

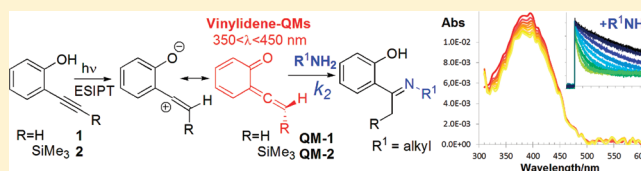
Vinylidene–Quinone Methides, Photochemical Generation and β -Silicon Effect on Reactivity

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S Supporting Information

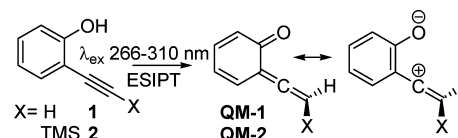
ABSTRACT: Irradiation of 2-alkynylphenols resulted in the generation of vinylidene–quinone methides (QMs), which were detected by laser flash photolysis in organic solvents and aqueous acetonitrile. QMs' spectroscopic properties and electrophilicity were both significantly affected by β -silicon effect. The hydration of the alkynyl moiety (22 and $900\text{ M}^{-1}\text{ s}^{-1}$ for **QM-1** and **QM-2**, in aqueous acetonitrile) was an acid- and base-catalyzed process. The addition of amines was fast ($9.2 \times 10^3\text{ M}^{-1}\text{ s}^{-1} < k_2 < 1.3 \times 10^8\text{ M}^{-1}\text{ s}^{-1}$), yielding ketimines, with primary amines.



Excited state intramolecular proton transfer (ESIPT) from an *ortho*-aromatic OH (phenol or naphthol) to unsaturated systems such as carbonyls,¹ alkenes,^{2,3} and aromatics^{4–6} has been extensively investigated in the last 15 years. While the proton transfer to a carbonyl group is a highly reversible process, the ESIPT to a carbon atom or to a leaving group are often irreversible ones, leading to further reactivity with the generation of reactive quinone methides (QMs).^{7–10} QMs received a great deal of attention thanks to their useful applications in organic synthesis¹¹ and as selective alkylating agents targeting DNA.^{12–19} The main effort on the mechanistic aspects of ESIPT to carbon atoms has been focused on alkenes and aromatics, collecting a great amount of spectroscopic and kinetic data related to substituted QMs.^{10,20–23} Despite the original and pioneering work on the photohydration of *o*-hydroxyphenylacetylenes by Ferris²⁴ and Yates and co-workers,²⁵ spectroscopic and kinetic data related to the intermediate generated by ESIPT have not yet been published. It is interesting to underline in this contest that a dipolar carbocation-like structure was suggested as key intermediate on the basis of product distribution analysis from the photohydration reaction of *o*-hydroxyphenylacetylene (**1**).^{24,25} Only 25 years later, such an intermediate has been rewritten as vinylidene–QM structure.²⁶ The lack of direct evidence for vinylidene–QMs combined to our interest in photogenerated alkylating species, prompted us to investigate the properties and reactivity of the vinylidene–quinone methides **QM-1** and **QM-2** (Scheme 1).

The *o*-hydroxyphenylacetylenes **1** and **2**,²⁷ which are potential precursors of **QM-1** and **QM-2**, respectively, were synthesized according to a Sonogashira protocol and subsequent TMS cleavage by fluoride (for **QM-1**).²⁷ Irradiation of aqueous ACN solutions of both **1** and **2** at 310 nm yielded *o*-hydroxyacetophenone as the only photoproduct, which was isolated by chromatography and characterized by comparison to a commercial sample. Under the same irradiation conditions (4 lamps, 15 W), **1** resulted twice as reactive as **2** (irradiation time: 90 min, 48% yield and 150 min, 44% yield, respectively).

Scheme 1. Photogeneration of Vinylidene–Quinone Methides



Photolysis of both **1** and **2** in ACN and CH_2Cl_2 solutions in the presence of propylamine (*n*-PrNH₂) was quantitative and completely stereoselective, yielding (*E*)-2-(1-propyliminoethyl)-phenol (**3**) (Scheme 2). The *E* stereochemistry of the resulting imine has been assigned on the basis of a NOE experiment, which highlighted the *cis* relationship between the methyl group and the CH_2 moiety on the imine (Supporting Information). The generation of **3** from **2** is probably the result of a fast thermal desilylation on the intermediate 2-(1-propylimino-2-trimethylsilyl)phenol (in brackets, Scheme 2), after the **QM-2** has been trapped by *n*-PrNH₂. Unfortunately, we have been unable to isolate and characterize the primary photoproduct, even at low conversion.

The formation and reactivity of both QMs in aqueous and organic solutions (neat ACN and CH_2Cl_2) were monitored by a nanosecond spectrometer equipped with pulsed Nd:YAG laser. Excitation of alkyne **2** in both argon purged ACN (Figure 1a) and CH_2Cl_2 (Figure 1c) with 10 ns 266 nm pulses of a Nd:YAG laser resulted in the formation of a short-lived transient with λ_{max} 330 nm, together with a long-lived species at λ_{max} 390–400 nm, which did not appreciably decay within 10 ms in neat ACN (Figure 1a, with a long time delay from the laser pulse, and 1b).

Excitation of alkyne **2** in aqueous ACN ($\text{H}_2\text{O}/\text{ACN} = 1:9$) at pH 7 generated a transient species that exhibited a very similar spectrum (37.6 μs after laser pulse; Figure 1d). However, in this

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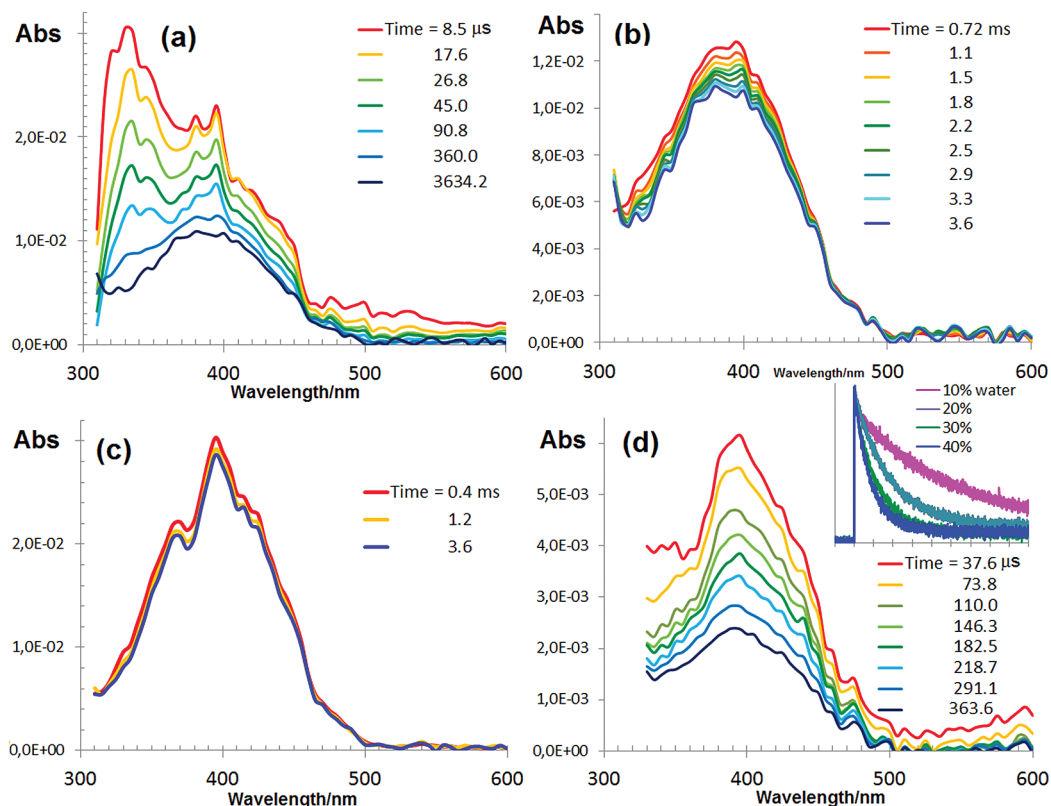
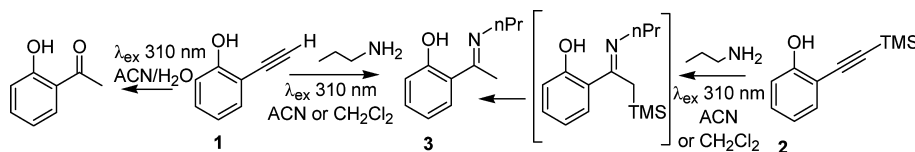
Scheme 2. Photohydration and Ketimine Formation by Irradiation of 1 and 2 at 310 nm in ACN, Aqueous ACN and CH₂Cl₂

Figure 1. Transient spectra obtained by photolysis of (a) an argon purged ACN solution of **2** (0.1 mM; from 8.5 μ s to 3.6 ms, after the laser pulse); (b) an air purged ACN solution of **2** (0.1 mM; from 0.72 to 3.6 ms, after the laser pulse); (c) an air purged CH₂Cl₂ solution of **2** (0.1 mM; from 0.4 to 3.6 ms, after the laser pulse); and (d) an air purged aqueous ACN solution (H₂O 10% v) of **2** at pH 7 (0.1 mM; from 37.6 to 363.6 μ s, after the laser pulse). Inset: effect of water on the **QM-2** kinetic in ACN solution.

case, the transient species followed a single exponential decay that became faster, increasing the amount of water added to ACN (inset of Figure 1d). Alkyne **1** exhibited a very similar spectroscopic behavior, but the long-lived species was blue-shifted by 25 nm (λ_{max} 375 nm) (Figure 2). The decay kinetic was dramatically affected by amine addition as highlighted in the inset of Figure 2.

The transient at 330 nm has been assigned to the triplet excited states of both alkynes **1** and **2**, as they were efficiently quenched by molecular oxygen. The identity of the longer lived species has been established on the basis of their reactivity toward water and several nucleophiles and from the results of the product distribution analysis obtained from both steady state and pulsed (by laser) irradiations. Taking also into account the striking similarity of their spectroscopic properties to that of the prototype *o*-QM,^{10,21} we have assigned them to the vinylidene-QM structures: **QM-1** and **QM-2**. They were both fairly long-lived in neat ACN and CH₂Cl₂, as no significant decay was recorded within the limit of our LFP equipment (time \leq 10 ms). Nevertheless, both slowly decayed in acetonitrile in the presence of small amount of water, with

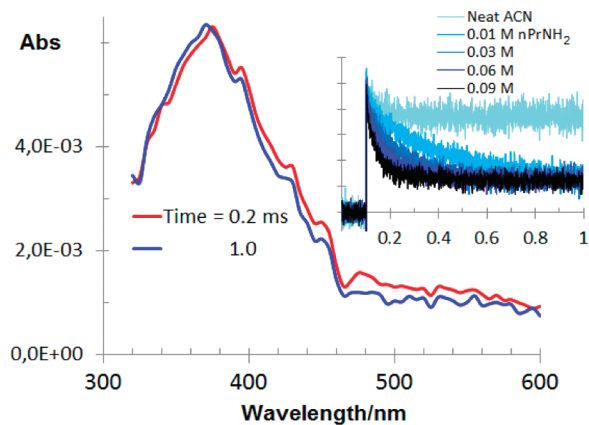
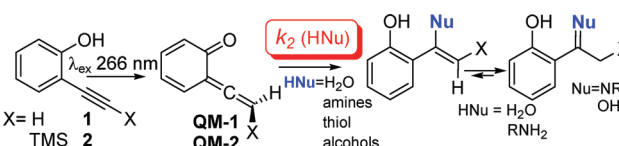


Figure 2. Transient spectra obtained by photolysis of an air purged solution of **1** (0.1 mM) in neat ACN (0.2 and 1.0 ms, after the laser pulse). Inset: effect of *n*-PrNH₂ (from 0.01 to 0.09 M in ACN) on the **QM-1** decay kinetics.

$k_2(\text{QM-1}) = 22 \text{ M}^{-1} \text{ s}^{-1}$ and $k_2(\text{QM-2}) = 900 \text{ M}^{-1} \text{ s}^{-1}$ at 25 °C, respectively. Addition of several amines both in CH₂Cl₂ and in

ACN accelerated the rate of the quenching processes [$10^4 \text{ M}^{-1} \text{ s}^{-1} \leq k_2(\text{QMs}) \leq 10^8 \text{ M}^{-1} \text{ s}^{-1}$, see Table 1). The quenching reactions

Table 1. Second Order Rate Constants for Addition Reactions to QM-1 and QM-2, Photogenerated by LFP at 266 nm, and Monitored at 375 and 395 nm, Respectively, in Organic Solvents (CH_2Cl_2 and ACN) and Aqueous ACN, at 25 °C



HNu	QM-1 $k_2/\text{M}^{-1} \text{ s}^{-1a}$		QM-2 $k_2/\text{M}^{-1} \text{ s}^{-1a}$		
	CH_2Cl_2	ACN	CH_2Cl_2	ACN	H_2O
<i>n</i> -PrNH ₂	7.8×10^4	2.2×10^5	8.9×10^5	9.3×10^6	
pentylamine	8.5×10^4	1.9×10^5	7.2×10^5	7.2×10^6	
<i>t</i> -BuNH ₂	9.2×10^3	5.6×10^4	2.2×10^5	6.4×10^6	
pyrrolidine	1.4×10^6	4.7×10^6	3.5×10^7	1.3×10^8	
piperidine	4.3×10^5	2.4×10^6	5.3×10^6	6.4×10^7	
<i>i</i> -Pr ₂ NH	1.8×10^4	9.9×10^4	2.0×10^5	9.8×10^6	
morpholine	4.2×10^5	4.2×10^5	1.1×10^6	8.4×10^6	
Et ₃ N	9.1×10^5	1.1×10^6	2.1×10^7	3.4×10^7	
<i>n</i> -Bu ₃ N	3.7×10^5	1.2×10^7	1.7×10^7		
<i>N</i> -Me-morph	4.6×10^4	1.2×10^5	1.8×10^6	4.7×10^6	
NH ₂ NH ₂		3.6×10^5	3.2×10^5	3.8×10^6	
H ₂ O		2.2×10^1	9.0×10^2		
CH ₃ OH			4.2×10^2	3.8×10^2	
H ₃ O ⁺					2.7×10^5
2-propanol			6.6×10^3		
OH [−]					1.4×10^6
octane-1-thiol			2.9×10^3		

^aEstimated errors on the reported values are 4%.

were identified as hydration and nucleophilic additions of the amines. In fact, *o*-hydroxyacetophenone was detected as the only product after 20 laser shots (at 266 nm) on an aqueous ACN solution of **1**. The replacement of water by *n*-PrNH₂, in ACN solution, resulted in the photogeneration of imine **3** as the only detectable product. The direct measurement of the second-order rate constants (k_2) listed in Table 1 (Figures S1–S4, Supporting Information) for the addition reactions on both QM-1 and QM-2 by several amines, water, methanol, and octane-1-thiol by LFP allowed a quantitative evaluation of the electrophilicity of QM-1 vs QM-2, together with the selectivity toward N (amines), O (water and alcohols), and S (thiols) nucleophiles. QM-1 and QM-2 are fast and efficient carbon electrophiles that are very selective toward amines. In fact, the reactivity of vinylidene-QMs spans 5 orders of magnitude on passing from water to amines. From this point of view, the chemical behavior of QM-1 and QM-2 mirrors that of prototype *o*-QM.²¹ Nevertheless, the modest reactivity toward thiols [$k_2(\text{QM-2}) = 2.9 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$] came as a surprise because, on the contrary, the prototype *o*-QM was much more reactive [$k_2(\text{o-QM}) = 1.9 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$].²¹ The reactivity toward amines is strongly affected by solvent polarity, as both QM-1 and QM-2 are much more reactive in ACN than in CH_2Cl_2 .

The difference in reactivity between QM-1 and QM-2 is also noteworthy, as the more bulky QM-2 is always much more reactive than the unsubstituted counterpart (QM-1, Table 1).

Such a reactivity gap has to be ascribed to a β -silicon effect.²⁸ In fact, the hyperconjugation in QM-2 is apparent in the orbital plots for the LUMO (Figure S5, Supporting Information) as sketched in Figure 3a. The LUMO for QM-2 is primarily a p_π orbital on the carbenium-like carbon (in the dipolar limit structure, Figure 3a) with an out-of-phase mixture of the

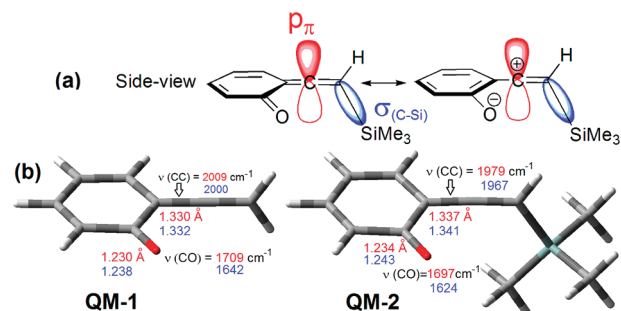


Figure 3. (a) Schematic representation of the β -silicon effect in QM-2, involving the p_π orbital on the carbenium-like carbon and the eclipsing $\sigma_{(\text{C-Si})}$ bond orbital. (b) Selected geometrical bond lengths (in Å) and vibrational frequencies (in cm^{-1}) computed for QM-1 and QM-2 at B3LYP/6-31+G(d,p) level of theory, in gas (red) and in ACN (blue).

eclipsing $\sigma_{(\text{C-Si})}$ bond orbital. Such a silicon hyperconjugation, involving the electrophilic carbon atom and the C–Si bond, should be responsible for the enhancement of the dipolar nature (described by the zwitterionic limit structure in Figure 3a) and hardness of QM-2 at β -carbon atom, in comparison to QM-1. In the past, it has been shown that the nucleophilic addition of NH₃ to the prototype *o*-QM exhibits a TS with an enhanced dipolar character in comparison to the reactant.²⁹ This should also be the case of amine addition to vinylidene–quinone methides, as the experimental kinetic data revealed a systematic higher reactivity in polar solvents. Therefore, it is reasonable to expect a selective stabilization of the TS, induced by β -silicon effect, which accounts for the improved reactivity passing from QM-1 to QM-2.

The antiperiplanar relationship between the two interacting orbital fragments, the empty p_π orbital on the carbenium carbon and the filled $\sigma_{(\text{C-Si})}$ (which is the key prerequisite for an effective beta-silicon effect) has been confirmed, optimizing the geometries of both QM-1 and QM-2 by computational means, at B3LYP/6-31+G(d,p) level of theory, in gas and condensed phase (ACN) (Figure 3b).

The enhanced dipolar nature of QM-2, in comparison to QM-1, is further supported by additional geometric and spectroscopic evidence computed at the same level of theory. In fact, the optimized geometries and the computed IR vibrational spectra in gas phase (in red, Figure 3b) suggested that both the C=O and the exocyclic C=C double bonds in QM-1 are shorter and stronger [CO = 1.230 Å; $\nu(\text{CO}) = 1709 \text{ cm}^{-1}$, CC = 1.330 Å; $\nu(\text{CC}) = 2009 \text{ cm}^{-1}$] than in QM-2 [CO = 1.234 Å, $\nu(\text{CO}) = 1697 \text{ cm}^{-1}$; CC = 1.337 Å; $\nu(\text{CC}) = 1979 \text{ cm}^{-1}$]. In addition, the solvation by a polar solvent (modeled by PCM solvation model at the same level of theory), further elongated the above bond lengths, reducing the frequencies of both C=O and asymmetric C=C stretching modes (in blue, Figure 3b). Such computational evidence unambiguously suggests that the electrophilicity and the dipolar character of the vinylidene-QMs (Figure 3a), which relates with its hardness, are enhanced by both β -silicon effect and

solvation. This also accounts for the lower reactivity of **QM-2** toward thiols, in comparison to the prototype *o*-QM.

In conclusion, we have described the photogeneration of vinylidene–quinone methides by ESIP in organic and aqueous solvents. Furthermore, we have characterized their UV–vis properties and the remarkable electrophilicity, which is enhanced by a β -silicon effect and solvent polarity. Despite some similarity with the prototype quinone methide (*o*-QM), at least with amines and water, vinylidene–quinone methides are much less reactive toward thiols than QMs because of their harder character. Because of the selectivity toward amines, they should be considered as promising activatable electrophiles to achieve a photogeneration of imines (photoimination) of amino acids and nucleic acids. Currently, work on water-soluble 2-alkynylphenols and derivatives of more complex structure is in progress.

EXPERIMENTAL SECTION

1 and **2** have been synthesized according to a published synthetic procedure.²⁷

General Methods. All organic solvents were dried and freshly distilled before use. Purification of products by column chromatography was performed using 40–63 μ m silica gel. All NMR spectra were recorded on a 300 MHz instrument in CDCl₃ and referenced to TMS. Solutions for photolysis were prepared using anhydrous CH₂Cl₂, HPLC grade water, and acetonitrile. Preparative photolyses were carried out using a photochemical reactor equipped with four fluorescent UV lamps (15 W, 310 nm).

Flash Photolysis Experiments. UV–vis spectra and rate measurements of **QM-1** and **QM-2** reactions were performed using a kinetic spectrometer by following spectral changes at 375 and 395 nm, respectively. Generation of **QM-1** and **QM-2** was achieved by photolysis of **1** and **2**, respectively, using the fourth (266 nm) harmonic of a Q-switched Nd:YAG laser, delivering 3 mJ pulses with a duration of ca. 10 ns. The signal from the spectrometer was digitized by an oscilloscope, and the data were processed on a PC system. The sample solution was kept constant at 25 °C. The disappearance of both **QM-1** and **QM-2** was followed, under pseudo-first-order conditions, by monitoring the absorbance decrease at 375 and 395 nm, respectively. Pseudo-first-order rate constants (k_{obsd}) were obtained from the fit of the absorbance data to a single exponential function and were reproducible to $\pm 4\%$. The second-order rate constants k_2 (M⁻¹ s⁻¹) for the reaction of nucleophiles with **QM-1** and **QM-2** were determined as the least-squares slopes of linear plots of k_{obsd} against the total concentration of the nucleophile (Figure S1–S4, Supporting Information). Amines were used from 2×10^{-3} to 0.75 M concentration range. Octane-1-thiol, methanol, and water required higher concentrations: 0.5–0.8 M, 2–8 M, 5–12 M, respectively.

Computational Details. All calculations were carried out using the Gaussian 2003 program packages.

The geometric structures of **QM-1** and **QM-2** were fully optimized in the gas phase and in water solution using the hybrid density functional method B3LYP with the 6-31+G(d,p) basis set. Frequency calculations have been performed at the same level of theory, and they have not been scaled. The bulk solvent effect on the geometries was calculated via the self-consistent reaction field (SCRf) method using the PCM as implemented in the C.02 version of Gaussian 2003.³⁰ The cavity was composed by interlocking spheres centered on non-hydrogen atoms with radii obtained by the HF parametrization of Barone known as the united atom topological model (UAHF).³¹

General Procedure for the Preparative Irradiation of 1 and 2 in the Presence of Propylamine. An argon-purged solution of the *o*-hydroxyphenylacetylene (**1** or **2**) (1.05 mmol) together with propylamine (0.59 g, 10 mmol) in dry CH₂Cl₂ (100 mL) was irradiated in 10 Pyrex tubes, using a multilamps reactor fitted with four 15 W lamps, with maximum emission centered at 310 nm. After 40 min (120 min, using **2**), the solutions were collected, and the solvent was removed under vacuum. The crude residue was purified by flash chromatography (cyclohexane/ethyl

acetate = 8:2) affording **3** (56 and 44% yields, starting from **1** and **2**, respectively).

(E)-2-(N-Propyl-1-iminoethyl)phenol (3). Pale yellow oil; ¹H NMR (CDCl₃) δ 1.07 (t, J = 7.4 Hz, 3H), 1.80 (m, 2H), 2.36 (s, 3H), 3.56 (t, J = 6.9 Hz, 2H), 6.77 (dt, J = 1.0, 7.3 Hz, 1H), 6.93 (dd, J = 1.0, 8.3 Hz, 1H), 7.29 (dt, J = 1.0, 7.3 Hz, 2H), 7.52 (dd, J = 1.0, 8.3 Hz, 2H), 16.5 (broad s, 1H); ¹³C NMR (CDCl₃) δ 11.8, 14.0, 23.4, 50.4, 116.3, 119.2, 127.8, 132.5, 165.3, 171.35. Anal. Calcd for C₁₁H₁₅NO: C, 74.54; H, 8.53; N, 7.90; O, 9.03. Found: C, 74.49; H, 8.22; N, 8.01.

ASSOCIATED CONTENT

Supporting Information

¹H NMR, ¹³C NMR, and COSY of **3**. **QM-1** and **QM-2** geometries and frequencies at B3LYP/6-31+G(d,p) level of theory in gas and ACN (by PCM). This material is available free of charge via Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Cuma, M.; Scheiner, S.; Kar, T. *J. Am. Chem. Soc.* **1998**, *120*, 10497.
- (2) Brousmiche, D. W.; Xu, M. S.; Lukeman, M.; Wan, P. *J. Am. Chem. Soc.* **2003**, *125*, 12961.
- (3) Chuang, W. T.; Hsieh, C. C.; Lai, C. H.; Lai, C. H.; Shih, C. W.; Chen, K. Y.; Hung, W. Y.; Hsu, Y. H.; Chou, P. T. *J. Org. Chem.* **2011**, *76*, 8189.
- (4) Lukeman, M.; Wan, P. *J. Am. Chem. Soc.* **2002**, *124*, 9458.
- (5) Lukeman, M.; Wan, P. *Chem. Commun.* **2001**, 1004.
- (6) Lukeman, M.; Xu, M. S.; Wan, P. *Chem. Commun.* **2002**, 136.
- (7) Barasic, N.; Zabcic, I.; Mlinaric-Majerski, K.; Wan, P. *J. Org. Chem.* **2010**, *75*, 102.
- (8) Verga, D.; Nadai, M.; Doria, F.; Percivalle, C.; Di Antonio, M.; Palumbo, M.; Richter, S. N.; Freccero, M. *J. Am. Chem. Soc.* **2010**, *132*, 14625.
- (9) Kulikov, A.; Arumugam, S.; Popik, V. V. *J. Org. Chem.* **2008**, *73*, 7611.
- (10) Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc.* **2002**, *124*, 6349.
- (11) Pathak, T. P.; Sigman, M. S. *J. Org. Chem.* **2011**, *76*, 9210.
- (12) Rossiter, C. S.; Modica, E.; Kumar, D.; Rokita, S. E. *Chem. Commun.* **2011**, 47, 1476.
- (13) Wang, H. A.; Rokita, S. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 5957.
- (14) Wang, H.; Wahl, M. S.; Rokita, S. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 1291.
- (15) Nadai, M.; Doria, F.; Di Antonio, M.; Sattin, G.; Germani, L.; Percivalle, C.; Palumbo, M.; Richter, S. N.; Freccero, M. *Biochimie* **2011**, *93*, 1328.
- (16) Di Antonio, M.; Doria, F.; Richter, S. N.; Bertipaglia, C.; Mella, M.; Sissi, C.; Palumbo, M.; Freccero, M. *J. Am. Chem. Soc.* **2009**, *131*, 13132.
- (17) Weng, X.; Ren, L.; Weng, L.; Huang, J.; Zhu, S.; Zhou, X.; Weng, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8020.
- (18) Zhou, Q.; Qu, Y.; Mangrum, J. B.; Wang, X. *Chem. Res. Toxicol.* **2011**, *24*, 402.

- (19) Doria, F.; Richter, S. N.; Nadai, M.; Colloredo-Mels, S.; Mella, M.; Palumbo, M.; Freccero, M. *J. Med. Chem.* **2007**, *50*, 6570.
- (20) Weinert, E. E.; Dondi, R.; Colloredo-Melz, S.; Frankenfield, K. N.; Mitchell, C. H.; Freccero, M.; Rokita, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 11940.
- (21) Modica, E.; Zanaletti, R.; Freccero, M.; Mella, M. *J. Org. Chem.* **2001**, *66*, 41.
- (22) Arumugam, S.; Popik, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 11892.
- (23) Arumugam, S.; Popik, V. V. *J. Org. Chem.* **2010**, *75*, 7338.
- (24) Ferris, J. P.; Antonucci, F. R. *J. Am. Chem. Soc.* **1974**, *96*, 2010.
- (25) Isaks, M.; Yates, K.; Kalanderopoulos, P. *J. Am. Chem. Soc.* **1984**, *106*, 2128.
- (26) Lukeman, M. In *Wiley Series on Reactive Intermediates in Chemistry and Biology: Quinone Methides*; Rokita, S. E., Ed.; Wiley: Hoboken, NJ, 2009; p 16.
- (27) Pirali, T.; Gatti, S.; Di Brisco, R.; Tacchi, S.; Zaninetti, R.; Brunelli, E.; Massarotti, A.; Sorba, G.; Canonico, P.-L.; Moro, L.; Genazzani, A.-A.; Tron, G.-C.; Billington, R.-A. *Chem. Med. Chem.* **2007**, *2*, 437.
- (28) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183.
- (29) Di Valentin, C.; Freccero, M.; Zanaletti, R.; Sarzi-Amadè, M. *J. Am. Chem. Soc.* **2001**, *123*, 8366.
- (30) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B. et al. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.
- (31) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995.