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Dye-Sensitized Photooxygenation of the C=N Bond. 5. Substituent Effects on the Cleavage of the C=N Bond of *C*-Aryl-*N*-aryl-*N*-methylhydrazones[1]

Ihsan Erden,* Pinar Ergonenc Alscher, James R. Keeffe,* and Colin Mercer

Department of Chemistry and Biochemistry, San Francisco State University, 1600 Holloway Avenue, San Francisco, California 94132

ierden@sfsu.edu; keeffe@sfsu.edu

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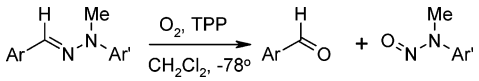

The title compounds are cleaved cleanly at the C=N bond by singlet oxygen ($^1O_2$, $^1\Delta_g$) yielding arylaldehydes and *N*-aryl-*N*-methylnitrosamines. These reactions take place more rapidly at −78 °C than at room temperature. The effects of substituent variation at both the *C*-aryl and *N*-aryl groups were studied using a competitive method. Good correlations of the resulting rate ratios with substituent constants (σ^- or σ^+) were obtained yielding small to very small ρ values indicative of small to very small changes in charge distribution between the reactant and the rate determining transition state. Electron withdrawing groups on the *C*-aryl moiety retard reaction somewhat by preferential stabilization of the hydrazone. Electron donors on the other hand slightly stabilize the rate determining transition state. Substituents on the *N*-aryl group have almost no effect. Inhibition by 3,5-di-*tert*-butylphenol was not observed showing that free (uncaged) radical intermediates are not involved in the mechanism. We postulate a mechanism in which the initial event is exothermic electron transfer from the hydrazone to $^1O_2$ leading to an ion−radical caged pair. Subsequent covalent bond formation between the hydrazone carbon and an oxygen atom is rate controlling. The transition state for this step also has a lower enthalpy than the starting reactants, but the free energy of activation is dominated by a large negative $T\Delta S^{\ddagger}$ term leading to the negative temperature dependence. Direct formation of a C−O bond in the initial step is not unambiguously ruled out. Subsequent steps lead to C−N cleavage.

Introduction

In previous studies we have shown that reaction of singlet oxygen, $^1O_2$ ($^1\Delta_g$), with the C=N bond requires the presence of good to very good electron donating groups attached to the doubly bonded nitrogen. For example, aryloximes and aryloxime ethers react sluggishly or not at all, but oximate anions react readily, as do nitronate anions, *O*-trimethylsilylnitronates, *C*-aryl-*N,N*-dimethylhydrazones, and nitrones.[2] For the reactions of $^1O_2$ with nitrones and *C*-aryl-*N,N*-dimethylhydrazones we have observed peroxidic intermediates by low-temperature NMR spectroscopy. The accumulated observations permitted mechanistic proposals to be made about these reactions which do not depend solely on identification of the products.[3]

In this study we report the reaction of singlet oxygen with *C*-aryl-*N*-aryl-*N*-methylhydrazones in which para substituents on the *C*-aryl and *N*-aryl rings have been systematically varied. Competition for singlet oxygen between different hydrazones was designed to allow determination of relative reaction rates for the differently substituted substrates, and these results permitted analysis with use of established substituent constant values.[4] The effect of temperature on reaction efficiency was also determined. To the best of our knowledge this is the first systematic study of purely electronic substituent effects on the reactivity of $^1O_2$ with a single substrate type.

Results

Four types of relative rate comparisons were made. In Set I hydrazones with X = variable and Y = H [see eq 1] were compared with the parent hydrazone for which X

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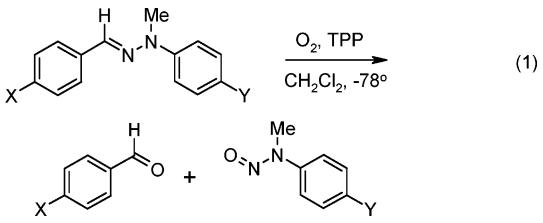

(1)

= Y = H. In Set II compounds with X = CH_3 and Y = variable competed with X = CH_3, Y = H. In Set III X = Cl and Y was again varied. These were compared with X = Cl and Y = H. Set IV, a smaller group, allowed both X and Y to vary and compete with X = Y = H. In all cases the reaction temperature was −78° C, initial subtrate concentrations were 0.05 M (in CH_2Cl_2), and the photosensitizer, TPP, was at 10^{-4} M. Reaction progress was monitored to no greater than 10% conversion to ensure approximately zero-order kinetics. See the Experimental Section for details. Relative rates were determined by ^{1}H NMR analysis of integrated areas of one or more characteristic product signals. Ten to fifteen replicates were run for each competition. The relative rate ratios for each set are given in Tables 1−4 along with the standard deviation of the mean.

In addition to the competition experiments just described, the reactions of the hydrazones with X = Y = H and X = CH_3O, Y = H were compared at two temperatures, −78 and ∼20 °C. In these experiments the stirring time prior to illumination was varied in order to test whether oxygen saturation of the reaction solutions had occurred. At short reaction times, just long enough to detect product formation for the slower reaction (10 min), the reactions at −78 °C were uniformly faster by an amount independent of prior stirring time. The ratio of reactivities at the two temperatures was found to be at least 45:1. We emphasize that this is a *minimum* ratio because by the time product formation could be detected for the slower reaction (∼1% conversion), product formation at −78° C had reached 40−70%, thus substrate concentration in that solution had fallen significantly.

Discussion

Structure of the Hydrazones. The preferred geometry about the C=N bond of *C*-aryl-*N*-aryl-*N*-methylhydrazones is taken as syn (*E*) rather than anti (*Z*) by analogy with the observations of Karabatsos[5] and Hegarty[6] and their respective co-workers. In this form the geometry is virtually planar about the C=N bond, and the amino nitrogen lone pair is able to conjugate more effectively with the C=N π bond provided the groups attached to the C=N carbon (H in our case) *and* the amino nitrogen are not large. Hegarty and co-workers also obtained convincing evidence that the syn to anti isomerization barrier is about 23 kcal/mol at room temperature for a hydrazone of our type, namely, Ph-CH=N-N(CH_3)Ar, where Ar = 4-nitrophenyl.[7] Our semiempirical molecular orbital calculations (AM1) support these conclusions, placing the *E* isomer 1.1 kcal/mol below the *Z* isomer, and showing the amino nitrogen better situated for conjugation.[8]

Inverse Temperature Dependence. An inverse temperature dependence on the rate of singlet oxygen

TABLE 1. Product Ratios (Relative Rates) for Compeititve Reaction with Singlet Oxygen, Set I: 4-X-C_6H_4-CH=N-N(CH_3)Ph vs Ph-CH=N-N(CH_3)Ph(−78 °C, CH_2Cl_2 solution)

X	product ratio[a]	standard deviation of the mean[b]
NO_2	0.115	0.003
Cl	0.752	0.007
$N(CH_3)_2$	0.93	0.001
CH_3	1.21	0.0012
OCH_3	1.52	0.002

[a] Reactions were run to no greater than 10% conversion of the more reactive substrate. Product ratios therefore measure relative reaction rates to a good approximation. [b] Ten to fifteen replicate compeititions were done for each pair.

TABLE 2. Product Ratios (Relative Rates) for Competitive Reaction with Singlet Oxygen, Set II: 4-CH_3-C_6H_4-CH=N-N(CH_3)C_6H_4-4-Y vs 4-CH_3-C_6H_4-CH=N-N(CH_3)Ph (−78 °C, CH_2Cl_2 solution)

Y	product ratio[a]	standard deviation of the mean[b]
NO_2	1.27	0.03
Cl	1.07	0.02
CH_3	0.94	0.03
OCH_3	0.75	0.04

[a] Reactions were run to no greater than 10% conversion of the more reactive substrate. Product ratios therefore measure relative reaction rates to a good approximation. [b] Ten to fifteen replicate competitions were done for each pair.

TABLE 3. Product Ratios (Relative Rates) for Competitive Reaction with Singlet Oxygen, Set III: 4-Cl-C_6H_4-CH=N-N(CH_3)C_6H_4-4-Y vs 4-Cl-C_6H_4-CH=N-N(CH_3)Ph (−78 °C, CH_2Cl_2 solution)

Y	product ratio[a]	standard deviation of the mean[b]
Cl	1.24	0.51
CH_3	0.89	0.06
OCH_3	0.65	0.047

[a] Reactions were run to no greater than 10% conversion of the more reactive substrate. Product ratios therefore measure relative reaction rates to a good approximation. [b] Ten to fifteen replicate competitions were done for each pair.

TABLE 4. Product Ratios (Relative Rates) for Competitive Reaction with Singlet Oxygen, Set IV: 4-X-C_6H_4-CH=N-N(CH_3)C_6H_4-4-Y vs Ph-CH=N-N(CH_3)Ph (−78 °C, CH_2Cl_2 solution)

X, Y	product ratio[al]	standard deviation of the mean[b]
NO_2, H	0.115	0.003
NO_2, OCH_3	0.91	0.002
OCH_3, H	1.52	0.002

[a] Reactions were run to no greater than 10% conversion of the more reactive substrate. Product ratios therefore measure relative reaction rates to a good approximation. [b] Ten to fifteen replicate competitions were done for each pair.

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reactions with hydrazones[2,9] and other substrates[10−12] has been noted previously. Several factors, physical and chemical, could play a role in determining this difference. Long and Kearns[13] have determined that in $CHCl_3$ solvent the lifetime of $^1O_2$ is decreased by only about 50% with a 100 °C increase in temperature. The temperature dependence of the solubility of oxygen in dichloromethane was not found in the literature by us. However, studies of oxygen solubility as a function of temperature in other solvents have been reported.[14] The results show a good deal of variability. For example, the solubility of O_2 in CCl_4 changes hardly at all over the range 0 to 60 °C. In chlorobenzene the solubility of oxygen steadily *increases* between 0 and 80 °C. In acetone the oxygen solubility is almost invariant with temperature between −78 and 40 °C, and in diethyl ether the solubility declines by a factor of 1.8 over the range −78 to 20 °C. Without information for dichloromethane a firm statement cannot be made, but it appears likely that the influences of increased lifetime of singlet oxygen and possibly increased solubility of oxygen at the lower temperature, countered by increased viscosity, hence a smaller diffusion rate at −78 °C, cannot account for the ca. 50-fold greater reactivity we see at the lower temperature

Other circumstances can lead to an inverse dependence of rate on temperature. Braderic and Leigh have discussed possible causes noting that this observation is not uncommon, especially for bimolecular reactions of reactive intermediates.[15] They write that there are two common mechanistic explanations for such behavior. In one case there is an initial exothermic formation of a complex that may revert to reactants or proceed to products, the product-forming path having a higher free energy barrier but a lower enthalpy barrier than formation of the complex or its reverse. The negative temperature dependence is then due to a dominant negative entropy of activation. To satisfy these requirements the initially formed complex would be relatively loose compared with the rate-determining transition state on the product-forming path. In fact, singlet oxygen reactions often do have near-zero enthalpies of activation and entropies of activation ranging from −25 to −40 cal/(deg·mol).[10−12] A second possibility is that the reaction is concerted, again with domination of $\Delta G^{\ddagger}$ by a large, negative $T\Delta S^{\ddagger}$ term.[16,17] Large negative entropies of activation are expected whenever a bimolecular process occurs, but especially when that process involves separation of charge in a relatively nonpolar medium.[18]

Substituent Effects. The relative rates compiled in Tables 1 through 4 were correlated with Hammett substituent constants[4] by using the following relationship, log(product ratio) = $a\sigma + b$. The original σ values

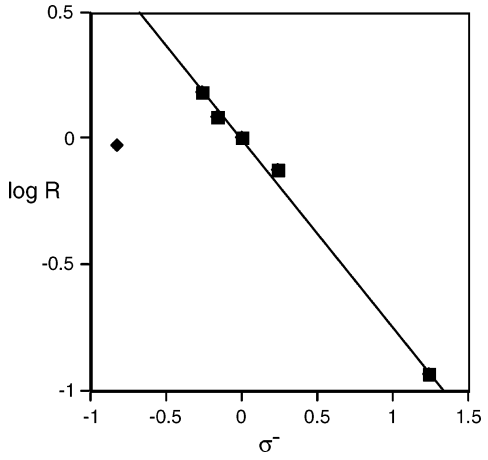

FIGURE 1. Plot of log(product ratio) vs σ^- for Set I. The diamond-shaped point is for the competition between 4-Me_2N-C_6H_4-CH=N-N(Me)Ph and Ph-CH=N-N(Me)Ph.

did not provide a good linear correlation with any of the data sets. Set I (*C*-ring substituents) were very well correlated with σ^- values, see eq 2. In this correlation the point for the *p*-dimethylamino group was 0.64 log unit below the correlation line established by the other substituents, see Figure 1. Tertiary amines (DABCO for example) are known to quench singlet oxygen, and we ascribe the apparent retardation for this compound to quenching by the substituent. Sets II and III (*N*-ring substituents) were best correlated with σ^+ values, see eqs 3 and 4.

$$\text{Set I:}\quad \log(\text{product ratio})_{\text{I}} = -0.74\sigma^- - 0.008;\ r^2 = 0.994,\ n = 5 \quad (2)$$

$$\text{Set II:}\quad \log(\text{product ratio})_{\text{II}} = 0.14\sigma^+ + 0.002;\ r^2 = 0.975,\ n = 5 \quad (3)$$

$$\text{Set III:}\quad \log(\text{product ratio})_{\text{III}} = 0.28\sigma^+ + 0.34;\ r^2 = 0.952,\ n = 4 \quad (4)$$

The most prominent result of these correlations is that the slopes (ρ values) are either small (Set I) or very small (Sets II and III). Set IV, a small set in which substituents on *both* rings were changed, gave only a fair correlation with ($\sigma^-_{\text{C}} + \sigma^+_{\text{N}}$). A rough value for that slope, $\rho \approx -0.5$, is in qualitative agreement with the difference between ρ (Set I) and ρ (Set II or III).

The small ρ values indicate that charge development in the rate determining transition state is not extensive; it is likely that the transition state is an early one. We interpret the result for Set I to signify that the reactant hydrazone is somewhat stabilized by electron withdrawing groups on the *C*-ring, especially those capable of a resonance interaction with the hydrazine function, as illustrated by structures **1a** and **1b**. Such stabilization is decreased in the rate-controlling transition state. Sets II and III show that reaction is slightly retarded by electron donors on the *N*-ring. The effect is so small that a convincing explanation is lacking.

Mechanism. Unlike our study of *C*-aryl-*N,N*-dimethylhydrazones,[3] we were unable to detect any intermediates in the reactions of the title compounds of this study.

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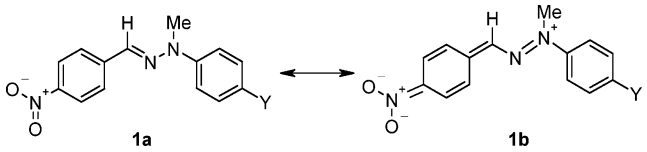

However, by analogy with the earlier study, and with the data gathered in this investigation, we postulate the mechanistic scheme shown below. Reaction begins with a bimolecular, exothermic step in which a complex is formed between hydrazone and singlet oxygen. The nature of such a complex has not been investigated. Then either electron transfer from the hydrazone to $^1O_2$ to form a radical−ion caged pair (not trapped by free radical scavengers) or direct formation of a bond between the hydrazone carbon and an oxygen atom occurs. This step is retarded by *C*-ring EWGs and accelerated by *C*-ring EDGs. If electron transfer is a distinct step, it would be followed by covalent bond formation. Whether electron transfer or covalent bond formation is rate controlling, it occurs with a transition state that is early with respect to charge development. It is likely that covalent bond formation, passing through a transition state structure that is slightly tighter than that of the complex, is rate controlling. The next step is unimolecular cyclization to a 3-aza-1,2-dioxetane, which undergoes facile cleavage to the observed products: an aryl aldehyde and a *N*-aryl-*N*-methylnitrosamine. However, we cannot unambiguously rule out initial complex formation or dioxetane formation as the rate controlling event.

Experimental Section

Materials. All hydrazones, except for two, were prepared in excellent yields by the method of Yao and Resnick in which a ring-substituted benzaldehyde is condensed with an *N*-aryl-*N*-methylhydrazine.[19] *C*-(4-Tolyl)-*N*-methyl-*N*-(4-nitrophenyl)-hydrazone and *C*-(4-chlorophenyl)-*N*-methyl-*N*-(4-nitrophenyl)-hydrazone were made by nitration of the corresponding *N*-phenylhydrazones at 0 °C in acetic anhydride, using concentrated nitric acid. The necessary *N*-aryl-*N*-methylhydrazines were prepared by reduction of the corresponding *N*-aryl-*N*-methylnitrosamines with zinc powder in acetic acid,[20,21] and the nitrosamines by treatment of *N*-aryl-*N*-methylamines with nitrous acid.[22] Melting points of hydrazones were in good agreement with literature values where these were found. Melting points and NMR features for those hydrazones not found in the literature are given in the Supporting Information. All NMR spectra were determined in $CDCl_3$ solution. The terms "major" and "minor" within the NMR data refer to the major (syn or *E*) forms and the minor (anti or *Z*) forms.

Product Studies. Four solutions of each hydrazone were made by dissolving the hydrazone (~2×10^{-4} mol, accurately weighed) in 4 mL of methylene chloride or in 4 mL of methylene chloride containing 10^{-4} M tetraphenylporphyrin (TPP). This produced 0.05 M solutions of each hydrazone, two of them with TPP present, and two of them without TPP. All four reaction flasks were subjected to a positive pressure of O_2 and the contents stirred. Two of the flasks, one with TPP, the other without, were cooled to −78 °C, and the other two were left at room temperature (~20 °C). After 30 min of stirring, irradiation of the four vessels with a 250-W sodium vapor lamp was begun. Irradiation was continued for 4 h. ^1H NMR analysis of the contents showed that the reaction solutions without TPP were unchanged. All solutions *with* TPP showed that the hydrazones had been partly or entirely cleaved at −78 °C yielding arylaldehydes and *N*-aryl-*N*-methylnitrosamines as the sole products, as demonstrated by comparison with the authentic samples available from our synthetic method. Most of the solutions (13 out of 21) containing TPP and reacting at room temperature also showed these oxidation products.

In a separate set of experiments reaction solutions were prepared as above for a more quantitative study of the temperature dependence of reaction efficiency. Hydrazones with X = Y = H, and X = CH_3O, Y = H were compared at −78 °C and at room temperature. The solutions were stirred under a positive pressure of oxygen for times ranging from 30 to 120 min, then irradiated for only the amount of time necessary for detection of product formation (~1%) in the slower reaction at room temperature. Percent-conversion at −78 °C exceeded that at room temperature by a factor of at least 45:1 and did not depend on the stirring time prior to irradiation (see Results). All the other hydrazones were also compared at the two temperatures, but, as described above, the irradiation times were 4 h, and the reactions at −78 °C were almost complete obviating quantitative comparisons.

We can characterize the dye-sensitized photooxygenation reactions as shown above in eq 1. The clean product composition stands in contrast to the reaction of *C*-aryl-*N,N*-dimethylhydrazones with singlet oxygen, which produces arylaldehydes, but also aromatic carboxylic acids, minute amounts of their methyl esters, *C*-aryl-*N*-formyl-*N*-methylhydrazones, and trace amounts of *N*-nitroso-*N,N*-dimethylamine.[3]

An experiment was carried out as described above, with TPP and at −78 °C, but with the singlet oxygen quencher DABCO (1,4-diazabicyclo[2.2.2]octane) added to the reaction mixture. No product formation was observed. This control verifies that singlet oxygen is the actual oxidant in these reactions. In another test the free radical scavenger 3,5-di-*tert*-butylphenol was added. Its presence failed to inhibit reaction, showing that free (uncaged) radicals do not lie on the pathway to products.

Competition Experiments. Competitive rates of reaction with singlet oxygen were studied by allowing differently substituted hydrazones, 0.05 M in CH_2Cl_2, to compete in a pairwise fashion at −78 °C. A known concentration of cyclohexane was present as an internal standard in order to assay percent reaction. In all cases reactions were allowed to proceed to 10% conversion or less in order to preserve the zero-order nature of the kinetics. In some cases the two hydrazones were in the same reaction vessel, in other cases in different vessels, but run in parallel. Concordant results were obtained with the two methods.

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Supporting Information Available: Physical constants and ^1H and ^{13}C NMR data for all previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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