

# Theoretical Study of the Reaction Formaldehyde with Singlet Oxygen. Fragmentation of the C=N Bond, Ene Reaction and Other Processes<sup>†</sup>

Benjamin Rudshiteyn<sup>1</sup>, Álvaro Castillo<sup>1</sup>, Ashwini A. Ghogare<sup>1</sup>, Joel F. Liebman<sup>2</sup> and Alexander Greer<sup>\*1</sup>

<sup>1</sup>Department of Chemistry, Graduate Center & The City University of New York (CUNY), Brooklyn College, Brooklyn, NY

<sup>2</sup>Department of Chemistry and Biochemistry, University of Maryland, Baltimore County (UMBC), Baltimore, MD

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## ABSTRACT

Photobiologic and synthetic versatility of hydrazones has not yet been established with <sup>1</sup>O<sub>2</sub> as a route to commonly encountered nitrosamines. Thus, to determine whether the “parent” reaction of formaldehyde and <sup>1</sup>O<sub>2</sub> 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-dioxazetidene in a 16 kcal/mol<sup>-1</sup> process. Reversible addition or physical quenching of <sup>1</sup>O<sub>2</sub> occurs either on the formaldehyde carbon for triplet diradicals at 2–3 kcal mol<sup>-1</sup>, or on the nitrogen (N(3)) atom forming zwitterions at ~15 kcal/mol<sup>-1</sup>, although the quenching channel by charge-transfer interaction was not computed. The computations also predict a facile conversion of formaldehyde and <sup>1</sup>O<sub>2</sub> 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 study, our goal was to theoretically study the reaction of formaldehyde **1** with singlet oxygen (<sup>1</sup>Δ<sub>g</sub> O<sub>2</sub>, abbreviated here as <sup>1</sup>O<sub>2</sub>), to gain a sense of the energetics required for nitrosamine release. Reactions of *N*-methyl-*N*-phenylhydrazones of *p*-tolualdehyde and *p*-acetyltoleuene with <sup>1</sup>O<sub>2</sub> have led to nitrosamine and carbonyl products at –78°C in CCl<sub>4</sub> or CH<sub>2</sub>Cl<sub>2</sub> (1,2). The reaction of <sup>1</sup>O<sub>2</sub> with hydrazones such as glucosazone or *N,N*-dimethylhydrazone has 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-<sup>1</sup>O<sub>2</sub> 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-dioxazetidene) intermediates is also an area of interest.

Dioxazetidene intermediates have been postulated in photooxidations of benzophenone oximes (9–11), oximes of aldehyde, aliphatic acyclic and cyclic ketones (12), acyclic α-diimines (13)

and nitromethyl alkylphosphonates (14). Dioxazetidene has also been suggested in thermal reactions, such as nucleophilic reactions of nitrosamines with peracids (15) and autoxidation reactions (16). Spectroscopic observations of dioxazetidene remain to be established, although there is matrix isolation evidence for unstable three-membered ring dioxaziridene (RNO<sub>2</sub>) (17,18). Theoretical studies have in the past focused on reactions of <sup>1</sup>O<sub>2</sub> reactions with alkenes (19–21), but not with hydrazones.

Here, we report CCSD(T)//DFT and Benson group type calculations for the formaldehyde-<sup>1</sup>O<sub>2</sub> 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-dioxazetidene **4** (path A). Reversible addition of <sup>1</sup>O<sub>2</sub> may occur as diradicals at carbon (C(4)) 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 (peroxide-like) intermediate **10** was not located (path D). The theoretical study described here provides insight into the energetics of hydrazone/<sup>1</sup>O<sub>2</sub> reactions, which is relevant to nitrosamine formation to develop this area for biological and synthetic chemistry. The formation of nitrosamine would require a hydrazone bearing no N–H quasi allylic hydrogens otherwise a facile ‘ene’ reaction with <sup>1</sup>O<sub>2</sub> takes place as it will be seen.

## METHODS

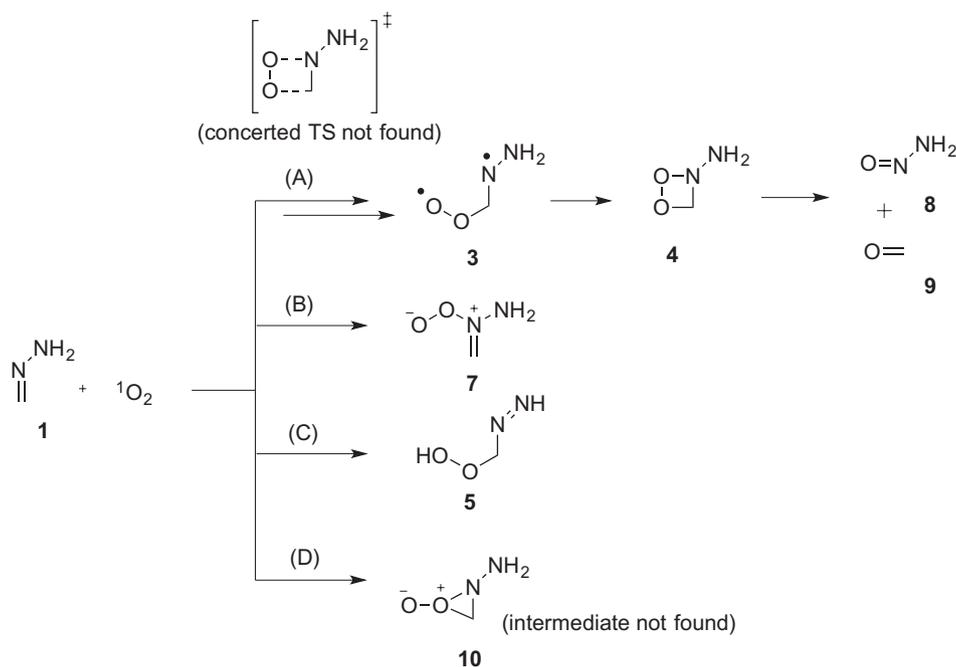
Calculations were performed with the Gaussian 09 program package (22) and visualized with Gaussview 5 (23). The ωB97X-D functional (24,25) was used along with standard protocols (26,27). The “D” indicates the functional accounts dispersion forces (28). The ωB97X functional produces results in good agreement with CCSD(T) (29,30) based on the reaction of ethene with <sup>1</sup>O<sub>2</sub> (31). In our case, geometries were optimized with ωB97X-D/6-311+G(d,p) followed by single-point energy calculations with CCSD(T)/aug-cc-pVTZ. Frequency calculations established the type of stationary point obtained. Intrinsic reaction coordinate calculations demonstrated that saddle points connected minima, except for TS34 and TS3'4, which connect **2–4** by **3** or **3'**, respectively, which are shallow points. We added the ωB97X-D/6-311+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 ωB97X-D/6-311+G(d,p) by means of a spin correction formula (32,33):

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

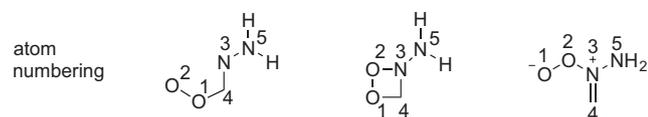
where  $E$  is the absolute energy,  $l$  and  $h$  represent the lower energy spin state (singlet) and the higher energy spin state (triplet), respectively. Also,

\*Corresponding author email: agreer@brooklyn.cuny.edu (Alexander Greer)

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Scheme 1.



Scheme 2.

$E_{sc}$  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 (34). To estimate the energy of  $^1\Delta_g$  oxygen, the experimental singlet-triplet gap of 22.5 kcal mol<sup>-1</sup> was added to the value computed for  $^3\Sigma_g^+$  oxygen, which appears in parentheses in Figs. 3–6. Although 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 Figs. 3–6 reflecting its higher error, and is analogous to the reports of Jensen *et al.* (35), McKee (36), Moss *et al.* (37), Rondan *et al.* (38) and Xu *et al.* (39) where the relative energy of sulfide/singlet oxygen or halocarbene/alkene reagents often have negative enthalpy barriers. Conceivably, multireference methods are advantageous for mixed species, such as in the case of radicals with resonance (40). Indeed, Table 1 shows  $T_1$  diagnostic values for many of our computed structures are above 0.02, which points to the need for multireference calculations (41). 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 formaldehyde diazene **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 formaldehyde diazene **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**

**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*	$\langle S^2 \rangle$ after annihilation*	$T_1^\dagger$	N(3) spin density <sup>†</sup>	O(2) spin density <sup>†</sup>
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

\* $\omega$ B97X-D/6-311G(d,p); <sup>†</sup>CCSD(T)/aug-cc-pVTZ.

and hydroperoxymethyl diazene **5**, the latter two species could theoretically arise from the formaldehyde diazene- $^1\text{O}_2$  reaction.

### Computed geometries

DFT computed structures are given in Figs. 1 and 2. Compounds **1–9**, **2T–3'T** and **5T** optimized to minima, where species labeled

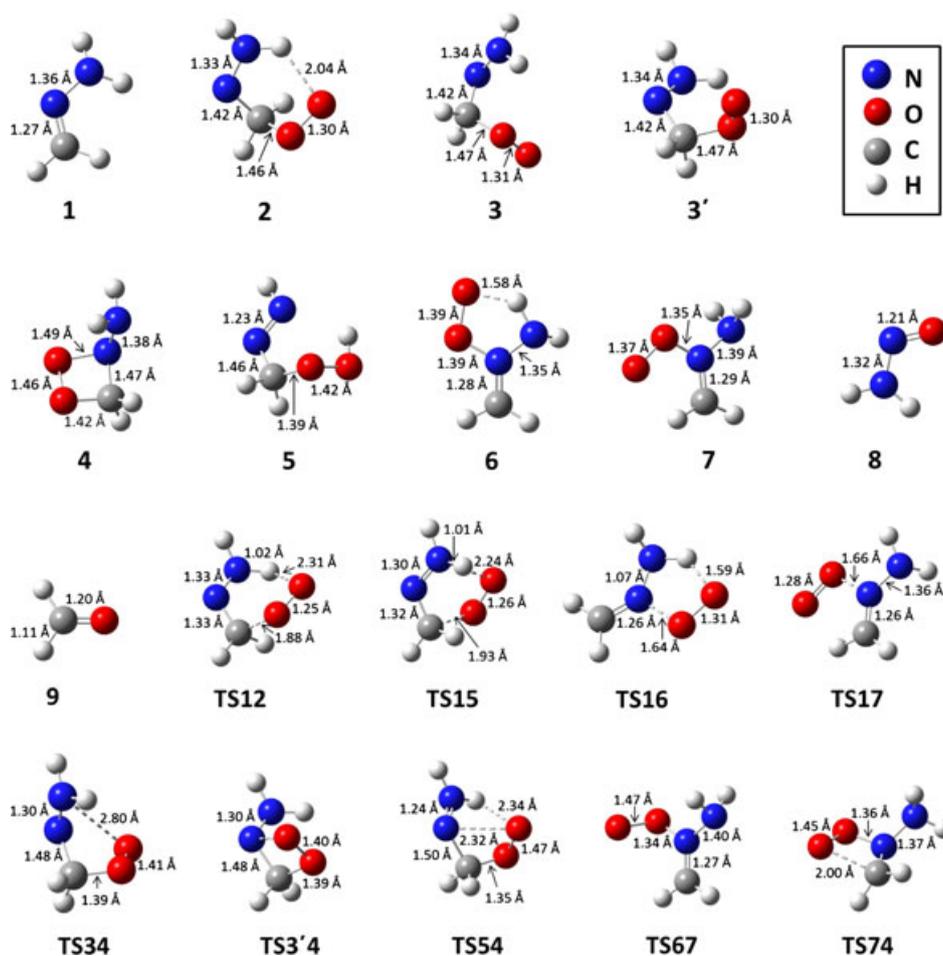


Figure 1.  $\omega$ B97X-D/6-311+G(d,p) minimum energy structures and transition states (TS) on the singlet surface.

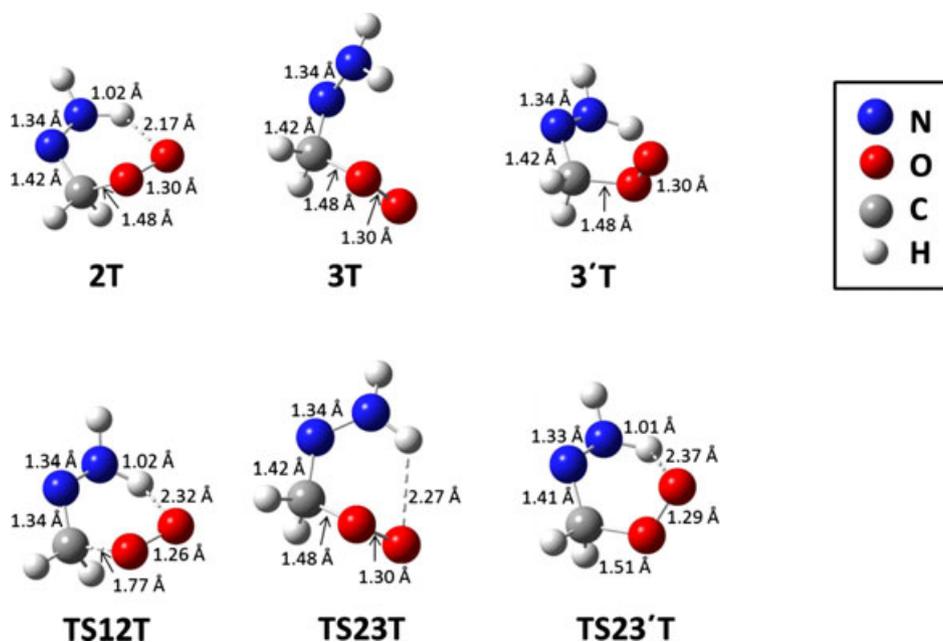


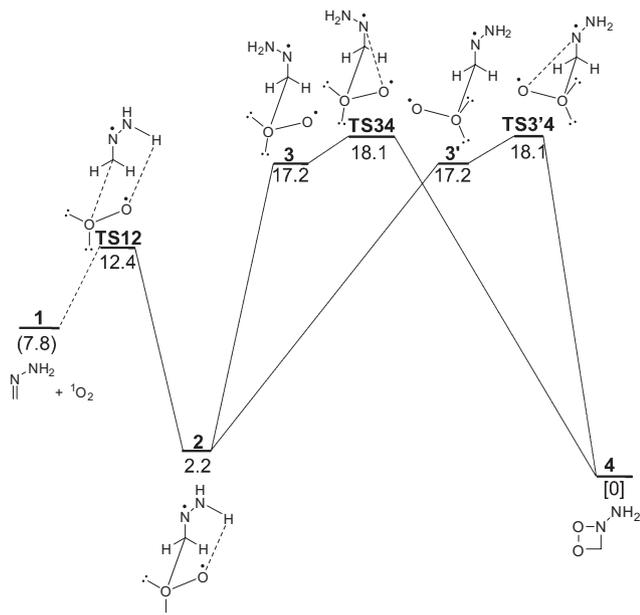
Figure 2.  $\omega$ B97X-D/6-311+G(d,p) computed structures and transition states (TS) on the triplet surface, thus the “T” designation.

“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 (42,43). 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) ( $\theta$ ) is 81.4°. Dioxazetidine **4** shows the expected deviation from planarity, where  $\theta$  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  $\theta$  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  $\text{H}_2\text{O}_2$  (1.475 Å) (44). In **6**,  $\theta$  is 172.7° and in **7** it is 180.0°.

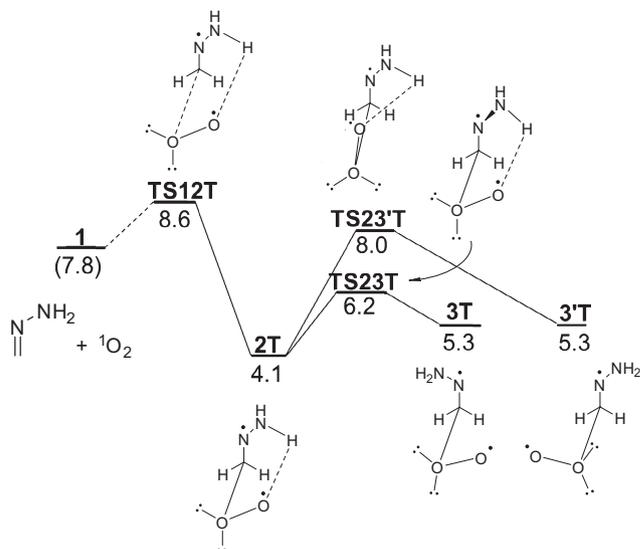
### Potential energy surfaces

We have explored the reaction of formaldehyde with  $^1\text{O}_2$  reaction in gas phase with CCSD(T)/aug-cc-pVTZ// $\omega$ B97X-D/6-311G(d,p) calculations (Figs. 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 $^{-1}$  (Fig. 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 $^{-1}$  (Fig. 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



**Figure 3.** CCSD(T)/aug-cc-pVTZ// $\omega$ B97X-D/6-311+G(d,p) computed singlet open-shell surface for path A in kcal mol $^{-1}$  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// $\omega$ B97X-D/6-311+G(d,p) computed triplet surface of path A in kcal mol $^{-1}$ . 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.

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 (45–47), a species that can transfer an oxygen to toluene (48) or cyclize to dioxaziridine (18).

The stationary points in Fig. 3 resemble those in Fig. 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 **3'T** 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 eight-membered ring diperoxide, 3,7-diamino-3,4,7,8-tetrahydro-1,2,5,6-tetraoxa-3,7-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 (49,50).

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 $^{-1}$ , respectively (Fig. 5). The activation energies to reach these species are 12.4 and 15.0 kcal mol $^{-1}$ , respectively. Furthermore, a saddle point which connects **7** and **4** has been located, but it is too high (27.3 kcal mol $^{-1}$ ) 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 (51), but such a quenching channel that includes a charge-transfer interaction was not modeled.

Finally, 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 $^{-1}$  (Fig. 6). The barrier between **1** +  $^1\text{O}_2$  and **5** is low (3.0 kcal mol $^{-1}$ ). Surprisingly, subsequent conversion of the hydroperoxymethyl

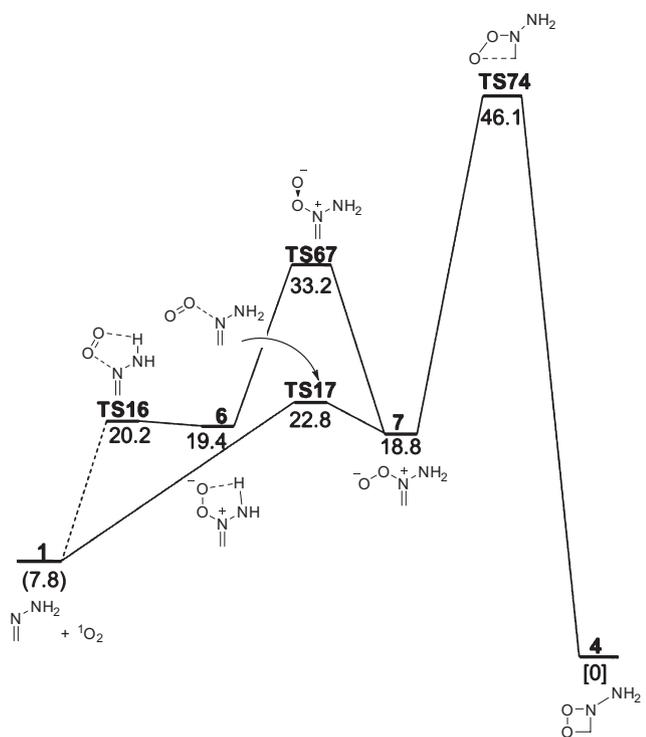


Figure 5. CCSD(T)/aug-cc-pVTZ// $\omega$ B97X-D/6-311+G(d,p) computed singlet open-shell surface for path B in kcal mol<sup>-1</sup>.

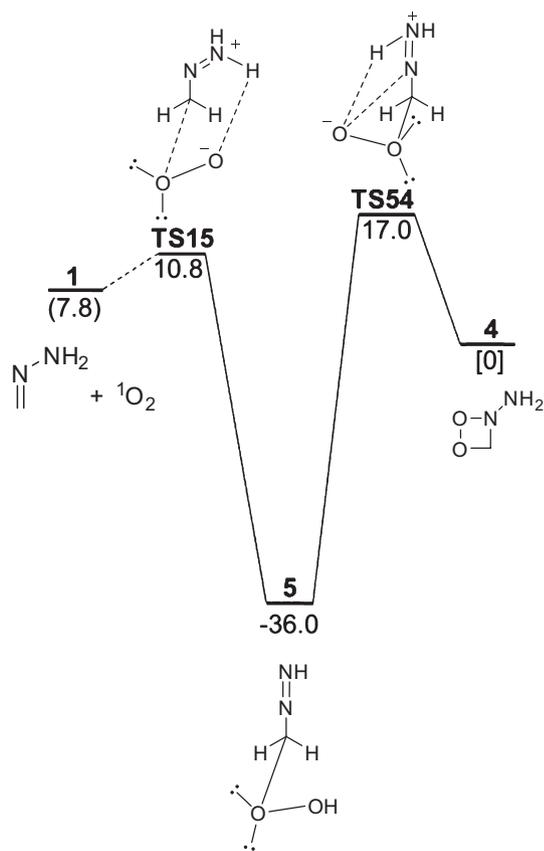


Figure 6. CCSD(T)/aug-cc-pVTZ// $\omega$ B97X-D/6-311+G(d,p) computed singlet closed-shell surface for path C in kcal mol<sup>-1</sup>.

diazene **5** to dioxazetidone **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<sup>-1</sup>).

The 2-amino-oxaziridine-*O*-oxide intermediate **10** was not found computationally. With  $\omega$ 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, BHandHLYP, CAM-B3LYP, M08-SO, B3LYP-D3 and TPSSTPSS.

### Enthalpies of formation

It may be asked if the calculated values of the relative enthalpies of formation in the current study are plausible: 3-amino-1,2,3-dioxazetidone **4**, 0.0 kcal mol<sup>-1</sup> (by definition); formaldehyde **1** (+singlet oxygen), 7.8 kcal mol<sup>-1</sup>; hydroperoxymethyl diazene **5**, -36.0 kcal mol<sup>-1</sup>. Relatedly, how plausible is the reaction exothermicity of 3-amino-1,2,3-dioxazetidone to form formaldehyde + nitrosamine of 67.1 kcal mol<sup>-1</sup> (the units in this section will be omitted in calculations for clarity, but kcal mol<sup>-1</sup> 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 (52)), 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-dioxazetidone (or any oxazetidone for that matter) and so the corresponding ring correction is not to be found in Ref. (52) and so must be "approximated." There are no species at all with measured enthalpies of formation with either -O-O-N- or -O-N-N- functionalities should we sensibly ignore multiply bonded species such as peroxy nitrites 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. (53) and (54) respectively). Said differently, while  $\Delta_f H^0$  (**4**) = C-(N)(O)(H)<sub>2</sub> + N-(N)(O)(C) + O-(O)(N) + O-(O)(C) + N-(N)(H)<sub>2</sub> + ring correction, but the group increments C-(N)(O)(H)<sub>2</sub>, O-(O)(N) and N-(N)(O)(C) and the ring correction must be derived de novo for the current study.

Starting with the increment C-(N)(O)(H)<sub>2</sub>, it is taken here as the average of C-(O)(O)(H)<sub>2</sub> (*i.e.* C-(O)<sub>2</sub>(H)<sub>2</sub>) [-17.7] and C-(N)<sub>2</sub>(H)<sub>2</sub> [-12.1],  $\frac{1}{2}$  ([-17.7] + [-12.1]) = <-14.9> (In the current study "square brackets" [and] around a numerical value will be used to denote it is from values from ref. (52), and the "angular brackets" < and > likewise to denote derived estimates for use in the current study.). Alternatively, the difference of C-(O)(O)(H)<sub>2</sub> [-17.7] - C-(N)(O)(H)<sub>2</sub> may be equated with C-(O)(C)(H)<sub>2</sub> [-8.5] - C-(N)(C)(H)<sub>2</sub> [-6.6] and so the desired increment C-(N)(O)(H)<sub>2</sub> is deduced to be [-17.7] - ([-8.5] + [6.6]) = <-15.8>. The two values for C-(N)(O)(H)<sub>2</sub> are close: a consensus value of -15 kcal mol<sup>-1</sup> will be taken.

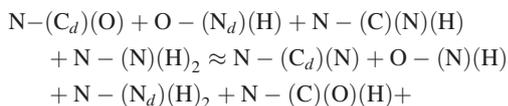
The value for O-(O)(N) is not available. The difference of O-(C)(N) and O-(O)(N) is approximated here by that of O-(C)<sub>2</sub>

and O–(O)(C), [–23.7]–[–4.5] = <–19.2>, of O–(C)(H) and O–(O)(H) = [–37.9]–[–16.3] = <–21.6> or better still, their average, <–20.4>. From the value for O–(C)(N) = [–0.9], we thus derive O–(O)(N) = [–0.9]–<–20.4> = <19>. Alternatively, the difference O–(O)(H) and O–(O)<sub>2</sub> = [–16.3]–<19.0> = <–35.3> and O–(O)(H) and O–(O)(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 O–(C)(N) [–14.1] and O–(O)(N), we derive O–(O)(N) = <–14.1> – <–34> = <20> nearly the same as before, and now taken as the consensus value of O–(O)(N) = 20 kcal mol<sup>–1</sup>.

Assuming N–(N)(C)<sub>2</sub> – N–(H)(C)<sub>2</sub> [29.2] – [15.4] ≈ N–(N)(C)(H) – N–(C)(H)<sub>2</sub> [20.9] – [4.8] ≈ N–(N)(O)(C) – N–(H)(O)(C) from N–(H)(O)(C) = [12.2], N–(N)(O)(C) ≈ <26> kcal mol<sup>–1</sup>.

The ring correction for 3-amino-1,2,3-dioxazetidine is taken here as 26 kcal mol<sup>–1</sup>, set equal that of other four-membered rings, cyclobutane and oxetane [26.2] and [26.4] kcal mol<sup>–1</sup>. Accordingly, Δ<sub>r</sub>H<sup>0</sup> (**4**) = C–(N)(O)(H)<sub>2</sub> + N–(N)(O)(C) + O–(O)(N) + O–(O)(C) + N–(N)(H)<sub>2</sub> + <ring correction> ≈ <–15> + <20> + <26> + [–4.5] + [11.4] + <26> ≈ 64 kcal mol<sup>–1</sup>.

Benson *et al.* (52) 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. (55), it is plausibly about half of that of glyoxal dioxime much as formaldehyde –26.0 kcal mol<sup>–1</sup>, is about half of glyoxal, 50.6 and ethylene, 12.5, is about half of 1,3-butadiene, 26.3. Benson, *et al.* (52) give the reader two reasoned estimates for glyoxal dioxime, 0 and 1.9 kcal mol<sup>–1</sup>, and so a value of 1 kcal mol<sup>–1</sup> 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<sup>–1</sup> 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<sup>–1</sup> for the enthalpy of formaldoxime. An overall consensus value for formaldoxime of ca. 3 kcal mol<sup>–1</sup> may thus be suggested. Reference (52) 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) ≈ 38 kcal mol<sup>–1</sup> is deduced for formalhydrazone. Accordingly species **1** has an enthalpy of formation of ca. 38 + 22.5 = 60 kcal mol<sup>–1</sup>. This is 4 kcal mol<sup>–1</sup> lower than that of the cyclic product **4**, 3-amino-1,2,3-dioxazetidine for which an enthalpy of formation of 64 kcal mol<sup>–1</sup> had been suggested earlier in this text. The earlier quantum chemical calculations suggest a difference of species **1** and **4** was 8 kcal mol<sup>–1</sup> 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<sup>–1</sup> in so many of our numbers, most obviously and unavoidably in the group increments.

What is Δ<sub>r</sub>H<sup>0</sup> (**5**)? Is it best to start with the preliminary enthalpy of formation of the parent species, the dehydroperoxylated methyl diazene itself? Whether by the use of Benson group increments or in this case, taking the average of the enthalpies of formation of N<sub>2</sub>H<sub>2</sub> and azomethane (dimethyl diazene), the value of  $\frac{1}{2}(50.2 + 44.3) = <47>$  kcal mol<sup>–1</sup> is found. Reintroducing the hydroperoxy group corresponds to the change of C–(N<sub>d</sub>)(H)<sub>3</sub> to C–(N<sub>d</sub>)(O)(H)<sub>2</sub> + O–(O)(C) + O–(H)(O). Equating this change with that of C–(N)(H)<sub>3</sub> to C–(N)(O)(H)<sub>2</sub> + O–(O)(C) + O–(H)(O), the change is from [–10.1] to <–15> + [–4.5] + [–16.3] or <–27> kcal mol<sup>–1</sup>. Accordingly, the predicted enthalpy of formation of species **5** ≈ <47> + <–27> ≈ 20 kcal mol<sup>–1</sup>. Formalhydrazone + singlet oxygen is thus predicted to be 38 + 22 – 20 ≈ 40 kcal mol<sup>–1</sup> higher in energy than hydroperoxymethyl diazene from the current analysis increments while the quantum chemical difference is 7.8 – (–36.0) ≈ 44 kcal mol<sup>–1</sup> in comforting agreement. Here, it is clear that the hydroxyperoxymethyl diazene is 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<sub>2</sub>) – N–(NO) ≈ O–(NO<sub>2</sub>)(C) – O–(NO)(C) = [–19.4] – [–5.9] ≈ <–14> kcal mol<sup>–1</sup>. No data are given for the enthalpy of formation of any nitramine in Ref. (50). No data for the enthalpy of formation of gaseous NH<sub>2</sub>NO<sub>2</sub> are known from experiment; accepting the high accuracy quantum chemically calculated value, 1 kcal mol<sup>–1</sup>, from Ref. (56) results in a suggested value of 1 + 14 ≈ 15 kcal mol<sup>–1</sup> for NH<sub>2</sub>NO. The enthalpies of formation of nitrosamine **8** and formaldehyde **9** sum to 15 – 27 = –12 kcal mol<sup>–1</sup> 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<sup>–1</sup> while the prediction made earlier in the current study is exothermic by but 67 kcal mol<sup>–1</sup>. While there is a disparity of 9 kcal mol<sup>–1</sup>, 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? Reference (53) 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 (J. E. Bartmess, personal communication). What about hydrazones and hydrazines? For the former, problems have long been enunciated (57). For the former, problems have recently been heralded (58).

## CONCLUSION

The reaction of formalhydrazone **1** with <sup>1</sup>O<sub>2</sub> was calculated using CCSD(T)//DFT in the gas phase to assess the energetics of the ‘ene’ and [2 + 2] pathways. Computations indicate a facile ‘ene’ reaction of **1** and <sup>1</sup>O<sub>2</sub> by **TS15** to hydroperoxymethyl diazene **5**. If there are no N–H allylic hydrogens, a step-wise reaction of hydrazone with <sup>1</sup>O<sub>2</sub> and then cleavage of the resulting dioxazetidine

makes the route to nitrosamine relevant from a biological or synthetic point of view. Dioxazetidone **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 10 different DFT functionals. The Benson-like analysis has been found to be in qualitative agreement with the quantum chemical calculations.

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