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Photo removal of protecting groups: 1,3dithiane conversion into carbonyl group. Mechanistic aspects

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Abstract

The photodeprotection of 1,3-dithianes in the presence of thiapyrylium to give back the parent carbonyl compound was performed and the mechanism studied by steady state photolysis, laser flash photolysis (LFP) and theoretical calculations. Electron transfer from dithianes to triplet sensitizer is extremely fast, and the decay of dithianes radical cations was not affected by the presence of water or oxygen, as a consequence of a

favorable unimolecular fragmentation pathway. Similar behaviors were observed for dithianes bearing electron-releasing or electron-withdrawing substituents on the aryl moiety, evidencing a C-S bond cleavage to form a distonic radical cation species. The lack of reaction under nitrogen atmosphere, the requirement of oxygen for a good conversion yields, the inhibition of the photodeprotection process by the presence of p-benzoquinone, and the absence of labelled carbonyl final product when the reaction is performed in the presence of $H_2^{18}O$, suggest that superoxide anion drives the deprotection reaction. DFT computational study on the reactions with water, molecular oxygen and superoxide radical anion supports the experimental findings.

Introduction

The protection of carbonyl groups is often a necessary step in organic synthesis, especially in the total synthesis of natural products and multifunctional organic compounds. Thioacetals and cyclic thioacetals such as 1,3-dithianes and 1,3-dithiolanes are protecting groups commonly used due to their easy access and high stability under both acidic and basic conditions.¹

Many procedures are available for thioacetal deprotection. It usually requires drastic conditions, like, e.g., a stoichiometric or an excess amount of toxic reactants such as Hg(II) or other heavy metal salts.² The later process has been recently used for sensitive and selective detection of Hg(II) and Cd(II).³ Furthermore, there are methods under heterogeneous conditions using a variety of Fe(III)⁴ and Cu(II)⁵ salts and other recent solvent-free methodologies.⁶ The deprotection of 1,3-dithianes and 1,3-dithiolanes have been also performed under irradiation in presence of a variety of sensitizers such as 2,4,6-triphenylpyrylium salts, chloranil (CA), dicyanoanthracene (DCA), methylene blue (MB) and methylene green (MG) under mild conditions.⁷

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Due to their low oxidation potential, cyclic thioethers are prompt to undergo singleelectron transfer (SET) oxidation. Thus, the participation of radical cation intermediates has been proposed for the oxidative cleavage of thioacetal.⁷ However, the operating mechanism as well as the source of oxygen in these reactions are a matter of controversy (Scheme 1).^{7, 8} The mechanism proposed for dithianes 1 deprotection by using indirect electrochemical oxidation procedure with tris(p-tolyl)amine as homogeneous electron donor⁹ or via SET oxidants such as SbCl₅,⁸ Cu(NO₃)₂ 2.5H₂O/K-10,^{6b} MG^{7d} or Fe(phen)₃(PF₆)₃ complexes,¹⁰ involves the participation of a radical cation 1^{•+} which fragments into a distonic radical cation. The one-electron oxidation of the later species to a sulfonium ion is the key step for dethioacetalization, which possibly involves H₂O as nucleophile (Scheme 1, pathway a).^{8, 10} In addition, during the photochemical dethioacetalization by 2,4,6-triphenylpyrylium tetrafluoroborate (TPPT) or methylacridinium perchlorate (MAP), fragmentation of 1^{++} into a distonic radical cation has been proposed to account for the formation of the carbonyl compound, after subsequent reaction with O₂ at the radical carbon center (Scheme 1, pathway b).^{7e} Participation of the superoxide anion has also been proposed when using DCA (Scheme 1, pathway c).^{7e} DCA indeed possesses a more negative reduction potential than O₂, and therefore the superoxide radical anion is in this case formed by a secondary ET from the sensitizer radical anion.





ACS Paragon Plus Environment On the other hand, for reactions in the presence of *meso*-tetraphenylporphine (TPP) and MB, the generation of singlet oxygen has been proposed so as to explain the photodeprotection reaction.^{7a}

Herein, we report for the first time the photorelease of several 1,3-dithianes carbonyl protecting groups by photoinduced oxidation using 2,4,6-triphenylthiapyrylium cation (5) as sensitizer (Scheme 2). The preparative aspect of the reaction was studied and a complete mechanistic picture of this photoreaction was established by using transient absorption spectroscopy. Additionally, we have used quantum chemical calculations (PCM(ACN)-[M06-2X/def2-TZVP]) for exploring all alternative reaction pathways.

Scheme 2. Dithiane deprotection using thiapyrylium cation 5 as sensitizer.



Results and Discussion

We studied the reaction between 2-aryl-1,3-dithianes and 2,4,6-triphenylthiapyrylium cation as sensitizer under both steady-state and time-resolved conditions, so as to assess the photophysical and photochemical behavior of the dithianes and to detect possible transients involved in the photodeprotection process.

Steady-state Photolysis. The photodeprotection of dithianes 1 was conducted in MeCN at $\lambda > 350$ nm using 5 as sensitizer and the results are gathered in Table 1.

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Benzaldehyde was obtained in 42 % yield, after 2 h irradiation of 2-phenyl-1,3-dithiane (**1a**) in air saturated solvent, while the reactant conversion was lower than 5 % under nitrogen atmosphere (Table 1, entries 1 and 2). Molecular oxygen is thus essential for the photodeprotection process. The photodeprotection of **1a** was also carried out in a sealed tube and after a 2 h irradiation, the product mixture was analyzed by GC-MS. In these conditions, it was possible to detect 1,2-dithiolane in similar amount (55 %) to benzaldehyde (Table 1, entry 3). Finally, the reaction was partially inhibited by *p*-benzoquinone, a well-established superoxide anion trap (Table 1, entry 4).¹¹ The lack of reaction under nitrogen atmosphere indicates that oxygen is required to get conversion yields. Moreover, inhibition of the photodeprotection in the presence of *p*-benzoquinone suggests that the superoxide anion might be the species responsible for the deprotection reaction.

The dethioacetalization process was then explored with other dithianes in order to evaluate the substitution effect at the phenyl ring as well as at the carbon center. Irradiation time was kept constant (2 h) for all dithianes **1a-e**. Table 1 shows that the presence of an electron-donating or an electron-withdrawing group on the phenyl ring leads to lower conversion yields (see Table 1, entries 5 and 6), whereas increasing substitution at the pro-carbonyl carbon improves the yield for ketone formation, namely acetophenone for **1d** and benzophenone for **1e** (see Table 1, entries 7 and 8). Finally, when the photodeprotection of **1e** was performed in the presence of H₂¹⁸O in a concentration similar to the dissolved O₂, no labeled ¹⁸O atom incorporation into the benzophenone product was detected by GC-MS (SIM mode). This last result rules out the participation of water as a nucleophile in the deprotection process.

Table 1. Photodeprotection of dithiane 1 in presence of 5.^a

S. R	$\begin{array}{c} & hv \\ X \\ X \\ 1 \\ R^2 \\ \end{array} \begin{array}{c} hv \\ O_2 \\ O_2 \\ Se \\ Se \end{array}$	$ = \frac{350 \text{ nm}}{2 - \text{MeCN}} \qquad $		
Entry		Dithiane	(1)	Product
		R^1	\mathbb{R}^2	$(4) (\%)^{b}$
1	1 a	Ph	Н	42
2^{c}	1 a	Ph	Н	< 5
3 ^d	1a	Ph	Н	55 ^e
4^{f}	1a	Ph	Н	23
5	1b	4-OMeC ₆ H ₄	Н	27
6	1c	$4-CNC_6H_4$	Н	27
7	1d	Ph	Me	76
8	1e	Ph	Ph	89
9 ^g	1e	Ph	Ph	85 ^{e,h}

^a Reaction performed in air saturated MeCN, [1] 10 mM.

^bQuantification by GC (internal standard method).

^c Under nitrogen atmosphere.

^dReaction performed in a sealed tube.

^e Relative areas determined by GC-MS together with a similar amount of 1,2-dithiolane.

^f In the presence of 100 % benzoquinone (BQ).

^g In the presence of 0.02 % of H_2^{18} O relatively to 1e.

^hNo incorporation of ¹⁸O in benzophenone was detected by GC-MS.

Characterization of transient species by Laser Flash Photolysis (LFP). Using LFP, it

was possible to detect the formation of radical cations $1a-d^{*+}$ (Scheme 3). Laser excitation of the thiapyrylium salt at 355 nm resulted in a broad transient absorption between 460 and 600 nm, with a lifetime of $2.5 \pm 0.2 \,\mu$ s in MeCN measured at 470 nm (Figure 1a), which was assigned to the known T-T transition of **5** according to previously published spectra.¹² In the presence of dithiane **1a**, the kinetic trace at 470 nm decays faster and pseudo-first-order treatment at low concentration of **1a** led to the

determination of the quenching rate constant k_q (Figure 1b). Concomitantly with the disappearance of the triplet 5, a broad band with a maximum close to 510 nm arises with a longer lifetime of ca. 20 µs (Figure 1c and Figure 2) at relatively high concentration of phenyldithiane (5 mM), which was assigned to the 1,3-dithiane radical cation $1a^{+}$. The same methodology was applied to the family of dithianes 1a-e. In all cases, the triplet state lifetime of the sensitizer in MeCN becomes shorter when increasing the concentration of **1a-e**, and the bimolecular quenching rate constants by these species ranges between 1.20 and 2.37 $\times 10^{10}$ M⁻¹ s⁻¹ (Table 2). These quenching rates were ascribed to the electron transfer process from dithianes to the sensitizer triplet state. The Gibbs free energy change for electron transfer ($\Delta G_{\rm ET}$) from the dithiane **1b** to the triplet excited state of 5 was estimated according to the Rehm-Weller equation (eq. 1)¹³ where $E_{D/D}^{++}$, the standard oxidation potential of the dithiane, and E_{A}^{++} , the standard oxidation potential of the thiapyranyl radical, were obtained from the literature.^{14, 15} A value of 52 kcal mol⁻¹ was used for the excitation energy (E^*), leading to -23 kcal mol⁻¹ for $\Delta G_{\rm ET}$, thus indicating that the ET is exergonic. This large driving force is also in agreement with the close to diffusion-controlled quenching rate constants measured for the dithianes investigated (Table 2).

$$\Delta G_{\rm ET} \,(\rm kcal \ mol^{-1}) = 23.06 \left[E_{D/D^{+}} - E_{A^{-}/A} \right] - E_{A}^{*} \quad (1)$$

The maximum absorption wavelengths for dithiane radical cations $1a-e^{+}$ as well as quenching rate constants for the electron transfer reactions between dithianes 1a-e and the triplet sensitizer are given in Table 2 (kinetic traces are shown on Figures S1-S5).



Scheme 3. Generation of radical cations 1a-e⁺⁺

е

Ph

Me Ph

`R²

d

1a-e

С

Н



(c)

Figure 1. (a) Decay trace of the T-T absorption of **5** (0.067 mM) obtained after laser excitation ($\lambda = 355$ nm) in MeCN, under argon, measured at 470 nm and (b) plot of $1/\tau$ against concentration of **1a**. (c) Decay trace at 510 nm of a mixture of **5** (0.067 mM) and **1a** (5 mM) obtained after laser excitation ($\lambda = 355$ nm) in MeCN, under argon.



Figure 2. Normalized transient absorption spectra obtained upon LFP ($\lambda = 355$ nm) of **5** (0.067 mM) in MeCN under argon: with no quencher (•) and with of 1 mM of **1a** (•). Spectra were recorded 0.6 µs after the laser pulse.

The fragmentation of the radical cation intermediates could be a unimolecular process or a bimolecular process assisted by a nucleophilic species. It appears that the decay of dithiane radical cations signal follows in all cases a first order kinetic behavior and was not affected by the presence of both water or molecular oxygen (see for example Figure S6 in the supporting Information), thus confirming the occurrence of a unimolecular decay mechanism in which the nucleophile does not partake. Similar decays profiles were obtained for dithianes bearing electron-releasing or electron-withdrawing substituents on the aryl moiety (Figure S7 and S8-S12 for the k_q measurements). Lifetimes for the radical cations **1a-e⁺⁺**, whose values are in the range 16 - 30 µs, are gathered in Table 2.

Table 2. Quenching rate constants between the triplet state of **5** and **1a-e**, and characteristics of the dithiane radical cations.^a

Entry	Dithiane	$k_{ m q}$	$\lambda_{ m max\ rad\ cat}$	$ au_{ m rad\ cat}$	k_Z/k_H^e
		$(10^{10} \mathrm{M}^{-1} \mathrm{s}^{-1})^b$	$(nm)^c$	$(\mu s)^d$	
1	1,3-dithiane	1.29	530	30.0	-
2	1 a	1.20	510	20.9	1
3	1b	1.40	520	16.0	1.31
4	1c	2.37	510	17.2	1.22
5	1d	1.35	500	16.7	1.25
6	1e	1.38	500	25.1	0.83

^{*a*} In MeCN under argon atmosphere, [**5**] = 0.076 mM, (λ_{exc} = 355 nm).

^{*b*} Obtained by using the Stern-Volmer equation: $1/\tau = 1/\tau_0 + k_q[Q]$ (at 470 nm).

^c Radical cation wavelength maximum absorption obtained for dithianes **1a-e** (concentration 5 mM).

^{*d*} Lifetime time for the radical cations $1a \cdot e^{+}$, assuming a first-order decay.

^{*e*} Normalized lifetime of the radical cation towards $1a^{+}$ (effect of the *para* substituent on the phenyl ring).

The dithiane radical cations are stabilized by forming sulfur-sulfur two-center threeelectrons bond (i.e., σ -type), as already reported for the radical cations of aliphatic sulfides.¹⁶ As a consequence, we expect small if any effect of substituent on the phenyl

ring in dithianes 1a-e. And indeed, the ratio k_Z/k_H shows very little variation in the whole family of compounds (Table 2), thus providing further evidence that C-S bond cleavage occurs without assistance of a nucleophilic reagent to form a distonic radical cation (Scheme 1), as detailed below.

Mechanism and theoretical calculations

Compound 5 is a well-known electron transfer sensitizer with a high singlet excitedstate energy (66 kcal mol⁻¹), a triplet excited-state energy of approximately 52 kcal mol⁻ ¹, an intersystem crossing quantum yield (Φ_{ISC}) of 0.94 and a reduction potential of – 0.21 V vs. SCE.¹⁵ In addition, the thiapyrylium salt used does not sensitize the formation of singlet oxygen $({}^{1}\Delta_{g})$.¹⁷ Our experimental results are consistent with an electron transfer reaction leading to the formation of a dithiane radical cation that further decays to a distonic radical cation. Two species may be formed: an open-benzyl cation (2) or a closed-benzyl radical (3) (Scheme 1). $^{7, 18}$ The fact that the decay rates for the radical cations do not depend on the nature of the substituents borne by the dithianes suggests that 3 predominates over 2. We have performed DFT calculations for 2a and **3a**, both being derived from C-S bond cleavage in $1a^{+}$ (Scheme 1). In agreement with experimental data (Table 2), the computational results (Table 3, entries 1 and 2) indicate that **3a** is the most stable structure (by ca. 9.3 kcal mol⁻¹). In addition, the transition state Gibbs free energy connecting these two structures equals to 8.3 kcal mol⁻¹ with respect to the open species. The high energy difference between the two structures points towards a strong predominance of the closed form (Figure 3).



Figure 3. Free energy profile for the close-open forms equilibrium resulting from C-S bond cleavage in the one electron oxidized compound $1a^{+}$. Relative Gibbs free energies are given in kcal mol⁻¹. Selected distances are given in Å.

It is worth noting that the spin density gives some hints on the reactivity of each species (Figure 4). In the open form, spin density on the radical cation is fully located on the external sulfur atom, whereas in its closed form it is partially delocalized between the benzylic carbon atom and the phenyl ring.



Figure 4. Spin density isosurface (isocontour 0.01 a.u.) for **2a** (left) and **3a** (right). Light blue: carbon; white: hydrogen; gold: sulfur.

As illustrated on Scheme 1, different nucleophilic species may be responsible for the deprotection reaction, namely, water, molecular oxygen O_2 (${}^{3}\Sigma_{g}$) or superoxide anion O_2^{\bullet} . It is commonly accepted that following the formation of the radical cation intermediate, a nucleophilic attack occurs at the benzylic carbon.⁷ Taking into account the spin density profiles of **2a** and **3a** depicted in Figure 4, it can be foreseen that H₂O would more likely react with the distonic radical cation **2a** at the benzylic carbocation, while $O_2({}^{3}\Sigma_g)$ would rather react with **3a** at the benzylic radical. Superoxide anion O_2^{\bullet} may react both as a nucleophile and as a radical. We thus performed a computational study of the reaction between the nucleophilic agents and 2-phenyl-1,3-dithiane radical cation in MeCN as solvent. All the reaction pathways were calculated at the PCM(ACN)-[M06-2X/def2-TZVP] level of theory.

Table 3. Relative electronic energy (zero point energy corrected) and Gibbs free energies (in kcal mol⁻¹) for reactions involving 2a and 3a.^a

Entry	Reaction	$\Delta E + Z P E^{b}$	ΔG^{b}
1	$2a \rightarrow 3a$	-9.7	-9.3
2	$2a \rightarrow TS(2a-3a)$	+0.6	+8.3
3	$2a + \mathrm{H_2O} \rightarrow TS(\mathrm{H_2O})$	+1.1 / +3.4	+16.6 / +18.8
4	$\mathbf{2a} + \mathrm{H_2O} \rightarrow \mathbf{INT(H_2O)}$	-18.9 / +2.3	-3.3 / +18.0
5	$\mathbf{3a} + O_2 (^{3}\Sigma_g) \rightarrow \mathbf{TS}(\mathbf{O_2})$	+7.1 / +5.5	+18.3 / +16.6
6	$\mathbf{3a} + \mathrm{O}_2 (^{3}\Sigma_{\mathrm{g}}) \rightarrow \mathbf{INT}(\mathbf{O}_2)$	-14.4 / -13.0	-2.5 / -1.9
7 ^c	$3\mathbf{a} + \mathrm{O_2}^{\div} \to \mathrm{TS}(\mathrm{O_2}^{\div})$	-13.8	-2.7
8 ^c	$3\mathbf{a} + \mathbf{O_2}^{-} \rightarrow \mathbf{P}$	-64.1	-52.8

^a Values were computed at the PCM(ACN)[M06-2X/def2-TZVP] level of theory.

^b Values for entries 3 to 6 correspond to attack of the nucleophilic specie from the internal face (left) and from the external face (right) relatively to the dithiane (see Figure 5, path A and path B, respectively).

^c Route A, attack of superoxide anion on **3a** (see Figure 6 and Scheme 3).

We first addressed the reaction with water. It has been repeatedly suggested that the presence of water is necessary for getting mild and efficient photochemical and thermal thioacetal deprotection reactions.^{7c, 19} The nucleophilic addition of H_2O at the positively charged benzylic carbon of **2a** may occur on two distinct faces. Our results indicate it takes place on the internal face close to both sulfur atoms (path A, Figure 5) and that the reaction goes through an early transition state where the hydrogen transfer from the

water to the sulfut transition states has species.²⁰ On the distribution state eiger Figure 5). $30.0 \\ 25.0 \\ 20.0 \\ 15.0 \\ 15.0 \\ 15.0 \\ 15.0 \\ 15.0 \\ 100 \\$

water to the sulfur is concerted with the formation the oxygen-carbon bond. Such transition states have been observed in reactions involving water molecule and radical species.²⁰ On the other hand, when the water molecule attacks on the external side the transition state eigenvector is characterized by the O-C bond formation only (path B, Figure 5).



Figure 5. Energy profile for the reaction of the opened 1,2-dithiolane distonic radical cation (**2a**) with water. Relative Gibbs free energies given in kcal mol⁻¹.

Both relative electronic energy and Gibbs free energy for the TS are given in Table 3 (entry 3). Path A (Figure 5) is favored both kinetically and thermodynamically. The adduct formed along path B is only 0.8 kcal mol⁻¹ below the energy of the corresponding transition state so that if addition of water was to take place along this route, the adduct would immediately evolve back into the reactants.

 O_2 (³ Σ_g) is also an efficient reactant for oxidation processes, like the well-known free radical oxidation of unsaturated lipids or aldehyde formation by alpha deprotonation of sulfide radical cations followed by oxygen addition to the carbon centered radical.²¹ It can be seen that the energy of the reaction $3a + O_2$ (${}^{3}\Sigma_{g}$) \rightarrow INT(O₂) is slightly exergonic by 2.5 and 1.9 kcal mol⁻¹ depending on the approach (Table 3). However the calculated energy barriers are high, i.e. 18.3 and 16.6 kcal mol⁻¹ for each reactive face respectively.

Finally, it has been suggested that the reaction of the sulfide radical cation with $O_2^{\bullet-}$ may also play a key role in the product formation of different sulfide compounds.²² Based on previous studies on radical cation sulfide derivatives, there are at least five main possible reactions between the dithiane radical cation and O2., as illustrated on Scheme 4. The first reaction (path A) is the nucleophilic addition to the carbon atom bearing a partial positive charge. The second reaction (path B) consists in the $O_2^{\bullet-}$ attack to the internal sulfur atom to yield persulfoxide (int-PSO) and/or thiadioxirane (int-**TDO**), as reported elsewhere.^{22a} Likewise, attack can occur at the external sulfur atom to give persulfenate (ext-PST) and/or thiadioxirane (ext-TDO),²³ along path C. Addition of O_2^{\bullet} to sulfide radical cation has been demonstrated to take place for other systems,^{22b, 24} but its efficiency depends on side reactions such as back electron transfer (path D) and deprotonation reaction (path E). Deprotonation following oxidation is a common reaction mechanism for benzyl sulfide derivates and it has been shown to be

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thermodynamically favored for some systems.²⁵ In the present case, abstraction of the benzylic proton by radical anion superoxide (path E) is thermodynamically unfavorable since ΔH^0 and ΔG^0 are 11.9 and 10.5 kcal mol⁻¹, respectively. On the other hand, the back electron transfer is highly exergonic, $\Delta G^0 = -37.9$ kcal mol⁻¹ (path D) and might affect the photooxidation reaction yield.



Scheme 4. Possible reactions of 2a and 3a with superoxide anion O_2^{-} : (A) direct nucleophilic addition; (B) attack to internal sulfur atom; (C) attack to external sulfur atom; (D) back electron transfer; and (E) deprotonation.

We have explored the various routes displayed in Scheme 4. Relative energies of the structures with respect to reactants are displayed in Figure S13. Gibbs free energy of the product **P** (path A, Scheme 4), formed by the direct attack of the O_2^{\bullet} to the electrophilic carbon, stands 52.8 kcal mol⁻¹ below the energy of the reactants. This value is in line with a barrierless attachment of O_2^{\bullet} . In fact, the energy of the transition state connecting **3a** to **P** is -2.7 kcal mol⁻¹ below **3a**, (Table 3, entry 7). The energy profile is presented in Figure 6, where the reaction with H₂O and O₂ (${}^{3}\Sigma_{g}$) were also included for

comparison, in blue and red respectively. From this picture it appears that the reaction between 3a and O_2^{\bullet} is the most favorable route for the deprotection process, both kinetically and thermodynamically.

Conversely to the addition of water and molecular oxygen, the approach of O_2^{\bullet} through the internal face of **2a** leads to the formation of persulfenate specie (**ext-PST**, path C in Scheme 4), that is 15.1 kcal mol⁻¹ more stable than the initial reagents. Cyclisation by reaction at the carbon atom leads to **Cycle-P** (see Figure S13) through a 3 kcal mol⁻¹ barrier, while the process is exergonic by 6.5 kcal mol⁻¹.



Figure 6. Energy profile for the reaction of **2a** and **3a** with water (blue line), O_2 (${}^{3}\Sigma_{g}$) (red line) and O_2^{\bullet} (black line). Relative Gibbs free energies given in kcal mol⁻¹.

Conclusions

The addition of O_2^{\bullet} to the internal sulfur of **3a** yielding to the thiadioxirane compound int-TDO (path B, Scheme 4) is slightly exothermic ($\Delta H^0 = -8.0 \text{ kcal mol}^{-1}$) but unfavorable in terms of Gibbs energy ($\Delta G^0 = 5.8 \text{ kcal mol}^{-1}$, see Figure S13). Similarly, the reaction leading to the persulfoxide adduct (int-PSO) is endergonic by 6.3 kcal mol⁻¹. The transition state connecting these two structures was found to be 17.9 kcal mol⁻¹ higher in energy with respect to the reactant energy and 12.1 kcal mol⁻¹ with respect to int-TDO (Figure S1). This is in good agreement with the values reported for the isomerization process with dimethyl sulfide.²⁶

We unraveled the mechanistic details of the photodeprotection reaction of 1,3-dithiane derivates by a combination of experimental and computational studies. Comparative experiments performed under nitrogen atmosphere and in the presence of the $H_2^{18}O$ indicate that oxygen is playing a crucial role on the reaction. Inhibition of the reaction with *p*-benzoquinone has further pointed out that superoxide radical anion is the most probable source of oxygen. Using laser flash photolysis experiments, we were able to characterize a dithiane radical cation species as an intermediate during the course of the reaction. Effect of both water, molecular oxygen and of the substituents on the aryl group on the decay rate constant of the intermediate support an unimolecular fragmentation.

All these experimental outcomes can be rationalized by a stepwise mechanism along which a first single electron transfer is followed by an unimolecular fragmentation, yielding a distonic radical cation which then quickly reacts with the superoxide anion. This picture is in agreement with theoretical calculations. Exploration of the various reaction routes indeed supports the proposal that the reaction of oxidized dithianes with superoxide radical anion is the most favorable pathway, on both kinetic and thermodynamic grounds.

Experimental Section

Materials and methods: Chemicals. Acetophenone, benzophenone were purchased. Acetonitrile (HPLC grade) was used without any further purification and stored over molecular sieves (4 Å). Ultrapure water from a Milli-Q station was used. All dithianes and 2,4,6-triphenylthiapyrylium perchlorate were synthesized and purified according to previously reported procedures.^{27, 28}

Absorption measurements were performed with a UV-Visible spectrophotometer.

Laser Flash Photolysis (LFP). Transient absorption spectra and quenching rate constants were determined using a Nd:YAG laser generating 355 nm laser pulse (10 mJ per pulse, ca. 10 ns pulse duration) as an excitation source. The spectrometer was a commercial set-up.

Computational Details. Theoretical calculations were performed with the GAUSSIAN 09 suite of programs.²⁹ All geometry optimizations were computed using the functional M06-2X³⁰ and the Ahlrich def2-TZVP basis set.³¹ The stationary points were located with the Berny algorithm³² using redundant internal coordinates. Analytical Hessians were computed to determine the nature of stationary points (one and zero imaginary frequencies for transition states and minima, respectively)³³ and to calculate unscaled zero-point energies (ZPEs) as well as thermal corrections and entropy effects using the standard statistical-mechanics relationships for an ideal gas.³⁴ Transition structures (TSs) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the

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reaction coordinate under consideration using the intrinsic reaction coordinate (IRC) method.³⁵ Unless otherwise stated, Gibbs energies have been computed at 298.15 K. For these calculations, the acetonitrile solvent was described by nonspecific solvent effects within the self-consistent reaction field (SCRF) approach in Tomasi's formalism.³⁶

Representative experimental procedure for the deprotection process. A solution of dithiane (0.1 mmol, 10 mM) and 2,4,6-triphenylthiapyrylium (1 mM) in acetonitrile was irradiated with a medium pressure Hg lamp in a Pyrex tube while being purged with a stream of oxygen. After irradiation the products were quantified by GC using the internal standard method.

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Keywords: photodeprotection, 1,3-dithianes, radical cation, electron transfer.

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23. Note that the term "thiadioxirane" refers to a compound with the formula R2SO2 where a three-membered ring is formed between the S and the two O atoms. Although ext-TDO is not strictly a thiadioxirane species, it keeps the main ring.

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