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Photosensitized Reactions of Oxime Ethers: A Steady-State and Laser Flash Photolysis Study

H. J. Peter de Lijser* and Chao-Kuan Tsai

Department of Chemistry and Biochemistry, California State University at Fullerton,
Fullerton, California 92834-6866.

pdelijser@fullerton.edu

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The mechanistic aspects of the photosensitized reactions of a series of oxime ethers were studied by steady-state (product studies) and laser flash photolysis methods. Nanosecond laser flash photolysis studies have shown that chloranil-sensitized reactions of the oxime ethers result in the formation of the corresponding radical cations. The radical cation species react with nucleophiles such as MeOH by clean second-order kinetics with rate constants of $(0.7-1.4) \times 10^6$ M^{-1} s^{-1}. Only a small steric effect is observed in these reactions, which is taken as an indication that the reaction center is not the *O*-alkyl moiety, but rather somewhere else in the molecule. Product studies in a polar nonnucleophilic solvent (MeCN) revealed that in order for the oxime ether radical cation to react more readily, α-protons must be available on the alkyl group. The *O*-methyl (**1**), *O*-ethyl (**2**), and *O*-benzyl (**3**) acetophenone oximes all reacted readily to give acetophenone oxime as the major product (as well as an aldehyde derived from the *O*-alkyl group), whereas *O*-*tert*-butyl acetophenone oxime (**4**) did not. The product formation can be explained by a mechanism that involves electron transfer followed by proton transfer (α to the oxygen) and subsequent β-cleavage. When using **3** in MeOH, a change in the product formation is observed, the most important difference being the presence of benzyl alcohol rather than benzaldehyde as the major product. On the basis of the data from LFP and steady-state experiments, it is suggested that the competing mechanism under these conditions involves electron transfer, followed by a nucleophilic attack on the nitrogen, a MeOH-assisted [1,3]-proton transfer, and subsequent loss of benzyl alcohol. This mechanism is supported by DFT (B3LYP/6-31G*) and AM1 calculations.

Introduction

Oximes and their derivatives have found widespread use in synthetic organic chemistry as protecting groups for carbonyl compounds.[1] In addition to their synthetic utility, many oximes are commonly used as pesticides[2] (including the structurally related carbamates) and drugs[3] (e.g., as antidotes for organophosphorus poisoning). As a result, oximes are obvious substrates for enzymatic or photochemical (sensitized or direct) oxidations. The expected intermediates in these reactions are excited-state oximes (singlet or triplet), oxime radical cations, or reactive species (radicals) derived from these such as iminoxyl radicals.

The photochemical reactions of oximes have received considerable attention.[4] A number of pathways are available to oximes in the excited state. Singlet excited-state oximes may rearrange to form oxaziridines. Direct photolysis may also result in the formation of amides (via a photo-Beckmann rearrangement) or carbonyl compounds. Photolysis of cyclic ketoximes also proceeds through oxaziridine intermediates; in this case the product formation was found to be solvent dependent. For example, photolysis of cyclohexanone oxime in MeOH gave ϵ-ca-

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* To whom correspondence should be addressed. Phone: (714) 278-3290. Fax: (714) 278-5316

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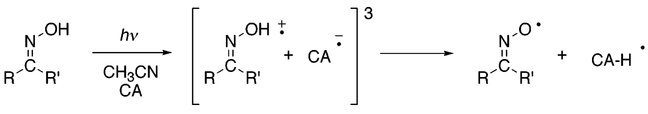
SCHEME 1



prolactam whereas in 2-propanol solution the caproamide was the major product.[4c] Haley and Yates investigated the photochemical deprotection of oximes to aldehydes and ketones.[4i,j] Both aromatic aldoximes and ketoximes undergo photohydrolysis via their lowest singlet state; however, the quantum yields for these processes were generally low ($\Phi = 0.01-0.15$) and certain substituents (e.g., nitro) prevented the photohydrolysis from taking place. Evidence was presented for the formation of an oxaziridine intermediate in these and other photolysis reactions. Some syn−anti isomerization was also observed, which is thought to occur from the lowest triplet excited state.

The available literature on the photochemistry of oxime ethers suggest that syn−anti isomerization is the major process.[5] Early work by Padwa and co-workers showed that triplet sensitization results in syn−anti isomerization although direct photolysis may give the same results via a singlet excited state.[5a−d] The isomerization process is affected by the environment[5e] (solvent and the presence of added species such as surfactants or salts) and the concentration of the oxime ethers (exciplexes and excimers have both been indicated as important species).[5d,f]

Recently, we reported that oximes react rapidly when irradiated in the presence of an appropriate (triplet) photosensitizer such as chloranil.[6] This is in stark contrast with direct photolysis reactions, which, in general, are much slower.[4] The proposed mechanism involves electron transfer (ET), followed by (in-cage) proton transfer to form an iminoxyl radical and the chloranil semiquinone radical ($CA\text{-}H^\bullet$). Spectroscopic information supports this proposed step (Scheme 1).[6b]

Iminoxyl radicals are also known to be important intermediates in chemical,[7] as well as biological,[8] oxidation processes of oximes. Contrary to these results, Shine and co-workers studied the reactions of several aldoximes with thianthrene perchlorate radical cation salt and proposed an oxaziridine radical cation intermediate to explain the formation of oxadiazoles.[9]

Much less is known about the ET reactions of oxime ethers. Kawamura and co-workers have reported that *O*-methylbenzophenone oxime derivatives undergo syn−anti isomerization in the presence of oxygen when using 9,10-dicyanoanthracene (DCA) as the sensitizer.[10] ET is favorable in these reactions and the DCA radical anion reacts with triplet oxygen to form ground-state DCA and superoxide. The isomerization process is explained on the basis of an *N*-methoxymethanimine radical cation−superoxide complex that reacts to give an intermediate 1,4-biradical, which isomerizes and then releases oxygen. Armesto and co-workers have studied the aza-di-π-methane (ADPM) rearrangements via radical cation intermediates using imines, oximes, and oxime ethers as substrates.[11] The DCA-sensitized reactions of oximes typically result in the formation of dihydroisoxazoles as well as the expected product from the ADPM rearrangement. Under similar conditions, oxime ethers react slower than the corresponding oximes and give either ADPM products in low yield or a complex mixture of products. The failure of oxime ethers to give isoxazole products seems consistent with the fact that no acidic protons are available (similar to those in the oxime radical cation); however, the proposed mechanism does not address this issue.

An important step in the photooxidation of oximes is the in-cage deprotonation of the oxime radical cation by the sensitizer radical anion.[6] To test the importance of the deprotonation step we have replaced the proton in the oximes with different alkyl groups and studied their behavior upon irradiation in the presence of chloranil as the photosensitizer. The results of these studies and the mechanistic implications are discussed.

Results and Discussion

A. Laser Flash Photolysis Studies of Oxime Ethers in the Presence of Chloranil.

The oxime ethers used in these photochemical studies are shown in Figure 1.

Previously we have shown that oximes quench the triplet state of chloranil (^3CA) with rates close to the diffusion-controlled limit.[6b] Similar results are obtained when using oxime ethers **1**−**4** as the quenchers (k_q; Table 1). This is consistent with the measured peak potentials for oxidation (E_p), which, when using the Weller equa-

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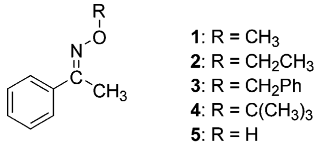

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FIGURE 1. Oxime ethers used in the chloranil-sensitized reactions.

TABLE 1. Summary of Kinetic Data Obtained from Nanosecond Laser Flash Photolysis Experiments of Oxime Ethers 1–4 and Acetophenone Oxime (5)

oxime ether	E_p (V)[a]	ΔG_{ET} (kcal mol^{-1})[b]	k_q (M^{-1} s^{-1})	k_{MeOH} (M^{-1} s^{-1})
1	2.12	−0.7	3.1×10^9	1.4×10^6
2	2.08	−1.6	4.3×10^9	1.2×10^6
3	2.10	−1.2	5.3×10^9	7.2×10^5
4	2.03	−2.8	3.8×10^9	7.5×10^5
5	1.65	−11.5	9.5×10^9	na

[a] Oxidation potentials measured by cyclic voltammetry (0.1 M tetraethylammonium perchlorate in CH_3CN, Ag/AgCl electrode). [b] Calculated with 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).

tion,[12] suggest that ET is favorable. For comparison, the peak potential and quenching rate for acetophenone oxime (**5**) are also included.

All oxime ethers rapidly quench ^{3}CA, which is expected when considering the measured (irreversible) peak potentials for oxidation. Compared to acetophenone oxime (**5**), the reactions are somewhat slower (by a factor of 2–3), which is most likely due to the higher peak potentials of the oxime ethers. On the basis of these quenching rates we propose that irradiation of mixtures of chloranil and the oxime ethers in MeCN results in an ET pathway generating the oxime ether radical cation and the chloranil radical anion.

These results are supported by the spectra obtained from laser excitation (355 nm) of a solution containing CA and oxime ether **1**. The spectrum (Figure 2) shows absorption bands around 400 and 650 nm, which decay slowly ($\tau = 500$ ns). 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 oxime ethers **2**–**4**.

The difference between these spectra and those obtained for oxime radical cations is significant; no signal for the oxime radical cation can be observed (Figure 3; dashed line), which is a result of the increased acidity of the oxime radical cation.

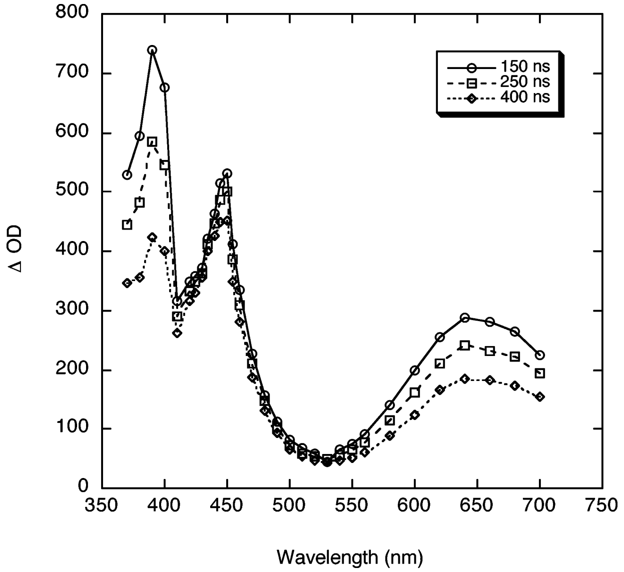

FIGURE 2. Spectra obtained from CA-sensitized laser photolysis (355 nm) of oxime ether **1** in MeCN taken 150, 250, and 400 ns after the laser pulse.

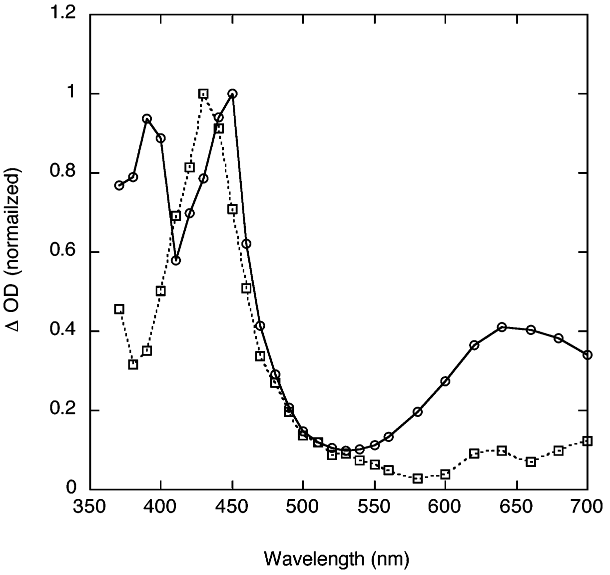

FIGURE 3. Comparison of the spectra obtained from CA-sensitized laser photolysis (355 nm) of oxime ether **1** (○) and oxime **5** (□) in MeCN, taken 400 ns after the laser pulse.

These results are in agreement with a study by Rhodes,[14] who used EPR to show that one-electron oxidation of benzophenone oxime results in the formation of the corresponding iminoxyl radical. Bordwell has calculated the acidities (pK_a) of oxime radical cations.[15] The pK_a of the acetophenone oxime radical cation was calculated to be −13,[15a] suggesting that the deprotonation step using the CA radical anion as the base will be extremely rapid. As a result, the two species expected to be present under these conditions are the iminoxyl radical and the semiquinone radical. From Figure 3 it can be seen that the maximum of the band absorbing between 425 and 525 nm appears either at 445 nm or at 435 nm depending on whether an oxime ether or an oxime is used. This difference in λ_{max} is most likely due

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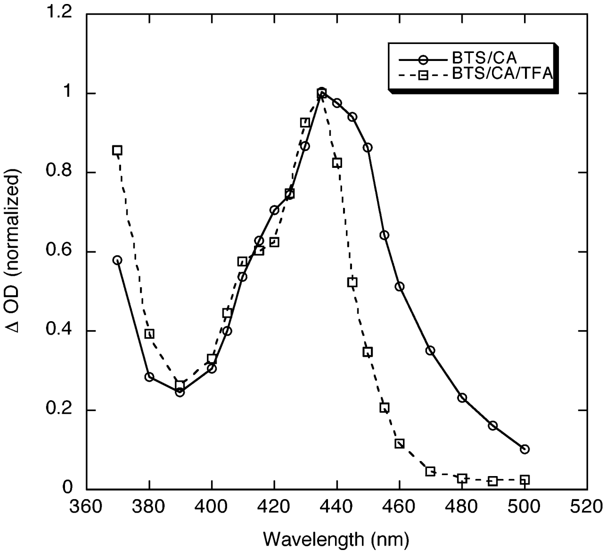

FIGURE 4. Comparison of the spectra of the chloranil radical anion (○) and the semiquinone radical (□), generated by excitation of chloranil in the presence of benzyltrimethylsilane with or without trifluoroacetic acid in MeCN.

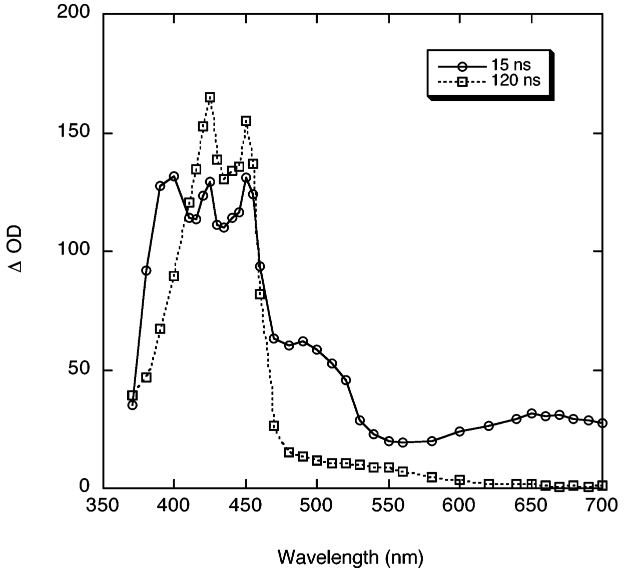

FIGURE 5. Spectra obtained from laser photolysis (355 nm) of chloranil and oxime ether **1** in MeOH, 20 ns (○) and 120 ns (□) after the laser pulse.

to the different chemistry of these compounds; the species present under these conditions are the chloranil radical anion ($\lambda_{\max} = 445$ nm; observed when using an oxime ether) or the semiquinone radical ($\lambda_{\max} = 435$ nm; observed when using an oxime). These results are in agreement with the previously reported spectra.[13]

Further attempts to prove the presence of the chloranil radical anion and/or the semiquinone radical were inconclusive. To obtain a spectrum of the CA radical anion, a solution containing chloranil and benzyltrimethylsilane in MeCN was subjected to the laser pulse. Benzyltrimethylsilane radical cation is expected to react with the solvent and cleave, rather than losing a proton.[16]

The spectrum obtained is shown in Figure 4 (solid line). In the presence of trifluoroacetic acid (TFA), the CA radical anion is no longer expected to exist and only the semiquinone radical should be present. The dashed line in Figure 4 represents the spectrum of the species present after addition of TFA to the solution. It is clear that the spectrum changes upon the addition of TFA; however, the overlap of the two bands is almost complete and distinguishing between these two species under the conditions of the experiment is challenging.

Despite the many indications that ET is the preferred pathway, it cannot be completely ruled out that instead of an ET pathway the reaction proceeds via a hydrogen atom abstraction pathway.[17] To obtain further evidence for the formation of the oxime ether radical cation under these conditions, the addition of variable concentrations of the electron donor (tris-*p*-anisylamine; TAA) was studied. Monitoring the spectrum upon addition of TAA revealed a decay of the signal at 710 nm as a function of the concentration of added TAA and the appearance of a new signal at 680 nm. The latter signal is assigned to the TAA radical cation, consistent with literature data.[18] The slope of the plot of the rate constant for the growth of the signal at 680 nm against the TAA concentration gave a bimolecular rate constant of 2.3×10^{10} $M^{-1}s^{-1}$. These experiments confirm that under the conditions of the reactions, ET occurs and the bands appearing between 370−410 and 550−750 nm in the spectrum shown in Figure 2 are assigned to the oxime ether radical cation. Also consistent with these observations is the fact that the lifetimes of the oxime ether radical cation species can be prolonged significantly in trifluoroethanol.[19] The species now have lifetimes on the order of microseconds compared to nanoseconds in MeCN.

As expected, the spectra change dramatically when a nucleophilic solvent (MeOH) is used. The spectrum obtained from laser photolysis of a MeOH solution containing **1** and CA is shown in Figure 5. At very short times, a short-lived residual (~29 ns) can be seen between 550 and 750 nm. Similar spectra are obtained for oxime ethers **2**, **3**, and **4**. These results suggest that the oxime ether radical cation is formed and that MeOH is nucleophilic enough to react with the radical cations.

The main features of the spectrum are the two bands at 425 and 450 nm, similar to that reported by Tsubomura and co-workers.[20] The fact that both bands form at the same time (and decay at the same rate) indicates that they belong to one and the same rather than two separate species. This species is long-lived; the spectrum does not show any significant changes when comparing the one taken 50 ns after the pulse to that taken 5 μs after the pulse. To determine which species was formed under these conditions, both the CA radical anion and the semiquinone radical signals were generated as before (using benzyltrimethylsilane with and without TFA).

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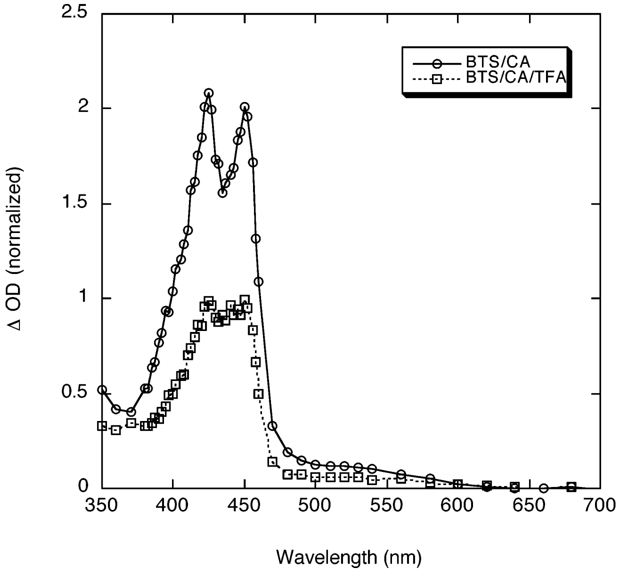
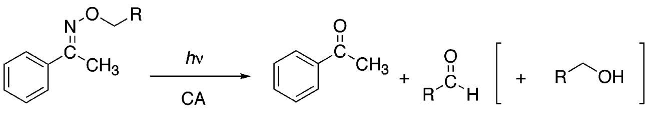


FIGURE 6. Spectrum of a species generated from chloranil in MeOH after ET from benzyltrimethylsilane with (○) and without (□) trifluoroacetic acid present; the spectra were recorded 2.5 μs after the laser pulse.

From Figure 6 it can be seen that the two spectra are similar although the intensity of the bands changes upon addition of TFA. The spectra show very little difference over a time frame of microseconds, suggesting that the observed signal is that of the semiquinone radical. Most likely, MeOH rather than TFA acts as a proton donor and as a result, the same (semiquinone radical) species is observed under both conditions.

The reactions of the oxime 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. Using these rate constants, we can calculate the lifetimes of the oxime ether radical cations in MeOH to be 29 ($\mathbf{1}^{\bullet+}$), 34 ($\mathbf{2}^{\bullet+}$), 56 ($\mathbf{3}^{\bullet+}$), and 54 ns ($\mathbf{4}^{\bullet+}$), consistent with the spectral data (Figure 5). On the basis of these results we conclude that steric effects are relatively unimportant in these reactions; the difference between $\mathbf{1}^{\bullet+}$ and $\mathbf{3}^{\bullet+}$ is only a factor of 2. Relatively small steric effects are not unusual in radical ion reactions.[21] For example, the reaction of *tert*-butyl alcohol with the phenylcyclopropane radical cation is slower by a factor of 2.2 compared to the reaction with MeOH.[21c] Similarly, the 9-fluorenyltrimethylsilane radical cation reacted faster with MeOH than with *tert*-butyl alcohol by only a factor of 3.5.[21e] However, it is interesting to note that the reactions of a series of benzyltrialkyl silane radical cations with MeOH resulted in significantly different rate constants.[21d] For example, the benzyltrimethylsilane radical cation reacts with MeOH with a rate constant of 2.9×10^9 M^{-1} s^{-1} in dichloromethane, whereas under identical conditions benzyltriisopropylsilane radical cation reacts with a rate constant of 8.9×10^5 M^{-1} s^{-1}. The large difference (>3000) was attributed to the fact that nucleophilic attack would have to occur on the silane and therefore is largely affected by steric effects. If this explanation is also applicable to the reactions of oxime ether radical cations, this observation suggests that nucleophilic attack is not occurring on the aliphatic carbon but rather somewhere else in the molecule.

SCHEME 2



1 - 3

6

TABLE 2. Summary of the Results from the Photosensitized Reactions of Oxime Ethers 1−4

			product yields[b]			
oxime ether	solvent	% C[a]	**6**	**7**	**8**	others[c]
1	MeCN	<10	100			
	MeOH	38	76			24
2	MeCN	<10	100			
	MeOH	56	91			9
3	MeCN	21	67	95		33
	MeOH	52	96	<1	92	12
4	MeCN	12				100
	MeOH	<10	70			30

[a] Conversion was calculated on the basis of the GC-FID peak area of the oxime before and after photolysis. [b] Product yields determined by calibrated GC/FID. [c] Products other than those listed depend on the solvent and the oxime ether used; see text for details.

The results of these LFP studies show that upon laser photolysis of a mixture containing CA and an oxime ether, ET occurs resulting in the formation of the oxime ether radical cation. In the presence of a nucleophilic solvent, the radical ions are short-lived due to follow-up reactions.

B. Steady-State Photolysis of Oxime Ethers in the Presence of Chloranil. In general, irradiations were carried out for 1 h on argon-purged (15 min) solutions (5 mL) containing the oxime ether (0.015 M) and chloranil (CA; 0.015 M) in Pyrex tubes, using a Rayonet photochemical reactor equipped with 16 RPR-3500 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 product(s) formed in these reactions depends on the structure of the alkyl group (Scheme 2); however, in general the reactions proceed cleanly although some secondary products were detected by GC-FID or GC-MS. Longer irradiation (for up to 4 h) resulted in the formation of the same major products as well as a number of minor products. No conversion of the starting material is observed when a solution of the oxime ether without any CA present is irradiated. Both syn and anti isomers of the oxime ethers can be detected and quantified by GC/FID.

The results of the steady-state photolysis experiments of oxime ethers **1**−**4** are summarized in Table 2. Irradiation of an argon-purged MeCN solution containing chloranil and *O*-methylacetophenone oxime (**1**) resulted in

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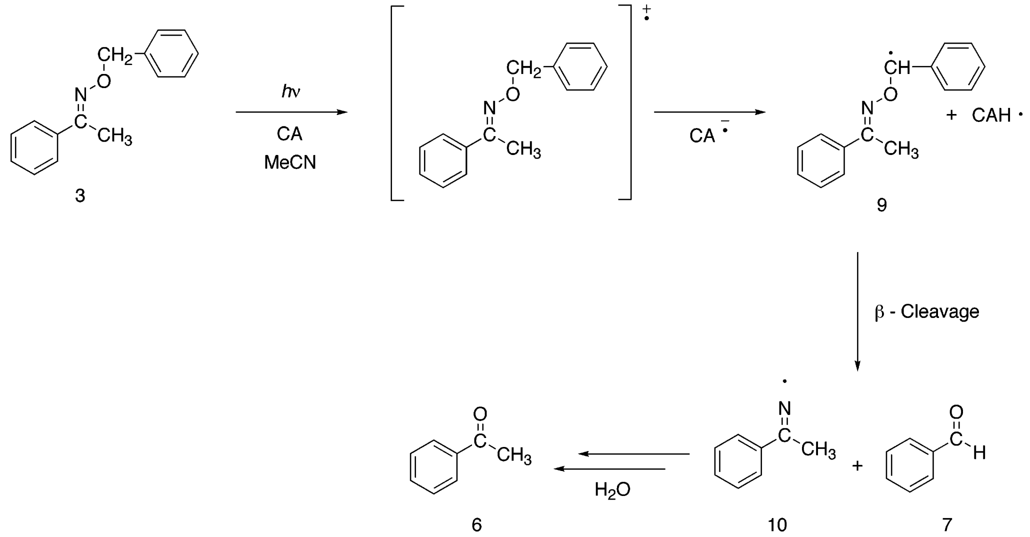
[21] (a) Dinnocenzo, J. P.; Todd, W. P.; Simpson, T. R.; Gould, I. R. *J. Am. Chem. Soc.* **1990**, *112*, 2462. (b) Dinnocenzo, J. P.; Lieberman, D. R.; Simpson, T. R. *J. Am. Chem. Soc.* **1993**, *115*, 366. (c) Dinnocenzo, J. P.; Simpson, T. R.; Zuilhof, H.; Todd, W. P.; Heinrich, T. *J. Am. Chem. Soc.* **1997**, *119*, 987. (d) Dockery, K. P.; Dinnocenzo, J. P.; Farid, S.; Goodman, J. L.; Gould, I. R.; Todd, W. P. *J. Am. Chem. Soc.* **1997**, *119*, 1876. (e) de Lijser, H. J. P.; Snelgrove, D. W.; Dinnocenzo, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 9698.

SCHEME 3



the formation of acetophenone (**6**) as the only product in low yield. The conversion of **1** and yield of **6** increase upon prolonged irradiation; however, it also results in the formation of an unknown with a mass of 163. Attempts to isolate this product by column chromatography were unsuccessful.

Irradiation of **1** and CA in MeOH for 1 h results in the formation of acetophenone (**6**) only and complete conversion of the starting material was achieved within 4 h. The faster reaction in MeOH is most likely due to the nucleophilic nature of this medium, consistent with the observations from the LFP experiments. Some syn−anti isomerization is observed at early reaction times; however, unlike other reports,[5,10] it never is a dominant reaction. In addition to the major product (**6**), small amounts of acetophenone dimethylacetal and 1-methoxy-1-phenylethylene were also present. Separate experiments have shown that these products are a result of the reaction of acetophenone with MeOH (in the presence of light and chloranil).

Similar results were obtained for the irradiation of *O*-ethylacetophenone oxime (Table 2). At short irradiation times, acetophenone is the only product observed; however, a small amount of an unknown compound was also formed upon longer irradiation. The mass spectrum was similar to that of the unknown obtained from the irradiation of **1** but its mass was 14 units higher (177), suggesting that the alkyl group that is originally present in the oxime ether is retained in the unknown product. Once again, attempts to isolate the product were unsuccessful. In MeOH, similar conversions are observed and the major product is acetophenone. Small amounts of the follow-up products were also present.

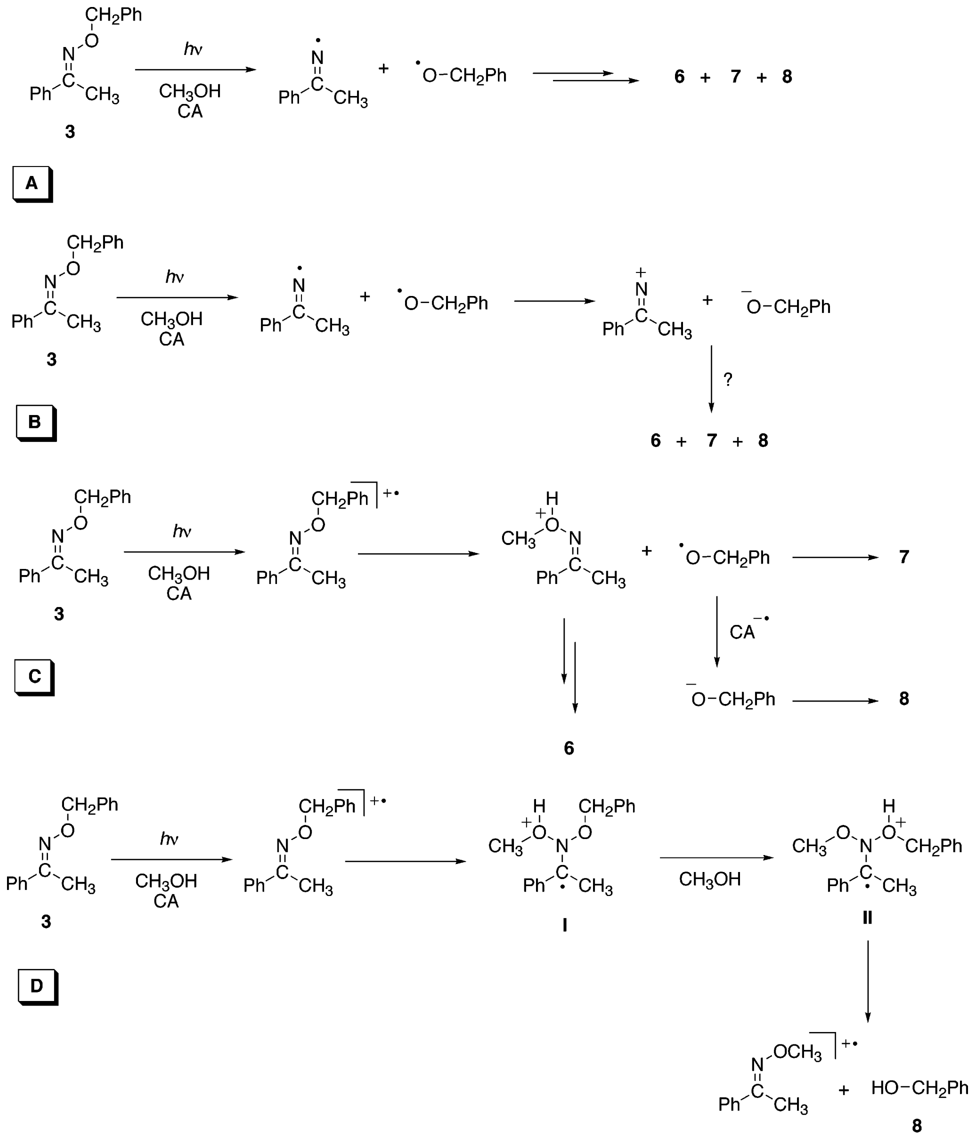
The CA-sensitized photolysis of *O*-benzylacetophenone oxime (**3**) in MeCN results in the formation of acetophenone (**6**) and benzaldehyde (**7**) as the major products (Table 2). In addition to these two products, a trace amount of acetophenone oxime was also detected. The same reaction in MeOH yields acetophenone (**6**) and benzyl alcohol (**8**) as the major products, and benzaldehyde (**7**) was formed in trace amounts only. Other products present in small amounts are benzaldehyde dimethylacetal and acetophenone dimethylacetal. These two products are a result of follow-up reactions of benzaldehyde and acetophenone, respectively.

The irradiation of *O-tert*-butylacetophenone oxime (**4**) gave completely different results (Table 2). After 1 h of irradiation some conversion is observed when using MeCN; however, acetophenone is not formed under these conditions. After prolonged irradiation, larger conversions of the starting material are observed, but the product mixture contains only a trace of acetophenone. The mixture turns dark suggesting that reactive species (radicals) are formed that can undergo polymerization. Some conversion is observed when using MeOH, with acetophenone (**6**) being the major product. Small amounts of acetophenone dimethylacetal were also present.

Although the data from the LFP experiments suggest that ET is the expected pathway, two additional steady-state experiments were carried out to confirm this. First, a solution containing oxime ether **3**, DCA (9,10-dicyanoanthracene), and biphenyl in MeCN was irradiated for 1 h in the Rayonet. Under these conditions acetophenone (**6**) and benzaldehyde (**7**) were the major products and some syn−anti isomerization of the starting material was observed as well. A similar experiment with benzophenone (BP) as the photosensitizer results in syn−anti isomerization only. Isomerization of oxime ethers upon triplet sensitization is a well-known phenomenon and is a result of energy transfer.[5] If ET becomes endothermic and unfavorable, the energy transfer pathway can be followed provided the triplet energy of the oxime ether is low enough for triplet−triplet energy transfer to take place. The free energies for ET (ΔG_{ET}) are calculated to be +2 (DCA) and +20 kcal/mol (BP). On the basis of these results we conclude that products **6** and **7** are the result of a photoinduced electron-transfer (PET) reaction. Some syn−anti isomerization is also observed when using DCA because the value for ΔG_{ET} is somewhat endothermic making energy transfer more competitive with ET.[10]

C. Mechanistic Interpretation of the Steady-State and Laser Flash Photolysis Data. Careful analysis of the data from the steady-state photolysis experiments of the oxime ethers **1**−**4** reveals two important observations. First, a sluggish reaction is observed when using a

SCHEME 4



substrate that does not have α-protons on the alkyl chain. Second, benzyl alcohol (**8**) is only observed when using **3** in MeOH, possibly suggesting a change in mechanism. For an explanation we will focus on the results obtained from oxime ethers **3** and **4**. Oxime ethers **1** and **2** in principle show the same behavior as **3**.

The observed reactions of oxime radical cations are in large part due to their acidic (hydroxylic) proton and the presence of a base within the solvent cage.[6] Oxime ether radical cations tend to react slower; however, the LFP experiments (as well as some of the steady-state experiments) have shown that the first step is a one-electron oxidation to generate the oxime ether radical cation. Combining this piece of information with the observation that the absence of α-protons on the alkyl chain results in a sluggish reaction suggests that a key step in the mechanism is ET followed by proton transfer. These two initial steps can be used to explain the behavior of oxime ethers **1**−**4** in MeCN. The proposed mechanism that is consistent with these observations is shown in Scheme 3 for oxime ether **3**. The initial ET and proton-transfer steps result in the formation of a radical species (**9**), which undergoes a β-cleavage to yield benzaldehyde (**7**) and an iminyl radical (**10**). The iminyl radical is expected to undergo hydrolysis to yield acetophenone (**6**). An identical mechanism is expected to operate for oxime ethers **1** and **2**; however, due to volatility issues, the products from these reactions (formaldehyde and acetaldehyde) cannot be observed.

This mechanism could also explain the product formation observed in MeOH, provided benzyl alcohol (**8**) were the result of a photoreduction of benzaldehyde. However, reacting benzaldehyde with ^{3}CA in MeOH yields benzaldehyde dimethylacetal instead of benzyl alcohol, ruling out the mechanism described above for the reactions in MeOH.

A priori, several pathways can be used to explain the product formation in MeOH, including bond homolysis (Scheme 4A),[22,23] bond homolysis followed by ET (Scheme 4B), nucleophile-induced mesolytic cleavage (Scheme 4C), and nucleophilic addition followed by a [1,3]-proton transfer and elimination (Scheme 4D).

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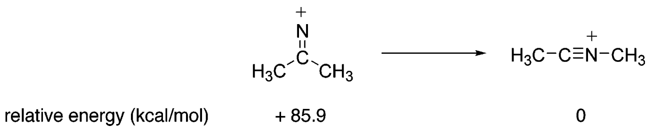
(22) Badr, M. Z. A.; Aly, M. M.; Mahgoub, S. A.; Fahmy, A. M.; Atallah, A. A. *Bull Chem. Soc. Jpn.* **1988**, *61*, 1779.

(23) Luo, Y.-R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: Boca Raton, FL, 2003.

SCHEME 5



Both pathways A and B involve the formation of the benzyloxy radical as an intermediate in the formation of **8**. To determine whether the benzyloxy radical is an intermediate in these reactions, experiments were conducted with CD_3OD and CH_3OD. If the benzyloxy radical is an intermediate in these reactions, reaction with the former should give benzyl alcohol-O-*d*, whereas a reaction with the latter should give benzyl alcohol-O-*h*. Both reactions resulted in the formation of benzyl alcohol-O-*d*, suggesting that the precursor for benzyl alcohol is not the benzyloxy radical, ruling out pathway A.

An alternative mechanism, similar to that proposed by Pincock and co-workers for the photochemical reactions of arylmethyl esters, would be homolytic bond cleavage followed by ET (pathway B).[24] This pathway is consistent with the observation of deuterium incorporation into product **8**; however, the ET step would result in the formation of an extremely reactive iminium ion, which is energetically unfavorable and is expected to undergo very rapid rearrangements. For example, the difference in energy between the two cations shown in Scheme 5 is 85.9 kcal/mol in favor of the nitrilium ion, and the iminium ion was found to rearrange spontaneously to the nitrilium ion.[25]

The best argument against pathways A and B is the fact that the results from the LFP studies on **1** and CA in MeOH (Figure 5) suggest the presence of the semiquinone radical, which is most likely a product from the reaction of the CA radical anion with MeOH. Furthermore, at early times the band of the oxime ether radical cation (550−750 nm) can be seen. Identical spectra are obtained when using any of the other oxime ethers. Thus, to explain the formation of **8**, we must take into account the fact that the reaction starts by an ET pathway, ruling out pathways A and B.

Pathways C and D both involve ET as the first step. In pathway C, the initial oxime ether radical cation is attacked by the nucleophile (MeOH) at the nitrogen resulting in N−O bond cleavage. In addition to the benzyloxy radical, this reaction also results in the formation of oxime ether **1** (after deprotonation). The fact that it is not observed under the conditions of the reaction suggests that it is consumed very rapidly via an ET pathway (consistent with LFP data which show that $\mathbf{1}^{\bullet+}$ reacts rapidly with MeOH). To explain the incorporation of deuterium in product **8**, a reduction step must be involved. One possible mechanism is the reduction of the benzyloxy radical via return ET from the CA radical anion. The LFP data show that the only species observed under the conditions used is the semiquinone radical. We have not been able to detect the CA radical anion in MeOH, suggesting a lifetime of 15 ns or less for this species. Furthermore, the return ET step is expected to be unfavorable energetically due to the very low oxidation potential (−0.02 V) of the CA radical anion. To the best of our knowledge, the reduction potential of the benzyloxy radical has not been determined; however, it seems reasonable to assume a value between −0.1 and −0.4 V for this process.[26] As a result, the free energy for this particular reaction could be endothermic by as much as 10 kcal mol^{-1}.

Pathway D is the most consistent with all the experimental observations. ET results in the formation of the oxime ether radical cation, which reacts with the nucleophile. Instead of a substitution, we propose an addition reaction (intermediate **I**), followed by a [1,3]-proton transfer to form intermediate **II**, which reacts to give benzyl alcohol and $\mathbf{1}^{\bullet+}$. The radical cation is much more reactive than the neutral species (as proposed in pathway C); the lifetime of $\mathbf{1}^{\bullet+}$ in MeOH is approximately 29 ns, and as a result it is not expected to form **1** as a product. This is consistent with the fact that **1** is not detected in this reaction.

The [1,3]-proton transfer step is not expected to occur as such, because it would require a four-membered transition state, which is energetically unfavorable. More likely, this step is assisted by a nucleophile (MeOH), which is known to accelerate these types of reactions.[27] For example, the 1,3-proton shift between the tautomers in a protonated peptide in the gas phase has a barrier of approximately 39.6 kcal/mol, whereas in the presence of MeOH, the barrier is lowered to only 22.0 kcal/mol.[27i] Although the overall mechanism requires two molecules of MeOH, the kinetic (LFP) data clearly show that the reaction of the oxime ether radical cations with MeOH proceeds via clean second-order kinetics. This observation suggests that addition of the nucleophile to the oxime ether is the rate-determining step. The [1,3]-proton-transfer step is expected to be fast.

The faster reaction of oxime ethers $\mathbf{1}^{\bullet+}$− $\mathbf{3}^{\bullet+}$ in MeOH can have two potential reasons. First, MeOH can act as a base and assist in the deprotonation of the oxime ether radical cation species. Second, MeOH can act as a nucleophile in the addition−elimination reaction. Earlier we have observed that oxime radical cations react slower in polar protic solvents such as MeOH.[6a] For oxime radical cations, the deprotonation step is very important, but it seems to be retarded due to interaction of the solvent with the chloranil radical anion, suggesting that MeOH is not a good enough base for the deprotonation step. Furthermore, if MeOH is involved in the deprotonation of $\mathbf{3}^{\bullet+}$, one would expect significant amounts of

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[24] For an overview of this work see: Pincock, J. A. *Acc. Chem. Res.* **1997**, *30*, 43.

[25] de Lijser, H. J. P.; Arnold, D. R. *J. Phys. Chem. A* **1998**, *102*, 5592.

[26] These numbers are proposed on the basis of the following data: the reduction potential of the *tert*-butoxy radical is −0.23 V (vs SCE),[26a] whereas that of the cumyloxy radical is −0.12 V.[26b] (a) Workentin, M. S.; Maran, F.; Wayner, D. D. M. *J. Am. Chem. Soc.* **1995**, *117*, 2120. (b) Antonello, S.; Musemeci, M.; Wayner, D. D. M.; Maran, F. *J. Am. Chem. Soc.* **1997**, *119*, 9541.

[27] (a) Grunwald, E.; Meiboom, S. *J. Am. Chem. Soc.* **1963**, *85*, 2047. (b) Roitman, J. N.; Cram, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 2225, 2231. (c) Menger, F. M.; Grossman, J.; Liotta, D. C. *J. Org. Chem.* **1983**, *48*, 905. (d) Lee, I.; Kim, C. K.; Seo, H. S. *Bull. Korean Chem. Soc.* **1986**, *7*, 395. (e) Soloshonok, V. A.; Ono, T. *Synlett* **1996**, 919. (f) Aune, M.; Gogoll, A.; Matsson, O. *J. Org. Chem.* **1995**, *60*, 1356. (g) Kukhar, V. P.; Soloshonok, V. A.; Galushko, S. V.; Rozhenko, A. B. *Dokl. Akad. Nauk SSSR* **1990**, *310*, 886; *Chem. Abstr.* **1990**, *113*, 78920w. (h) Hussénius, A.; Mattson, O.; Bergson, G. *Chem. Commun.* **1998**, 2693. (i) Rodriquez, C. F.; Cunje, A.; Shoeib, T.; Chu, I. K.; Hopkinson, A. C.; Siu, K. W. M. *J. Phys. Chem. A* **2000**, *104*, 5023. (j) Hjelmencrantz, A.; Berg, U. *J. Org. Chem.* **2002**, *67*, 3585.

TABLE 3. Calculated (B3LYP/6-31G*) Energies, Bond Lengths, and Charge and Spin Densities of Oxime Ethers 1−4 and Their Radical Cations

	1			**2**			**3**			**4**		
	neutral	ion	Δ	neutral	ion	Δ	neutral	ion	Δ	neutral	ion	Δ
E_{rel}[a]	0	172.8		0	171.0		0	168.1		0	168.8	
charge density												
C═	0.228	0.296	0.068	0.227	0.297	0.070	0.229	0.298	0.069	0.227	0.302	0.075
═N	−0.156	−0.041	0.115	−0.152	−0.039	0.113	−0.156	−0.047	0.109	−0.158	−0.044	0.114
−O−	−0.414	−0.251	0.163	−0.425	−0.255	0.170	−0.417	−0.249	0.168	−0.428	−0.253	0.175
−C	−0.303	−0.320	−0.017	−0.096	−0.112	−0.016	−0.105	−0.117	−0.012	0.286	0.277	−0.009
spin density												
C═		0.025			0.036			0.047			0.061	
═N		0.278			0.268			0.250			0.248	
−O−		0.266			0.277			0.285			0.295	
−C		−0.010			−0.010			−0.009			−0.009	
bond length[b]												
C═N	1.290	1.343	0.053	1.290	1.344	0.054	1.290	1.343	0.053	1.290	1.346	0.056
N−O	1.395	1.325	−0.070	1.394	1.322	−0.072	1.396	1.322	−0.074	1.390	1.315	−0.075
O−C	1.423	1.456	0.033	1.432	1.477	0.045	1.438	1.496	0.058	1.459	1.525	0.066

[a] Relative energies in kcal mol^{-1}; [b] Bond lengths in Å.

benzaldehyde (or the dimethyl acetal), yet only small amounts are actually formed. As a result, we conclude that under these conditions the predominant reaction involves nucleophilic attack by the solvent on the oxime ether radical cation.

A similar explanation is not valid for compound **4**. Although acetophenone is formed as the major product in MeOH (which is not the case in MeCN), the conversion is much smaller compared to that of compounds **1**−**3** under similar conditions. Most likely this is due to steric hindrance, preventing the nucleophile from attacking the substrate. To learn more about the proposed mechanism involving nucleophilic attack on the nitrogen, as well as the steric effects involved in these reactions, we have further examined these species by theoretical computations, the results of which are described below.

D. Quantum Chemical Calculations. The unusual observations for the experiments in MeOH prompted us to investigate the starting reactants and the intermediates by means of theoretical computations, including molecular mechanics (MMFF),[28] semiempirical (AM1),[29] and the density functional hybrid method B3LYP using the 6-31G* basis set.[30] The relative energies for the global minima of the neutral oxime ethers and the radical cation species as well as selected spin and charge densities are listed in Table 3.

The calculated ionization potentials are in agreement with the observed quenching rates listed in Table 1. The bond lengths in oxime ethers **1**−**4** upon ionization are similar in all cases; the C═N and O−C bonds lengthen whereas the N−O bond shortens. The O−C bond lengthening is somewhat dependent on the steric bulk of the alkyl group; the largest change is observed for the *O-tert*-butyl derivative (**4**).

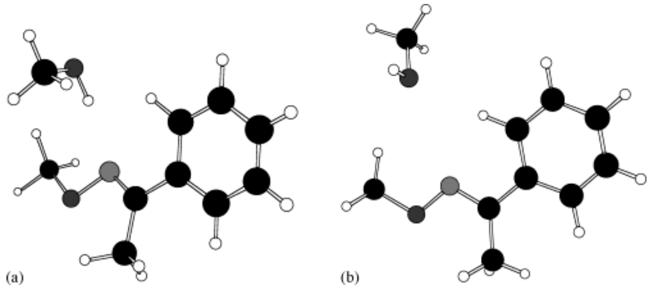

FIGURE 7. (a) Optimized (B3LYP/6-31G*) geometry of neutral *O*-methylacetophenone oxime (**1**) in the presence of a MeOH molecule; the hydrogen bond (1.998 Å) is clearly visible. (b) Optimized (B3LYP/6-31G*) geometry of *O*-methylacetophenone oxime radical cation in the presence of a MeOH molecule. The orientation of the MeOH molecule is now such that the nucleophilic oxygen is directed toward the electrophilic nitrogen.

To explain the proposed behavior in MeOH (nucleophilic attack on nitrogen), the calculated charge densities are useful parameters. However, the calculated charge densities for **4**$^{\bullet+}$ suggest that nucleophilic attack will occur on the α-carbon rather than the nitrogen. Similarly, for species **1**−**3** the largest charge density is located on the carbon of the iminyl group and not on the nitrogen. Obviously, these parameters are not correct in explaining the observed reactivity, and therefore we have opted to look at the change (Δ) in charge density upon ionization. From Table 3 it can be seen that in all cases the largest change in charge density occurs on the nitrogen and oxygen atoms of the oxime moiety. This is consistent with the proposed mechanism in which the nucleophile attacks the nitrogen (attack on oxygen by the nucleophile would be highly unlikely).

Further evidence for the proposed mechanism (pathway D) comes from the optimization (B3LYP/6-31G*) of the structure of oxime ether **1** in the presence of a MeOH molecule. When using the neutral oxime ether, the hydroxylic proton of MeOH is oriented in such a way that a hydrogen bond (1.994 Å) is formed with the nitrogen of the oxime ether (Figure 7a). The O−H−N angle is 170.5°, which is close to the optimum value of 180°. Optimization of the ionized oxime ether (**1**$^{\bullet+}$) in the presence of a MeOH molecule leads to a conformation in which the nucleophilic oxygen from MeOH is directed toward the nitrogen of the oxime moiety (Figure 7b). The

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(28) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490.

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(30) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.

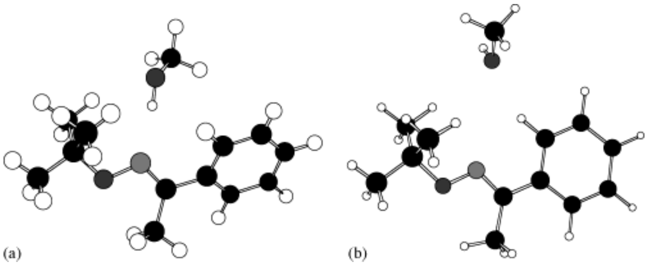
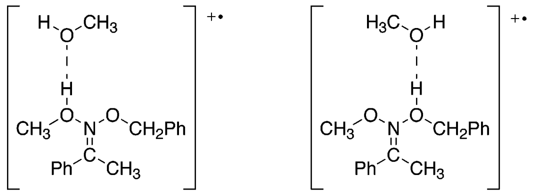


FIGURE 8. (a) Optimized (B3LYP/6-31G*) geometry of neutral *O-tert*-butylacetophenone oxime (**4**) in the presence of a MeOH molecule; the deviation in the O−H−N angle of the hydrogen bond (1.998 Å) is clearly visible. (b) Optimized (B3LYP/6-31G*) geometry of *O-tert*-butylacetophenone oxime radical cation in the presence of a MeOH molecule. The orientation of the MeOH molecule is now such that the nucleophilic oxygen is directed toward the electrophilic nitrogen; however, steric hindrance (three protons) prohibits the nucleophile from attacking the nitrogen as easily as in less sterically hindered substrates.

SCHEME 6



I-A **II-A**

distance between the oxygen and the nitrogen is 3.324 Å.

Calculations on the neutral *tert*-butyl derivative show similar features (Figure 8). In the neutral molecule, a hydrogen bond is formed between the hydroxylic proton of the MeOH and the nitrogen of the oxime (Figure 8a). The distance between the hydroxylic proton and the nitrogen nucleus is 2.007 Å, slightly longer than the 1.994 Å observed for [**1** + MeOH]. The O−H−N angle is 168.2°, which is similar to that calculated for [**1** + MeOH]. In the ionized species, the MeOH molecule is oriented such that the oxygen atom is directed toward the center of the positive charge (Figure 8b). The distance between the oxygen of the MeOH and the nitrogen of the oxime is 3.805 Å, significantly longer than that observed in [$\mathbf{1}^{\bullet+}$ + MeOH]. In addition, the oxygen of the MeOH is "surrounded" by three protons in the oxime: one from each of the two methyl groups that are pointed toward the nucleophile and the ortho proton of the aromatic ring. This conformational (steric) limitation is likely to have an effect on the reactivity. This is consistent with the experimentally observed behavior of these molecules.

To test the viability of the [1,3]-proton-transfer step as proposed in pathway D of Scheme 4, both intermediates (**I** and **II**) were analyzed by means of molecular mechanics (MMFF) calculations. Several low-energy conformers were identified for both intermediates. The difference in energy between the lowest energy conformers of **I** and **II** is approximately 10 kcal/mol in favor of **II**.

As discussed earlier, it is well established that [1,3]-proton transfers typically must be assisted by nucleophilic solvents such as water or MeOH.[27] To determine the effect of a second molecule of MeOH on the proton-transfer reaction, complex **I-A** (Scheme 6) was optimized by using AM1.

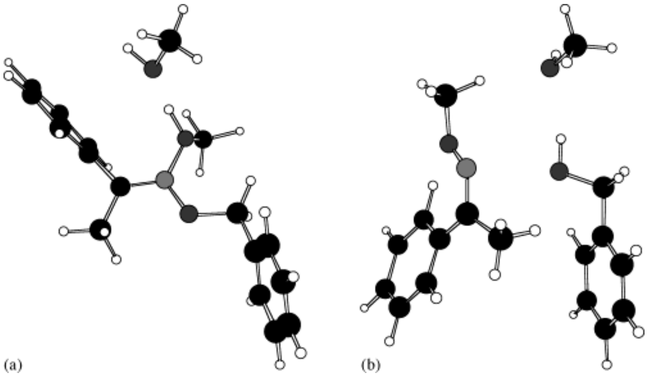


FIGURE 9. Geometries of the conformations of complex **I-A** (a) before optimization and (b) after (AM1) optimization.

The final result of this optimization, shown in Figure 9, clearly illustrates the fact that this particular proton-transfer step is now favorable. The products from this reaction are benzyl alcohol, MeOH, and $\mathbf{3}^{\bullet+}$. As expected, there is a residual interaction between the hydroxyl proton of the benzyl alcohol and the oxygen of the MeOH. Similar results were obtained when using complex **II-A** as the starting point, or when using different starting conformations of **I-A**. These results provide solid support for the proposed ET−nucleophilic addition−[1,3]-proton transfer−elimination pathway in the one-electron oxidation reactions of oxime ethers in nucleophilic solvents.

One of the original goals of this research was to provide more support for the deprotonation step proposed for the reactions of oxime radical cations. The results discussed above show that (i) oxime ether radical cations react slower than the corresponding oxime radical cations and (ii) oxime ether radical cations without α-hydrogens react significantly slower than those that have α-hydrogens on the alkyl chain. Both observations are in accord with the deprotonation mechanism of oxime radical cations. The fact that under these conditions oxime ethers react slower than the corresponding oximes is most likely due to a decreased acidity. Although no pK_a values are available for oxime ether radical cations, calculations show that the charge density on the α-protons is significantly smaller than that of the hydroxylic proton in an oxime radical cation, which is in agreement with the proposed mechanism.

Further studies (experimental and theoretical) on the scope and limitations of these reactions, pathways, and the reactive intermediates involved are currently underway.

Conclusions

Chloranil-sensitized reactions of oxime ethers result in the formation of the oxime ether radical cation and the chloranil radical anion. Follow-up reactions depend on the structure of the oxime ether as well as the medium. The presence of α-protons on the alkyl chain is necessary for products to form cleanly. In the absence of α-protons, the reactions become sluggish and lead to a number of products, many of which are likely due to free radical side reactions. In nonnucleophilic solvents the major products are proposed to be the result of an α-deprotonation followed by a β-cleavage to yield an iminyl radical that reacts further to give the observed acetophenone. In nucleophilic solvents such as MeOH, nucleophilic attack on the oxime radical cation competes with the deprotonation step and gives a different product mixture. Nucleophilic attack involves (most likely) an addition to nitrogen followed by a nucleophile (MeOH)-assisted [1,3]-proton transfer and elimination of an alcohol. Quantum mechanical calculations support this conclusion. The reactions of oxime ethers are slower than those of the corresponding oximes, which is due to the fact that the oxime ether radical cations are less acidic than oxime radical cations.

Experimental Section

General Techniques. ^{1}H NMR spectra were recorded on a 90-MHz FT spectrometer. Chemical shifts are reported in ppm and are relative to tetramethylsilane (TMS). Gas chromatography (with flame ionization or mass selective detection) was carried out as described before.[6] The oxidation potentials of the oximes were determined by cyclic volatammetry at a scan rate of 100 mV/s. The reported potentials were referenced to the Fc$^+$/Fc couple. All measurements were carried out under an argon atmosphere.

Materials. All chemicals other than the oxime ethers were commercially available. The oxime ethers were prepared from reaction of acetophenone (MC&B, 99%) with the commercially available *O*-alkylhydroxylamine hydrochloride salts (see below). Acetonitrile (Fisher) and methanol (Aldrich) were of HPLC purity and were used as received. Methyl-d_3 alcohol-d_1 (99.8+ atom % D) and methyl alcohol-d_1 (99.5+ % D) were purchased from Aldrich.

Synthesis of *O*-Alkyl Acetophenone Oximes. All acetophenone oximes were prepared according to literature procedures with some slight modifications.[31] The purity was checked by gas chromatography with flame ionization detection (GC-FID; >99% peak area), gas chromatography with mass spectrometry (GC-MS), ^{1}H NMR, and FT-IR.

***O*-Methylacetophenone Oxime (1).** To a mixture containing methoxylamine hydrochloride (Aldrich, 98%; 2.78 g, 33.3 mmol) and acetophenone (2.01 g, 16.7 mmol) in 50 mL of 95% ethanol was added several drops of concentrated hydrochloric acid after which the solution was refluxed for 24 h. Evaporation of the solvent under reduced pressure produced an oily yellow residue. Purification by column chromatography (hexanes−ether gradient) gave a colorless oil (1.94 g, 78%). ^{1}H NMR (CDCl$_3$) δ 7.75−7.10 (m, 5 H), 3.98 (s, 3 H), 2.20 (s, 3 H).[31b]

***O*-Ethylacetophenone Oxime (2). 2** was prepared according to the method described above with *O*-ethylhydroxylamine hydrochloride (Aldrich, 97%; 3.25 g, 33.3 mmol) and acetophenone (2.00 g, 16.6 mmol). Yield: 2.03 g, 75% (colorless oil). ^{1}H NMR (CDCl$_3$) δ 7.89−7.10 (m, 5 H), 4.24 (q, 2 H), 2.21 (s, 3 H), 1.31 (t, 3 H).[31c]

***O*-Benzylacetophenone Oxime (3). 3** was prepared according to the method described above with *O*-benzylhydroxylamine hydrochloride (Aldrich, 99%; 2.65 g, 16.6. mmol) and acetophenone (1.02 g, 8.5 mmol). Yield: 1.31 g, 68% (colorless oil). ^{1}H NMR (CDCl$_3$) δ 7.75−6.95 (m, 10 H), 5.23 (s, 2 H), 2.20 (s, 3 H).[31d]

***O*-*tert*-Butylacetophenone Oxime (4). 4** was prepared according to the method described above with *O*-*tert*-butylhydroxylamine hydrochloride (Aldrich, 99%; 1.00 g, 8 mmol) and acetophenone (0.48 g, 4 mmol). Yield: 0.64 g, 84% (colorless oil). ^{1}H NMR (CDCl$_3$) δ 7.75−7.15 (m, 5 H), 2.19 (s, 3H), 1.36 (s, 9H).[31e]

Steady-State Photolysis Experiments. Appropriate amounts of the *O*-alkyl acetophenone 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, 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 up to 4 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 after 1 h of irradiation.

Laser Flash Photolysis. The apparatus used for the laser flash photolysis (LFP) experiments was of standard design,[32] and the details have been described elsewhere.[33] 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 oxime 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 oxime radical cations. A solution containing the oxime 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 uL) of MeOH 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 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 oxime (10 mM) and chloranil (OD ∼ 0.5−1).

Computational Methods. Molecular mechanics (MMFF), semiempirical (AM1), and DFT **(**B3LYP) calculations were performed with Spartan 2002,[34] installed on a PowerMac G4. For the DFT calculations, the 6-31G* basis set[35] implemented within the program was used. The lowest energy conformers were obtained from an MMFF conformer distribution search.

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