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Effect of β-Alkylthioethyl Substitution in 1,3-Dithianes: Quasianchimeric Assistance in Photoinduced Electron Transfer?

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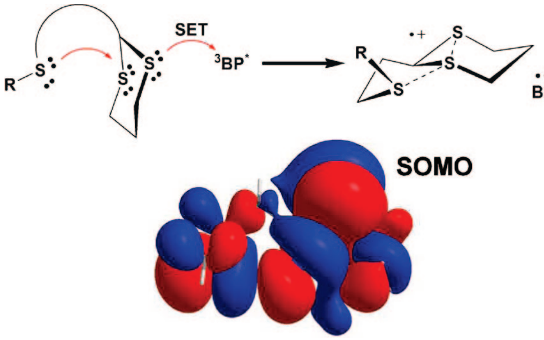
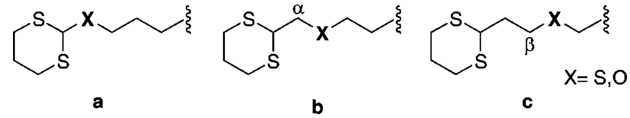


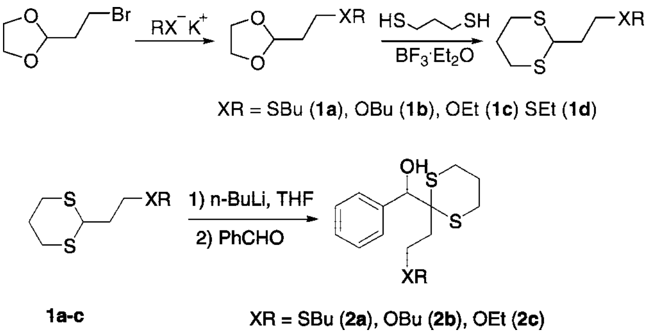
Nanosecond laser flash photolysis (LFP) experiments show that the rates of ET quenching of triplet benzophenone by 2-alkyldithianes significantly decrease with bulkier substitution. Introduction of sulfur at the β-position of the flexible alkyl chain reverses this trend, whereas such substitution at the α-position has negligible effect. This is rationalized in terms of the three electron two center bonds, favorable due to the formation of five-membered cyclic radical cations in the case of β-substitution, which is supported by DFT computations.

Detection of molecular recognition events aided by chemical encoding with photolabile tags is under extensive development in our laboratory. This methodology is based on externally sensitized photofragmentation in α-hydroxyalkyldithianes,[1] which can be made contingent on a molecular recognition event and therefore can be used to detect and report such events at a molecular level. We have demonstrated that this methodology can be utilized to encode and screen solution phase combinatorial libraries, either unsupported or immobilized on nanosized carriers too small for mechanical manipulations.[2] The encoding dithiane tags are released into solution only when a binding event occurs between the tagged ligand and the receptor, outfitted with an electron-transfer sensitizer. The released tags are detected by ubiquitous analytical techniques, such as GCMS, revealing the identity of the lead ligand or narrowing the range of potential leads. We have demonstrated that 2-alkyldithianes can be excellent tags because they do not interfere with biological interactions, are easy to separate from the aqueous screening environment due to their lipophilicity, and can be detected with very high sensitivity.

SCHEME 1



SCHEME 2



As high dimensional combinatorial libraries require a larger set of tags, we have been systematically searching for additional photolabile pendants in a form of other di- or trisulfides which can be utilized as photoactive molecular encoding tags. One alternative is a diverse auxiliary set of mass-differentiated 2,6,7-trithiabicyclo[2.2.2]octanes (TTBO), which can be readily synthesized and used for combinatorial encoding.[3]

Another systematic way to generate such sets is to progressively replace CH$_2$-groups in the alkyl substituent of dithianes by a heteroatom, e.g., sulfur or oxygen. This general topology is sketched in Scheme 1.

The TTBO system falls under the "**a**" category in Scheme 1 (X = S), where the sulfur atom replaces the first methylene in the alkyl chain. These bicyclic thioorthoesters and their adducts with benzaldehyde and benzophenone were found to have comparable photophysical properties to that of alkyldithiane adducts.[3] The alkylthio*methyl*dithianes (i.e., α-sulfides, case "**b**") eliminate alkylthiolates when treated with *n*-butyllithium, triggering an unexpected anionic dimerization of the elimination product, methylenedithiane.[4] Case "**c**" is the focus of this paper, where we examine the effect of heteroatom substitution in the third position of the alkyl chain (i.e., β-sulfides) on the initial rate of electron transfer quenching and quantum efficiencies of the photoinduced fragmentation in the adducts of alkylthio*ethyl*dithianes with carbonyl compounds.

2-Alkylthioethyl and 2-alkoxyethyl substituted dithianes are synthesized starting with 2-(2-bromoethyl)-1,3-dioxolane as shown in Scheme 2.

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[1] McHale, W. A.; Kutateladze, A. G. *J. Org. Chem.* **1998**, *63*, 9924–9931.

[2] Kottani, R.; Valiulin, R. A.; Kutateladze, A. G. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 13917–13921.

[3] Valiulin, R. A.; Kutateladze, A. G. *J. Org. Chem.* **2008**, *73*, 335–338.

[4] Valiulin, R. A.; Halliburton, L. M.; Kutateladze, A. G. *Org. Lett.* **2007**, 4061–4063.

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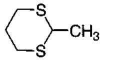
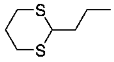
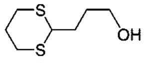
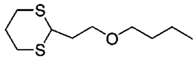
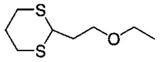
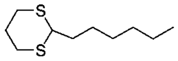
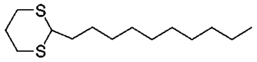
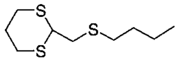
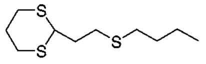
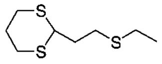
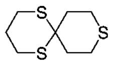
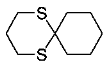
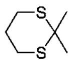
TABLE 1. Electron Transfer Rate Constants for Dithiane−Carbonyl Adducts in MeCN

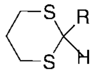
Entry	Dithianes	k_{ET}, M^{-1} s^{-1}
1		$15.2 \pm 1.1 \times 10^8$ [ref. 6]
2		$12.3 \pm 0.3 \times 10^8$
3		$10.1 \pm 0.3 \times 10^8$
4	 **(1b)**	$9.2 \pm 0.4 \times 10^8$
5	 **(1c)**	$10.5 \pm 0.5 \times 10^8$
6		$12.9 \pm 0.4 \times 10^8$
7		$10.0 \pm 0.4 \times 10^8$
8		$11.3 \pm 0.5 \times 10^8$
9	 **(1a)**	$15.8 \pm 0.6 \times 10^8$
10	 **(1d)**	$18.0 \pm 0.7 \times 10^8$
11	 **(1e)**	$10.3 \pm 0.4 \times 10^8$
12	 **(1f)**	$5.5 \pm 0.3 \times 10^8$
13	 **(1g)**	$8.9 \pm 0.5 \times 10^8$

Alternatively, the addition of thiolates to acrolein can be used to access alkylthioethyldithianes as described earlier.[5] Dithianes **1** were then lithiated and reacted with benzaldehyde to furnish photoactive adducts **2a**−**c** in high yields of 80−90%.

To address the mechanistic questions we first carried out a nanosecond laser flash photolysis (LFP) study of the quenching of triplet benzophenone by the parent (i.e., alkyl-, alkylthiomethyl-, and alkylthioethyl-) dithianes. As Table 1 shows, the initial rate of the quenching varies modestly from 5.5×10^8 to 18×10^8 M^{-1} s^{-1}, and generally decreases with increased alkyl substitution. Introduction of an α-sulfide (entry 8) does not change this trend. However, the rate of the electron transfer (ET) quenching by butylthio*ethyl*dithiane (**1a**)—which is sterically more congested than many of them but has a butylthio-group in the *β*-position—recovers and exceeds that of methyldithiane. The quenching by another *β*-sulfide, slightly less sterically congested *ethyl*thioethyldithiane (**1d**), is faster yet at 18×10^8 M^{-1} s^{-1}. In contrast, oxygen substitution, as in **1b** and **1c** (entries 4 and 5), does not have an effect on the electron transfer rate.

Clearly, the rate of the electron transfer quenching correlates inversely with steric congestion. However, the presence of an alkylsulfide group in the *β*-position of the flexible alkyl tail facilitates the photoinduced electron transfer. We suggest that this behavior of **1a** and **1d** can be rationalized in terms of formation of the five-membered cation radical containing the dithiane-1,2-dithiolane fused ring system.

TABLE 2. Nonvertical Ionization Potentials Calculated at the B3LYP/6-311++G(2d,p) Level (ZPE Corrected)

Entry	Dithiane 	IP, eV
1	R = H	7.84
2	R = Me	7.66
3	R = Et	7.58
4	R = Pr	7.55
5	R = SMe	7.66
6	R = CH_2SMe	7.47
7	R = CH_2CH_2SMe	>> **7.23** <<
8	R = CH_2CH_2OMe	7.56

The butylthio*methyl*dithiane (Table 1, entry 8) is only capable of forming a four-membered ring, which is not beneficial. In fact even hexyldithiane (entry 6) is a somewhat better quencher, which can be explained by the reported acceptor ability of C−S bonds in the alkyl chain.[6] Another manifestation of the effect of *β*-substitution can be found in comparison of entries 11 and 12. *β*-Sulfide **1e** does not offer any particular rate enhancement over the compounds shown in entries 2−8. However, when appropriately compared with its sulfur-less counterpart **1f** (entry 12) the *β*-sulfide **1e** does show a factor of 2 increase in the rate. It is plausible that additional steric shielding affects the rates in 2,2-disubstituted dithianes. For example, the rate of ET quenching in 2,2-dimethyldithiane (entry 13) is 40% slower than that of 2-methyldithiane (entry 1).

Our DFT (Density Functional Theory) calculations support the LFP experimental observations.[7] The values of nonvertical ionization potentials, IP, calculated at the B3LYP/6-311+G(2d,p) level of theory and corrected for zero-point vibrational energy, are listed in the last column of Table 2 (methylthio/methoxy substitution is used for computational simplicity). These values stay in the vicinity of 7.5−7.6 eV for the majority of substituted dithianes, but precipitously drop to 7.23 eV for the bicyclic radical cation, possessing the exocyclic 2-center-3-electron bond (entry 7).

Figure 1 illustrates that the most stable conformation of cation radicals of both α- (R = CH_2SMe, left) and *β*- (R = CH_2CH_2SMe, right) substituted systems is adopted to involve the third sulfur in the delocalization of charge density. Their singly occupied MOs (SOMOs) are primarily the out-of-phase antibonding combination of three unshared orbitals on sulfur atoms (shown). The exocyclic partial S−S bond in the α-substituted case is slightly shorter (2.93 Å) than the endocyclic S−S bond (2.97Å), while in the *β*-case this trend is reversed: 2.95 Å for the exocyclic bond and 2.91 Å for endocyclic. However, the *β*-substituted cation radical is significantly, about 5.4 kcal/mol, more stable than that of the α-substituted dithiane.

Analysis of the LFP kinetic data clearly indicates that there is on average a 50% rate enhancement in the case of *β*-sulfides and virtually no enhancement in the case of α-substitution. The question remains whether the observed acceleration is the result of quazianchimeric assistance of electron transfer[8] or a mere

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(6) Vath, P.; Falvey, D. E.; Barnhurst, L. A.; Kutateladze, A. G. *J. Org. Chem.* **2001**, *66*, 2886–2890.

(7) Alabugin, I. V.; Zeidan, T. A. *J. Am. Chem. Soc.* **2002**, *124*, 3175–3185.

(8) Although DFT computations are not ideal for odd electron systems due to the self-interaction error, examples of successful computations are plentiful in the literature, including radical cations of cyclic sulfides:Hennig, H.; Schumer, F.; Reinhold, J.; Kaden, H.; Oelssner, W.; Schroth, W.; Spitzner, R.; Hartl, F. *J. Phys. Chem. A* **2006**, *110*, 2039–2044.

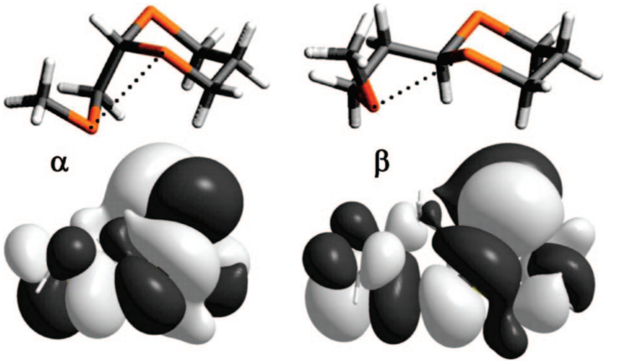


FIGURE 1. B3LYP/6-311+G(2d,p) optimized structures/SOMOs of dithianyl radical cations featuring α- (left) and *β*- (right) substitution.

TABLE 3. Quantum Yields (QY) of Photoinduced Fragmentation in MeCN

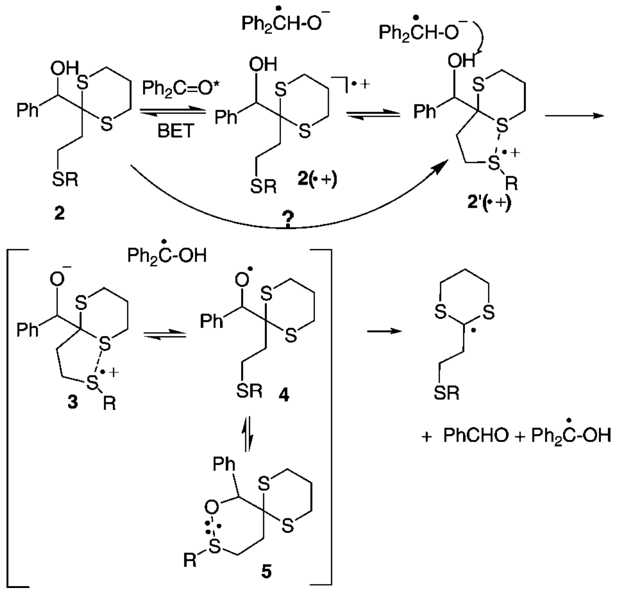
benzaldehyde adducts	absolute QY, %	relative QY
2a	10.1 ± 2.5	0.65
2b	13.6 ± 1.8	0.88
2c	15.4 ± 1.3	0.99
methyldithiane adduct	15.6 ± 0.4	(1.0)

addition of the third atom of sulfur increasing the number of donor atoms by a formal 50%. However, the rate dependence on the position of this third sulfur implies the anchimeric assistance.

Radical cations of conformationally flexible **1a** or **1d** are the most stable in the series. Sensitivity of dithianes detection by GCMS with electron impact ionization is expected to follow the same trend as stability of their radical cations. Such sensitivity is a critical feature for chemical encoding of combinatorial libraries with photolabile dithiane tags. Ready synthetic availability of a diverse set of 2-(*β*-alkylthioethyl)-1,3-dithianes (such as **1a** and **1d**) makes them particularly attractive in this respect. Their aldehyde adducts are synthesized in high yields and with no complications. The measured quantum yields of fragmentation for typical benzaldehyde adducts are shown in Table 3.

On the basis of our prior observations and the results of the current study, the mechanism of photoinduced fragmentation in adducts **2a−c** in the presence of benzophenone as an electron transfer (ET) sensitizer most likely involves photoinduced ET from the dithiane moiety to excited triplet benzophenone, followed by mesolytic fragmentation in the generated cation radical (Scheme 3). The fragmentation is facilitated by the benzophenone radical anion, which is capable of deprotonating the benzylic hydroxy group in the cation radical.

SCHEME 3



The close proximity of the third sulfur atom in **2** may slightly alter the mechanism toward the formation of a three electron two center bond with one of the dithiane sulfurs to furnish a five-membered ring, as in **2′**(•+), thus stabilizing the generated cation radical. Earlier we have demonstrated that the deprotonation step may also be coupled with intramolecular electron transfer from oxygen to the electron deficient sulfur(•+),[9,10] yielding the oxygen-centered radical, which then undergoes spontaneous fragmentation. In the context of the current study, such ET-coupled deprotonation of **2′**(•+) would have to produce radical **4**, which lost its three electron two center bond between the two sulfurs. We note that the conformational flexibility and the size of the bis-methylene tether could conceivably allow for another cyclization—the O-centered radical attacking the third sulfur to yield an O−S three electron bond (**5**). Reactions of alkoxy or hydroxy radicals with sulfides are well precedented in the literature, and so are the formations of the three electron two center bonds between two sulfur atoms.[11]

One notices that the quantum yield of fragmentation in **2a** is slightly lower than that of its oxa-counterparts **2b**, **2c**, or methyldithiane adduct. This is in keeping with the rationale that the initial electron transfer is not rate limiting. It is not surprising because in acetonitrile the excited triplet benzophenone has a reduction potential of −1.68 V vs SCE,[12] which is at least half a volt greater than what is needed to oxidize an average alkyl dithiane in the same solvent (oxidation potentials of various substituted dithianes are in the range of 0.7−1.2 V vs SCE[13]). At this point we can only speculate that the actual mechanism for further stabilization of the (deprotonated) radical intermediate **4** may involve formation of oxathiane **5** (Scheme 3), which is reluctant to fragment and reverts to the starting material **2** by hydrogen abstraction from benzophenone ketyl radical. Computationally the two lowest energy conformations of the “open-chain” radical **4** and cyclic oxathiane **5** are nearly degenerate (Figure 2), with the latter being only 1.1 kcal/mol higher in energy at the B3LYP/6-311+G(2d,p) level of theory.

The effect on experimental quantum efficiencies of fragmentation, however, is not strongly pronounced and the fragmentation can be easily driven to high conversions upon irradiation.

In conclusion, we have found that 2-substituted 1,3-dithianes containing the *β*-sulfide moiety in the substitution chain quench triplet benzophenone much faster than their all-carbon alkyl counterparts. In contrast, dithianes containing ether groups do

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(10) Li, Z.-G.; Kutateladze, A. G. *J. Org. Chem.* **2003**, *68*, 8236–8239.

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(13) Roth, H. D.; Lamola, A. A. *J. Am. Chem. Soc.* **1974**, *96*, 6270–6275.

(14) Glass, R. S.; Petsom, A.; Wilson, G. S. *J. Org. Chem.* **1986**, *51*, 4337–4342.

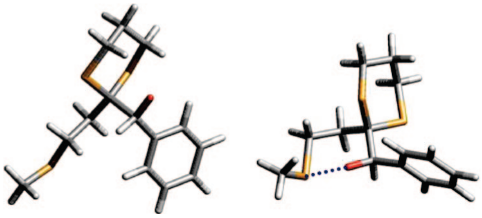

FIGURE 2. B3LYP/6-311+G(2d,p) optimized structures of an oxygen centered radical of type **4** (left) and a cyclic 1,2-oxathiane radical of type **5** (right). The structures are nearly energy-degenerate.

not show appreciable acceleration of the initial electron transfer. The same is true for α-sulfides. The rationale for this behavior of conformationally flexible β-sulfides is that their radical cations are additionally stabilized by the formation of a partial exocyclic S−S bond. This hypothesis is supported by DFT calculations, which show that such stabilization can be as significant as 7 kcal/mol.

A diverse set of mass differentiated 2-(2-alkylthioethyl)-1,3-dithianes is now made readily accessible via a straightforward modular synthetic approach, which makes them suitable photoactive tags for combinatorial encoding.

Experimental Section

General Procedures for Preparation of 2-(2-Alkylthioethyl)- and 2-(2-Alkoxyethyl)-1,3-dithianes. Step A: Alkanethiol or alkanol was dissolved in 20−30 mL of THF (for thiols) or DMF (for alcohols), then NaH (60% in mineral oil, prewashed with hexane) was slowly added and the resulting mixture was stirred for 15−20 min at room temperature.

Step B: The formed thiolate/alcoholate (from step **A**) was added to a solution of 2-(2-bromoethyl)-1,3-dioxolane in THF or DMF and the resulting mixture was refluxed overnight. The reaction mixture was washed several times with water and brine and extracted with 20 mL of CH_2Cl_2. The organic layer was dried over anhydrous $NaSO_4$ and removed under vacuum.

Step C: 2-(2-alkoxyethyl)-1,3-dioxolane or 2-(2-alkylthioethyl)-1,3-dioxolane (from step B) and 1,3-propanedithiol were dissolved in 100 mL of CH_2Cl_2, $BF_3 \cdot Et_2O$ was added dropwise over 15−20 min, and the resulting mixture was stirred overnight at 25 °C. The reaction mixture was washed with 5% aqueous NaOH (2 × 200 mL) and 50 mL of H_2O. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and dried to furnish crude 2-(2-alkylthioethyl)-1,3-dithiane or 2-alkyloxyethyl)-1,3-dithiane, which were subjected to gel filtration with pentane and pentane/ether (15:1) as eluent.

2-(2-Butylthioethyl)-1,3-dioxolane. From 2 g (22.2 mmol) of 1-butanethiol, 1.17 g (28.9 mmol) of NaH, and 4.8 g (26.7 mmol) of 2-(2-bromoethyl)-1,3-dioxolane in THF; yield 92.5%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (t, 1H, $J = 4.6$ Hz), 4.01−3.90 (m, 2H), 3.90−3.80 (m, 2H), 2.71−2.55 (m, 2H), 2.55−2.47 (m, 2H), 1.94 (m, 2H), 1.56 (quint, 2H, $J = 7.4$ Hz), 1.38 (sextet, 2H, $J = 7.4$ Hz), 0.90 (t, 3H, $J = 7.4$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 103.5, 65.1, 34.3, 32.1, 31.9, 26.6, 22.2, 13.9.

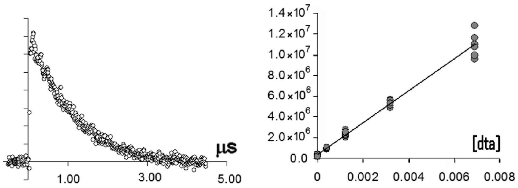

FIGURE 3. A typical waveform collected at 520 nm and a typical concentration series for triplet benzophenone (10^{-4} M) being quenched by 2-(2-butylthioethyl)-1,3-dithiane (**1a**).

2-(2-Butylthioethyl)-1,3-dithiane (1a). From 4.27 g (22.5 mmol) of 2-(2-butylthioethyl)-1,3-dioxolane, 2.5 mL (24.9 mmol) of 1,3-propanedithiol, and 12.0 mL (94.6 mmol) of $BF_3 \cdot Et_2O$ in CH_2Cl_2 (150 mL); yield 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (t, 1H, $J = 7.0$ Hz), 2.94−2.76 (m, 4H), 2.69 (t, 2H, $J = 7.4$ Hz), 2.51 (t, 2H, $J = 7.4$ Hz), 2.17−2.06 (m, 1H), 2.02 (dt, 2H, $J = 7.0$, 7.4 Hz), 1.94−1.80 (m, 1H), 1.56 (quint., 2H, $J = 7.4$ Hz), 1.40 (sext., 2H, $J = 7.4$ Hz), 0.91 (t, 3H, $J = 7.32$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 46.2, 35.4, 31.9, 31.9, 30.4, 29.1, 26.2, 22.2, 13.9. MS *m/z* 236 (M+, 100), 179 (25), 146 (35).

Laser flash photolysis experiments were performed with use of the Applied Photophysics nanosecond LFP system. The third (355 nm) harmonic output from a Q-switched Nd:YAG laser was used as the excitation source; the light is absorbed by the sensitizer and not by the dithianes/adducts. The solvent for irradiations was acetonitrile. The decay of triplet benzophenone (initial concentration of benzophenone was 10^{-4} M) as a function of the concentration of quencher was measured at 520 nm (Figure 3). Every sample was degassed for 20−35 min by bubbling argon gas through the solution.

Photochemistry and quantum yield determination were performed in the Rayonet carousel photoreactor, using RPR-3500 lamps (max irradiance at λ 350 nm). The samples were irradiated for 1−5, 10, and 20 min. Quantum yields were determined at low conversions (5 min of irradiation). A solution of benzophenone (0.1 M) and benzhydrol (1.0 M) was used as a reference actinometer. The sample contained the adduct (0.01 M) and benzophenone as a sensitizer (0.1 M).

Theory and Calculation. DFT computations were carried out at the B3LYP/6-311+G(2d,p) level. The geometries were fully optimized and were subjected to vibrational analysis; all energies are ZPE-corrected. The computations were carried out on a quadruple processor Dell workstation equipped with 32 GB of RAM with use of Gaussian 03, Revision C.02.

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Supporting Information Available: Additional experimental information, spectra, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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