JOC Notes

Anomalous C−C Bond Cleavage in Sulfur-Centered Cation Radicals Containing a Vicinal Hydroxy Group

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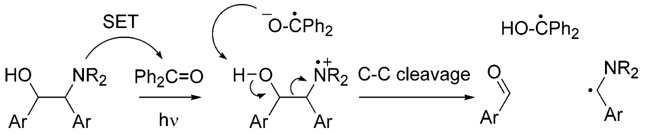
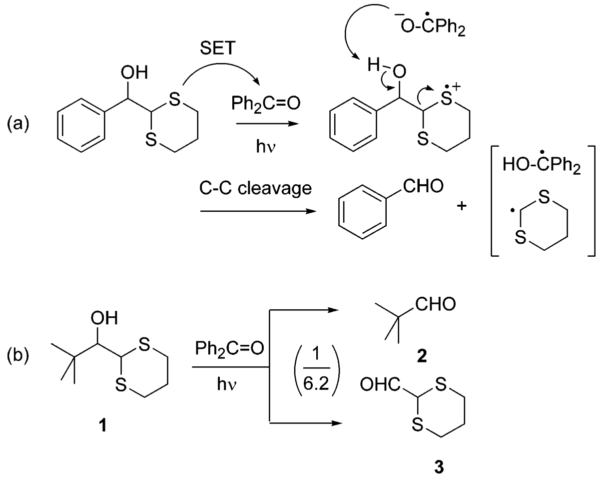
Abstract: 1,3-Dithianyl cation radicals having α-hydroxyneopentyl or similar groups in position 2, which are generated via oxidative photoinduced electron transfer, undergo anomalous fragmentation necessitating refinement of the accepted mechanism. Experimental and computational data support a rationale in which proton abstraction from the hydroxy group in the initial cation radical does not cause a Grob-like fragmentation, but rather produces a neutral radical species, the alkoxy radical, that undergoes fragmentation in either direction, i.e., cleaving the C−C bond to dithiane or to the tertiary alkyl group.

Oxidative electron transfer-induced fragmentations in vicinal amino alcohols and diols have been known for a long time and their mechanism has been exhaustively studied.[1] The accepted mechanistic rationale includes photoinduced electron transfer to an ET-sensitizer, e.g. benzophenone, followed by a mesolytic cleavage in the generated cation radical, assisted by the benzophenone anion radical deprotonating the vicinal hydroxy group. It was noted earlier that the C−C bond cleavage step is reminiscent of the Grob fragmentation in closed shell systems.[2]



Similar photoinduced fragmentation of 2-(α-hydroxybenzyl)-1,3-dithianes was recently reported by us, Scheme 1a, and its mechanism was investigated utilizing classical physical organic methods such as the Hammett substituent effect and kinetic isotope effect studies[3] and also a laser flash photolysis study.[4] In this note we report an anomalous fragmentation in sulfur-centered cation radicals containing vicinal hydroxy groups—an experimental observation of fundamental interest, necessitating a refinement of the accepted mechanism.

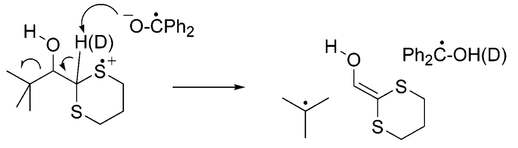
SCHEME 1



All our previous observations were in keeping with the mechanism shown in Scheme 1a, until we tested photoinduced fragmentation in the *tert*-butyl derivative **1**, which in addition to the expected pivalaldehyde **2** ("normal" cleavage) produced dithiane-2-carboxaldehyde **3** as a major product in 1:6.2 ratio, Scheme 1b. Isolation of considerable amounts of α-(*tert*-butyl)benzhydrol, $Ph_2C(OH)tBu$, indirectly confirmed the formation of *tert*-butyl radical as the second product of the fragmentation.

Clearly the quasi-Grob electron pushing rationale, i.e., the benzophenone anion radical is *pushing* and the heteroatom-centered cation radical is *pulling*, needed refinement, because compound **1** was primarily cleaving the wrong bond.

First we tested if the formation of **3** were a result of the abstraction of the dithiane's C-2 proton yielding the enol form of **3**:



1$^{\bullet+}$or **1-D**$^{\bullet+}$ **3-enol**

Deuteration of **1** changed the ratio of products **2** to **3** slightly, from 1:6.2 to 1:4.9, indicating that there is no primary kinetic isotope effect on formation of **3**. In fact, completely blocking position 2 in the dithiane ring with a methyl group did not shut off the anomalous fragmentation, although the product ratio changed significantly, with pivalaldehyde **2** becoming the major product (**2**:**5** = 1.8:1).

These experiments ruled out the competitive O−H vs S_2C−H deprotonation, leaving us with one possibility. It appears that deprotonation of the hydroxy group in the generated cation radical does not result in the formation

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(1) For review see: Gaillard, E. R.; Whitten, D. G. *Acc. Chem. Res.* **1996**, *29*, 292.

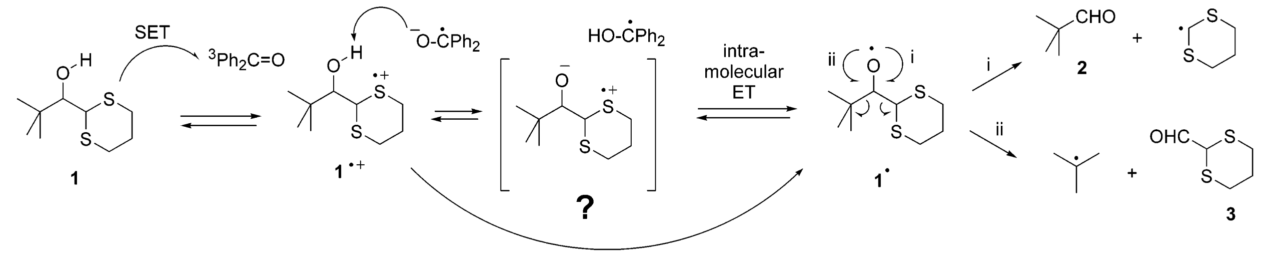
(2) (a) Ci, X.; Whitten, D. G. *J. Am. Chem. Soc.* **1987**, *109*, 7215. (b) Ci, X.; Whitten, D. G. *J. Am. Chem. Soc.* **1989**, *111*, 3459.

(3) McHale, W. A.; Kutateladze A. G. *J. Org. Chem.* **1998**, *63*, 9924.

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

10.1021/jo035001z CCC: $25.00

SCHEME 2



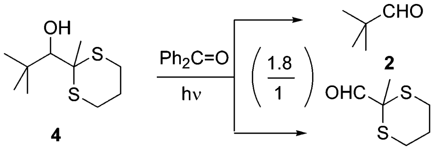
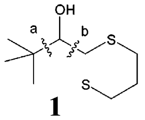
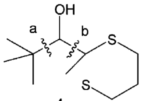
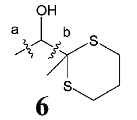
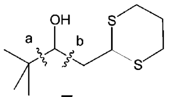
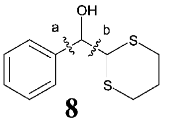
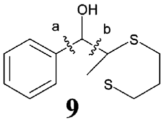
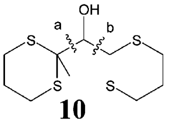
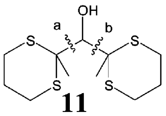
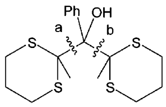


TABLE 1. Quantum Yields of Fragmentation in Acetonitrile

Compound	Φ_{tot}	Φ_a [a]	Φ_b [a]	Φ_a/Φ_b
 **1**	.125	.108	.017	6.2:1
 **4**	.258	.091	.167	1:1.8
 **6**	.122	0.0	.122	-
 **7**	.10	.10	0.0	-
 **8**	.091	0.0	.091	-
 **9**	.238	0.0	.238	-
 **10**	.24	.224	.016	14:1
 **11**	.45	(.225)	(.225)	(1:1)
 **12**	.56	(.28)	(.28)	(1:1)

[a] Partial quantum yields of cleavage "a" (to the left) and "b" (to the right), respectively

of a charge separated "Grob-like" precursor $^-O-C-C-S^{+\bullet}-R$ but rather produces a neutral oxygen-centered radical (or a species behaving as one), via intramolecular electron transfer. The O-radical undergoes subsequent fragmentation in either direction, with the partition correlating with the stability of the produced radicals, Scheme 2.[5] We also compared the results of the fragmentation in methylene chloride and acetonitrile, which constitutes almost an order of magnitude difference in dielectric constant, and did not see any difference in the partitioning within experimental error. The combined experimental and computational results seem to indicate that a charge-separated species does not exists or at best is in fast equilibrium with the alkoxy radical.

The overall mode of fragmentation is somewhat similar to cleavage in 4-methoxybenzyl alcohol radical cations reported by Baciocchi and Steenken.[6] At the same time, as was shown by Asmus and co-workers in numerous studies,[7] intermolecular reaction of oxy-radicals (e.g., hydroxy, generated by pulse radiolysis) with sulfides eventually leads to the formation of sulfur-centered cation radicals, not vice versa. What is unusual in our case is that the intramolecular charge transfer in α-hydroxyalkyl dithianes seems to occur in the opposite direction, with the net result of the S-centered cation-radical oxidizing the alkoxide.

Additional examples presented in Table 1 show that cleaving the bond to the methyldithiane moiety is by far the most efficient mode of fragmentation in this series. Comparison of fragmentation ratios in **1** and **4** and also of an unbiased competition between methyl dithianyl and dithianyl departure in bis-adduct **9** shows that methyl stabilization increases Φ_b by a factor of 11 to 14. If the rate-determining step is the fragmentation in oxy-radical **1**•, then the "normal" to "abnormal" ratio should simply correlate with the relative stabilities of the radicals produced as a result of such fragmentation.[8] The change in fragmentation ratios for **1** and **4** (from 1:6.2 to 1.8:1) corresponds to an approximately 1.4 kcal/mol relative change in free energy of activation. We used Pasto's[9] isodesmic reaction, $^{\bullet}CH_{3-n}X_n + CH_4 \rightarrow X_nCH_{4-n} + {}^{\bullet}CH_3$, as the definition to compute the additional resonance stabilization energy for 2-methyldithianyl radical at the

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(5) β-Alkylthio-ethoxy radicals were implicated in the dissociation of hydroxyl radical adducts of (alkylthio)ethanol derivatives: Schöneich, C.; Bobrowski, K. *J. Am. Chem. Soc.* **1993**, *115*, 6538.

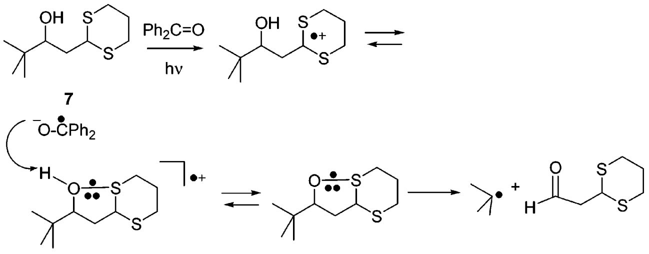
(6) (a) Baciocchi, E.; Bietti, M.; Steenken, S. *J. Am. Chem. Soc.* **1997**, *119*, 4078. (b) Baciocchi, E.; Bietti, M.; Steenken, S. *Chem. Eur. J.* **1999**, *5*, 1785.

(7) Bonifacic, M.; Schaefer, K.; Moeckel, H.; Asmus, K. D. *J. Phys. Chem.* **1975**, *79*, 1496. Asmus, K.-D. *Acc. Chem. Res.* **1979**, *12*, 436.

B3LYP/6-31g* level and found it to be 0.8 kcal/mol, which indeed is in a reasonably good agreement with experiment.

Formation of conjugated carbonyl improves the efficiency of photocleavage by a factor of 2 (cf. **6** and **9**). These results point to the *late* transition state of the C−C bond cleavage.

Strikingly, separation of the hydroxy group from the dithiane moiety with an extra methylene had virtually no effect on Φ_a (cf. **1** and **7**), although the through-bond communication between the sulfur-centered cation radical and the oxygen atom was expected to diminish. Conceivably this deficiency is offset by a direct interaction, i.e., via a two-center three-electron bond. While stable four-membered structures of this type have never been observed,[10] five-membered oxathiolane intermediates have previously been postulated.[5]



The rationale shown above could be an attractive alternative to the mechanism presented in Scheme 2. However, we did not find any computational evidence for S−O three-electron bond formation in cation radicals of 1,2-thioalcohols **1**, **4**, **6**, and **8**−**11** that can only form four-membered rings, which, as mentioned above, is in keeping with experimental observations.

Bis-dithianes **11** and **12** showed a significant increase in quantum yields of fragmentation in part due to a statistical factor of 2: both directions of fragmentation lead to the formation of the table 2-methyl-1,3-dithian-2-yl radical.

In addition to the statistical factor, upon close examination one can see that the efficiency Φ_a of the methyldithiane cleaving off in both bis-dithianyl systems **10** and **11** (0.224 and 0.225, respectively) is higher than that for **4** (0.167) or **6** (0.122). We suggest that this is due to additional stabilization of the respective cation radicals $\mathbf{10}^{+\bullet}$ and $\mathbf{11}^{+\bullet}$, which makes electron transfer less reversible. AM1 computations show that two kinds of S−S three-electron bonds could exist in $\mathbf{11}^{+\bullet}$, i.e., the intra-dithiane (internal two-center three-electron bond forming a three-membered ring, reported earlier[11]) and the inter-dithiane S−S bond (i.e., the five-membered ring), Figure 1. The latter is calculated to be 21.8 kcal/mol more stable, which is in remarkably good agreement with the reported effects of ring size on the stability of cation radicals from cyclic dithia compounds reported by Asmus and coworkers.[12] They showed that the $\sigma \rightarrow \sigma^*$ band corresponding to the intramolecular three-electron S−S bond in the 1,3-dithiane cation radical has $\lambda_{\max}$ of 600 nm, or 47.7 kcal/mol, whereas the cation radical of 1,5-dithia-cyclooctane, capable of forming a more stable 5-membered cycle with the three-electron S−S bond, showed a considerable blue shift of this band to 400 nm (or 71.5 kcal/mol), with the difference of 23.8 kcal/mol.

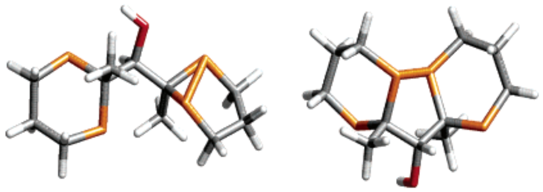


FIGURE 1. AM1 geometries of $\mathbf{11}^{+\bullet}$ with intra- (left) and inter-dithiane three-electron bonds.

In conclusion, dithianyl cation radicals having α-hydroxy-neopentyl or similar groups in position 2 undergo an unusual fragmentation that necessitates refinement of the previously proposed mechanism. Our experimental and computational data support a rationale in which deprotonation of the initial cation radical produces a neutral radical species, most probably the alkoxy radical that undergoes fragmentation in either direction. Ab initio computations indicate that the deprotonation is coupled with intramolecular electron transfer, although experimentally we cannot rule out the possibility that it is a two-step process, i.e., deprotonation followed by the intramolecular electron transfer in the initially formed charge separated species. In such a case both channels of fragmentation, the Grob-like fragmentation in the radical zwitterionic intermediate and the fragmentation in the O-centered neutral radical, may be operational and competing.

These results may have implications for the general mechanism of fragmentation in heteroatom-centered cation radicals containing vicinal hydroxy groups, although at this point we are not ready to generalize whether the same argument is applicable to mesolytic cleavage in cation radicals of vicinal amino alcohols.

Experimental Section

General Procedure for the Preparation of Dithiane Adducts with Aldehydes or Epoxides. To 1,3-dithiane or 2-methyl-1,3-dithiane (5 mmol), dissolved in 20 mL of THF and stirred at −25 °C under a nitrogen atmosphere, was added 1.1 molar equiv of *n*-butyllithium (1.6 M in hexane). The mixture was stirred at −25 °C for 3 h, the temperature was then reduced to −78 °C, and the corresponding aldehyde or epoxide (5 mmol) in 5 mL of THF was added. The mixture was stirred at −78 °C for an additional 3 h and stored at −25 °C overnight. Saturated ammonium chloride was added, and the aqueous phase was extracted twice with dichloromethane. The combined organic solution was washed twice with water and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography.

Deuterated **1-d** was obtained according to this general procedure, starting with 2,2-dideuterio-1,3-dithiane, which in

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[8] For a recent paper correlating radical stabilities in fragmentations of alkoxy radicals see: Nakamura, T.; Watanabe, Y.; Suyama, S.; Tezuka, H. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1364 and references therein.

[9] Pasto, D. J.; Krasnansky, R.; Zercher, C. *J. Org. Chem.* **1987**, *52*, 3062.

[10] (a) Hiller, K.-O.; Asmus, K.-D. *Int. J. Radiat. Biol.* **1981**, *40*, 597. (b) Asmus, K.-D.; Göbl, M.; Hiller, K.-O.; Mahling, S.; Mönig, J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 641.

[11] See: Maity, D. K. *J. Am. Chem. Soc.* **2002**, *124*, 8321 and references therein.

[12] Asmus, K.-D.; Bahnemann, D.; Fischer, C.-H.; Veltwisch, D. *J. Am. Chem. Soc.* **1979**, *101*, 5322.

turn was obtained by three consecutive lithiations of 1,3-dithiane followed by quenching with D_2O.

Compounds **1**,[13] **4**,[14] **6**,[15] **8** and **12**,[16] and **9**[17] were described previously.

1-(1,3-Dithian-2-yl)-3,3-dimethylbutan-2-ol (7) (99%): ^{1}H NMR ($CDCl_3$) δ 4.27 (dd, $J_1 = 10.3$ Hz, $J_2 = 3.7$ Hz, 1H), 3.57 (d, $J = 10.3$ Hz, 1H), 2.98−2.80 (m, 4H), 2.17−1.70 (m, 5H), 0.9 (s, 9H); ^{13}C NMR NMR (100 MHz, $CDCl_3$) δ 75.9, 45.1, 37.4, 34.8, 30.6, 30.1, 26.2, 25.7. Anal. Calcd for $C_{10}H_{20}OS_2$: C, 54.50; H, 9.15. Found: C, 54.64; H 9.18.

(1,3-Dithian-2-yl)-(2-methyl-1,3-dithian-2-yl)-methanol (10). 10 was prepared from lithiated 1,3-dithiane and 2-formyl-2-methyl-1,3-dithiane.[16] ^{1}H NMR (400 MHz, CD_3CN) δ 4.79 (d, $J = 1.5$ Hz, 1H), 4.10 (dd, $J_1 = 1.5$ Hz, $J_2 = 4.4$ Hz, 1H), 3.44 (d, $J = 4.4$ Hz, 1H), 3.07−2.56 (m, 8H), 2.09−1.98 (m, 2H), 1.83−1.67 (m, 2H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.4, 53.6, 47.9, 30.8, 29.7, 26.4, 26.0, 25.7, 24.0, 22.9. Anal. Calcd for $C_{10}H_{20}OS_2$: C, 42.51; H, 6.42. Found: C, 42.65; H 6.50.

Bis(2-methyl-1,3-dithian-2-yl)-methanol (11). 11 was prepared from lithiated 2-methyl-1,3-dithiane and 2-formyl-2-methyl-1,3-dithiane.[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (d, $J = 1.5$ Hz, 1H), 3.60 (d, $J = 1.5$ Hz, 1H), 3.17−3.01 (m, 4H), 2.85−2.73 (m, 4H), 2.09−2.01 (m, 2H), 1.98−1.89 (m, 2H), 1.86 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.6, 54.4, 27.6, 26.8, 25.4, 24.1. Anal. Calcd for $C_{10}H_{20}OS_2$: C, 44.55; H, 6.80. Found: C, 44.68; H 6.80.

Acknowledgment. Support of this research by the National Science Foundation (CHE-314344) is gratefully acknowledged.

Supporting Information Available: NMR spectra of compounds **1**, **1-D**, **4**, and **6**−**11** and computed geometries and energies of $\mathbf{11}^{+\bullet}$ and of dithiane−dithianyl radical and methyldithiane−methyldithianyl radical pairs for the isodesmic reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] Kang, J.; Kim, J. I.; Lee, J. H. *Bull. Korean Chem. Soc.* **1994**, *15*, 865.

[14] Katzenellenbogen, J. A.; Bowlus, S. P. *J. Org. Chem.* **1973**, *38*, 627.

[15] Tietze, L. F.; Weigand, B.; Wuff, C. *Synthesis* **2000**, 69.

[16] Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

[17] Wan, Y.; Kurchan, A.; Kutateladze, A. *J. Org. Chem.* **2001**, *66*, 1894.