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Photolysis of N-phenylhydroxylamine: a novel photochemical disproportionation reaction in N–O bond cleavage assisted by hydrogen bonding

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Abstract

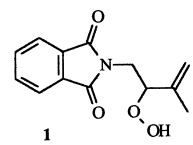
The photochemistry of N-phenylhydroxylamine (**9**) has been examined in the solution phase and in the solid state. The major products are aniline and nitrosobenzene. The nitrosobenzene quickly reacts with **9** to generate azoxybenzene and with aniline to produce azobenzene. The quantum yields for the disappearance of **9** are reasonably high (0.25–0.29) and suggest that the photochemical reactions proceed from a hydrogen-bonded dimer.

Keywords: Photolysis; N-Phenylhydroxylamine; Hydrogen bonding; Azobenzene

1. Introduction

In the past several years, considerable advances have been made in both the design and the preparation of new substances that serve as nucleic acid cleaving reagents. These act as structural probes as well as therapeutic agents and two reviews have recently appeared [1,2]. Specifically, there has been interest in the preparation of cleaving agents for nucleic acids that are photochemically activated. Much interest has been targeted toward the photochemical production of hydroxyl radicals because of their destructive nature, but they show little selectivity. It has been proposed that some reagents, e.g., hydrogen peroxide and some alkylhydroperoxides provide hydroxyl radicals directly, but others, e.g., pyridine oxides and hydroxylamines undergo electron transfer to molecular oxygen to generate eventually hydroxyl radicals through the superoxide anion by a Haber–Weiss type reaction [3].

In search of reagents that produce hydroxyl radicals in a facile photoreaction, the hydroperoxides **1** [4] and **3** [1] as well as the N-oxide **2** [5] have been examined in both organic and aqueous media



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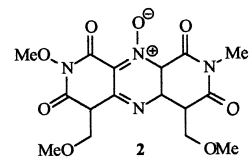

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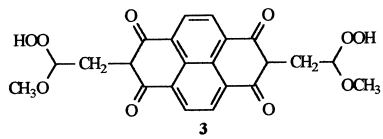

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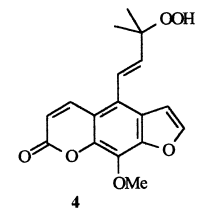

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There have been some problems associated with the study of these molecules as hydroxyl radical sources. For example, the photolysis of hydroperoxide **1** effects the nicking of plasmid DNA by hydroxyl radical production. Hydroperoxide **3** effects the photonicking of DNA, but a mechanistic study showed that the photocleavage was not due to hydroxyl radical production because **3** binds strongly to DNA so that photonicking may precede hydroxyl radical production. The N-oxide **2** is photoactive in water but not in acetonitrile. One of the most efficient hydroperoxides is furocoumarin **4** [6,7], which acts as an intercalating photo-Fenton reagent with a high quantum yield for hydroperoxide consumption.

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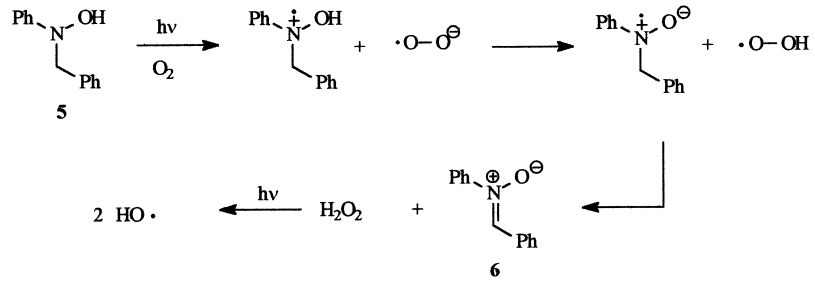
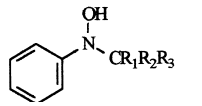


Scheme 1.

Recent work has also tried to exploit the photochemical cleavage of the N–O bond of benzohydroxamic acid derivatives to generate either hydroxyl or alkoxyl radicals. However, results from these studies have been somewhat sporadic. While in some work it was postulated that the photolysis of benzohydroxamic acid derivatives leads to N–O bond cleavage [8,9], other studies have shown that processes such as the Norrish Type II or electron transfer reactions account for the observed photoproducts [10,11].

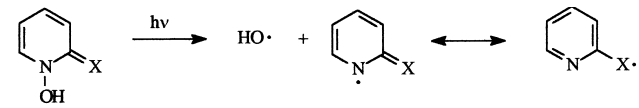
Recently, N-phenyl-N-benzylhydroxylamine (**5**) has been shown to be an efficient reagent for DNA cleavage by hydroxyl radicals [12]. However, its mode of action is not the direct photochemical production of hydroxyl radicals; ultimately, the photochemical reaction with molecular oxygen affords the nitrone (**6**) and hydrogen peroxide, the latter is photolyzed under the reaction conditions to produce hydroxyl radicals. (Scheme 1).

On these studies a patent has been issued for N-arylamine-N-alkylhydroxylamines (**7**) as photolytic sources of hydrogen peroxide [13].



7a: R_1=R_2=H, R_3=CH_3
7b: R_1=H, R_2=R_3=Ph
7c: R_1=R_2=H, R_3=C_6H_{11}

There has been considerable work on the photochemistry of pyridone derivatives (**8a,b**) as photochemical precursors for hydroxyl radicals (Scheme 2). The intervention of hydroxyl radicals has been examined by the conversion of 2-propanol to acetone [14], by trapping with triethyl phosphite [15], and by laser studies [16]. Unfortunately, the photolysis of the pyridine-2-thione (**8a**) is not as clean as desired for photobiological studies [17]; however, Kochevar [18] has recently reported that the related pyridine-2-one (**8b**) is a convenient and efficient (Φ_{diss} 0.61 in acetonitrile



8 a: X=S
8 b: X=O

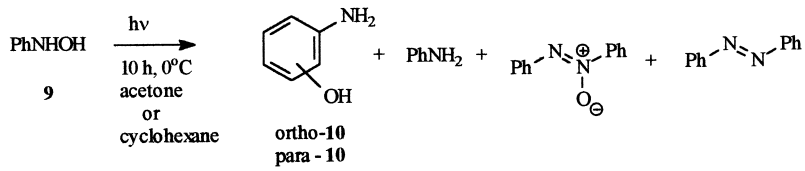
Scheme 2.

and 0.49 in methanol) source of hydroxyl radicals by photochemical cleavage of the N–O bond. Also, in the photolysis of N-phenylhydroxylamine (**9**), products are formed [19], notably *ortho*- and *para*-hydroxyanilines (**10**), which imply the generation of hydroxyl radicals (Scheme 3).

However, the long reaction times required for the photolysis suggest a very inefficient photochemical cleavage of the N–O bond compared to pyridine-2-one. In addition, the GC analyses may have led to unreliable results since any remaining starting material would decompose or undergo rearrangement due to the high temperatures in the GC injection port. Finally, although the Bamberger reaction in which N-phenylhydroxylamine is converted to the hydroxyanilines **10** is an acid-catalyzed rearrangement, their formation is not consistent with the reaction of hydroxyl radicals with aniline [20]. Problems on the photochemistry of hydroxylamine **9** demanded a restudy of its photochemistry and we report our results herein.

2. Experimental

N-phenylhydroxylamine [21] and azoxybenzene [22] were prepared by literature methods, the former was recrystallized twice from ethyl ether/petroleum ether before photolysis. Aniline, azobenzene and the *ortho*- and *para*-



Scheme 3.

hydroxyanilines were commercially available and either distilled or recrystallized before use. Acetonitrile, methanol and water were all hplc grade.

Reversed-phase hplc analyses were carried out on a Kontron instrument, equipped with a Kontron model 430 detector system (set at 254 nm), a Kontron T 414 pump and a 100-C18 column. The eluent was 50/50 (v/v) acetonitrile/water mixture, the flow rate was 0.6 ml/min, and toluene was used as an internal standard. The UV spectral determinations were run on a Hitachi U-3200 spectrometer, and the irradiations were carried out in a Rayonet Photochemical Reactor supplied with 16 RPR-3000 lamps and a merry-go-round accessory.

For the photolyses, ca. 10^{-2} M solutions of N-phenylhydroxylamine were used, which were purged with argon gas for 20 min prior to irradiation. After irradiation, toluene (internal standard) was added and the mixture analyzed directly by hplc. Quantum yield determinations were carried out in the same apparatus with azoxybenzene as the external actinometer [23], the conversion was kept to less than 15%. The solid-state reaction was conducted by placing crystalline N-phenylhydroxylamine (**9**) in an NMR tube, which was purged with argon gas for 20 min, placed into the Rayonet reactor and photolyzed for 5 min. After irradiation, the contents were dissolved in acetonitrile, an exact amount of toluene added as the internal standard and the mixture analyzed by hplc at the conditions specified above.

3. Results and discussion

The UV spectra of the hydroxylamine **9** in acetonitrile, methanol and cyclohexane are essentially the same as those of aniline. Thus, λ_{max} values for both amines are located at 282, 281 and 278 nm and the molar absorptivities at 300 nm in these three solvents are 310, 278 and 50 M^{-1} cm^{-1}, respectively.

The photolysis of N-phenylhydroxylamine (**9**) at 300 nm in both acetonitrile and methanol proceeded rapidly (ca. 50% conversion in 20 min in acetonitrile and 40 min in methanol). The product studies are summarized in Table 1; clearly, the major products are aniline and nitrosobenzene. The nitrosobenzene is found in lower yield because it reacts with **9** to generate azoxybenzene [24].

In addition, azobenzene, nitrobenzene and 2-hydroxyazobenzene (**11**) are formed in minor amounts. The latter is formed as a secondary photoproduct of azoxybenzene [23]. In our experiments, the hydroxyanilines **10** were detected in only trace amounts (<4%), as determined by hplc analysis, which is in contrast with previous work [19]. Indeed, a control experiment confirmed that the substantial amounts of the hydroxyanilines **10** were produced through thermal decomposition of the unaltered hydroxylamine **9** in the injection port.

The quantum yields for the disappearance of hydroxylamine **9** in acetonitrile ($\Phi = 0.29 \pm 0.013$) and in methanol ($\Phi = 0.25 \pm 0.020$) are a little lower than for pyridone (**8b**), but are reasonably efficient in terms of N–O bond cleavage. Attempts were made to determine the quantum yields of disappearance in the less polar solvent tetrahydrofuran; however, in tetrahydrofuran, the photoreaction was so rapid that the initially formed nitrosobenzene reacted with the hydroxylamine **9** to generate azoxybenzene, which rendered measurements of the consumption of starting material unreliable.

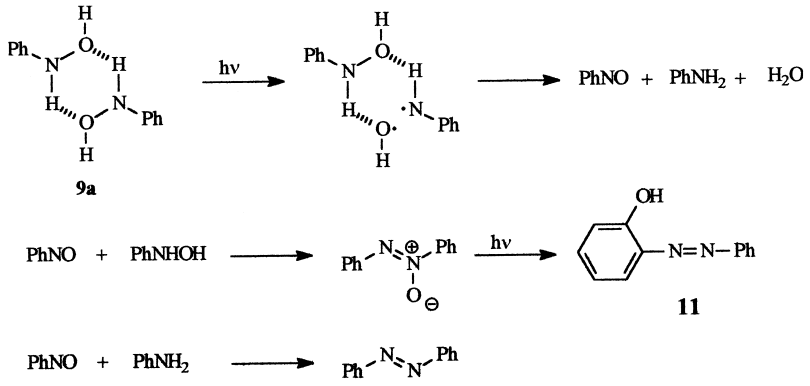
The high amounts of both aniline and nitrosobenzene that are formed during the relatively short irradiation periods of the hydroxylamine **9** suggest an efficient photochemical reaction mode. We propose the novel disproportionation reaction of the intermolecularly hydrogen-bonded dimer **9a** for this photolysis (Scheme 4). Bordwell [25] has found that the N–H bond is slightly more acidic than the O–H bond, which makes the hydrogen bonded structure **9a** plausible. Former infrared studies on **9** in carbon tetrachloride solution confirm this proposal [26]. These spectra showed that a broad infrared band for the intermolecularly hydrogen bonded –OH and –NH groups disappeared in dilute solutions and were replaced by two sharper peaks at 3584 and 3325 cm^{-1} which belonged to the monomeric species in solution.

It has been observed that the ease of hydrogen abstraction processes in the crystalline state is dependent upon geometric requirements [27] and that intramolecular hydrogen bonding facilitates this process [28]. Our observation that

Table 1
Product distribution in the photolysis of N-phenylhydroxylamine (**9**)[a,b]

Solvent	Φ_{diss}	Conversion (%)	Mass balance (%)	$PhNH_2$	PhNO	PhN=NPh	PhN = N(O)Ph	**11**[c]	$PhNO_2$
MeCN	0.29 ± 0.013	52[d]	79	0.47	0.18	0.01	0.048	0.072	0.01
MeOH	0.25 ± 0.020	60[e]	75	0.48	0.098	0.026	0.082	0.066	Trace
Solid		6[f]	89	0.46	0.42				

[a]Amounts given in mol product/mol N-phenylhydroxylamine consumed.
[b]HPLC analysis (RP C-18 column, 50 : 50 MeCN/H_2O), and a flow rate of 0.6 ml/min, error ±2% of the stated values normalized to 100%.
[c]2-hydroxyazobenzene.
[d]20 min in acetonitrile.
[e]40 min in methanol.
[f]5 min.



Scheme 4.

the 5 min photolysis of the hydroxylamine **9** in the solid state to generate nitrosobenzene and aniline as the two major products in nearly equal amounts as in the solution phase is in accordance with our mechanistic proposal in Scheme 4.

This reaction also occurs thermally [29], when hydroxylamine **9** is heated under reflux for 2 h in chloroform to result in aniline and azoxybenzene. Under these conditions, the initially formed nitrosobenzene condenses with the hydroxylamine **9** to afford azoxybenzene [24].

In summary, the photochemistry of N-phenylhydroxylamine (**9**) is characterized by efficient N–O bond cleavage to generate both aniline and nitrosobenzene as the major products through disproportionation of its hydrogen bonded dimer **9a**. This unprecedented process is responsible for the low yield of hydroxyl radicals that are set free in the photolysis and, hence, only traces of hydroxyanilines **10** are observed.

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