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Photochemistry of N-Phenyl Dibenzothiophene Sulfoximine†

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ABSTRACT

Sulfoximines are popular scaffolds in drug discovery due to their hydrogen bonding properties and chemical stability. In recent years, the role of reactive intermediates such as nitrenes has been studied in the synthesis and degradation of sulfoximines. In this work, the photochemistry of N-phenyl dibenzothiophene sulfoximine [5-(phenylimino)-5H-5,4-dibenzo[h,d]thiophene S-oxide] was analyzed. The structure resembles a combination of N-phenyl iminodibenzothiophene and dibenzothiophene S-oxide, which generate nitrene and O (3P) upon UV-A irradiation, respectively. The photochemistry of the N-phenyl dibenzothiophene sulfoximine was explored by monitoring the formation of azobenzene, a photoproduct of triplet nitrene, using direct irradiation and sensitized experiments. The reactivity profile was further studied through direct irradiation experiments in the presence of diethylamine (DEA) as a nucleophile. The studies demonstrated that N-phenyl dibenzothiophene sulfoximine underwent S–N photocleavage to release singlet phenyl nitrene which formed a mixture of azepines in the presence of DEA and generated moderate amounts of azobenzene in the absence of DEA to indicate formation of triplet phenyl nitrene.

INTRODUCTION

Sulfoximines have recently regained popularity as an important functional group in drug discovery and medicinal chemistry (1–7). The functional group, when added to lead compounds for generating analogues, has shown to increase chemical and metabolic stability and improve solubility (1,2,5). The focus on synthetically incorporating sulfoximine in drug molecules has resurfaced due to recent viable and safe methods described in the literature (8–16). Reactive intermediates in the context of sulfoximine have been often profiled in the discussion of synthesizing them (17–22), but recently focus has also shifted in analyzing reactive intermediates as a by-product of their degradation through S-heteroatom bond cleavages (23). Nitrenes are one of the reactive intermediates that have been outlined in the synthesis of sulfoximines (13,20,24). Thus, the photolysis of sulfoximines through S–N photocleavage would likely generate a nitrene, very similar to N-substituted iminodibenzothiophene photolysis that generates nitrenes (25).

While S–N bond cleavage would be the expected initial photodegradation pathway for sulfoximines, the known photodeoxygenation of dibenzothiophene S-oxide (DBTO) that leads to the production of atomic oxygen [O(3P)] suggests sulfoximines could be capable of generating two reactive intermediates in tandem (26). Studies exploring the product profile from photolysis of aryl sulfoxides and alkyl aryl sulfoxides have revealed pathways consistent with α-cleavage and racemization (27,28). However, Gurria and Posner studied the photolysis of aryl sulfoxides and reported a series of aromatic sulfoxides where the corresponding sulfides were generated in high yields through photodeoxygenation (29). In this study, DBTO was noted to yield its corresponding sulfide in approximately 95% yield (29). Further exploration into the UV-A light-driven photodeoxygenation of DBTO suggested that ground-state atomic oxygen [O(3P)] was a photo-product from S–O bond cleavage (26). Due to lack of spectroscopic techniques for detecting short-lived intermediates such as O(3P) in condensed phase, creative studies using nanocapsule barriers between DBTO derivative and O(3P)-acceptor molecules (30) and product profile investigations with O(3P)-acceptor molecules from photodeoxygenation of DBTO and its derivative (26,31) demonstrated that O(3P) was the likely diffusing electrophilic oxidant. These findings were followed by an array of successful attempts on derivatizing DBTO and its core structure to design exploratory studies to probe O(3P)’s reactivity and study its effect on biomolecules using DBTO derivatives as O(3P)-precursors (32–39).

Atomic oxygen [O(3P)] is a highly reactive oxidant but interestingly it also exhibits unique selectivity with its reactivity in gas and condensed phase (40–43). In the gas phase, it has shown a preference for thiols, alkenes and sulfides compared with aldehydes, alcohols and alkanes (41,42). Likewise, it has shown higher reactivity for primary thiols, conjugated aromatic alkenes and sulfoxides in the condensed phase (43). Studies of O(3P) in solution had been hindered by a lack of “good” sources due to the high energy photons needed to generate O(3P) from reported...
methods (31,40,44–46). However, with the discovery of O(1P) as a product of UV-A irradiation of DBTO (26), the ease of exploring and exploiting the unique selectivity of reactive O(1P) significantly increased. Efforts to derivatize DBTO and its core structure for higher wavelength energy-driven photolysis and aqueous solubility resulted in a series of synthetic and associated photochemical studies (32–34,47,48). These improvements in physical properties through benzannulation and addition of hydrophilic substituents in the DBTO core structure allowed for biological studies to evaluate the effect of O(1P) (35–39). Examining the effect of O(1P) on proteins revealed its selectivity for cysteine residues (35,39), and analyzing its reaction with lipids revealed unique product distribution that included aldehydes (37,38). These reports have demonstrated the exclusive reactivity of O(1P) and the possibilities for DBTO derivatives as O(1P) precursors being used as tools to deliver O(1P) in a targeted specific way in cells.

Similar to O(1P)’s reactivity and biological applications, nitrenes—the likely photoproduction from S–N cleavage of sulfoximines—have been widely referenced in literature for their role in photoaffinity labeling to study protein interactions and complex biomembranes (49). Their longer lifetimes compared with other photoactive species such as carbenes allow for efficient targeting due to greater diffusion (49). Aryl azides have served as primary precursors for introducing nitrenes for photoaffinity labeling since the first ary1 azide photoinactive agent synthesized by Fleet et al. in 1969 (50). Since then, ary1 azido groups have been linked to phospholipids (49,51) to study protein–lipid interactions (52), human erythrocyte membrane proteins (53) and analyzing the subunits of ATP-synthase TF,0,F; in P53 bacterium (54). However, ary1 azides are problematic as they require to be photoradiated close to the absorption maxima of nucleic acids and proteins (49). This uniquely positions N-ar1 substituted sulfoximines as viable ary1 nitrene precursors that can be irradiated at higher wavelengths and circumvent exciting UV-sensitive groups in nucleic acids and proteins.

Nitrenes have been referred to as the chemical equivalent of carbenes in nitrogen chemistry, and much like carbenes, they are synthetically relevant through rearrangements, hydrogen abstraction and insertion reactions (55). These reactions have allowed for the introduction of various nitrogen functional groups such as imines, amines and aziridines in hydrocarbons (55–58). Nitrenes are often generated through thermolysis and photolysis of alkyl or aromatic azides (56,58,59). However, the use of these photo and thermally generated nitrenes in synthesis is limited by its inefficiency in terms of yield and selectivity (55). Metal catalysts address this ineffective reactivity by highly selective nitrene transfers (60–67), allowing these nitrene transfer reactions to be a method for synthesizing sulfoximines (13,24,68).

Among the list of ary1 nitrenes, phenyl nitrene is notable for its complicated spectroscopical, kinetic and reactivity footprint (69,70). The complex reactivity of phenyl nitrene has been explored through photolysis of phenyl azide, and characterizing the generated transient has been used as an insightful indicator to predict product distribution and reactivity (69,71–73). The two intermediates that have been identified in condensed phase are singlet phenyl nitrene (PhN1) and triplet phenyl nitrene (PhN3) (Scheme 1) (70). The singlet transient, PhN1, undergoes rapid ring expansion to form [A] which can be trapped by secondary amine like diethylamine (DEA) to form [B] and the triplet transient PhN3 dimerizes to form azobenzene (69,70,72). The pathway that generates singlet nitrene is also implicated in photolabeling reactions with biomembranes and proteins (49). Additionally, the reactivity observed has been shown to be dependent on concentration of phenyl azide (72), temperature (70) and nucleophile (70–72).

In this work, we have explored the photochemistry of N-phenyl dibenzothiophene sulfoximine [5-(phenylimino)-5H-S,S'-diazo[6,5-d]thiophene S-oxide], 1 (74), which represents a combination of the core structures of dibenzothiophene-S-oxide (DBTO, 2) and N-phenyl iminodibenzothiophene (3) (Scheme 2). This resemblance in the core structure of sulfoximine 1 with compounds 2 and 3 presents the framing of a hypothesis wherein 1 generates the reactive intermediates, nitrene and O(1P), upon photoirradiation (Scheme 2, eqs. 1–3) (25,26). In this report, we attempt to understand the sequence in which the reactive intermediates are generated, and further investigate the photochemistry of 1 through trapping the photoproducts using substrates, common intermediate tests and triplet sensitization reactions. These experiments were designed to determine the events of photolysis, mechanisms at play and possible applications of 1.

Materials and Methods

All reagents and solvents used in this work were purchased from Sigma-Aldrich or Fisher Scientific unless indicated otherwise. HPLC grade acetonitrile was used for photochemical and mechanistic studies. Bruker NMR 400 MHz Avance III or Bruker Avance Neo 600 were used to obtain NMR spectra, and associated analysis was performed on TopSpin 4.0.6 or MestReNova software packages. Thermo Scientific NanoDrop 2000c was used to acquire UV-visible spectra. Agilent 1200 series (Quad pump, DAD with autosampler) with a 5 µL CIPEUS C-18 column (150 × 4.6 mm) was used for HPLC analysis. Photoreactions were performed in Luchem photo reactor with 14 L2C UV-A bulbs (Hitachi FL3B-L-B, fwhm 325–375 nm) or a Photon Technologies International monochromator with a Xenon Short Arc Lamp (75 W). A Q-Exactive Orbitrap equipped with a nanospray ion source (Thermo Scientific) was used for MS analysis at a spray voltage of 1.75 kV in positive ionization mode at a resolution of Rfwhm = 140 K and capillary temperature of 200 °C. MS1 spectra were acquired from m/z 50–750. All products were detected within 1 ppm (approximately 0.2 ppm mass error). A 1.5 cm × 50 µm capillary column packed with Waters Atlantis 3 µm C18 stationary phase was used for separation. Mobile phases were LC-MS grade water (A) and acetonitrile (B), both with 0.1% formic acid. The gradient was as follows (minute, %B): 0 min, 0%; 2 min, 0%; 8 min, 98%; 9.5 min, 98%; 10 min, 0%. The synthesis of sulfoximine 1 is described in the Supporting Information (SI) in detail (SI, Data S1–S3). Statistical analyses were performed on Microsoft Excel and GraphPad Prism.

Energy calculations to estimate sequence of events in photolysis. Bond dissociation energies were calculated by optimizing geometry of 1 using HSEH1PBE/6-311G (d,p) level of theory in Gaussian 09 suite of programs (SI, Data S4) (75–77). The enthalpies for S–N and S–O cleavage reactions for sulfoximine 1 were calculated from energy calculations at different levels of theory using coordinates from the HSEH1PBE/6-311G(d,p) optimized geometry (SI, Section 4) (75). The bond dissociation enthalpies were determined by including a temperature (298.15 K) and an unscaled zero-point energy correction from the HSEH1PBE/6-311G(d,p) frequency calculation (SI, Data S4) (78). Optimized geometries were visualized using Chemcraft (79).

Quantum yield determination. The experiment was performed by dissolving 1 in acetonitrile (3.2 mM), and an optical density of the resulting solution was recorded to be 2.630 (>2) at 325 ± 3 nm. Then, 4 mL of the solution was added to a quartz cuvette and sparged with argon for 15 min. The solution was photolyzed in a monochromator (Photon Technologies International with a Xenon Short Arc Lamp) for 4 h. The experiment was performed at low conversion [corresponding sulfoxide 2, (approximately 3%)]. The concentration of sulfoxide was determined using injections and calibration curves in HPLC. Two trials
were performed, and the error was calculated at 95% confidence interval. Photolysis of azobenzene in alkaline ethanolic conditions was used as a chemical actinometer to determine flux (80).

**Trapping of nitrene using 1-octene.** A solution with sulfoximine 1 (0.08 mmol, 7.6 mM) and 1-octene (8.35 mmol, 835 mM, 110 eq) was prepared in acetonitrile and irradiated for 20 h 39 min in a monochromator with 75 W Xe arc lamp. The solution was then analyzed by HPLC and Shimadzu LC-MS-2010EV. Two trials were performed, and the error was calculated at 95% confidence interval.

**Comparative study of azobenzene formation.** Sulfoximine 1 was dissolved in acetonitrile at varying concentrations (0.16–3.4 mM) in acetonitrile. The solutions were then transferred (4–6 mL) to a quartz test tube with a Micro Spinbar, which was then sealed using a rubber septum. The solution was sparged using argon gas for 15–20 min to minimize dissolved oxygen. The quartz tubes were placed in a Luzchem photoreactor with 14 UV-A LZC-A bulbs (fswm, 325–375 nm), and the solutions were irradiated for different durations (between 15 min and 3.5 h). Concentration and yields for azobenzene, dibenzothiophene (DBTO), and error was calculated at 95% confidence interval. Two trials were performed, and peak areas from LC-MS/MS chromatogram were used to analyze the azepine product profile.

A triplet sensitization reaction was also performed where 1.6 nm solution of 1 was prepared with 3.7 mM of anthraquinone and 1.6 mM of DEA in acetonitrile. The solution (4 mL) was irradiated using a monochromator at 355 ± 5 nm for approximately 18.5 h after degassing with argon. The solution was then analyzed by HPLC and LC-MS/MS.

**RESULTS AND DISCUSSION**

**Photolysis of 1**

Photolysis of N-substituted iminodibenzothiophene and DBTO releases nitrene and O(3P), respectively (25,26). Since sulfoximine 1 resembles a combination of the core structure of N-substituted iminodibenzothiophene and DBTO, the irradiation of sulfoximine 1 can be expected to produce either phenyl nitrene (PhN:) or O(3P) initially (Scheme 3). It was posited that the ratio of nitrene to O(3P) would be dependent upon the difference in the bond energy of the S–N and S–O bond in 1. The S–N bond energy for a series of sulfoximines using MP2(full)/6-31 + G* level has been reported, and the S–N BDE for sulfoximine and N-methyl sulfoximine was calculated to be 51.35 and 41.28 kcal mol⁻¹, respectively (81). In this report, we used B3LYP and HSEH1PBE level of theories in Gaussian 09 suite of programs to compute the S–N and S–O bond dissociation energies (BDE) (75). The methodology of using DFT calculations to predict pathways has been discussed for its uncertainty (82–85), but due to the lack of experimental BDE values for sulfoximines, we relied on this approach to predict the sequence of photoproducts.

**Scheme 1.** Eq. (1): Photoirradiation of phenyl azide leading to formation of singlet and triplet nitrene; eq. (2): singlet phenyl nitrene undergoing ring expansion to form dehydroazepine [A] and forming 2-(diethylamino)-3H-azepine [B]; eq. (3): triplet phenyl nitrene dimerizing to form azobenzene.
much higher than previously reported values for sulfoximines (81), but the structural differences between 1 and the sulfoximines studied in the referenced report are significant. In sulfoximine 1, the sulfur atom is included in a conjugated aromatic system and nitrogen atom is linked to a phenyl group, whereas for sulfoximines studied by Kumar et al. in 2005, the sulfoxide functional group is linked to two hydrogens and nitrogen atom is linked to H, Me, Cl and F (81). The S–N BDE for 1 was calculated to be approximately 70 kcal mol$^{-1}$, which was roughly 40 kcal mol$^{-1}$ less than S–O bond. This significant difference between the calculated two BDE was a strong indicator that S–N bond cleavage would occur before S–O bond cleavage upon irradiation. Another way to rationalize the cleavage of S–N bond before S–O bond is to compare the electronic effects of O and N atoms. Oxygen atom being more electronegative (86) and sulfur with its large size and polarizability (86) render the S–O bond with higher partial charge separation when compared to S–N bond. This partial charge separation is lower in S–N bond because of N atom’s lower electronegativity and larger size when compared to the O atom. This reasoning makes the S–N bond weaker than the S–O bond due to lower differences in electronegativity between S and N atoms. Therefore, we expected the S–N bond to cleave before S–O bond in our bench studies.

To observe the sequence of events experimentally, we performed a reaction where we irradiated a 1.4 mM solution of 1 in acetonitrile after degassing with a monochromator (75 W Xe) at 325 ± 5 nm for 24 h alongside a thermal control. The solution was analyzed on HPLC, and the major peak observed other than 1 was DBTO. Other moderate and minor peaks were observed corresponding to DBT, azoxybenzene and azobenzene. Two trials were performed, and 61 ± 11% (mean ± 95% CI) of sulfoximine 1 was calculated to be converted to DBTO. The thermal control showed no formation of products. This supported our hypothesis that S–N bond was being cleaved upon photolysis of 1 and DBTO was being produced.

**Scheme 2.** N-phenyl dibenzothiophene sulfoximine (1) represents the core structure of dibenzothiophene-S-oxide (DBTO, 2) and N-phenyl iminodibenzothiophene (3); eq. (1): DBTO generates O($^3$P) on UV-A irradiation and dibenzothiophene (DBT) (26); eq. (2): N-substituted iminodibenzothiophene generates corresponding nitrene on UV-A irradiation (25); eq. (3): hypothesis—photoirradiation of 1 will generate phenyl nitrene and O($^3$P).

**UV absorbance and quantum yield**

The ground-state absorption spectrum of 1 presented in Fig. 1 shows the two absorbance bands with maxima at 274 and 319 nm, respectively. We used this UV-trace to determine the wavelength for measurement of photodenitrenation efficiency of 1. Since quantum yield is a measure of photodenitrenation efficiency of 1, we determined quantum yield with respect to the formation of DBTO at 325 ± 3 nm. The $\Phi_{DBTO}$ of 1 was experimentally found to be 0.0141 ± 0.0017. This measurement
was used as a benchmark for experiments designed to probe the mechanism behind photolysis of 1.

**Mechanism of photolysis of 1**

*Trapping photogenerated intermediate using 1-octene.* The S–N bond cleavage through UV-A irradiation and the photoproducts generated further by a reaction with 1-octene were explored. This strategy was used as olefins react with nitrenes from photolysis of N-substituted iminodibenzothiophene to produce aziridines (25). In the reaction with 1-octene, the reaction products were analyzed using HPLC and LC-MS. Sulfoximine 1 underwent 9.4% conversion to DBTO, and we observed peaks on HPLC and LC-MS corresponding to DBTO, DBT, azoxybenzene and azobenzene (Scheme 4). The DBT photoproduct on HPLC accounted for 0.24% yield relative to DBTO formation. This result indicated that S–N bond was being cleaved first and possibly phenyl nitrene was being generated; however, since aziridine product was not detected, questions about the spin state of the generated transient remained. The aziridine product was not detected even when the photolysis was carried out in neat 1-octene. Inconsistency in product profile for phenyl nitrene with alkenes has been noted previously in the literature (70,87). In order to infer the mechanism behind photolysis of 1 and characterize the identity of the generated transient, experiments were designed based on findings presented in a study by Schrock and Schuster (72), which focused on determining the chemical properties of phenyl nitrene generated from photolysis of phenyl azide.

**Comparative study of azobenzene formation.** One of the ways to confirm the identity of the transient intermediate generated on photodissociation is to perform common intermediate experiments. These experiments can be used to establish the identity of the intermediate generated from a new compound by replicating...
the products or results from an established compound known to generate the hypothesized intermediate. If the product profile of the new compound resembles that of the known compound, then the intermediate generated is inferred to be the same for both the compounds. Since the study with 1-octene showed the generation of azobenzene, common intermediate experiments to explore the photochemistry of 1 were performed based on previous work on phenyl azides to characterize whether the transient generated was triplet nitrene, PhN₃ (72). These experiments were designed to photoirradiate 1 at different concentrations in acetonitrile using a photoreactor and monitor the formation of azobenzene, which is the dimer product of PhN₃.

The azobenzene yields from the experiments on sulfoximine 1 are presented independently in Fig. 2A, and comparison with azobenzene yields from photolysis of phenyl azide as reported by Schrock and Schuster in 1984 is included in Fig. 2B. On analyzing the azobenzene yields from photoirradiation of 1 at different concentrations in acetonitrile using a photoreactor and moniter the formation of azobenzene, which is the dimer product of PhN₃.

Overall, the yields for each concentration studied in this work were comparable to each other. The yield of azobenzene being largely independent of the concentration of 1 was consistent with PhN₃ not reacting with the starting material or products.

When comparing the yields in this study to the measurements in the work by Schrock and Schuster where phenyl azide was irradiated using a Rayonet photoreactor with 254 nm lamps or with “an Ultraviolet Products Model SCT-1 Hg lamp” (72), it was noted that the azobenzene yield for 1.6 mM of 1 at low conversion was near identical to the yield observed for 1.5 mM of phenyl azide (Fig. 2B). However, there was less agreement between the results obtained for the other concentrations studied at either high or low conversion with the yields observed for different phenyl azide concentrations comparable to concentrations of 1. This variance in data between the two studies could be due to differences in experimental setup including lamps used for photolysis and their associated flux. In the study by Schrock and Schuster (72), azobenzene was observed to have high yields for low concentrations of phenyl azide at high percent conversion and the azobenzene yields were lower for high concentrations of phenyl azide at low percent conversion. Unlike the results for phenyl azide, the results in Fig. 2A,B demonstrated that the yields of azobenzene do not strongly depend on the concentration of 1 or extent of conversion. This shows that the reactivity of 1 on photoexcitation may not be exactly similar to the reactivity of phenyl azide. At the same time, these findings imply the formation of PhN₃ and concomitant azobenzene yields are largely consistent throughout the study for 1 at high or low conversion. The low yields of azobenzene from 1 throughout these trials require further examination of the fate of the rest of...
the PhN: generated. The generation of azobenzene is strongly indicative of two possible pathways: one where PhN\(^+\) is generated after S–N bond cleavage from excited singlet state of \(\text{I}\) which further undergoes intersystem crossing (ISC) to produce PhN\(^{3+}\), or singlet excited \(\text{I}\) undergoes ISC to generate triplet \(\text{I}\) (\(\text{T}\)) that then undergoes S–N cleavage to generate PhN\(^{3+}\).

**Triplet sensitization of \(\text{I}\) using anthraquinone.** We proceeded to perform triplet sensitization experiment to resolve the pathway in photodenitrenation of \(\text{I}\). In order to select a triplet sensitizer, the triplet energy state (\(\text{T}\)) of \(\text{I}\) was calculated using HSEH1PBE level of theory with 6-311G(d,p) basis set in Gaussian 09 suite of programs (75–77). The triplet energy (\(\text{T}\)) was found to be 47.9 kcal mol\(^{-1}\). Anthraquinone was selected because of its triplet energy (approximately 63 kcal mol\(^{-1}\)) being 15 kcal mol\(^{-1}\) higher than \(\text{I}\) (89). It is worth noting that the S–N BDE values calculated in Table 1 are higher than the computed \(\text{T}\) energy. This suggests the values calculated in Table 1 are only suitable for comparing the relative strength of S–N bond against S–O bond and should not be relied on for accuracy. A 0.4 mM solution of \(\text{I}\) in acetonitrile in the presence of 3.8 mM of anthraquinone was irradiated at 355 ± 5 nm (Fig. 3A). It is worth noting that molar absorptivity of \(\text{I}\) (log \(\text{e}\) 3.18) is higher than anthraquinone (log \(\text{e}\) 2.75) at 355 nm (Fig. 3B). Therefore, the anthraquinone concentration used was ninefold that of \(\text{I}\) to ensure that almost all photons were absorbed by anthraquinone. The results of the study are summarized in Fig. 3C where a control experiment without anthraquinone was also performed for comparison with direct irradiation.

The azobenzene yield for the triplet sensitization of \(\text{I}\) using anthraquinone as the sensitizer was significantly higher than the control (direct irradiation of \(\text{I}\)). This reaction proceeded through the triplet state of \(\text{I}\), which suggested that azobenzene was the primary product from triplet \(\text{I}\). It is also notable that almost all of the sulfoximine \(\text{I}\) was converted to DBTO in the triplet sensitization experiment as compared to only 8.2% of \(\text{I}\) being converted to DBTO on direct irradiation. The \(\Phi_{\text{DBTO}}\) and \(\Phi_{\text{azobenzene}}\) observed for the sensitized reaction was 0.057 and 0.020 at 355 nm as compared to 0.0055 and 0.0038 for direct irradiation, respectively. This illustrates that the efficiency of the sensitized reaction of \(\text{I}\) in the presence of anthraquinone to produce DBTO and azobenzene is significantly higher than direct irradiation of \(\text{I}\).

**Concentration-dependent study of \(\text{I}\) in the presence of DEA.** We advanced to explore photoradiation of \(\text{I}\) in the presence of DEA to find out if PhN\(^{3+}\) was one of the intermediates generated (Fig. 4A). In this analysis, a solution in acetonitrile with 1.6 mM of \(\text{I}\) was irradiated for approximately 18 h using a monochromator at 325 ± 5 nm where the sulfoximine was expected to undergo 40–50% conversion (~0.8 mM DBTO) and DEA was added to amount to 0.40 equivalents (0.32 mM DEA), 1 equivalent (0.80 mM DEA), and 2 equivalents (1.6 mM DEA) of the estimated DBTO generated. These experiments were designed with varying concentrations of DEA to examine whether the azobenzene and azepine yields were dependent on the concentration of the nucleophile. The results from these photoreactions were also expected to reveal insights into the outcome of photo-generated PhN: that do not form azobenzene and further explain the underlying mechanism in photodenitrenation of \(\text{I}\).

Tandem mass spectrometry (LC-MS/MS) was used to detect the azepine product profile from the reactions. Interestingly, two peaks were observed in the chromatogram for m/z 165 that possibly suggested the formation of two azepine isomers,
1H-azepine and 3H azepine (Fig. 4B). Even though previous studies strongly suggest 2-(diethylamino)-3H-azepine is the principal isomer when PhN1 reacts with DEA, there is evidence for the formation of 1H-azepine through aziridine intermediate followed by valence tautomerization presented in Scheme 5 (71,72). Based on these previous mechanistic studies, we assigned the peak at 8.33 min as 1H-azepine and at 8.50 min as 3H-azepine. The formation of 1H-azepine has been concluded to be independent of amine concentration and has also been implicated in eventually leading to the formation of 3H-azepine (71,72).

The sample with 0.80 mM DEA was treated as the standard for comparison because the DEA concentration in sample preparation was correlated with the expected DBTO concentration postphotolysis in a 1:1 ratio. From our results summarized in Fig. 4C and D, we concluded that there was a significant difference for the formation of 1H-azepine at 0.80 mM DEA as compared to 1.6 mM DEA. Similar difference in peak area is observed for 3H-azepine at 0.32 mM DEA as compared to 0.80 mM DEA. Azobenzene formation was not notably observed for 0.80 mM and 1.6 mM DEA, but samples with 0.32 mM DEA showed 21 ± 27% (Mean ± 95% CI) azobenzene yield. These results with high error bars reflect that azobenzene is not a primary photoprotect for sulfoximine 1 photosynthesis in the presence of DEA. We also explored the possibility of the formation of aniline as previous work has cited aniline-like products from phenyl nitrene derivatives (70,90). Even though dimerization of triplet nitrene has been noted as the dominant pathway, H-atom abstraction or electron transfer in the presence of amine has been posited to result in the formation of aniline-like product from triplet substituted phenyl nitrenes (72, 91–94). We monitored product formation postirradiation using HPLC, and no major peaks consistent with aniline were detected in our analysis. The trend overall illustrates that reactivity of sulfoximine 1 is dependent on the presence of DEA and azepine formation may slightly be dependent on amine concentration. Amine concentration did not affect rate of photodenitrenation significantly as conversion to DBTO largely remained the same among the different concentrations of 1 (SI, Data S5).

Triplet sensitization of a 1.6 mM solution of 1 with 3.7 mM of anthraquinone in the presence of 1.6 mM DEA was performed at 355 ± 5 nm for 18 h. The results are presented alongside the previously discussed findings in Fig. 4C and D. In triplet sensitized photolysis of 1 in the presence of DEA, almost all of sulfoximine 1 was converted to DBTO and significant DBT formation from DBTO photolysis was observed as opposed to 43% conversion to DBTO for direct irradiation of 1.6 mM of 1 in the presence of 1.6 mM DEA (SI, Section 5.4). Additionally, we observed that 3H-azepine was the primary azepine product, but the peak area was significantly lower than the direct irradiation trial with 0.80 mM DEA. The small amount of 3H-azepine observed can be attributed to direct irradiation of 1 as sulfoximine 1 absorbs at 355 nm (log ε 3.18). The observations that sensitized 1 in the presence of DEA does not generate azepines in considerable yields and azobenzene generation plummets when 1 is directly irradiated in the presence of DEA suggest the formation of PhN3 ceases in the presence of DEA when 1 is directly irradiated. This indicates that ISC to triplet 1 which then releases PhN3 is somewhat unlikely. The most likely pathway for directly irradiated 1 is wherein PhN3 is the species that branches out to form (a) azirine which eventually reacts with DEA to form...
azepine and (b) also undergoes ISC to PhN\textsuperscript{3} which dimerizes to azobenzene. This set of DEA experiments further added some clarity to the mechanism behind the photoexcitation of sulfoximine \textit{1}.

At this stage, based on the profile of the photoproducts in the presence of DEA, we deduce that sulfoximine \textit{1} photolyzes to cleave the S–N bond that likely releases PhN\textsuperscript{1}. This PhN\textsuperscript{1} possibly undergoes three pathways (Scheme 6): pathway (A) ring expansion to form dehydroazepine that forms 3\textit{H}-azepine in the presence of secondary amine (dominant pathway), pathway (B) formation of 1\textit{H}-azepine from azirine reacting with secondary amines and pathway (C) intersystem crossing to form triplet nitrene and subsequently generating azobenzene. However, the pathway of sulfoximine 1 undergoing ISC to generate 1\textit{3} and then subsequently cleaving S–N bond to yield PhN\textsuperscript{3} cannot be entirely ruled out. The pathways very closely resemble the reactivity footprint of phenyl azide and postulate the use of sulfoximines with appropriate linkers as red-shifted photoaffinity labels to study biomembranes as pathway A is likely the predominant mechanism of photodenitrenation. Additionally, sulfoximines can be conceived as O(3\textit{P})-delivery agents within biomembranes with concurrent biolabeling to study the targeted effect of oxidative stress in phospholipids.

CONCLUSION

The photochemistry of sulfoximine 1 was explored as the structure posited the release of PhN\textsuperscript{3} and O(3\textit{P}) on UV-A irradiation. We predicted S–N bond cleavage before S–O bond cleavage using computational studies on structure optimization of 1 and possible photoproducts along with BDE values for S–N and S–O bonds. This prediction was supported through photochemistry studies where photodenitrenation was observed before photodeoxygenation to release DBTO with a quantum yield of 0.014.
at 325 nm. The photochemistry of 1 was further explored by irradiation in the presence of octene but the nondetection of aziridine reflected the complex reactivity profile of aryl nitrenes. Azobenzene yields as an indicator of PhN3 were studied at different concentrations of 1 at high and low conversions. The yields for azobenzene were largely found to be independent of concentration of 1 and percent conversion to DBTO. Additionally, triplet sensitization reaction using anthraquinone revealed a significant increase in azobenzene yield, whereas azobenzene as a major photoproduct was not detected when 1 was irradiated in the presence of DEA as a nucleophile. Instead, in the presence of DEA a mixture of 1H-azepine and 3H-azepine products was detected. Based on these exploratory analyses, we concluded that the reactivity of 1 is dependent on the presence of a nucleophile like DEA and the azobenzene yield in the absence of a nucleophile like DEA ranges from approximately 20–30%. The data from the experiments also strongly suggest that the photodenitration pathway for 1 is closely related to phenyl azide where PhN3 is released on photoexcitation which then rearranges to form azirine to release a mixture of azepines in the presence of DEA; concurrently, PhN3 undergoes ISC to form PhN3 which dimerizes to release azobenzene.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article:
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