye laser. When RB was used as sensitizer, samples were excited with the second harmonic (532 nm, ca. 9 mJ per pulse) of 6-ns light pulse of a Quantel Brilliant Q-Switched Nd:YAG laser. The emission of singlet oxygen produced by photosensitization was detected by using a liquid nitrogen-cooled North Coast model EO-817P germanium photodiode detector equipped with a built-in preamplifier. The detector was coupled to the cell

in a right-angle geometry. An interference filter (1270 nm, Spectrogon US, Inc.) and a cut-off filter (995 nm, Andover Corp.) were the only elements between the cell face and the diode cover plate. The preamplifier output was fed into the 1 MΩ input of a digitising oscilloscope Hewlett Packard model 54540 A. Computerized experiment control, data acquisition and analysis were performed by LabView-based software developed in our laboratory [17].

The determination of the total rate constant by steady-state competitive techniques was done using TPP as sensitizer ($\lambda_{max} = 414$ nm) following the inhibition of consumption of 9,10-dimethylanthracene upon drug addition [18]. The irradiation was performed with a visible Par lamp, 150 W, using a Schott cut-off filter at 400 nm.

GLC chromatograms were obtained in a Hewlett Packard 5890 chromatograph, equipped with an NPD detector and a Hewlett Packard Ultra-2 capillary column. UV-Vis absorption experiments were performed in a thermostated Unicam UV-4 spectrophotometer. ^{1}H NMR spectra were obtained in a Bruker DRX-300 spectrometer.

Equation coefficients and statistical parameters were obtained by multilineal correlation analysis with STAT VIEW 5.0 (SAS Institute Inc.). Results were chosen on the basis of the *t*-statistic of the descriptors, correlation coefficients, standard deviations, and the Fisher index of equation reliability. Only coefficients at the 0.95 significance level were considered. The number of solvents included in the correlation was as large as possible and at least three times the number of parameters used in the generalized equation. When the variance inflation factor (VIF) parameter was too large, the less significant variable was removed. This permits to solve the problem of crossed correlation [19]. This implies that the number of accepted independent variables have the smallest collinearity. The number of measured k_T values in the solvent set and those included in the correlation equation could differ because data points with a residual biggest than twice of S.D. were not included in the correlation. This criteria improves the fitting between the experimental and calculated k_T values.

3. Results and discussion

The total (physical and chemical) quenching rate constant, k_T, for the reaction of $O_2(^1\Delta_g)$ with antimalarial drugs in several solvents was obtained from the experimentally measured first order decay of $O_2(^1\Delta_g)$ in the absence (τ_0^{-1}) and presence of the antimalarial drug (τ^{-1}) according to

$$\tau^{-1} = \tau_0^{-1} + k_T[\text{drug}] \quad (1)$$

In these solvents, the triplet decay of the sensitizer (TPP) was not affected by the addition of the antimalarials even at concentrations higher than those used to quench the excited oxygen. Linear plots of τ^{-1} versus drug concentration were obtained for all the solvents employed (Fig. 2). The intercept of these plots corresponds to the singlet oxygen lifetime

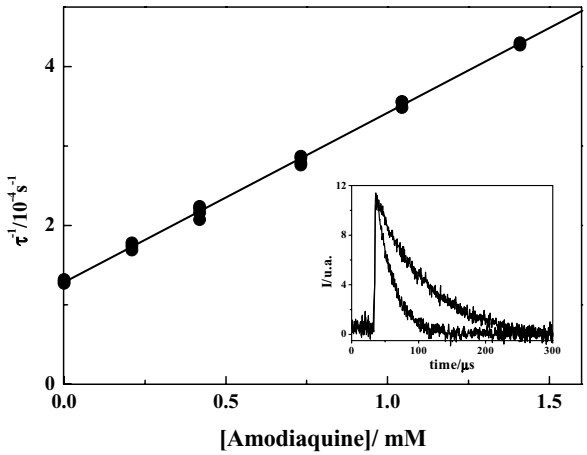


Fig. 2. Stern–Volmer plot for singlet oxygen deactivation by amodiaquine in acetonitrile with RB as sensitizer. Inset: singlet oxygen phosphorescence decay at 1270 nm, following dye laser excitation at 532 nm. Curve with decreasing lifetime represent an experiment with 1.4 mM amodiaquine.

in the solvent employed. In all the experiments these values closely matched the singlet oxygen lifetimes determined independently in a large set of experiments performed in our laboratory during past few years. The k_T values calculated from the slope of these plots are given in Table 1. These results show that the quenching is most efficient in polar non-protic solvents and decreases considerably in non-polar and in protic solvents. Possible rapid chemical changes of samples during illumination or interference of the $O_2(^1\Delta_g)$ luminescence with the scattered laser light, and the tail end of the sensitizer fluorescence [20] can be disregarded since the rate constant measured in some solvents by using competitive steady-state method afforded the same value as that obtained by the time-resolved method (data not shown). In steady-state experiments, the possible quenching of the sensitizer excited states by the antimalarials can be ignored since, in competitive experiments with DMA, linear plots were obtained over a wide range of drug concentrations.

Data in Table 1 show that the total quenching rate constants for the four drugs are in the order of 10^7 M^{-1} s^{-1}, indicating that antimalarial drugs are efficient quenchers of singlet oxygen. The most reactive compounds with singlet oxygen were QU, CQ and QC. Also, the k_T values were found to be solvent-dependent for all compounds. For example the k_T value for quinine increases by a factor 40 when the solvent is changed from methanol to dioxane. The rate constants for QC and CQ increase by more than one order of magnitude when the solvent is changed from protic to polar non-protic. The lesser solvent effect is shown by AQ. These results cannot be associated only with changes in the macroscopic dielectric constant, suggesting that specific solute–solvent interactions are important in determining reactivity of antimalarial drugs towards singlet oxygen. In this case it is appropriate to use linear solvent free-energy relationships to correlate the experimental rate constant with

Table 1
Values of k_T ($\times 10^7\ M^{-1}\ s^{-1}$) for the reaction between $O_2(^1\Delta_g)$ and antimalarial drugs in different solvents

Solvent	TEA[a]	QU	CQ	AQ	QC
Methanol	1.27 ± 0.05	0.61 ± 0.08	0.96 ± 0.03	1.20 ± 0.07	0.97 ± 0.04
Ethanol	2.36 ± 0.14	1.11 ± 0.05	1.72 ± 0.07	0.70 ± 0.03	1.53 ± 0.08
1-Propanol	1.48 ± 0.07	1.14 ± 0.05	1.55 ± 0.09	0.50 ± 0.02	2.00 ± 0.09
1-Butanol	2.23 ± 0.11	1.19 ± 0.06	1.61 ± 0.04	0.49 ± 0.03	2.08 ± 0.09
Hexyl alcohol	2.22 ± 0.10	1.04 ± 0.04	1.74 ± 0.08	0.53 ± 0.03	2.68 ± 0.32
1-Octanol	3.04 ± 0.16	1.26 ± 0.06	1.92 ± 0.06	0.49 ± 0.02	2.35 ± 0.10
1-Pentanol	1.97 ± 0.12	1.14 ± 0.07	1.54 ± 0.06	0.48 ± 0.03	1.63 ± 0.07
Benzyl alcohol	1.52 ± 0.08	0.75 ± 0.03	1.66 ± 0.14	2.50 ± 0.09	2.00 ± 0.15
Ethylene glycol	1.71 ± 0.09	0.91 ± 0.05	1.30 ± 0.07	4.17 ± 0.22	2.58 ± 0.13
Acetonitrile	16.5 ± 0.66	7.95 ± 0.32	12.3 ± 0.61	2.13 ± 0.08	11.9 ± 0.91
Benzonitrile	25.4 ± 0.91	10.8 ± 0.48	13.5 ± 0.67	1.76 ± 0.07	14.9 ± 0.66
Formamide	2.16 ± 0.11	–	1.18 ± 0.05	1.71 ± 0.06	2.02 ± 0.26
N,*N*-dimethylformamide	34.8 ± 1.00	21.7 ± 0.94	25.1 ± 0.88	3.93 ± 0.14	23.0 ± 0.75
Propylencarbonate	25.8 ± 0.89	10.9 ± 0.41	17.1 ± 0.74	4.78 ± 0.17	15.7 ± 0.93
Diethylether	9.15 ± 0.32	10.1 ± 0.39	3.95 ± 0.19	0.57 ± 0.02	4.48 ± 0.21
Ethyl acetate	19.0 ± 0.76	8.30 ± 0.42	9.58 ± 0.54	1.17 ± 0.04	8.75 ± 0.33
Acetone	21.7 ± 0.76	12.0 ± 0.58	13.2 ± 0.52	1.22 ± 0.05	10.9 ± 0.49
Benzene	19.9 ± 0.71	9.12 ± 0.49	6.69 ± 0.39	0.45 ± 0.03	7.12 ± 0.71
Toluene	13.7 ± 0.62	13.1 ± 1.01	4.86 ± 0.23	0.48 ± 0.02	6.08 ± 0.24
Hexane	6.62 ± 0.26	0.79 ± 0.03	0.95 ± 0.05	–	1.17 ± 0.05
Heptane	6.88 ± 0.34	0.86 ± 0.03	1.02 ± 0.05	–	1.38 ± 0.07
Chloroform	4.53 ± 0.23	2.33 ± 0.12	2.66 ± 0.17	0.93 ± 0.04	2.64 ± 0.41
Dichloromethane	12.8 ± 0.51	4.54 ± 0.25	5.69 ± 0.34	1.06 ± 0.12	5.40 ± 0.32
Dioxane	27.5 ± 0.91	24.2 ± 0.98	13.5 ± 0.53	1.23 ± 0.08	14.3 ± 0.75
Trifluoroethanol	0.16 ± 0.01	–	–	0.71 ± 0.04	–

[a] From Ref. [21].

solvent properties. To obtain insight of solvent effect on the interaction of singlet oxygen with antimalarial drugs, we analysed the quenching rate constant dependence on the microscopic solvent characteristics by using the semiempirical solvatochromic equation (LSER) of Kamlet and co-workers (Eq. (2)) [22–24]:

$$\log k = \log k_0 + s\pi^* + \mathrm{d}\delta + a\alpha + b\beta + h\rho_H^2 \quad (2)$$

where π^* accounts for dipolarity and polarizability of solvents [23,24], δ is a correction term for polarizability, α is related to the hydrogen bond donor solvent ability, β indicates the solvent capacity as a hydrogen bond acceptor, and ρ_H is the Hildebrand parameter. This parameter corresponds to the square root of the solvent cohesive density [24] and is a measure of solvent–solvent interactions that are disrupted in creating a solute cavity [22]. The coefficients of Eq. (2) obtained by multilineal correlation analysis for the dependence of k_T on the solvent parameters are given in Table 2. These correlation equations result from purely statistical criteria. The sample size, *N*, the correlation coefficient, *R*, the standard deviation, S.D., and the Fisher index of equation reliability, *F*, indicate the overall correlation equation quality. The reliability of each term is indicated by the standard error, ±, the 2-tail probability, *P*(2-tail), and the *t*-statistics. Good quality is indicated by large *F*- and *t*-statistics values, and small S.D. The results show that not all the descriptors are significant. Descriptor coefficients accepted in the correlation equation were those having a significance level ≥0.95. For this reason, ρ_H was not included in the LSER correlation. According to the coefficients of Eq. (2), QU, CQ, and QC show the same behaviour. The values of k_T depend on microscopic solvent parameters π^*, α, and β, increasing in solvents with largest capacities to stabilize charges and dipoles, diminishing in solvents with high α values, and increasing in HBA solvents. This solvent dependence is similar to that observed in aliphatic amines of similar reactivity, such as triethylamine, TEA. The LSER analysis for this compound is also included in Table 2 [21]. These results indicate that the reaction of singlet oxygen with QU, CQ, and QC is compatible with the formation of a charge transfer exciplex, with the reactive centre being the tertiary amine group of the side chain substituent. The increase of k_T in polar non-protic solvents is explained in terms of the charge transfer-exciplex stabilization by dipolar interactions. Stabilization increases if these solvents have a large capacity as a hydrogen bond acceptor because of the stabilizing interaction with the positive charge developed on the reactive amine nitrogen. HBD solvents inhibit the reaction by blocking sterically the reactive centre through hydrogen bonding interactions with the lone pair on the reactive nitrogen.

AQ is lesser reactive than the other antimalarial drugs studied, and shows a different dependence of k_T with microscopic solvent parameters. For this compound, LSER analysis shows that the total rate constant depends on solvatochromic parameters π^*, δ, and α, with a high statistical weight associated to π^*. This molecule presents several potentially reactive sites towards singlet oxygen: the ter-

Table 2
LSER correlation equations for the reactions of singlet oxygen with antimalarial drugs

Compound	$\log k_0$	s	d	a	b	N	R	S.D.	F
QU	7.091	0.851	–	−1.448	0.930	18	0.971	0.135	77.715
CQ	7.168	0.711	–	−1.441	1.049	24	0.949	0.155	63.453
QC	7.197	0.782	–	−1.187	0.848	23	0.965	0.118	85.731
AQ	6.181	1.628	−0.376	−0.203	–	22	0.962	0.106	73.843
TEA	7.925	0.323	–	−1.300	0.356	29	0.948	0.196	74.057

tiary and secondary amine groups on the side substituent, the quinoline ring, and the phenol ring. However, the electrophilic attack of singlet oxygen on the tertiary amine group cannot be the main reaction path because the k_T values for AQ are smaller than those for TEA [21] as observed in Table 1 and LSER analysis is non-compatible with the formation of a charge transfer exciplex involving the tertiary amine nitrogen. The relative importance of the α parameter is smaller than that typically observed for charge-transfer reaction with amines. We propose that the tertiary amine group is blocked by an intramolecular interaction that hinders the singlet oxygen attack, as shown in Fig. 3. This interaction would be most important in non-protic solvents. In protic media, both intramolecular interaction and/or solvent hydrogen bonding with the amine nitrogen sterically hinder singlet oxygen attack.

This proposition is supported by the kinetics data. Table 1 shows that the k_T values in protic solvents for AQ are between a factor of 2–4 smaller than those for QU, QC, and CQ, whereas in non-protic solvents in which intramolecular hydrogen bonding interaction is favourable, k_T values for AQ are between a factor 4–20 smaller than those for the other antimalarials. For example, in benzene, k_T for AQ is $0.45 \times 10^7\ M^{-1}\ s^{-1}$, whereas k_T values for the other antimalarials are a factor 15–20 larger (9.12×10^7, 6.69×10^7 and $7.12 \times 10^7\ M^{-1}\ s^{-1}$ for QU, CQ, and QC, respectively). Moreover, equal values of k_T were measured for AQ in ethanol and trifluoroethanol, which has the largest α character in the solvent set employed. The dependence of k_T with α clearly apart from behaviour of TEA [21,25], whose k_T diminishes by about of a factor 15 when the solvent is changed from ethanol to trifluoroethanol, indicating that reaction of AQ with singlet oxygen does not involve the tertiary amine group. Clennan et al. [26] have studied the effect of intramolecular hydrogen bonding on the kinetic of reactions of singlet oxygen with amines. They found that the substitution of a terminal methyl group by an hydroxyl group in the butyl substituent of *N*,*N*-dimethyl-*N*-butylamine diminishes the rate constant for reaction with singlet oxygen by a factor 6 in benzene and practically does not change in solvents with very high α values such as trifluoroethanol. Comparison of k_T value for AQ in benzene, acetone or *N*,*N*-dimethylformamide with those measured for the other antimalarial drugs shows that the effect of intramolecular hydrogen bonding in AQ is greater than that reported by Clennan et al. [26]. In addition, reaction of singlet oxygen with the quinoline ring in AQ is highly improbable because the k_T values for reactions of 7-chloroquinaldine and 6-chloroquinoline with singlet oxygen (to be published) are in the order of $10^4\ M^{-1}\ s^{-1}$. On the other hand, the *p*-aminophenol substituent would be the reactive centre. Briviba et al. [27] demonstrated that *p*-aminophenol reacts efficiently with singlet oxygen ($k_T = 1 \times 10^8\ M^{-1}\ s^{-1}$), giving hydroxyquinone. Also, Bartlett et al. [28], have reported that the rate constants for reaction of singlet oxygen with substituted anilines correlate with the ionisation potential of the aniline and the slope is larger than that for aliphatic amines.

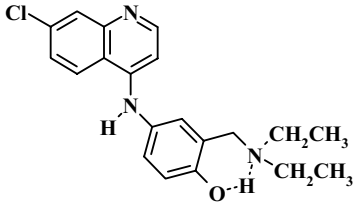
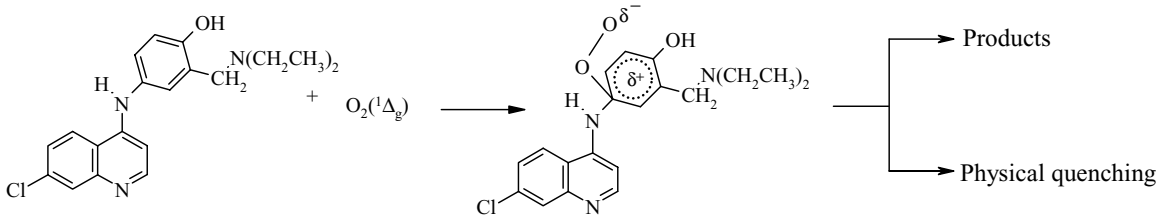


Fig. 3. Intramolecular hydrogen bonding interaction in amodiaquine.

Considering these results, we propose that the AQ reaction with singlet oxygen mainly involves the aminophenol substituent in position 4 on the quinoline ring. The dependence of k_T with solvent microscopic parameters is easily understood in terms of a mechanism involving a partially concerted cycloaddition to give a dipolar intermediate as shown in Scheme 1.

Dependence on the π^* parameter is explained in terms of the stabilizing effect of solvents with high capacity to stabilize charges and dipoles. The relatively weak inhibition of the reaction in HBD solvents (negative but small dependence on parameter α) can be understood by considering that the interaction of HBD solvents with the amino group in position 4 diminishes the electron-donating capacity of the amino substituent toward the phenol ring, reducing the negative charge on it.

In conclusion, the four antimalarial drug studied are efficient quenchers of singlet oxygen. QU, CQ, and QC react most likely through a charge transfer complex involving the tertiary amino group on the side chain, whereas AQ behaves differently. In the latter case, intramolecular hydrogen bonding diminishes the electron density on the amino group, consequently, singlet oxygen probably attacks the phenol ring to give a dipolar intermediate.



Scheme 1.

Acknowledgements

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References

[1] H.H. Tønnesen, S. Kristensen, K. Nord, in: H.H. Tønnesen (Ed.), The Photostability of Drugs and Drugs Formulations, Taylor & Francis, Washington, DC, 1996.
[2] D.E. Moore, V.J. Hemmens, Photochem. Photobiol. 36 (1982) 71–77.
[3] S. Kristensen, A.L. Orsteen, S.A. Sande, H.H. Tønnesen, J. Photochem. Photobiol. B: Biol. 26 (1994) 87–95.
[4] H.H. Tønnesen, D.E. Moore, Int. J. Pharm. 70 (1991) 95–101.
[5] J.D. Spikes, J. Photochem. Photobiol. B: Biol. 42 (1998) 1–11.
[6] S. Kristensen, R.H. Wang, H.H. Tønnesen, J. Dillon, J.E. Roberts, Photochem. Photobiol. 61 (1995) 124–130.
[7] S. Kristensen, L. Grinberg, H.H. Tønnesen, Eur. J. Pharm. Sci. 5 (1997) 139–146.
[8] S. Kristensen, K. Nord, A.L. Orsteen, H.H. Tønnesen, Pharmazie 53 (1998) 98–103.
[9] A.G. Motten, L.J. Martínez, N. Holt, R.H. Sik, K. Reszka, C.F. Chignell, H.H. Tønnesen, J.E. Roberts, Photochem. Photobiol. 69 (1999) 282–287.
[10] H.H. Tønnesen, A.L. Grislingaas, S.O. Woo, J. Karlsen, Int. J. Pharm. 43 (1988) 215–219.
[11] K. Nord, J. Karlsen, H.H. Tønnesen, Int. J. Pharm. 72 (1991) 11–18.
[12] S. Kristensen, A.L. Grislingass, J.V. Greenhil, T. Skjetne, J. Karlsen, H.H. Tønnesen, Int. J. Pharm. 100 (1993) 15–23.
[13] A. Brossi, W. Gessner, C.D. Hufford, J.K. Baker, F. Homo, P. Millet, I. Landau, FEBS Lett. 223 (1987) 77–81.
[14] K. Briviba, L.O. Klotz, H. Sies, Biol. Chem. 378 (1997) 1259–1265.
[15] L.M. Hultén, M. Holmström, B. Soussi, Free Radic. Biol. Med. 27 (1999) 1203–1207.
[16] E. Lemp, A.L. Zanocco, E.A. Lissi, Curr. Org. Chem. 7 (2003) 799–819.
[17] A.L. Zanocco, G. Günther, E. Lemp, J.R. de la Fuente, N. Pizarro, Photochem. Photobiol. 68 (1998) 487–493.
[18] A.L. Zanocco, E. Lemp, G. Günther, J. Chem. Soc., Perkin Trans. II (1997) 1299–1302.
[19] D.A. Besley, E. Kuh, R.E. Welsh, Regression Diagnosis, Wiley, New York, 1980.
[20] A. Michaeli, J. Feitelson, Photochem. Photobiol. 59 (1994) 284–289.
[21] A.L. Zanocco, G. Günther, E. Lemp, J.R. de la Fuente, N. Pizarro, J. Photochem. Photobiol. A: Chem. 140 (2001) 109–115.
[22] C. Reichardt, Solvents and Solvent Effects in Organic Chemistry, VCH, Weinheim, 1990.
[23] M.J. Kamlet, J.L.M. Abboud, M.H. Abraham, R.W. Taft, J. Org. Chem. 48 (1983) 2877–2887.
[24] M.H. Abraham, R.M. Doherty, M.J. Kamlet, J.M. Harris, R.W. Taft, J. Chem. Soc., Perkin Trans. II (1987) 913–920.
[25] C. Schweitzer, R. Schmidt, Chem. Rev. 103 (2003) 1685–1757.
[26] E.L. Clennan, L.J. Noe, T. Wen, E. Szneller, J. Org. Chem. 54 (1989) 3581–3584.
[27] K. Briviba, T.P.A. Devasagayam, H. Sies, S. Steenken, Chem. Res. Toxicol. 6 (1993) 548–553.
[28] P.D. Bartlett, G.D. Mendenhall, D.L. Durham, J. Org. Chem. 45 (1980) 4269–4271.