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Reaction of singlet molecular oxygen, $O_2(^1\Delta_g)$, with the *Cinchona* tree alkaloids
Effect of absolute configuration on the total rate constant

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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 the total reaction rate constant, k_T, and the reactive reaction rate constant, k_R, for the reaction between singlet oxygen and the *Cinchona* tree alkaloids, cinchonidine, cinchonine, quinine and quinidine in several solvents. In most solvents, the k_T values were close to 10^7 M^{-1} s^{-1}, indicating that these compounds are good singlet oxygen quenchers. The reactive rate constants are smaller than 10^4 M^{-1} s^{-1}, implying that quenching is essentially a physical process. The analysis of solvent effect on k_T by using LSER equations indicates that singlet oxygen deactivation by these drugs is accelerated by solvents with large π^* and β values, being inhibited by hydrogen bond donor (HBD) solvents. Correlations employing theoretical solvent parameters, TLSER, give similar results. These data support the formation of an exciplex with charge transfer character, resulting from the singlet oxygen electrophilic attack on the quinuclidine moiety nitrogen. In most solvents, cinchonidine is more reactive than cinchonine and quinine is more reactive than quinidine although reactivity differences are small and only in a few solvents k_T values of the *S*,*R*-isomer are about twice than those of *R*,*S*-isomer. The higher reactivity of *S*,*R*-isomers in these solvents is explained by the geometrically favorable intra-exciplex stabilizing interaction between the non-bonded pernitrone oxygen and the hydrogen of the hydroxyl substituent at C(9).
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Keywords: Antimalarial drugs; *Cinchona* tree alkaloids; Singlet oxygen; Solvent effect; LSER; Time resolved kinetics

1. Introduction

Linear solvation energy relationship, LSER, and theoretical linear solvation energy relationship, TLSER, are very useful frameworks to analyze solvent effects on singlet oxygen reactions with several kinds of molecules. Treatments allow quantitative evaluation of solvent effects and are helpful tools for interpreting the mechanism of the process. These equations have also been employed to determine the main reaction center in polyfunctional compounds, to detect changes in the reaction mechanism with solvent properties and to evaluate the relative contribution of tautomers in equilibrium to the total reaction rate [1,2].

Cinchona alkaloids, the natural compounds extracted from barks of *Cinchona* tree have an ancient therapeutic heritage [3]. They have multiple biological activities, among them, the widely known antimalarial and antiarrhytmic properties. The most abundant constituents of *Cinchona* bark are the so-called *erythro* isomers: cinchonidine (**1**), quinine (**2**), cinchonine (**3**) and quinidine (**4**), which differ from each to other by the absence or presence of the methoxy substituent in the quinoline moiety and/or in the absolute configuration of two carbon atoms, C(8) and C(9), while the configuration of C(3) and C(4) is the same for all the alkaloids of this group.

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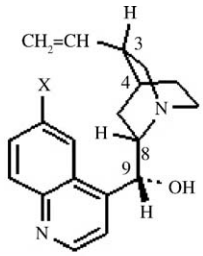
Until relatively recently, quinine was the only remedy to treat malaria, the most awful disease for world civilization over the past three centuries [4], which caused the death of millions of peoples (over 1.1 million in 2001) [5]. Compounds (**1**)–(**4**) are antimalarials of comparable activity, unlike their C(9) epimers that are practically inactive. Since the beginning of the last century, synthetic antimalarials have also been employed to treat the disease. Most antimalarials have pharmacological activities beyond those for treating malaria, consequently a number of them have been used with several degrees of success to treat medical conditions other than malaria including lupus erythematosus, polymorphous light eruption, cutaneous lymphoma, and rheumatoid arthritis [6]. The majority of antimalarials derived from quinoline possessed undesirable photosensitizing properties that produce toxic side effects both in the skin and the eye [7–9]. Cutaneous and ocular effects, probably caused by light, include changes in the skin pigmentation, corneal opacity, cataract formation and other visual disturbances, including irreversible retinal damage that may lead to blindness [6]. The precise mechanisms for these reactions in humans remain unknown, although singlet molecular oxygen, $O_2(^1\Delta_g)$, and free radicals including superoxide/hydroperoxyl or peroxyl adduct, carbon- and nitrogen-centered radicals have been invoked as responsible of these phototoxic effects [10–14]. On the other hand, it is well known that singlet molecular oxygen ($^1\Delta_g$) reactions are important in biological systems, where it can play deleterious (damaging valuable biomolecules) and/or beneficial roles (photodynamic therapy of cancer) [15,16]. Furthermore, the relevance of the singlet oxygen-mediated photosensitizing effects of the antimalarials will be related to the efficiency with which the drug produces $O_2(^1\Delta_g)$ and/or to the reactivity of the molecule towards this active species of oxygen. Bimolecular rate constants for quenching of singlet oxygen by antimalaric drugs have been determined in D_2O at pD = 7.4 by Motten et al. [14] and by Zanocco and coworkers in several solvents [17]. In view of the current interest in antimalarial drugs photoreactions due to their photosensitizing properties and the possible role of the singlet molecular oxygen to generate photooxidation products from the drugs that can also be photochemically active, we want to determine how reactive these compounds may be with singlet oxygen. If the structures of antimalarial drugs included in Fig. 1 are analyzed, several reactive centers can be visualized: the aromatic ring, the quinoline nitrogen and the bicyclic nitrogen that can interact with $O_2(^1\Delta_g)$. In addition, if the reactive center is the bicyclic nitrogen, the absolute configuration of the two carbon atoms, C(8) and C(9) could affect substrate reactivity towards singlet oxygen. In this study, we report on the LSER and TLSER analysis of the reactions of *Cinchona* tree alkaloids with singlet oxygen to determine if this framework provides information about the influence of carbon configuration in the vicinity of the reactive centre on substrate reactivity.



Compound	Absolute Configuration		X
	C(8)	C(9)	
Cinchonidine (1)	S	R	H
Quinine (2)	S	R	OCH_3
Cinchonine (3)	R	S	H
Quinidine (4)	R	S	OCH_3

Fig. 1. Molecular structures of the principal *Cinchona* tree alkaloids.

2. Experimental

Cinchonidine hydrochloride and cinchonine hydrochloride (Sigma), 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP), 9,10-dimethylanthracene (DMA) and rubrene (Aldrich) were used without further purification. Rose Bengal (Fluka) was recrystallized from ethanol prior to use. All solvents (Merck) were of spectroscopic or HPLC grade. Quinine and quinidine (Sigma) were recrystallized from ethanol before used.

Free bases of cinchonidine and cinchonine were obtained by dissolving the corresponding salt in water, followed by addition of 10% NaOH until pH 12 and several extractions with chloroform or diethylether. The organic phase was dried over anhydrous sodium sulphate and the solvent removed. Both compounds were purified by at least three recrystallizations from ethanol. Purity of the free bases was assessed by its melting points, ^{1}H NMR spectrum and GC-NPD chromatogram.

The measurements of total quenching rate constants, k_T, by time-resolved experiments were carried out observing the phosphorescence of $O_2(^1\Delta_g)$ at 1270 nm. TPP was irradiated by the 500 ps light pulse of a PTI model PL-202 dye laser (414 nm, ca. 200 μJ per pulse). When Rose Bengal 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 singlet oxygen emission 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 a cuvette (1 cm optical path) 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 cuvette face and the diode cover plate. The output of the preamplifier was fed into the 1 MΩ input of a digitizing oscilloscope Hewlett Packard model 54540 A. Computerized experiment control, data acquisition

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