

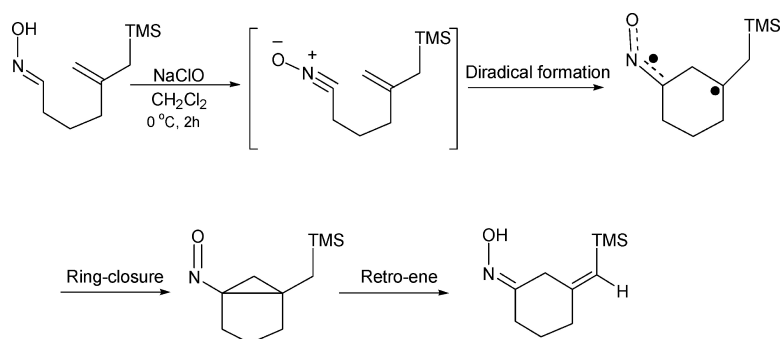
Article

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J. Am. Chem. Soc., **2003**, 125 (45), 13825-13830 • DOI: 10.1021/ja0376487 • Publication Date (Web): 17 October 2003

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Intramolecular 1,3-Dipolar Ene Reactions of Nitrile Oxides Occur by Stepwise 1,1-Cycloaddition/Retro-Ene Mechanisms

Zhi-Xiang Yu and K. N. Houk*

Contribution from the Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

Received July 30, 2003; E-mail: houk@chem.ucla.edu

Abstract: Density functional theory studies of intramolecular ene-like (or the so-called 1,3-dipolar ene) reactions between nitrile oxides and alkenes (Ishikawa, T.; Urano, J.; Ikeda, S.; Kobayashi, Y.; Saito, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1586) show that this reaction is a three-step process involving a stepwise carbenoid addition of nitrile oxide to form a bicyclic nitroso compound, followed by a retro-ene reaction of the nitrosocyclopropane intermediate. The competitive reactions, either the intramolecular (3+2) reactions between nitrile oxides and alkenes or the intermolecular dimerizations of nitrile oxides to form furoxans, can overwhelm the intramolecular 1,3-dipolar ene reactions when the tether joining the nitrile oxide and alkene is elongated or some substituents such as trimethylsilyl are absent.

1. Introduction

The synthetic utility¹ and mechanisms² of 1,3-dipolar cycloadditions have been actively explored for nearly half a century. In addition to the common concerted and very rare stepwise-diradical mechanisms, a third alternative was proposed by Huisgen, the originator of the field: the 1,3-dipole could act as a carbene or nitrene in a cheletropic 1,1-cycloaddition to form a three-membered ring intermediate, followed by a hetero-vinylcyclopropane rearrangement to furnish the final (3+2) cycloadduct.³ Although elegant experiments by Huisgen et al. ruled out this carbene-type mechanism for most 1,3-dipolar cycloadditions,^{3c} Padwa, Steglich, Mukai, and others discovered that the 1,1-cycloaddition resembling a carbene addition to a C=C double bond (carbene-like addition) can be achieved in some intramolecular reactions.⁴ A novel intramolecular ene-like reaction of a nitrile oxide with an alkene was recently reported by Ishikawa, Saito, and co-workers (reaction 1, Scheme 1).⁵⁻⁷ Similar intramolecular ene-like reactions were observed with ether and amine tethers.⁶ Although a concerted mechanism

was proposed, this is a formally forbidden 8-electron process. We have used quantum mechanical calculations to explore whether various stepwise alternatives might occur. The theoretical studies uncovered a novel three-step mechanism, involving a stepwise carbene-like 1,1-cycloaddition mechanism to form bicyclic intermediate **5**, followed by a retro-ene reaction to furnish cyclic oxime *cis-7*. We have also shown the origin of the stereoselective formation of *cis-7* (Scheme 1).

Experiments indicate that when the trimethylsilyl (TMS) group is absent, the final products are furoxan derivatives formed via dimerization (reaction 2, Scheme 2). Second, when the tether has one more carbon atom than that in reaction 1, and the double bond is internal instead of terminal, the final product is a (3+2) cycloadduct (reaction 3, Scheme 3). Theoretical explorations and explanations of these phenomena are reported in the paper.

2. Computational Methods

All of the calculations were performed with the Gaussian 98 program.⁸ The hybrid B3LYP functional⁹ in conjunction with the 6-31G* basis set¹⁰ was applied for the optimization of all of the stationary points in the gas phase. Singlet diradical transition states and intermediates were located with UB3LYP/6-31G*. Frequency calculations were performed to confirm that each stationary point is

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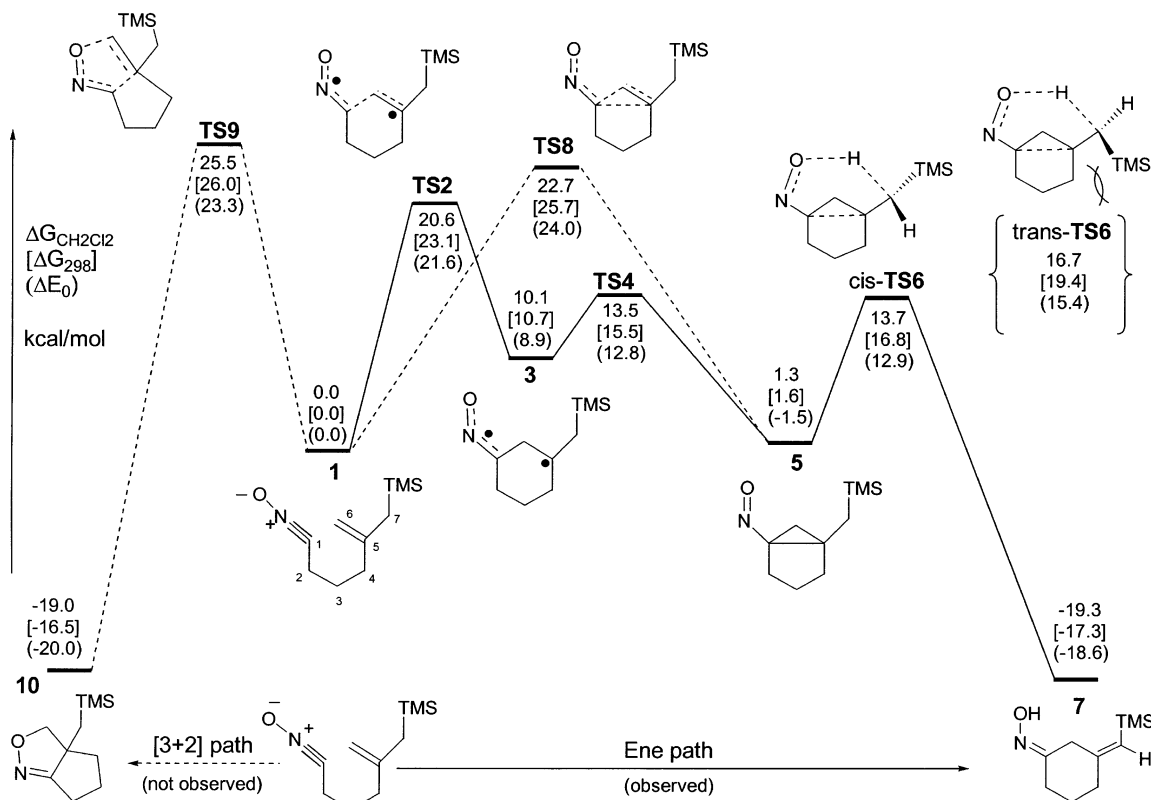
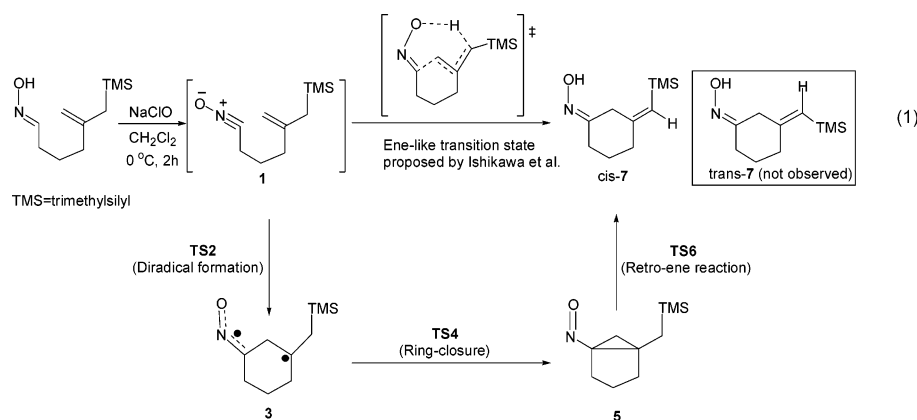
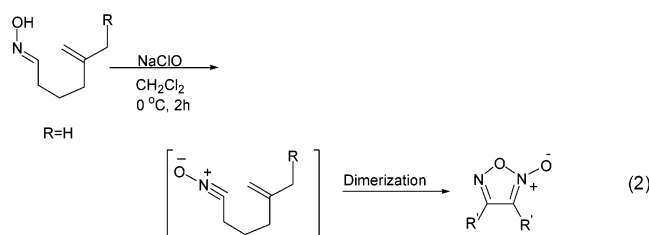


Figure 1. Energies of reactions of 1 (reaction 1).

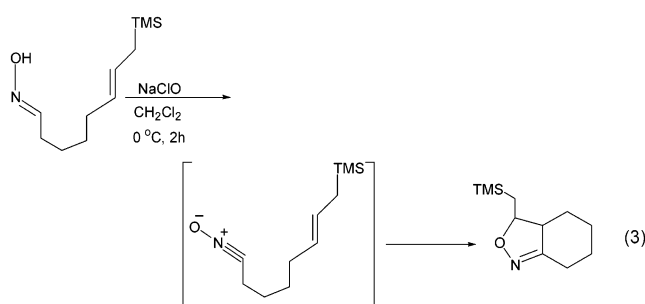
Scheme 1



Scheme 2



Scheme 3



either a minimum or a transition structure. IRC¹¹ calculations were used to confirm the connection between the reactant, product, and transition state. Solvent effects were computed by the PCM model¹² using the gas-phase optimized structures. The $\Delta G_{\text{CH}_2\text{Cl}_2}$ values in dichloromethane were calculated by adding the solvation energies to the computed gas-

phase relative free energies (ΔG_{298}). ΔE_0 is the zero-point energy (ZPE)-corrected relative electronic energy in the gas phase. For diradical species, the YJH spin-projection scheme¹³ has been used to approximate energies without spin contamination. The computed $\langle S^2 \rangle$ values are given in the Supporting Information.

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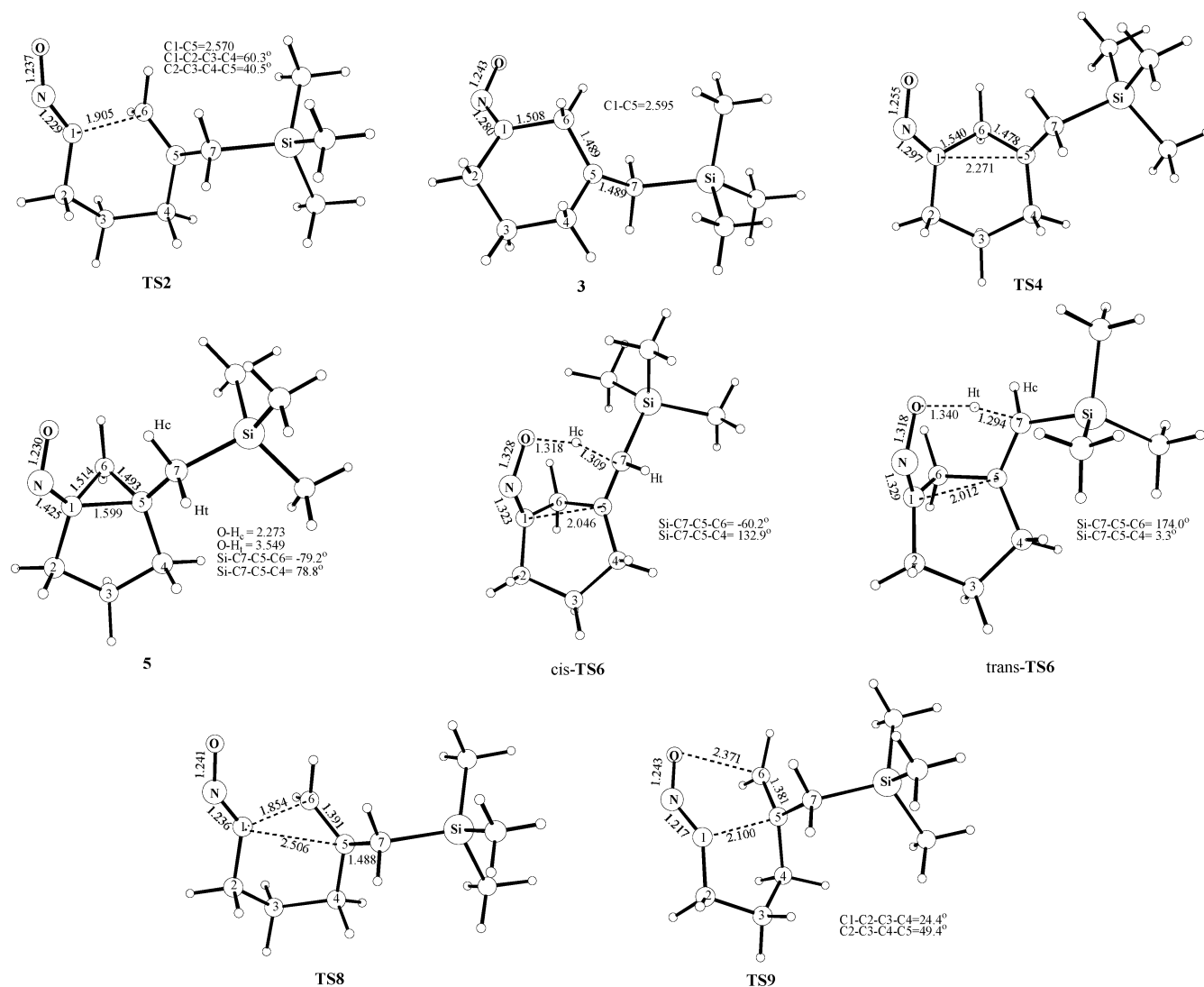


Figure 2. The B3LYP/6-31G* computed structures for the transition structures and intermediates for reactions of **1**. Distances in Å.

3. Results and Discussion

3.1. Reaction 1. (a) The Ene Path. Efforts to locate a one-step, concerted ene-like transition state proposed by Ishikawa et al.⁵ for reaction 1 were unsuccessful. Such an ene-like transition state is an orbital symmetry forbidden 8-electron process.¹⁴ The reaction path to *cis*-**7** occurs through a three-step mechanism involving a stepwise carbene-like 1,1-cycloaddition followed by a retro-ene reaction, as shown in Figure 1. The key computed structures involved in this path and a competing (3+2) path for reaction 1 are given in Figure 2.

The 1,1-cycloaddition proceeds via **TS2** to form diradical intermediate **3**, which is then transformed to bicyclic intermediate **5** via **TS4**. A concerted 1,1-cycloaddition (carbene addition) transition state **TS8** can also be located, but it has higher activation energy as compared to **TS2**, even though both **TS2** and **TS8** have similar geometries (Figure 2). **TS2** is the rate-determining transition state and is higher than the reactant by 23.1 kcal/mol in terms of free energy in the gas phase. Solvent

effects are beneficial to this ene reaction, as indicated by the about 2.5 kcal/mol reduction of the activation free energy for the 1,1-cycloaddition step in dichloromethane.

The transformation of bicyclic intermediate **5** to form **7** is a retro-ene reaction. This is similar to the retro-ene reaction of *cis*-1-methyl-2-vinylcyclopropane to *cis*-1,4-hexadiene and can be also described as a [1,5] sigmatropic shift.¹⁵ The nitroso group of **5** could abstract either hydrogen Hc or Ht. The abstraction of Hc to generate *cis*-**7** is found to be easier, because **trans-TS6** leading to *trans*-**7** has steric repulsions caused by the proximity of SiMe₃ with the C4 atom. The Si-C7-C5-C4 angle is 133° in *cis*-**TS6**, whereas it is only 3° in *trans*-**TS6**. The computed energy difference between *cis*- and *trans*-**TS6** is over 2.5 kcal/mol, suggesting that *cis*-**7** will be generated exclusively. This is consistent with the experimental observation.⁵

(b) The (3+2) Path. The (3+2) cycloaddition of **1** has not been observed. Indeed, the (3+2) transition state **TS9** shown in Figure 2 lies higher in energy than the rate-determining **TS2**

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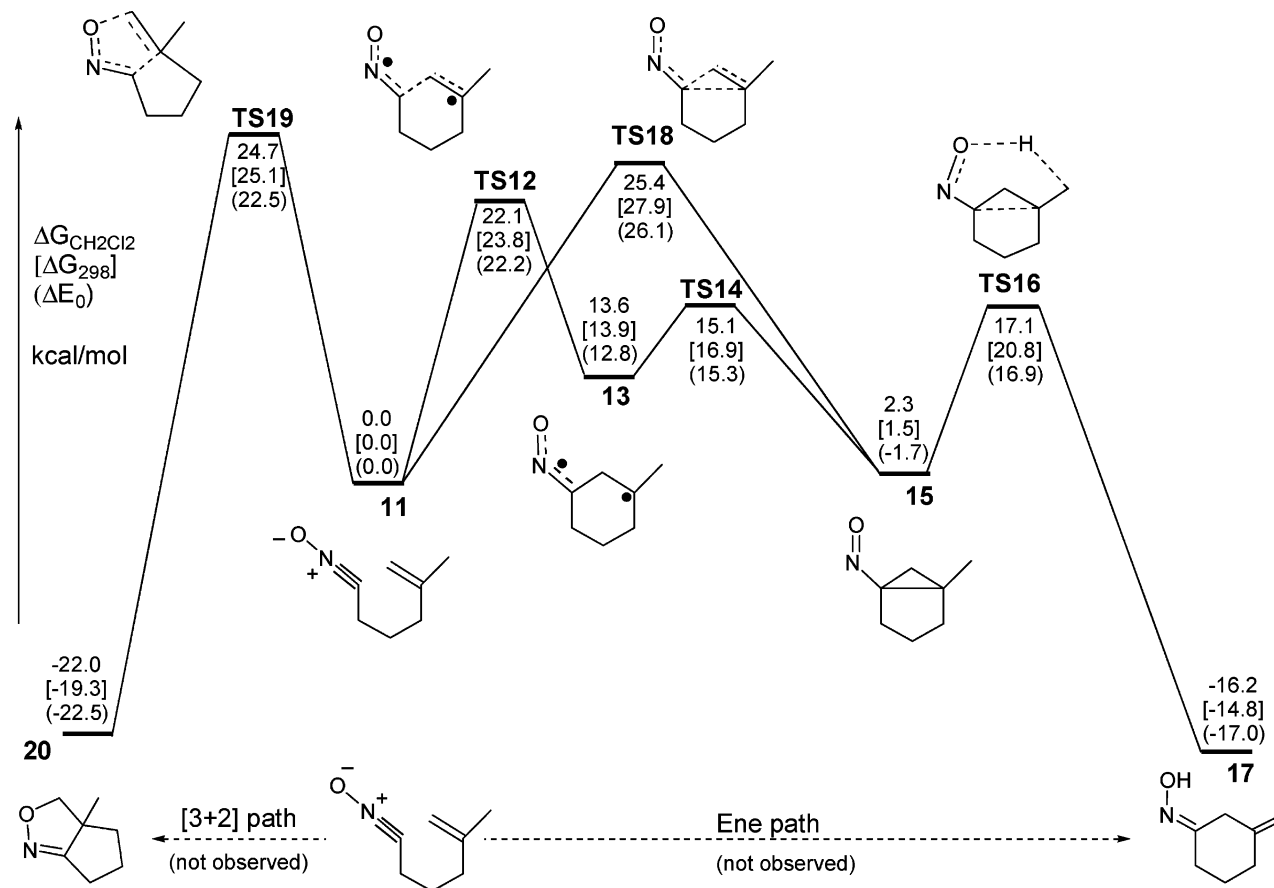


Figure 3. Energies of reactions of **11** (reaction 2).

of the ene path in both the gas phase and dichloromethane (Figure 1).¹⁶ The preference for **TS2** over **TS9** is attributed to strain in the latter, arising from partial eclipsing about C1–C2–C3–C4, which has a dihedral angle of 24°. This dihedral angle is 60° in **TS2** (Figure 2). On the basis of this above analysis, it is expected that when the tether is lengthened, the (3+2) path could become favored.¹⁸ Reaction 3 follows this trend. Calculations on model reaction 4, which differs from reaction 3 in that the TMS group is replaced by a hydrogen atom, support the experimental finding (Figure 4).⁵ The dihedral angle of C1–C2–C3–C4 in the (3+2) transition structure **TS22** is now 40°, and the activation energy drops by about 4 kcal/mol as compared to the (3+2) path of reaction 1. The relatively higher strain energy in the five-membered ring C1–C2–C3–C4–C5 of **TS9** with respect to the six-membered ring C1–C2–C3–C4–C5–C6 of **TS22** is also responsible for the lower activation energy of the (3+2) process of reaction 4. The concerted (3+2) path is now favored over the stepwise ene path in reaction 4.

3.2. Reaction 2. Why does the absence of the TMS group in **11** in reaction 2 lead to a reaction path different from that of reaction 1? Figure 3 shows the PES of reaction 2 to form ene and (3+2) products. These paths are very similar to those in reaction 1. The computed structures of intermediates and

transition states are also very similar to their counterparts in reaction 1 (see Figure S1 in the Supporting Information for their detailed structures). The ene path is still favored over the (3+2) path due to the short tether (three carbon atoms) between the nitrile oxide and alkene. As compared to reaction 1, however, the activation free energy for reaction 2 in dichloromethane is 1.5 kcal/mol higher. This relatively high activation free energy is responsible for the change of reaction path from ene to dimerization, which will be addressed in section 3.3.

As shown in Figures 1 and 3, the ene path of reaction 1 has a slightly lower activation energy than that of reaction 2 due to electronic donation by the silyl and a gentler solvent effect on the slightly more polar reaction of **1**. The TMS group significantly lowers the activation barrier for the retro-ene reaction step of reaction 1 as compared to the retro-ene reaction step of reaction 2 (14.4 vs 18.6 kcal/mol), but this step is not rate-determining. The reduction of activation energy in the retro-ene step by the TMS group occurs because TMS acts as a good sigma donor, while the nitroso group in **5** acts as an electron acceptor to facilitate the reaction via favorable donor–acceptor (push–pull) interaction.¹⁹

3.3. The Competitive Dimerization Processes in Reactions 1 and 2. In addition to the (3+2) path, dimerization competes with the ene path. The dimerization of acetonitrile oxide was

(16) In addition to **TS9**, there is another approach for the (3+2) path involving addition of C1 to C5 and O to C6. This path can be ruled out according to Bredt's rule.¹⁷ No transition state for this path could be located computationally.

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(18) Another possible path to form the (3+2) product is through the isomerization of **5** to **10**. This is similar to the isomerizations of vinylcyclopropanes to cyclopentenes. We could not locate such a transition state, suggesting this path is not possible. For reviews of the isomerizations of vinylcyclopropanes to cyclopentenes, see: (a) Baldwin, J. E. *J. Comput. Chem.* **1998**, *19*, 222. (b) Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197.

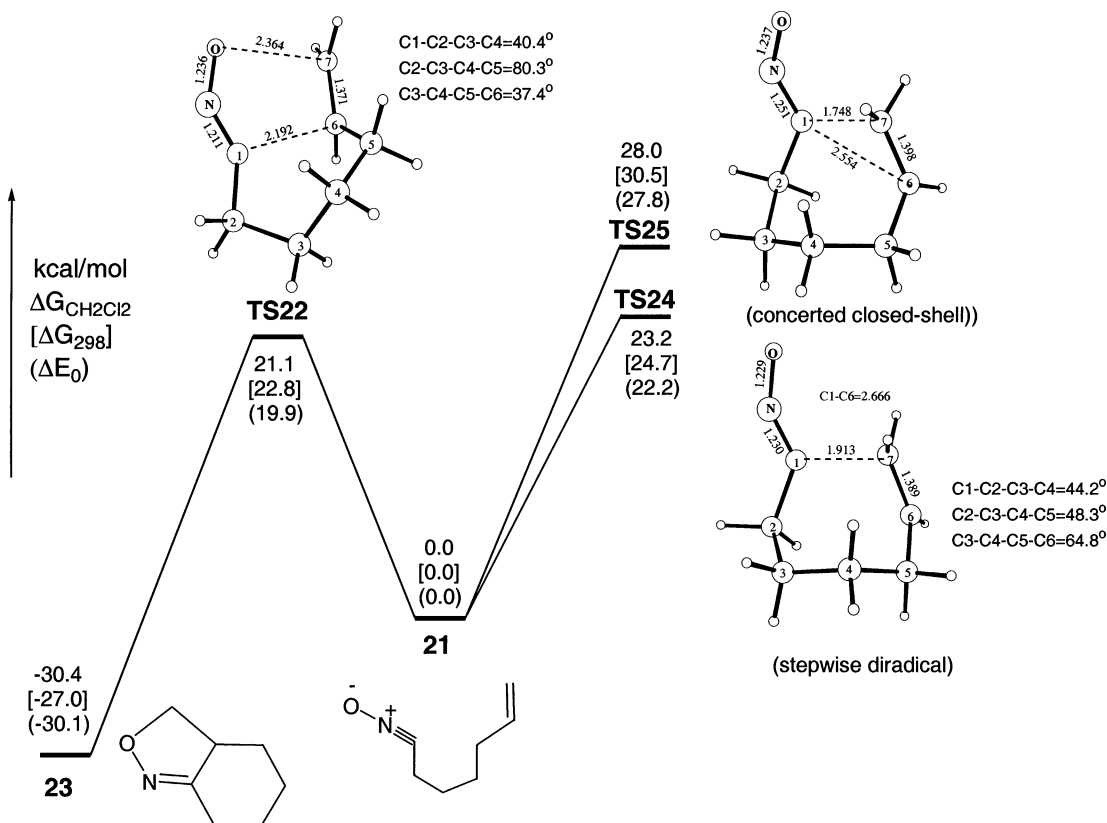


Figure 4. Energies of reactions of **21** (reaction 4).

used to explore this process. The potential energy surface for the dimerization of CH_3CNO to dimethylfuroxan is given in Figure 5. Details are given elsewhere.²⁰ The dimerization is found to be a stepwise process with the formation of a dinitrosoethene, which is found to be a diradical species. In the gas phase, the dimerization has an activation energy of only 11.1 kcal/mol. When the entropy contribution is taken into account, the dimerization has an activation free energy of 22.0 kcal/mol, 0.4 kcal/mol higher than the rate-determining step of the ene path in reaction 1, suggesting that the dimerization and ene paths for reactant **1** are very competitive in the gas phase.

In dichloromethane, the dimerization activation free energy is 25.7 kcal/mol, 5.1 kcal/mol higher than that of the rate-determining step of the ene path in reaction 1. The computed entropy contribution for a bimolecular reaction in solvent is sometimes overestimated by the procedure used here. For example, it was found that the entropy contribution in aqueous solution for bimolecular reaction is found to be overestimated by 50–70%.²¹

Experimentally, the dimerizations of *para*-chlorobenzonitrile in various solvents have activation free energies of 21.5–22.6

kcal/mol.²² The computed activation energy of dimerization of *para*-chlorobenzonitrile in the gas phase is 3.1 kcal/mol higher than that required for dimerization of acetonitrile oxide (14.2 vs 11.1 kcal/mol).²⁰ Therefore, the activation free energies for CH_3CNO and simple alkyl nitrile oxides should be in the range of 19 kcal/mol.

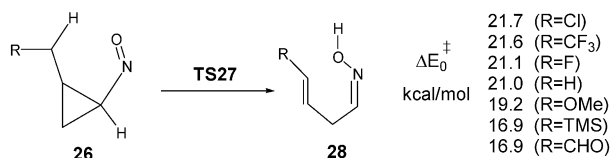
The ratio of reaction rates of dimerization vs. the ene process for the nitrile oxides can be expressed as follows:

$$k_{\text{dimer}}/k_{\text{ene}} = [\text{nitrile-oxide}] \exp[-(\Delta G_{\text{dimer}}^\ddagger - \Delta G_{\text{ene}}^\ddagger)/RT]$$

This expression means that the preference of dimerization or ene path depends on both the difference of the activation free energies of the two paths and the concentration of the reactant, [nitrile-oxide]. The last term ($\exp[-\Delta\Delta G^\ddagger/RT]$) in $k_{\text{dimer}}/k_{\text{ene}}$ is about 5.0 in reaction 1, suggesting that when the concentration of nitrile oxide is greater than 0.2 M, dimerization will dominate over the ene path. The concentration of the in situ generated reactant is expected to be far less than this value, and, consequently, the ene path in reaction 1 is observed.

However, in reaction 2, the value of $\exp[-\Delta\Delta G^\ddagger/RT]$ in $k_{\text{dimer}}/k_{\text{ene}}$ is 22.2, implying that the concentration of nitrile oxide needed for a dimerization is only 0.05 M. Therefore, dimerization is favored in reaction 2 under similar conditions.

(19) Computational evidence to support this argument is that the retro-ene reactions shown below have lower activation energies when R is an electron-donating group as compared to the case when R is an electron-withdrawing group. When R is a good π -electron-withdrawing group, such as CHO, the acidity of the (R)C–H is increased and the corresponding transition state **TS27** is only 16.9 kcal/mol higher than **26**.



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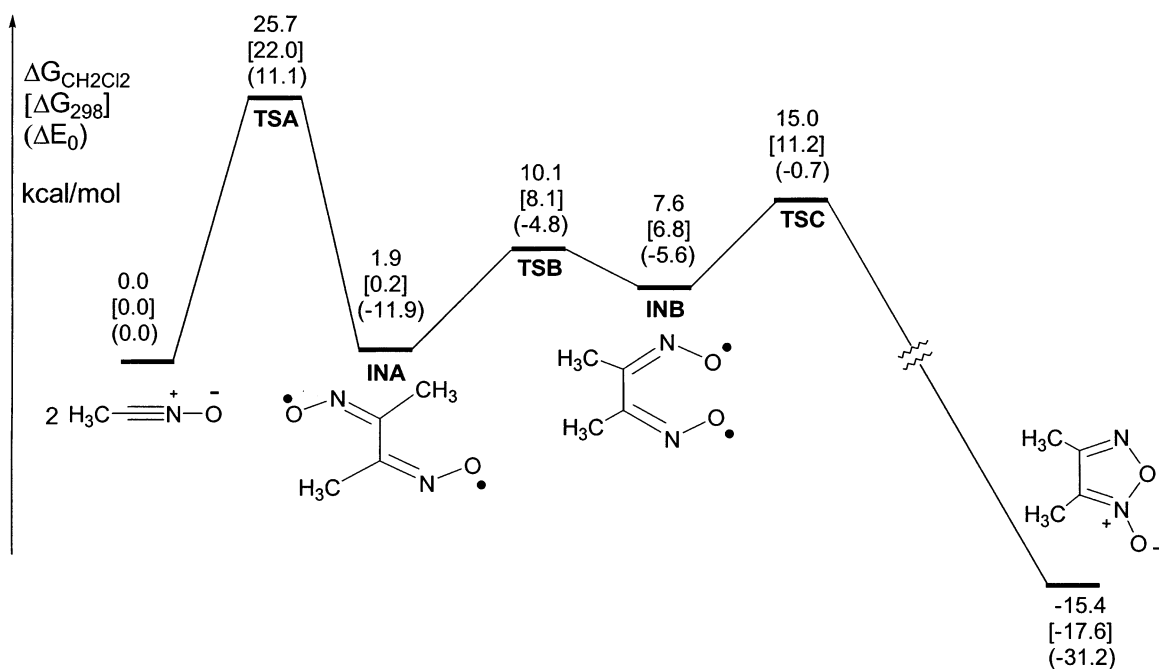


Figure 5. Energies of dimerization of acetonitrile oxide to furoxan.

4. Conclusions

DFT calculations reveal that the intramolecular ene-like reaction between a nitrile oxide and an alkene is a three-step process involving a stepwise carbene-like 1,1-cycloaddition and a stereoselective retro-ene reaction. The stereoselective formation of one cyclic oxime product involving the TMS group is a steric effect. The achievement of the ene path is due to the ring strain in the competing (3+2) reaction path.

Acknowledgment. We are grateful to the National Science Foundation for financial support of this research.

Supporting Information Available: The DFT computed structures and energies for all species discussed (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA0376487