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# Quinone Methide Generation via Photoinduced Electron Transfer

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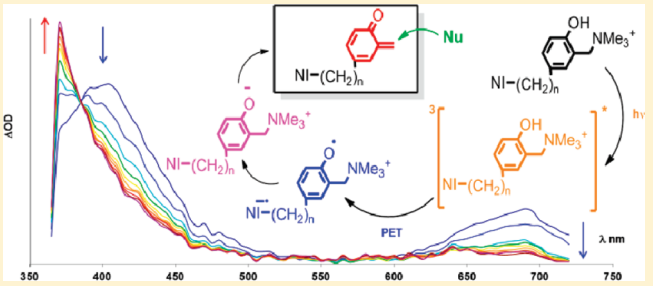
Supporting Information

**ABSTRACT:** Photochemical activation of water-soluble 1,8-naphthalimide derivatives (NIs) as alkylating agents has been achieved by irradiation at 310 and 355 nm in aqueous acetonitrile. Reactivity in aqueous and neat acetonitrile has been extensively investigated by laser flash photolysis (LFP) at 355 nm, as well as by steady-state preparative irradiation at 310 nm in the presence of water, amines, thiols, and ethyl vinyl ether. Product distribution analysis revealed fairly efficient benzylation of the amines, hydration reaction, and 2-ethoxychromane generation, in the presence of ethyl vinyl ether, resulting from a [4 + 2] cycloaddition onto a transient quinone methide. Remarkably, we found that the reactivity was dramatically suppressed under the presence of oxygen and radical scavengers, such as thiols, which was usually associated with side product formation. In order to unravel the mechanism responsible for the photoreactivity of these NI-based molecules, a detailed LFP study has been carried out with the aim to characterize the transient species involved. LFP data suggest a photoinduced electron transfer (PET) involving the NI triplet excited state ($\lambda_{max}$ 470 nm) of the NI core and the tethered quinone methide precursor (QMP) generating a radical ions pair $NI^{\bullet-}$ ($\lambda_{max}$ 410 nm) and $QMP^{\bullet+}$. The latter underwent fast deprotonation to generate a detectable phenoxyl radical ($\lambda_{max}$ 390 and 700 nm), which was efficiently reduced by the radical anion $NI^{\bullet-}$, generating detectable QM. The mechanism proposed has been validated through a LFP investigation at 355 nm exploiting an intermolecular reaction between the photo-oxidant *N*-pentylnaphthalimide (NI-P) and a quaternary ammonium salt of a Mannich base as QMP (**2a**), in both neat and aqueous acetonitrile. Remarkably, these experiments revealed the generation of the model *o*-QM ($\lambda_{max}$ 400 nm) as a long living transient mediated by the same reactivity pathway. Negligible QM generation has been observed under the very same conditions by irradiation of the QMP in the absence of the NI. Owing to the NIs redox and recognition properties, these results represent the first step toward new molecular devices capable of both biological target recognition and photoreleasing of QMs as alkylating species, under physiological conditions.




## INTRODUCTION

1,8-naphthalimide derivatives (NIs) have been studied extensively over the past few years because of their very interesting photophysical properties[1−5] as well as their wide biological applicability. In fact, these compounds present two characteristic features, namely, high and tunable fluorescence properties and the excellent accepting character of the NI core, which has greatly increased the use of NI-based molecules for the synthesis of new devices with emission behavior, such as dyes,[6] organic LEDs,[7] pH and metal cation sensors,[8−11] as well as anions sensors.[12−14]

Moreover, it has been shown that such a class of molecules acts both as effective DNA intercalating agents,[15,16] and potent topoisomerase II inhibitors.[17,18] This has resulted in the wide ranging applications of NI-based molecules for the development and design of new antitumor drugs.[19−23]

The high tendency of the NI core to undergo photoinduced electron transfer (PET), as well as the affinity toward biological substrates such as DNA, has also been exploited to induce selective DNA damage. In particular, selective photo-oxidation[24] and photocleavage[25] processes have been extensively investigated in the past few years. Furthermore, it has been demonstrated that NIs directly tethered to double-stranded oligonucleotides, provided with a variable length A−T base pair spacer, are capable of undergoing intramolecular PET, generating a couple of radical ions, namely $NI^{\bullet-}$ and $A^{\bullet+}$. Although the charge recombination process should be favored, the quick reoxidation of $NI^{\bullet-}$ by $O_2$ and the possibility of a hole hopping between $A^{\bullet+}$ and G to form $G^{\bullet+}$ can strongly compete with the latter. By confirmation of that, it has been observed that DNA damage is greatly affected by the rate of the reoxidation process, both by the length of the A−T base pair linker and G oxidation potential.[26,27] On the other hand, several groups have achieved covalent modification of DNA by direct photoactivation of *o*-hydroxybenzylic alcohols (**1**) or Mannich base derivatives of phenols (**2**) and binols (**3**), in water solution, and such a

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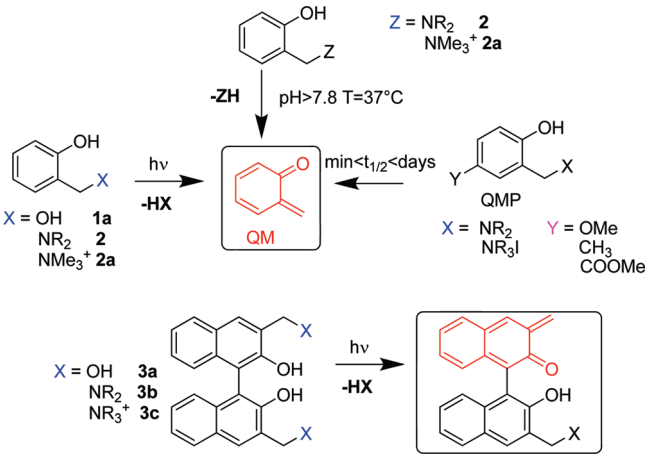
reactivity can also be triggered by thermal digestion, base catalysis, and the presence of fluoride anions.[28−41] More recently, binol derivatives, functionalized with benzylic amino acids side chains, showed DNA photoalkylation properties and photocytotoxicity comparable to, and in some cases higher than, psoralene.[42] Moreover, purine selective alkylation toward DNA has been achieved by direct photogeneration of naphthoquinone methides.[43]

The key intermediates shared between all these processes are the transient quinone methides (QMs). Their formation showed a strong dependence on the leaving group attached at the benzylic position of their precursor (QMP). Furthermore, the generation of QMs has been proven to be highly responsive to the presence of electron-withdrawing and electron-donating groups. In more detail, electron-donating groups greatly facilitate QM generation, whereas electron-withdrawing substituents strongly suppress such a process.[44] This peculiar feature of QMP has been recently exploited to develop a brand new reductive protocol for the release of the QM transient. In particular, the monoelectronic reduction of a naphthalendiimide (NDI) acts as a reactivity switch for the directly tethered QMP, owing to the properties of the electron-donating group of the stable NDI radical anion generated, as summarized in Schemes 1 and 2.[45]

Although the above mechanism represents an original and biologically suitable activation protocol for generation of QMs, very stable and long living radical anion intermediates are required in order to trigger the reactivity, thus allowing the formation of byproducts such as reactive oxygen species (ROS).

In our present work, we describe the synthesis and the unexpected photochemical reactivity of a new class of NI derivatives, bearing two different QMPs at the imide moiety (Scheme 3) by irradiation of the NI core. Moreover, we rationalize the photogeneration of the transient QM (**6**) through a PET mechanism between the phenolic precursors and the NI core. Such a reactivity represents the first case of non-direct phototriggering of QMs via PET involving a tethered peripheral moiety.

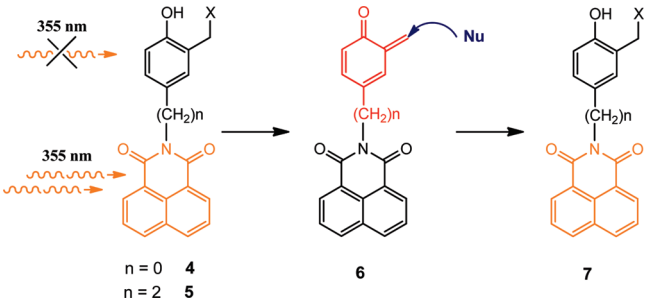
**Scheme 1. Thermal and Photoinduced Generation of QM and Substituent Effect on the Reactivity of QM Precursor (QMP)**



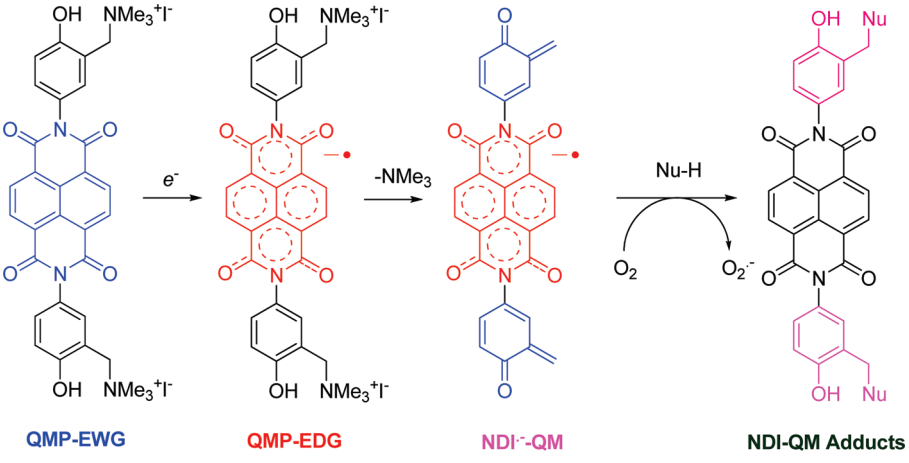

## RESULTS AND DISCUSSION

**Synthesis.** Already published studies showed how the PET mechanism in naphthalimide−donor dyads is strongly affected by the linker length between the NI accepting core and the donor.[2,4] In order to evaluate how this effect could be translated in terms of photoreactivity, we decided to synthesize two different NI derivatives. By tethering the (5-amino-2-hydroxybenzyl)trimethylammonium iodide, as QMP precursor, to the 1,8-naphthalene anhydride (**8**) we obtained molecule **11**. The latter represents a directly linked donor−acceptor system.

**Scheme 3. Generation of QMs by PET Activation of Substituted NIs at 355 nm**




**Scheme 2. Generation of the NDI Radical Anion ($NDI^{\bullet-}$) as Electron-Donating Substituent, Triggering the QM Formation**





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Alternatively, using [5-(2-aminoethyl)-2-hydroxybenzyl]trimethylammonium iodide, we obtained molecule **14**, which allowed us to separate the donor QMP from the NI core with a conformationally flexible spacer (Scheme 4).

Attempts to achieve a direct coupling between the anhydride **8** and (5-amino-2-hydroxybenzyl)trimethylammonium iodide, according published procedures,[6] were hampered by the thermal instability of the quaternary ammonium salts. In fact, it is well-known how such substrates can easily decompose into free QM and amine in the presence of electron-donating groups on the aromatic ring.[44] Consequently, both the adduct **11** and **14** were synthesized by a three-step procedure starting from the coupling of the anhydride **8** to *p*-aminophenol or tyramine, respectively, exploiting a microwave synthetic protocol herein discussed. The above coupling was followed by a Mannich reaction and $CH_3I$ methylation (Scheme 4). This synthetic route allowed us to obtain NIs **11** and **14** by using only one chromatographic purification step in excellent yield.

After the synthesis of **11** and **14** was accomplished, we started to investigate photoactivation protocols under mild conditions, in order to study the reactivity of such molecules as photoalkylating agents. Moreover, to evaluate their thermal intrinsic reactivity and to discriminate it from the photoreactivity, two more activation pathways have been studied: (i) buffered neutral thermal digestion and (ii) base-catalyzed thermal digestion. In both cases, the reaction of **11** and **14** was performed at 45 °C in the presence of several nucleophiles (thiols and amines), in aqueous acetonitrile solutions ($CH_3CN/H_2O$ 1:1).

**Photoreactivity.** The photoactivation of *o*-hydroxybenzyl alcohols, Mannich bases, and their quaternary ammonium salts as alkylating agents via QM generation has been studied. In fact, it is well-known how QMs could be efficiently generated by direct irradiation of phenol-like chromophores. Indeed, the acidic QMPs singlet excited state leads to a facile deprotonation, which eventually results in QM generation.[31,46] Surprisingly, we found that the photoreactivity observed for the NI derivatives herein synthesized was not due to such a mechanism. This conclusion was suggested by two key experimental observations: (i) the high absorptivity of the NI core in the 310 and 360 nm spectroscopic window, compared to the negligible absorbance of the QMP moiety, and (ii) the absence of photoreactivity of the amine analogues (**10**, **13**). In fact, it is widely known that QM generation by direct irradiation of Mannich bases also occurs, with very similar photoefficiency to their quaternary ammonium salts.[47] Despite this, irradiation of molecules **11** and **14** showed high photoreactivity toward basic nucleophiles such as piperidine, ethylbutylamine, and *tert*-butylamine. In fact, both molecules upon irradiation at 310 nm in a $CH_3CN:H_2O$ 1:1 Ar purged solution gave conversion into the corresponding alkylated adducts ranging between 15 and 50%, after only 5 min of irradiation (using four lamps, 15 W; Tables 1 and 2). A similar behavior toward neutral nucleophiles, such as water and thiols, has been observed for longer irradiation times (30 min; Tables 1 and 2), resulting in the hydration adducts **15** and **21**. This difference could easily be explained by the higher electron donor character of the phenolate anion generated in the presence of basic nucleophiles. Indeed, performing the irradiation in carbonate buffered conditions (pH >8.5) the hydration reaction became as efficient as the trapping of basic nucleophiles. In fact, almost complete conversion to the hydration adducts **15** and **21** was observed after 30 min of irradiation under this condition (Tables 1 and 2), whereas similar conversions to those observed for amines were obtained for 5 min irradiation. Notably, poor photoreactivity toward thiol-based nucleophiles has been observed, which is in marked contrast to the reactivity studied by generating the transient QM by direct irradiation. Therefore, in order to clarify the conditions of the photo- and thermal activation, a blank has been prepared for each photoreaction batch, which was made and treated under the very same conditions but not exposed to light. Alkylating adducts have never been detected for the nonirradiated blank solutions, in the presence of the same nucleophiles for equal or longer reaction times (at least for an additional hour). This result confirmed that the observed conversions were due to photochemical process only.

**Base Catalytic Activation.** Activation by base catalysis takes advantage of the low p$K_a$ (~8) of the quaternary ammonium salts of the Mannich bases, which allows the generation of a

**Scheme 4. Synthesis of the NI Derivatives (11 and 14)**

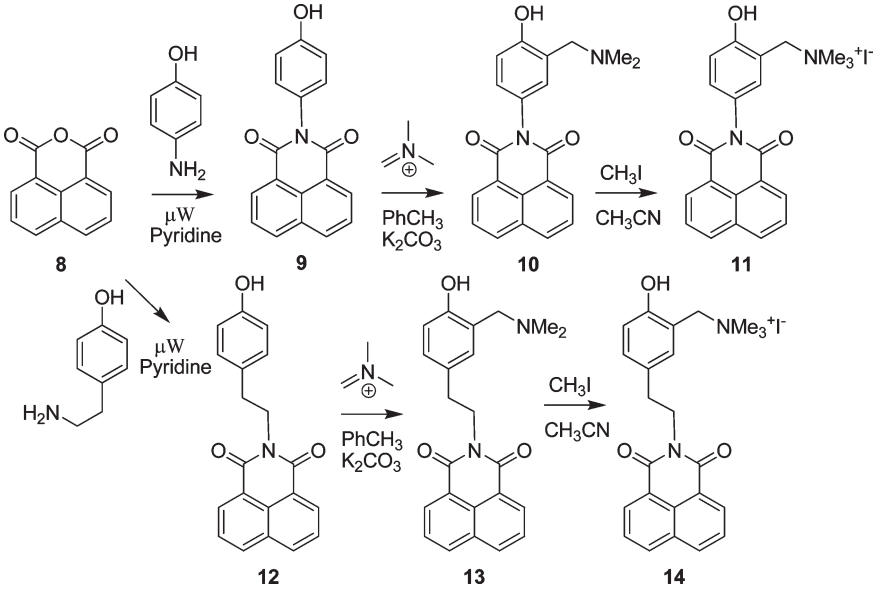



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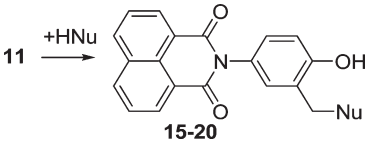
**Table 1. Reactivity of 11 by Base Catalysis and Irradiation at 310 nm**




15-20

| Adduct | Nu | Base Catalysed Activation | Photoactivation |
|---|---|---|---|
| | | Conditions, (Yield)[a] | Conditions, (Yield)[b] |
| **15** | HO- | 30 min; 45°C; (10) [c] | 30 min; 25°C; (33) [e] |
| | | 90 min; 45°C; (-) [d] | 30 min; 25°C; (76) [f] |
| **16** |  | 5 min; 45°C; (3)[d] | 5 min; 25°C; (49) [e] |
| | | 30 min; 25°C; (1) [d] | 10 min; 25°C; (99) [e] |
| **17** |  | 5 min; 45°C; (8)[d] | 5 min; 25°C; (55) [e] |
| | | 30 min; 25°C; (4) [d] | 10 min; 25°C; (100) [e] |
| **18** |  | 5 min; 45°C; (-)[d] | 5 min; 25°C; (13) [e] |
| | | 30 min; 25°C; (-) [d] | 30min; 25°C; (65) [e] |
| **19** | *t*-BuNH- | 5 min; 45°C; (5)[e] | 5 min; 25°C; (15) [e] |
| | | 60 min; 25°C; (-) [d] | 30 min; 25°C; (45) [e] |
| **20** | HO-$(CH_2)_2$S- | 60 min; 45°C; (23)[c] | 30 min; 25°C; (7) [e] |
| | | 90 min; 25°C; (-)[d] | 60 min; 25°C; (22) [e] |

[a] Reaction time; *T*/°C. $CH_3CN$:$H_2O$ = 1:1, [**11**] or [**14**] = $5 \times 10^{-4}$ M, [HNu] = $5 \times 10^{-3}$ M, kept in the dark. [b] Reaction time; *T*/°C. $CH_3CN$:$H_2O$ = 1:1, [**11**] or [**14**] = $5 \times 10^{-4}$ M, [HNu] = $5 \times 10^{-3}$ M, 310 nm irradiation. Reaction yields (%) are reported in parentheses. [c] Condition A, carbonate buffered (pH ≥8.5). [d] Condition A, not buffered. [e] Condition B, not buffered. [f] Condition B, carbonate buffered (pH ≥8.5)

reactive zwitterionic form at pH ≥8 and generates alkylating QM after mild thermal activation.

Basic amines such as piperidine, *tert*-butylamine, and ethylbutylamine ($pK_a$ > 10.7) gave almost quantitative conversion after 1 h of digestion (45 °C, in $CH_3CN$:$H_2O$ 1:1; reaction condition A, Tables 1 and 2). Amines displaying lower basicity ($pK_a$ ≤8), namely, morpholine, as well as neutral nucleophiles, such as water and thiols, require carbonate-buffered conditions (pH ≥8.5, reaction condition C) and longer reaction times (Tables 1 and 2). Remarkably, under these conditions reactivity toward thiols has been recovered. The results described above suggest that the activation of **11** and **14** as alkylating agent is not efficient at rt but only under strong basic conditions (pH >8.5, 45 °C), when the phenol is mainly deprotonated, and under higher temperatures. Similarly to the prototype quaternary ammonium salt **2a**, also for **11** and **14**, the zwitterionic form has to be populated to lower the barrier for the QM generation.

**Hetero-Diels–Alder Reactivity.** In order to confirm that a QM transient species was responsible of the alkylating reactivity observed, irradiation in the presence of ethyl vinyl ether (EVE) has been carried out. Although the QM-hydration pathway is competitive in aqueous acetonitrile ([EVE] = 0.1 M), the irradiation of the NIs **11** and **14** leads to the formation of the 2-ethoxychromanes **27** and **28**. Such reactivity could be allowed only by the formation of a QM transient capable of reacting with EVE via [4 + 2] hetero-Diels–Alder cycloaddiction, as depicted in Scheme 5.

**Photochemical Efficiency. Quantum Yield Measurements.** In order to evaluate the efficiency of NI derivatives **11** and **14** as photoalkylating agents, quantum yield experiments have been carried out. In more detail, we investigated the efficiency of the QM generation in water, trapping the resulting QM (i) by water in a buffered solution and (ii) by a nitrogen nucleophile, such as ethylbutylamine. In particular, for both derivatives **11** and **14**, two diluted solutions of the NIs ($2.5 \times 10^{-4}$ M in $H_2O$:$CH_3CN$ 1:1) have been prepared: (i) a phosphate-buffered one at pH 7 and (ii) an unbuffered one in the presence of freshly distilled ethylbutylamine ($2.5 \times 10^{-3}$ M). Both solutions have been irradiated for 10 min at 315 nm, and both the alcohols **15** and **21** together with the amines **17** and **23** have been detected and measured by HPLC. In addition, it is worthy to underline that **2a**, which is the precursor of a QM by direct irradiation, is not reactive under the conditions described above, as its absorbance at 315 nm is negligible.

Although the quantum yields in Table 3 clearly suggest that the photoactivation efficiency of these NIs is quite low (<0.07), they can be activated at much longer wavelength (355 nm) than the quaternary ammonium salt **2a** (254–280 nm).


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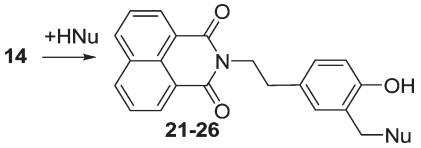
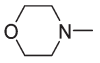
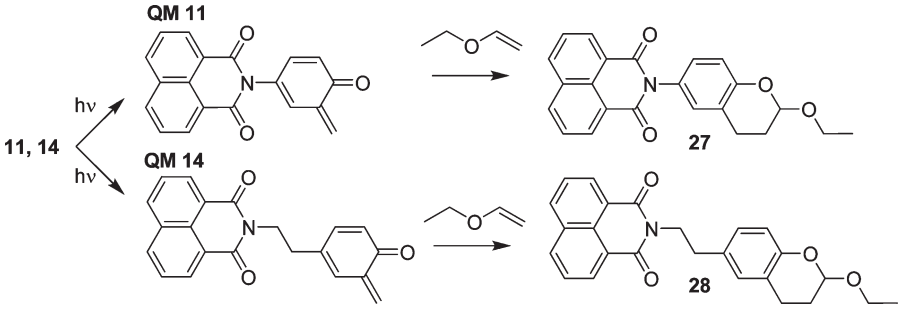
**Table 2. Reactivity of 14 by Base Catalysis and Irradiation at 310 nm**




| Adduct | Nu | Base Catalysed Activation | Photoactivation |
|---|---|---|---|
| | | Conditions, (Yield)[a] | Conditions, (Yield)[b] |
| **21** | HO- | 30 min; 45°C; (17) [c] | 30 min; 25°C; (22) [e] |
| | | 90 min; 25°C; (-) [c] | 30 min; 25°C; (58) [f] |
| **22** |  | 5 min; 45°C; (19)[c] | 5 min; 25°C; (24) [e] |
| | | 60 min; 25°C; (6) [d] | 30 min; 25°C; (56) [e] |
| **23** |  | 5 min; 45°C; (19)[c] | 5 min; 25°C; (25) [e] |
| | | 60 min; 25°C; (4) [d] | 30 min; 25°C; (52) [e] |
| **24** |  | 5 min; 45°C; (-)[c] | 5 min; 25°C; (3) [e] |
| | | 30 min; 25°C; (-)[c] | 30 min; 25 °C; (22) [e] |
| **25** | *t*-BuNH- | 5 min; 45°C; (11)[d] | 5 min; 25°C; (5) [e] |
| | | 60 min; 25°C; (-) [d] | 30 min; 25°C; (31) [e] |
| **26** | HO-$(CH_2)_2$S- | 60 min; 45°C; (39)[c] | 30 min; 25°C; (2) [e] |
| | | 90 min; 25°C; (-)[d] | 60 min; 25°C; (12) [e] |

[a] Reaction time; *T*/°C. $CH_3CN$:$H_2O$=1:1, [**11**] or [**14**] = $5 \times 10^{-4}$ M, [Hnu] = $5 \times 10^{-3}$ M, kept in the dark. [b] Reaction time; *T*/°C. $CH_3CN$:$H_2O$=1:1, [**11**] or [**14**] = $5 \times 10^{-4}$ M, [HNu] = $5 \times 10^{-3}$ M, 310 nm irradiation. Reaction yields (%) are reported in parentheses. [c] Condition A, carbonate buffered (pH ≥8.5). [d] Condition A, not buffered. [e] Condition B, not buffered. [f] Condition B, carbonate buffered (pH ≥8.5)

**Scheme 5. Generation of Ethoxychromanes 27 and 28 by Trapping QMs (QM 11 and QM 14)**




**Intermolecular QM generation by PET. Direct Evidence for QM Generation.** The well-known electron-accepting properties of 1,8-naphthalimide derivatives described by Majima and co-workers[3] suggest that the photoalkylation reactions described above may be initiated by a photoinduced electron transfer (PET) involving the triplet excited NI and the phenol moiety. In order to support such a hypothesis, we began a laser flash photolysis (LFP) investigation on the model intermolecular photoreaction between *N*-pentylnaphthalimide [NI-P (**29**); see the Supporting Information] and the quaternary ammonium salt of the mannich base **2a**. The transient absorption spectra resulting from flashing a diluted solution of NI-P ($2 \times 10^{-4}$ M) in the presence of **2a** by LFP using 355 nm laser excitation in both neat $CH_3CN$ and aqueous $CH_3CN$ have been recorded (Figures 1 and 2). The NI-P triplet excited state ($^3$NI-P*) at 470 nm[48,49] was efficiently quenched by **2a** with second-order rate constants $k_2 = 1.4 \times 10^8$ and $1.3 \times 10^8$ $M^{-1}$ $s^{-1}$ in neat $CH_3CN$ and aqueous $CH_3CN$, respectively. In neat acetonitrile, a longer time

**Table 3. Quantum Yields ($\Phi$)[a] for NIs Photoreactivity, Measured for 11 and 14 ($2.5 \times 10^{-4}$ M) in Aqueous Acetonitrile Solutions ($H_2O$:$CH_3CN$ 1:1) under Buffered (Phosphate Buffered, pH 7) and Unbuffered Conditions**

| NI derivative | conditions | $\Phi$[a] |
|---|---|---|
| **11** | $H_2O$:$CH_3CN$, pH 7 | 0.022[b] |
| **11** | $2.5 \times 10^{-3}$ M ethylbutylamine | 0.069[c] |
| **14** | $H_2O$:$CH_3CN$, pH 7 | 0.016[b] |
| **14** | $2.5 \times 10^{-3}$ M ethylbutylamine | 0.043[c] |

[a] By potassium ferrioxalate actinometry (monitored by UV−vis). [b] Quantum yield for the formation of **15** and **21** by hydration reaction $H_2O$:$CH_3CN$ 1:1, $10^{-2}$ M phosphate buffer, pH 7. [c] Quantum yield for the formation of **21** and **23** in the presence of $2.5 \times 10^{-3}$ M ethylbutylamine in $H_2O$:$CH_3CN$ 1:1.

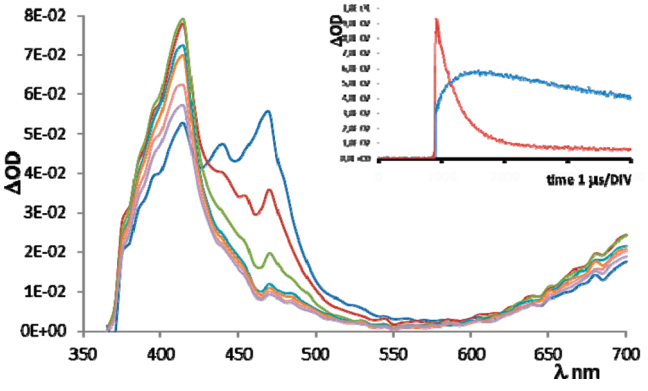



**Figure 1.** Transient absorption spectra of a solution NI-P ($2 \times 10^{-4}$ M) and **2a** ($2 \times 10^{-4}$ M) in neat and argon-purged $CH_3CN$, recorded 0.82, 1.14, 1.77, 2.09, 2.41, 2.73, and 3.37 $\mu$s after the laser pulse (355 nm). (Inset) Overlapping decay traces at 410 and 470 nm recorded in neat $CH_3CN$ under argon.

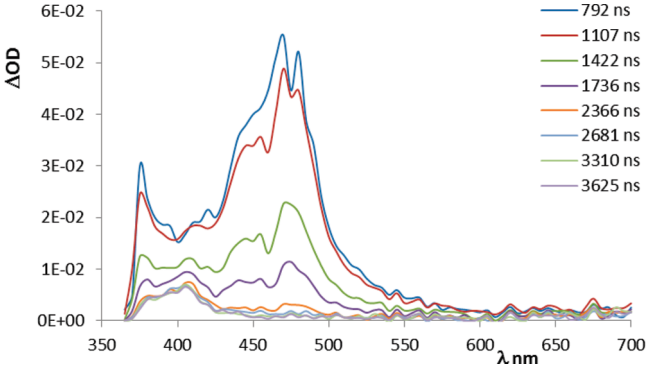



**Figure 2.** Transient absorption spectrum of a solution of NI-P ($2 \times 10^{-4}$ M) and **2a** ($2 \times 10^{-4}$ M) in argon-purged 1:1 aqueous acetonitrile solution, recorded 0.79, 1.11, 1.42, 1.73, 2.36, 2.68, 3.31, and 3.62 $\mu$s after the laser pulse.

scale (>1 $\mu$s) revealed the evolution of the triplet into a blue-shifted transient absorption, centered at 410 nm with a broad absorption around 700 nm. Figure 1 shows the parallel time course of the absorbance at both wavelengths 470 and 410 nm. At the shorter wavelength (410 nm), the formation kinetic of this transient was seen, and this buildup was mirrored by the decay at 470 nm (inset of Figure 1).

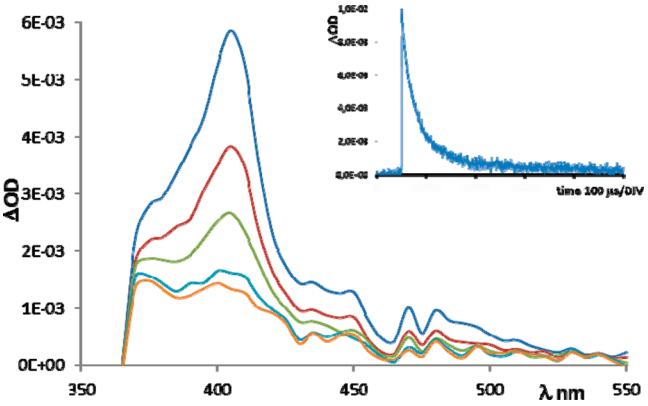



**Figure 3.** Transient absorption spectrum of a solution of NI-P ($2 \times 10^{-4}$ M) and **2a** ($4 \times 10^{-3}$ M) in argon-purged 1:1 aqueous acetonitrile solution, recorded after 0.11, 0.18, 0.22, 0.29, and 0.36 ms the laser pulse (355 nm). (Inset) Decay trace monitores at 400 nm.

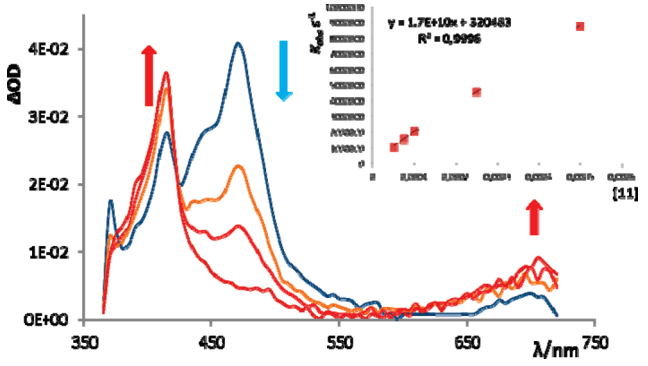



**Figure 4.** Transient absorption spectrum of **11** in oxygen-free $CH_3CN$, recorded 2.14, 2.55, 3.37, and 3.78 $\mu$s after the 355 nm laser pulse. (Inset) $^3$**11*** pseudo-first-order rate constants as a function of the concentration of **11**.

The transient species that was generated from the decay of the triplet excited state, with a maximum absorbance at 410 nm, exhibited a longer lifetime, decaying with a first-order kinetic. It was partially quenched by $O_2$. Literature data suggest that both the phenol radical cation and NI radical anion absorb at similar wavelength (410 nm).[50,51] Therefore, in the absence of reactivity, from product distribution analysis in neat $CH_3CN$, such a decay process may be assigned to back electron transfer.

In aqueous acetonitrile, the $^3$NI-P* absorbance (470 nm) and its decay still are clearly visible, but the resulting intense transient at 410 nm has disappeared, been replaced by a much weaker and long-living transient centered at 400 nm (Figure 2). The intensity of the absorbance related to the last species has been enhanced by the rising of the quencher (**2a**) concentration. Both the spectroscopic and the kinetic properties of this long-living species suggest assigning the above transient to a quinone methide (QM) (Figure 3), which has been detected only in aqueous acetonitrile.

**Laser Flash Photolysis on NI−QMP Dyads. Solvent Effect on Intermolecular vs Intramolecular PET.** We have been able to infer the nature of the key transient species (QMs) by studying the photoactivation of the NIs **11** and **14** by product distribution analysis and by investigating the parallelism between the photoactivation and the base-catalyzed process. In addition, the LFP investigation on the intermolecular reactivity, described in the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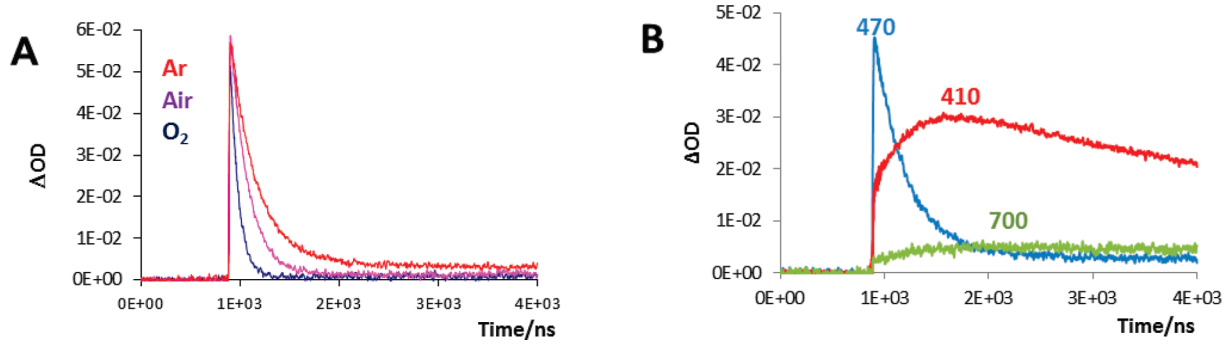



**Figure 5.** (A) Decay traces of a $CH_3CN$ diluted solution of **11** ($5 \times 10^{-4}$ M) at 470 nm recorded flashing at 355 nm under argon (red), air (fuchsia), and oxygen (blue line). (B) Overlapping decay traces at 410, 470, and 700 nm, under argon.

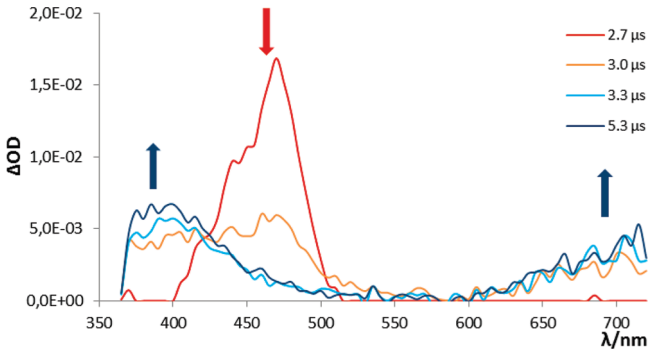



**Figure 6.** Transient absorption spectrum of **11** in an oxygen-saturated $CH_3CN$ solution recorded 2.7, 3.0, 3.3, and 5.3 $\mu$s after the laser pulse.

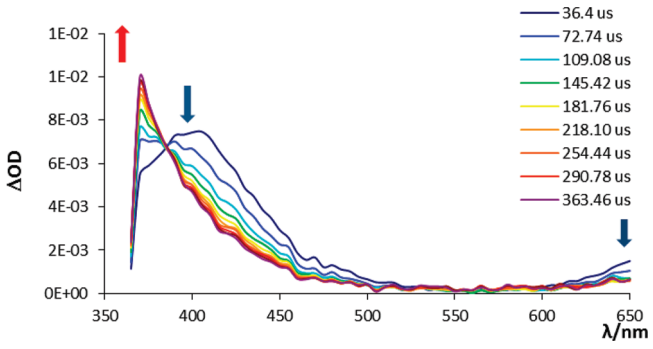


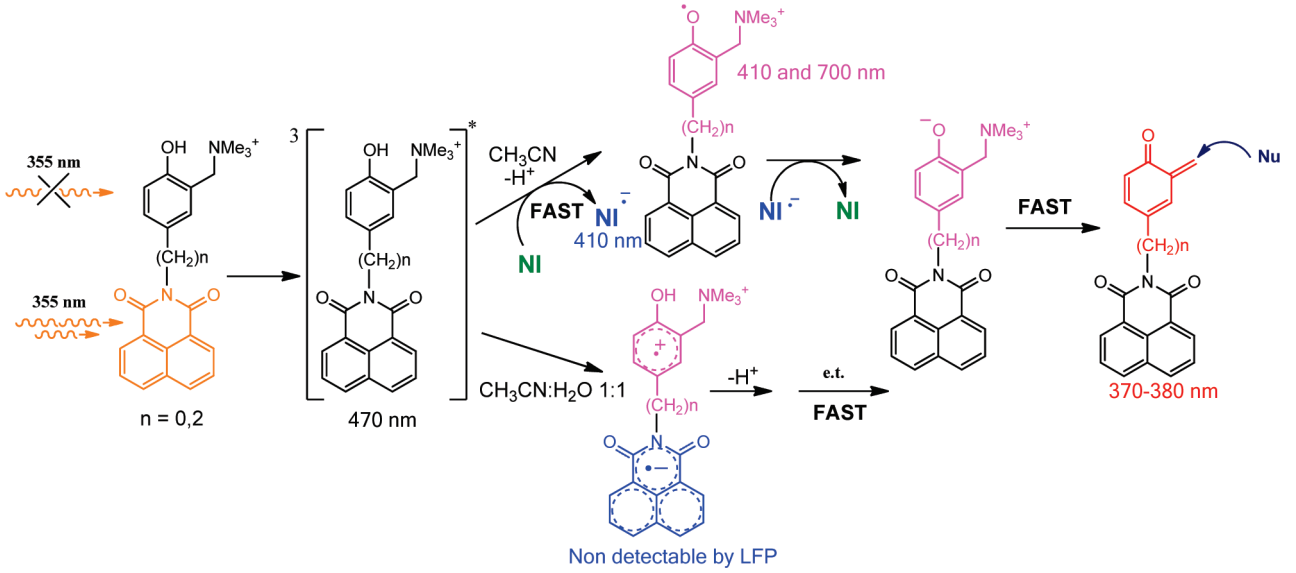

**Figure 7.** Transient absorption spectrum of **11** in an oxygen-free $CH_3CN$ solution recorded from 36.4 to 363.5 $\mu$s after the laser pulse.

previous chapter, clearly suggests the role of a PET mechanism in the activation of the alkylating QM at 355 nm. Therefore, we decided to investigate further such QM activation novelty, flashing at 355 nm the NI−QMP dyads **11** and **14** by LFP. Photolysis of an argon-purged acetonitrile solution of **11** ($5 \times 10^{-4}$ M) resulted in a transient spectrum exhibiting, at pulse end, an absorption centered at 470 nm (Figure 4). This transient, decaying with a pseudo-first-order rate constant $k_{obs} = 3.6 \times 10^6$ s$^{-1}$ in Ar-purged $CH_3CN$, was quenched by $O_2$. The quantitative effect of $O_2$ on the triplet lifetime is reported in Figure 5A (air-purged $CH_3CN$, $k = 6.33 \times 10^6$ s$^{-1}$, $\tau = 158$ ns; $O_2$ purged $CH_3CN$, $k = 1.22 \times 10^7$ s$^{-1}$, $\tau = 82$ ns). Therefore, it was assigned to the triplet state of **11** ($^3$**11***), on the basis of both the published triplet−triplet absorption spectra of similar NIs[52,53] and the striking similarity to the $^3$NI-P* described above. Interestingly, the $^3$**11*** lifetime was a linear function of **11** concentration, in the absence of $O_2$. Plotting the $^3$**11*** pseudo-first-order rate constants in neat acetonitrile as a function of **11** concentration, we have been able to calculate the second-order rate constant $k_2 = 1.7 \times 10^{10}$ M$^{-1}$ s$^{-1}$ for the intermolecular quenching of $^3$**11*** by **11**, which is diffusion-controlled (see Figure 4 inset). Similarly to the intermolecular reaction between NI-P and **2a**, a longer time scale revealed the evolution of the $^3$**11*** into a blue-shifted transient absorption, centered at 410 nm with a broad and weak absorption around 700 nm. Figure 5B shows the parallel time course of the absorbance at wavelengths 470, 410, and 700 nm. At the shorter wavelength, the formation kinetic of this transient was seen, and this buildup was mirrored by the decay at 470 nm.

The transient that was generated from the decay of the triplet excited state, with a maximum absorbance at 410 nm, exhibited a longer lifetime ($k = 4.48 \times 10^4$ s$^{-1}$) and it was partially quenched by $O_2$ (air-purged $CH_3CN$, $k = 6.29 \times 10^6$ s$^{-1}$; $O_2$ purged $CH_3CN$, $k = 2.02 \times 10^7$ s$^{-1}$). The oxygen did not bleach completely the transient centered at 410 nm, leaving a decay trace that did not returned back to zero absorbance (Supporting Information Figure S1). Upon recording a full transient spectra in the presence of $O_2$ (Figure 6), it became clear that a second weaker transient centered at 390−400 nm (retaining the broad band at 700 nm) was present, but it was partially hidden by the intense absorbance at 410 nm in the absence of $O_2$. The absorption spectra of the transient centered at 410 nm was very similar to the published NI radical anion spectra (NI$^{\bullet-}$, $\lambda_{max}$ 410 nm).[54] This spectroscopic evidence, together with its quenching by $O_2$, suggests that the intense absorbance at 410 nm has to be ascribed mainly to the radical anion of the NI **11** (**11**$^{\bullet-}$). It is also clear that **11**$^{\bullet-}$ absorption partially overlaps to a second transient (centered at 390−400 nm), which became visible only in the presence of $O_2$. This species, which exhibits also broad absorption beyond 650 nm, has been assigned to the phenoxyl radical of the Mannich base moiety (**11**$^{\bullet}$), due to its similarity to phenoxyl radical spectra already published.[55,56] In spite of the fairly close similarities between phenoxyl radical and phenol radical cation spectra,[57] **11**$^{\bullet}$ cannot be mistaken for the phenol radical cation **11**$^{\bullet+}$ because it is stable on a microsecond time scale in the presence of $O_2$ (Supporting Information, Figure S2). Conversely, phenol radical cations decay within 1−2 $\mu$s in neat acetonitrile.[57]

LFP of **11** was then carried out in diluted aqueous $CH_3CN$ containing a variable amount of water from 5 to 100 mM. After the laser pulse, all the transients due to (i) the triplet, (ii) the NI radical anion **11**$^{\bullet-}$, and (iii) the phenoxyl radical **11**$^{\bullet}$ were observed at 470, 410, and 700 nm, respectively. In aqueous

**Scheme 6. The Intermolecular and Intramolecular PET Mechanisms Triggering the QM Reactivity**




$CH_3CN$, with water concentration below 0.1 M, the $^3$**11*** lifetime was unaffected. Conversely, both the transients absorbing at 410 nm (**11**$^{\bullet-}$) and 700 nm (**11**$^{\bullet}$) showed a strong water dependence on their lifetimes. In addition, water (from 5 to 50 mM) was responsible for a dramatic reduction of both their lifetimes (Supporting Information, Figure S3). Nevertheless, for 75 mM water concentrations, the formation of a more stable third species became detectable. In fact, longer time scale (>30 $\mu$s) revealed the parallel evolution of both **11**$^{\bullet-}$ and **11**$^{\bullet}$into a blue-shifted (370−380 nm) stable absorption and a broad tail up to 450 nm (Figure 7). The striking similarity of all the transients detected in the intermolecular reaction NI-P (**29**) + **2a**, including the direct detection of the prototype *o*-QM, with those characterized for the dyad NI−QMP (**11**) suggests that the last forming species should be ascribed to the QM conjugated to the NI core.

Surprisingly, the intensity of the $^3$**11*** absorption rapidly decreased under aqueous solutions for water concentrations higher than 0.1 M. We have not been able to detect the triplet $^3$**11*** nor the following transient species in aqueous acetonitrile 1:1, with our LFP equipment. This aspect, together with the fact that (i) in steady-state irradiations both photohydration−alkylation reactions reach their maximum efficiencies and (ii) the presence of amines does not quench the alkylating reactivity, suggests an intramolecular quenching of the NI triplet excited state, by the donor moiety, in aqueous acetonitrile 1:1.

The NI **14** exhibited a very similar LFP behavior, with the generation of (i) the triplet excited state of **14**, (ii) its NI radical anion **14**$^{\bullet-}$, and (iii) the homologue phenoxyl radical **14**$^{\bullet}$ observed at 470, 410, and 700 nm, respectively (Supporting Information, Figure S4). Therefore, according to the experimental evidence, we could rationalize the observed QM generation within the dyads **11** and **14** mainly through an intermolecular PET process in diluted aqueous acetonitrile (<0.1 M $H_2O$), which generates a couple of radical ions, NI$^{\bullet-}$ and QMP$^{\bullet+}$. Conversely, in aqueous acetonitrile with water concentration >0.1 M the PET becomes mainly intramolecular with a higher efficiency of the QM generation, since the phenol radical cation deprotonation is faster. The presence of a proximal quaternary ammonium salt moiety further enhances the acidity of the phenolic radical cation, which undergoes fast deprotonation, generating a phenoxy radical. The latter is detectable only in the intermolecular process. Deprotonation efficiently competes with the back electron transfer, only when water is present in solution and the resulting phenoxy radical can be reduced to the anion NI−QMP$^{-}$. Indeed, according to the already reported reduction potentials of phenoxyl radicals,[58] as well as the good reductive character of the NI$^{\bullet-}$,[59] the reduction of the phenoxyl radical to phenolate results in a thermodynamically favored process. Such a mechanism is consistent with the poor reactivity observed in the presence of radical scavengers and oxidants such as thiols and oxygen (see Scheme 6).

## CONCLUSIONS

In conclusion, we have described a novel, mild QM generation pathway, triggered by a PET mechanism involving a naphthalene imide core and a tethered QMP. The transient species, as well as the mechanism involved in different solvent conditions, have been clarified by performing detailed LFP investigations on both an intermolecular model reaction and on the dyads NI−QMP.

To the best of our knowledge, this reactivity represents the very first case of alkylating QM photogeneration triggered by a photoinduced electron transfer with a peripheral moiety. The reactivity of the photogenerated QM toward several nucleophiles, together with a thorough LFP investigation, revealed the generation of the QM as a key intermediate using a longer wavelength than that required for direct irradiation of the quinone methide precursors. Owing to the wide applicability of NI-based molecules in selective biological targeting, such reactivity represents the first step toward the development of molecular devices capable of undergoing photodelivery of QM using UV−visible light.

## EXPERIMENTAL SECTION

**Microwave Imidization of 1,8-Naphthalic Anhydride (9, 12). General Procedure.** Although the synthesis of similar NI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derivatives has already been published,[6] we developed a microwave-based methodology suitable for aromatic amines. In this way, the reaction has been carried out in 1 h instead of 16 h, with higher yields. In more detail, 500 mg (2.5 mmol) of 1,8-naphthalic anhydride and 3.1 mmol of the respective amine (4-aminophenol, tyramine) were suspended in 6 mL of pyridine. The mixture was irradiated for 1 h in a CEM oven, kept at constant temperature (130 °C) with a maximal power output of 200 W. After cooling, the pyridine was removed under reduced pressure. The crude solid was then suspended in an HCl aqueous solution, filtered, and washed first with acidic water and then twice with anhydrous EtOH.

The crude imides **9** and **12** were obtained as gray-violet (97% yield) and white-yellow solids (95% yield) respectively. These compounds have been used without further purification. The spectroscopic data found for the imide **9** were in agreement with those reported in the literature. [60](See the Supporting Information.)

***N*-[(4-Hydroxyphenyl)ethyl]-1,8-naphthalimide (12).** Mp: 225−227 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 2.80 (t, 2H, $J$ = 8.0 Hz), 4.17 (t, 2H, $J$ = 8.0 Hz), 6.69 (d, 2H, $J$ = 8.4 Hz), 7.06 (d, 2H, $J$ = 8.4 Hz), 7.81−7.86 (m, 2H), 8.44 (m, 4H), 9.24 (s, 1H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 32.7, 41.3, 115.2, 121.9, 127.2, 128.7, 129.5, 130.6, 131.2, 134.3, 155.8, 163.2. Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.70, H, 4.76; N, 4.41; O 15.13. Found: C, 75.72, H, 4.73; N, 4.48.

**Mannich Reaction (10, 13). General Procedure.** A 500 mg portion of the respective 1,8-naphthalimide (**9**, **12**) was dissolved in anhydrous toluene (60 mL), and 1.2 equiv of *N*,*N*-dimethylmethyleniminium chloride and 1.6 equiv of $K_2CO_3$ were added to the solution. This mixture was allowed to reflux with vigorous stirring under nitrogen atmosphere for 4 h. After TLC control (EtOAc/MeOH 8:2), the solid suspension was filtrated and washed with 30 mL of ethyl acetate. The filtrated organic solution was dried under vacuum and the crude residue was purified by flash chromatography (EtOAc/MeOH 8:2), affording **10** (59% yield) or **13** (40% yield).

***N*-[3-(Dimethylamino)methyl-4-hydroxyphenyl]-1,8-naphthalimide (10).** Mp: 210−211 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.30 (s, 6H), 3.70 (s, 2H), 6.90 (d, 1H, $J$ = 2.3 Hz), 7.0 (d, 1H, $J$ = 8.5 Hz), 7.15 (dd, 1H, $J$ = 2.4, 8.5 Hz), 7.79−7.84 (m, 2H), 8.30 (d, 2H, $J$ = 7.6 Hz) 8.70 (d, 2H, $J$ = 7.3 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 44.3, 62.4, 108.3, 116.9, 122.2, 122.8, 126.0, 126.9, 128.2, 128.7, 131.5, 131.6, 134.1, 158.2, 164.6. Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09; O,13.86. Found: C, 72.79; H, 5.27; N, 8.03.

***N*-[(3-(Dimethylamino)methyl-4-hydroxyphenyl)ethyl]-1,8-naphthalimide (13).** Mp: 185−188 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.30 (s, 6H), 2.94 (t, 2H, $J$ = 8.4 Hz), 3.61 (s, 2H), 4.37 (t, 2H, $J$ = 8.4 Hz), 6.78 (d, 1H, $J$ = 8.2 Hz), 6.97 (d, 1H, $J$ = 2.0 Hz), 7.17 (dd, 1H, $J$ = 2.1, 8.2 Hz), 7.74−7.80 (m, 2H), 8.22 (d, 2H, $J$ = 7.4 Hz), 8.61 (d, 2H, $J$ = 7.0 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 33.3, 41.9, 44.3, 62.7, 115.8, 121.8, 122.6, 126.8, 128.0, 128.8, 128.9, 129.1, 131.0, 131.5, 133.7, 156.5, 164.0. Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48; O, 12.82. Found: C, 73.79; H, 5.89; N, 7.45

**Exhaustive Methylation of Mannich Bases (11, 14). General Procedure.** A 500 mg portion of the respective Mannich base (**10**, **13**) were dissolved in $CH_3CN$ (30 mL), and $CH_3I$ (5 equivalents) was added dropwise. The solution was stirred at rt under nitrogen atmosphere until precipitation of a white solid is observed. To enhance the solid's precipitation, 10 mL of $Et_2O$ could be added. The white solid was collected by filtration and washed twice with cold $CH_3CN$ to give **11** (73% yield) or **14** (75% yield).

***N*-[3-(Trimethylamino)methyl-4-hydroxyphenyl]-1,8-naphthalimide Iodide (11).** Mp: 256−257 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 3.34 (s, 9H), 4.62 (s, 2H), 7.15 (d, 1H, $J$ = 8.6 Hz), 7.35 (d, 1H, $J$ = 2.4 Hz), 7.48 (dd, 1H, $J$ = 2.3, 8.5 Hz), 7.90−7.95 (m, 2H), 8.50 (d, 2H, $J$ = 7.8 Hz), 8.58 (d, 2H, $J$ = 7.3 Hz). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 52.0, 62.8, 114.7, 116.3, 122.5, 126.8, 127.3, 127.8, 130.8, 131.4, 132.7, 134.5, 134.9, 157.0, 163.8. Anal. Calcd for $C_{22}H_{21}IN_2O_3$: C, 54.11; H, 4.33; I, 25.99; N, 5.74; O, 9.83. Found: C, 54,10; H, 4.38; I, 25.90; N, 5.72.

***N*-[(3-(Trimethylamino)methyl-4-hydroxyphenyl)ethyl]-1,8-naphthalimide Iodide (14).** Mp: 251−256 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 2.87 (t, 2H, $J$ = 7.6 Hz), 2.97 (s, 9H), 4.22 (t, 2H, $J$ = 7.5 Hz), 4.39 (s, 2H), 6.85 (d, 1H, $J$ = 8.3 Hz), 7.18 (dd, 1H, $J$ = 1.8, 8.3 Hz), 7.27 (d, 1H, J = 1.8 Hz), 7.82−7.88 (m, 2H), 8.42−8.46 (m, 4H), 10.14 (s, 1H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 32.5, 41.1, 51.8, 63.0, 114.5, 116.1, 121.9, 127.2, 129.4, 130.7, 131.3, 132.4, 134.4, 134.7, 155.7, 163.3. Anal. Calcd for $C_{24}H_{25}IN_2O_3$: C, 55.82.01; H, 4.88; I, 24.58; N, 5.43; O, 9.30. Found: C, 55.80; H, 4.90; I, 24.55; N, 5.45.

**Photoactivation. General Procedure.** The determination of the photoreactivity of molecules **11** and **14** as alkylating agents has been performed according the following procedure. A Pyrez tube was filled with 10 mL of a $5 \times 10^{-4}$ M solution of **11** or **14** in $H_2O/CH_3CN$ 1:1. To this solution the freshly distilled nucleophile was added until its concentration reaches $5 \times 10^{-3}$ M, and a purge with $N_2$ flush was performed for 5 min. After that time the tube was irradiated in a multilamp reactor fitted with four lamps centered at 310 nm for the required time (5−60 min). Conversion has been followed by analytical HPLC ($H_2O$ added with 0.1% TFA and $CH_3CN$ as eluent system).

**Activation by Base Catalysis. General Procedure.** The alkylating properties of molecules **11** and **14** toward different nucleophiles (amines, thiols, and water) have also been investigated under thermal base catalysis. To a $5 \times 10^{-4}$ M solution of **11** or **14** in a 1:1 mixture of $H_2O/CH_3CN$ was added the freshly distilled nucleophile until its concentration reaches $5 \times 10^{-3}$ M. Basic catalysis has been achieved according two different strategies: (i) by using strong basic nucleophiles, such as amines, or (ii) by performing the reaction in a carbonate buffered media (pH 10, $NaHCO_3/Na_2CO_3$) with nucleophiles displaying poor basicity. Conversion has been followed by analytical HPLC ($H_2O$ added with 0.1% TFA and $CH_3CN$ as eluent system).

***N*-[4-Hydroxy-3-(hydroxymethyl)phenyl]-1,8-naphthalimide (Adduct 15).** Yellow oil. $^1$H NMR (DMSO-$d_6$): $\delta$ 4.54 (s, 2H), 5.07 (bs, 1H), 6.88 (d, 1H, $J$ = 8.4 Hz), 7.02 (dd, 1H, $J$ = 2.4, 8.4 Hz), 7.23 (d, 1H, $J$ = 2.2 Hz), 7.9 (t, 2H, $J$ = 7.7 Hz), 8.49−8.51 (m, 4H), 9.6 (bs, 1H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 58.0, 114.6, 122.7, 126.8, 127.2, 127.4, 127.6, 127.8, 129.2, 130.7, 131.4, 134.3, 153.7, 163.9. Anal. Calcd for $C_{19}H_{13}NO_4$: C, 71.47; H, 4.10; N, 4.39. O, 20.04. Found: C, 71.49; H, 4.09; N, 4.41.

***N*-[4-Hydroxy-3-(piperidin-1-ylmethyl)phenyl]-1,8-naphthalimide (Adduct 16).** Yellow needles. Mp: 214−215 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.66−1.74 (m, 6H), 3.20−3.24 (m, 4H), 3.75 (bs, 2H), 6.90 (d, 1H, $J$ = 2.4 Hz), 7.0 (d, 1H, $J$ = 8.5 Hz), 7.15 (dd, 1H, $J$ = 2.5, 8.5 Hz), 7.76−7.82 (m, 2H), 8.25 (d, 2H, $J$ = 8.0 Hz), 8.65 (d, 2H, $J$ = 8.2 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 22.0, 25.6, 44.6, 53.8, 116.9, 121.9, 122.7, 126.0, 126.9, 128.4, 128.5, 128.5, 131.5, 131.6, 134.1, 158.2, 164.6. Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25; O, 12.42. Found: C, 74.40; H, 5.85; N, 7.32.

***N*-[3-(Butylethylamino)methyl-4-hydroxyphenyl]-1,8-naphthalimide (Adduct 17).** Pale yellow needles. Mp: 128−129 °C. $^1$H NMR ($CDCl_3$): $\delta$ 0.90 (t, 3H, $J$ = 7.3 Hz), 1.20 (t, 3H, $J$ = 7.2 Hz), 1,35−1.48 (m, 2H), 1.60−1.65 (m, 2H), 2.67−2.80 (m, 2H), 2.95−3.06 (m, 2H), 4.00 (s, 2H), 6.90 (d, 1H, $J$ = 2.2 Hz), 7.0 (d, 1H, $J$ = 8.5 Hz), 7.15 (dd, 1H, $J$ = 2.3, 8.3 Hz), 7.78−7.84 (m, 2H), 8.30 (d, 2H, $J$ = 8.2 Hz), 8.70 (d, 2H, $J$ = 7.3 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 10.5, 13.8, 20.3, 27.9, 47.0, 52.5, 56.4, 117.36, 121.6, 122.8, 126.1, 126.9, 128.8, 129.0, 131.5, 131.6, 134.1, 158.1, 164.5. Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96; O, 11.93. Found: C, 74.55; H, 6.72; N, 7.05.

***N*-[4-Hydroxy-3-(morpholin-4-ylmethyl)phenyl]-1,8-naphthalimide (Adduct 18).** Yellow needles. Mp: 222−224 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.65 (bs, 4H), 3.77−3.80 (m, 6H), 6.90 (d, 1H, $J$ = 2.3 Hz), 7.0 (d, 1H, $J$ = 8.5 Hz), 7.15 (dd, 1H, $J$ = 2.3, 8.5 Hz), 7.78−7.83 (m, 2H), 8.30 (d, 2H, $J$ = 8.3 Hz), 8.70 (d, 2H, $J$ = 8.3 Hz). $^{13}$C NMR

($CDCl_3$): δ 52.9, 6.5, 66.7, 116.9, 121.2, 122.7, 126.4, 126.9, 128.4, 128.7, 128.9, 131.6, 131.5, 134.1, 157.7, 164.6. Anal. Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21; O, 16.48. Found: C, 71.35; H, 5.10; N, 7.05.

***N*-[3-(*tert*-Butylamino)methyl-4-hydroxyphenyl]-1,8-naphthalimide (Adduct 19).** Yellow needles. Mp: 153−155 °C. $^1$H NMR (DMSO-$d_6$): δ 1.30 (s, 9H), 4.00 (s, 2H), 6.90 (d, 1H, *J* = 8.5 Hz), 7.15 (dd, 2H, *J* = 2.3, 8.5 Hz), 7.88−7.93 (m, 2H), 8.51 (m, 4H). $^{13}$C NMR (DMSO-$d_6$): δ 26.6, 40.9, 42.1, 115.6, 122.0, 122.5, 126.5, 127.2, 127.8, 129.6, 129.9, 130.7, 131.4, 134.4, 157.0, 163.9. Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48; O, 12.82. Found: C, 73.53; H, 5.98; N, 7.52.

***N*-[4-Hydroxy-3-((2-hydroxyethylthio)methyl)phenyl]-1,8-naphthalimide (Adduct 20).** White dust. Mp: 215−216 °C. $^1$H NMR (DMSO-$d_6$): δ 2.79−2.82 (m, 2H), 3.55 (bs, 2H), 3.73 (s, 2H), 4.74 (bs, 1H), 6.93 (d, 1H, *J* = 8.4 Hz), 7.04 (dd, 1H, *J* = 2, 8 Hz), 7.16 (d, 1H, J = 2 Hz), 7.88 (t, 2H, *J* = 8 Hz), 8.45−8.48 (m, 4H), 9.7 (s, 1H). $^{13}$C NMR (DMSO-$d_6$): 33.4, 37.5, 60.5, 114.7, 122.1, 124.8, 126.1, 126.6, 127.2, 127.7, 129.8, 130.2, 130.9, 133.7, 154.3, 163.3. Anal. Calcd for $C_{21}H_{17}NO_4S$: C, 66.47; H, 4.52; N, 3.69; O, 16.87; S, 8.45. Found: C, 66.45; H, 4.55; N, 3.72; S, 8.43.

***N*-[(4-Hydroxy-3-(hydroxymethyl)phenyl)ethyl]-1,8-naphthalimide (Adduct 21).** Yellow oil. $^1$H NMR (DMSO-$d_6$): δ 2.81 (t, 2H, *J* = 8.3 Hz), 4.19 (t, 2H, *J* = 8.2 Hz), 4.47 (d, 2H, *J* = 5.3 Hz), 4.96 (t, 1H, *J* = 5.3 Hz), 6.71 (d, 1H, *J* = 8.0 Hz), 6.91 (dd, 1H, *J* = 2.4, 8.0 Hz), 7.25 (d, 1H, *J* = 2.4 Hz), 7.87−7.92 (m, 2H), 8.46−8.54 (m, 4H), 9.18 (s, 1H). $^{13}$C NMR (DMSO-$d_6$): 33.0, 41.5, 58.2, 114.6, 122.1, 125.0, 127.2, 127.4, 127.5, 128.6, 129.5, 130.7, 131.3, 134.3, 152.6, 163.3. Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03; O, 18.42. Found: C, 72.60; H, 4.95; N, 4.02.

***N*-[(4-Hydroxy-3-(piperidin-1-ylmethyl)phenyl)ethyl]-1,8-naphthalimide (Adduct 22).** White solid. Mp: 145−150 °C. $^1$H NMR ($CDCl_3$): δ 1.58−1.63 (m, 6H), 2.46 (bs, 4H), 2.89−2.94 (m, 2H), 3.62 (s, 2H), 4.32−4.37 (m, 2H), 6.76 (d, 1H, *J* = 8.2), 6.96 (d, 1H, *J* = 1.8 Hz), 7.16 (dd, 1H, *J* = 2.0, 8.1 Hz), 7.72−7.77 (m, 2H), 8.19 (d, 2H, *J* = 7.6 Hz), 8.50 (d, 2H, *J* = 7.0 Hz). $^{13}$C NMR ($CDCl_3$): δ 23.9, 25.7, 33.3, 41.9, 53.7, 61.9, 115.8, 121.5, 122.5, 126.8, 128.0, 128.9, 128.9, 131.0, 131.4, 133.8, 156.5, 163.9. Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76; O, 11.58. Found: C, 75.35; H, 6.30; N, 6.72.

***N*-[(3-(Butylethylamino)methyl-4-hydroxyphenyl)ethyl]-1,8-naphthalimide (Adduct 23).** Yellow needles. Mp: 112−115 °C. $^1$H NMR ($CDCl_3$): δ 0.92 (t, 3H, *J* = 7.2 Hz), 1.08 (t, 3H, *J* = 7.2 Hz), 1.26−1.43 (m, 2H), 1.48−1.56 (m, 2H), 2.49−2.62 (m, 4H), 2.90−2.95 (m, 2H), 3.74 (s, 2H), 4.33−4.38 (m, 2H), 6.76 (d, 1H, *J* = 8.1 Hz), 6.99 (s, 1H), 7.15 (dd, 1H, *J* = 1.5, 8.0 Hz), 7.73−7.78 (m, 2H), 8.21 (d, 2H, *J* = 8.2 Hz), 8.60 (d, 2H, *J* = 8.0 Hz). $^{13}$C NMR ($CDCl_3$): 10.8, 13.8, 20.4, 28.5, 33.3, 42.0, 46.5, 52.5, 57.3, 115.9, 122.0, 122.5, 126.8, 128.0, 128.9, 131.0, 131.5, 133.8, 156.6, 163.9. Anal. Calcd for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02; N, 6.51; O, 11.15. Found: C, 75.35; H, 7.00; N, 6.55.

***N*-[(4-Hydroxy-3-(morpholin-4-ylmethyl)phenyl)ethyl]-1,8-naphthalimide (Adduct 24).** White powder. Mp: 182−185 °C. $^1$H NMR ($CDCl_3$): δ 2.48 (bs, 4H), 2.87−2.93 (m, 2H), 3.64 (s, 2H), 3.71 (bs, 4H), 4.29−4.35 (m, 2H), 6.76 (d, 1H, *J* = 8.2 Hz), 6.96 (d, 1H, *J* = 1.8 Hz), 7.16 (dd, 1H, *J* = 2.0, 8.1 Hz), 7.70−7.75 (m, 2H), 8.18 (d, 2H, *J* = 8.2 Hz), 8.56 (d, 2H, *J* = 7.23 Hz). $^{13}$C NMR ($CDCl_3$): 33.2, 41.8, 52.7, 61.7, 66.7, 115.9, 120.5, 122.5, 126.8, 128.0, 129.3, 129.4, 131.0, 131.4, 133.8, 155.9, 163.7. Anal. Calcd for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73; O, 15.37. Found: C, 72.15; H, 5.78; N, 6.70.

***N*-[(3-(*tert*-Butylamino)methyl-4-hydroxyphenyl)ethyl]-1,8-naphthalimide (Adduct 25).** Yellow solid. Mp 132−135 °C. $^1$H NMR (DMSO-$d_6$): δ 1.07 (s, 9H), 2.77 (t, 2H, *J* = 7.3 Hz), 3.78 (s, 2H), 4.15 (t, 2H, *J* = 7.3 Hz), 6.59 (d, 1H, *J* = 8.2 Hz), 6.57−6.97 (m, 2H), 7.80−7.85 (m, 2H), 8.41−8.45 (m, 4H). $^{13}$C NMR (DMSO-$d_6$): δ 27.9, 32.7, 41.4, 44.5, 50.5, 115.6, 121.9, 124.4, 126.9, 127.1, 127.7, 128.1, 128.2, 130.6, 131.2, 134.2, 156.6, 163.2. Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96; O, 11.93. Found: C, 74.62; H, 6.49; N, 6.94.

***N*-[(4-Hydroxy-3-((2-hydroxyethylthiomethyl)phenyl)ethyl]-1,8-naphthalimide (Adduct 26).** White solid. Mp: 190−194 °C. $^1$H NMR ($CDCl_3$): δ 2.56−2.60 (m, 2H), 2.97 (t, 2H, *J* = 7.3 Hz), 3.75−3.84 (m, 2H), 3.84 (s, 2H), 4.42 (t, 2H, *J* = 7.3 Hz), 6.5 (bs, 1H), 6.75 (d, 1H, *J* = 6.1 Hz), 7.07 (dd, 1H, *J* = 2.0, 6.0 Hz), 7.14 (d, 1H, *J* = 2.0 Hz), 7.75−7.81 (m, 2H), 8.25 (d, 2H, *J* = 8.8 Hz), 8.59 (d, 2H, *J* = 8.2 Hz). $^{13}$C NMR ($CDCl_3$): δ 30.8, 32.0, 32.5, 33.1, 41.7, 61.5, 116.8, 122.4, 126.9, 129.7, 130.8, 131.2, 131.3, 131.5, 134.0, 143.5, 153.6, 164.1. Anal. Calcd for $C_{23}H_{21}NO_4S$: C, 67.79; H, 5.19; N, 3.44; O, 15.71; S, 7.87. Found: C, 67.82; H, 5.15; N, 3.42; S, 7.89.

***N*-[2-Ethoxychroman-6-yl]-1,8-naphthalimide (Adduct 27).** White needles. Mp: 273−274 °C. $^1$H NMR ($CDCl_3$): δ 1.23−1.28 (m, 3 H), 2.01−2.09 (m, 2H), 2.67−2.72 (m, 1H), 2.95−3.06 (m, 1H), 3.65−3.68 (m, 1H), 3.93−3.99 (m, 1H), 5.32 (bs, 1H), 6.98−7.08 (m, 3H), 7.79−7.85 (m, 2H), 8.30 (d, 2H, *J* = 8.3 Hz), 8.67 (d, 2H, *J* = 7.3 Hz). $^{13}$C NMR ($CDCl_3$): δ 15.0, 20.5, 26.1, 63.7, 97.0, 117.8, 122.8, 123.5, 126.9, 127.1, 127.5, 128.4, 128.9, 131.5, 131.6, 134.1, 152.4, 164.6. Anal. Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75; O, 17.14. Found: C, 73.85; H, 5.03; N, 3.70.

***N*-[(2-Ethoxychroman-6-yl)ethyl]-1,8-naphthalimide (Adduct 28).** White needles. Mp: 168−170 °C. $^1$H NMR (CDCl3): δ 1.22 (t, 3H, *J* = 7.0 Hz), 1.95−2.06 (m, 2H), 2.60−2.71 (m, 1H), 2.92−2.97 (m, 3H), 3.63−3.69 (m, 1H), 3.88−3.94 (m, 1H), 4.35−4.40 (m, 2H), 5.26 (bs, 1H), 6.82 (d, 1H, *J* = 7.8 Hz), 7.10 (s, 1H), 7.15 (d, 1H, *J* = 8.2 Hz), 7.75−7.81 (m, 2H), 8.23 (d, 2H, *J* = 8.2 Hz), 8.63 (d, 2H, *J* = 7.2 Hz). $^{13}$C NMR ($CDCl_3$): 15.0, 20.43, 26.5, 33.4, 42.0, 63.5, 96.8, 116.8, 122.4, 122.6, 126.8, 127.7, 128.0, 129.6, 130.7, 131.0, 131.5, 133.8, 150.7, 163.9. Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49; O, 15.94. Found: C, 74.82; H, 5.73; N, 3.52.

## ■ ASSOCIATED CONTENT

**Supporting Information.** $^1$H NMR and $^{13}$C NMR for the NIs **11** and **14**, their synthetic precursors, and the adducts **15**−**28**; further LFP data; and NI-P (**29**) synthetic procedure and spectroscopic data. This material is available free of charge via Internet at http://pubs.acs.org.

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