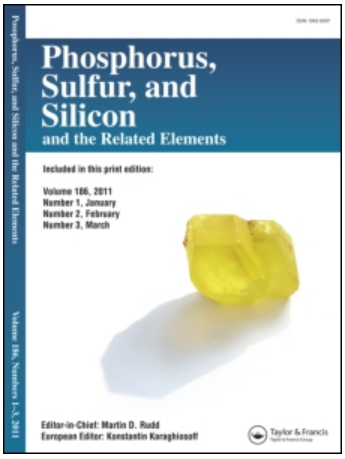

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Dithiane, Trithiane, and Dithiazane-Based Photolabile Scaffolds for Molecular Recognition: Mechanism and Efficiency of the Photoinduced Fragmentation in Aqueous Reductive Environments

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To cite this Article Kutateladze, Andrei G. , Kottani, Rudresha , Kurchan, Alexei N. , Majjigapu, Janaki R. R. and Shirk, Samuel M.(2005) 'Dithiane, Trithiane, and Dithiazane-Based Photolabile Scaffolds for Molecular Recognition: Mechanism and Efficiency of the Photoinduced Fragmentation in Aqueous Reductive Environments', Phosphorus, Sulfur, and Silicon and the Related Elements, 180: 5, 1379 — 1384
To link to this Article: DOI: 10.1080/10426500590912673
URL: http://dx.doi.org/10.1080/10426500590912673

Phosphorus, Sulfur, and Silicon, 180:1379–1384, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500590912673

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Photoinduced fragmentation in dithiane and trithiane adducts of aromatic ketones and aldehydes was studied in aqueous reductive environments. Density functional computations were carried out for thioxanthone derivatives bearing donor and acceptor substituents in the aromatic ring to identify the substitution pattern that is most promising for the productive irreversible electron transfer.

Keywords Mesolytic fragmentation; photoinduced electron transfer; sulfur-centered cation radicals; thioxanthone

INTRODUCTION

We are developing a general strategy for assembly and photoinduced disassembly of modular photolabile molecular objects, designed for applications in chemical biology.[1] At the core of this approach is the recently discovered photofragmentation in dithiane or trithiane adducts of aldehydes and ketones,[2] which we equip with various elements of molecular recognition, including the biologically relevant groups capable of hydrogen bonding. The ultimate goal is to release a biological effector, with such a release being contingent on a molecular recognition event taking place. This is achieved by separating the functions of chromophore/sensitizer from the actual photocleavable unit and outfitting

Received July 9, 2004; accepted October 5, 2004.
Support of this research by the National Science Foundation, Grant CHE-314344, is gratefully acknowledged.
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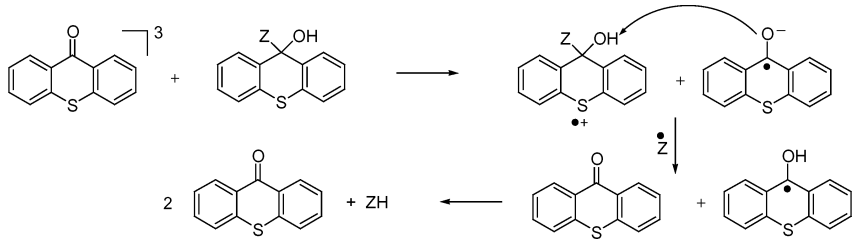
the individual molecules with complementary elements of molecular recognition. As such, the approach relies on the efficiency of the intermolecular single electron transfer oxidation of sulfur-containing species by the excited triplet aromatic ketone sensitizer. The relatively low oxidation potential of dithianes (+0.7 to +1.2 V) allows us to carry out these reactions selectively in the presence of other reducing functional groups. To further optimize the selectivity of this reaction, a group of sensitizers that are least affected by the reductive medium has to be identified. In this communication we describe our most recent mechanistic findings and our results in optimizing the efficiency of the photoinduced fragmentation as we progress from the model systems in organic solvents to aqueous reductive environments relevant to biological applications.

RESULTS AND DISCUSSION

We have been utilizing unsubstituted benzophenone, with only a few exceptions, as the electron transfer sensitizer for fragmentations in dithiane-carbonyl adducts in acetonitrile and aqueous acetonitrile. For the bioapplications that we are developing, the sensitizer and/or the dithiane adduct has to be tethered *via* a polyethylene glycol (PEG) linker (for example, the TentaGel beads), which creates a potentially reducing environment for excited carbonyls. For the purpose of the present mechanistic study, we modeled such environment by carrying out the reactions in 80% aqueous dioxane. We have found that although benzophenone was still capable of initiating the desired photofragmentation, it was also reduced to a considerable extent by the major component of the solvent, dioxane. The main reduction product was found to be tetraphenyl pinacol, although traces of benzhydrol and a product of ketyl radical recombination with dioxanyl radical were also present in the reaction mixture. The latter was identified by GC MS.

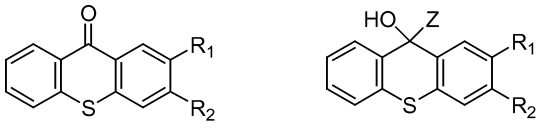
Hydrogen atom abstraction by the ketones that have a low laying $n \rightarrow \pi^*$ triplet state is a well-known phenomenon. The problem is that the mechanism of formal hydrogen *atom* abstraction from heteroatom-containing substrates often involves a single electron transfer oxidation followed by ketyl anion-radical abstraction of a *proton*. This makes it difficult to improve the productive electron transfer channel for the fragmentation and concurrently prevent nonproductive hydrogen abstraction from the solvent. With that we turned our attention to ketones that are known to have the $\pi \rightarrow \pi^*$ triplet excited state, *e.g.* thioxanthone. Irradiation of 10 mM thioxanthone in aqueous dioxane showed much slower reduction than that of benzophenone under the same conditions, but the ability of thioxanthone to sensitize the fragmentation was also diminished. The addition of lithiated methyldithiane to thioxanthone

disrupts the conjugation through carbonyl, which effectively means that a diphenyl sulfide moiety is created as a result of such addition. Diphenyl sulfides have low oxidation potential: therefore, addition of any (carbon) nucleophile, not just dithianes or trithianes, to thioxanthones creates a potentially photocleavable system, as long as *Z* is a good radical leaving group (compare to other studies[3]). The photoinduced reaction sequence with thioxanthone sensitizing fragmentation of an adduct of the same thixanthone is shown in Scheme 1. The reaction involves single electron-transfer oxidation of the adduct by triplet thioxanthone, followed by a mesolytic cleavage in the generated cation-radical, which is assisted by thioxanthone anion-radical.



SCHEME 1

This system lends itself to "fine tuning" because the same substitution at positions 2 or 3 that modulates reactivity of the excited thioxanthone also alters the oxidation potential of the diphenyl sulfide fragment in the adduct. To better understand how the driving force for electron transfer is affected by such substitution, we have carried out a density functional study at the b3lyp/6-31g* level of theory, analyzing the effects of donors or acceptors in positions 2 or 3 of thioxanthone. We concentrated on the first step—the bimolecular quenching of the triplet ketone by the diphenyl sulfide moiety of the adduct, which produces the radical ion pair. The prediction of the substituent effect on the driving force of the one electron oxidation (Scheme 1) is not at all straightforward. The same electron withdrawing group that is expected to improve electron transfer by making the reduction potential of the triplet excited ketone more negative also impedes the oxidation of the adduct by increasing the oxidation potential of the thioxanthene moiety deconjugated from the carbonyl group (*i.e*, the diphenyl sulfide moiety). Figure 1 shows the five species involved in our computations. The ketone (an acceptor, A) is represented by three species: (i) A_S—singlet ground state, (ii) A_T—the triplet state and (iii) A_{AR}—the anion-radical. Only two species of the alcohol (a donor, D) need to be taken into account: (i) D_S—the singlet ground state and (ii) D_{CR}—the cation-radical. The



A_S, A_T, A_{AR} D_S, D_{CR} (Z=H)

a, $R_1 = R_2 = H$
b, $R_1 = OH$, $R_2 = H$
c, $R_1 = NO_2$, $R_2 = H$
d, $R_1 = H$, $R_2 = NO_2$
e, $R_1 = CONH_2$, $R_2 = H$
f, $R_1 = H$, $R_2 = CONH_2$
g, $R_1 = NHCHO$, $R_2 = H$
h, $R_1 = H$, $R_2 = NHCHO$

FIGURE 1 2,3-disubstituted thioxanthones and thioxanthenes investigated in this study.

driving force for the forward electron-transfer oxidation is then approximated by the energy difference of $(D_{CR} + A_{AR}) - (D_S + A_T)$. The back electron transfer, on the other hand, is not the reverse of this expression. Because the ketone is regenerated in its ground state, the back electron-transfer driving force is approximated by $D_S + A_S - (D_{CR} + A_{AR})$.

For these energies to be compared in a meaningful fashion, we present their values in a form of relative energies ΔE_{ET} and ΔE_{BET}. The difference of these two values, *i.e.* $\Delta\Delta E = \Delta E_{ET} - \Delta E_{BET}$, gives an estimate as to how favorable the productive (irreversible) electron transfer is. Each of the five species (A_S, A_T, A_{AR}, D_S, and D_{CR}) was introduced into the computations as a set of eight structures outfitted with donor or acceptor substituents (**a–h**). The geometries were generated by Chem3D, preoptimized using a semi-empirical method, AM1 or PM3, and then fully optimized at B3LYP/6-31G(d) level using Gaussian-98 computational package. The DFT energies in Hartrees are listed in Table I,

TABLE I DFT Energies of the Five Species in Hartrees*

	A_S	A_T	(E_T)*	A_{AR}	D_S	D_{CR}
(a) H	−973.63155	−973.52861	*(64.6)*	−973.64393	−974.81492	−974.54969
(b) 2-OH	−1048.84597	−1048.75070	*(59.8)*	−1048.85926	−1050.03053	−1049.77641
(c) 2-NO2	−1178.13089	−1178.02664	*(65.4)*	−1178.16838	−1179.31664	−1179.03260
(d) 3-NO2	−1178.12941	−1178.03827	*(57.2)*	−1178.18615	−1179.31528	−1179.03330
(e) 2-CONH2	−1142.33175	−1142.22798	*(65.1)*	−1142.35222	−1143.51749	−1143.24870
(f) 3-CONH2	−1142.33282	−1142.23474	*(61.5)*	−1142.36354	−1143.51667	−1143.24856
(g) 2-NHCHO	−1142.32229	−1142.22798	*(59.2)*	−1142.34740	−1143.50449	−1143.24714
(h) 3-NHCHO	−1142.32366	−1142.21392	*(68.9)*	−1142.34618	−1143.50410	−1143.23591

*Triplet energy E_T is in kcal/mol. The level of calculations appears to be adequate for these structures; the calculated triplet energy of thioxanthone (64.6 kcal/mol) is within 2.2% of its experimental value of 63.2 kcal/mol obtained by K. Meier and H. Zweifel, *J. Photochem*, **35,** 353 (1986).

TABLE II Selected Relative Energies for Forward ET and BET, Kcal/mol

	$A_T \rightarrow A_{AR}$	$D_S \rightarrow D_{CR}$	ΔE_{ET}*	ΔE_{BET}	$\Delta\Delta E$
(a) H	0.0	0.0	0.0	0.0	0.0
(b) 2-OH	4.2	−7.0	−2.7	7.5	−10.3
(c) 2-NO2	−16.6	11.8	−4.8	3.9	−8.7
(d) 3-NO2	−20.4	10.5	−9.9	17.3	−27.3
(e) 2-CONH2	−5.6	2.2	−3.4	2.8	−6.2
(f) 3-CONH2	−8.5	1.8	−6.7	9.7	−16.4
(g) 2-NHCHO	−2.6	−4.9	−7.5	12.9	−20.4
(h) 3-NHCHO	−10.6	1.9	−8.8	4.5	−13.3

*ΔE_{ET} can also obtained as the sum of the first two columns, referenced to H.

while Table II has the calculated energy values in kcal/mol relative to the unsubstituted thioxanthone (*a*).

Analysis of the ΔE_{ET} values clearly shows the importance of both the electron-withdrawing substituent effect on facilitating $A_T \rightarrow A_{AR}$ reduction by stabilizing the excess negative density of the generated anion-radical, and at the same time electron-donating substituent effect on facilitating the $D_S \rightarrow D_{CR}$ oxidation by stabilizing the positive charge density of the cation radical. The 3-nitro group makes the forward ET step 9.9 kcal/mol more exothermic than the unsubstituted case. The 2-NHCHO group also affects the driving force in the same direction, making the ET step about 7.5 kcal/mol more exothermic than the unsubstituted thioxanthone. A careful analysis reveals, however, that the similar net effects are produced for completely different reasons—additional stabilization in the anion radical, A_{AR}, in the 3-nitro case (*d*) *vs* the additional stabilization of the cation-radical, D_{CR}, in the 2-formylamino case (*g*). As follows from Table 2, the 3-nitro group offers a 17.9 kcal/mol advantage over the 2-formylamino group at the reduction of the triplet ketone ($A_T \rightarrow A_{AR}$, first column). At the oxidation step ($D_S \rightarrow D_{CR}$, second column), however, the advantage is almost completely lost, 10.5 – (– 4.9) = 15.4 kcal/mol, leaving the two ΔE_{ET} within about 2.4 kcal/mol. A stronger donor, the hydroxy group, helps make the oxidation step even more exothermic (rel. –7.0 kcal/mol) but the reduction of triplet 2-hydroxythioxanthone is prohibitively costly (24.6 kcal/mol less favorable than that of the 3-nitro compound) with net result of the 3-nitrothioxanthone ET step being 7.2 kcal/mol more exothermic than the 2-hydroxy compound (*i.e.*, −9.9 kcal/mol and −2.7 kcal/mol respectively). Overall, the donors in the position 2 help facilitate the $D_S \rightarrow D_{CR}$ oxidation, at the expense of the $A_T \rightarrow A_{AR}$ reduction,

whereas the electron-withdrawing groups in the position 3 of the thioxanthone do precisely the opposite. The effect of placing the formylamino group into the position 3 is nearly evenly split between moderate destabilization of both the reduction and the oxidation components (as compared with 3-NO_2 and 2-OH respectively). The overall result is $\Delta E_{ET} = -8.8$ kcal/mol, competing with that of 3-NO_2.

The calculated relative driving force for back electron transfer was the most unfavorable in the case of 3-nitrothioxanthone (*d*) because the nitro group is in extended conjugation with the carbonyl, lowering the ketone's LUMO and stabilizing the anion-radical. However, the 2-formylamino substituent showed the next best ΔE_{BET} value, which is 12.9 kcal/mol higher than that of the unsubstituted thioxanthone. For this reason the 2-(formylamino)-thioxanthone (*g*) was second best in the series (Table 2, last column; more negative values correspond to less reversible electron transfer).

We have therefore demonstrated that, by varying the substitution, photoinduced fragmentation of adducts of substituted thioxanthones sensitized by the same (free) ketones can be fine-tuned to allow running the fragmentation reactions in reductive medium, such as aqueous dioxane. While the introduction of donor substituents inevitably diminishes the quantum efficiency of the fragmentation, this is offset by the fact that the sensitizer survives longer in the reductive medium, leading to higher total fragmentation yields. Despite the large calculated $\Delta\Delta E$'s for the 3-nitro substituted compound, it is not practical to utilize thioxanthones bearing strong electron-withdrawing substituents, because they are too easily reduced. Our experiments with 2- and 3-nitro thioxanthones showed that the reduction is by far the major channel for their photoreactions in reductive media. In fact, even thioxanthone itself was considerably reduced upon 20 min irradiation in 80% aqueous dioxane, whereas 2-(butanoylamino)-thioxanthone was barely affected.

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