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Intramolecular Electron Transfer Initiated Cation and Radical Formation through Carbon–Carbon Bond Activation

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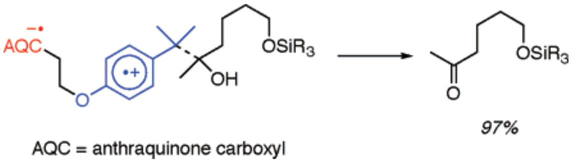
ABSTRACT



Radical cations can be formed in a spatially and temporally controlled manner by appending a sacrificial photooxidant to an easily oxidized substrate, leading to intramolecular electron transfer upon irradiation. The anthraquinone carboxyl group is an effective photooxidant that can promote single electron oxidation from an appended arene. The resulting intermediates undergo a cleavage reaction through carbon–carbon bond activation to provide either cations or radicals that react to form a range of products.

Photoinitiated deprotection reactions[1] are powerful tools for liberating molecules in a spatially and temporally precise manner on surfaces[2] and in cells.[3] Developing new methods that employ photocleavage reactions to yield synthetically versatile reactive intermediates rather than stable functional groups would expand the structural diversity that can be accessed in this manner. In this regard, utilizing photoinitiated electron-transfer processes is attractive because of the wealth of reactions that proceed through radical ion intermediates.[4] We have developed a series of transformations based on carbon−carbon bond-cleavage reactions of radical cations that arise from bimolecular single electron-transfer processes.[5] These reactions, however, cannot be applied to spatially and temporally controlled syntheses because of the potential for photooxidant diffusion and, for biological applications, the statistical improbability of bimolecular electron transfer. Tethering a photooxidant to the cleavage substrate would solve these problems by promoting reactions through intramolecular electron transfer rather than intermolecular electron transfer. Herein we report that anthraquinone carboxylates are suitable photooxidants for effecting intramolecular single electron oxidations of homobenzylic alcohols and ethers, that the resulting charge separated intermediates undergo carbon−carbon bond cleavage reactions, and that, in addition to the expected cationic intermediates, radicals can be formed from electron transfer following the initial cleavage.

We envisioned a modular design for cleavage substrates in which a photooxidant is appended to an electroauxiliary that is attached to a cargo unit by a cleavable linker (Scheme 1).[6] Photoirradiation will yield a charge-separated intermediate through intramolecular electron transfer. Provided that the radical cation fragment of the molecule reacts in an analogous manner to related species that arise from intermolecular electron transfer, the cargo will be released as a

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[1] Bochet, C. G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 125.

[2] (a) Pirrung, M. C. *Chem. Rev.* **1997**, *97*, 473. (b) McGall, G. H.; Barone, A. D.; Diggelmann, M.; Fodor, S. P. A.; Gentalen, E.; Ngo, N. *J. Am. Chem. Soc.* **1997**, *119*, 5081.

[3] (a) Adams, S. R.; Tsien, R. Y. *Annu. Rev. Physiol*. **1993**, *55*, 755. (b) Dormán, G.; Prestwich, G. D. *Trends Biotechnol*. **2000**, *18*, 64. (c) *Dynamic Studies in Biology: Phototriggers, Photoswitches, and Caged Biomolecules*, Goeldner, M., Givens, R., Eds.; Wiley-VCH GmbH and Co.: Weinheim, Germany, 2005.

[4] (a) Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2550. (b) Baciocchi, E.; Bietti, M.; Lanzalunga, O. *Acc. Chem. Res.* **2000**, *33*, 243.

[5] (a) Kumar, V. S.; Floreancig, P. E. *J. Am. Chem. Soc.* **2001**, *123*, 3842. (b) Aubele, D. L.; Floreancig, P. E. *Org. Lett.* **2002**, *4*, 3443. (c) Wang, L.; Seiders, J. R., II; Floreancig, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 12596.

[6] For a related approach, see: Majjigapu, J. R. R.; Kurchan, A. N.; Kottani, R.; Gustafson, T. P.; Kutateladze, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 12458.

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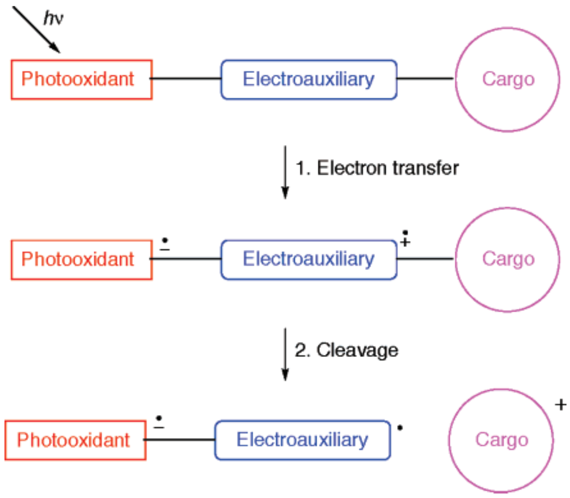
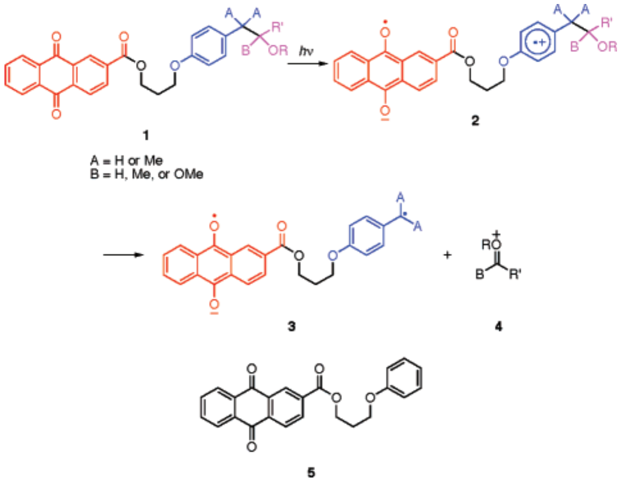
Scheme 1. Strategy for Intramolecular Electron Transfer and Bond Cleavage



cation that can either engage in a cyclization reaction or be quenched by solvent.

For this approach to be effective, return electron transfer in the charge-separated intermediate must be sufficiently slow to allow bond cleavage to be a competitive process. Because a spin flip must precede return electron transfer, enhanced lifetimes of charge-separated states are observed[7] when photooxidants react through triplet excited states rather than singlet states. Whitten has reported[8] that the anthraquinone carboxylate group is a suitable photooxidant for promoting long-lived charge separated intermediates. Substituted arenes are exceptionally versatile electroauxiliaries and function even when appended to complex structures through ether linkages.[9] Incorporating these elements into a composite design led to prototypical substrate **1** (Scheme 2). Photoexcitation of the anthraquinine group in **1** is expected to provide charge separated intermediate **2**, which will cleave to form **3** and **4**. Subsequent reactions of **4** can lead to a range of products. To confirm that intramolecular electron transfer is feasible in this system we prepared noncleavable analogue **5**. The characteristic fluorescence emission bands from the anthraquinone carboxylate group at 466 and 500 nm were completely quenched by arene substitution, consistent with efficient photoinitiated intramolecular electron transfer.[10]

Scheme 2. Anthraquinone Carboxylate Substrates



To test the capacity of these structures to undergo bond cleavage, we prepared substrates **6**−**9** based on observations that related substrates smoothly undergo cleavage upon bimolecular oxidation.[8] These substrates were irradiated (medium-pressure mercury lamp, Pyrex filtration) in aqueous CH_3CN to provide carbonyl-containing products[11] as summarized in Table 1. Several observations from Table 1 are noteworthy. Weakening the benzylic carbon−carbon bond,[5c] either by using a tertiary alcohol rather than a secondary alcohol or by introducing alkyl groups at the benzylic position, enhances both the rate and the efficiency of the cleavage reaction. Remarkably effective ketone formation was noted when both strategies were employed (entry 3). Free hydroxyl groups are not required for cleavage, as demonstrated by the reaction of acetal **9**, though the process is slower (entry 4). Baciocchi has observed[12] that alcohols undergo cleavage faster than ethers in the presence of base, presumably reflecting heightened electron donation. Acetal substrates yield esters, thereby broadening the range of oxidation states that can be accessed through this protocol. To the best of our knowledge entry 4 depicts the first report of ester formation through photochemical cleavage in a

Table 1. Bond Cleavage through Intramolecular Electron Transfer[a]

6: A, B, R = H
7: A, R = H, B = Me
8: A, B = Me, R = H
9: A = H, B = OMe, R = Me

10: B = H
11: B = OH
12: B = Me
13: B = OMe

entry	substrate[b]	time (h)	product(s)	yield (%)[c]
1	**6**	1.5	**10**	61
			11	6
2	**7**	1	**12**	89
3	**8**	1	**12**	97
4	**9**	2	**13**	77

[a] AQC = anthraquinone carboxylate. Reaction conditions: hν (medium-pressure Hg lamp, Pyrex filter), NaOAc, CH_3CN, H_2O (20:1). [b] See the Supporting Information for synthetic schemes to prepare the substrates. [c] Yields are reported for isolated, purified materials.

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[7] Jones, G., II; Haney, W. A.; Phan, X. T. *J. Am. Chem. Soc.* **1988**, *110*, 1922.

[8] Leon, J. W.; Whitten, D. G. *J. Am. Chem. Soc.* **1993**, *115*, 8038.

[9] Liu, H.; Wan, S.; Floreancig, P. E. *J. Org. Chem.* **2005**, *70*, 3814.

[10] See the Supporting Information for fluorescence quenching data.

[11] For other examples of photoinitiated ketone and aldehyde release, see: (a) Blanc, A.; Bochet, C. G. *J. Org. Chem.* **2003**, *68*, 1138. (b) Lu, M.; Fedoryak, O. D.; Moister, B. R.; Dore, T. M. *Org. Lett.* **2003**, *5*, 2119.

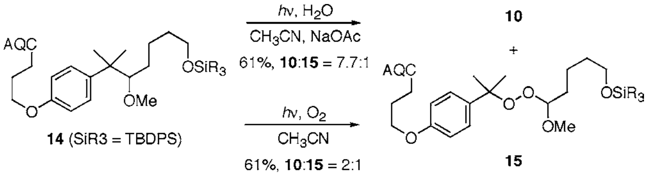
[12] Baciocchi, E.; Bietti, M.; Putignani, L.; Steenken, S. *J. Am. Chem. Soc.* **1996**, *118*, 5952.

nonalcoholic solvent. Cleaving secondary alcohol **6**, in addition to the expected aldehyde **10**, provided a small amount of carboxylic acid **11**. This result was unexpected on the basis of related bimolecular reactions[8] that did not result in overoxidation. All of these reactions were conducted in 5% aqueous acetonitrile, demonstrating that water does not have a deleterious effect on the process. A control substrate in which the anthraquinone carboxylate and linker groups were replaced by a methyl group underwent photoinitiated cleavage at a rate that was approximately 2 orders of magnitude slower than that of the parent structures (data not shown), confirming the importance of intramolecular electron transfer in promoting the reaction.

While no direct comparison of these cleavage reactions to similar reactions that proceed through intermolecular electron transfer is possible, a general comparison of reactivity patterns is instructive. Notably, for reactions that proceed through intermolecular electron transfer the presence of a *para*-alkoxy group on the arene completely suppresses oxidative cleavage unless substituents are appended to the benzylic position to weaken the carbon−carbon bond. Benzylic substituents promote smoother cleavage for reactions that utilize intramolecular electron transfer, but they are not necessary. This effect can most likely be attributed to an inherently enhanced reactivity for the charge separated intermediates relative to simple radical cations and/or to intramolecular electron transfer producing higher concentrations of reactive intermediates than the corresponding intermolecular processes.

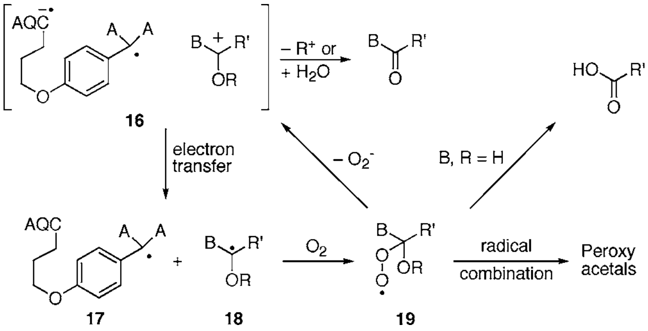
To explore the scope of the process further, we prepared secondary ether **14** to determine whether oxocarbenium ions could be generated in this manner as an entry to cyclization reactions. Direct irradiation of **14** under the standard conditions (Scheme 3) indeed provided aldehyde **10** in 54% yield, though the reaction was slower (5.5 h) than the reactions in Table 1 and the unusual peroxyacetal **15** was formed in a 7% yield. Interestingly, when the reaction was conducted in the absence of water but in the presence of O_2, **15** was formed in 21% yield while the yield of **10** dropped to 40%. These results suggest that the intermediacy of alkoxyalkyl radicals is possible in these cleavage reactions.

Scheme 3. Cleavage of a Secondary Ether



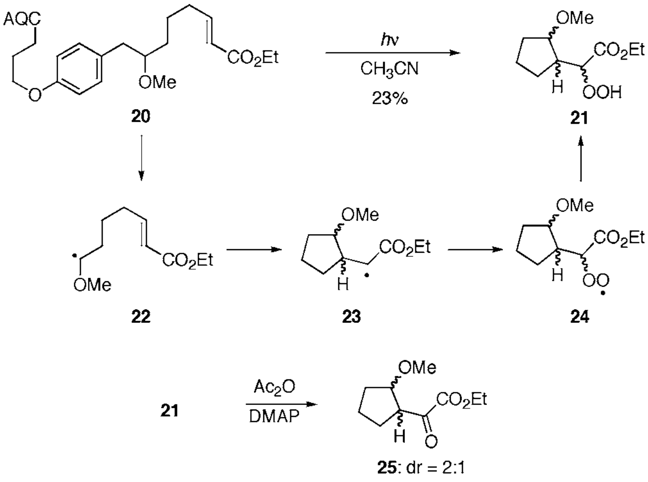
Isolating acid **11** from **6** and peroxyacetal **15** from **14** indicates that the reaction pathways following intramolecular electron transfer and bond cleavage can diverge from those that are observed when cleavage is initiated by intermolecular electron transfer. Reaction of the intermediate carbocations with water either through nucleophilic addition or deprotonation to form the expected products appears to be the dominant pathway (Scheme 4). However, the radical anion−cation pair from the cleavage reaction (**16**) can undergo an electron-transfer reaction to form radicals **17** and **18** when the reaction with water is slow because neutral product formation through proton loss is not a viable pathway (as for **14**) or because the driving force for reducing a relatively unstabilized intermediate oxocarbenium ion is high (as for **6**). The enhanced production of peroxyacetal **15** in anhydrous conditions supports this hypothesis. We have not previously observed this process because the driving force for cation reduction by the benzylic radical leaving groups that we normally employ is significantly lower than for reduction by the radical anion in **16**. The resulting oxyalkyl radical (**18**) can react with O_2 to form peroxy radical **19**. The peroxy radical can either recombine with the benzylic radical to form a peroxy acetal, collapse to form a carbonyl group, or lose superoxide to regenerate the oxocarbenium ion intermediate.

Scheme 4. Reaction Pathways Following Cleavage



In further exploration of radical intermediates on this pathway, and in an attempt to use these intermediates in productive bond formation, we prepared substrate **20** with the expectation that alkoxyalkyl radical formation would result in a cyclization through addition into the electron deficient alkene. Indeed, irradiating **20** (Scheme 5) in the absence of added water resulted in the formation of peroxide **21** as a mixture of stereoisomers. This process proceeded

Scheme 5. Photoinitiated Radical Cyclization



through cleavage and electron transfer to form alkoxyalkyl radical **22** followed by cyclization into the pendent alkene to form **23**. Radical trapping by O_2 to form peroxy radical **24** and hydrogen abstraction completed the sequence to form **21**. Product characterization was facilitated by converting the multiple diastereomers of **21** to keto ester **25**,[13] which was isolated as a 2:1 mixture of stereoisomers. While the yield for this reaction was modest, the results are consistent radical formation through oxocarbenium ion reduction since reaction between the electron deficient alkene and a cationic intermediate is unlikely, particularly given the observed regiochemical outcome.

We have developed a method for cleaving carbon−carbon bonds through photoinitiated intramolecular electron-transfer processes. These fragmentations proceed to form oxocarbenium ions and radical anions, and are most efficient when the intermediate cations are highly stabilized or when a neutral product can be formed through deprotonation. Ketones, aldehydes, and esters can be released in good to excellent yields. When the cationic fragment cannot form a neutral molecule through deprotonation, radical formation through electron transfer from the radical anion to the oxocarbenium ion becomes a competitive process, as evidenced by the isolation of peroxide and radical cyclization products. In principle the modular substrate design will allow for the incorporation of a wide range of photooxidants and electroauxiliaries in response to the needs of a particular application, such as altered excitation wavelength or electrophore oxidation potential. The ability to access reactive intermediates rather than stable molecules should substantially broaden the range of structures that can be accessed in a spatially and temporally controlled manner. Further studies directed toward these objectives are currently in progress

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Supporting Information Available: Synthetic schemes for all cleavage substrates and experimental procedures and characterization data for all cleavage reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] Matsushita, Y.; Sugamoto, K.; Matsui, T. *Chem. Lett.* **1992**, 2165.