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Theoretical Study of the Reaction Formalhydrazone with Singlet Oxygen. Fragmentation of the C=N Bond, Ene Reaction, and Other Processes†

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Abstract

Photobiologic and synthetic versatility of hydrazones has not yet been established with ¹O₂ as a route to commonly encountered nitrosamines. Thus, to determine whether the “parent” reaction of formalhydrazone and ¹O₂ leads to facile C=N bond cleavage and resulting nitrosamine formation, we have carried out CCSD(T)//DFT calculations and analyzed the energetics of the oxidation pathways. A [2 + 2] pathway occurs via diradicals and formation of 3-amino-1,2,3-dioxazetidine in a 16 kcal/mol process. Reversible addition or physical quenching of ¹O₂ occurs either on the formalhydrazone carbon for triplet diradicals at 2–3 kcal/mol, or on the nitrogen (N(3)) atom forming zwitterions at ~15 kcal/mol, although the quenching channel by charge-transfer interaction was not computed. The computations also predict a facile conversion of formalhydrazone and ¹O₂ to hydroperoxymethyl diazene in a low-barrier ‘ene’ process, but no 2-amino-oxaziridine-*O*-oxide (peroxide-like) intermediate was found. A Benson-like analysis (group increment calculations) on the closed shell species are in accord with the quantum chemical results.

INTRODUCTION

In this paper, our goal was to theoretically study the reaction of formalhydrazone **1** with singlet oxygen (¹Δ_g O₂, abbreviated here as ¹O₂), to gain a sense of the energetics required for nitrosamine release. Reactions of *N*-methyl-*N*-phenylhydrazones of *p*-tolualdehyde and *p*-acetyltoleune with ¹O₂ have led to nitrosamine and carbonyl products at –78 °C in CCl₄ or CH₂Cl₂ (1,2). The reaction of ¹O₂ with hydrazones, such as glucosazone or *N,N*-dimethylhydrazone have led to carbonyl compounds under mild conditions (3–6).

Biologically, nitrosamines are powerful toxins and mutagens in many reactions with DNA (7,8). They are implicated in diseases such as cardiovascular disease and cancer. Although hydrazone-¹O₂ reactions give rise to nitrosamines, information is limited on their involvement in biological photooxidation reactions. How nitrosamines arise from four-membered ring (3-amino-1,2,3-dioxazetidine) intermediates is also an area of interest.

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Dioxazetidine intermediates have been postulated in photooxidations of benzophenone oximes (9,10,11), oximes of aldehyde, aliphatic acyclic and cyclic ketones (12), acyclic α -diimines (13), and nitromethyl alkylphosphonates (14). Dioxazetidines have also been suggested in thermal reactions, such as nucleophilic reactions of nitrosamines with peracids (15) and autoxidation reactions (16). Spectroscopic observations of dioxazetidines remain to be established, although there is matrix isolation evidence for unstable three-membered ring dioxaziridines (RNO_2) (17,18). Theoretical studies have in the past focused on reactions of $^1\text{O}_2$ reactions with alkenes (19), but not with hydrazones.

Here, we report CCSD(T)//DFT and Benson group type calculations for the formalhydrazone- $^1\text{O}_2$ reaction (Schemes 1 and 2). The computational data point to a [2 + 2] reaction via cyclization of diradicals for formation of 3-amino-1,2,3-dioxazetidine **4** (path A). Reversible addition of $^1\text{O}_2$ may occur as diradicals at carbon (C(1)) or as zwitterions at nitrogen (N(3)) (paths A and B). The energetics also point to an 'ene' pathway with abstraction of an allylic proton and formation of hydroperoxymethyl diazene **5** (path C). A 2-amino-oxaziridine-*O*-oxide (perepoxide-like) intermediate **10** was not located (path D). The theoretical study described here provides insight into the energetics of hydrazone/ $^1\text{O}_2$ reactions, which is relevant to nitrosamine formation to develop this area for biological and synthetic chemistry. The formation of nitrosamine would require a hydrazine bearing no N-H quasi allylic hydrogens otherwise a facile 'ene' reaction with $^1\text{O}_2$ takes place as it will be seen.

METHODS

Calculations were performed with the Gaussian 09 program package (20) and visualized with Gaussview 5 (21). The $\omega\text{B97X-D}$ functional (22,23) was used along with standard protocols (24,25). The "D" indicates the functional accounts dispersion forces (26). The ωB97X functional produces results in good agreement with CCSD(T) (27,28) based on the reaction of ethene with $^1\text{O}_2$ (29). In our case, geometries were optimized with $\omega\text{B97X-D}/6\text{-311+G(d,p)}$ followed by single-point energy calculations with CCSD(T)/aug-cc-pvtz. Frequency calculations established the type of stationary point obtained. IRC calculations demonstrated that saddle points connected minima, except for **TS34** and **TS3'4**, which connect **2** to **4** by **3** or **3'** respectively, which are shallow points. We added the $\omega\text{B97X-D}/6\text{-311+G(d,p)}$ thermal corrections for enthalpy at 298.15 K and 1 atm to the CCSD(T) result. The broken-symmetry method is used and yields mixed singlet and triplet states. Thus, spin corrected values are reported for $\omega\text{B97X-D}/6\text{-311+G(d,p)}$ by means of a spin correction formula (31,32):

$$E_{sc}^l \approx E_{BS}^l + \frac{(\langle S^2 \rangle^l)}{\langle S^2 \rangle^h - \langle S^2 \rangle^l} (E_{BS}^l - E^h)$$

where E is the absolute energy, l and h represent the lower energy spin state (singlet) and the higher energy spin state (triplet). Also, E_{sc} is the spin corrected energy, E_{bs} is the broken symmetry (BS) (i.e., contaminated) energy, and $\langle S^2 \rangle$ is the expectation value for the total spin angular momentum squared. $\langle S^2 \rangle$ is normally 0 for a singlet ($(0)(0 + 1)$), 0.75 for a doublet ($(1/2)(1/2 + 1)$), and 2.0 for a triplet ($(1)(1 + 1)$), but since the BS method is being used, the $\langle S^2 \rangle$ for a singlet diradical is equal to 1 due to mixture of the triplet solution (30). To estimate the energy of $^1\Delta_g$ oxygen, the experimental singlet-triplet gap of 22.5 kcal/mol was added to the value computed for $^3\Sigma_g^+$ oxygen, which appears in parentheses in Figures 3–6. While the energy gap of $^1\Delta_g$ and $^3\Sigma_g^+$ oxygen can be calculated with reasonable accuracy, the error associated with the initial part of the reaction of $^1\Delta_g$ oxygen with **1** lead us to use **4** as the reference point. The initial part of the reaction is labeled with a dashed line

in Figure 3–6 reflecting its higher error, and is analogous to the reports of Jensen et al. (33), McKee (34), Moss et al. (35), Houk et al. (36), and Doubleday et al. (37) where the relative energy of sulfide/singlet oxygen or halocarbene/alkene reagents often have negative enthalpy barriers. Conceivably, multi-reference methods are advantageous for mixed species, such as in the case of radicals with resonance (38). Indeed, Table 1 shows T_1 diagnostic values for many of our computed structures are above 0.02, which points to the need for multi-reference calculations (39). However, we consider the single reference method described here as a good first step.

RESULTS AND DISCUSSION

We report the results of a theoretical study for the reaction of formalhydrazone **1** with $^1\text{O}_2$, and has three parts. First, we describe the computed geometries of intermediates and transition structures produced in the reaction. Second, we examine the attack of $^1\text{O}_2$ on formalhydrazone **1** and pathways such as the one leading to the 3-amino-1,2,3-dioxazetidine **4**. Third, we describe the computed heats of formation ($\Delta_f H^0$) of **1**, and also dioxazetidine **4** and hydroperoxymethyl diazene **5**, the latter two species could theoretically arise from the formalhydrazone- $^1\text{O}_2$ reaction.

(1) Computed geometries

DFT computed structures are given in Figures 1 and 2. Compounds **1–9**, **2T–3'T**, and **5T** optimized to minima, where species labeled “TS” are saddle points. Structures **3** and **3'** are enantiomers. In **1**, the C=N bond length was calculated to be 1.27 Å and the N-N bond length was 1.36 Å, and the amino group is pyramidal in accord with previous calculations (40,41). Upon formation of the O-C bond (1.46 Å) in **2**, the C=N bond lengthens to 1.42 Å. In **3**, the dihedral angle O(2)-O(1)-C(4)-N(3) (θ) is 81.4°. Dioxazetidine **4** shows the expected deviation from planarity where ϕ equals 15.3°. Bond distances in the dioxazetidine **4** include the C-N bond = 1.47 Å; C-O bond = 1.42 Å; O-O bond = 1.46 Å; and O-N bond = 1.49 Å. The θ angle in this case is 15.9°. In **6**, upon formation of the O-N bond (1.39 Å) with $^1\text{O}_2$, the N-N reduces to a length of 1.35 Å. The O-O bond distance in **5** is 1.42 Å, which is shorter than the O-O bond distance of H_2O_2 (1.475 Å) (42). In **6**, θ is 172.7° and in **7** it is 180.0°.

(2) Potential energy surfaces

We have explored the reaction of formalhydrazone with $^1\text{O}_2$ reaction in gas phase with CCSD(T)/aug-cc-pvtz// ω B97X-D/6-311G(d,p) calculations (Figures 3–6).

We first focused on the [2 + 2] route (path A). A transition structure for a concerted [2 + 2] reaction was not found. Instead, the reaction between **1** and $^1\text{O}_2$ gives singlet diradical **2**, which is computed to be exothermic by 5.6 kcal/mol (Figure 3). Diradical **2** can cyclize to **4** by enantiomers **3** and **3'**. Diradicals **3** and **3'** were “pseudominima” (shallow minima), which lead to enantiomeric **TS34** or **TS3'4** and then onto **4**. These singlet diradicals had $\langle S^2 \rangle$ values fairly close to 1 before and after spin annihilation with large Mulliken spin densities on atoms N(3) and O(2) of opposite signs. The triplet surface was also computed, where the reaction between **1** and $^1\text{O}_2$ gives diradical **2T**, which is computed to be exothermic by 3.7 kcal/mol (Figure 4). Diradical **2T** converts to enantiomers **3T** and **3'T** by **TS23** and **TS23'T**, respectively. These triplet diradicals had $\langle S^2 \rangle$ values close to 2 before and after spin annihilation with large Mulliken spin densities on atoms N(3) and O(2), but of the same sign. As expected, diradicals **2T**, **3T**, and **3'T** are nearly isoenergetic with each other, and bear some resemblance to nitroso-*O*-oxide (43–45), a species that can transfer an oxygen to toluene (46) or cyclize to dioxaziridine (18).

The stationary points in Figure 3 resemble those in Figure 4 where the energetics are similar. We note that **3T** is curled and brings radical sites into close proximity of each other, but do not reach triplet **4** since it is not a minimum. It is possible that enantiomers **3T** and **3T'** can reach singlet **4** by surface crossing, but we did not investigate this pathway, nor did we scrutinize the energetics for conversion of the diradicals to the 8-membered ring diperoxide, 3,8-diamino-3,4,7,8-tetrahydro-1,2,5,6-tetraoxa-4,8-diazocine. Thus, theoretical evidence has been collected for the existence of dioxazetidine **4**. We have not computed the transition structures connecting **4** with **8** and **9** that must be computed in both the ground and excited states. By analogy, excited-state carbonyl products are formed in the decomposition of conventional 1,2-dioxetanes (47,48).

Next, we focused on the route to peroxy nitrogen species (path B). The reaction between **1** and $^1\text{O}_2$ gives closed-shell, zwitterionic peroxy nitrogen species **6** and **7** that are calculated to be endothermic by 11.6 and 15.0 kcal/mol, respectively (Figure 5). The activation energies to reach these species are 12.4 and 15.0 kcal/mol, respectively. Furthermore, a saddle point which connects **7** and **4** has been located, but it is too high (27.3 kcal/mol) for ring closure at experimentally relevant conditions. Interaction of singlet oxygen with the nitrogen atoms of **1** is likely lead to a physical quenching process, as has been detected with hydrazines (49), but such a quenching channel that includes a charge-transfer interaction was not modeled.

Lastly, we focused on the 'ene' route (paths C and D). The reaction between **1** and $^1\text{O}_2$ gives hydroperoxymethyl diazene **5**, and is calculated to be exothermic by 43.8 kcal/mol (Figure 6). The barrier between **1** + $^1\text{O}_2$ and **5** is low (3.0 kcal/mol). Surprisingly, subsequent conversion of the hydroperoxymethyl diazene **5** to dioxazetidine **4** was also found. A saddle point which connects **5** and **4** has been located, but the activation energy is very high (53 kcal/mol).

The 2-amino-oxaziridine-*O*-oxide intermediate **10** was not found computationally. With $\omega\text{B97X-D/6-311+G(d,p)}$, various start geometries collapsed to species associated with paths A–C. The 2-amino-oxaziridine-*O*-oxide also does not optimize to a minimum with the following DFT functionals and the 6-31+G(d,p) basis set: HSEH1PBE, LC-wPBE, M06-2X, O3LYP, BH and HLYP, CAM-B3LYP, M08-SO, B3LYP-D3, and TPSSPTSS.

(3) Enthalpies of formation

It may be asked if the calculated values of the relative enthalpies of formation in the current paper are plausible: 3-amino-1,2,3-dioxazetidine **4**, 0.0 kcal/mol (by definition); formalhydrazone **1** (+ singlet oxygen), 7.8 kcal/mol; hydroperoxymethyl diazene **5**, -36.0 kcal/mol. Relatedly, how plausible is the reaction exothermicity of 3-amino-1,2,3-dioxazetidine to form formaldehyde + nitrosamine of 67.1 kcal/mol (the units in this section will be omitted in calculations for clarity, but kcal/mol is assumed throughout)? To answer this requires defining the word "plausible" – it is here taken to mean that these values are in rough accord with that predicted by additivity relations such as Benson group increments with associated ring corrections (in the particular, those from the pioneering study (50)), a particularly well-known simple (i.e., nonquantum chemical) approach.

Use of Benson group increments and ring corrections in the current situation is complicated by the paucity, and occasionally, complete absence of data from which these numbers can be directly obtained: we cannot simply add, or even tabulate, a set of long-known increments. In the case of species **4**, the "central" compound of our current study, there are no thermochemical data for 3-amino-1,2,3-dioxazetidine (or any oxazetidine for that matter) and so the corresponding ring correction is not to be found in ref. (50) and so must be "approximated". There are no species at all with measured enthalpies of formation with either -O-O-N- nor -O-N-N- functionalities should we sensibly ignore multiply bonded

species such as peroxyxynitrites and azoxy compounds. (For a review of the thermochemistry of hydroxylamine derivatives and a survey of cyclic species with the –O–O–N– functionality see refs. (51) and (52) respectively.) Said differently, while $\Delta_f H^0(\mathbf{4}) = \text{C}(\text{N})(\text{O})(\text{H})_2 + \text{N}(\text{N})(\text{O})(\text{C}) + \text{O}(\text{O})(\text{N}) + \text{O}(\text{O})(\text{C}) + \text{N}(\text{N})(\text{H})_2 + \text{ring correction}$, but the group increments $\text{C}(\text{N})(\text{O})(\text{H})_2$, $\text{O}(\text{O})(\text{N})$ and $\text{N}(\text{N})(\text{O})(\text{C})$ and the ring correction must be derived de novo for the current study.

Starting with the increment $\text{C}(\text{N})(\text{O})(\text{H})_2$, it is taken here as the average of $\text{C}(\text{O})(\text{O})(\text{H})_2$ (i.e. $\text{C}(\text{O})_2(\text{H})_2$ [–17.7] and $\text{C}(\text{N})_2(\text{H})_2$ [–12.1], $\frac{1}{2}([–17.7] + [–12.1]) = <–14.9>$. (In the current paper “square brackets” [and] around a numerical value will be used to denote it is from values from ref. (50), and the “angular brackets” < and > likewise to denote derived estimates for use in the current study. Alternatively, the difference of $\text{C}(\text{O})(\text{O})(\text{H})_2$ [–17.7] – $\text{C}(\text{N})(\text{O})(\text{H})_2$ may be equated with $\text{C}(\text{O})(\text{C})(\text{H})_2$ [–8.5] – $\text{C}(\text{N})(\text{C})(\text{H})_2$ [–6.6] and so the desired increment $\text{C}(\text{N})(\text{O})(\text{H})_2$ is deduced to be [–17.7] – ([–8.5] + [6.6]) = <–15.8>. The two values for $\text{C}(\text{N})(\text{O})(\text{H})_2$ are close: a consensus value of –15 kcal/mol will be taken.

The value for $\text{O}(\text{O})(\text{N})$ is not available. The difference of $\text{O}(\text{C})(\text{N})$ and $\text{O}(\text{O})(\text{N})$ is approximated here by that of $\text{O}(\text{C})_2$ and $\text{O}(\text{O})(\text{C})$, [–23.7] – [–4.5] = <–19.2>, of $\text{O}(\text{C})(\text{H})$ and $\text{O}(\text{O})(\text{H})$ = [–37.9] – [–16.3] = <–21.6> or better still, their average, <–20.4>. From the value for $\text{O}(\text{C})(\text{N})$ = [–0.9], we thus derive $\text{O}(\text{O})(\text{N})$ = [–0.9] – <–20.4> = <19>. Alternatively, the difference $\text{O}(\text{O})(\text{H})$ and $\text{O}(\text{O})_2$ = [–16.3] – <19.0> = <–35.3> and $\text{O}(\text{O})(\text{H})$ and $\text{O}(\text{O})(\text{C})$, [–37.9] – [–4.5] = <–33.4>. The average of these two increments, $\frac{1}{2}(<–35.3> + <–33.4>) = <–34>$ are nearly equal. Assuming this average difference is the same as for $\text{O}(\text{C})(\text{N})$ [–14.1] and $\text{O}(\text{O})(\text{N})$, we derive $\text{O}(\text{O})(\text{N})$ = <–14.1> – <–34> = <20> nearly the same as before, and now taken as the consensus value of $\text{O}(\text{O})(\text{N})$ = 20 kcal/mol.

Assuming $\text{N}(\text{N})(\text{C})_2 - \text{N}(\text{H})(\text{C})_2$ [29.2] – [15.4] $\approx \text{N}(\text{N})(\text{C})(\text{H}) - \text{N}(\text{C})(\text{H})_2$ [20.9] – [4.8] $\approx \text{N}(\text{N})(\text{O})(\text{C}) - \text{N}(\text{H})(\text{O})(\text{C})$ from $\text{N}(\text{H})(\text{O})(\text{C})$ = [12.2], $\text{N}(\text{N})(\text{O})(\text{C}) \approx <26>$ kcal/mol.

The ring correction for 3-amino-1,2,3-dioxazetidine is taken here as 26 kcal/mol, set equal that of other 4-membered rings, cyclobutane and oxetane [26.2] and [26.4] kcal/mol. Accordingly, $\Delta_f H^0(\mathbf{4}) = \text{C}(\text{N})(\text{O})(\text{H})_2 + \text{N}(\text{N})(\text{O})(\text{C}) + \text{O}(\text{O})(\text{N}) + \text{O}(\text{O})(\text{C}) + \text{N}(\text{N})(\text{H})_2 + <\text{ring correction}> \approx <–15> + <20> + <26> + [–4.5] + [11.4] + <26> \approx 64$ kcal/mol.

Benson and his coworkers (50) provide little help for species **1** and **5** in that there are few data given for hydrazines and azo compounds, and for hydroxylamines and oximes, and none for hydrazones and monoalkyldiazenes. Nonetheless, we may assume that

Equivalently, should thermoneutrality be assumed for

It is necessary to know the enthalpy of formation for formaldoxime. From ref. (53), it is plausibly about half of that of glyoxal dioxime much as formaldehyde 26.0, is about half of glyoxal, 50.6, and ethylene, 12.5, is about half of 1,3-butadiene, 26.3. Benson, et al. (50) gives the reader two reasoned estimates for glyoxal dioxime, 0 and 1.9 kcal/mol, and so a value of 1 kcal/mol may be suggested for formaldoxime. Or we may demethylate

acetaldoxime with its enthalpy of formation of -6.3 . This demethylation enthalpy is ca 11 kcal/mol using the enthalpies of formation of ethene and propene, $12.5 - 4.9 = 7.6$, formaldehyde and acetaldehyde, $-26.0 - (-39.7) = 13.7$. This results in 5 kcal/mol for the enthalpy of formaldoxime. An overall consensus value for formaldoxime of ca. 3 kcal/mol may thus be suggested. Ref. (50) gives us a value of 22.8 and -12.0 for the enthalpies of formation of methylhydrazine and N-methylhydroxylamine. From all of this an enthalpy of formation of $3 + 22.8 - (-12.0) \approx 38$ kcal/mol is deduced for formalhydrazone. Accordingly species **1** has an enthalpy of formation of ca. $38 + 22.5 = 60$ kcal/mol. This is 4 kcal/mol lower than that of the cyclic product **4**, 3-amino-1,2,3-dioxazetidine for which an enthalpy of formation of 64 kcal/mol had been suggested earlier in this text. The earlier quantum chemical calculations suggest a difference of species **1** and **4** was 8 kcal/mol favoring the dioxazetidine. Which is more stable then, the formalhydrazone or the dioxazetidine? This is hard to decide given uncertainties of a few kcal/mol in so many of our numbers, most obviously and unavoidably in the group increments.

What is $\Delta_f H^0(\mathbf{5})$? It is best to start with the preliminary with enthalpy of formation of the parent species, the dehydroperoxylated methyldiazene itself? Whether by the use of Benson group increments or in this case, taking the average of the enthalpies of formation of N_2H_2 and azomethane (dimethyldiazene), the value of $\frac{1}{2} (50.2 + 44.3) = \langle 47 \rangle$ kcal/mol is found. Reintroducing the hydroperoxy group corresponds to the change of $C-(N_d)(H)_3$ to $C-(N_d)(O)(H)_2 + O-(O)(C) + O-(H)(O)$. Equating this change with that of $C-(N)(H)_3$ to $C-(N)(O)(H)_2 + O-(O)(C) + O-(H)(O)$, the change is from $[-10.1]$ to $\langle -15 \rangle + [-4.5] + [-16.3]$ or $\langle -27 \rangle$ kcal/mol. Accordingly, the predicted enthalpy of formation of species **5** $\approx \langle 47 \rangle + \langle -27 \rangle \approx 20$ kcal/mol. Formalhydrazone + singlet oxygen is thus predicted to be $38 + 22 - 20 \approx 40$ kcal/mol higher in energy than hydroperoxymethyl diazene from the current analysis increments while the quantum chemical difference is $7.8 - (-36.0) \approx 44$ kcal/mol in comforting agreement. Here it is clear that the hydroxyperoxymethyl diazene is the more stable.

Compare now briefly 3-amino-1,2,3-dioxazetidine and its decomposition products nitrosamine **8** + formaldehyde **9**. There are no increments available for nitrosamines – assume then that the difference of nitrosamines and corresponding nitramines is the same as for nitrites and nitrates, $N-(NO_2) - N-(NO) \approx O-(NO_2)(C) - O-(NO)(C) = [-19.4] - [-5.9] \approx \langle -14 \rangle$ kcal/mol. No data is given for the enthalpy of formation of any nitramine in ref. (50). No data for the enthalpy of formation of gaseous NH_2NO_2 is known from experiment; accepting the high accuracy quantum chemically calculated value, 1 kcal/mol, from ref. (54) results in a suggested value of $1 + 14 \approx 15$ kcal/mol for NH_2NO . The enthalpies of formation of nitrosamine **8** and formaldehyde **9** sum to $15 - 27 = -12$ kcal/mol and so the decomposition of 3-amino-1,2,3-dioxazetidine **4** to these acyclic species is predicted to be $64 - (-12) = 76$ kcal/mol while the prediction made earlier in the current paper is exothermic by but 67 kcal/mol. While there is a disparity of 9 kcal/mol, it is unequivocal that the dioxazetidine is unstable relative to the nitrosamine + formaldehyde.

The quantum chemical calculations and Benson-like analysis are in qualitative agreement. Numerical agreement is less satisfactory. From where do discrepancies arise? The answer may arise in part because so many of the species are possibly thermochemically problematic. For example, do we trust the data for hydroxylamines and oximes? Ref. (51) reminds us of problems here, or at least there is a paucity of data from which to derive conclusions. What about nitrosamines? These data are seemingly problematic (55). What about hydrazones and hydrazines? For the former, problems have long been enunciated (56). For the former, problems have recently been heralded (57).

CONCLUSION

The reaction of formalhydrazone **1** with $^1\text{O}_2$ was calculated using CCSD(T)//DFT in the gas phase in order to assess the energetics of the 'ene' and [2 + 2] pathways. Computations indicate a facile 'ene' reaction of **1** and $^1\text{O}_2$ by **TS15** to hydroperoxymethyl diazene **5**. If there are no N-H allylic hydrogens, a step-wise reaction of hydrazone with $^1\text{O}_2$ and then cleavage of the resulting dioxazetidine makes the route to nitrosamine relevant from a biological or synthetic point of view. Dioxazetidine **4** is predicted to be higher in energy than hydroperoxymethyl diazene **5**. The reaction of $^1\text{O}_2$ at the nitrogen atom (N(3)) gives rise to a reversible reaction via peroxy nitrogen species **6** and **7**. The 2-amino-oxaziridine-*O*-oxide intermediate **10** does not arise as an intermediate from an end-on attack of $^1\text{O}_2$ with the C=N bond of **1**. We do not find the 2-amino-oxaziridine-*O*-oxide as an intermediate with ten different DFT functionals. The Benson-like analysis has been found to be in qualitative agreement with the quantum chemical calculations.

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References

1. Castro C, Dixon M, Erden I, Ergonenc P, Keeffe JR, Sukhovitsky A. Dye-sensitized photooxygenation of the carbon-nitrogen double bond. *J Org Chem*. 1989; 54:3732–3738.
2. Erden I, Alscher PE, Keeffe JR, Mercer C. Dye-sensitized photooxygenation of the CN Bond. 5. Substituent effects on the cleavage of the CN bond of *C-aryl-N-aryl-N-methylhydrazones*. *J Org Chem*. 2005; 70:4389–4392. [PubMed: 15903316]
3. Ito Y, Kyono K, Matsuura T. Temperature- and substituent-dependence in the photosensitized oxygenation of *N,N-disubstituted hydrazones*. *Tetrahedron Lett*. 1979; 20:2253–2256.
4. Friedrich E, Lutz W, Eichenauer H, Enders D. Mild cleavage of *N,N-dimethylhydrazones to carbonyl compounds with singlet oxygen*. *Synthesis*. 1977; 1977:893–894.
5. Enders D, Wortmann L, Peters R. Recovery of carbonyl compounds from *N,N-Dialkylhydrazones*. *Acc Chem Res*. 2000; 33:157–169. [PubMed: 10727205]
6. Vaidya VK. Sensitized photooxidation of osazone by singlet oxygen. *J Photochem Photobiol A: Chem*. 1994; 81:135–137.
7. Loeppky, RN. Nitrosamines and related N-nitroso compounds: Chemistry and biochemistry. Vol. 553. American Chemical Society; 1994. p. 1-18.
8. Lijinsky, W. Chemistry and biology of N-nitroso compounds. Cambridge University Press; 1992. p. 173-201.
9. Wamser CC, Herring JW. Photooxidation of benzophenone oxime and derivatives. *J Org Chem*. 1976; 41:1476–1477.
10. Kawamura Y, Takayama R, Nishiuchi M, Tsukayama M. Curious oxygen effect on photosensitized electron-transfer reactions of benzophenone oxime. *O-methyl ethers: one-way photoisomerization of an iminic double bond*. *Tetrahedron Lett*. 2000; 41:8101–8106.
11. Kawamura Y, Abe T, Tsukayama M. One-way and two-way geometrical isomerizations of 1,1-diarylketone oxime. *O-methyl ethers induced by photosensitized electron transfer*. *Int J Mod Phys B*. 2003; 17:1487–1491.
12. Yang Y, Zhang D, Wu LZ, Chen B, Zhang LP, Tung CH. Photosensitized oxidative deprotection of oximes to their corresponding carbonyl compounds by platinum(II) terpyridyl acetylide complex. *J Org Chem*. 2004; 69:4788–4791. [PubMed: 15230603]
13. Lemp E, Zanocco AL, Günther G, Pizarro N. Solvent effect on the sensitized photooxygenation of cyclic and acyclic α -diimines. *Tetrahedron*. 2006; 62:10734–10746.

14. Savignac, P.; Iorga, B. *Modern Phosphonate Chemistry*. Taylor & Francis; 2003. p. 192-193.
15. Corbett MD, Corbett BR. Reaction of nitroso aromatics with glyoxylic acid. A new path to hydroxamic acids. *J Org Chem*. 1980; 45:2834–2839.
16. Yao HC, Resnick P. Azo-hydrazone conversion. III. The autoxidation of benzaldehyde phenylhydrazones. *J Org Chem*. 1965; 30:2832–2834.
17. Harder T, Wessig P, Bendig J, Stösser R. Photochemical reactions of nitroso oxides at low temperatures: The first experimental evidence for dioxaziridines. *J Am Chem Soc*. 1999; 121:6580.
18. Sawwan N, Greer A. Rather exotic types of cyclic peroxides: Heteroatom dioxiranes. *Chem Rev*. 2007; 107:3247–3285. [PubMed: 17592878]
19. For example: Singleton DA, Hang C, Szymanski MJ, Meyer MP, Leach AG, Kuwata KT, Chen JS, Greer A, Foote CS, Houk KN. Mechanism of ene reactions of singlet oxygen. A two-step no-intermediate mechanism. *J Am Chem Soc*. 2003; 125:1319–1328. [PubMed: 12553834] Sheppard AN, Acevedo O. Multidimensional exploration of valley–ridge inflection points on potential-energy surfaces. *J Am Chem Soc*. 2009; 131:2530–2540. [PubMed: 19193015] Leach AG, Houk KN, Foote CS. Theoretical prediction of a perepoxide intermediate for the reaction of singlet oxygen with *trans*-cyclooctene contrasts with the two-step no-intermediate ene reaction for acyclic alkenes. *J Org Chem*. 2008; 73:8511–8519. [PubMed: 18834182]
20. RA; Frisch, GWTMJ.; Schlegel, HB.; Scuseria, GE.; Robb, JRCMA.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, HNGA.; Caricato, M.; Li, X.; Hratchian, HP.; Izmaylov, JBAF.; Zheng, G.; Sonnenberg, JL.; Hada, M.; Ehara, KTM.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, OKY.; Nakai, H.; Vreven, T.; Montgomery, JA., Jr; Peralta, FOJE.; Bearpark, M.; Heyd, JJ.; Brothers, E.; Kudin, VNSKN.; Kobayashi, R.; Normand, J.; Raghavachari, ARK.; Burant, JC.; Iyengar, SS.; Tomasi, J.; Cossi, NRM.; Millam, JM.; Klene, M.; Knox, JE.; Cross, JB.; Bakken, CAV.; Jaramillo, J.; Gomperts, R.; Stratmann, RE.; Yazyev, AJAO.; Cammi, R.; Pomelli, C.; Ochterski, JW.; Martin, KMRL.; Zakrzewski, VG.; Voth, GA.; Salvador, JJD.; Dapprich, S.; Daniels, AD.; Farkas, JBFO.; Ortiz, JV.; Cioslowski, J. Gaussian 09. G and D J Fox Inc; Wallingford CT: 2009.
21. Dennington, R.; Keith, T.; Millam, J. Gaussview. Semichem Inc; Shawnee Mission KS: 2009.
22. Chai JD, Head-Gordon M. Systematic optimization of long-range corrected hybrid density functionals. *J Chem Phys*. 2008; 128:084106–15. [PubMed: 18315032]
23. Chai JD, Head-Gordon M. Long-range corrected hybrid density functionals with damped atom-atom dispersion corrections. *Phys Chem Chem Phys*. 2008; 10:6615–6620. [PubMed: 18989472]
24. Cramer, CJ. *Essentials of Computational Chemistry*. Wiley; Chichester, U.K: 2004. p. 249-300.
25. Jensen, F. *Introduction to Computational Chemistry*. Wiley; Chichester, U.K: 2007. p. 177-203.
26. Kuwata KT, Valin LC, Converse AD. Quantum Chemical and Master Equation Studies of the Methyl Vinyl Carbonyl Oxides Formed in Isoprene Ozonolysis. *J Phys Chem A*. 2005; 109:10710–10725. [PubMed: 16863120]
27. Bartlett RJ, Purvis GD. Many-body perturbation theory, coupled-pair many-electron theory, and the importance of quadruple excitations for the correlation problem. *Int J Quantum Chem*. 1978; 14:561–581.
28. Pople JA, Krishnan R, Schlegel HB, Binkley JS. Electron correlation theories and their application to the study of simple reaction potential surfaces. *Int J Quantum Chem*. 1978; 14:545–560.
29. Saito T, Nishihara S, Kataoka Y, Nakanishi Y, Kitagawa Y, Kawakami T, Yamanaka S, Okumura M, Yamaguchi K. Reinvestigation of the Reaction of Ethylene and Singlet Oxygen by the Approximate Spin Projection Method. Comparison with Multireference Coupled-Cluster Calculations. *J Phys Chem A*. 2010; 114:7967–7974. [PubMed: 20666543]
30. Abe M. Diradicals. *Chem Rev*. 2013 in press. 10.1021/cr400056a
31. Yamanaka S, Kawakami T, Nagao H, Yamaguchi K. Effective exchange integrals for open-shell species by density functional methods. *Chem Phys Lett*. 1994; 231:25–33.
32. Yamaguchi K, Jensen F, Dorigo A, Houk KN. A spin correction procedure for unrestricted Hartree-Fock and Möller-Plesset wavefunctions for singlet diradicals and polyradicals. *Chem Phys Lett*. 1988; 149:537–542.

33. Jensen F, Greer A, Clennan EL. Reaction of Organic Sulfides with Singlet Oxygen. A Revised Mechanism. *J Am Chem Soc.* 1998; 120:4439–4449.
34. McKee ML. A Theoretical Study of Unimolecular Reactions of Dimethyl Persulfoxide. *J Am Chem Soc.* 1998; 120:3963–3969.
35. Moss RA, Wang L, Zhang M, Skalit C, Krogh-Jespersen K. Enthalpy versus Entropy in Chlorocarbene/Alkene Addition Reactions. *J Am Chem Soc.* 2008; 130:5634–5635. [PubMed: 18393413]
36. Rondan NG, Houk KN, Moss RA. Transition states and selectivities of singlet carbene cycloadditions. *J Am Chem Soc.* 1980; 102:1770–1776.
37. Xu L, Doubleday CE, Houk KN. Dynamics of Carbene Cycloadditions. *J Am Chem Soc.* 2011; 133:17848–17854. [PubMed: 21961828]
38. Vereecken L, Francisco JS. Theoretical studies of atmospheric reaction mechanisms in the troposphere. *Chem Soc Rev.* 2012; 41:6259–6293. [PubMed: 22660412]
39. Lee TJ, Taylor PR. A diagnostic for determining the quality of single-reference electron correlation methods. *Int J Quantum Chem.* 1989; 36:199–207.
40. Armstrong DR, Walker GT. The electronic structure of CH_2NCH_3 , CH_2NNH_2 , CH_2NOH and CH_2NF . *J Mol Struct Theochem.* 1987; 149:369–389.
41. do Monte S, Ventura E, da Costa T, Santana S. Ab initio and DFT conformational study on nitrosamine ($\text{H}_2\text{N}-\text{N}=\text{O}$) and N-Nitrosodimethylamine [$(\text{CH}_3)_2\text{N}-\text{N}=\text{O}$]. *Struct Chem.* 2011; 22:497–507.
42. Redington RL, Olson WB, Cross PC. Studies of hydrogen peroxide: The infrared spectrum and the internal rotation problem. *J Chem Phys.* 1962; 36:1311–1326.
43. Srinivasan A, Kebede N, Saavedra JE, Nikolaitchik AV, Brady DA, Yourd E, Davies KM, Keefer LK, Toscano JP. Chemistry of the diazeniumdiolates. 3. Photoreactivity. *J Am Chem Soc.* 2001; 123:5465–5472. [PubMed: 11389628]
44. Chainikova EM, Safiullin RL, Spirikhin LV, Abdullin MF. A revised mechanism of thermal decay of aryl nitroso oxides. *J Phys Chem A.* 2012; 116:8142–8147. [PubMed: 22803653]
45. Gritsan NP. Study of photochemical transformations of organic azides by matrix isolation techniques and quantum chemistry. *Russ Chem Rev.* 2007; 76:1139–1160.
46. Ishikawa S, Nojima T, Sawaki Y. Reactivity of nitroso oxides: effect of polar substituents and reaction mechanism. *J Chem Soc, Perkin Trans 2.* 1996; 1:127–132.
47. Nkepank G, Pogula PK, Bio M, You Y. Synthesis and singlet oxygen reactivity of 1,2-diaryloxyethenes and selected sulfur and nitrogen analogs. *Photochem Photobiol.* 2012; 88:753–759. [PubMed: 22268454]
48. Bartusik D, Aebischer D, Ghogare A, Ghosh G, Abramova I, Hasan T, Greer A. A fiberoptic (photodynamic therapy type) device with a photosensitizer and singlet oxygen delivery probe tip for ovarian cancer cell killing. *Photochem Photobiol.* 2013; 89:936–941. [PubMed: 23495787]
49. Clennan EL, Noe LJ, Szneler E, Wen T. Hydrazines: new charge-transfer physical quenchers of singlet oxygen. *J Am Chem Soc.* 1990; 112:5080–5085.
50. Benson SW, Cruickshank FR, Golden DM, Haugen GR, O'Neal HE, Rodgers AS, Shaw R, Walsh R. Additivity rules for the estimation of thermochemical properties. *Chem Rev.* 1969; 69:279–324.
51. Slayden, SW.; Liebman, JF. *PATAI'S Chemistry of Functional Groups*. John Wiley & Sons, Ltd; 2009. The Organic Thermochemistry of Hydroxylamines, Oximes, Hydroxamic Acids and their Derivatives; p. 53-83.
52. Slayden, SW.; Greer, A.; Liebman, JF. *PATAI'S Chemistry of Functional Groups*. John Wiley & Sons, Ltd; 2009. Peroxynitrogen: A Study of Nitrogen/Oxygen Heterocycles with N-O and O-O or N-O-O Bonding; p. 549-576.
53. Liebman JF. The relative conjugation energies of dienes and α -diketones. *Struct Chem.* 1992; 3:449–450.
54. Szakács PT, Csontos JZ, Das S, Kállay MI. High-accuracy theoretical thermochemistry of atmospherically important nitrogen oxide derivatives. *J Phys Chem A.* 2011; 115:3144–3153. [PubMed: 21428388]
55. Bartmess, JE. personal communication.

56. Kharasch MS. Heats of combustion of organic compounds. *Bur Stand J Res.* 1929; 2:359–430.
57. Notario R, Klapötke TM, Liebman JF. The gas phase enthalpies of formation of hydrazine, its methylated derivatives, and the corresponding values for ammonia and its methylated derivatives. *Struct Chem.* 2013 in press. 10.1007/s11224-013-0235-z

Figure 1. ω B97X-D/6-311+G(d,p) minimum energy structures and transition states (TS) on the singlet surface.

Figure 2.
 ω B97X-D/6-311+G(d,p) computed structures and transition states (TS) on the triplet surface, thus the “T” designation.

Figure 3.

CCSD(T)/aug-cc-pvtz// ω B97X-D/6-311+G(d,p) computed singlet open-shell surface for path A in kcal/mol relative to **4** as a reference point. The dashed line from **1** + $^1\text{O}_2$ indicates greater error in calculating it compared to other parts of the PES.

Figure 4.

CCSD(T)/aug-cc-pvtz// ω B97X-D/6-311+G(d,p) computed triplet surface of path A in kcal/mol. Stationary points marked with a “T” are triplet open-shell species. The dashed line from **1** + ${}^1\text{O}_2$ indicates greater error in calculating it compared to other parts of the PES.

Figure 5. CCSD(T)/aug-cc-pvtz// ω B97X-D/6-311+G(d,p) computed singlet open-shell surface for path B in kcal/mol.

Figure 6. CCSD(T)/aug-cc-pvtz// ω B97X-D/6-311+G(d,p) computed singlet closed-shell surface for path C in kcal/mol.

Scheme 1.

atom
numbering

Scheme 2.

Table 1

Calculated $\langle S^2 \rangle$ Values, T_1 Diagnostic Values, and Mulliken Spin Densities on N(3) and O(2)

compound	$\langle S^2 \rangle$ before annihilation ^a	$\langle S^2 \rangle$ after annihilation ^a	T_1 ^b	N(3) spin density ^b	O(2) spin density ^b
2	0.886	0.043		-0.856	0.920
3	1.007	0.064	0.367	-0.527	0.040
3'	1.007	0.064	0.367	0.527	-0.040
4	0	0.0			
5					
6	0	0			
7	0	0	0.040		
8	0	0	0.015		
9	0	0	0.020		
TS12	0.995	0.225	0.045	0.718	-0.824
TS15					
TS16	0	0	0.046		
TS17	0	0	0.033		
TS34	0.491	0.009	0.044	-0.855	1.095
TS3'4	0.493	0.009	0.044	0.856	-1.094
TS54	0	0			
TS67	0	0	0.026		
TS74	0	0	0.036		
2T	2.009	2.000	0.028	0.871	0.908
3T	2.008	2.000		0.897	0.935
3'T	2.008	2.000	0.027	0.897	0.935
TS12T	2.036	2.000	0.035	0.755	0.839
TS23T	2.009	2.000		0.926	0.931
TS23'T	2.009	2.000	0.028	0.865	0.892

^a ω B97X-D/6-311G(d,p)

^b CCSD(T)/aug-cc-pvtz