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Mechanism of Photochemical O-Atom Exchange in Nitrosamines with Molecular Oxygen

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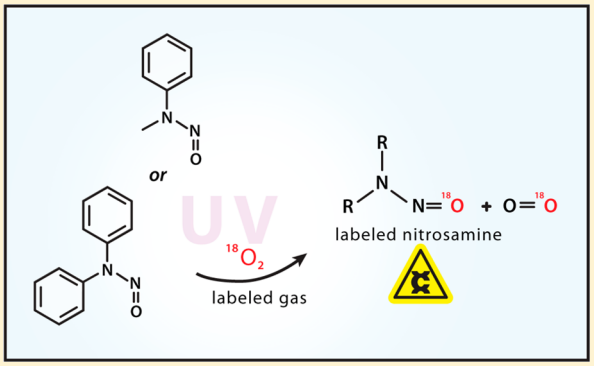
Supporting Information

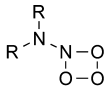
ABSTRACT: The detection of an oxygen-atom photoexchange process of *N*-nitrosamines is reported. The photolysis of four nitrosamines (*N*-nitrosodiphenylamine **1**, *N*-nitroso-*N*-methylaniline **2**, *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine **3**, and *N*-nitrosodiethylamine **4**) with ultraviolet light was examined in an $^{18}O_2$-enriched atmosphere in solution. HPLC/MS and HPLC-MS/MS data show that ^{18}O-labeled nitrosamines were generated for **1** and **2**. In contrast, nitrosamines **3** and **4** do not exchange the ^{18}O label and instead decomposed to amines and/or imines under the conditions. For **1** and **2**, the ^{18}O atom was found not to be introduced by moisture or by singlet oxygen [$^{18}(^1O_2\ ^1\Delta_g)$] produced thermally by $^{18}O-^{18}O$ labeled endoperoxide of *N,N′*-di(2,3-hydroxypropyl)-1,4-naphthalene dipropanamide (DHPN$^{18}O_2$) or by visible-light sensitization. A density functional theory study of the structures and energetics of peroxy intermediates arising from reaction of nitrosamines with O_2 is also presented. A reversible head-to-tail dimerization of the *O*-nitrooxide to the 1,2,3,5,6,7-hexaoxadiazocane (30 kcal/mol barrier) with extrusion of O=^{18}O accounts for exchange of the oxygen atom label. The unimolecular cyclization of *O*-nitrooxide to 1,2,3,4-trioxazetidine (46 kcal/mol barrier) followed by a retro [2 + 2] reaction is an alternative, but higher energy process. Both pathways would require the photoexcitation of the nitrooxide.

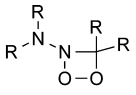


INTRODUCTION

Despite the decades-long interest in *N*-nitrosamine organic chemistry and toxicity,[1,2] no photochemical O-atom exchange process with molecular oxygen has been reported. One paper[3] speculated that an O-atom exchange between singlet oxygen ($^1O_2$) and *N*-nitrosamine would proceed by a 1,2,3,4-trioxazetidine intermediate (cycloNO$_3$ species) (Scheme 1).

Scheme 1


1,2,3,4-trioxazetidine


1,2,3-dioxazetidine

In related papers,[4−9] experimental and theoretical evidence have pointed to the intermediacy of a 1,2,3-dioxazetidine (cycloCNO$_2$ species) in the reaction of $^1O_2$ with hydrazones, which cleaves the hydrazone C=N bond yielding carbonyls and *N*-nitrosamines.

Little is known of the intermediates involved in the direct photolysis of nitrosamines in the presence of O_2 and the formation of peroxy intermediates. Early studies of Tanikaga[10] and Chow et al.[11] were done in air-saturated solutions. Formed aminium radical cations ($R_2NH^{+\cdot}$), from protonation of aminyl radicals ($R_2N^{\cdot}$), were thought not to react with O_2 due to unaffected absorption signals at 10^{-3} M O_2 concentrations.[12] Past studies had focused on nitrosamine excited states, NO· release, and the formation of amine and imine, not on *photooxygen atom* exchange chemistry. Indeed, nitrosamine photolysis studies mainly focused on N_2-degassed solutions.[11−16]

Here, we review nitrosamine photochemistry to set the stage for our work. Using N_2-degassed solutions, the direct photolysis of nitrosamines can lead to the homolysis of the N−N bond[17,18] via excitation to the S_1 and S_2 states.[19−21] For diarylnitrosamines, photodissociation of NO· occurs from the singlet excited state.[15,22,23] The triplet state of diarylnitrosamine has a low propensity to dissociate NO·.[15] Later we will show that photoexpulsion of NO· from **1** and **2** is minor pointing to the importance of a triplet reaction in our system. For *N*-nitrosodimethylamine, the first excited singlet state ($1^1A''$)

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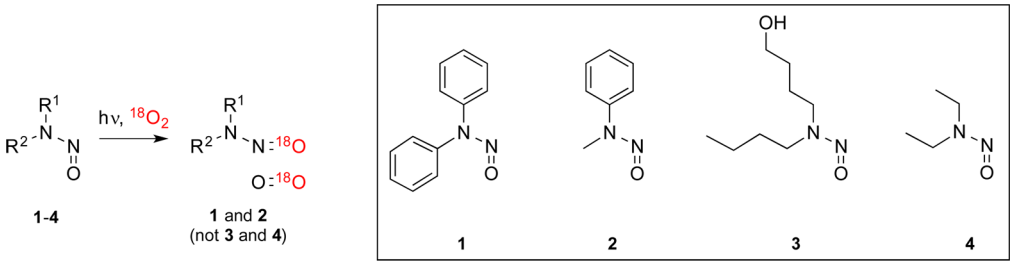
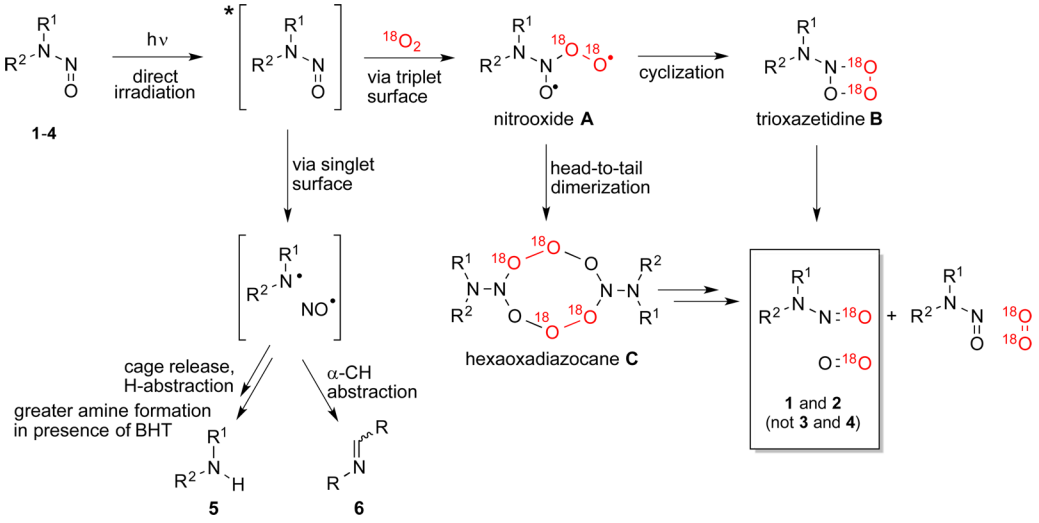
Scheme 2. Photo ^{18}O Exchange Process and Generation of ^{18}O-Labeled Nitrosamines



Scheme 3. Proposed ^{18}O Exchange Mechanism for Generating the ^{18}O-Labeled Nitrosamine



contains $np_O \rightarrow \pi^*_{NO}$ character, while the second excited singlet state ($2^1A'$) contains $np_N \rightarrow \pi^*_{NO}$ character.[20] Chow et al.[16] also found a direct excitation route [$S_0 \rightarrow T_1$ ($n \rightarrow \pi^*$) transition] for *N*-nitrosodimethylamine at 453 nm. The photolysis of alkyl nitrosamines leads to NO· release and aminyl radicals or aminium radical cations after protonation[20,21] in the presence of acid.[13] On the S_1 excited surface, CASSCF calculations show that *N*-nitrosodimethylamine can lose NO· by loss of $R_2N-N{=}O$ planarity,[20,24] where subsequent reactions were stymied due to high-energy barriers so that recombination of NO· and R_2N· is favored and regenerates ground-state nitrosamine. When originating from the S_1 state, aminyl radicals can have lifetimes (τ) upward of 0.5 s.[16] Consistent with a long lifetime, Geiger et al. found that UV photolysis of *N*-nitrosodimethylamine led to isotopic exchange for ^{15}NO· from the $S_0 \rightarrow S_1$ transition but not the $S_0 \rightarrow S_2$ transition.[25,26] Chow et al.[16] also found that excitation *N*-nitrosodimethylamine to S_2 led to NO· release and products such as imines ($CH_2{=}NHCH_3$ and $CH_2{=}NH$) and a methyl radical (CH_3·). Photolysis of *N*-nitrosopiperidine also yielded imines.[11,16] On the other hand, UV photolysis of **1** started with NO· release and led to Ph_2NH and, after extended photolysis, carbazole as a secondary product. Photorelease of NO· has been recognized in other compounds, such as diazeniumdiolates.[27−30] With time-dependent DFT calculations, an O_2-dependent process is known for $n \rightarrow \pi^*$ excitation of $CH_3CH_2NHN{=}O$ with isomerization and H-abstraction to reach $CH_3CH{=}NH$.[31]

Today, the potential for photochemical O-atom exchange in nitrosamines with O_2 remains unexplored. We thought that an oxygen isotope labeling study would be useful since its use in rearrangement and cleavage reactions has helped deduce mechanisms in the past. For example, ^{18}O isotope labeling has helped deduce the mechanism of the Robinson−Gabriel oxazole synthesis[32] and has proved useful in tracking peroxynitrogen and -sulfur species in reactions,[33,34] and other oxygen-transfer reactions.[35−39] One example of ^{18}O labeling described phenyl dioxaziridine (cycloNO$_2$ species) arising in the photooxidation of phenyl azide[40−47] and accompanying calculations.[48,49]

Here, we describe a scrambling of O-atoms in the photolysis of nitrosamines in the presence of $^{18}O_2$. We report experiments and calculations that suggest a new oxygen atom exchange scheme. One feature is the presence of an intermediate, trioxazetidine (cycloNO$_3$ species), as playing an important role in the reaction mechanism. HPLC/MS and HPLC-MS/MS were used to examine the photochemistry of four nitrosamines (*N*-nitrosodiphenylamine **1**, *N*-nitroso-*N*-methylaniline **2**, *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine **3**, and *N*-nitrosodiethylamine, **4**). These nitrosamines, **1**−**4**, were chosen to vary in their number of phenyl and alkyl groups. The intention was to uncover a possible photoexchange process and evaluate a substituent dependence for the process. DFT and TD-DFT calculations were also carried out. Experimental and theoretical evidence that supports the reaction in Scheme 2 is described next.

RESULTS AND DISCUSION

We thought that the research should focus on the photooxygen atom exchange mechanism of nitrosamines **1**−**4** because observations of the intermediates in O_2-saturated solution have not yet been sought. Experimental and theoretical

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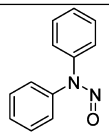
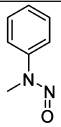
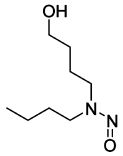
Table 1. HPLC/MS Data of the Nitrosamine Percent ^{18}O Exchange and Decomposition in the Presence of $^{18}O_2$ in $CHCl_3$

nitrosamine	irradiation time (h)	relative abundance of isotopes (%) [a]			percent decomposition (%) [b]
		$[M+H]^+$	$[(M+1)+H]^+$	$[(M+2)+H]^+$	
 **1** (m/z = 199)	0	100±0	17±2	1±0	0
	3	65±4	11±2	8±2	35±4
 **2** (m/z = 137)	0	100±0	8±1	0±0	0
	3	50±2	4±0	12±3	50±2
 **3** (m/z = 175)	0	100±0	12±1	1±0	0
	1	30±3	4±1	0±0	70±3
 **4** (m/z = 103)	0	100±2	6±0	1±1	0
	0.5	48±2	3±0	0±0	52±2

[a]Relative to the sum of area of the $[M + H]^+$, $[(M + 1) + H]^+$, and $[(M + 2) + H]^+$ peaks. [b]Based on the amount of reactant remaining after photolysis.

calculations have been conducted for determining the likely intermediates produced upon excitation of nitrosamine in the presence of $^{18}O_2$. The proposed reaction scheme is shown in Scheme 3. The experimental photoexchange results will be discussed first, followed by product analyses and theoretical calculations.

Direct Excitation of Nitrosamines 1−4 in the Presence of Labeled Molecular Oxygen ($^{18}O_2$). Photolyses of **1**−**4** (5 mM) in $^{18}O_2$-saturated $CHCl_3$ solutions were carried out at room temperature by irradiation with a metal halide or tungsten light source. Table 1 shows that the ^{18}O-label was exchanged into nitrosamines **1** and **2**, but not **3** and **4**, as it will be discussed below. Figure 1 shows mass spectral data for **1** prior to and after photolysis for 3 h. The base peak at m/z = 199.08 is unlabeled **1** $(M + H)^+$, and the peak with a +2 Da mass increase ($[(M + 2) + H)]^+$, m/z = 201.08) is ^{18}O-labeled **1**. Peaks with m/z = 200 and 201 correspond to the natural abundance of isotopomers containing 1.1% ^{13}C and 0.21% ^{18}O, respectively. The small peak at m/z = 202 is due to the isotopomer with the ^{18}O label and the natural abundance of ^{13}C (1.1%). Figure S7 (Supporting Information) shows mass spectral data for **2** prior to and after photolysis where a peak with a +2 Da mass increase is found for ^{18}O-labeled **2**. Table 1 shows that the ^{18}O-label is photoexchanged with limited efficiency, which led us to analyze decomposition yields and byproduct formation.

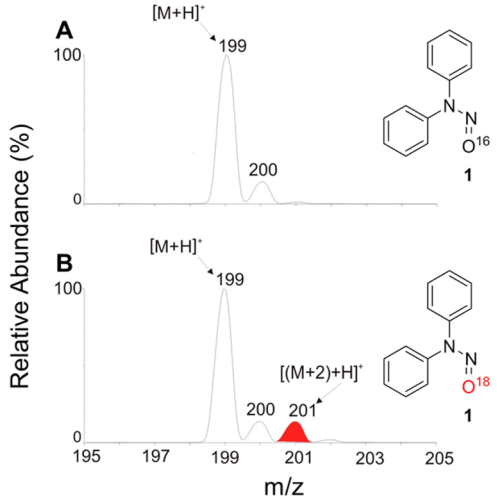


Figure 1. HPLC-MS/MS analysis of (A) **1** prior to photolysis and of (B) **1** with the ^{18}O-label photochemically introduced.

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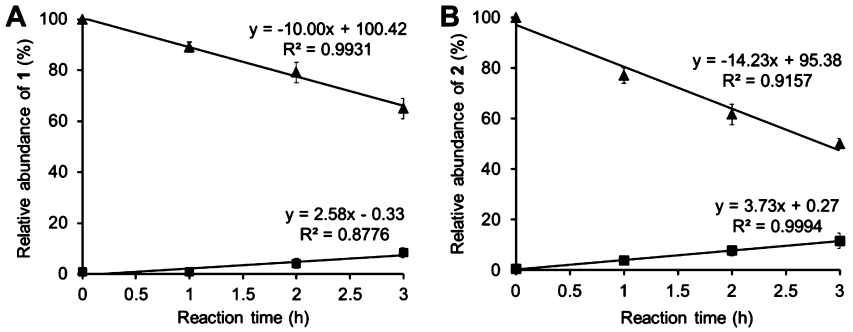
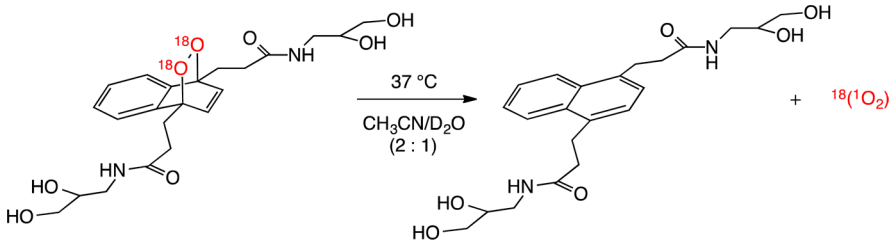


Figure 2. HPLC/MS isotopic abundances of nitrosamine reagent $[M + H]^+$ (▲) and ^{18}O-labeled nitrosamine product $[(M + 2) + H]^+$ (■) as a function of photolysis time of **1** (A) and **2** (B) with $^{18}O_2$ in acetonitrile. The sum of the isotopic abundance of the two peaks and $[(M + 1) + H]^+$ was normalized to 100%.

Scheme 4



Nitrosamine Photolytic Instability. HPLC-MS/MS was used to determine the percent yields of products in the photolysis of **1**−**4** (Figures S3, S7, S11, and S14, Supporting Information). It is clear that nitrosamine photodecomposition rates are increased as the number of alkyl groups are increased. The di- and monophenyl nitrosamines **1** and **2** only photodecomposed by 35 ± 4% and 50 ± 2% photodegradation after 3 h, respectively. In contrast, the amount of **3** and 4 remaining was far less. After 1 h of photolysis, the amount of starting material remaining of **1** was 89%, of **2** was 77%, of **3** was 30%, and of **4** was 4%. Figure 2 shows the rate of appearance of ^{18}O-labeled **2** is 1.4-fold greater than that of ^{18}O-labeled **1**, but that the rate of the photodegradation of **2** is greater by 1.5-fold than that of **1**. Clearly, the dialkyl substituted nitrosamines decompose rapidly. The time to fully photodegrade **3** and **4** was and 3 h and 2 h, respectively. The photolysis of nitrosamines **1** and **2** for 3 h led to the detection of amines, namely *N,N*-diphenylamine $[m/z = 170\ (M + H)^+]$ and *N*-methylaniline $[m/z = 108\ (M + H)^+]$, in 17% and 28% yields, respectively. As seen in the Supporting Information, amines and/or imines were detected upon the photolysis of nitrosamines **3** and **4.**

Effects of Added Radical Scavenger BHT. Because Crumrine et al.[15] found that the photolysis of nitrosamines leads to NO· and aminyl radicals where amine product formation was increased in protic solvents, we hypothesized that BHT scavenging of the aminyl radical by a H-atom transfer agent will decrease the α-C−H abstraction reaction to imine **6**. This is indeed what we find. In the presence of BHT and $^{18}O_2$, UV photolysis of **3** was carried out for 1 h and followed by HPLC-MS/MS. The formation of amine **5** increased from 42% to 60% and the formation of imine **6** decreased from 24% to 2%. The result suggests that the aminyl radical arises following NO· release and rapidly abstracts a hydrogen atom in the presence of BHT. Because of the possible instability due to moisture, we next examined whether the source of the ^{18}O in photolyzed **1** and **2** was due to adventitious trapping of H_2O.

The Photo-oxygen Exchange by Adventitious $H_2{}^{18}O$ is Ruled Out. When the photolysis reaction was carried out in an $^{16}O_2$-saturated atmosphere in CH_3CN in the presence of <1% w/v $H_2{}^{18}O$ for 3 h, the ^{18}O-atom was found not to exchange into nitrosamines **1** or **2**. Similarly, the ^{18}O-atom exchange did not occur with $H_2{}^{18}O$ addition in N_2 degassed photolysis experiments in the absence of $^{18}O_2$. Thus, the involvement of $H_2{}^{18}O$ in the exchange of ^{18}O can be ruled out. To provide further insight into the formation of these ^{18}O labeled nitrosamines, we have conducted a study to explore whether the exchange process derived from singlet oxygen.

Experiments with ^{18}O-Labeled Singlet Oxygen ($^{18}O_2$). ^{18}O-Labeled singlet oxygen was generated by photochemical or chemical methods. Visible-light irradiation [metal-halide lamp with a cutoff filter (λ < 500 nm) as the light source] of 0.2 mM $SiPcCl_2$ or methylene blue in the presence of **1**−**4** (5 mM) was used in $^{18}O_2$-saturated $CHCl_3$ solutions. We found no evidence for the exchange of an ^{18}O-atom in the nitrosamines. Scheme 4 shows that $^{18}(^1O_2)$ was generated from a chemical source [^{18}O−^{18}O labeled naphthalene endoperoxide of *N,N′*-di(2,3-hydroxypropyl)-1,4-naphthalene dipropanamide (DHPN$^{18}O_2$)],[50] which also failed to exchange an ^{18}O atom into **1**. The thermal decomposition of DHPN$^{18}O_2$ was carried out in the presence of **1** in CH_3CN/D_2O buffer phosphate (2:1) at pD 7.4 and also in a two-phase $CHCl_3/D_2O$ buffer phosphate (2:1) system at pD 7.4 with stirring for 1 h at 37 °C. Figure S6 (Supporting Information) shows the HPLC-MS/MS of ^{18}O-labeled endoperoxide of DHPN$^{18}O_2$ before and after its thermal decomposition. Theoretical evidence that supports the reaction in Scheme 3 is described next.

Computed Energetics. DFT calculations were conducted to predict bond dissociation energies (BDE), excited state energetics, and geometries and energetics of the reagents and intermediates in the nitrosamine/O_2 photoreaction.

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First, we discuss the N−N BDEs that have been computed. Table 2 shows that the BDEs are about 14−18 kcal/mol lower for **1** and **2** compared to **3** and **4**. This is a telling result because the lower N−N BDEs of **1** and **2** *do not* result in greater loss of NO·, but instead a greater propensity for ^{18}O-photoexchange. Our BDE values are similar to previous theoretical studies for N−N BDEs of ∼35 kcal/mol (when X is an aromatic substituent) and X−NH−NO ranging from 48 kcal/mol (when X is an alkyl substituent).[51] Due to resonance, the aminyl radicals derived from the nitrosamines **1** and **2** (i.e., Ph_2N· and Ph(Me)N·) are stabilized and account for the lower N−N BDE relative to the aliphatic aminyl radicals derived from **3** and **4**. Nitrosamines **1** and **2** also have longer N−N bond lengths compared to **3** and **4** as anticipated for weaker N−N bonds. Table 2 and Figure 3 show our TD-DFT computed vertical electronic excitation energy from the ground state (S_0) to the S_1 and T_1 states of nitrosamines **1**−**4** and **7**. Our values are in fairly good agreement with previously reported experimental values.[16] For example, for *N*-nitrosodimethylamine, the experimental reported excited singlet state is 72−73 kcal/mol and the excited triplet state is 58−59 kcal/mol.[16]

Table 2. Energetics and Parameters of Nitrosamines 1−4 with DFT and TD-DFT Calculations

nitrosamine	BDE (kcal/mol)[a]	N−N bond distance (Å)[b]	S_1 (kcal/mol)[c]	T_1 (kcal/mol)[c]
1	28.6	1.35	71.9	48.4
2	32.6	1.34	76.6	53.0
3	47.8	1.32	79.3	55.6
4	46.4	1.32	79.1	55.5

[a]DFT computed enthalpies with UωB97XD/6-31+G(d,p) where BDE = [(R_2N· + NO·) − $R_2NN{=}O$]. [b]ωB97XD/6-31+G(d,p) optimized geometries. [c]TD-DFT computed enthalpies with B3LYP/6-311+G-(d,p).

Next, gas-phase calculations were performed to access the factors that are likely to influence nitrosamine ^{18}O-photoexchange with the aim of evaluating the viability of peroxy intermediates. Our calculations did not take into account solvation. Saddle points do not directly connect **7** + $^3O_2$ with **A** or **B**. Instead, a stepwise pathway endothermic by 46.2 kcal/mol (green line depicted in Figure 3) was found for the reaction of $^3O_2$ with nitroamine **7** to reach *syn-O*-nitrooxide **A**. The *syn-O*-nitrooxide conformer **A** is 2.0 kcal/mol more stable than the *anti-O*-nitrooxide and is related by a rotation around the N−OO bond (structures not shown). The structural integrity of intermediates **A**−**C** was supported by their successful optimization with DFT. But only singlet **A**−**C** exist as well-defined minima on the PES. Minimization attempts of triplet **A**−**C** led to their dissociation of the O_2 molecule. A dimerization of nitrooxide **A** yielded hexaoxadiazocane **C** which was endothermic by 29.6 kcal/mol (blue line depicted in Figure 3). We did not find a transition state for this closure of **A** to **B**. In contrast, a stepwise route from **7** + $^3O_2$ to **B** was found by a large barrier via consecutive transition states, **TS7/B** and **TS7/B′**. Although dioxaziridine *N*-oxide (**8**) is similar to dioxaziridines and peroxy acid dioxiranes (**9**)[52] that can exchange an ^{18}O peroxy acid oxygen (Scheme 5), we do not find evidence for **8** on the potential energy surface after a detailed search of conformational space. We note the addition of $^1O_2$ to **7** is also computed, but it is tempting to suggest charge-transfer $^1O_2$ physical quenching to $^3O_2$, a channel that is significant in azides, amines, and hydrazines,[53−56] where tertiary

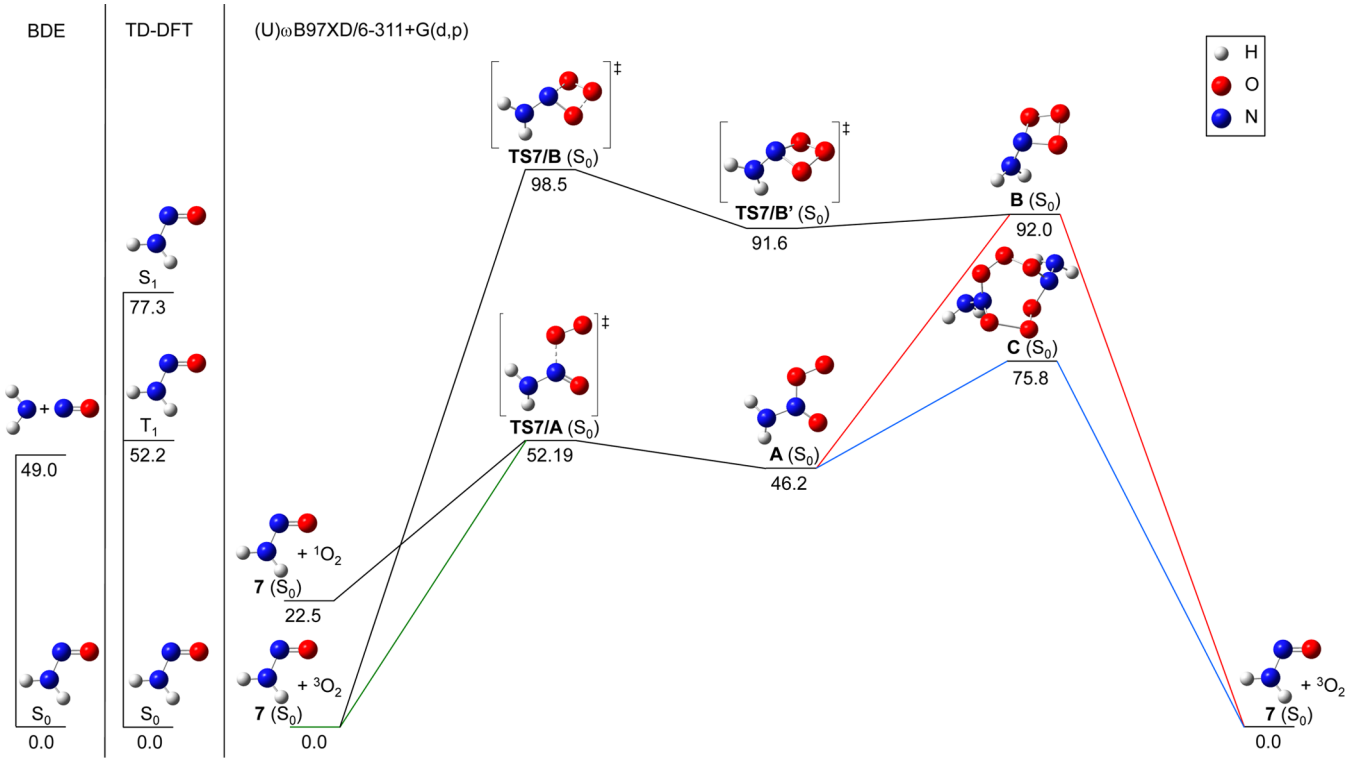

Figure 3. DFT and TD-DFT computed BDE and excited states of nitrosamine **7**. DFT potential energy surface with structures and transition states (TS) for the reaction nitrosamine **7** with triplet and singlet oxygen. The experimental value for $^3O_2/^1O_2$ gap (22.5 kcal/mol) has been used. Energetics in kcal/mol.

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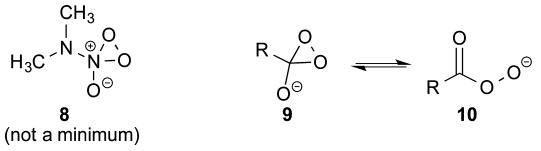
Scheme 5



amines can even chemically react with $^1O_2$ leading to C−N bond cleavage.[57,58]

Mechanism. To assess the factors that underlie nitrosamine photochemistry in the presence of O_2, three mechanistic aspects were considered. One emanates from the ^{18}O exchange reaction of nitrosamines with O_2 via hexaoxadiazocane and trioxazetidine intermediates that cleave apart, the second from unimolecular NO· release and formation of amine and/or imine products, and the last is the viability of the peroxy intermediates.

(i). O-Atom Exchange. That the photoexchange occurs with $^{18}O_2$ is viewed as evidence for a reaction with triplet nitrosamine. Assuming nitrooxide **A** is sufficiently long-lived, subsequent dimerization of the nitrooxide to yield the hexaoxadiazocane **C** with loss of O═^{18}O can lead to the exchange of the oxygen atom label. Alternatively, but higher in energy, is the conversion of nitrooxide **A** to trioxazetidine **B**, which is followed by the unimolecular collapse of the trioxazetidine to nitrosamine and oxygen.

(ii). Nitrosamine Photodecomposition. The aliphatic substituents on nitrosamine play a key role in facilitating the photodecomposition. α-C−H groups are labile to hydrogen abstraction by radicals and offer an explanation to the rapid photodecomposition of **3** and **4**, and the slightly faster decomposition of **2** compared to **1** in our series. Oxygen-derived radicals would be expected to react with the nitrosamines and contribute to their decomposition. For example, nitrosamines[16] (and amines[59]) bearing α-C−H groups can more easily photodecompose than aromatic nitrosamines (and amines). Furthermore, the dialkylaminium radical can react with an aliphatic nitrosamine via α-C−H abstraction leading to an alkylidenimine product.[60] There are reports of nitrosamines losing NO· where the exciting wavelength modulates the NO· donor activity, where the aminyl radical can persist for longer periods from the S_1 state.[14,16] That NO· formation in **1** and **2** is minor also argues for a triplet process. Expulsion of NO· occurs but is not the main reaction route of the aryl nitrosamines **1** and **2**. It was interesting and unexpected that lower nitrosamine N−N BDEs correlate with the ease of O-atom photoexchange since the exchange nets an identity reaction, not a N−N bond broken compound.

(iii). Reactive Intermediates in the ^{18}O Exchange Process. The mechanism in Scheme 3 is tentative and is based on nitrosamines **1** and **2** and the dimerization of their corresponding nitrooxides in preference to the unimolecular cyclization of nitrooxides. Computations indicate high-energy barriers for the nitrooxide dimerization to hexaoxadiazocane **C** and for the conversion of nitrooxide **A** to trioxazetidine **B**. Thus, photochemical interconversions would be necessary to overcome the high barriers. We note there are similarities between our work and the previous literature. That is, nitrooxide **A** bears similarity to the nitrosooxide, an intermediate formed in the reaction of nitrenes with $^3O_2$.[40−49,61,62] Relatedly, the trioxazetidine **B** is reminiscent of the 1,2,3,4-dioxadiazete, which along with its radical cation (cycloN_2O_2 species) has been postulated in gas-phase ion−molecule reactions.[63] The dimerization of nitrooxide **A** to hexaoxadiazocane **C** is reminiscent of the coupling of a carbonyl oxide yielding a dimeric benzophenone peroxide[64] and also nitrosooxide yielding a tetraoxadiazine.[27] Furthermore, the photocyclization of **A** and **B** is similar to that reported for the photocyclization of nitrosooxide to dioxaziridine,[35,42,65] where ^{18}O labeling also showed aryl dioxaziridines arise in the photooxidation of aryl azides (λ > 350 nm) using $^{18}O_2$ gas by photocyclization of the aryl nitrosooxide.[40,41]

In summary as described above, a photochemical process that transposes an ^{18}O label from molecular oxygen $^{18}O_2$ was seen for nitrosamines **1** and **2**, but not for **3** and **4**. The ^{18}O-atom source was found not to be from moisture based on control photolysis experiments with ^{18}O-labeled H_2O. Thermal or visible-light sensitized production of singlet $^{18}O_2$ to give ^{18}O-labeled nitrosamine was not observed. In these reactions, physical quenching of $^1O_2$ to $^3O_2$ is likely a key pathway. An ordinary [2 + 2] cycloaddition of $^1O_2$ to the nitrosamine N═O bond is not operating as a means to reach the trioxazetidine and scramble the ^{16}O and ^{18}O atoms.

■ CONCLUSION

Four nitrosamines **1**−**4** were irradiated in the presence of ^{18}O-labeled molecular oxygen gas to examine a substituent dependence in the *O*-atom exchange process. Di- and monophenyl nitrosamines **1** and **2** are more photostable than the dialkyl nitrosamines **3** and **4**. Nitrosamines are generally recognized not to be good sources of NO·,[23,66] even under a N_2 atmosphere, due to the formation of byproducts. Whether triplet sensitization of nitrosamines is also a viable strategy to reach the nitrooxide is a question that we are also exploring. The formation of non-nitrosamine products, such as nitroamine in photooxidation reactions, is currently being explored. Another question yet to be addressed is related to possible chemiluminescence from the trioxazetidine (by analogy to 1,2-dioxetanes).[67,68] Time-resolved IR methods[69−72] would also provide insight into the mechanism. Lastly, the discovery of an oxygen exchange route in nitrosamine photochemistry and the formation of peroxy intermediates derived from this reaction is described here and may provide a clue to new factors significant in nitrosamine phototoxicity.

■ EXPERIMENTAL SECTION

Reagents. Diphenylamine, *N*-methyl-*N*-(*p*-tolyl) amine, silicon phthalocyanine dichloride ($SiPcCl_2$), methylene blue, butylated hydroxytoluene (BHT), $K_2Cr_2O_7$, CH_3CN, $CHCl_3$, $CDCl_3$, $H_2{}^{18}O$ (96.9%), $^{18}O_2$ gas (99% ^{18}O) from a gas cylinder, *N*-nitrosodiphenylamine **1**, *N*-nitroso-*N*-methylaniline **2**, *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine **3**, and *N*-nitrosodiethylamine **4** were purchased commercially. (*Caution: nitrosamines are carcinogenic.*)

Instrumentation. Positive ion mode electrospray ionization mass spectrometry data were collected as previously described.[73] The analysis was done by direct injection to a mass spectrometer with a *Z*-spray atmospheric pressure ionization source. Samples were dried and reconstituted in acetonitrile prior to injection into the mass spectrometer. HPLC-MS/MS refers to liquid chromatography coupled to an electrospray ionization tandem mass spectrometry instrument[74] that was used. HPLC/MS data were collected as has been described in our previous work.[75] NMR data were recorded on an instrument operating at 400 MHz for ^1H NMR and 100.6 MHz for ^{13}C NMR. UV−visible and GC/MS data were also collected. Micromass software was also used to generate theoretical spectra of nitrosamines to calculate the natural abundance of isotopomers.

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^{18}O-Photoexchange Reactions. Photooxidations were carried out in a 3 mL sealed glass vial at 27 °C with periodic $^{18}O_2$ bubbling and irradiation with two 400-W metal halide lights or two 500-W tungsten lights. Experiments were conducted in 1 mL $CHCl_3$ or CH_3CN solutions of 1 mM or 5 mM **1**−**4**. Prior to photolysis, one of two methods was used to introduce $^{18}O_2$ gas: (i) $CHCl_3$ solutions were frozen and thawed in liquid N_2 and kept under vacuum, then the system was connected to an $^{18}O_2$ gas cylinder, and the system was kept closed during the photolysis; or (ii) CH_3CN solutions were sparged with N_2 for 15 min and then $^{18}O_2$ gas for 5 min. During the photolysis, at 30 min intervals, samples were sparged with $^{18}O_2$ gas for 3 min periods. $CHCl_3$ contains trace ethanol as a stabilizer, which was not removed. The results were reproducible and nearly identical in either $CHCl_3$ or CH_3CN solutions. Reaction mixtures were analyzed by HPLC/MS and HPLC-MS/MS. For the HPLC/MS, the column used for **1**−**4** was a 2.1 mm × 30 mm, 3.5 μm SB-C18 column. For the HPLC-MS/MS, the column used for **1** and **2** was a 25 cm × 2.1 mm, 5 μm Supelcosil LC18-S column, and for **3** and **4** it was a 25 cm × 4.6 mm, 5 μm C18 Gemini column.

UV Photolysis of *N*-Nitrosodiphenylamine 1. HPLC/MS: t_R = 5.48 min; HRMS (+ESI) calcd for labeled $C_{12}H_{11}N_2{}^{18}O$ = 201.0938, found 201.0958; calcd unlabeled $C_{12}H_{11}N_2O$ = 199.0871, found 199.0872. When followed by HPLC-MS/MS, peaks were observed for **1** (m/z = 199) and ^{18}O-exchanged **1** (m/z = 201) at 24.69 min and diphenylamine (m/z = 170) at 26.51 min. Spiking a commercial sample of diphenylamine led to an increase in the m/z = 170 peak.

UV Photolysis of *N*-Nitroso-*N*-methylaniline 2. HPLC/MS: t_R = 3.91 min; HRMS (+ESI) calcd for labeled $C_7H_9N_2{}^{18}O$ = 139.0757, found 139.0755; calcd unlabeled $C_7H_9N_2O$ = 137.0715, found 137.0724. When followed by HPLC-MS/MS, peaks were observed for *N*-methylaniline (m/z = 108) at 4.81 min and **2** (m/z = 137) and ^{18}O-exchanged **2** (m/z = 139) at 12.69 min.

UV Photolysis of *N*-Butyl-*N*-(4-hydroxybutyl)nitrosamine 3 and nitrosodiethylamine 4. When followed by HPLC-MS/MS, peaks were observed for parent **3** and **4**, but not ^{18}O-exchanged **3** and **4**. The photolysis of **3** led to an imine 4-((1-hydroxybutyl)imino)-butan-1-ol or isomer [m/z = 144 $(M + H)^+$] at 5.87 min and 4-(butylamino)butan-1-ol [m/z = 146 $(M + H)^+$] at 7.26 min. The photolysis of **4** led to diethylamine (m/z = 74) at 3.92 min.

Photochemical and Chemical Generation of Singlet Oxygen [$^{18}(^1O_2)$]. Experiments were conducted in 1 mL $CDCl_3$ or CH_3CN solutions of 1 mM or 5 mM **1**−**4**. The experiments for a photochemical source of $^{18}(^1O_2)$ used a photosensitizer, 0.1 mM $SiPcCl_2$ or methylene blue, in which samples were irradiated through a cutoff filter (λ < 500 nm) solution of 0.2 M $K_2Cr_2O_7$ in 0.5% v/v H_2SO_4. The experiments for a chemical source of $^{18}(^1O_2)$ used an $^{18}O-{}^{18}O$ labeled endoperoxide [*N*,*N*′-di(2,3-dihydroxypropyl)-1,4-naphthalene dipropanamide ($DHPN_{18}O_2$)] that was synthesized as described previously.[7]

Computational Methods. Calculations were performed with Gaussian 09 (revision D.01)[76] and visualized with Gaussview 5.0.[77] Geometries were optimized with unrestricted ωB97X-D, which includes empirical dispersion[78] along with the 6-311+G(d,p) basis set. These calculations yielded results in reasonably good agreement with CCSD(T) based on the reaction of ethene with $^1O_2$.[79] The energetics are reported as the thermal enthalpies. BDEs were determined by UωB97X-D/6-311+G(d,p) calculations of optimized geometries of **1**−**4** and the corresponding aminyl radicals and NO· with the formula: BDE = [(R_2N· + NO·) − $R_2NN{=}O$]. For the potential energy surface (PES) in Figure 3, frequency calculations established the nature of the stationary point obtained. Vibrational analyses showed that species were minima with the exception **TS7/A** which is a first-order saddle point connecting to **A**, and **TS7/B** and **TS7/B′**, which are consecutively connected transition structures, the latter connecting to **B**. TD-DFT[80] with B3LYP/6-311+(d,p) calculations was used without thermal corrections to determine the S_0, S_1, and T_1 of **1**−**4** and **7**.

■ ASSOCIATED CONTENT

Supporting Information

Details on experimental conditions for the ^{18}O exchange, as well as HPLC-MS/MS, HPLC/MS, HRMS and UV−visible spectra and DFT computed data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00633.

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Notes

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