Photochemistry and Photobiology, 2006, 82: 110–118

# Quinone-sensitized Steady-state Photolysis of Acetophenone Oximes Under Aerobic Conditions: Kinetics and Product Studies†

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**Received 23 April 2005; accepted 18 July 2005; published online 22 July 2005 DOI: 10.1562/2005-04-23-RA-496**

## ABSTRACT

**Oxidation of oximes via photosensitized electron transfer (PET) results in the formation of the corresponding ketones as the major product via oxime radical cations and iminoxyl radicals. The influence of electron-releasing and electron-accepting substituents on these reactions was studied. The observed substituent effect strongly supports formation of iminoxyl radicals from the oximes via an electron transfer–proton transfer sequence rather than direct hydrogen atom abstraction. Correlation of the relative conversion of the oximes with Hammett parameters shows that radical effects dominate for the *meta*-substituted acetophenone oximes ($\rho_{rad}/\rho_{pol} = 5.4$; $r^2 = 0.93$), whereas the *para*-substituted oximes are influenced almost equally by radical and ionic effects ($\rho_{rad}/\rho_{pol} = -1.1$; $r^2 = 0.98$). From these data sets we conclude that the follow-up reactions proceed through a number of intermediates with both radical and ionic character. This was confirmed by product studies with the use of an isotopically labeled nucleophile. In addition to the major oxidation product (ketone), a chlorine-containing product was often identified as well. Studies on the formation of this product show that the most likely pathway is either via a direct nucleophilic addition in a complex formed between the oxime radical cation and the chloranil radical anion or via a radical substitution ($S_H2$) mechanism. These studies show that with the increasing use of oximes as drugs and pesticides, intake of these chemicals followed by enzymatic oxidation may result in the formation of a variety of reactive intermediates, which may lead to cell and tissue damage.**

## INTRODUCTION

The use of oximes and related compounds in pesticides (1,2) and drugs (3–6) has increased in recent years, leading to a larger availability in the environment (7) and an increased risk of uptake by organisms. Detoxification of such xenobiotics typically involves oxidative pathways (8), which, in the case of oximes, can result in the formation of reactive oxygen species (ROS) such as iminoxyl radicals (9–16). Little is known about these reactive intermediates. Oxime radical cations and iminoxyl radicals are the proposed intermediates in the nitric oxide synthase (NOS) catalyzed metabolism of l-arginine to l-citrulline (17,18). Iminoxyl radicals have also been proposed as intermediates in the formation of nitric oxide from oximes (19,20). It was shown that the *in vivo* metabolism of cyclohexanone oxime (an intermediate in the synthesis of Nylon-6) in rats resulted in excessive nitric oxide (NO) formation, which may be responsible for the toxicity of this compound (21). A number of alkyl- and aryloximes have been shown to act as nitric oxide donors under oxidative conditions; in fact, some are commercially available and were reported to produce significant vasorelaxation in isolated dog coronary arteries and the rat aorta (22–24). However, cyclohexanone oxime and structurally related oximes were shown to be animal carcinogens (25,26). Clearly, a good understanding of the structure-reactivity relationships in different types of oximes as well as the actual intermediates involved would be very beneficial.

We recently reported on our initial photochemical studies involving a series of *ortho*-, *meta*-, and *para*-substituted acetophenone oximes (27). With the use of laser flash photolysis (LFP) it was shown that substituents have a significant effect on the initial electron transfer step. Triplet chloranil ($^3$CA) is rapidly quenched by the oxime ($4 \times 10^7 - 2 \times 10^{10} M^{-1} s^{-1}$). Correlation of the quenching rate constants with Hammett substituent coefficients suggested that steric, polar and radical effects are important for *ortho*-substituted acetophenone oximes, polar effects are important for *para*-substituted oximes, and radical stabilization is more important than polar effects for the *meta*-substituted substrates. Although these results seem consistent with an electron transfer–proton transfer sequence, it cannot be ruled out that the formation of the iminoxyl radicals proceeds via a hydrogen atom transfer (HAT) process (Fig. 1).

Free-radical processes are known to be sensitive to both radical and polar effects (28,29), which could explain the observations. One argument against a HAT process is the fact that the calculated bond dissociation energies in substituted acetophenone oximes were reported to be relatively independent of the substituent (30,31). Consequently, one would expect little effect on the HAT

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† This paper is part of a special issue dedicated to Professor J. C. (Tito) Scaiano on the occasion of his 60th birthday.

*Abbreviations:* BA, bromanil; CA, chloranil; CP, chlorinated product; DFT, density functional theory; ET-PT, electron transfer–proton transfer; FA, fluoranil; HAT, hydrogen atom transfer; IP, ionization potential; LFP, laser flash photolysis; NOS, nitric oxide synthase; PET, photosensitized electron transfer; ROS, reactive oxygen species; SS, steady-state; TCHQ, 2,3,5,6-tetrachlorohydroquinone.

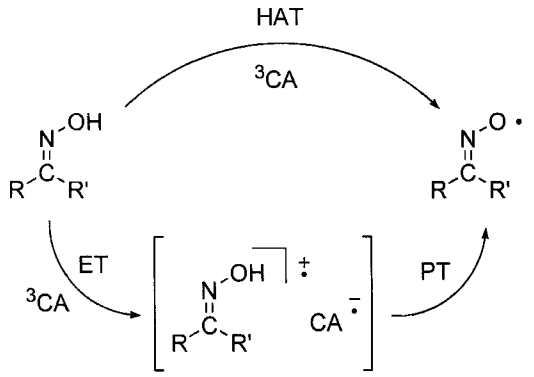


**Figure 1.** Possible steps for the formation of iminoxyl radicals from oximes via hydrogen atom transfer (HAT) and electron transfer–proton transfer (ET-PT) sequences.

process by the substituent. The measured rates for quenching of triplet chloranil by the substituted acetophenone oximes showed a dramatic effect, suggesting a different process. However, the methodology that was used recently for obtaining the O–H bond strengths in substituted oximes was called into question. It was shown that as a result of these measurements significant deviations of certain bond strengths were obtained (32).

It is important to note that the LFP data only reflect the initial electron transfer step and do not take into account any follow-up reactions. A number of pathways can be proposed involving a variety of intermediates, both radicals and cations (Fig. 2). Depending on the structure of the intermediate(s), the effect of the substituents on the overall reaction is likely to be different from those on the first (electron transfer) step.

To address these issues we have undertaken a more extensive study involving the steady-state (SS) photolysis of *meta*- and *para*-substituted acetophenone oximes. The photochemical experiments were complemented by electrochemical data as well as density functional theory (DFT) calculations on the neutral compounds and the radical cation species.

## MATERIALS AND METHODS

*Materials.* All substituted acetophenone oximes were synthesized from their respective ketones, which were commercially available. Acetophenone oxime (98%), 3-methylacetophenone (98%), 3-(trifluoromethyl)acetophenone (98+%), 4-methylacetophenone (96%), 4-(trifluoromethyl)acetophenone (98+%), 3-chloroacetophenone (98+%), 4-chloroacetophenone (97%), 3-fluoroacetophenone (98%) and 4-fluoroacetophenone (98%) were obtained from Lancaster Synthesis, Inc. (Windham, NH). Acetophenone was obtained from Matheson, Coleman, and Bell (Norwood, OH). Benzophenone (98%), benzil (98%), anthracene (99%), *p*-chloranil (98+%), hydroxylamine hydrochloride (98%), 3-nitroacetophenone (99%), 4-nitroacetophenone (98%), 3-methoxyacetophenone (97%), 4-methoxyacetophenone (99%), 3-cyanoacetophenone (97%) and 4-cyanoacetophenone (99%), and 2,3,5,6-tetrabromohydroquinone (98%) were obtained from Sigma-Aldrich (Milwaukee, WI). *p*-Bromanil (98%) and 2,3,5,6-tetrachlorohydroquinone (98%) were obtained from TCI America (Portland, OR). *p*-Fluoranil (97%) was obtained from Acros (Fairlawn, NJ) and tetraethylammonium perchlorate was purchased from Eastman Kodak (Kingsport, TN). All solvents were HPLC grade and used as such. Anhydrous acetonitrile and water-$^{18}$O, normalized, 95 atom% $^{18}$O were obtained from Sigma-Aldrich.

*Synthesis of substituted acetophenone oximes.* All oximes were prepared according to standard literature procedures (33). In general, hydroxylamine hydrochloride (15 mmol) was dissolved in 5 mL of water and 3 mL of 3 *M* sodium hydroxide solution, and the appropriate ketone (7.5 mmol) was added. To this mixture was added approximately 20–25 mL of 95% ethanol to create a clear solution, which was refluxed for 1 h. The solvent was removed via rotary evaporation, and the resulting product collected and dried by vacuum filtration. The crude product was dissolved in ether and extracted with water (~25 mL). The organic layer was dried over magnesium sulfate and the solvent was removed via rotary evaporation. The residue was further purified by recrystallization or column chromatography. The synthesized compounds were characterized by $^1$H-NMR spectroscopy, infrared (IR) spectroscopy and melting point.

*Instrumentation.* The gas chromatography analyses were performed on a Perkin-Elmer (Boston, MA) Autosystem equipped with a flame ionization detector (FID) and on a Hewlett-Packard (Agilent, Palo Alto, CA) 5890 series II coupled to a Hewlett-Packard mass selective detector (MSD) 5917 series. The Perkin-Elmer GC/FID was equipped with a Chrompack CP-Si-5-Cb capillary column (30 m × 0.32 mm i.d., film thickness 0.25 μm). The Hewlett-Packard GC/MS was equipped with an HP-5 capillary column (30 m × 0.25 mm i.d.; film thickness: 0.25 μm).

*Photochemical reactors.* The irradiations were carried out in a Rayonet RPR-100 photochemical reactor equipped with 16 RPR-3500A (black-phosphor) bulbs (Southern New England Ultraviolet Company, Branford, CT). The output wavelength range of these bulbs is between 300 and 400 nm, with the maximum output (~90%) at 350 nm.

*Oxidation potentials.* All electrochemical experiments were performed on a Bioanalytical Systems (BAS, West Lafayette, IN) C3 Electrochemistry Cell Stand with the use of a CV-50 Voltammetric Analyzer. Oxidation potentials were recorded with the use of a platinum working electrode, a platinum wire counter/auxiliary electrode, and a Ag/AgCl reference electrode. Tetraethyl ammonium perchlorate (0.1*M*) served as an electrolyte salt in acetonitrile. The redox potential of the electrolyte solution was recorded first, followed by that of the oxime (~5 mmol). The scan rate was 100 mV/s. The system was calibrated by recording the oxidation potential of ferrocene.

*Steady-state photolysis experiments and sample analysis.* Appropriate amounts of the *meta*- or *para*-substituted oxime (0.015*M*), acetophenone oxime (0.015*M*), and chloranil (CA, 0.005*M*) were weighed out and dissolved in 5 mL acetonitrile. The solution was placed in a Pyrex tube (8 mL volume, cutoff wavelength = 300 nm) and photolyzed in the Rayonet reactor for 60 min. The solutions were analyzed by GC/MS and GC/FID and showed the corresponding ketones as the major products. Other (minor) products, tentatively identified as (1-chloroethyl)arenes, were observed as well. Quantification of the products was accomplished by calibrated GC/FID with the use of authentic materials; the relative conversions over time were used as a measure of the rates of the reactions.

## RESULTS AND DISCUSSION

### Oxidation potentials of *meta*- and *para*-substituted acetophenone oximes

The measured peak potentials for the *meta*- and *para*-substituted acetophenone oximes are listed in Table 1. The oxidative scans are

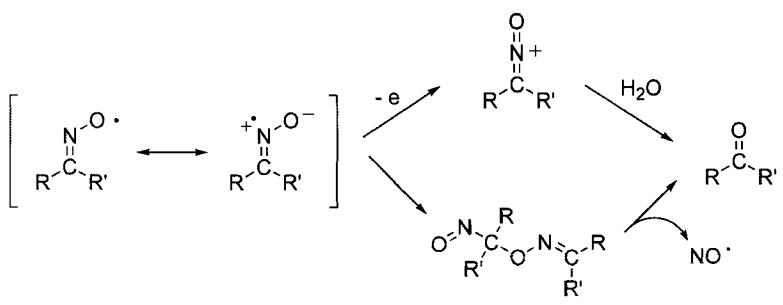


**Figure 2.** Possible follow-up reactions of iminoxyl radicals.

**Table 1.** Peak potentials, ionization potentials, and photolysis data of *meta*- and *para*-substituted acetophenone oximes and Hammett substituent constants for polar ($\sigma_{pol}$, $\sigma_{mb}$) and radical ($\sigma_{rad}$, $\sigma_{JJ}$) effects.

| X | $E_p$ (V) | IP (kcal mol$^{-1}$) | Conv. (%)* | Rel. Conv† | Log (%X/%H)‡ | $\sigma_{pol}$§ | $\sigma_{mb}$‖ | $\sigma_{rad}$¶ | $\sigma_{JJ}$‖ |
|---|---|---|---|---|---|---|---|---|---|
| *p*-$CF_3$ | 2.13 | 186.00 | 6 | 0.43 | −0.40 | 0.54 | 0.49 | 0.08 | −0.01 |
| *m*-CN | 2.15 | 189.38 | 8 | 0.57 | −0.23 | 0.56 | 0.89 | −0.12 | 0.11 |
| *m*-$CF_3$ | 2.13 | 185.24 | 9 | 0.64 | −0.19 | 0.43 | 0.39 | −0.07 | −0.07 |
| *p*-CN | 2.19 | 188.05 | 9 | 0.64 | −0.18 | 0.66 | 0.86 | 0.46 | 0.42 |
| *m*-Cl | n/a | 182.00 | 11 | 0.79 | −0.09 | 0.373 | 0.12 | −0.04 | −0.05 |
| *p*-$NO_2$ | 2.18 | 192.74 | 11 | 0.79 | −0.09 | 0.778 | 0.86 | 0.57 | 0.36 |
| *m*-F | n/a | 181.32 | 12 | 0.86 | −0.07 | 0.337 | 0.23 | −0.05 | 0.03 |
| *p*-Cl | 1.73 | 178.47 | 14 | 0.98 | −0.01 | 0.227 | 0.11 | 0.12 | 0.22 |
| *p*-H | 1.87 | 177.70 | 14 | 1.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| *m*-$CH_3$ | 1.66 | 174.47 | 14 | 1.03 | 0.01 | −0.069 | −0.20 | 0.03 | 0.00 |
| *p*-F | 1.77 | 177.53 | 15 | 1.07 | 0.03 | 0.06 | −0.24 | −0.08 | −0.02 |
| *m*-$NO_2$ | 2.24 | 191.21 | 16 | 1.14 | 0.06 | 0.71 | 0.69 | −0.11 | 0.001 |
| *p*-$CH_3$ | 1.60 | 172.32 | 36 | 2.57 | 0.41 | −0.17 | −0.29 | 0.11 | 0.15 |
| *m*-$OCH_3$ | 1.65 | 168.61 | 67 | 4.79 | 0.68 | 0.115 | −0.11 | −0.02 | 0.10 |
| *p*-$OCH_3$ | 1.46 | 163.36 | 80 | 5.71 | 0.77 | −0.268 | −0.77 | 0.24 | 0.23 |

* Conversion of the oxime after 1 h photolysis (350 nm) in the presence of CA.
† Relative conversion (relative to conversion of the unsubstituted oxime).
‡ Ratio of the conversion of the substituted oxime to that of the unsubstituted oxime.
§ Constants were taken from Reference 39.
‖ Constants were taken from Reference 40.
¶ Constants were taken from References 41 and 42.

broad and irreversible in every case. For certain compounds (*m*-Cl, *m*-F), no reliable data could be obtained. Plotting the measured peak potentials against the measured rate for quenching triplet chloranil ($k_q$) gives an excellent correlation ($r^2 = 0.93$; Fig. 3A).

The ionization potentials (IP) of these oximes were determined by theoretical methods. All *syn* and *anti* isomers were considered; the lowest energy conformers were found by a conformational search (MMFF) and were further optimized by AM1 calculations (34). The geometries of all the oxime isomers were then optimized by DFT calculations with the use of Becke's three-parameter functional and the nonlocal correlation of Lee, Yang and Parr (B3LYP) (35,36) with the 6-31G* basis set (37) implemented within Spartan 2002 (38). The geometry of the optimized neutral compound was used as a starting point for a geometry optimization of the corresponding radical cation species.

The results show that the *anti* isomers are of lower energy than the corresponding *syn* isomers. A plot of the measured peak potentials against the calculated IP (*anti* isomers) also gives an excellent correlation ($r^2 = 0.93$; Fig. 3B). These results are most consistent with an initial electron transfer step rather than hydrogen atom transfer.

Further analysis of the electrochemical data revealed that they also correlate well with several σ values such as $\sigma_{pol}$ ($r^2 = 0.896$) and $\sigma_{mb}$ ($r^2 = 0.898$), but not with $\sigma_{JJ}$ ($r^2 = 0.010$), or $\sigma_{rad}$ ($r^2 = 0.001$). This indicates that the electrochemical process results in the formation of cationic species rather than radicals, which is consistent with a study by Benchariff, Tallec and Tardivel, who have proposed a sequence of reactions at the electrode very similar to those proposed for the photoinduced electron transfer reactions (39).

### Photosensitized reactions of *meta*- and *para*-substituted acetophenone oximes

The kinetic studies involved steady-state (SS) photolysis experiments in which a mixture of the substituted oxime and the unsubstituted oxime (0.015 *M* each) as well as the sensitizer (CA, 0.005 *M*) in acetonitrile was photolyzed for 1 h. The experiments were carried out several times, and the relative conversions of the substituted oximes (%X/%H; average of three or four separate experiments) were correlated against different sets of substituent constants in order to determine the importance of radical and polar effects on these reactions. The results of these photolysis experiments are listed in Table 1. At first glance the reactivity seems to follow roughly that which would be expected on the basis of electron-accepting and donating properties. The *p*-methoxyacetophenone oxime is the most reactive and reacts almost six times as fast as the unsubstituted oxime. The slowest reaction is observed for *p*-(trifluoromethyl)acetophenone oxime; overall, the difference between the fastest and the slowest substrate is approximately 13. The correlation between the reactivity (kinetic) data and the measured peak potentials ($r^2 = 0.51$), the calculated IPs ($r^2 = 0.64$), or the measured quenching rates ($r^2 = 0.63$) are all poor. This suggests that the initial electron transfer step and the experimental data representing it ($E_p$, IP, $k_q$) cannot be used to draw conclusions on the overall outcome of the reaction. To look for trends and patterns of the overall reaction, the kinetic data (relative conversion;

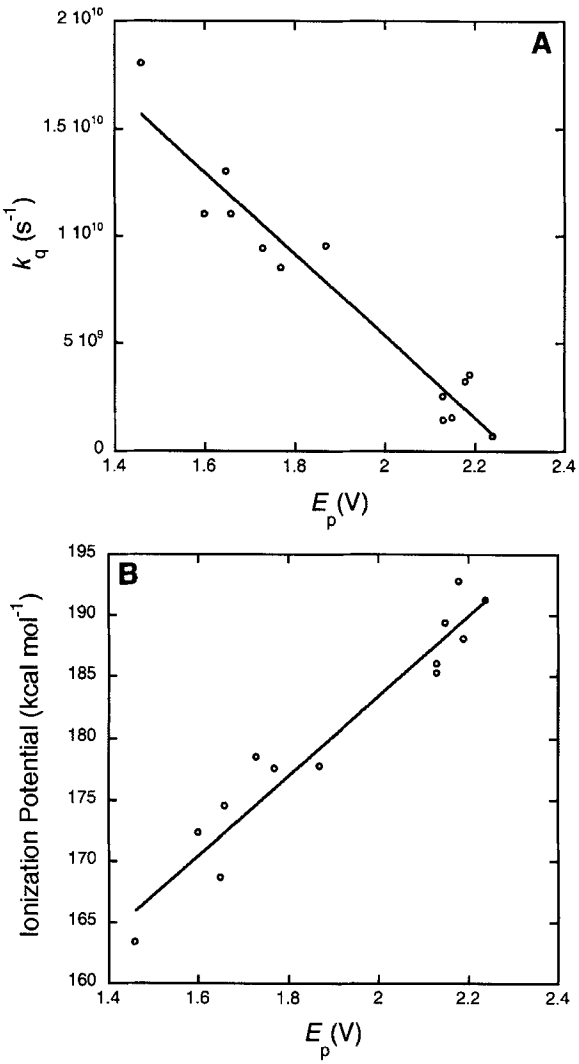


**Figure 3.** Correlation of the measured peak potential ($E_p$) with (A) the previously measured quenching rates ($k_q$) and (B) the calculated ionization potentials.

**Table 2.** Comparison of Hammett data obtained from steady-state (SS) and laser flash photolysis (LFP) experiments on *meta*- and *para*-substituted acetophenone oximes.

| | *meta* | | *para* | |
|---|---|---|---|---|
| | ρ (SS) | ρ (LFP) | ρ (SS) | ρ (LFP) |
| Single parameter | | | | |
| $\sigma_{pol}$ | −0.35 (0.12) | −1.63 (0.79) | −0.75 (0.65) | −0.73 (0.88) |
| $\sigma_{rad}$ | +1.75 (0.11) | +8.46 (0.79) | −0.10 (0.00) | −0.62 (0.20) |
| $\sigma_{mb}$ | −0.35 (0.24) | −1.15 (0.82) | −0.52 (0.68) | −0.49 (0.83) |
| $\sigma_{JJ}$ | +1.51 (0.13) | +1.08 (0.02) | +0.22 (0.01) | −0.36 (0.04) |
| Dual parameter* | | | | |
| $\sigma_{pol}$ | −28.7 (0.93) | −7.10 (0.94) | −1.20 (0.98) | −0.89 (0.93) |
| $\sigma_{rad}$ | −155 (0.93) | −30 (0.94) | +1.26 (0.98) | +0.44 (0.93) |
| $\sigma_{mb}$ | −0.43 (0.39) | −1.22 (0.95) | −0.69 (0.95) | −0.56 (0.91) |
| $\sigma_{JJ}$ | +2.71 (0.39) | +3.16 (0.95) | +1.29 (0.95) | +0.56 (0.91) |

* Dual-parameter correlations used for data analysis are ($\sigma_{pol} + \sigma_{rad}$) and ($\sigma_{mb} + \sigma_{JJ}$).

$\log[k_X/k_H]$) was correlated with various Hammett parameters (Table 1). For these studies we have focused on two polar ($\sigma_{pol}$ and $\sigma_{mb}$) (40,41) and two radical ($\sigma_{rad}$ and $\sigma^{\bullet}_{JJ}$) (41–43) substituent constants. Analysis of the complete data set (both *meta*- and *para*-substituted oximes are included) gave only moderate correlations when using any of the single substituent constants. Some improvement was observed when a dual-parameter set was used; however, the best results only gave a correlation ($r^2$) of 0.63.

In our earlier studies (27) we noted that analysis of the data yielded better results when the *meta*- and the *para*-substituted compounds were separated. Similar results were obtained this time (Table 2). Significant improvements are noticeable when dual correlations are used (Fig. 4). For example, using the polar and radical substituent constants gives correlations of 0.93 for the *meta* data and 0.98 for the *para* data. The contribution of the radical constants is remarkable, especially for the *meta*-substituted acetophenone oximes. In this case, $\rho_{rad}/\rho_{pol} = -5.4$, which is similar to the previously (LFP) observed ratio of −4.2. For the *para*-substituted oximes the polar and radical contributions are approximately equal ($\rho_{rad}/\rho_{pol} = -1.05$). Analysis of the data with the use of the Jiang and Ji polar ($\sigma_{mb}$) and radical ($\sigma^{\bullet}_{JJ}$) substituent constants (41) gives similar results for the *para* data set ($\rho_{JJ}/\rho_{mb} = -1.9$; $r^2 = 0.95$), but the correlation for the *meta* data set is significantly worse ($r^2 = 0.39$), although the importance of radical effects is seen again ($\rho_{JJ}/\rho_{mb} = -6.3$).

It is interesting to note that for the *para* data only two substituents are significantly influenced by the radical substituent coefficients. Comparing Figs. 4B,C clearly shows that both *p*-$NO_2$ and *p*-CN acetophenone oximes deviate from the line when a polar substituent coefficient is used. Without these data points, the correlations would be 0.91 ($\rho_{mb} = -0.91$) and 0.86 ($\rho_{pol} = -1.30$). These results are consistent with those from the dual-parameter correlations; for the *para*-substituted acetophenone oximes, polar effects are more important than radical effects.

Overall, these observations are in reasonable agreement with those of the earlier LFP (quenching) studies (Table 2). The most obvious difference is the observation that in the LFP studies good correlations are often obtained with single parameters, whereas in the SS experiments dual-parameter correlations are necessary in order to observe clear trends. This is in agreement with the fact that in the LFP experiments only the first step is important and a single

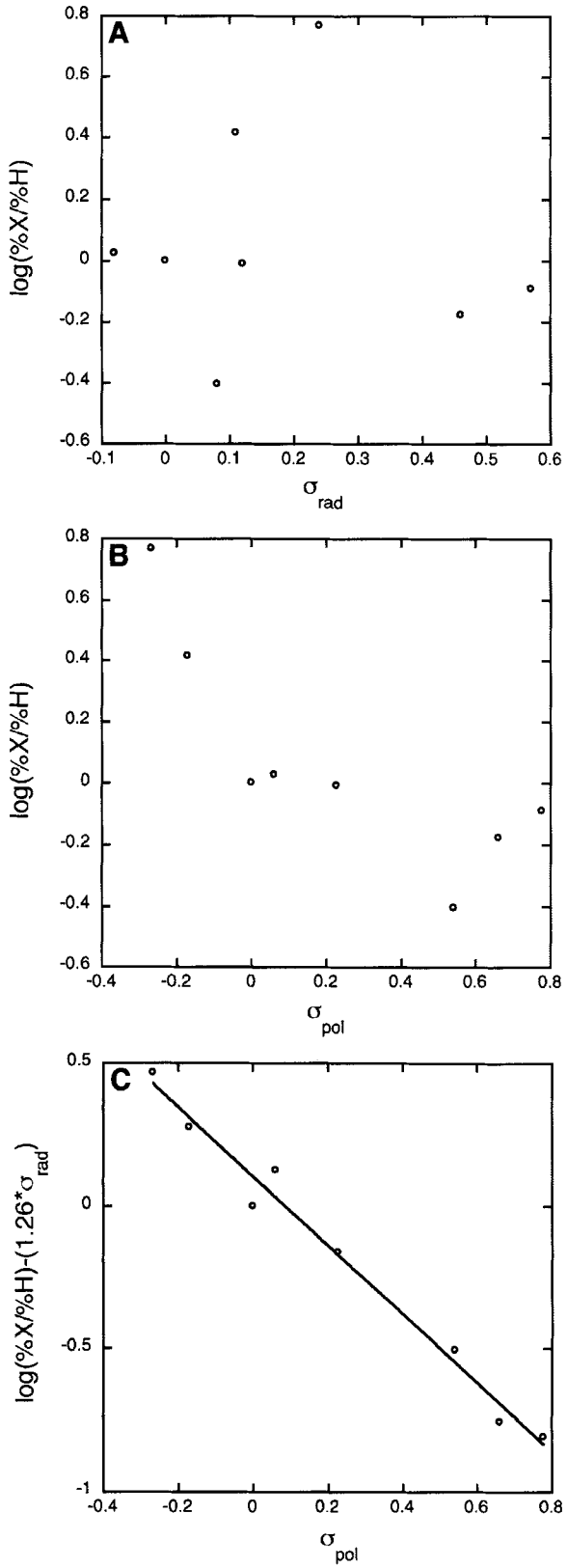


**Figure 4.** Semilogarithmic plots of the relative conversions of *para*-substituted acetophenone oximes (*%X/%H*) *versus* radical ($\sigma_{JJ}$, $\sigma_{rad}$) and polar ($\sigma_{pol}$, $\sigma_{mb}$) substituent constants. Plots **A** and **B** are one-parameter plots representing radical and polar contributions, respectively; plot **C** is a two-parameter plot incorporating both radical and polar contributions.

species (with both radical and polar character) is generated. In the SS experiments, there are a number of follow-up steps involving *several* types of intermediates, each of which are influenced by polar and radical effects in *different* ways.

### Product ketone formation in the photosensitized reactions of *meta*- and *para*-substituted acetophenone oximes

The CA-sensitized reactions resulted in the formation of the corresponding ketone as the major product and a minor side product tentatively identified as the (1-chloroethyl)aryl derivative. In the case of *p*-methoxyacetophenone oxime, the major product was found to be the corresponding amide; this unusual observation is further discussed below. The use of CA as a sensitizer in PET reactions is well established (44). Triplet chloranil ($^3$CA) is a powerful oxidant ($E^*_{red}$ = 2.15 V), capable of oxidizing a wide variety of substrates, including arenes, alkenes, alcohols, and amines (45–48). However, one early report has suggested the formation of HCl in the photosensitized reactions of CA with aldehydes (49). Clearly, formation of HCl under our conditions could be responsible for the observed products as well. To rule out the involvement of HCl in these reactions, the irradiations were also carried out with other sensitizers such as benzophenone and 9,10-dicyanoanthracene (DCA). In both cases, the oxime was converted into the corresponding carbonyl compounds. These results, together with those discussed above, strongly support an initial electron transfer step.

The exact mechanistic pathway for formation of the carbonyl compound so far remains unknown; however, the results presented above clearly suggest that the initial electron transfer step is followed by other steps, resulting in the formation of ionic and/or radical species. A key issue to unraveling this mechanism would be to identify the origin of the carbonyl oxygen. Earlier experiments have ruled out the involvement of molecular oxygen and singlet oxygen in these reactions (50). One possible pathway for an intramolecular oxygen transfer process involves dimerization of the iminoxyl radical intermediate followed by bond cleavage processes (Fig. 5) (51). The mechanism proposed by Ingold and co-workers also involved carbon–carbon bond cleavage with formation of a nitrile (51). This pathway is only expected to be important if a stable radical species can be formed; otherwise the iminyl radical will be hydrolyzed.

A second option would be an intermolecular reaction of a nucleophile (water) with the oxime radical cation or another electrophilic species. To differentiate between intermolecular and intramolecular reactions we have carried out the PET reactions of different oximes (acetophenone oxime, benzaldehyde oxime, and deoxybenzoin oxime) in anhydrous MeCN to which was added oxygen-18 labeled water ($H_2O$*; 95% $^{18}$O). A solution containing the oxime (0.025*M*) and CA (0.025*M*) in MeCN with added $H_2O$* (total $H_2O$* concentration: 0.82*M*) was irradiated for 1 h (350 nm). The reaction was carried out under aerobic (oxygen-purged) and anaerobic (argon-purged) conditions. Analysis of the mixture after photolysis by GC/MS revealed >90% incorporation of the oxygen-18 label in the product ketone or aldehyde (Fig. 6). There was no difference between the aerobic and anaerobic experiments.

These results show that formation of the carbonyl compound involves nucleophilic attack by water on the intermediate oxime radical cation or another electrophilic species derived from it. The intramolecular oxygen transfer pathway can be ruled out because

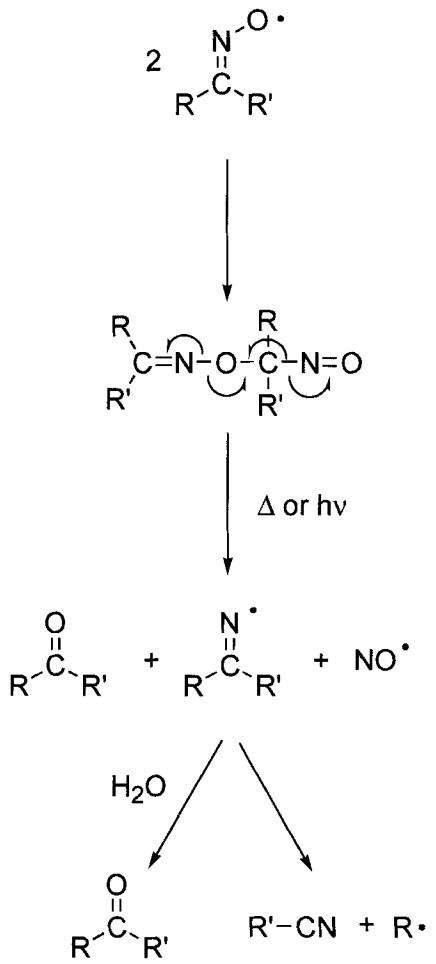


**Figure 5.** Possible pathways for the conversion of iminoxyl radicals into carbonyl compounds via an intramolecular oxygen transfer.

only a maximum of 50% of the carbonyl compound would be expected to carry the oxygen-18 label.

Earlier studies have suggested that the initial oxidation step is followed rapidly by a deprotonation step to form an iminoxyl radical (27,50), which may be too fast for nucleophilic attack to compete with. So far we have been unable to directly measure the rate of reaction between oxime radical cations and nucleophiles; however, based on spectroscopic data we predict that the oxime radical cation lifetime is on the scale of nanoseconds as a result of the fast deprotonation step (27). Oxime ether radical cations are much longer lived, and their reactions with nucleophiles are relatively slow ($10^5$–$10^6 M^{-1}$ $s^{-1}$) (52). Assuming a similar rate for the reaction of oxime radical cations with nucleophiles, nucleophilic attack is too slow to compete with the deprotonation step. We propose that deprotonation of the oxime radical cation results in the formation of an iminoxyl radical, which may undergo a second oxidation to form an α-nitroso-type cation. Although the oxidation potentials of iminoxyl radicals are unknown, it is well known that certain radicals with heteroatoms in the β-position can have very low, sometimes negative, oxidation potentials (53). Assuming a low oxidation potential for iminoxyl radicals, even ground state CA ($E_{red}$ = +0.02 V) could oxidize this radical, which would result in the formation of an electrophilic species that can react with water to form the corresponding carbonyl compound (Fig. 7).

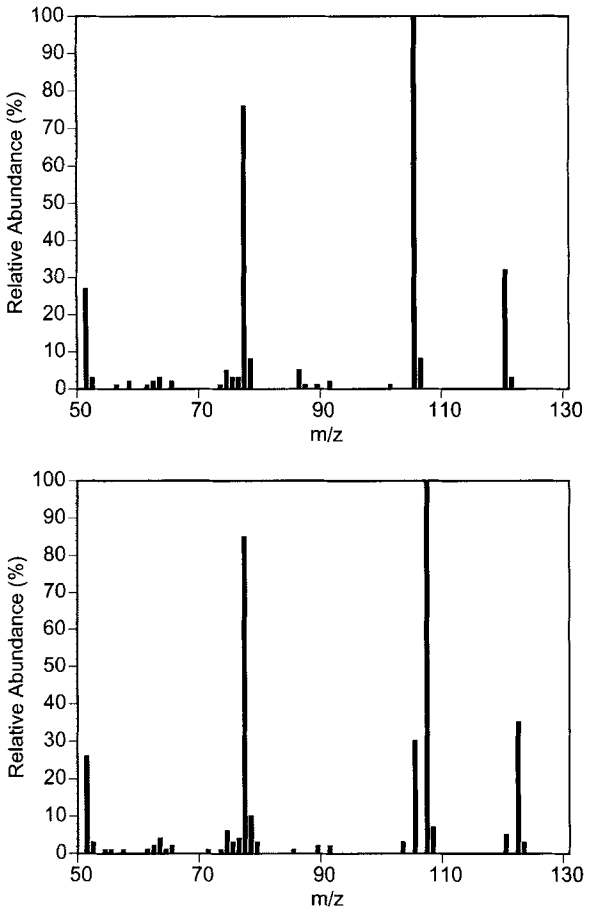


**Figure 6.** Mass spectra of acetophenone (top) and acetophenone-$^{18}$O (bottom). The top spectrum was obtained from a normal experiment irradiating acetophenone oxime and CA in acetonitrile; the bottom spectrum was obtained upon irradiating acetophenone oxime and CA in MeCN with added $^{18}$O-labeled water.

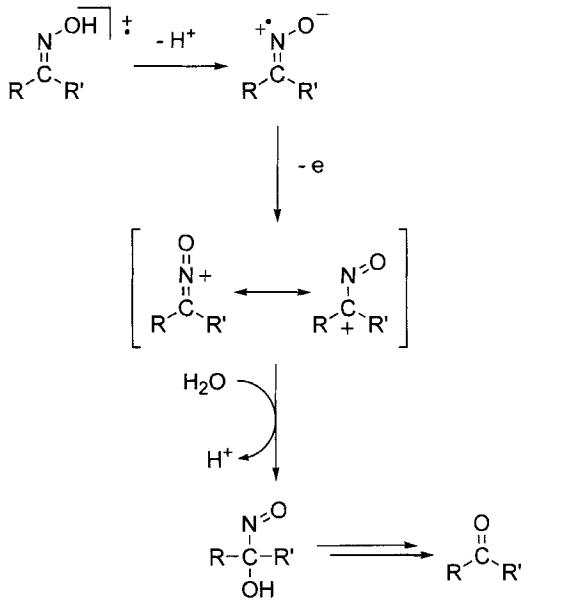


**Figure 7.** Proposed follow-up reactions in the PET reactions of oximes. Oxidation of the intermediate iminoxyl radical results in the formation of an electrophilic species that reacts with water to produce the observed carbonyl compound.

Preliminary results from AM1 and DFT calculations on simple α-nitroso-type cations seem to confirm the viability of this mechanism. Optimization of these structures in the presence of a water molecule leads to a structure in which the nucleophilic oxygen is directed toward the carbon, in agreement with the proposed mechanism.

## Formation of chlorinated side products

Irradiation of acetophenone oximes and CA in MeCN results in the formation of the corresponding ketone as the major product. In addition to the major carbonyl compound we often noticed the presence of a second product. On the basis of its mass spectrum it was tentatively identified as the (1-chloroethyl)aryl derivative (Fig. 8). Comparison with an authentic sample confirmed the identity of this chlorinated product (CP).

In general the yield of CP is small (typically less than 20%); however, at earlier reaction times the yield is usually significantly higher (Fig. 9).

Irradiation of the product ketone with CA in MeCN does not result in the formation of the CP, suggesting that it is formed from either the oxime or another intermediate on the pathway to the ketone. Further experiments have shown that the chloride comes directly from chloranil. Addition of free chloride anion (using potassium chloride and 18-crown-6) did not increase the chlorinated product yield. Other chlorinated sensitizers, such as 2,3-dichloronaphthoquinone and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, also yielded the CP but in much lower yields.

At early reaction times (20–30 min) the product mixture contains almost equal amounts of ketone and CP. At lower CA concentrations the CP/ketone ratio is much smaller, but increasing the CA concentration resulted in higher CP yields. Similarly, increasing the oxime concentration also leads to higher CP/ketone ratios. These results suggest that the reactive intermediate and CA must be close together to react; a substitution reaction involving a complex between the oxime and the sensitizer would explain these results.

If this reaction were indeed a direct substitution, one would expect other sensitizers to display similar or different behavior depending on the group that is transferred. For example, using bromanil (2,3,5,6-tetrabromo-1,4-benzoquinone, BA) might give similar or better results, whereas using fluoranil (2,3,5,6-tetrafluoro-1,4-benzoquinone, FA) is not expected to yield any significant amount of fluorinated products because fluoride is a poor leaving group. The results of experiments with different sensitizers partially confirm this hypothesis. Using FA as the sensitizer did not yield any fluorinated products, as predicted. When BA was used as the sensitizer, the brominated product (BP) was detected; however, the yield was somewhat lower than that of the corresponding chlorinated product in the reaction with CA. Interestingly, in the reaction with BA the amount of *syn–anti* isomerization was much larger than in the reaction with CA. Previously we have suggested that the probability for *syn–anti* isomerization increases when the free energy for electron transfer ($\Delta G_{ET}$) as calculated by the Weller equation (54) becomes less favorable (27,50). Although the reported reduction potentials of BA (0.0 V) and CA (+0.02 V) are very similar (55), our results suggest that BA is not as effective a sensitizer as CA. Additionally, steric effects may become more important as well. BA may not be able to approach the oxime as readily as CA due to the larger bromine atoms (one of which

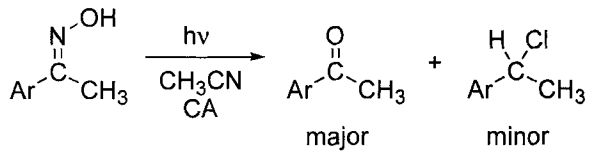


**Figure 8.** Product formation in the chloranil (CA) sensitized reactions of *meta*- and *para*-substituted acetophenone oximes. Both the corresponding ketone (major) and a chlorinated product (minor) were present in the product mixture.

needs to be transferred). Finally, the transfer of the halide may not occur in the rate-limiting step, which could also explain these observations.

In methanol the chlorinated product is not observed. There are two possible explanations for this result. First, we have shown that CA reacts rapidly with MeOH to form the semiquinone radical (56), which may cause the reactive chlorinating species (*e.g.* chloranil radical anion) to be trapped and thus prevent the chlorination reaction from taking place. Second, the chlorination reaction proceeds through an electrophilic intermediate, which is captured more rapidly by the solvent. One possible argument against the latter explanation is the fact that no other products are observed when MeOH is used as the solvent. For example, if this were a simple exchange of nucleophiles, one would expect to see (1-methoxyethyl)benzene derivatives; however, no such species were formed in this reaction.

A second option to be considered is a free-radical substitution reaction ($S_H2$). Assuming that the initial electron transfer step is followed rapidly by the deprotonation step, the species responsible for the chlorine atom transfer would have to be the semiquinone radical (Fig. 10).

One potential argument against the free-radical process is the fact that less of the CP was observed when the reaction was carried out in dichloromethane. Even in carbon tetrachloride the reaction did not yield a significantly larger amount of the CP. Although these results do not support a free-radical process, it is possible that formation of the CP occurs within the solvent cage, which would exclude participation of the solvent to any great extent.

Recently, Pragnacharyulu and Abushanab reported the formation of chlorinated species from reaction of 5,6-dihydropyrimidine nucleosides with DDQ (57). On the basis of their studies they proposed an intermediate involving 2,3-dicyano-5,6-dichloro-*p*-dihydroquinone that protonates the substrate and then delivers chloride to the resulting electrophilic species. Separate experiments with the hydroquinone species confirmed its involvement. Earlier we have shown that under certain conditions, hydroquinones such as 2,3,5,6-tetrachlorohydroquinone (TCHQ) can act as photoacids (56). The proposed mechanism for the formation of the acidic species was one-electron oxidation to generate the quinol radical cation, followed by loss of a proton. However, these reactions were only observed in MeOH and other protic solvents but not in acetonitrile. Nevertheless, there seems to be some precedent for the involvement of this type of species, and therefore we have also investigated the photosensitized reactions of acetophenone oximes with TCHQ. Irradiation (350 nm) of a solution containing *p*-fluoroacetophenone oxime and TCHQ for 2 h resulted in little conversion (less than 10%), and no CP was formed. On the basis of these results we conclude that TCHQ is not involved in the formation of the chlorinated product. At this point we conclude that the formation of the CP occurs via a chloride anion transfer within

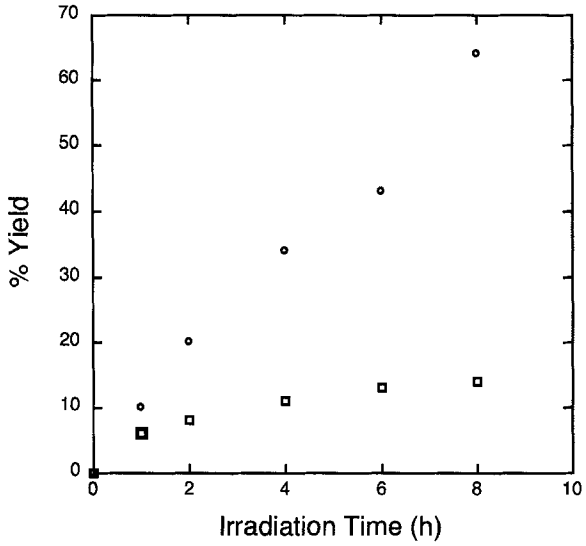


**Figure 9.** Formation of *p*-fluoroacetophenone (circles) and 1-(1-chloroethyl)-4-fluorobenzene (squares) as a function of time in the CA-sensitized reaction of *p*-fluoroacetophenone oxime.

a complex formed between the oxime radical cation and the chloranil radical anion or via a free-radical substitution reaction involving the iminoxyl radical and the semiquinone radical. Further studies on this reaction are currently under way.

## Formation of amides from oximes via photosensitized electron transfer reactions

Irradiation of *p*-methoxyacetophenone oxime in the presence of CA ($E_S$ = 266 kJ/mol; $E_T$ = 206 kJ/mol) or BA resulted in the formation of the corresponding amide via a Beckmann rearrangement. The direct photolysis of oximes is known to produce amides

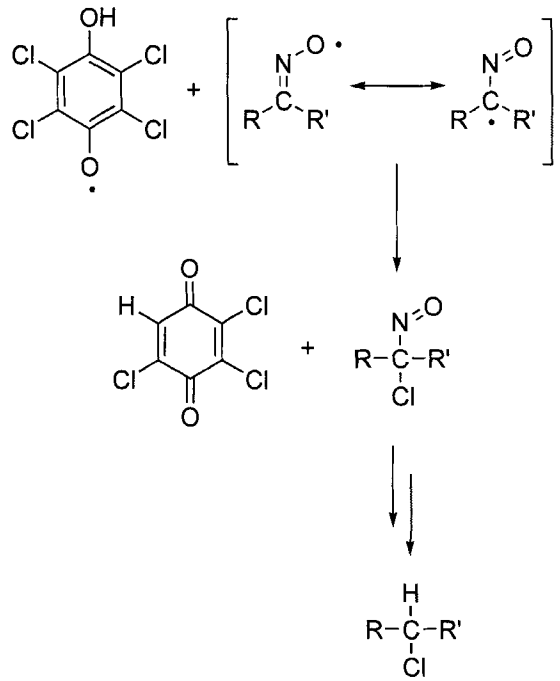

**Figure 10.** Formation of the CP via a radical substitution ($S_H2$) process, involving the iminoxyl radical and the semiquinone radical.

(58–60); however, this was shown to occur from the lowest excited singlet state. *Syn–anti* isomerization was proposed to occur from the lowest excited triplet state (61). Earlier, we also observed the formation of amides from oximes under PET conditions, although it was not a general reaction (50). Normally, the Beckmann rearrangement is an acid-catalyzed process (62). Radical cations are known to be acidic (e.g., the estimated $pK_a$ of acetophenone oxime radical cation is −13 [30]) and an intermolecular proton transfer from the oxime radical cation to a neutral oxime could possibly explain the observed Beckmann rearrangement. Additionally, the formation of other acidic species (e.g., HCl from photolysis of CA) might also explain this observation. However, it would seem strange that only *p*-methoxyacetophenone oxime undergoes this rearrangement. There is no reason why *m*-methoxyacetophenone oxime or *p*-methylacetophenone oxime should not undergo a similar reaction; however, no amide was formed in these reactions. Further studies with other triplet and singlet sensitizers gave different results. Benzophenone ($E_S$ = 316 kJ/mol; $E_T$ = 287 kJ/mol) (63), benzil ($E_S$ = 247 kJ/mol; $E_T$ = 227 kJ/mol) (63) and anthracene ($E_S$ = 318 kJ/mol; $E_T$ = 178 kJ/mol) (63) to a certain extent all sensitize the formation of *p*-methoxyacetophenone but not the amide. These preliminary results indicate that the rearrangement occurs as a result of an electron transfer process rather than singlet or triplet energy transfer. This is of interest for enzymatic systems because only oximes that are easily oxidized are expected to be suitable substrates; however, if amides are produced, these reaction products themselves may then become substrates. Enzymatic oxidation of these metabolites would result in the formation of *N*-arylhydroxamic acids, which are considered carcinogens (64). We are currently further exploring this interesting behavior of oximes.

## CONCLUSIONS

We have shown that the photooxidation of oximes results in the formation of a number of reactive intermediates, including radical cations, cations and free radicals. The transformation of oxime to ketone requires multiple steps, each of which is governed by polar and/or radical effects as shown by the results from the Hammett study. For *para*-substituted acetophenone oximes polar effects are typically more important than radical effects, with the exception of *p*-$NO_2$ and *p*-CN derivatives, which deviate from the best-fit line. The results are significantly different for the photooxidation studies of *meta*-substituted acetophenone oximes, which are dominated by radical effects. In addition, it was shown that quinones and other carbonyl compounds could act as sensitizers for these oxidative processes but may also participate in side reactions, especially when nucleophilic atoms or groups (*e.g.* halides) are present. In our studies with chloranil as the sensitizer, we have observed the formation of chlorinated compounds, which is believed to involve a direct nucleophilic transfer of chloride anion from the chloranil radical anion to the oxime radical cation, although at this point a chlorine atom transfer cannot be ruled out completely. Finally, certain oximes with low oxidation potentials seem to be susceptible to other pathways such as rearrangement to an amide (a Beckmann rearrangement). Therefore, the oxidation of oximes and related compounds may lead directly or indirectly to the production of carcinogenic species. These results clearly indicate the potential risk that oximes and related compounds pose if they were taken up by an organism and subjected to enzymatic (one-electron) oxidation or detoxification. Our studies will be helpful in assessing the factors involved in these oxidation reactions, and how to predict the reactivity on the basis of structural features, which eventually may lead to safer alternatives.

*Acknowledgements*—This work was supported by Research Corporation (CC5107), the State of California, and California State University, Fullerton. Part of this work was supported by the National Science Foundation under grant 0097795.

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