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ARTICLE

Photophysics and Photochemistry of the β -Lapachone Derived Diphenyldihydrodioxin: Generation and Characterization of Its Cation Radical

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José Carlos Netto-Ferreira^{a,b*}, Virginie Lhiaubet-Vallet^b, Bauer Bernardes^a, Aurelio Baird Buarque Ferreira^a and Miguel Ángel Miranda^b

Abstract The photophysics and photochemistry of the β -lapachone derived diphenyldihydrodioxin **3** were investigated using steady-state and time resolved techniques. Laser excitation of **3** leads to the formation of its cation radical **4** (absorption maxima at 410 and 450 nm and a lifetime of 10 μ s), which was confirmed by its thermal generation employing tris(2,4-dibromophenyl)-aminium hexachloroantimonate (BAHA) as the electron acceptor. The cation radical **4** was also formed *via* the triplet excited state of **3**, through a triplet sensitized process using benzophenone ($E_1=69$ kcal mol⁻¹) as the sensitizer.

Introduction

The photocycloaddition of *ortho*-quinones to olefins can lead to the formation of oxetanes ($[2\pi+2\pi]$ Paternò-Büchi reaction) and/or dioxins ($[4\pi+2\pi]$ reaction, Schönberg adduct).¹ It has been suggested that the keto-oxetane is photochemically unstable and can be converted back to reagents, with olefin isomerization,¹ and to a dioxol.²⁻⁴ With the *ortho*-quinones 1,2-naphthoquinone,⁵⁻⁷ tetrachloro-*ortho*-benzoquinone,^{8,9} acenaphthenequinone¹⁰ and 9,10-phenanthrenequinone¹¹ this reaction preferentially results in the formation of the $[4+2]$ photocyclization product, although in some cases keto-oxetanes are obtained as the main product.¹²⁻¹⁴ From our preliminary results, steady-state irradiation of β -lapachone (**1**) with simple olefins (including stilbene) does not result in the usual $[2\pi+2\pi]$ photocycloaddition (Paternò-Büchi) reaction, *i.e.* oxetane formation.¹⁵ However, when electron-rich olefins such as 2,3-diphenyl-1,4-dioxene (**2**) are employed, the only product observed is the corresponding dioxin, resulting from a $[4\pi+2\pi]$ photocycloaddition. Thus, the photoreaction of β -lapachone with **2** results in the formation of the Schönberg adduct, diphenyldihydrodioxin **3** (3,3-dimethyl-*cis*-9a,13a-diphenyl-2,3,9a,11,12,13a-hexahydro-1*H*-benzo[*h*][1,4]dioxino[2',3':5,6] [1,4]dioxino[2,3-*f*] chromene), as recently reported by us (Scheme 1).¹⁵ The main characteristic of this compound is the *cis*

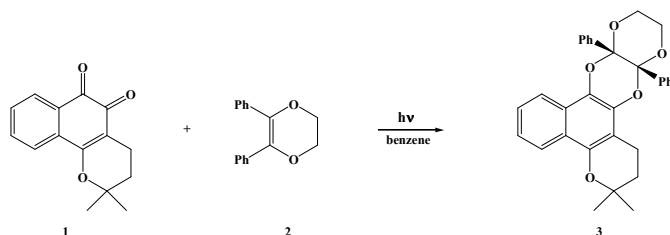
arrangement of the two phenyl groups at atoms C13 and C16, having a dihedral angle C23-C16-C13-C17 of 51.5(2)°, with the angle between the planes of the phenyl rings measuring 82.07(7)°.

Diphenyldihydrodioxins can undergo cycloreversion and despite the importance of this reaction for biological systems due to the fact that dihydrodioxins derived from pyrene-4,5-dione are efficient photoactivatable DNA-damaging agents,^{16,17} little is known about this process. Since *ortho*-quinones are extremely reactive, for their effective delivery to a DNA site it is necessary that they are masked and in this case their release will occur only upon binding to the target site. In this sense, diphenyldihydrodioxins such as **3** can be significantly promising to recognize and bind selectively to a specific DNA sequence.

The β -lapachone-mediated cytotoxicity in human cells is related to the two-electron oxidoreductase, NQO-1,¹⁸ with this enzyme being the responsible for the catalysis of the one-step two-electron reduction of β -lapachone, which is the principal determinant of its cytotoxicity to human cells.^{19,20}

Although **3** does not seem to hydrolyze easily on treatment with hydrochloric acid,²¹ it is expected to regenerate β -lapachone quite readily under photochemical or oxidative conditions, based on previous work performed with other dihydrodioxins.^{16,17} This raises the possibility of incorporating these regeneration processes into a protection-deprotection

cycle for *ortho*-quinones similar to **1**. Thus, in this work the photophysics and photochemistry of the β -lapachone (**1**) derived diphenyldihydrodioxin **3**, as well as the generation and characterization of its corresponding cation radical, was studied by nanosecond laser flash photolysis and ground state absorption spectroscopy.



Scheme 1

Experimental

Materials and Methods

The solvents, acetonitrile, benzene, dichloromethane, 1,4-dioxane, methanol and 2-propanol (Aldrich, spectrograde) were used as received. Naphthalene, tris(2,4-dibromophenyl)-aminium hexachloroantimonate (BAHA), 1,4-cyclohexadiene, benzophenone, from Aldrich, were used as received (purity >99%).

The olefin 2,3-diphenyl-1,4-dioxene (**2**) and the diphenyldihydrodioxin **3** were synthesized following procedures from the literature.^{15,22} A detailed description of the synthesis for these compounds can be found in the Supporting Information, together with their spectroscopic and spectrometric data (Figures 1S-4S).

Instruments

Ground state absorption spectra were measured using an HP diode array spectrophotometer model 8452A. Steady-state fluorescence emission was recorded in a Photon Technology Instruments spectrofluorometer, equipped with a lamp power supply (LPS-220B), working at room temperature. The excitation wavelength for emission spectra was 355 nm. Quantum yields were measured using naphthalene in acetonitrile as standard ($\Phi_{\text{fluor}}=0.21$)²³. For relative emission quantum yield measurements, the excitation bandwidth was 1 nm, and the absorbance of the sample and of naphthalene were fixed at a value of 0.1 at the excitation wavelength (295 nm). Samples used for emission spectra and quantum yield determinations were placed into quartz cells of 1 cm path length and purged with N₂ for 20 min.

Steady-State Photolysis

Solutions containing the diphenyldihydrodioxin **3** (0.1 mmol L⁻¹) in acetonitrile were irradiated in a multilamp photoreactor equipped with 10 lamps (Osram Sylvania, F15T8/BLB) from 310 to 410 nm with a maximal output (1 mW cm⁻²) at ca. 360 nm. The reaction was followed by GC-MS (quadrupole mass selective detector connected to a gas chromatograph (Agilent), equipped with a DB-1 capillary column (15 m, film thickness 1 mm, i.d. 0.25 mm) - conditions: initial temperature=100 °C (5 min); ramp of 20 °C/min, from 100 to 280 °C; final temperature=280 °C (5 min).

Time resolved fluorescence emission

Time resolved fluorescence emission experiments were performed employing an Edinburgh FLS-920 spectrofluorimeter equipped with a picosecond light emitting diode from Edinburgh Instruments ($\lambda_{\text{exc}}=280$ nm; 850 ps/pulse; 1,8 μ W/pulse).

Laser flash photolysis

These experiments were carried out using the 3rd harmonic ($\lambda_{\text{exc}}=355$ nm) of a Quantel pulsed Nd:YAG spectrum laser system instrument. The single pulses were ca. 10 ns duration, and the energy was ca. 35 mJ per pulse. A Xenon lamp was employed as detecting light source. The laser flash photolysis apparatus consisted of the pulsed laser, the Xe lamp, a monochromator, and a photomultiplier (PMT) system made up of side-on PMT, PMT housing, and a PMT power supply. The output signal from the Tektronix oscilloscope was transferred to a personal computer for study. Samples were contained in 10 × 10 mm cells made of Suprasil quartz and were deaerated for at least 20 min with dry nitrogen prior to the experiments. The concentration for the samples was adjusted to yield an absorbance of $\square 0.3$ at the excitation wavelength. Stock solutions of quenchers were prepared so that it was only necessary to add microliter volumes to the sample cell in order to obtain appropriate concentrations of the quencher.

Results and Discussion

The ground state absorption spectrum for the diphenyldihydrodioxin **3** shows bands at 212 and 245 nm together with a broad band from 270 to 360 nm, with maximum at 317 nm, in acetonitrile (Figure 5S, Supporting information). Its fluorescence emission spectrum displays a strong emission at 384 nm in acetonitrile and is the mirror image of its excitation spectrum, which matches the absorption spectrum in the 280-360 nm region of the spectrum (Figure 6S, Supporting information). This emission is dependent on

the solvent polarity and in benzene the maximum is blue-shifted by 13 nm, compared to the methanol (Figure 7S, Supporting information). A fluorescence quantum yield of 0.06 was measured in acetonitrile, using naphthalene as standard. Time resolved fluorescence emission experiments revealed a lifetime associated to this emission of 2.5 ± 0.1 ns.

Laser excitation (355 nm) of a 1 mmolar solution of **3**, in acetonitrile, leads to the formation of a new transient, **4**, showing absorption maxima at 410 and 450 nm (Figure 1) and a lifetime of 10 μ s. This species is not quenched by common triplet quenchers such as 1,3-cyclohexadiene and β -carotene.²³ Furthermore, even after the addition of a large amount of 1,3-cyclohexadiene no changes could be observed in both the decay lifetime and in the intensity at 410 nm recorded right after the laser pulse. These results lead us to conclude that this transient is neither the triplet excited state of **3** nor is derived from a triplet precursor. It is important to note that the triplet excited state of naphthalene derivatives usually has a lifetime of the order of microseconds.²³ These results led us to conclude that in this case the probable precursor for this transient is the singlet excited state of **3**.

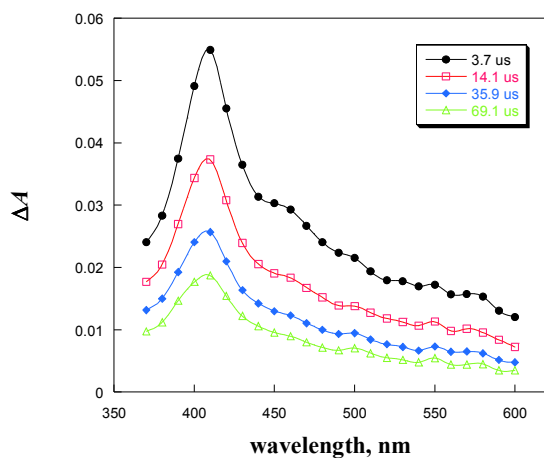
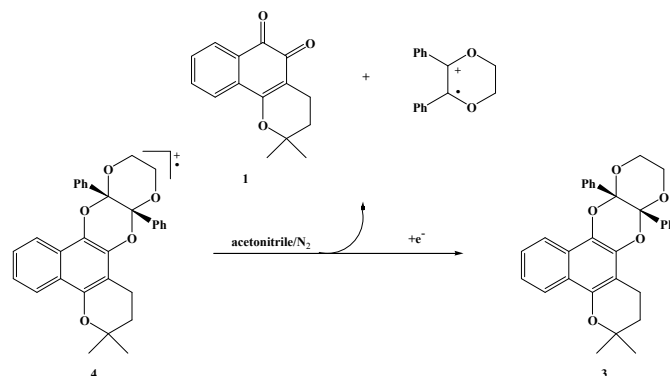


Figure 1. Transient absorption spectra obtained upon excitation at 355 nm of a solution of the diphenyldihydrodioxin **3** in acetonitrile.

It is known that dihydrodioxins are able to form stable cation radicals in solution upon direct excitation as a consequence of electron ejection.¹⁶ Assuming that the radical cation **4** is formed from the irradiation of **3**, the pair β -lapachone/2,3-diphenyl-1,4-dioxene cation radical is expected to be formed. The alternative fragmentation to yield the cation radical derived from β -

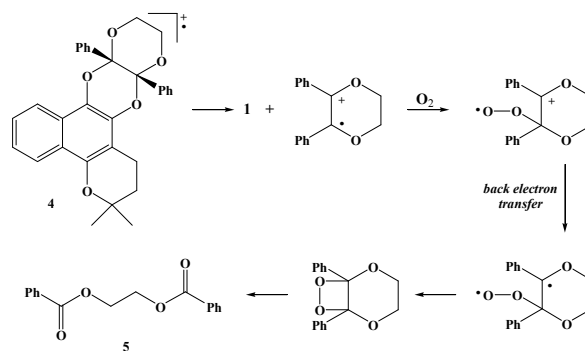
lapachone and 2,3-diphenyl-1,4-dioxene (**2**) can be ruled out on energetic grounds.

To get some insight on the fate of the radical cation **4**, steady-state irradiation ($\lambda_{\text{exc}}=355$ nm) of a millimolar deoxygenated solution of **3** in acetonitrile was performed. The reaction was analyzed by GC-MS and the only products observed were β -lapachone (**1**) and 2,3-diphenyl-1,4-dioxene (**2**) (Figures 8S-10S, Supporting Information).



Scheme 2

However, when the reaction was performed in the presence of oxygen, we still could observe the formation of β -lapachone, but there was no indication of the presence of the dioxene **2**. In this case, a new product was observed (retention time 12.18 min; MW=270) which was identified by mass spectrometry as the diester ethylene dibenzoate (**5**) (Figure 11S). Its formation, under oxygenated conditions, possibly involves a dioxetane intermediate, resulting from the interaction between molecular oxygen and the 2,3-diphenyl-1,4-dioxene radical cation formed from the decay of **4** (Scheme 3), as previously proposed in the literature.²⁴ From these results we can conclude that the preferential decay mode for **4** involves formation of the 2,3-diphenyl-1,4-dioxene radical cation.



Scheme 3

To further confirm the nature of the intermediate formed upon photolysis of **3**, the thermal generation of the radical cation **4** was performed by employing tris(2,4-dibromophenyl)-aminium hexachloroantimonate (BAHA) as the electron acceptor.²⁵ Ground state absorption spectra were recorded after successive additions of μL aliquots (from 0 to 600 μL) of a 1.0 mmol L^{-1} solution of BAHA to a 1.0 mmol L^{-1} solution of diphenyldihydrodioxin **3**, in dichloromethane. (Figure 12S in supporting information shows all absorption spectra obtained after these additions). The initially colorless solution of **3** became reddish, with the new species formed displaying absorption maxima at 407 and 460 nm (Figure 2).

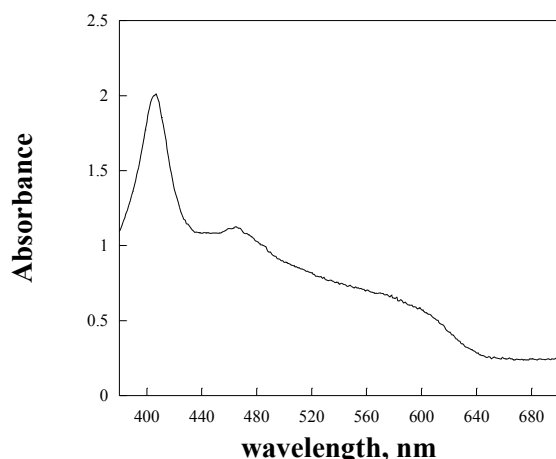


Figure 2. Absorption spectrum for **4** generated thermally and obtained after addition of a 600 μL aliquot of 1.0 mmol L^{-1} solution of BAHA to a 1.0 mmol L^{-1} solution of **3** in dichloromethane.

The absorption spectrum obtained after BAHA addition to the diphenyldihydrodioxin matches with that observed in the laser flash photolysis experiments (Figure 13S, supporting information), to which we previously assigned the radical cation **4** (Figure 1). The small hypsochromic shift observed in the absorption spectrum of the thermal generated cation radical may be due to a solvent effect. These results unequivocally demonstrate that **4** can be formed either by direct photolysis or thermally.

It is worth noting that the radical cation **4** generated through the thermal electron transfer from the diphenyldihydrodioxin **3** to BAHA has a decay time of

the order of hours. Figure 3 shows all absorption spectra corresponding to the decay of **4** as a function of time, from 0 to 300 min, and the *inset* in Figure 3 displays the kinetic trace corresponding to this decay.

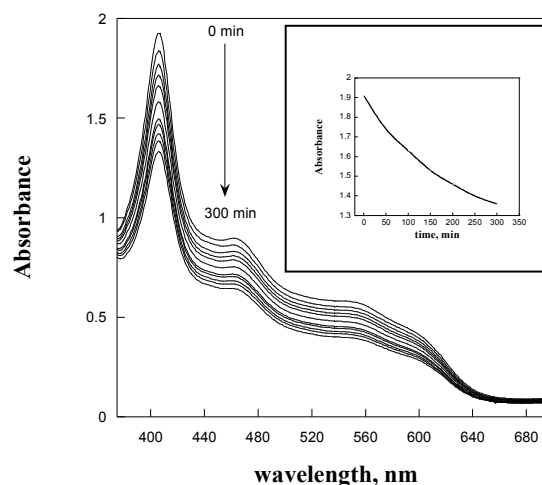


Figure 3. Absorption spectra corresponding to the decay of **4** as a function of time, from 0 to 300 min. The cation radical **4** was obtained by addition of a 600 μL aliquot of 1.0 mmol L^{-1} solution of BAHA to a 1.0 mmol L^{-1} solution of **3**, in dichloromethane. *Inset:* Kinetic trace corresponding to this decay, monitored at 410 nm.

Interestingly, this decay is much slower than observed when **4** is formed upon direct irradiation ($\tau=10\text{ }\mu\text{s}$), which can be due to a fast back electron transfer in the latter case, with this process not being effective for the thermal reaction employing BAHA. Similar behavior was observed in the case of pyrenedi hydrodioxin.¹⁶ The above results seem to indicate that the formation of the radical cation **4** through the direct excitation of the diphenyldihydrodioxin **3** occurs from its singlet excited state. Based on this, we decided to investigate the possibility of the formation of **4** *via* the triplet excited state of **3**, which has to be formed through a triplet sensitization process. Benzophenone ($E_{\text{T}}=69\text{ kcal mol}^{-1}$)²³ was chosen as the triplet sensitizer since it is very well known that naphthalenes are good quenchers of benzophenone triplet.²⁶

Laser excitation ($\lambda_{\text{exc}}=355\text{ nm}$) of a millimolar solution of benzophenone, in acetonitrile, yields a transient absorption at 525 nm due to triplet benzophenone (Figure 4A),²⁷ which was readily quenched in the

presence of the diphenyldihydrodioxin **3** (up to 0.1 millimolar). A linear quenching plot (Figure 14S – Supporting Information) following equation 1 was obtained,²⁸ resulting in a rate constant of $k_q = (9.7 \pm 0.2) \times 10^9 \text{ L mol}^{-1} \text{ s}^{-1}$, close to the diffusion control limit for acetonitrile ($k_{\text{diff}} \sim 1 \times 10^{10} \text{ L mol}^{-1} \text{ s}^{-1}$).²³ This indicates that the benzophenone triplet is being quenched by **3** through a triplet–triplet energy transfer mechanism.

$$k_{\text{obs}} = k_o + k_q[Q] \quad \text{eq.1}$$

where: k_{obs} is the pseudo-first order rate constant for the triplet decay; k_o is the triplet decay rate constant in the absence of quencher; k_q is the triplet decay rate constant in the presence of the quencher and $[Q]$ is the quencher concentration in mol L^{-1} .

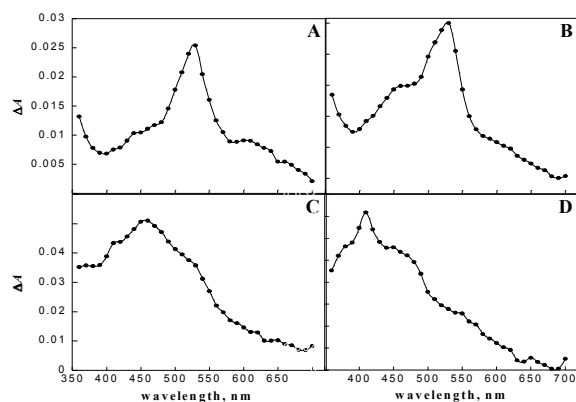


Figure 4. Transient absorption spectra for: (A) triplet-triplet absorption for 1 mM benzophenone in acetonitrile recorded 400 ns after the laser pulse; (B) transient formed after addition of a 0.1 mM solution of **3** and recorded 1 μs after the laser pulse; (C) same as (B), recorded 5 μs after the laser pulse; (D) same as (B), recorded 15 μs after the laser pulse

The transient absorption spectrum obtained upon laser excitation of a solution containing benzophenone (1.0 mM) and the diphenyldihydrodioxin **3** (1.0 mM), in ACN, and recorded 400 ns after the laser pulse, clearly shows that beside the absorption due to the benzophenone triplet, at 525 nm, a new species is growing-in at 460 nm (Figure 4B). This species is fully formed 1.0 μs after the laser pulse (Figure 4C) and was tentatively assigned to the triplet excited state of **3**. Meanwhile, the triplet benzophenone completely disappeared. The transient absorption spectrum for this same mixture recorded 15 μs after the laser pulse is completely replaced by a new transient with absorption maxima at 410 and 460 nm (Figure 4D). In fact, the absorption spectrum for this transient perfectly matches

those obtained in Figures 1 and 2, to which we assigned the radical cation **4**. These results unequivocally demonstrate that **4** can be formed through either the singlet or the triplet excited state of **3**.

It is worth noting that since the decay of **4** leads to β -lapachone (**1**) formation as shown in Scheme 2, two possibilities arise: 1) the triplet of the later can be further formed upon excitation, and quenching of this triplet through electron transfer from another molecule of the diphenyldihydrodioxin **3**, can lead to the formation of its cation radical **4**, releasing another molecule of β -lapachone; 2) excited diphenyldihydrodioxin is preferentially quenched by electron transfer to previously formed **1**, also leading to **4**. Either way an autocatalytic reaction could be involved.

Conclusions

Formation of the cation radical derived from β -lapachone diphenyldihydrodioxin is proposed to occur through both singlet and triplet excited state mechanisms, with these results being supported by steady-state and time resolved techniques. This assignment was confirmed by the thermal generation of this radical cation employing tris(2,4-dibromophenyl)-aminium hexachloroantimonate (BAHA) as the electron acceptor. Product studies clearly indicate that the main decay mode of this cation radical involves the pair β -lapachone/2,3-diphenyl-1,4-dioxene radical cation. Since the cation radical derived from β -lapachone diphenyldihydrodioxin can regenerate β -lapachone quite readily under photochemical or thermal conditions, this raises the possibility of incorporating these regeneration processes into a protection-deprotection cycle for *ortho*-quinones in general.

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Notes and references

- ^aDepartamento de Química – Universidade Federal Rural do Rio de Janeiro, Antiga Rio São Paulo, km 47, Seropédica 23970-000 RJ, Brazil.
- ^bInstituto de Tecnología Química UPV-CSIC, Universitat Politècnica de València, Avda. de los Naranjos s/n, 46022 Valencia, Spain.

Electronic Supplementary Information (ESI) available. Synthesis of 2,3-diphenyl-1,4-dioxene and diphenyldihydrodioxin **3**; IR, MS, ^1H and ^{13}C NMR, UV-visible and fluorescence spectra for **3**; GC traces for **1**, **2**, and **3** under different conditions; absorption spectra for the thermal generation of the diphenyldihydrodioxin cation radical **4** and Stern-Volmer plot for the quenching of benzophenone triplet by diphenyldihydrodioxin **3**.

See DOI: 10.1039/b000000x/

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