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Synthesis of a Stereochemically Defined 1,2-Diazetine *N*,*N*′-Dioxide and a Study of Its Thermal Decomposition

Gary W. Breton,* Lindsey H. Oliver, and Justine E. Nickerson

Department of Chemistry, Berry College, P.O. Box 495016, Mount Berry, Georgia 30149

gbreton@berry.edu

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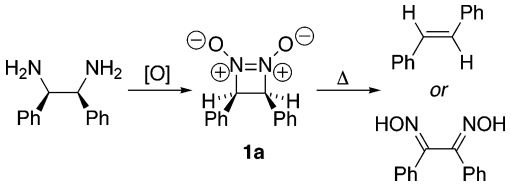
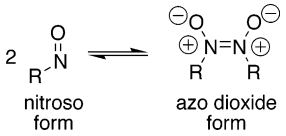


Diazetine dioxide **1a** has been synthesized in a single step via oxidation of *meso*-2,3-diphenyl-1,2-ethanediamine with dimethyldioxirane, albeit in low yield (7%). Thermal decomposition of **1a** afforded predominantly either *trans*-stilbene or diphenyl glyoxime depending on solvent, temperature, and the presence of an amine catalyst. Reaction in chloroform at 69 °C favored elimination of NO and formation of *trans*-stilbene. The stereospecific formation of *trans*-stilbene suggests a mechanism of decomposition in which C−N bond cleavage leads to a diradical intermediate stabilized by the phenyl group. Bond rotation followed by cleavage of the second C−N bond accounts for the *trans*-stilbene. At 25 °C in chloroform, while *trans*-stilbene was still the major product, some diphenyl glyoxime was also observed (4% yield). However, **1a** as a solution in chloroform in the presence of Et_3N, or **1a** as a solution in DMSO-d_6, afforded predominantly diphenyl glyoxime. These results are interpreted in terms of two closely competing reactions subject to the effects of entropic contributions.

Introduction

1,2-Diazetine *N*,*N*′-dioxides (diazetine dioxides, **1** in Figure 1) are a class of strained four-membered ring azo dioxide heterocycles. Although the first report of a diazetine dioxide was as early as 1971, only a handful of such compounds are currently known.[1−5] Diazetine dioxides have been used as highly effective low-energy triplet quenchers in photochemical reactions,[6] and have recently been investigated for their biological activity as potent vasorelaxant and antiaggregant agents.[3−5,7] Despite their promise for utility, diazetine dioxides remain little explored.

Diazetine dioxides are formally ring-closed 1,2-dinitroso compounds.[8] Nitroso compounds are dimeric in the solid form as azo dioxides, but retain their monomeric form (or some equilibrium between the two forms) in solution.[8,9] The mono-



meric forms are easily recognized by their characteristic deep blue color.[10] Several bisnitroso compounds also exhibit this behavior in solution, and are in equilibrium with their ring-

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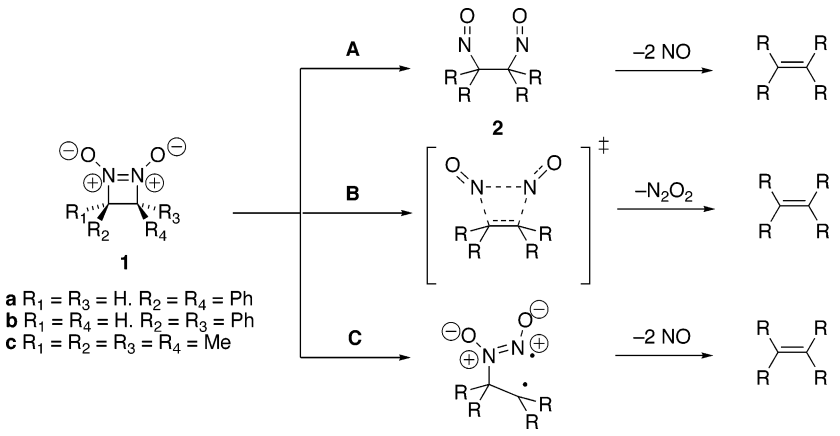


FIGURE 1. Possible mechanisms for the decomposition of diazetine dioxides.

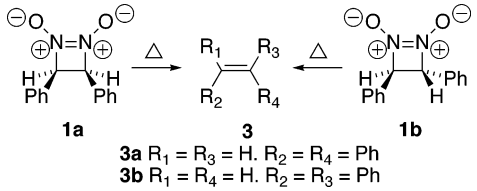


FIGURE 2. Possible products from the decomposition of diazetine dioxides **1a** and **1b**.

closed forms to afford cyclic azo dioxide compounds.[8,9] However, none of the known diazetine dioxides exhibit ready equilibrium between the open (i.e., 1,2-dinitroso) and closed (i.e., diazetine dioxide) forms in solution.[8a] One of the more intriguing aspects of the reactivity of diazetine dioxides is their tendency to liberate 2 equiv of nitric oxide (NO) upon decomposition to yield the corresponding alkene (see Figure 1).[1,3] It is the production of the biologically active molecule NO that has suggested the possibility of using diazetine dioxides as pharmaceutical agents.[3,7] The mechanism by which NO is liberated still remains a question.[8,9]

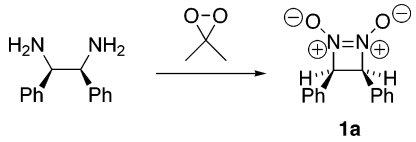
There are several mechanistic possibilities for the decomposition of diazetine dioxides (Figure 1). Mechanism A in Figure 1 results from initial breaking of the azo dioxide N═N bond (akin to the monomerization of azo dioxides mentioned above) to form a dinitroso intermediate (**2**), which could then release two molecules of NO to generate the alkene product. Mechanism B represents a concerted loss of two molecules of NO (or a molecule of N_2O_2 that would rapidly dissociate to two molecules of NO) along with generation of the alkene. Both a symmetrical and an asymmetrical version of mechanism B could be envisioned. In support of the feasibility of this mechanism an asymmetrical, yet concerted, elimination of N_2 has been put forth as the likely mode of decomposition for the related 1,2-diazetine compounds.[11] Mechanism C depicts single bond scission to form a diradical intermediate, followed by loss of N_2O_2 and formation of the alkene product.

To begin to differentiate between these mechanistic possibilities, we sought to investigate the decomposition of a suitably substituted diazetine dioxide such that the stereochemical outcome of the decomposition process could be ascertained (see Figure 2). For example, decomposition of dioxides **1a** and **1b** could occur stereospecifically (i.e., to afford **3a** from **1a**, and **3b** from **1b)** or nonspecifically to afford a mixture of stereoisomeric products (i.e., a mixture of **3a** and **3b** from either **1a** or **1b**). Stereospecific elimination is most consistent with mechanism B, while a mixture of stereoisomers would be expected from mechanisms A and C where the formation of intermediates allows time for rotation about the central C−C bond prior to elimination of NO.

Results

The prevailing method for the synthesis of diazetine dioxides is via oxidation of the corresponding 1,2-bishydroxylamines.[1,2,12] We found one brief report, however, on the direct oxidation of a 1,2-diamine (i.e., 2,3-dimethyl-1,2-diaminobutane) to diazetine dioxide **1c** with use of the strong oxidizing agent dimethyldioxirane.[13]

Subjecting commercially available *meso*-2,3-diphenyl-1,2-ethanediamine to a freshly prepared solution of dimethyldioxirane (5 equiv) at 0 °C resulted in rapid decoloration of the characteristic pale yellow color of the dimethyldioxirane and ultimately afforded *cis*-3,4-diphenyl diazetine dioxide (**1a**) in



low yield (7%) after chromatographic purification. At least part of the low yield of this reaction is attributable to the unexpectedly high reactivity of this compound toward thermal decomposition (vide infra). Benzaldehyde and benzonitrile were identified as the major byproducts of the reaction by GCMS analysis of the crude product mixture. Other oxidants tested (*m*CPBA and trifluoroperacetic acid) did not afford the desired product. Interestingly, attempts at oxidizing *d*,*l*-2,3-diphenyl-1,2-ethanediamine with dimethyldioxirane under identical conditions led to only trace amounts of suspected diazetine dioxide product **1b** and this process was not pursued further.

Diazetine dioxide **1a** was characterized by NMR, IR, and UV spectroscopy. Of particular note was the strong absorbance at 264 nm corresponding to the azo dioxide absorption in the

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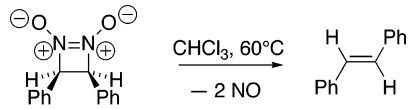
UV spectrum (ϵ = 19 000), which is similar to that reported for **1c** (λ_{max} = 255, ϵ = 10 000).[8a] In addition, the stretch in the IR spectrum at 1541 cm^{-1} corresponding to the azo dioxide stretch matches well with the same stretch in **1c** (reported at 1540 cm^{-1}).[8a] Both the ^1H and ^{13}C NMR spectra verified the symmetrical nature of the compound's structure. Finally, the thermal reactivity of the compound (described below) corroborates the proposed structure for the compound.

Heating a chloroform solution of **1a** to reflux for 0.5 h resulted in the liberation of a dark reddish-brown gas characteristic of N_2O_4 (apparently generated via air oxidation of liberated NO gas). ^1H NMR, TLC, and GCMS analysis of the resulting product mixture identified the major product (96% yield) as *trans*-stilbene (**3b**) and lesser amounts of benzaldehyde



1a **3b**

(~2%) and (*Z*)-1,2-diphenyl-1-nitroethylene (<1%). When the decomposition was effected in the heated injector port of the GCMS (350 °C), only **3b** and NO were observed, suggesting that the other products were formed from secondary reactions of **3b** with NO and/or N_2O_4.

We were interested in the rate of decomposition of **1a** relative to the known diazetine dioxide **1c**. Kinetic data reported for a variety of diazetine dioxides suggested similar rates of decomposition regardless of substitution patterns or the nature of substituents.[5,7c] We conducted our own rate studies on the decomposition of **1c** using sealed NMR tubes (in DMSO-d_6) and followed the loss of starting dioxide relative to an internal standard (dichloroethane) via integration. The well-behaved first-order kinetics observed at 90 ($k = (3.10 \pm 0.03) \times 10^{-5}$ s^{-1}), 100 ($k = (8.9 \pm 0.1) \times 10^{-5}$ s^{-1}), and 110 °C ($k = (3.2 \pm 0.1) \times 10^{-4}$ s^{-1}) afforded $\Delta H^{\ddagger}$ = 31.5 kcal/mol. The major product formed was identified as 2,3-dimethyl-2-butene (by ^1H NMR and GCMS) as expected from previous studies.[1] Lesser amounts of other products were observed presumably deriving from secondary reactions of the alkene product with liberated NO. As with **1a**, only the corresponding alkene (i.e., 2,3-dimethyl-2-butene) and NO were observed when the decomposition was carried out in the heated injector port of the GCMS.

Interestingly, when we set up a similar kinetics run for compound **1a** in a sealed NMR tube, we found that it readily decomposed in DMSO-d_6 even at 29 °C ($k = (8.1 \pm 0.2) \times 10^{-4}$ s^{-1}). The rate of decomposition of **1a** is therefore 2.2 × 10^5 times greater than the rate predicted for **1c** at 29 °C. However, the major product formed under these conditions was not **3b** as had been observed in chloroform. Instead, a number of products were formed, the most significant of which was diphenyl glyoxime **4** (27% yield, identified by ^1H NMR and GCMS). When the reaction was repeated in an open vessel rather than a sealed tube, only **4** was observed by GCMS, again

1a **4**

suggesting that the remaining products were formed from subsequent oxidation reactions (presumably from trapped NO and/or N_2O_4). Similarly, decomposition of **1a** was followed in $CDCl_3$ (sealed NMR tube) at 29 °C, and while the major product observed was still **3b** (~70% yield) as had been observed in boiling chloroform, a product distribution similar to that in DMSO-d_6 was observed, including the observance of small amounts of **4** (4% yield). The rate of decomposition ($k = (1.2 \pm 0.2) \times 10^{-4}$ s^{-1}) was 7 times slower than the reaction in the more polar solvent DMSO-d_6. Decomposition of **1a** in the presence of Et_3N (33% solution in $CHCl_3$) afforded **4** as the major product.

Discussion

Decomposition of diazetine dioxides leading to NO and the corresponding alkenes is the pathway of thermal decomposition observed for all reported diazetine dioxides thus far to our knowledge. As mentioned above, available data suggest that the rates of decomposition of diazetine dioxides are very similar. The significantly enhanced rate of decomposition of **1a** (in $CDCl_3$) relative to **1c** (in both cases leading to NO and the corresponding alkene) suggests that decomposition of **1a** is favored relative to diazetine dioxides that are not substituted with phenyl groups. This is probably most consistent with mechanism C in Figure 1 where phenyl substitution could stabilize a radical intermediate relative to the simple alkyl substituents found in other diazetine dioxides. Rapid rotation about the C−C bond prior to rupture of the remaining C−N bond to relieve the steric strain of the proximate phenyl groups would rationalize the formation of *trans*-stilbene **3b** rather than the stereochemically retained cis isomer **3a**. Mechanism B in Figure 1 is unlikely given that the stereochemistry of the resulting alkene is inverted relative to the starting material. Furthermore, Mechanism A is also unlikely given that there was no evidence of even transient formation of **2**, which would have given rise to the characteristic deep blue color associated with alkyl nitroso compounds (as well as bisnitroso compounds)[8] during the decomposition of **1a**.

The isomerization of **1a** to **4** is possible due to the presence of available hydrogen atoms at the 3- and 4-positions of the heterocyclic ring. However, prior to this study, isomerizations of other 3,4-dialkyl diazetine dioxides with similarly available hydrogens had either not been observed or had not been reported.[14] In contrast, for nitroso compounds and acyclic azo dioxides that have available hydrogens α to the nitrogen, isomerization to oximes is a well-known process, and several experimental and theoretical studies have been reported.[15−17] Thus, heating the cis dimer of nitrosomethane to 80 °C is reported to lead to the formation of formaldoxime, while at higher temperatures (~95 °C) monomeric nitrosomethane is formed.[16] Heating the trans dimer leads only to nitrosomethane (with no concurrent formation of either cis dimer or formaldoxime).[17] Furthermore, theoretical studies on nitrosomethane have suggested that uncatalyzed isomerization to formaldoxime

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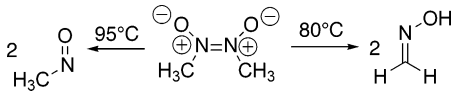

generally has a higher activation barrier than C−N bond cleavage leading to loss of NO.[16a,17] The picture that emerges from these various studies suggests that formation of formadoxime occurs exclusively from the *cis*-azo dioxide form (by an as yet unknown mechanism), while monomerization (and ensuing C−N bond scission) occurs at higher temperatures.

In one regard, compound **1a** is essentially an azo dioxide constrained to a cis conformation.[9] Its thermal behavior appears to parallel that of the cis dimer of nitrosomethane. Low-temperature decomposition (ca. room temperature) leads to diphenyl glyoxime as the major product in the highly polar solvent DMSO-d_6 and as a competing reaction product in $CDCl_3$. Isomerization probably results from direct conversion of the diazetine dioxide rather than via initial ring opening to the bisnitroso compound **2** since, as mentioned earlier, there is no evidence for even transient formation of **2**. The direct Et_3N-catalyzed conversion of **1a** to diphenyl glyoxime in $CHCl_3$ is consistent with previous studies of base-catalyzed isomerizations of azo dioxide compounds to the corresponding oximes.[18]

Thermal decomposition of diazetine dioxide **1a** apparently takes place via two closely competing routes: (i) isomerization to diphenyl glyoxime and (ii) C−N bond scission to form a transient diradical intermediate followed by loss of N_2O_2 to form *trans*-stilbene **3b**. We computed the energies of the compounds involved in both of these transformations at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) levels and the results are summarized in Table 1. The isomerization pathway to form glyoxime **4** is predicted to be exothermic by 26 kcal/mol, while loss of NO to form **3b** is predicted to be endothermic by 5 kcal/mol. However, the formation of **3b** will almost certainly be favored entropically. Thus at room temperature (and especially in the base-catalyzed reaction) the isomerization process is able to compete, while at higher temperatures, where entropic effects are more strongly exerted, NO elimination is favored. Notice that formation of the bisnitroso compound **2** (via mechanism A) is predicted to be endothermic by 8 kcal/mol and that formation of the stereochemically retained *cis*-stilbene **3a** (via mechanism B) is predicted to be endothermic by 10 kcal/mol, which further suggests that these pathways are less likely than the alternative modes of decomposition. We are currently extending our computational studies on model compounds to more closely examine the transition states expected from the various possible modes of decomposition.

Experimental Section

3,4-Diphenyl-1,2-diazetine 1,2-dioxide (1a). To 122 mL of a freshly prepared solution of dimethyldioxirane in acetone[19] at 0 °C (~0.07 M, 5 equiv) was added 0.364 g (1.72 mmol) of *meso*-1,2-diphenylethylenediamine (Aldrich) as a solid at one time. The solution quickly became blue-green in color, which then dissipated within 30 s. The solution was stirred for 1 h and the acetone removed under reduced pressure. Column chromatography (SiO_2, 1:1 hexane/EtOAc) afforded 0.11 g of a pale yellow solid. This solid was chromatographed a second time (SiO_2, CH_2Cl_2) to afford 26.2 mg of **1a** (7% yield) as a white solid. ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.24 (s, 10H), 6.43 (s, 2H); ^{13}C NMR (15 MHz, $CDCl_3$) δ 129.9, 129.5, 129.3, 128.6, 78.6; IR (solid) cm^{-1} 3065, 2993, 1541, 1452, 692; UV (CH_3OH) λ_{max} = 264 (ϵ = 19 000).

TABLE 1. Computed Energies of Compounds Relevant to the Decomposition of Diazetine Dioxide 1a[a]

compd	E[a] (hartrees)
1a	−800.71679
3a	−540.83905
3b	−540.84665
NO	−129.93143
4	−800.75874
2	−800.70326[b]

[a] B3LYP/6-311+G(d,p)// B3LYP/6-32G(d). [b] Computed at the most stable conformation as determined by a Monte Carlo distribution generated by a MMFF calculation.

Thermolysis of 1a. Diazetine dioxide **1a** (16 mg, 0.07 mmol) was dissolved in 1 mL of $CHCl_3$ (passed through a column of Al_2O_3 to remove acidic impurities) and the solution was quickly heated to reflux in a 5 mL conical vial fitted with a reflux condenser and drying tube. A reddish-brown gas evolved quickly from the heated solution and dissipated within 30 min. The solution was cooled and the $CHCl_3$ removed under reduced pressure. ^{1}H NMR analysis of the resulting white solid showed only *trans*-stilbene (identified by comparison to a commercially available sample). Analysis by GCMS revealed small amounts of benzaldehyde (2%) and (*Z*)-1,2-diphenyl-1-nitroethylene (<1%) in addition to *trans*-stilbene. The reaction products were identified (GC retention times and mass spectral data) by comparison to commercially available samples. A control run established that *trans*-stilbene is not isomerized to *cis*-stilbene even at the high temperatures of the GC injection port (350 °C).

Determination of the Rate of Decomposition of 1a by ^{1}H NMR Spectroscopy. Diazetine dioxide **1a** (20 mg, 0.08 mmol) was dissolved in either DMSO-d_6 or $CDCl_3$ and 5 μL of 1,2-dichloroethane was added as an internal standard. The resulting solution was transferred to an NMR tube. For the high-temperature kinetics runs, the sample was frozen under vacuum and the tube flame sealed. The samples were submerged in a silica gel bath heated to the desired temperature and removed at regular intervals for analysis by NMR spectroscopy. For the 29 °C runs (i.e., temperature in the cavity of the NMR instrument), the NMR tube was tightly capped and sealed with paraffin. In all cases, the rate of decrease of the proton signal corresponding to the hydrogens at the 3- and 4-positions of the diazetine dioxide ring was determined relative to the internal standard by integration. An average of at least three runs were taken in each case. The reaction mixtures were analyzed directly by GCMS. The reaction products were identified (GC retention times and mass spectral data) by comparison to commercially available samples.

Decomposition of 1a in the Presence of Triethylamine. Diazetine dioxide **1a** (20 mg, 0.08 mmol) was dissolved in a mixture of 1 mL of $CHCl_3$ and 0.5 mL of Et_3N. The solution was allowed to sit for 3 h after which it was directly analyzed by GCMS.

Computational Details

All of the computations reported in this paper were obtained with the Becke3LYP density functional as implemented within the Spartan '02 program.[20] Geometries and frequencies were computed

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with the B3LYP/6-31G(d) basis set and followed up with single-point calculations with the B3LYP/6-311+G(d,p) basis set. All reported geometries were fully optimized in the gas phase without imposing geometrical constraints. The computed frequencies confirmed that each structure was at a minimum by ensuring the absence of negative frequencies. Energies are uncorrected. Where many possible conformations might exist, the most stable conformation was determined by a Monte Carlo calculation with use of the MMFF force field.

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Supporting Information Available: Cartesian coordinates and total energies for calculated structures and ^{1}H NMR spectrum of compound **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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