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A Phenolic Antioxidant Releasing Nitric Oxide on Demand

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A novel molecular conjugate (**1**) that combines radical scavenging properties to light-regulated release of nitric oxide (NO) has been designed and synthesized by a straightforward procedure. This compound integrates a catecholic unit and a suitable NO photodonor, separated by an alkyl spacer, into the same molecular skeleton. The radical scavenging properties of **1** were evaluated by investigating its reactivity toward hydrogen abstraction by *tert*-butoxy radical by using laser flash photolysis techniques. The catecholic function of **1** is transparent to visible light, which, in contrast, is exclusively absorbed by the NO photodonor, resulting in the photocontrolled release of this radical species, monitored by an ultrasensitive NO electrode. A comparison of the value of the hydrogen abstraction rate constant and the amount of NO photoreleased with those of reference models demonstrates the retention of the single properties into the new molecular entity. This characteristic together with its water solubility make **1** a potential model system in the perspective of "multitarget" compounds for biomedical research studies.

Introduction

The design and development of multitarget drugs is one of the most intriguing challenges in the wide arena of biomedical research.[1] Namely, these compounds are single chemical entities able to address simultaneously more than one target with the aim of enhancing efficacy relative to drugs that address only a single target and, in principle, can be used for the treatment of complex diseases.[1–3] This strategy represents a significant step forward with respect to the "one-target, one-disease" approach that continues to dominate the pharmaceutical industry today and anticipates some benefit compared to the use of a monotarget drug cocktail.[1]

One of the most interesting cases of multitarget compounds is that of nitric oxide (NO)-donor phenol hybrids.[4] This interest is strongly motivated by the key role NO plays in a broad array of physiological processes,[5] encompassing hormone secretion, neurotransmission and vasodilatation, as well as by the well-known antioxidant properties of synthetic and naturally occurring phenolic compounds (ArOH).[6] Recently, Gasco and co-workers have shown a series of phenols containing NO-donor hybrids as potential candidates to tackle some forms of cardiovascular diseases.[7] However, it should be stressed that NO can act as a *double-edged sword* as far as its biological effects are concerned, being either beneficial or detrimental depending on the dose.[8] Considering than NO formation in vivo is precisely regulated by enzymes and signal transduction machinery, NO donors with controllable release of NO seem indispensable for developing potential therapeutic agents.

The easy manipulation of photons associated with the instantaneous initiation/stopping of photochemical reactions depending on the presence or not of the illumination make *light* the most appealing external on/off trigger to accurately regulate the NO dosage. Furthermore, photons offer the additional advantages to make the NO delivery both spatially and temporally controlled,[9] without affecting important physiological parameters such as pH, temperature, ionic strength, and so on, which is advantageous in view of biomedical applications. As a consequence, the combination of phenol-like antioxidant centers with suitable NO-photodonor appendages represents a valuable objective to pursue. In principle, these compounds would offer the possibility to act as radical scavengers in the dark with the additional property of NO delivery with great accuracy of the dosage, when stimulated by light.

Prompted by our ongoing interest in developing functional NO photoreleasing systems,[10] in this paper we demonstrate the above *proof of concept* by designing and synthesizing conjugate **1** (Scheme 1) as a potential multitarget compound. It integrates a catecholic unit as a radical scavenging center and a nitroaniline derivative, which we have recently discovered to be a good NO photodonor.[10b–10g,11] The rationale behind the choice of catechol as the antioxidant center is that phenols with two *ortho*-hydroxy groups are known to be among the most active antioxidants[12] and, in this case, are also transparent to visible light. This latter feature makes the nitroaniline derivative the only chromogenic center absorbing the visible light, resulting in

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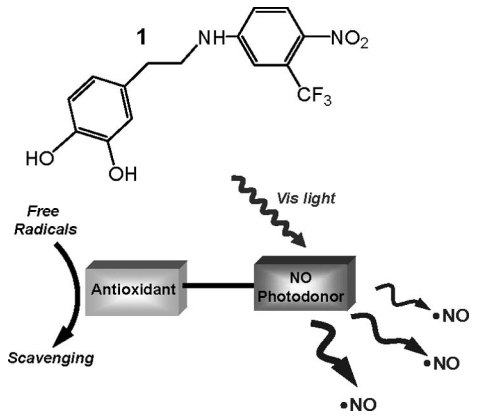
the regulated release of NO without affecting the radical scavenging properties of the catecholic unit.



Scheme 1. The molecular structure of **1** and its working principle.

Results and Discussion

Conjugate **1** was easily synthesized in two steps and its absorption spectrum together with those of suitable model compounds is reported in Figure 1. The absorption features of **1** (Figure 1, *a*), reflect very well those of the equimolar mixture of the single components (Figure 1, *b* and *c*), accounting for negligible mutual interaction between the two functional units in the ground state.

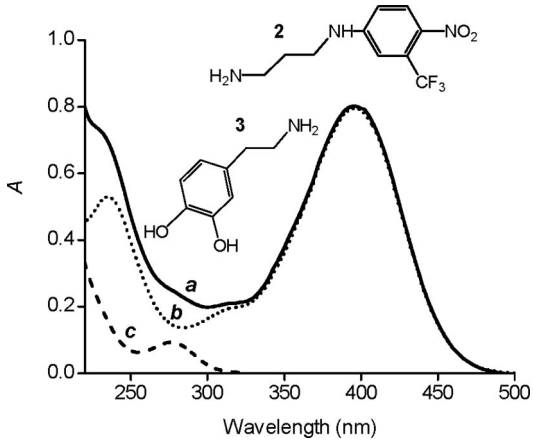


Figure 1. Absorption spectrum of a 10^{-4} M aqueous solution of **1** (*a*) and model compounds **2** (*b*) and **3** (*c*).

Phenolic antioxidants are prototypic chain-breaking antioxidants exerting their therapeutic action via the transfer of a hydroxylic H atom to the chain carrying free radicals at a rate faster than that of chain propagation.[13] The better antioxidant activity of catecholic derivatives is largely due to the stabilization of the aryloxyl radical (derived after hydrogen abstraction) due to the formation of intramolecular hydrogen bonding with the adjacent hydroxy group,[14] which is obviously absent in other phenols.

The radical scavenging properties of **1** were evaluated by investigating its reactivity toward hydrogen abstraction by *tert*-butoxyl radicals. The choice of these radicals as the oxidizing agents is not casual. In fact, existing literature data on their reactivity with catechol and other substituted phenols[15] will allow us to compare the free radical scavenging of **1** with that of the isolated antioxidant center.

The experiments were carried out in *tert*-butyl peroxide as solvent and *tert*-butoxyl radicals were generated in situ by fast laser flash photolysis (within the duration of the laser pulse of ca. 6 ns) of di-*tert*-butyl peroxide [Equation (1)], using the third harmonic of a Nd-YAG laser (λ_{exc} = 355 nm) as the excitation light source:

$$t\text{BuOO}t\text{Bu} \xrightarrow{h\nu} 2\ t\text{BuO}^{\bullet} \quad (1)$$

tert-Butoxyl radicals may decay by β-cleavage and reaction with the solvent [Equation (2)].[16] However, in the presence of hydrogen-atom donors, such as ArOH, the *tert*-butoxyl radicals are capable of abstracting a hydrogen atom from the phenolic OH groups, generating, therefore, a phenoxyl radical [(ArO•; Equation (3)].

$$t\text{BuO}^{\bullet} \xrightarrow{k_2} \text{decay} \quad (2)$$

$$t\text{BuO}^{\bullet} + \text{ArOH} \xrightarrow{k_3} \text{ArO}^{\bullet} + t\text{BuOH} \quad (3)$$

Laser flash photolysis with nanosecond time-resolution is a powerful tool for obtaining spectroscopic and kinetic features of phenoxyl radicals. Indeed, these species are generally characterized by lifetimes in the microsecond scale and spectral absorptions in the UV/Vis region.[15]

Following irradiation of di-*tert*-butyl peroxide with 355 nm laser excitation in the presence of **1**, we could readily monitor the appearance of a transient with absorption bands in the 380–420 nm region (Figure 2). According to

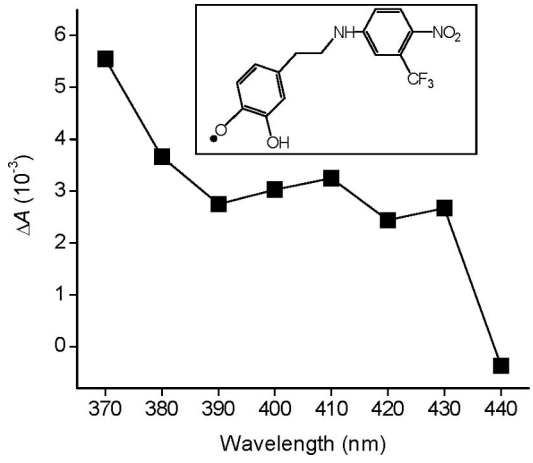


Figure 2. Transient absorption spectrum observed 10 μs after 355 nm laser excitation of a N_2-saturated di-*tert*-butyl peroxide solution containing compounds **1** (0.2 mM). $E_{355} \approx 5$ mJ/pulse.

the literature,[17] this transient species can be safely assigned to the semiquinone radical resulting from H abstraction from **1** (see inset Figure 2).

Figure 3 shows a typical build-up trace (following laser excitation) at 370 nm observed for the growth of the phenoxyl radicals from **1** in Equation (3). In order to determine the absolute rate constants k_3 we used low laser pulse energy (<6 mJ/pulse). Such a weak laser impulse ensures that (*i*) the initial concentrations of *t*BuO$^{\cdot}$ radicals is small and (*ii*) the heating of the solution is negligible. Under these experimental conditions, the loss of *tert*-butoxyl radicals by the reverse of Equation (1) is negligible and the observed rate constant, k_{obs}, for the growth of ArO$^{\cdot}$ [Equation (3)], is related to the concentration of ArOH via simple linear Equation (4).

$$k_{obs} = k_2 + k_3[\text{ArOH}] \quad (4)$$

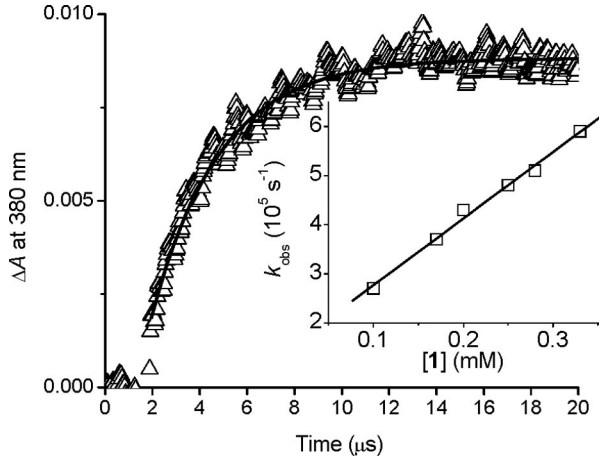


Figure 3. Representative experimental trace showing the buildup of phenoxyl radicals observed after 355 nm laser excitation of a di-*tert*-butyl peroxide solution of **1** (0.2 mM) and related first-order fitting. $E_{355} \approx 5$ mJ/pulse. The inset shows the plot of k_{obs} as a function of the concentration of **1** according to Equation 4.

The inset of Figure 3 reports the plots k_{obs} vs. [ArOH] obtained by changing the concentration of **1** and by determining the corresponding values of k_{obs} for the growth of ArO$^{\cdot}$.[18] Equation (4) appeared to be valid under all the experimental conditions employed. The slopes of the straight lines afforded a k_3 value of 1.4×10^9 M^{-1} s^{-1}. This value is basically similar to that reported for the same radicals with catechol (1.9×10^9 M^{-1} s^{-1})[15] and provides strong evidence that the radical scavenging properties of the antioxidant center are preserved in conjugate **1**.

For a complete characterization of the physicochemical properties of **1**, we also monitored the fate of the phenoxyl radical over time. Figure 4 shows the decay profile of this species at 380 nm. It is possible to note that the experimental trace is best fitted by a second-order function and the transient absorption does not go to zero. These results are in excellent agreement with the disproportionation pathway commonly expected for semiquinone radicals, which, as extensively known from the literature[17a,19] and exemplified in the inset of Figure 4 for **1**, lead to orthoquinone species strongly absorbing at ca. 380 nm.

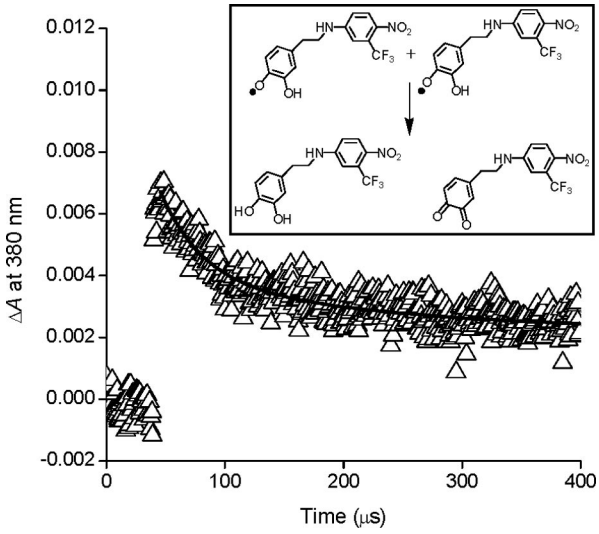
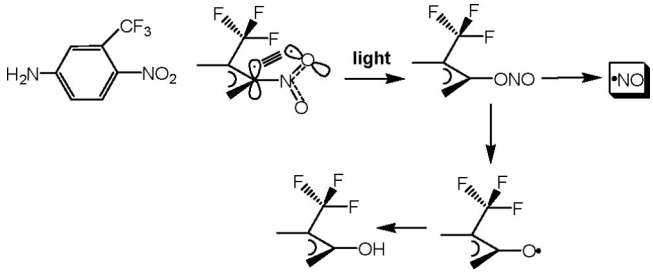


Figure 4. Representative experimental trace showing the decay of the phenoxyl radical observed after 355 nm laser excitation of a di-*tert*-butyl peroxide solution of **1** and related second-order fitting. $E_{355} \approx 5$ mJ/pulse.

The mechanism leading to NO photorelease from the photoactive unit of **1** has been described in our previous works.[10a–10g] However, we consider it useful to recall it in Scheme 2 for the sake of clarity.



Scheme 2. The NO photodonor unit and its mechanism of NO release.

Briefly, due to the presence of the CF_3 substituent the nitro group is placed almost perpendicularly to the aromatic plane. This *out of plane* geometry makes the p orbital of the oxygen atom have a constructive overlap with the adjacent p orbital of the aromatic ring in the ground state. Such a twisted conformation is crucial in triggering NO photorelease, which takes place through a nitro to nitrite photorearrangement followed by the rupture of the O–NO bond, leading to the concomitant generation of NO and a phenoxyl radical that, eventually, gives a phenol derivative as the only stable product. It is noteworthy that, analogously to some dimethylnitrobenzene derivatives, the photoactive center of **1** is unique in its mechanism of NO release.

The capability of **1** to generate NO under the exclusive control of light excitation was demonstrated by using an ultrasensitive electrode that detects directly and in real time this ephemeral radical species with nM concentration resolution, by an amperometric technique. From the absorption spectra of Figure 1 one can promptly note that our design ensures that the visible light radiation used in the experiments (λ_{exc} = 420 nm) is selectively absorbed by the NO photodonor unit. As shown in Figure 5, irradiation **1** results in the linear generation of NO, which promptly stops when the light is turned off and restarts as the light is turned on again, providing unambiguous evidence for the exclusive light-controlled generation of NO.

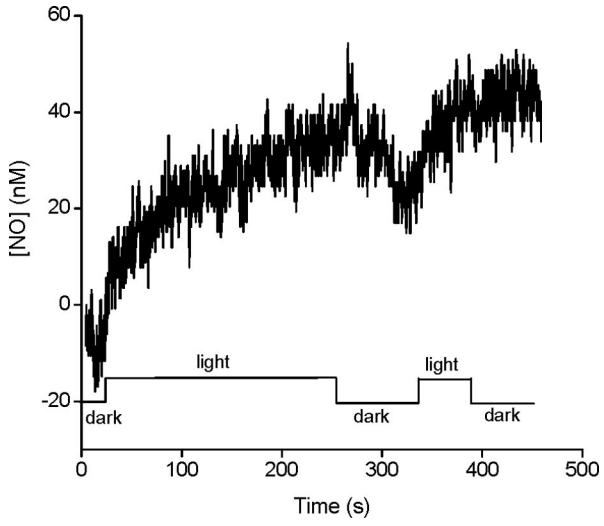


Figure 5. NO released upon 420 nm light irradiation of a water/MeOH (99:1) solution of **1** at 25 °C.

From the linear portions of the chronoamperogram, an average rate for NO release of ca. 0.25 nM s^{-1} can be estimated. Such a value is very close to that observed in the case of model compound **2** (ca. 0.30 nM s^{-1}) under identical experimental conditions and indicates that the photoexcited NO photodonor in conjugate **1** is not involved in any significant intramolecular interaction (i.e., photoinduced electron transfer)[20] with the antioxidant unit, retaining its own photochemical properties. That the mechanism for NO release reported in Scheme 2 applies also in the case of conjugate **1** was also confirmed by additional photolysis experiments. Figure 6 reports the spectral changes observed after different intervals of irradiation of a solution of **1**. The photolysis profile is virtually identical to that noted upon irradiation of the isolated NO photodonor unit (data not shown), accounting for no changes in the nature of the main photochemical reaction. The ESI-MS analysis of the crude reaction mixture carried out immediately after the photolysis experiments further validates this point. In fact, a main peak with a $[M + 1]^+$ value of 314.4 corresponding to the phenol derivative reasonably expected after NO release was revealed, besides that of the remaining starting compound. This represents an uncommon advantage in view of the potential bioapplications of **1**. In fact, one of the main problems associated with the NO donor is the formation of toxic side products. In the present case, the phenol derivative generated after NO release is expected to be biocompatible, and moreover, in light of the presence of the hydroxy functions, it is also expected to exhibit radical scavenging properties. Studies in this concern are currently in progress in our laboratory.

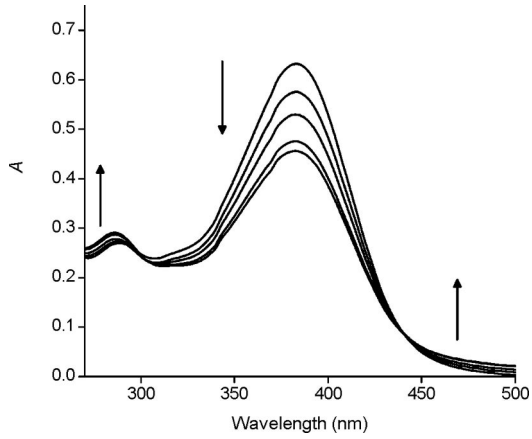


Figure 6. Absorption spectral changes observed upon 0, 10, 20, and 40 min irradiation (λ_{exc} = 420 nm) of a water/MeOH (99:1) solution of **1**. The arrows indicate spectral evolution with time.

Conclusions

We report the successful design of a novel, water soluble, potential multitargeted compound merging radical scavenging properties with the ability to release NO under the input of visible light stimuli. The suitable choice of the two independent units is, of course, crucial for the single properties to be retained in the new molecular conjugate, offering the possibility of joining, in a single compound, two functional molecules without any loss of their effectiveness. We would like to emphasize that, in contrast to nonphotoactivated compounds, the preservation of the properties of two independent units once merged into the same molecular skeleton is not obvious in the case of photoactivable molecular systems. In most of these cases, the properties of the conjugate can be in fact considerably affected due to the occurrence of intramolecular photoinduced energy and/or electron-transfer processes that preclude the final goal.

The concept of balance between the independent units is central in the multitarget approach. In the case of the NO-donor–antioxidant hybrids known to date, for example, the capacity of NO release is commonly adjusted by changing the structure of the NO-donor moiety appropriately. In this concern, photoactivable conjugate **1** may represent a valid alternative to these systems, as NO release can be immediately activated, stopped, or accurately tuned depending on the light intensity. We finally believe that our *proof-of-concept* logical design can, in principle, be extended to a variety of *ad-hoc* chosen antioxidant and NO photodonor functional molecules, paving the way for the development of

novel classes of multitarget compounds for biomedical research.

Experimental Section

Materials: All chemicals were purchased from Sigma–Aldrich and used as received. Di-*tert*-butyl peroxide was purchased from Aldrich and was passed through alumina before use. All solvent used (from Carlo Erba, Milan) were analytical grade. Model compound **2** was synthesized according to our previously reported procedure,[10f] whereas model compound **3** was purchased from Sigma–Aldrich and used as received.

4-(2-{[4-Nitro-3-(trifluoromethyl)phenyl]amino}ethyl)benzene-1,2-diol (1): Compound **1** was synthesized by a two-step synthesis reported in the following. Syntheses were carried out under a low intensity level of visible light.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-4-nitro-3-(trifluoromethyl)aniline (1a):** 2-(3,4-Dimethoxyphenyl)ethanamine (500 mg, 2.76 mmol), 4-chloro-1-nitro-2-(trifluoromethyl)benzene (622 mg, 2.76 mmol), and sodium carbonate (230 mg, 2.76 mmol) were heated at reflux in CH_3CN (15 mL) under continuous stirring for 16 h. After cooling down to ambient temperature the resulting suspension was filtered. The organic solution was concentrated under reduced pressure and purified by column chromatography (silica gel; CH_2Cl_2/cyclohexane, 7:3) to give **1a** (4.1 g, 76%). $C_{17}H_{17}F_3N_2O_4$ (370.33): calcd. C 55.13, H 4.63, N 7.56; found C 54.32, H 4.78, N 7.15. MS (ESI): *m*/*z* (%) = 371.2 (100) $[M + H]^+$. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 9.2 Hz, 1 H, ArH), 7.15 (d, *J* = 2.4 Hz, 1 H, ArH), 6.84 (d, *J* = 8.2 Hz, 1 H, ArH), 6.75 (dd, *J* = 8.2, 1.8 Hz, 1 H, ArH), 6.71 (d, *J* = 1.8 Hz, 1 H, ArH), 6.64 (dd, ^{1} = 9.2, 2.4 Hz, 1 H, ArH), 4.58 (br. s, 1 H, NH), 4.26 (t, *J* = 7.2 Hz, 2 H, NH*CH*$_2$), 3.88 (s, 6 H, OCH_3), 2.91 (t, *J* = 7.2 Hz, 2 H, Ar*CH*$_2$) ppm.

4-(2-{[4-Nitro-3-(trifluoromethyl)phenyl]amino}ethyl)benzene-1,2-diol (1): Compound **1a** (120 mg, 0.32 mmol) was dissolved in anhydrous CH_2Cl_2 (12 mL) and cooled to –78 °C. Afterwards, BBr_3 (1 M in CH_2Cl_2, 2.1 mL) was added dropwise. The reaction mixture was stirred for 2 h at this temperature and then overnight (16 h) at room temperature. Upon completion, the reaction mixture was quenched by adding water and extracted with CH_2Cl_2. The organic layer was washed with water, dried with anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (2–6% MeOH in CH_2Cl_2) to afford desired product **1** (80 mg, 73%). $C_{15}H_{13}F_3N_2O_4$ (342.27): calcd. C 52.64, H 3.83, N 8.18; found C 52.12, H 3.95, N 7.95. MS (ESI): *m*/*z* (%) = 343.3 (100) $[M + H]^+$. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 9.2 Hz, 1 H, ArH), 7.53 (d, *J* = 2.4 Hz, 1 H, ArH), 6.98 (d, *J* = 1.9 Hz, 1 H, ArH), 6.85 (d, *J* = 7.8 Hz, 1 H, ArH), 6.83 (dd, *J* = 7.8, 1.9 Hz, 1 H, ArH), 6.64 (dd, *J* = 9.2, 2.4 Hz, 1 H, ArH), 5.83 (br. s, 1 H, NH), 4.21 (t, *J* = 7.2 Hz, 2 H, NH*CH*$_2$), 2.98 (t, *J* = 7.2 Hz, 2 H, Ar*CH*$_2$) ppm.

Instrumentation: ^{1}H NMR spectra were recorded with a Varian INOVA 200 spectrometer, using TMS as internal standard. Mass spectra were recorded with an Agilent 1100 series ESI/MSD spectrometer. Experimental conditions were as follows: capillary voltage, 3.5 KV; fragmentor, 100 V; source temperature, 350 °C; drying gas, N_2 (10 L/min), carrier solvent, methanol (0.4 mL/min). The samples were dissolved in methanol containing trifluoroacetic acid. UV/Vis absorption spectra were recorded with a Jasco V-560 spectrophotometer. Photolysis experiments were carried out in a thermostatted quartz cell (1 cm path length, 3 mL capacity) by using a Rayonet photochemical reactor equipped with 8 RPR lamps with an emission in the 380–480 nm range with a maximum at 420 nm in the presence of a 400 nm cut-off filter. The incident photon flux on quartz cuvettes was ca. 1×10^{15} quanta/sec.

Laser Flash Photolysis: The samples were excited with the third harmonic of a Nd-YAG Continuum Surelite II-10 laser system (pulse width 6 ns FWHM, at λ = 355 nm) and the excited solutions were analyzed at a right angle geometry by using a mini mLFP-111 apparatus developed by Luzchem Research. Briefly, the monitoring beam was supplied by a ceramic xenon lamp and delivered through quartz fiber optical cables. The laser pulse was probed by fiber that synchronized the mLFP system with a Tektronix TDS 3032 digitizer operating in the pretrigger mode. The signals from a compact Hamamatsu photomultiplier were initially captured by the digitizer and then transferred to a personal computer that controlled the experiment with Luzchem software developed in the LabView 5.1 environment from National Instruments. The energy of the laser pulse was measured at each laser shot by a SPHD25 Scientech pyroelectric energy monitor. Oxygen was removed by vigorously bubbling the solutions with a constant flux of argon previously passed through a water trap. The solution (in a flow cell of 1 cm path length) was renewed after each laser shot. The sample temperature was 295 ± 2 K.

NO Detection: NO release was measured with a World Precision Instrument, ISO-NO meter, equipped with a data acquisition system, and based on direct amperometric detection of NO with short response time (<5 s) and sensitivity range 1 nM–20 μM. The analog signal was digitalized with a four-channel recording system and transferred to a PC. The sensor was accurately calibrated by mixing standard solutions of $NaNO_2$ with 0.1 M H_2SO_4 and 0.1 M KI according to the Equation (5).

$$4H^+ + 2I^- + 2NO_2^- \rightarrow 2H_2O + 2NO + I_2 \quad (5)$$

NO photorelease experiments were performed in a thermostatted quartz cell (1 cm path length, 3 mL capacity) by using the monochromatic radiation of 420 nm of a fluorimeter Fluorolog-2 (mod. F-111) as the light source. NO measurements were carried out with the electrode positioned outside the light path in order to avoid false NO signal due to photoelectric interference on the ISO-NO electrode.

Acknowledgments

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[18] We could not explore concentrations of **1** higher than those reported in the inset of Figure 3 because of the significant ground-state absorption of compounds **1** at the excitation wavelength.

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