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Solvent effects on the sensitized photoxygenation of lidocaine

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Abstract

Detection of $O_2(^1\Delta_g)$ phosphorescence emission, $\lambda_{max} = 1270$ nm, following laser excitation and steady state methods were employed to determine both the total constant, k_T^{LID}, and the chemical reaction rate constants, k_R^{LID}, for reaction between the anaesthetic lidocaine and singlet oxygen in several solvents. Values of k_T^{LID} range from $0.20 \pm 0.09 \times 10^6$ M^{-1} s^{-1} in trifluoroethanol to $45.8 \pm 2.40 \times 10^6$ M^{-1} s^{-1} in *N,N*-dimethylacetamide. Values of k_R^{LID} are at least one order of magnitude lower than k_T^{LID} values in a given solvent. Solvent effect on quenching rates shows that reaction mechanism involves formation of a charge transfer exciplex. Correlation of k_T^{LID} values with solvent parameters does not follow that observed for a typical tertiary amine such as triethylamine. Although k_T^{LID} values are lower in hydrogen bond donor solvents, this solvent effect is significantly smaller than that for triethylamine, and no expected decrease in lidocaine reactivity with change from aprotic to protic solvents was found. This result is ascribed to weaker hydrogen bonding between the amino moiety in lidocaine and the solvent. Otherwise, hydrogen bond acceptor solvents increase k_T^{LID} to a greater extent than that triethylamine. This can be explained by intra-molecular hydrogen bonding or electrostatic interactions that stabilize lidocaine and hydrogen bond acceptor solvents disrupt these interactions.

Keywords: Singlet oxygen; Lidocaine; Photosensitization; Solvent effect; LSER; TLSER

1. Introduction

Lidocaine, 2-(diethylamino)-*N*-(2,6-dimethylphenyl)-acetamide, is a local anaesthetic that reduces ventricular arrhythmia associated with myocardial infarction, myocardial infarct size and ischemic myocardial injury [1–3]. The protective effects of lidocaine have been attributed to its membrane stabilizing properties by acting as a short-lived free radical scavenger [4]. Furthermore, Das and Misra [4], has proposed lidocaine as a powerful scavenger of singlet oxygen and found that lidocaine was more effective than β-carotene, sodium azide and histidine in singlet oxygen quenching. However, there are no kinetic data accounting for its reactivity towards singlet oxygen and nor information about this reaction mechanism.

This paper reports kinetic results obtained on the sensitized photo-oxidation of lidocaine using both steady state and time-resolved methods. In addition, a semi-empirical solvatochromic equation, LSER, and a theoretical linear solvation relationship, TLSER, were employed to analyze kinetic solvent effects and explain differences between lidocaine reactivity and that of a typical aliphatic amine. The strong electron withdrawing acetamido group present in lidocaine (Fig. 1) will affect the reactivity of the diethylamino group towards singlet oxygen and may also interact intra-molecularly, e.g. by hydrogen bonding, which will be solvent dependent.

2. Experimental

Lidocaine (Sigma), phenazine, rubrene, 5,10,15,20-tetraphenyl-21H,23H-porphine (TPP), sodium azide, 9,10-dimethylanthracene (DMA), 9-anthrylmethanol and 1,3-diphenylisobenzofurane (DPBF) (Aldrich) were used without further purification. Rose bengal (Fluka) was recrystallized from ethanol prior to use. Triethylamine (TEA) (Aldrich Chemical Co.) was distilled twice before use. All solvents (Merck) were of spectroscopic or HPLC grade.

UV–VIS absorption spectra and steady state competitive kinetic experiments were performed in a Unicam UV-4 spectrophotometer. A Fisons MD-800 GC–MS system with a Hewlett-Packard Ultra-2 (25 m) capillary column was used to obtain electron impact and chemical ionization mass spectra.

Chemical reaction rate constants were determined in methanol, acetonitrile and *N,N*-dimethylformamide using

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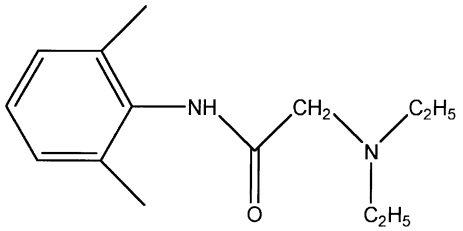


Fig. 1. Structure of lidocaine.

a 10 ml double wall cell, light-protected by black paint. A centred window allowed irradiation with light of a given wavelength using Schott cut-off filters. Circulating water maintained the cell temperature at 22 ± 0.5°C. The irradiation of the sensitizer, rose bengal, was performed with a visible, 200 W, Par lamp. A Hewlett-Packard 5890 gas chromatograph equipped with a NPD detector and a Hewlett-Packard Ultra-2 capillary column was used to monitor lidocaine consumption. 9,10-Dimethylanthracene and 1,3-diphenylisobenzofurane were used as actinometers in methanol or acetonitrile and *N,N*-dimethylformamide, respectively. Fresh 1,3-diphenylisobenzofuran solutions prepared in a dark room and appropriate cut-off filters were used. Auto-oxidation of this compound, followed by UV–VIS spectrophotometry, was <1% under our experimental conditions.

Time-resolved phosphorescence measurements were carried out in 1 cm path fluorescence cells. Phenazine was excited by the third harmonic (355 nm, ca. 15 mJ per pulse) of the 6 ns light pulse of a Quantel Brilliant Q-Switched Nd:YAG laser. When TPP or rose bengal was the sensitizer, samples were excited with the 500 ps light pulse of a PTI model PL-202 dye laser (419 or 556 nm, ca. 200 μJ per pulse). A PTI model PL-2300 nitrogen laser was used to pump the dye laser. A liquid-nitrogen cooled North Coast model EO-817P germanium photodiode detector with a built-in pre-amplifier was used to detect infrared radiation from the cell. The detector was coupled to the cell at a right-angle. 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 pre-amplifier output was fed into the 1 MΩ input of a digitizing oscilloscope Hewlett-Packard model 54540 A. Computerized experiment control, data acquisition and analysis were performed with a LabView-based software developed in our laboratory.

Unreliable quenching data of $O_2(^1\Delta_g)$ were obtained with time resolved methods due to the low water solubility of lidocaine. Then, competitive methods were employed to determine values of k_T^{LID} with rose bengal as sensitizer and 9-anthrylmethanol as actinometer. Disappearance of the anthracene derivative was followed by decrease in fluorescence intensity [5]. In heptane, k_T^{LID} values were determined from inhibition of the rubrene auto-oxidation rate [6]. These steady state competitive experiments were performed in a thermoregulated (22 ± 0.5°C) cell. A Schott cut-off filter was used to select light of a given wavelength from a visible, 150 W, Par lamp. The distance between the light source and cell was set for each experiment so that the initial substrate concentration diminished by about 50% in 15 min.

Regardless of the sensitizer employed to evaluate k_T^{LID}, these methods are applicable only if lidocaine does not quench the sensitizer excited states, singlet or triplet under the experimental conditions [7]. We discarded this possibility for several reasons: (i) in steady state experiments, k_T^{LID} values were independent of the initial rubrene concentration; (ii) linear Stern–Volmer type plots were obtained over a wide range of lidocaine concentrations (up to 10 mM); (iii) data obtained in double quenching experiments (using sodium azide) were compatible with those expected from competition for $O_2(^1\Delta_g)$; (iv) sensitizer consumption was not observed in time-resolved measurements. Mair's method was used to analyse peroxides [8].

Multi-linear correlation analysis with STAT VIEW 5.0 (SAS Institute Inc.) permitted to obtain the equation coefficients and statistical parameters. Sample size, *N*, the product correlation coefficient, *R*, the standard deviation, S.D., and the Fisher index of equation reliability, *F*, were used to determine the quality of the overall correlation equation. The reliability of each term is indicated by the standard error, ±, the 2-tail probability, *P* (2-tail), the *t*-statistic (*t*-stat.), and the variance inflation factor, VIF. Good quality was indicated by large *F*- and *t*-stat. values, small S.D. values and *R* and VIF close to one. Only coefficients at the 0.95 significance level were considered. The number of solvents included in the correlation was as large as possible and was at least three times the number of LSER or TLSER parameters used in the generalized equation. When the VIF (variance inflation factor) parameter was too large, the least significant variable was removed. This permits to solve the problem of crossed correlation [9].

3. Results and discussion

3.1. Chemical reaction of lidocaine with singlet oxygen

Rate constants for the chemical reaction between lidocaine and $O_2(^1\Delta_g)$, k_R^{LID}, from slopes of first-order plots are $(1.05 \pm 0.061) \times 10^5\ M^{-1}\ s^{-1}$, $(1.42 \pm 0.073) \times 10^5\ M^{-1}\ s^{-1}$ and $(0.61 \pm 0.046) \times 10^5\ M^{-1}\ s^{-1}$ in acetonitrile, methanol and *N,N*-dimethylformamide, respectively.

Chemical reaction of singlet oxygen with amines yield hydroperoxides and dehydrogenation compounds as the main reaction products [10–13]. According to reported results, hydroperoxide, olefinic and/or imino derivatives of lidocaine should be detected if photosensitized oxidation is performed with long irradiations.

By using the Mair method [8] for hydroperoxide determination, a concentration equivalent to 0.0153 M of hydroperoxide was found when 0.03 M lidocaine in acetonitrile

was irradiated for 12 h in the presence of rose bengal. The amount of hydroperoxide produced agrees with the consumption of lidocaine. Although we could not isolate reaction products in quantities adequate for spectroscopic characterization, a rough idea of the product distribution was obtained by GC–MS analysis of the main lidocaine derivatives produced in the photo-oxidations. When 0.03 M lidocaine was irradiated for 12 h in the presence of rose bengal, the results shown in Fig. 2(a) were obtained with the mass spectrometer in the positive chemical ionization (CI+) mode. There were only four peaks in the chromatogram. Unreacted lidocaine corresponded to the main one with a retention time of 15.59 min. Fig. 2(b) shows that the mass spectrum is that of lidocaine. The CI+ and

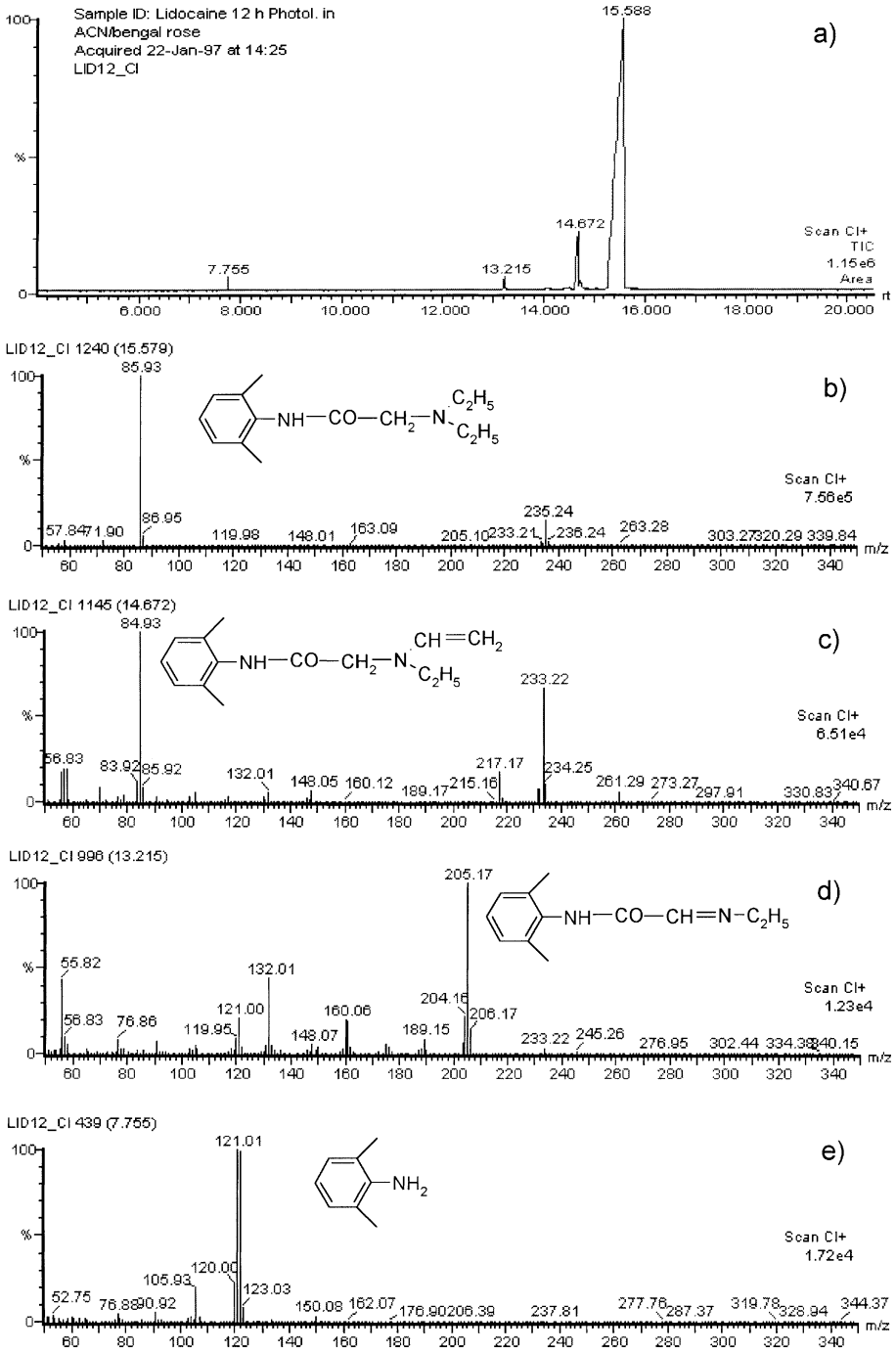


Fig. 2. (a) GC–MS chromatogram of 30 mM lidocaine in acetonitrile after 12 h of irradiation in the presence of rose bengal; (b) CI+ mass spectrum of compound with retention time 15.58 m; (c) CI+ mass spectrum of compound with retention time 14.67 m; (d) CI+ mass spectrum of compound with retention time 13.22 m; (e) CI+ mass spectrum of compound with retention time 7.76 m.

EI (not included) mass spectra corresponding to peaks at retention times of 14.57, 13.22 and 7.77 min, indicated that 2-(ethylvinylamino)-*N*-(2,6-dimethylphenyl)-acetamide, 2-(1-azapropily-den)-*N*-(2,6-dimethyl-phenyl)-acetamide and 2,6-dimethylaniline are the probable main products of lidocaine photo-oxidation. Fig. 2(c–e), show the CI+ mass spectra and corresponding structures.

3.2. Physical quenching of singlet oxygen by lidocaine

In most of the studied solvents, total rate constants, k_T^{LID}, for the reaction of lidocaine with $O_2(^1\Delta_g)$, were determined by using time-resolved phosphorescence. Fig. 3 shows a typical Stern–Volmer plot for the quenching of singlet oxygen by lidocaine. Values of k_T^{LID} in different solvents were obtained from slopes of these plots (Eq. (1)). The insert shows the luminescence decay of singlet oxygen at 1270 nm in acetone as solvent and rose bengal as sensitizer. The insert also shows the decays obtained over several lidocaine concentrations. The lifetime of $O_2(^1\Delta_g)$ was obtained from single exponential decays in the absence or presence of variable concentrations of lidocaine.

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

Table 1 includes values of k_T^{LID} in different solvents from the various methods.

A comparison of k_R^{LID} and k_T^{LID} values shows that k_T^{LID} is greater than k_R^{LID} by between one and two orders of magnitude in the same solvent, indicating that the main path for interaction of lidocaine with singlet oxygen corresponds to physical quenching. Thus, for this process, the quenching rate constant, k_Q, approximately equals

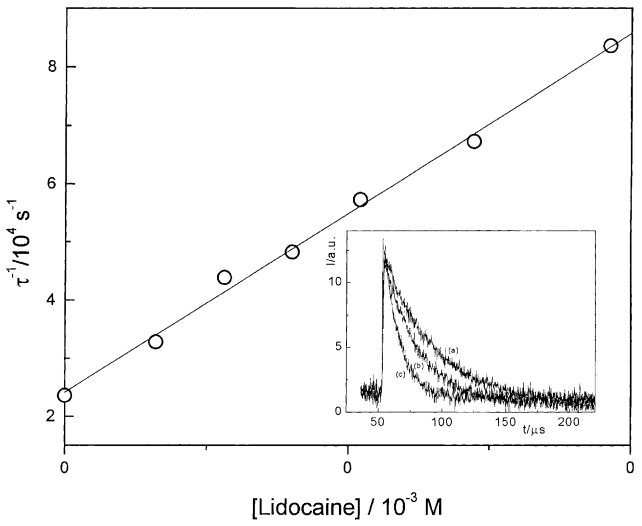


Fig. 3. Stern–Volmer plot for deactivation of singlet oxygen by lidocaine in acetone as the solvent: (a) singlet oxygen phosphorescence decay at 1270 nm, following dye laser excitation at 414 nm, with rose bengal as sensitizer in acetone; (b) and (c) as (a), but with 1.6 and 9.6 mM of lidocaine, respectively.

Table 1
Total rate constants for reactions of $O_2(^1\Delta_g)$ with lidocaine, k_T^{LID}, and triethylamine, k_T^{TEA}, in different solvents

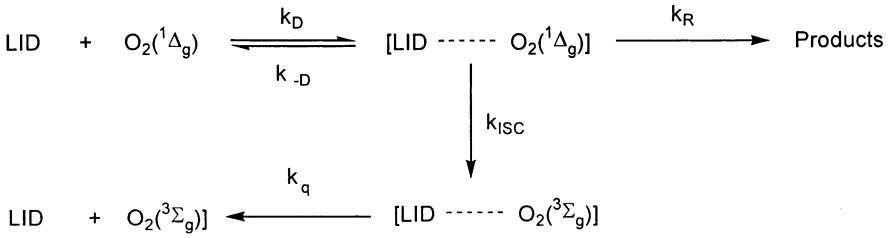
	Solvent	$k_T^{LID}/10^6$ ($M^{-1}\,s^{-1}$)	$k_T^{TEA}/10^6$ ($M^{-1}\,s^{-1}$)
1	*n*-Heptane	1.10 ± 0.08[a]	68.8 ± 3.4
2	*n*-Hexane	1.24 ± 0.05[b]	66.2 ± 2.6
		1.29 ± 0.06[c]	
3	Diethylether	3.30 ± 0.16[c]	91.5 ± 3.2
4	Dioxane	2.53 ± 0.13[c]	275.2 ± 9.1
5	Ethyl acetate	5.26 ± 0.17[c]	190.4 ± 7.6
6	Tetrahydrofurane	7.02 ± 0.32[c]	221.1 ± 6.6
7	Benzene	2.00 ± 0.11[a]	198.5 ± 7.1
		2.69 ± 0.09[b]	
8	Tributylphosphate	39.4 ± 0.16[c]	71.4 ± 3.5
9	Anisole	3.67 ± 0.19[c]	314.8 ± 9.4
10	Propylene carbonate	8.15 ± 0.36[c]	258.1 ± 8.9
11	*N,N*-Dimethylformamide	31.70 ± 1.27[c]	347.6 ± 10
12	*N,N*-Dimethylacetamide	45.8 ± 2.40[b]	422.2 ± 12
13	Benzonitrile	4.28 ± 0.21[c]	254.2 ± 9.1
14	Acetone	6.14 ± 0.28[c]	216.7 ± 7.6
15	Methylene chloride	1.42 ± 0.06[c]	128.4 ± 5.1
16	Acetonitrile	2.36 ± 0.09[d]	165.1 ± 6.6
		3.17 ± 0.15[b]	
		4.10 ± 0.19[c]	
17	Chloroform	0.98 ± 0.05[b]	45.3 ± 2.3
		0.90 ± 0.04[c]	
18	Benzylic alcohol	2.48 ± 0.11[c]	15.2 ± 0.8
19	Formamide	2.81 ± 0.12[b]	21.6 ± 1.1
20	i-Propanol	4.30 ± 0.22[c]	27.8 ± 1.4
21	*n*-Octanol	3.40 ± 0.16[c]	30.4 ± 1.6
22	*n*-Hexanol	–	22.2 ± 1.0
23	i-Pentanol	3.04 ± 0.13[c]	19.7 ± 1.2
24	*n*-Pentanol	3.52 ± 0.16[c]	26.2 ± 1.3
25	*n*-Butanol	3.54 ± 0.14[c]	22.3 ± 1.1
26	*n*-Propanol	2.96 ± 0.12[b]	14.8 ± 0.7
27	Ethanol	2.72 ± 0.13[d]	23.6 ± 1.4
		2.93 ± 0.15[b]	
28	Methanol	2.08 ± 0.09[b]	12.7 ± 0.5
29	Trifluoroethanol	0.20 ± 0.09[b]	–

[a] Sensitizer: rubrene, steady state method.
[b] Sensitizer: phenazine or TPP, Nd:YAG laser.
[c] Sensitizer: TPP or rose bengal, dye laser.
[d] Sensitizer: rose bengal, steady state method.

k_T^{LID}. Furthermore, k_T^{LID} depends on the solvent characteristics (Table 1). While in non-polar solvents, such as *n*-heptane, $k_T^{LID} \approx 10^6\,M^{-1}\,s^{-1}$, in polar solvents such as *N,N*-dimethylformamide, k_T^{LID} is approximately $3 \times 10^7\,M^{-1}\,s^{-1}$. Besides, singlet oxygen quenching by lidocaine is approximately 7 times faster in water at pH = 10 ($k_T^{LID} = 51.4 \times 10^7\,M^{-1}\,s^{-1}$) than at pH = 5 ($k_T^{LID} = 7.1 \times 10^7\,M^{-1}\,s^{-1}$).

Quenching of singlet oxygen by aliphatic amines is well studied [14,15] and is explained in terms of reversible formation of an exciplex via charge-transfer interactions due to the electrophilic attack of excited oxygen on the amino group. The exciplex yields products by chemical reaction or undergoes intersystem crossing to regenerate amine and triplet oxygen.

This behavior, expected for lidocaine, fits our steady state and time resolved experiments. Photo-oxidation product



Scheme 1.

distribution, hydroperoxide detection, dependence of k_T^{LID} on pH for reaction in aqueous solution and the increase of lidocaine reactivity towards singlet oxygen in more polar aprotic media indicate that reaction between singlet oxygen and lidocaine occurs via formation of a charge-transfer exciplex followed by physical quenching or chemical reaction. Scheme 1 shows a mechanism compatible with these observations.

Although these results are consistent with a common mechanism for reactions of lidocaine or aliphatic amines with singlet oxygen, several differences require additional explanations. In particular, k_T^{LID} values are between one and two orders of magnitude lower than those previously reported for typical tertiary amines [10,11]. This lower reactivity of lidocaine relative to tertiary amines is not easily understood in terms of steric effects and we note that dependence of k_T^{LID} on solvent has a different pattern from that for amines [10]. For instance, k_T values in acetonitrile are $(2.36 \pm 0.09) \times 10^6$ and $33.3 \times 10^7\ M^{-1}\ s^{-1}$ [16] while in methanol, they are $(2.08 \pm 0.09) \times 10^6$ and $1.3 \times 10^7\ M^{-1}\ s^{-1}$ [11] for lidocaine and triethylamine, respectively. Tertiary aliphatic amines dramatically decrease their reactivities towards singlet oxygen when the media changes from aprotic polar solvents, such as acetonitrile or methylene chloride, to protic polar solvents such as aliphatic alcohols. In contrast to this well-established behavior, lidocaine reactivity in aprotic polar solvents is very close to that in aliphatic alcohols.

In order to understand the solvent effect on k_T^{LID} and explain the lower reactivity of the drug, we determined the rate constant for the reaction between triethylamine (a typical tertiary amine) and singlet oxygen, k_T^{TEA}, in the solvents employed to determine k_T^{LID}. These results are included in Table 1.

3.3. LSER and TLSER analysis of solvent effect on k_T^{LID} and k_T^{TEA}

With the aim of rationalizing differences in lidocaine reactivity relative to that typical of aliphatic amines and solvent effects on k_T^{LID}, we analyzed the k_T dependence on microscopic solvent characteristics by using the semi-empirical solvatochromic equation (LSER) of Taft, Kamlet et al. [17–19] (Eq. (2)).

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

where the parameters π^*, δ, α, β and ρ_H have been previously defined [17,20–24].

We also analyzed the k_T^{LID} dependence on the solvent by using a theoretical set of correlation parameters determined solely from computational methods [25–27]. Theoretical linear solvation relationship (TLSER) descriptors have been developed to give optimal correlation with the LSER descriptors [25,26]. The generalized TLSER equation proposed by Famini et al. [25–28] (Eq. (3)), can be used to analyze chemical reactivity.

$$\log k = \log k_0 + a\rho_H^2 + b\pi_1 + c\varepsilon_b + dq_- + e\varepsilon_a + fq_+ \quad (3)$$

In Eq. (3), the bulk/steric term is described by the Hildebrand parameter, ρ_H. The index of polarizability corresponds to π_1 and accounts for the ease of moving or polarizing electron cloud. π_1 is obtained by dividing the polarizability volume by the molecular volume. The hydrogen bond acceptor basicity (HBAB) involves covalent, ε_b, and electrostatic, q_-, terms. Similarly, the hydrogen bond donor acidity (HBDA) includes covalent, ε_a, and electrostatic, q_+, terms [25,28].

Table 2 shows the correlation equations for the dependence of k_T^{LID} and k_T^{TEA} on the solvent parameters. These equations were obtained through purely statistical analyses. The results show that not all the descriptors are significant. We accepted the descriptor coefficients having a significance level ≥ 0.95. For this reason, the δ parameter and the Hildebrand solubility parameter, ρ_H^2, were not included in LSER correlation. Similarly, the bulk/steric term, ρ_H^2, and the covalent terms for acidity, ε_a, and basicity, ε_b, were not included in the TLSER correlation.

From the correlation equations listed in Table 2 for the LSER approach applied to the reactions of singlet oxygen with lidocaine and triethylamine is observed that: (i) π^* coefficients for both lidocaine and triethylamine are very similar. This supports the proposed formation of an exciplex with a considerable charge transfer character for reactions of singlet oxygen with amines (as expected in the systems under study); (ii) α coefficient is negative for both lidocaine and TEA and is statistically more significant in the equation for TEA; (iii) β coefficients are positive for both lidocaine and TEA, and correlation equations indicate that HBA solvents contribute to exciplex stabilization. In the LSER equation for lidocaine, the β parameter coefficient is the most important

Table 2
LSER and TLSER correlation equations for the reactions of singlet oxygen with lidocaine and triethylamine

	$\log k = \log k_0 + a\pi^* + b\alpha + c\beta$ [a,b]				$\log k = \log k_0 + d\pi_1 + eq_+ + fq_-$ [c,d]			
	$\log k_0$	a	b	c	$\log k_0$	d	e	f
TEA								
Coefficient	7.924	0.321	−1.305	0.362	6.465	15.031	−6.047	1.254
±	0.111	0.151	0.134	0.184	0.487	4.109	0.647	0.372
t-Statistic	71.126	2.121	−9.705	1.967	13.278	3.658	−9.344	3.374
P (2-tail)	<0.0001	0.0444	<0.0001	0.0609	<0.0001	0.0015	<0.0001	0.0029
VIF		1.068	1.721	1.869		1.109	1.160	1.193
LIDOCAINE								
Coefficient	5.946	0.425	−0.813	1.318	4.734	12.022	−2.655	2.717
±	0.096	0.128	0.081	0.121	0.633	5.309	0.901	0.514
t-Statistic	62.106	3.318	−10.074	10.872	7.476	2.264	−2.947	5.290
P (2-tail)	<0.0001	0.0029	<0.0001	<0.0001	<0.0001	0.0343	0.0077	<0.0001
VIF		1.014	1.144	1.159		1.143	1.193	1.164

[a] $N = 28$, $R = 0.927$, S.D. $= 0.200$, $F = 48.995$ (TEA).
[b] $N = 28$, $R = 0.941$, S.D. $= 0.173$, $F = 61.306$ (LIDOCAINE).
[c] $N = 25$, $R = 0.919$, S.D. $= 0.215$, $F = 37.967$ (TEA).
[d] $N = 25$, $R = 0.786$, S.D. $= 0.299$, $F = 11.323$ (LIDOCAINE).

and larger than the corresponding parameter in the TEA equation.

TLSER equation gives similar results to those obtained with LSER. In Table 2, coefficients corresponding to the solvent polarizability, π_1, are very similar for both lidocaine and TEA, having the largest statistical significance in the correlations. The TLSER treatment also shows that HBD solvents inhibit the reaction of singlet oxygen with both lidocaine and TEA. However, the q_+ coefficient in the TEA equation is more than a factor two larger than that in the lidocaine equation. Concerning this point, we note that TLSER analysis indicates that influences of HBD solvents are mainly electrostatic, because only q_+ is included in the correlation equation, although for the solvent set studied, α shows a very good correlation with the theoretical parameters ε_A and q_+ ($\alpha = 0.820 - 5.803\,\varepsilon_A + 4.723\,q_+$; $R = 0.975$; $F = 211.94$). In addition, TLSER equation shows that HBA solvents increase the reaction rate, although the relative importance of the coefficient associated with the q_- parameter is lower than that for β in the LSER analysis.

The meaningful differences found for solvent effects on k_T^{LID} and k_T^{TEA} can be understood if solvents have specific effects on lidocaine and TEA reactions. The decrease of k_T^{TEA} in HBD solvents is explained in terms of hydrogen bonding interactions between the solvent and the amino nitrogen, which sterically hinders $O_2(^1\Delta_g)$ access to this nitrogen inhibiting exciplex formation. The effect of HBD solvents on k_T^{LID} is more complex. Lidocaine has an electron withdrawing amido group near the reaction site, which decreases the electronic density of the reactive nitrogen atom as predicted by simple semi-empirical quantum mechanical calculations. Determinations of charge densities by using MOPAC 97 with AM1 Hamiltonian show that electron density on the aminic nitrogen of lidocaine is lower than that on the nitrogen of TEA, which explains the lower reactivity of lidocaine towards singlet oxygen as compared with TEA. However, the expected decrease in lidocaine reactivity with a change from aprotic to protic solvents was not observed. This behavior may be rationalized if inductive electron withdrawal by the amido group is modified by solvent–lidocaine interactions or if hydrogen bonding between the nitrogen atom of the amino group and the solvent is weaker than in a typical tertiary amine, such as triethylamine. ^{13}C NMR spectra of lidocaine in methanol, methanol-D_4, and carbon tetrachloride show that in methanol and in methanol-D_4, the signal corresponding to the carboxylic carbon of the amido group is at 172.5 and 172 ppm, respectively, whereas in carbon tetrachloride it is at 167.5 ppm. These results allow us to disregard changes in electron withdrawal by the amido group as being responsible for the unexpectedly high reactivity of lidocaine in aliphatic alcohols. Furthermore, we expect that the strength of hydrogen bonding interactions will be decreased due to the low electron density on the amino nitrogen of lidocaine as compared with that in TEA. In addition, a cooperative participation of the amido oxygen to hydrogen bonding that weakens the HBD solvent-aminic nitrogen interaction may be considered. Both effects may explain the lower dependence of k_T on the α parameter for reaction between lidocaine and singlet oxygen. Rate effects of HBA solvents on the reaction of singlet oxygen with lidocaine and TEA can be understood in terms of stabilization of the exciplex by solvents with the highest β or q_- values. We can also conclude that the interaction between HBA solvents and the exciplex is mainly electrostatic, because the TLSER correlation shows that the reaction rate depends largely on the q_- parameter and is almost independent of ε_B. We note that in the solvents employed in this study, there is a reasonable correlation for the dependence of β with ε_B and q_- ($\beta = 0.494 - 3.555\,\varepsilon_B + 1.826\,q_-$; $R = 0.782$; $F = 17.273$).

The larger statistical significance of β (or q_-) for lidocaine as compared with TEA can be explained by intra-molecular interactions between the amido NH and the tertiary amino group. Thus, HBA solvents compete for the anilide H-bond donor group of lidocaine, diminishing the tendency for intra-molecular hydrogen bonding or intra-molecular electrostatic stabilization with the tertiary amino centre. As result, HBA solvents free the reactive centre for interaction with singlet oxygen, thus, increasing the quenching rate.

In conclusion, our data show that lidocaine is a moderate quencher of singlet oxygen. Our data also show that the lower reactivity of lidocaine towards singlet oxygen relative to that of triethylamine, is a consequence of electronic factors and that steric effects are not significant. Additionally, the solvent dependence of singlet oxygen quenching rate by lidocaine, as distinct from that for typical tertiary amines, is due to the presence of the amido group in lidocaine. LSER and TLSER analyses are valuable tools in understanding these results.

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