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Mechanistic Aspects of the Formation of Aldehydes and Nitriles in Photosensitized Reactions of Aldoxime Ethers

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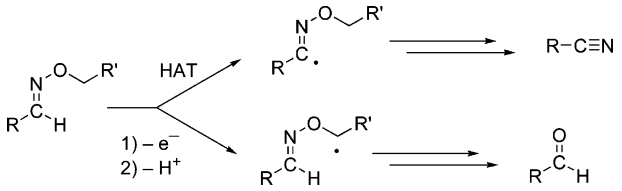

The photooxidation of a series of aldoxime ethers was studied by laser flash photolysis and steady-state (product studies) methods. Nanosecond laser flash photolysis studies have shown that chloranil (CA)-sensitized reactions of the *O*-methyl (**1**), *O*-ethyl (**2**), *O*-benzyl (**3**), and *O*-*tert*-butyl (**4**) benzaldehyde oximes result in the formation of the corresponding radical cations. In polar non-nucleophilic solvents such as acetonitrile, there are several follow-up pathways available depending on the structure of the aldoxime ether and the energetics of the reaction pathway. When the free energy of electron transfer (ΔG_{ET}) becomes endothermic, *syn*−*anti* isomerization is the dominant pathway. This isomerization pathway is a result of triplet energy transfer from CA to the aldoxime ether. For substrates with α-protons (aldoxime ethers **1**−**3**), the follow-up reactions involve deprotonation at the α-position followed by β-scission to form the benziminyl radical (and an aldehyde). The benziminyl radical reacts to give benzaldehyde, the major product under these conditions. A small amount of benzonitrile is also observed. In the absence of α-hydrogens (aldoxime ether **4**), the major product is benzonitrile, which is thought to occur via reaction of the excited (triplet) sensitizer with the aldoxime ether. Abstraction of the iminyl hydrogen yields an imidoyl radical, which undergoes a β-scission to yield benzonitrile. An alternative pathway involving electron transfer followed by removal of the iminyl proton was not deemed viable based on charge densities obtained from DFT (B3LYP/6-31G*) calculations. Similarly, a rearrangement pathway involving an intramolecular hydrogen atom transfer process was ruled out through experiments with a deuterium-labeled benzaldehyde oxime ether. Studies involving nucleophilic solvents have shown that all aldoxime ethers reacted with MeOH by clean second-order kinetics with rate constants of 0.7 to 1.2 × 10^7 M^{-1} s^{-1}, which suggests that there is only a small steric effect in these reactions. The steady-state experiments demonstrated that under these conditions no nitrile is formed. This is explained by a mechanistic scheme involving nucleophilic attack on the nitrogen of the aldoxime ether radical cation, followed by solvent-assisted [1,3]-proton transfer and elimination of an alcohol, similar to the results obtained for a series of acetophenone oxime ethers.

Introduction

The use of oximes as drugs (antidotes for organophosphorus poisoning, NO-donors),[1,2] pesticides,[3] and industrial chemicals (e.g., cyclohexanone oxime in the synthesis of caprolactam)[4] has dramatically increased in recent years. Their prevalence in the environment can result in uptake by organisms, that could lead to the formation of reactive intermediates by means of enzymatic oxidation processes.[5] The enzymes responsible for oxidative degradation of xenobiotics are the cytochromes P450 (CYP). CYP3A4 is the most abundant human liver microsome

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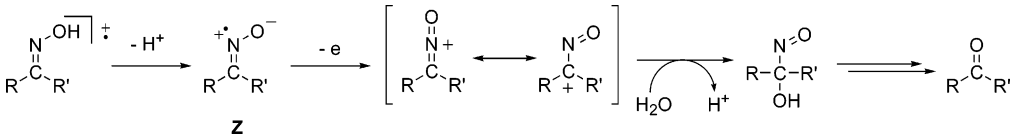
SCHEME 1



Z

SCHEME 2

and has a broad substrate specificity. In fact, this isoform is responsible for metabolizing more than 50% of the clinically used drugs.[6] The CYP enzymes are known to oxidize substrates via hydrogen atom transfer (HAT) or single electron transfer (SET) reactions.[7] One-electron oxidation of oximes can result in the formation of reactive intermediates such as radical cations and iminoxyl radicals,[8,9] which are harmful to organisms.[10] Oximes have also found use as NO-donors,[2] and iminoxyl radicals have been proposed as intermediates in this process.[2,11]

We have previously used photooxidation as a tool to generate these reactive intermediates and to study their behavior. Our initial studies have shown that ketoximes react to give the corresponding carbonyl compounds via the sequence given in Scheme 1.[9] The main intermediate in this reaction pathway is the iminoxyl radical, **Z**.

Recently we have focused on the reactivity of aldoximes, which under similar conditions react to give both aldehydes and nitriles.[9e] The pathway for aldehyde formation is thought to be via an iminoxyl radical in analogy to ketone formation above (Scheme 1, R′ = H). However, the nitrile formation was proposed to result from a different intermediate, most likely an imidoyl radical. We have also studied the photooxidation reactions of oxime ethers derived from ketones.[9c] On the basis of nanosecond laser flash photolysis and steady-state photolysis (product) studies, we have proposed that these compounds react via a pathway that does not involve the formation of iminoxyl radicals. In non-nucleophilic solvents such as acetonitrile, the reaction proceeds via deprotonation at the α-carbon followed by β-scission and follow-up reactions (Scheme 2).

To further study the possible involvement of iminoxyl and imidoyl radicals in the formation of nitriles in the photooxidation of aldoximes, we have studied a series of aldoxime ethers. The working hypothesis was that if nitriles are formed via iminoxyl radical intermediates, no nitriles should be formed in the photooxidation of oxime ethers, since oxime ethers do not react to give iminoxyl radicals. The results of these studies and the mechanistic implications are discussed.

Results and Discussion

A. Laser Flash Photolysis Studies of Aldoxime Ethers in the Presence of Chloranil. The benzaldehyde oximes used in these photochemical studies are shown in Figure 1.

Previously we have used laser flash photolysis (LFP) to show that both oximes and ketoxime ethers quench the triplet state of chloranil (^{3}CA) with rates close to the diffusion-controlled limit.[9] Similar results are obtained when using aldoxime ethers **1**−**4** as the quenchers (k_q; Table 1). On the basis of the Weller equation,[12] SET is not favorable; however, it cannot be ruled out as a pathway, although others must be considered as well.

Support for an initial SET step comes from the spectra obtained from laser excitation (355 nm) of a solution containing CA and aldoxime ether **1**. The spectrum (Figure 2A) shows absorption bands around 400 and 650 nm. The lifetime of the intermediate formed in these reactions ((τ = 200 ns) is significantly shorter than the *O*-alkyl acetophenone oxime radical cations (τ = 500 ns).[9c] The band at 450 nm decays slower than those at 400 and 650 nm and is most likely due to either the chloranil radical anion or the semiquinone radical, which are known to absorb in the region of 425−525 nm.[13] Similar spectra were obtained for aldoxime ethers **2**−**4** (Figures 2B−

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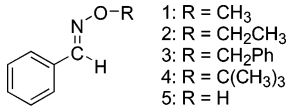

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FIGURE 1. Benzaldehyde oximes used in the chloranil-sensitized reactions.

TABLE 1. Summary of Kinetic Data Obtained from Nanosecond Laser Flash Photolysis Experiments of Aldoxime Ethers 1−4

aldoxime ether	E_p (V)[a]	ΔG_{ET} (kcal mol^{-1})[b]	k_q (M^{-1} s^{-1})	k_{MeOH} (M^{-1} s^{-1})
1	2.48	+7.6	3.22×10^9	1.15×10^7
2	2.42	+6.2	4.74×10^9	1.00×10^7
3	2.44	+6.7	3.44×10^9	1.21×10^7
4	2.32	+3.9	5.18×10^9	7.13×10^6

[a] Oxidation potentials measured by cyclic voltammetry (0.1 M tetraethyl ammonium perchlorate in CH_3CN, Ag/AgCl electrode); each value was corrected by +0.29 V in order to convert the reference to SCE. [b] calculated using the Weller equation (ref 12): $\Delta G_{ET} = 23.06[E^{ox} - E^{red} - E_T]$ kcal/mol; E_T is the triplet energy of CA (2.13 eV) and E^{red} is the reduction potential of CA (+0.02 V vs SCE).

D). These spectra are very similar to those obtained for ketoxime ether radical cations.[9c]

Similar spectra were obtained when *N*-ethylquinolinium tetrafluoroborate (NEQ) was used as the sensitizer (Figure 3). When the signals from ^{3}CA, the CA radical anion, and the semiquinone radical are absent, it becomes obvious that the band between 390 and 410 nm belongs indeed to the aldoxime ether (**1**) radical cation. As noted before,[9c] the spectra of oxime radical cations cannot be observed under these conditions. This is most likely because the aldoxime radical cation is a strongly acidic species[14] and will readily give up a proton to any available base.

To obtain further evidence for the formation of the aldoxime ether radical cation under these conditions, the addition of variable concentrations of the electron donor (4,4′-dimethoxystilbene; DMS) was studied. Monitoring the spectrum upon addition of DMS revealed a decay of the signal at 665 nm as a function of the concentration of added DMS and the appearance of a new signal at 530 nm. The latter signal is assigned to the DMS radical cation, consistent with literature data.[15] The slope of the plot of the rate constant for the growth of the signal at 530 nm against the DMS concentration gave a bimolecular rate constant of $\sim 2 \times 10^{10}$ M^{-1} s^{-1}. As expected for an electron-transfer process, this rate constant is close to the diffusion-controlled limit. These experiments confirm that under the conditions of the reactions, SET occurs and the aldoxime ether radical cations species are formed. The bands appearing between 390−410 nm and 550−750 nm in the spectra shown in Figure 2 are assigned to the aldoxime ether radical cations.

The reactions of the aldoxime ether radical cations with MeOH as a nucleophile (k_{MeOH}) were studied separately (in MeCN), and the rate constants for these reactions are listed in Table 1. There is little difference between the rate constants of the reactions of aldoxime ethers **1**−**3** with MeOH, but aldoxime ether **4** reacts somewhat slower. On the basis of the previously

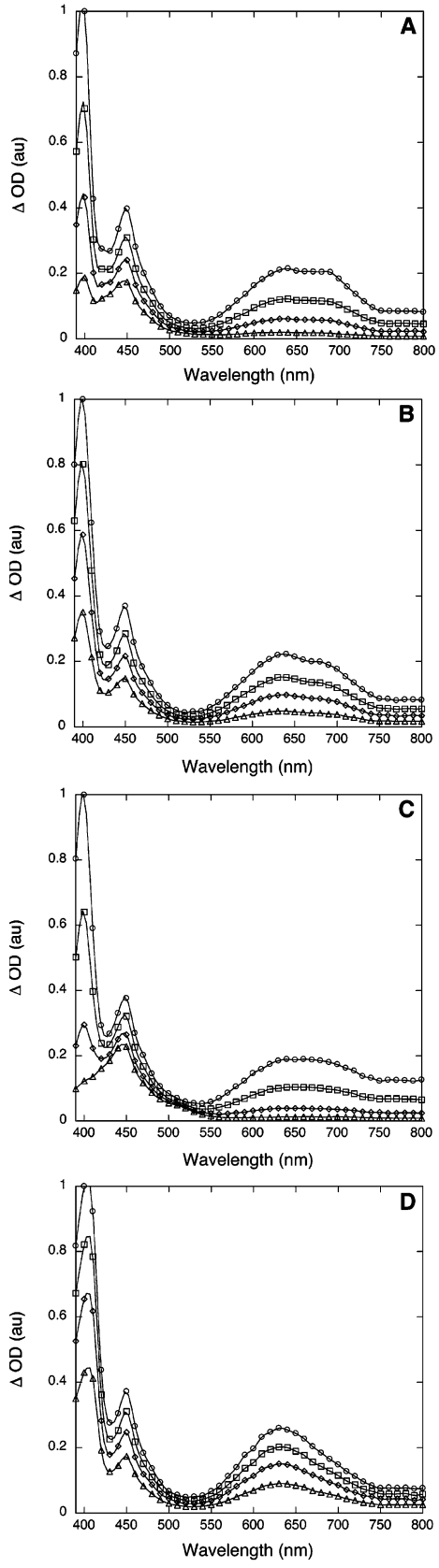

FIGURE 2. Spectra obtained from CA-sensitized laser photolysis (355 nm) of (A) aldoxime ether **1** in MeCN, (B) compound **2** in MeCN, (C) compound **3** in MeCN, and (D) compound **4** in MeCN. The spectra were taken 65 ns (○), 200 ns (□), 450 ns (◇), and 1 μs (△) after the laser pulse.

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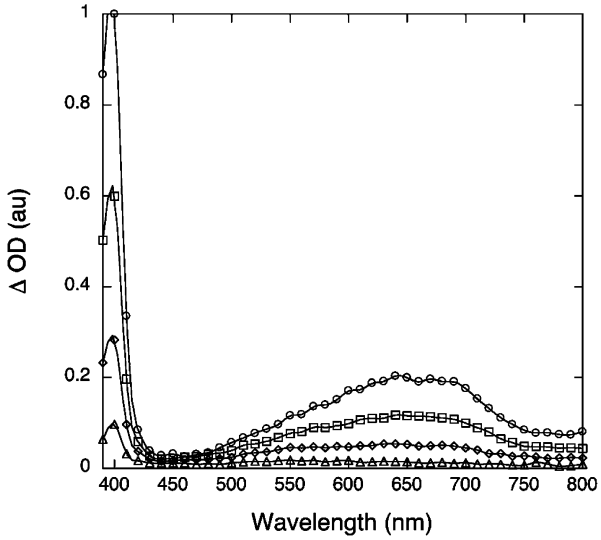
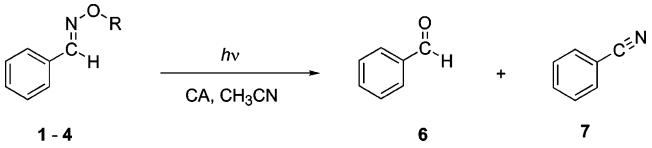


FIGURE 3. Spectra obtained from NEQ-sensitized laser photolysis (355 nm) of aldoxime ether **1** in MeCN. The spectra were taken 65 ns (○), 200 ns (□), 450 ns (◇), and 1 μs (△) after the laser pulse.

SCHEME 3



postulated mechanism for nucleophilic attack on the nitrogen of the ketoxime ether radical cation,[9c] the lifetime differences are best explained by a small steric effect. Similar results were observed in a series of ketoxime ethers derived from acetophenone,[9c] as well as in the reactions of other radical cation species with nucleophiles.[16] The results of these LFP studies show that upon laser photolysis of a mixture containing CA and an aldoxime ether, SET occurs resulting in the formation of the aldoxime ether radical cation. In the presence of a nucleophilic solvent, the radical ions are short-lived because of follow-up reactions.

B. Steady-State Photolysis of Aldoxime Ethers in the Presence of Chloranil. In general, irradiations were carried out for 2 h on argon-purged (15 min) acetonitrile or methanol solutions (5 mL) containing the aldoxime ether (0.015 M) and chloranil (CA; 0.015 M) in Pyrex tubes using a Rayonet photochemical reactor equipped with 16 RPR-3500A bulbs. UV−vis analysis of the mixtures with and without CA showed that under the conditions of the reactions only CA absorbs the incident light. The reactions were followed by gas chromatography with flame ionization detection (GC-FID) or with mass spectrometry (GC-MS). The major products formed in these reactions are benzaldehyde (**6**) and benzonitrile (**7**) (Scheme 3). The reactions typically proceed cleanly although some secondary products were detected by GC-FID or GC-MS. No conversion of the starting material is observed when a solution of the aldoxime ether without any CA present is irradiated. Both *syn* and *anti* isomers of the aldoxime ethers can be detected and quantified by GC-FID.

TABLE 2. Summary of the Results from the Photosensitized Reactions of Aldoxime Ethers 1−4 with CA in MeCN

aldoxime ether	%C[a]	product yields[b]			
		6	**7**	%I[c]	**6**:**7**
1	41	17	7	74	2.4
2	45	28	5	66	5.6
3	20	37	4	64	9.3
4	15	4	96	-	0.04

[a] Conversion was calculated on the basis of the GC-FID peak area of the aldoxime ether before and after photolysis. [b] Product yields determined by calibrated GC-FID. [c] *Syn*−*anti* isomerization.

The results of the steady-state photolysis experiments of aldoxime ethers **1**−**4** are summarized in Table 2. Irradiation of an argon purged MeCN solution containing chloranil and *O*-methyl benzaldehyde oxime (**1**) resulted in the formation of benzaldehyde (**6**) and benzonitrile (**7**) in moderate yield. The aldehyde−nitrile ratio (**6**:**7**) is approximately 2. The main product, however, is a result of *syn*−*anti* isomerization of the starting material. Isomerization of oxime ethers upon triplet sensitization is a well-known phenomenon and is a result of energy transfer.[17] If SET becomes endothermic and unfavorable, the energy transfer pathway can be followed provided the triplet energy of the aldoxime ether is low enough for triplet−triplet energy transfer to take place, although nonvertical energy transfer could also be responsible.[17i,j] From Table 1 it can be seen that the free energy for SET (ΔG_{ET}) is endothermic (+7.6 kcal/mol), suggesting that energy transfer is likely competitive with SET, and therefore *syn*−*anti* isomerization is a dominant reaction pathway.

Similar results were obtained for the irradiation of *O*-ethyl benzaldehyde oxime (**2**). Both benzaldehyde and benzonitrile are formed; the aldehyde−nitrile ratio is higher than for aldoxime ether **1**. Again, a significant amount of isomerization was observed, which is in agreement with the calculated free energy of electron transfer.

The CA-sensitized photolysis of *O*-benzyl benzaldehyde oxime (**3**) in MeCN results in the formation of benzaldehyde (**6**) and benzonitrile (**7**) as the major products (Table 2). The ratio of aldehyde−nitrile is higher than in the case of aldoxime ethers **1** and **2**. Isomerization of the starting material remains the major pathway, in agreement with the calculated energetics.

The irradiation of *O*-*tert*-butyl benzaldehyde oxime (**4**) gave different results (Table 2). The reaction is slower compared to those of aldoxime ethers **1**−**3**; however, no isomerization is observed. On the basis of the energetics, this reaction is the most favorable of all four aldoxime ethers, which may (in part) explain the absence of *syn*−*anti* isomerization. The major

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SCHEME 4

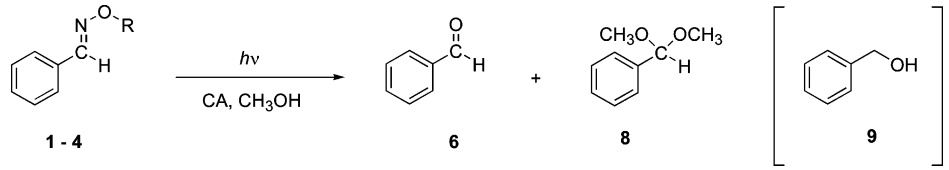

TABLE 3. Summary of the Results from the Photosensitized Reactions of Aldoxime Ethers 1−4 with CA in MeOH

aldoxime ether	%C[a]	product yields[b]			
		6	**7**	**8**	**9**
1	11	6	-	94	-
2	25	3	-	97	-
3	38	5	-	98	97
4	4	6	-	93	-

[a] Conversion was calculated on the basis of the GC-FID peak area of the aldoxime ether before and after photolysis. [b] Product yields determined by calibrated GC-FID.

product from the reaction is benzonitrile (**7**). A small amount of benzaldehyde is formed as well but the aldehyde−nitrile ratio is now only 0.04.

The presence of a nucleophile on the reaction was tested by carrying out the photolysis of **1**−**4** in methanol as the solvent (Scheme 4).

The results are listed in Table 3. Irradiation of **1** and CA in MeOH for 2 h results in the formation of benzaldehyde dimethyl acetal (**8**) as the major product and a small amount of benzaldehyde (**6**). No benzonitrile (**7**) was detected under these conditions and no *syn*−*anti* isomerization is observed. We have reported earlier on the photosensitized acetalization of aldehydes and ketones; under the conditions of the reaction, aldehydes (and ketones) react to form the dimethyl acetals in almost quantitative yield.[18] Hence, it is fair to assume that the initial (and major) product in these reactions is benzaldehyde.

Similar results were obtained for aldoxime ethers **2** and **4**. The reaction of **3** in MeOH yields equal amounts of benzaldehyde (in the form of the acetal) and benzyl alcohol (**9**). Separate experiments have shown that irradiation of a solution of CA and benzaldehyde in methanol does not yield any benzyl alcohol. The formation of benzyl alcohol is best explained by a nucleophilic attack−proton transfer−elimination sequence similar to that proposed for *O*-alkyl acetophenone oximes.[9c] Similar reactions are proposed to occur for aldoxime ethers **1**, **2**, and **4**; however, the corresponding alcohols (MeOH, EtOH, and *t*-BuOH) cannot be detected due to their volatility.

C. Mechanistic Interpretation of the Steady-State and Laser Flash Photolysis Data. The laser flash photolysis data shown for aldoxime ethers **1**−**4** is consistent with an initial SET step. On the basis of the similarities between the previously studied reactions of *O*-alkyl acetophenone oximes and those of *O*-alkyl benzaldehyde oximes **1**−**4** in acetonitrile, the formation of benzaldehyde is concluded to be a result of an electron transfer−deprotonation−β-scission mechanism (Scheme 2; R′ = H). This mechanism is the main pathway for aldoxime ethers **1**, **2**, and **3** (ignoring the isomerization pathway). In MeOH the mechanism changes; the main products are now benzaldehyde dimethyl acetal (formed from benzaldehyde) and benzyl alcohol (in the case of **3**). The proposed mechanism for formation of these products is shown in Scheme 5A. Nucleophilic attack on the oxime radical cation proceeds via addition of MeOH to nitrogen followed by a nucleophile (MeOH)-assisted[1,3]-proton transfer and elimination of an alcohol.[9c] An alternative mechanism involving hydrogen atom abstraction (by ^{3}CA) followed by β-scission (Scheme 5B) can be ruled out because it would also yield benzonitrile (**7**), which is not observed under these conditions.

The reactivity of aldoxime ether **4** in MeCN does not follow that of aldoxime ethers **1**−**3** because it does not have α-protons. Although aldoxime ether **4** reacts slower than aldoxime ethers **1**−**3**, it is not much slower than **3**, suggesting that an alternative pathway is available. Together with the observation that formation of the nitrile is now the dominant pathway suggests that these two facts are related. Previously it was observed that *O*-*tert*-butyl acetophenone oxime reacted sluggishly upon photolysis in MeCN with CA as the sensitizer.[9c] It was concluded that because of the lack of α-hydrogens no viable reaction pathway was available and therefore no reaction was observed. The only difference between aldoxime ether **4** and *O*-*tert*-butyl acetophenone oxime is the availability of the iminyl hydrogen in **4**. We have recently suggested that abstraction of the iminyl hydrogen in benzaldehyde oximes may be responsible for the formation of nitriles.[9e] The results presented here seem to support that hypothesis. It must be noted that aldoxime ethers **1**, **2**, and **3** also produce a small amount of nitrile, suggesting that a similar pathway is available in these aldoxime ethers. However, benzonitrile (**7**) is only a minor product in those reactions, and therefore the pathway to the nitrile is clearly not favored. Nevertheless, in the following discussion we will include all possible pathways for aldoxime ethers, including those with available α-hydrogens.

In principle there are three different pathways that can lead to the imidoyl radical. Following the proposed mechanism as shown in Scheme 2, electron transfer and deprotonation at the α-carbon yields the α-radical. Intramolecular hydrogen atom transfer (HAT) would yield the imidoyl radical, which can react to give the observed nitrile and benzyloxy radical (Scheme 6; path A). In addition it would be possible to form the imidoyl radical via a direct HAT mechanism using ^{3}CA (path B). The third possibility would involve removal of the iminyl proton from the aldoxime ether radical cation (path C).

Of the three potential pathways, path C seems the least likely despite the fact that the spectrum of the radical cation was observed in the LFP experiments discussed above. Previously we have also observed the spectrum of the radical cation of *O*-*tert*-butylacetophenone oxime; however, steady-state experiments did not show any significant conversion or product formation over time. This suggests that electron-transfer may be favorable (energetically); however, if there is no convenient reaction pathway available, no reaction (other than return electron-transfer) will occur. There are several other observations that support this conclusion. First, the change in product distribution in a series of substituted benzaldoximes was directly related to the substituent on the aromatic ring.[9e] An increase in

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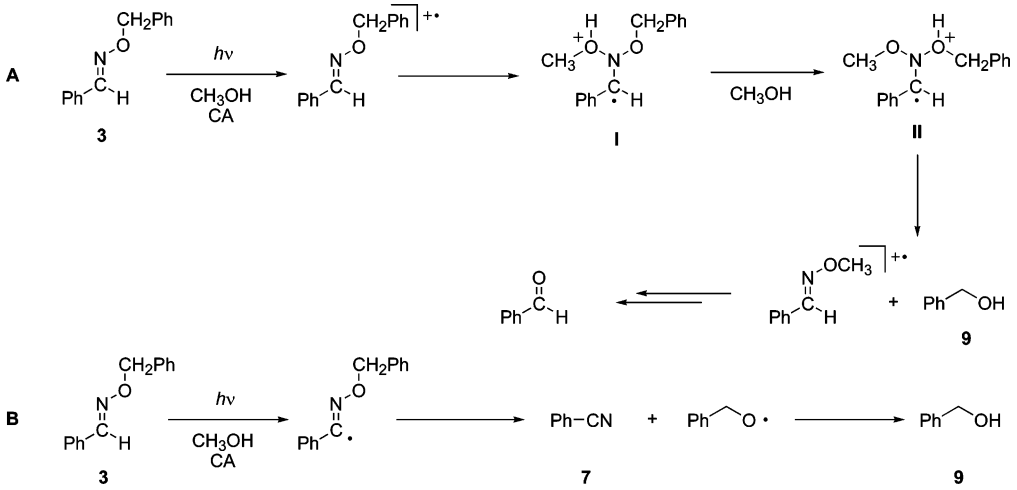
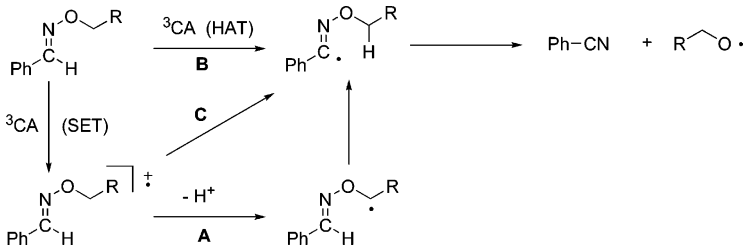
SCHEME 5



SCHEME 6

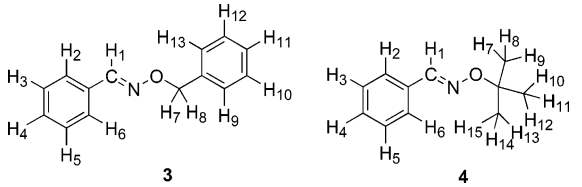


nitrile was observed for aldoximes bearing electron-withdrawing substituents. It was suggested that the presence of the electron-withdrawing group increased the oxidation potential of the aldoxime and therefore made SET less favorable. Under those conditions, the mechanism is believed to switch from SET to HAT. Second, calculations on the aldoximes and aldoxime ethers have shown that there is no significant charge development on the iminyl hydrogen. In the aldoximes, the most acidic proton is the hydroxyl proton, whereas in aldoxime ethers the charges on most hydrogens in the entire molecule are very similar. A summary of the calculated (B3LYP/6-31G*) charge densities in aldoxime ethers **3** and **4** is listed in Table 4. At this point we conclude that the data are not consistent with pathway C.

The fact that aldoxime ether **4** does not have α-hydrogens available rules out pathway A. However, that same pathway cannot be ruled out *a priori* for aldoxime ethers **1**−**3**. To distinguish between pathways A and B, we have prepared and studied the reactivity of *O*-benzyl *p*-methoxybenzaldehyde-*d* oxime (**10**). In the case of pathway A (Scheme 7; clockwise starting from **10**), intramolecular HAT should eventually yield both benzaldehyde-*d* (**6-*d***) and benzaldehyde-*h* (**6**), whereas pathway B (Scheme 7; counterclockwise starting from **10**) should only yield benzaldehyde-*h* (**6**) (Scheme 7).

A solution of aldoxime ether **10** and CA in MeCN was irradiated, and the reaction mixture was analyzed by GC-MS. Because **6** and **6-*d*** are eluted simultaneously, the data were analyzed in terms of relative abundance of specific ions observed in the mass spectrum. To interpret the results, a number of standard solutions containing varying amounts of **6** and **6-*d*** were prepared and analyzed, and the ion abundances of the ions of interest were determined. The relative abundance data obtained from the reaction mixture was then compared to the data obtained from the standard solutions (Table 5). It can be seen

TABLE 4. Calculated (B3LYP/6-31G*) Charge Densities on Hydrogen Atoms in Aldoxime Ethers 3 and 4. Both Mulliken and Natural Population Charges Are Listed



	3		**4**	
atom	Mulliken	natural	Mulliken	natural
H1	0.215519	0.249024	0.214745	0.248742
H2	0.194302	0.263480	0.196442	0.264305
H3	0.202221	0.273752	0.204431	0.275015
H4	0.200590	0.273299	0.210363	0.269727
H5	0.208103	0.268694	0.202140	0.274127
H6	0.206895	0.273467	0.205603	0.272287
H7	0.206577	0.255450	0.181026	0.255813
H8	0.206554	0.255404	0.181024	0.255811
H9	0.151936	0.243995	0.190785	0.265622
H10	0.168279	0.255332	0.192886	0.268011
H11	0.169945	0.256348	0.178111	0.253194
H12	0.168207	0.255342	0.179496	0.254203
H13	0.151884	0.243926	0.179506	0.254208
H14	-	-	0.192890	0.268009
H15	-	-	0.178102	0.253186

that the data from the reaction mixture most closely resembles that of the standard solution containing only **6**, suggesting that under these conditions, **6-*d*** is not formed. This, in turn, implicates that the intramolecular HAT pathway is negligible. The formation of benzonitrile from aldoxime ethers most likely proceeds via an imidoyl radical, which is formed via a direct hydrogen atom abstraction process by ^{3}CA. It must be reiterated that loss of an iminyl proton from the radical cation would give

SCHEME 7

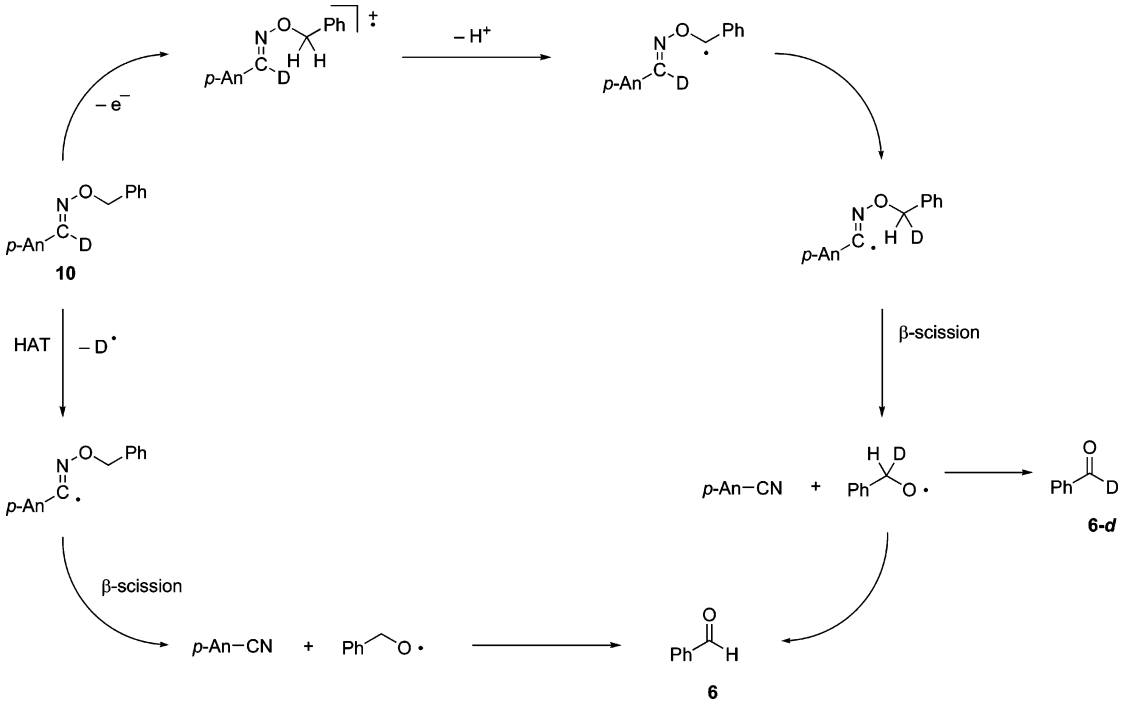
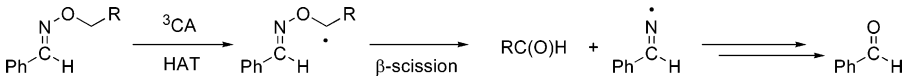


TABLE 5. Results from Experiments with Deuterated Aldoxime Ether 10

	mass				ratios	
%D	105	106	107	108	105:106	105:107
0	249.2	265.7	20.4	1.0	0.9	12.2
20	41.9	33.2	13.7	1.0	1.3	3.1
33	32.3	22.4	13.0	1.0	1.4	2.5
50	25.6	15.1	12.6	1.0	1.7	2.0
66	33.3	23.6	13.7	1.0	1.4	2.4
80	39.0	30.6	14.3	1.0	1.3	2.7
100	11.9	1.2	12.4	1.0	9.8	1.0
reaction 1	318.6	342.1	25.4	1.0	0.9	12.5
reaction 2	328.1	357.4	27.2	1.0	0.9	12.1

[a] The mass spectra of solutions with varying amounts of benzaldehyde (**6**) and benzaldehyde-*d* (**6-*d***) were analyzed. Masses 105 and 106 occur predominantly in **6** whereas masses 107 and 108 are associated with **6-*d***. All data is relative to mass 108. For simplicity, the data was also analyzed in terms of the ratios 105:106 and 105:107. The data from the irradiated sample (listed at the Bottom) was compared to that of the stock solutions. The reaction was carried out twice.

SCHEME 8



a similar result; however, based on our earlier discussion, we do not favor that particular pathway.

Finally, it must be noted that a HAT pathway could also explain the formation of the aldehyde. Reaction of ^{3}CA at the α-C−H position with aldoxime ether **1**, **2**, or **3** would produce the α-radical species, which can undergo a *β*-scission to eventually yield benzaldehyde (Scheme 8).

An argument in favor of this mechanism would be the observation that the major pathway for most aldoxime ethers under these conditions is *syn*−*anti* isomerization, which suggests that energy transfer rather than SET is dominant. On the other hand, two arguments can be made against this mechanism. The first argument would be the observation of the spectra of the aldoxime ether radical cations suggesting an initial SET step. The second argument would involve bond dissociation energies (BDE). The major product in each case (provided α-hydrogens are available) is the aldehyde. On the basis of available BDE values, this is not an expected outcome. Previously we have suggested that the BDE for the iminyl C−H bond is approximately the same as the C−H bond in benzaldehyde (88 kcal mol^{-1}).[9e] Bordwell has suggested a BDE of 94.9 kcal mol^{-1} for the α-C−H bond in benzamidoxime *O*-methyl ether.[14a] On the basis of these numbers, we would expect hydrogen abstraction from the iminyl carbon to be the dominant pathway and the major product should be the nitrile. However, it must be pointed out that the accuracy of Bordwell's methods for determining BDE values has recently been disputed,[19] and the actual number may be different.[20] On the basis of the results obtained so far, we currently favor the SET mechanism for the

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formation of the aldehyde product and the HAT pathway for the formation of the nitrile. However, we continue to explore the β-scission pathways of these and other reactive intermediates.

Conclusions

Chloranil-sensitized photooxidation of aldoxime ethers in acetonitrile results in the formation of aldoxime ether radical cations (and chloranil radical anion). Follow-up reactions may involve deprotonation at the α-position, yielding a radical species that undergoes β-scission. The major product under these conditions is benzaldehyde (**6**), but a small amount of benzonitrile (**7**) is also formed. In the absence of α-hydrogens (i.e., aldoxime ether **4**), the major product is benzonitrile (**7**), which is produced via a different pathway. Although SET is favorable, it does not lead to products. Instead, the triplet sensitizer abstracts the iminyl hydrogen to yield an imidoyl radical, which undergoes a β-scission to yield a nitrile. A similar pathway is most likely responsible for the formation of benzonitrile from aldoxime ethers that do have α-hydrogens; however, for those substrates it is only a minor pathway. A third pathway that was observed involves energy transfer, which leads to *syn*−*anti* isomerization. This pathway is observed when the free energy for electron transfer (ΔG_{ET}) becomes endothermic but usually competes with ET (as seen by the presence of both isomerization and oxidation products). In nucleophilic solvents such as methanol, the major photooxidation product is benzaldehyde. No nitrile is observed, which is explained by a mechanistic scheme involving nucleophilic attack on the nitrogen of the aldoxime ether radical cation, followed by proton-transfer and elimination as was observed for a series of acetophenone oxime ethers.

Experimental Section

Materials. All chemicals other than the aldoxime ethers were commercially available. The aldoxime ethers were prepared from benzaldehyde and commercially available *O*-alkylhydroxylamine hydrochloride salts (see below). Acetonitrile and methanol (spectrophotometric grade) were used as received.

Synthesis of *O*-Alkyl Benzaldehyde Oximes. All benzaldehyde oxime ethers were prepared according to literature procedures with minor modifications.[21] The aldoxime ethers were chromatographed on silica gel and were analyzed for purity by gas chromatography with flame ionization detection (GC-FID; >99% peak area); their identity was verified by mass spectrometry and ^{1}H NMR.

***O*-Methyl Benzaldehyde Oxime (1)**. To a mixture containing methoxylamine hydrochloride (1.01 g, 12 mmol) and benzaldehyde (1.01 g, 10 mmol) in 50 mL of 95% ethanol was added several drops of concentrated hydrochloric acid after which it was refluxed for 2−6 h. Evaporation of the solvent under reduced pressure produced an oily yellow residue. Purification by column chromatography (hexane−ether gradient) gave a colorless oil (0.91 g, 71%). ^{1}H NMR ($CDCl_3$): δ 8.06 (1 H, s), 7.57 (2 H, m), 7.36 (3 H, m), 3.97 (3 H, s).

***O*-Ethyl Benzaldehyde Oxime (2)**. Prepared according to the method described above using *O*-ethylhydroxyl amine hydrochloride (2.02 g, 21 mmol) and benzaldehyde (2.00 g, 19 mmol). Yield: 1.60 g, 57% (colorless oil). ^{1}H NMR ($CDCl_3$): δ 8.07 (1 H, s), 7.58 (2 H, m), 7.35 (3 H, m), 4.24 (2 H, q, J = 7.1 Hz), 1.34 (3 H, t, J = 7.1 Hz).

***O*-Benzyl Benzaldehyde Oxime (3)**. Prepared according to the method described above using *O*-benzylhydroxylamine hydrochloride (2.22 g, 14 mmol) and benzaldehyde (2.21 g, 21 mmol). Yield: 1.11 g, 58% (colorless oil). ^{1}H NMR ($CDCl_3$): δ 8.15 (1 H, s), 7.59−7.25 (10 H, m), 5.20 (2 H, s).

***O*-*tert*-Butyl Benzaldehyde Oxime (4)**. Prepared according to the method described above using *O*-*tert*-butylhydroxylamine hydrochloride (1.01 g, 9 mmol) and benzaldehyde (1.01 g, 9 mmol). Yield: 1.58 g, 91% (colorless oil). ^{1}H NMR ($CDCl_3$): δ 8.04 (1 H, s), 7.61−7.55 (2 H, m), 7.36−7.31 (3 H, m), 1.36 (9H, s).

***O*-Benzyl 4-Methoxybenzaldehyde-α-*d* Oxime (10)**. Prepared according to the method described above using *O*-benzylhydroxylamine hydrochloride (1.00 g, 14 mmol) and 4-methoxybenzaldehyde-α-*d* (0.51 g, 21 mmol). Yield: 0.45 g, 50% (white powder), mp = 42−44 °C. ^{1}H NMR ($CDCl_3$): δ 7.56 (2 H, d, J = 8.8 Hz), 7.47−7.32 (5 H, m), 6.92 (2 H, d, J = 8.8 Hz), 5.22 (2 H, s), 3.85 (3 H, s).

Steady-State Photolysis Experiments. Appropriate amounts of the *O*-alkyl benzaldehyde oxime (0.015 M) and chloranil (0.015 M) were weighed out and dissolved in 5 mL of solvent. For experiments where oxygen was to be excluded, and the solution was purged with argon for 15 min prior to photolysis. The solution was placed in a Pyrex tube and irradiated in a Rayonet RPR-100 photochemical reactor, equipped with 16 RPR-3500A (black light phosphor) bulbs (λ = 350 nm) for 2 h. The progress of the reactions was followed by GC-FID, and the products were identified by GC-MS. Conversion of the starting material and product yields were determined by calibrated GC-FID. The products were confirmed by comparison with authentic (commercially available) samples.

Electrochemistry. The oxidation potentials of the aldoxime ethers were determined by cyclic voltammetry at a scan rate of 100 mV/s in MeCN with tetraethyl ammonium perchlorate (0.1 M) as the electrolyte using a Ag/AgCl reference electrode. The reported potentials were referenced to SCE by adding 0.29 V to the measured values. All measurements were carried out under an argon atmosphere.

Laser Flash Photolysis. The apparatus used for the laser flash photolysis (LFP) experiments was of standard design,[22] and the details have been described elsewhere.[23] The quenching rates were obtained as follows. An MeCN (spectrophotometric grade) solution containing chloranil (CA; OD ~ 0.5−1) in a glass cuvette was purged with argon for about 5 min. The sample was subjected to the laser pulse (355 nm, 10 Hz, 0.5−2 mJ/pulse; 4 ns pulse width), and the decay of ^{3}CA at 510 nm was observed. Small amounts (10−25 uL) of the quencher (~0.015 M aldoxime ether standard solutions in MeCN) were added to the solution after which the decay was measured. The quenching rate was obtained from a plot of the measured decay rates against the quencher concentration. A similar methodology was used to obtain the rates for the reaction of MeOH with the aldoxime ether radical cations. A solution containing the aldoxime ether (10 mM) and chloranil (OD ~ 0.5−1) was subjected to the laser pulse, and the decay of the radical cation at 650 nm was observed. Small amounts (25−100 μL) of MeOH were added to the solution after which the decay was measured. The quenching

(20) Recent experiments in our laboratory suggest that the iminyl C−H bond is indeed weaker than the α-C−H bond. Chlorination of *O*-alkyl benzaldehyde oximes with *N*-chlorosuccinimide proceeds selectively and results in the formation of the corresponding *N*-alkoxy iminoyl chlorides; no chlorination at the α-carbon is observed.

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rate was obtained from a plot of the measured decay rates against the MeOH concentration.

Spectra were obtained by flash photolysis (355 nm, 10 Hz, 0.5−2 mJ/pulse; 4 ns pulse width) of argon-saturated solutions (3 mL) in a glass cuvette containing the aldoxime (10 mM) and chloranil (OD ∼ 0.5−1).

Computational Methods. Semiempirical (AM1)[24] and DFT (B3LYP)[25] calculations were performed with Spartan 2004,[26] installed on a PowerMac G4. For the DFT calculations, the 6-31G* basis set[27] implemented within the program was used.

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Supporting Information Available: Total energies and Cartesian coordinates for the optimized structures of the radical cations of compounds **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0703707

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