JOC Article

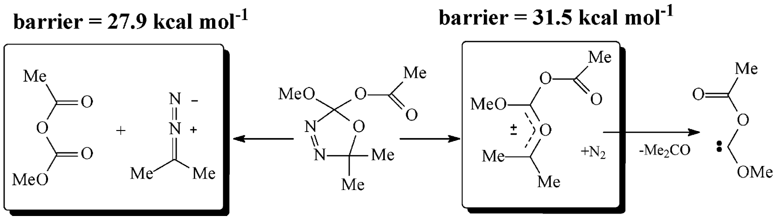
Density Functional Theory Computational Study on the Thermal Cycloreversion of 2-Acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline: Evidence for a Carbonyl Ylide Intermediate

Wojciech Czardybon, John Warkentin,* and Nick Henry Werstiuk*

Department of Chemistry, McMaster University, Hamilton, ON, Canada, L8S 4M1

warkent@mcmaster.ca; werstiuk@mcmaster.ca

Received June 10, 2005



Three [3 + 2] cycloreversions of 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazolines were examined by computation at the density functional level of theory. The lowest activation energies are those for cycloreversion to 2-diazopropane and acetic methylcarbonic anhydride and for cycloreversion to N_2 and a carbonyl ylide. Those are the reactions that are observed experimentally. A third cycloreversion, to acetoxy(methoxy)diazomethane and acetone, has a much larger barrier. The carbonyl ylide is a real intermediate, but it fragments easily to acetone and acetoxy(methoxy)carbene. The lifetime of the ylide may be so short, in some cases, as to blur the distinction between a two-step cycloreversion of the oxadiazoline and a concerted process that generates three fragments in one step.

Introduction

Recently we reported that 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**1**) (also known as 2-acetoxy-2,5-dihydro-2-methoxy-5,5-dimethyl-1,3,4-oxadiazole) undergoes two competing cycloreversions upon thermolysis in benzene at 110 °C.[1] The cycloreversions were essentially balanced, affording 2-diazopropane (**2**) together with mixed anhydride **3** on one hand and N_2 as well as carbonyl ylide **4** on the other, as shown in Scheme 1. The ylide was assumed to be the initial product of the extrusion of N_2; the actual materials identified were acetone and methyl pyruvate (**6**), the latter from rearrangement of acetoxy(methoxy)carbene (**5**) formed by fragmentation of ylide **4**.

We now report computations on three cycloreversions, two of which (Scheme 1) were observed experimentally in essentially 1:1 ratio. The existence of an intermediate carbonyl ylide **4** was also probed because Smith[2] had proposed that a carbonyl ylide is not a necessary intermediate in the thermolysis of oxadiazoline **7**[3] (Scheme 2). His calculations, at low levels of theory (semiempirical PM3 and ab initio HF/3-21G), indicated that the oxadiazoline could fragment in a concerted process to afford N_2, acetone, and carbene **9** in a single step, avoiding carbonyl ylide **8**.

Although we had gathered some experimental support for the intermediacy of carbonyl ylides of type **8** in the thermolysis of analogous oxadiazolines, the evidence was not compelling. Perhaps the strongest case was obtained from **10** (Scheme 3) where **12**, from apparent intramolecular reaction of ylide **11**, was isolated in 2% yield.[4] Even in that case, the intermediacy of **11** in the thermolysis of **10** remained in some doubt, particularly because the low yield meant that other, less likely, mechanisms leading to **12** could be envisioned.

Finally, the observed fragmentation of **1** to 2-diazopropane (Scheme 1) raised the question as to whether cycloreversion occurred to yield acetoxy(methoxy)diazomethane (**13**) that could, in principle, also decompose

---

[1] Czardybon, W.; Klys, A.; Warkentin, J.; Werstiuk, N. H. *Can. J. Chem.* **2003**, *81*, 1438.

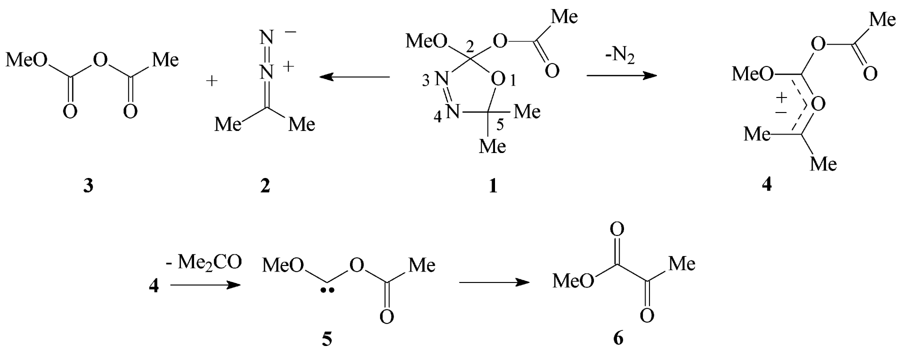
[2] Smith, W. B. *J. Org. Chem.* **1995**, *60*, 7456.

[3] Kassam, K.; Warkentin, J. *J. Org. Chem.* **1994**, *59*, 5071.

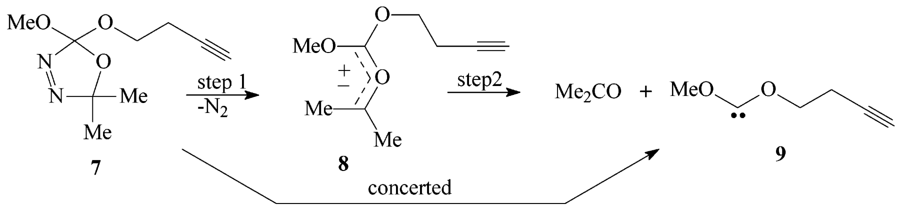
[4] Merkley, N.; Warkentin, J. *Can. J. Chem.* **2002**, *80*, 1187.

10.1021/jo0511750 CCC: \$30.25

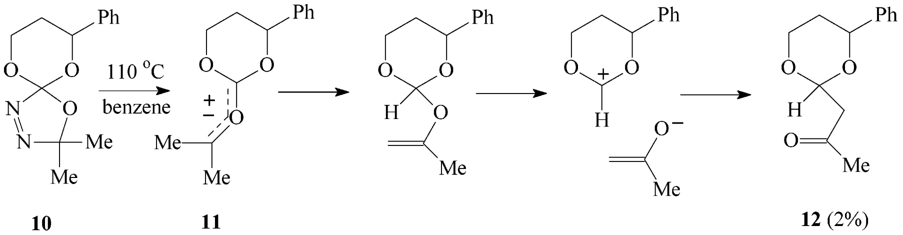
SCHEME 1



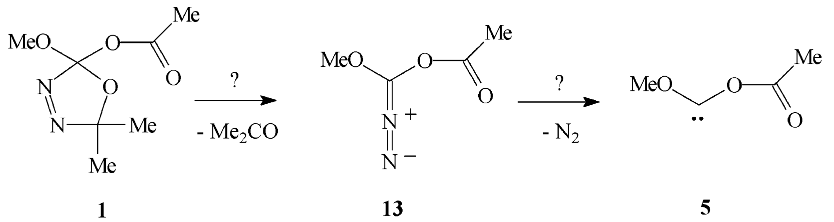
SCHEME 2



SCHEME 3



SCHEME 4



at 110 °C to yield acetoxy(methoxy)carbene (Scheme 4). The results of our computational studies are reported and discussed below.

Computational Methods

Optimized equilibrium geometries and transition states were obtained at the B3PW91/6-311+G(2df,p) level which includes the three parameter Becke–Perdew–Wang exchange-correlation potential[5] using either Gaussian 98[6] or Gaussian 03.[7] Calculations using the same method, but with a smaller basis set, were also carried out for comparison. The effect of solvent was probed with solvent-field calculations using the Onsager method; single-point calculations with the benzene dielectric constant were carried out with previously optimized geometries. Scan calculations were performed at the UB3PW91/6-31+G(d,p) level. Total energies and Z matrixes are included as Supporting Information. Frequency calculations were performed for all structures to characterize optimized geometries and transition states. While $\Delta E^{\ddagger}_{\text{elec}}$ values are discussed in the text, $\Delta E^{\ddagger}_{110°\text{C}}$ values are also presented in square brackets in the Figures. Computational results are collected in Table 1.

Results and Discussion

Conformational Properties. To ensure that we were dealing with the lowest energy pathways, we studied the conformational properties of **1** and also checked two conformers of **TS1** and **TS2**. Two low-energy conformers

---

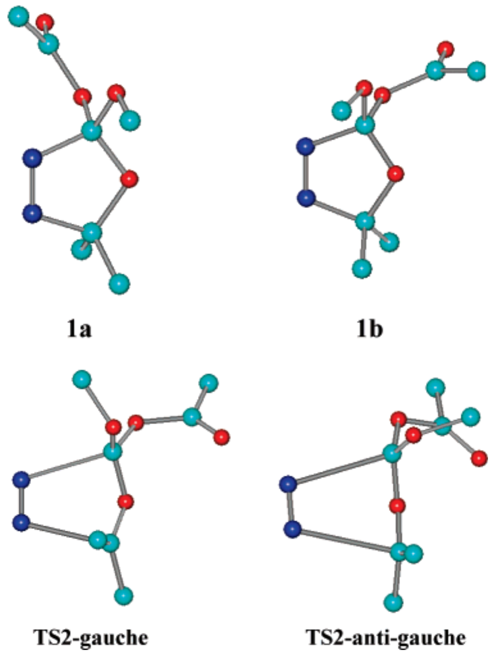
[5] Perdew J. P.; Wang Y. *Phys. Rev. B.* **1992**, *45*, 13244.

[6] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople J. A. *Gaussian 98*; Gaussian, Inc., Pittsburgh, PA, 1998.

TABLE 1. Thermochemical Data for 4, TS1, TS2, TS3, and TS5 Expressed Relative to 1

			TS1		TS2			
thermochemical parameter[a]	1	4 (singlet) (+N2)	gauche	antigauche	gauche	antigauche	TS3 (+N2)	TS5
ΔE_{elec}[b]	0	30.59[g]	29.23	27.87	31.49	33.43	33.59	49.70
ΔE_{o}[c]	0	24.78	26.73	25.35	27.91	28.63	27.23	46.70
$\Delta E_{110°\mathrm{C}}$[d]	0	26.30	25.91	26.15	29.33	30.71	28.44	47.52
$\Delta H_{25°\mathrm{C}}$[e]	0	26.82	27.40	26.06	29.09	30.41	29.09	47.32
$\Delta H_{110°\mathrm{C}}$	0	27.06	27.48	26.14	29.29	30.71	29.23	47.48
$\Delta G_{25°\mathrm{C}}$[f]	0	12.77	25.59	23.87	26.00	25.38	15.46	46.27
$\Delta G_{110°\mathrm{C}}$	0	8.7	25.06	23.23	25.09	23.91	11.55	45.95
ΔE_{elec}[b] (at B3PW91/6-31+G(d,p))	0	35.08		31.79	36.48		39.23	53.71

[a] At the B3PW91/6-311+G(2df,p) level in kcal mol^{-1} unless stated otherwise. [b] E_{elec} is the uncorrected total energy. [c] $E_{\mathrm{o}} = E_{\mathrm{elec}} + \mathrm{ZPE}$. [d] $E = E_{\mathrm{o}} + E_{\mathrm{vib}} + E_{\mathrm{rot}} + E_{\mathrm{trans}}$. [e] $H = E + RT$. [f] $G = H - TS$. [g] The values in this column correspond to ΔE_{elec}, ΔE_{o}, $\Delta E_{110°\mathrm{C}}$, $\Delta H_{25°\mathrm{C}}$, $\Delta H_{110°\mathrm{C}}$, $\Delta G_{25°\mathrm{C}}$, and $\Delta G_{110°\mathrm{C}}$.



1a **1b**

TS2-gauche **TS2-anti-gauche**

FIGURE 1. Confomers **1a** and **1b** of oxadiazoline **1** and gauche and antigauche conformers of **TS2** for extrusion of N_2. Hydrogen atoms are omitted for clarity.

of oxadiazoline **1** shown as **1a** and **1b** (Figure 1) were considered with the acetoxy group either syn (**1a**) or anti (**1b**) to the diazo group. The difference in energy between the conformers is small, and **1a** is marginally lower in energy than **1b**; $\Delta E_{\mathrm{elec}}(\mathbf{1a}-\mathbf{1b}) = -0.54$ kcal mol^{-1}. All the barriers reported in this paper were calculated relative to **1a**. The two conformers of **TS2, TS2-gauche** and **TS2-anti-gauche**, defined on the basis of the relative orientations of the methoxy and acetoxy substituents, are also shown in Figure 1. In fact, we found that the gauche conformation **TS2-gauche** is preferred for N_2 extrusion and an antigauche conformation was favored for diazopropane formation via **TS1**. As reported in the Table 1, differences in activation energies between the gauche and antigauche conformations in the cases of **TS1** and **TS2** are small.

Thermolysis of Oxadiazoline 1 to 2-Diazopropane. Figure 2 shows the potential energy surface for the thermolysis of **1** to form 2-diazopropane (**2**) and mixed anhydride **3** via the first cycloreversion (CR1) studied. Transition state **TS1** involves concerted breaking of the C−O and C−N bonds with the barrier $\Delta E^{\ddagger}_{\mathrm{elec}}$ being 27.87 kcal mol^{-1} ($\Delta E^{\ddagger}_{110°\mathrm{C}}$ is 26.14 kcal mol^{-1}).

Thermolysis of Oxadiazoline 1 to Ylide 4. Figure 3 shows the potential-energy surface for the competing cycloreversion (CR2) of **1** in to N_2 and ylide **4**. CR2, involving **TS2**, has a barrier of 31.49 kcal mol^{-1} (29.29 at 110 °C) with the products (ylide **4** and N_2) located only 0.91 kcal mol^{-1} below **TS2**. In the next step, ylide **4** undergoes fragmentation to acetone and carbene **5**. The barrier for this step is very low (3.00 kcal mol^{-1} (2.17 at 110 °C), indicating that the lifetime of ylide **4** is very short.

Most of the published experimental work on dialkoxycarbenes from oxadiazoline precursors has involved dimethoxycarbene. Consequently, we also modeled ylide **14** with two methoxy groups. A transition state **TS4** for loss of acetone, with formation of dimethoxycarbene, was found (Figure 4). It is only 1.60 (0.35 at 110°C) kcal mol^{-1} higher in energy than the ylide precursor, in support of the postulate that thermolysis of dialkoxyoxadiazolines is a stepwise process, with cycloreversion to N_2 and a carbonyl ylide as the first step. Fragmentation of the ylide to acetone and a dialkoxycarbene is a fast second step, with a very small barrier. Thus **14**, at best, has a shorter lifetime than **4**.

Our calculations yielded **TS4** with longer breaking bonds than those computed by Smith[2] for oxadiazoline **7** (C^2-N^3 at 2.394 and C^5-N^4 at 2.350 Å vs 1.688 and 2.088 Å). The important point is that the barrier to fragmentation of a carbonyl ylide such as **4**, **8**, or **14** is very small and that the ylide might not be a true intermediate in the case of some C-2 substituents. In theory, loss of N_2, which is the reverse of a 1,3-dipolar cycloaddition, would involve a carbonyl ylide intermediate. There is a large

---

(7) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*; Gaussian, Inc., Pittsburgh, PA, 2003.

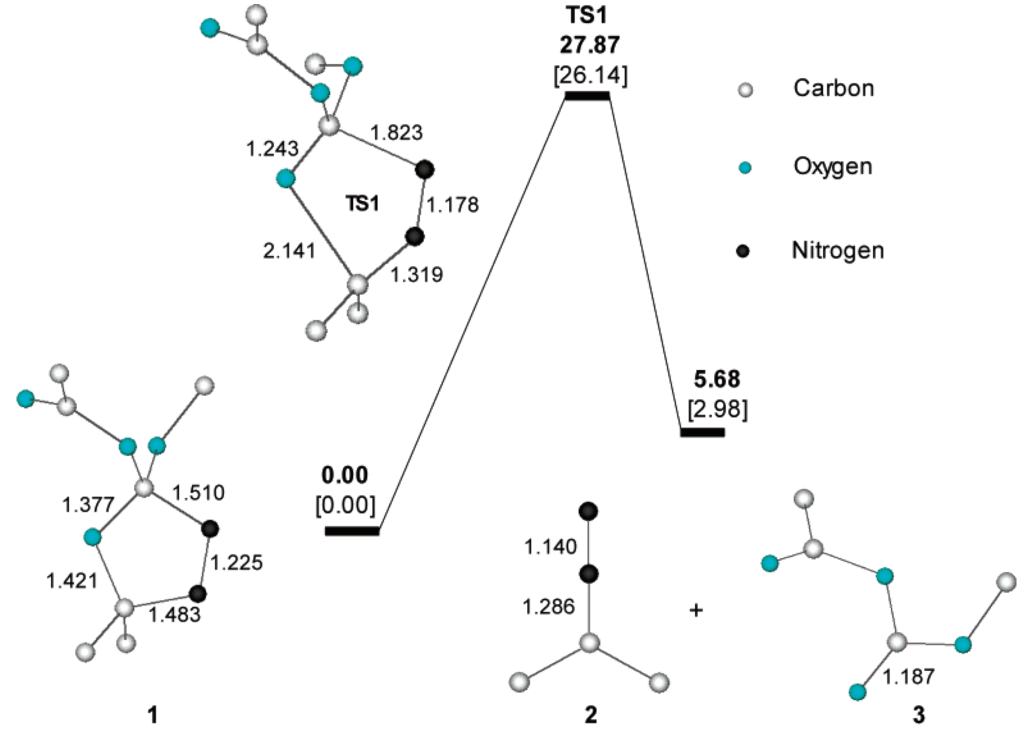


FIGURE 2. Potential-energy surfaces for cycloreversion (CR1) of **1** with formation of 2-diazopropane (**2**) and mixed anhydride (**3**) computed at the B3PW91/6-311+G(2df,p) level. Bolded values determined from E_{elec} and values in square brackets from $E_{110°\mathrm{C}}$. Bond distances are in angstroms.

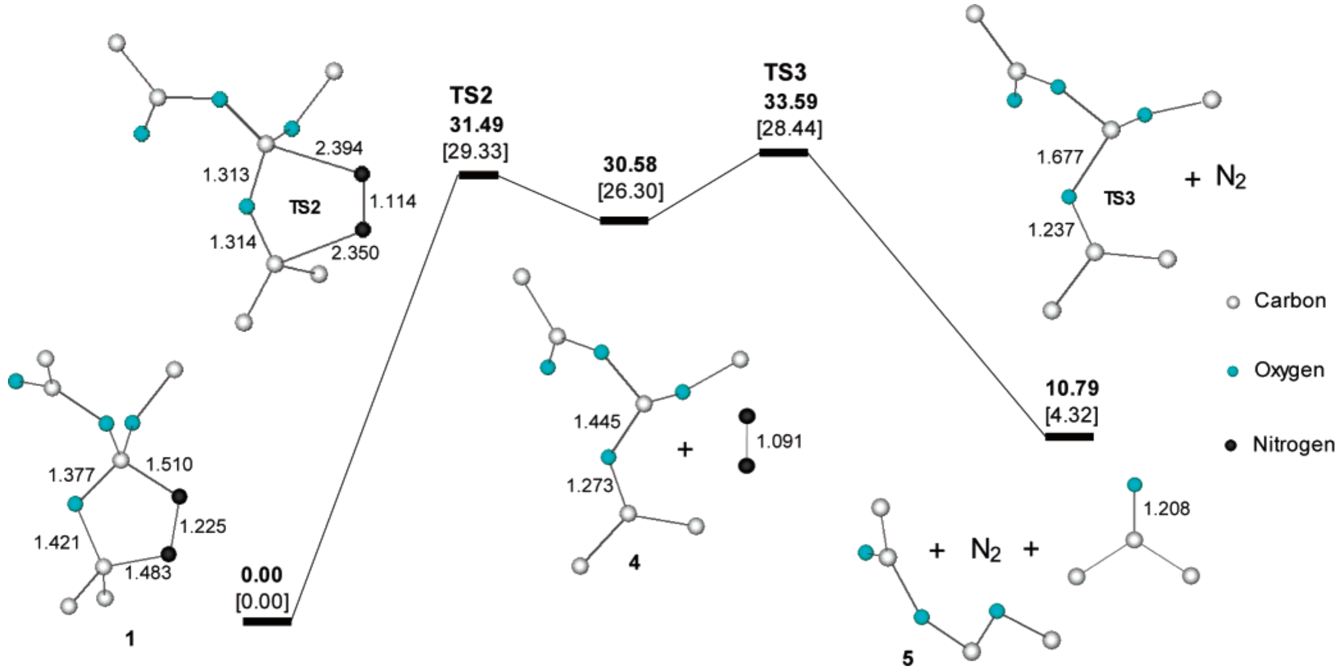


FIGURE 3. Potential-energy surfaces for cycloreversion (CR2) of **1** to N_2 and carbonyl ylide **4** and fragmentation of ylide **4** to carbene **5** and acetone at the B3PW91/6-311+G(2df,p) level. Bolded values determined from E_{elec} and values in square brackets from $E_{110°\mathrm{C}}$. Bond distances are in angstroms. Note that the diagram, which does not include entropies, does not imply that the free-energy barrier to addition of the ylide to N_2 is small. E_{elec} and $E_{110°\mathrm{C}}$ of N_2 were added to place the products on the same potential energy surface as **1** and **TS2**.

body of literature concerning cycloreversions that generate carbonyl ylides, as well as cycloadditions of carbonyl ylides to substrates with double or triple bonds.[8]

The carbonyl carbon of the incipient acetone (C^5) changes its character from pyramidal to planar along the reaction path (starting from **1** and ending with acetone). Table 2 shows how much O^1 lies out of the plane defined by C^5 and both methyl groups. We performed the IRC calculation to show clearly that **TS2** connects oxadiazoline **1** with the ylide **4**. Smith had concluded earlier that

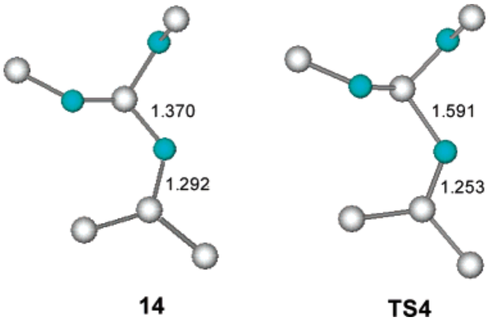


FIGURE 4. Ylide **14** and **TS4** optimized at the B3PW91/6-311+G(2df,p) level.

TABLE 2. Selected Geometrical Parameters of 1, TS2, 4, and TS3

compound	1	TS2	4	TS3
deviation from planarity of O^1 [deg]	32.0	12.4	5.7	3.7

possibly an ylide is not an intermediate in the thermolysis of oxadiazoline **7** to carbene **9**.

Stepwise Extrusion. We also carried out a series of calculations to probe for stepwise reaction paths for dinitrogen and diazopropane extrusion but were unable to locate unsymmetrical transition states leading to diradical intermediates that could yield N_2 or diazopropane. To estimate the barrier of a hypothetical reaction leading to a diradical intermediate, we performed a scan calculation at the UB3PW91/6-31+G(d,p) level to stretch the C2−N3 bond, lengthened stepwise in 0.1 Å increments, of the oxadiazoline ring starting with the optimized geometry of **1a.** The energy profile is displayed as Figure 5. The points after the maximum correspond to complexes with N_2 separated from the ylide, the remaining fragment of **1**. An attempt to locate a diradical transition state starting with the 2.4-Å geometry (highest point on the curve, $\Delta E^{\ddagger}_{\mathrm{elec}}$, 37.4 kcal mol^{-1}) failed; a transition state calculation on this structure ends with the complex of the ylide and N_2. We take this result as an indication that N_2 is not extruded stepwise through a diradical intermediate with a barrier that is lower than ΔE_{elec} for the concerted process (36.5 kcal mol^{-1}).

Thermolysis of Oxadiazoline 1 to Diazo Compound 13. Figure 6 shows the potential-energy surface for the third possible cycloreversion pathway (CR3). This reaction has the highest barrier ($\Delta E^{\ddagger}_{\mathrm{elec}}$, 49.70 kcal mol^{-1} and $\Delta E^{\ddagger}_{110°\mathrm{C}}$, 47.52 kcal mol^{-1}) of the three paths studied. **TS5** is very productlike. The C5−O1 bond length in **TS5** (1.257 Å) is only 0.04 Å longer than in acetone. This result clearly establishes that acetoxy(methoxy)carbene is not formed via a acetoxy(methoxy)diazomethane pathway.

A comparison of the three cycloreversions shows that CR1 and CR2, the pathways proposed on the basis of experimental data[1], have similar barriers, with $\Delta\Delta E^{\ddagger}_{\mathrm{elec}}$ being 3.62 kcal mol^{-1}. At 110 °C, the difference ($\Delta\Delta E^{\ddagger}_{110°\mathrm{C}}$) decreases to 3.17 kcal mol^{-1}. While $\Delta\Delta G^{\ddagger}_{25°\mathrm{C}}$ (2.13 kcal mol^{-1}) and $\Delta\Delta G^{\ddagger}_{110°\mathrm{C}}$ (1.86 kcal mol^{-1}) values correlate better with the experimental result, that the cycloreversions were essentially balanced, entropy calculations for molecules with many degrees of freedom can be problematic. That $\Delta\Delta E^{\ddagger}_{\mathrm{elec}}$ (5.72 kcal mol^{-1}) is considerably larger at a lower level (B3PW91/6-31+G(d,p)) indicates that it is desirable to study cycloreversions of this type at a fairly high level of theory.

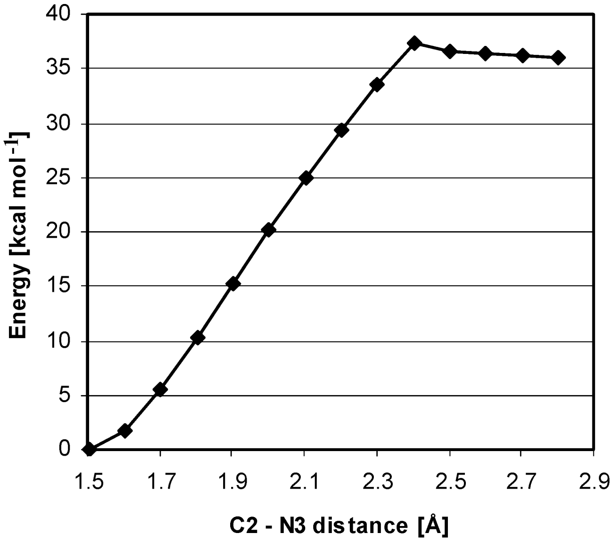


FIGURE 5. Energy profile for stretching C2−N3 bond.

Solvent Effect. Solvent field calculations with the benzene dielectric constant using the Onsager model yielded ΔE_{elec} values of 27.91 and 31.95 kcal mol^{-1} for CR1 and CR2 and 30.81 and 33.78 for **4** and **TS3**, respectively. These values are virtually identical to values (27.87 and 31.49 for CR1 and CR2 and 30.58 and 33.59 for **4** and **TS3**) we calculated for the gas-phase reactions showing, as might be expected, that nonpolar solvents have little effect on the activation energies of concerted reactions involving relatively nonpolar transition states.

Conclusions

A computational study of the potential cycloreversions of 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**1**) supports the experimental findings. The lowest-energy cycloreversion (CR1) yields 2-diazopropane (**2**) and mixed anhydride **3** while the second lowest-energy process (CR2) leads to carbonyl ylide **4** and N_2. Solvent field calculations change the barriers for CR1 and CR2 only very slightly. Overall, the results are in reasonable agreement with the experimental findings that **1** decomposes 55% via CR2 and 45% via CR1. A comparison of the results obtained at the 6-311+G(2df,p) and 6-31+G(d,p) levels shows that both methods give similar results, but the barriers calculated at the 6-311+G(2df,p) level correlate best with the experimental results, indicating that cycloreversion reactions of oxadiazolines should be studied at a relatively high level of theory. An alternative third cycloreversion (CR3), to acetoxy(methoxy)diazo-

---

(8) (a) Houk, K. N.; Rondan, N. G.; Santiago, C.; Gallo, C. J.; Gandour, R. W.; Griffin, G. W. *J. Am. Chem. Soc.* **1980**, *102*, 1504. (b) Clawson, P.; Whiting, D. A. *Tetrahedron Lett.* **1987**, 28, 3155. (c) Bonneau, R.; Liu, M. T. H. *J. Am. Chem. Soc.* **1990**, *112*, 744. (d) Hojo, M.; Aihara, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* **1996**, *37*, 9241. (e) Meier, K. R.; Linden, A.; Mloston, G.; Heimgartner, H. *Helv. Chim. Acta* **1997**, *80*, 1190. (f) Weingarten, M. D.; Prein, M.; Price, A. T.; Snyder, J. P.; Padwa, A. *J. Org. Chem.* **1997**, *62*, 2001. (g) Bussenius, J.; Keller, M.; Eberbach, W. *Liebigs Ann.* **1995**, 1503.

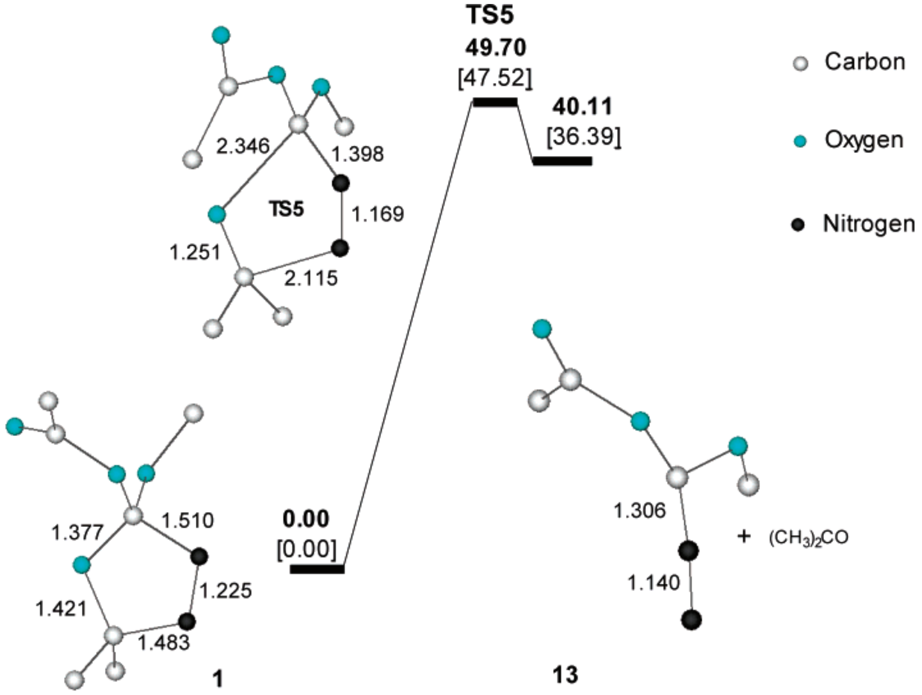


FIGURE 6. Potential-energy surface for cycloreversion (CR3) of **1** with formation of diazo compound **13** and acetone at the B3PW91/6-311+G(2df,p) level. Bolded values determined from E_{elec} and values in square brackets from $E_{110\,°\text{C}}$. Bond distances are in angstroms.

methane (**13**) and acetone, which could not be ruled out experimentally, has a barrier about 20 kcal mol^{-1} higher than the first two reactions and obviously does not need to be considered in the thermolysis of **1**. The intermediacy of a carbonyl ylide, pathway CR2, is supported at both levels.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada (NSERCC) for financial support and SHARCNET (Shared Hierarchical Academic Research Computing Network (of Ontario)) for providing computing resources at McMaster University.

Supporting Information Available: Z matrixes of optimized geometries and transition states along with total energies in hartrees. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0511750