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Theoretical Evidence for Oxygenated Intermediates in the Reductive Cyclization of Nitrobenzenes

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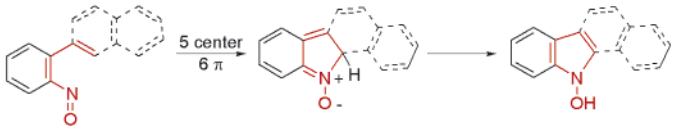
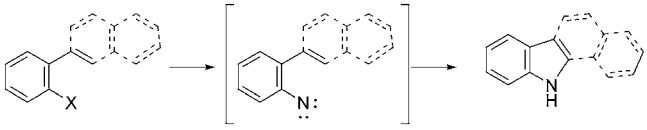
ABSTRACT



Deoxygenation of nitroaromatics is a classic synthetic method for the construction of nitrogen heterocycles. The generally accepted mechanism involves exhaustive deoxygenation to a singlet nitrene. We present theoretical evidence for an alternative, 6π-electron 5-atom electrocyclization of nitroso-styrenes, -stilbenes, and -biphenyls to nitronates. A downstream 1,5-H shift and tautomerization leads to *N*-hydroxy heterocycles.

Deoxygenation of functionalized nitroaromatics to give heterocycles was first realized by Waterman and Vivian in 1940 using iron oxalate at 200 °C.[1] The Cadogan deoxygenation of nitroaromatics using boiling triethyl phosphite is now a classic synthetic method for the construction of a wide range of nitrogen-containing aromatic heterocycles (Scheme 1).[2] Recent examples of the use of this method from

Scheme 1



1a X = NO_2
1b X = N_3
2
3

these laboratories include the synthesis of natural products tjipanazole B, D, E, and I[3] and 1*H*-indol-2-yl-1-*H*-quinolin-2-ones, which are potent KDR kinase inhibitors.[4]

The generally accepted mechanism for the formation of heterocyclic products from nitroaromatics **1a** involves exhaustive deoxygenation to a singlet nitrene **2**, which undergoes insertion into the π-bond of the adjacent olefin or arene followed by a hydrogen migration to give a formal C−H insertion product. This rationalization is primarily supported by the product distribution from reactions of aromatic nitro compounds and their analogous azides **1b**.[5,6] However, *N*-hydroxy and *N*-ethoxy indoles have been observed by Sundberg in the reduction of *ortho*-nitrostilbene, which suggests that a competitive pathway might be available involving partially deoxygenated intermediates.[7]

There is additional precedent from catalytic reactions using CO as the terminal reductant that provides a sound basis for

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(1) Waterman, H. C.; Vivian, D. L. U.S. Patent 2,292,808, 1942. Waterman, H. C.; Vivian, D. L. *J. Org. Chem.* **1949**, *14*, 289.

(2) Cadogan, J. I. G. *Synthesis* **1969**, *1*, 11. Cadogan, J. I. G. *Organophosphorus Reagents Org. Synth.* **1979**, 269. Cadogan, J. I. G. *Lect. Heterocycl. Chem.* **1978**, *4*, 17.

(3) Kuethe, J. T.; Wong, A.; Davies, I. W. *Org. Lett.* **2003**, *5*, 3721.

(4) Kuethe, J. T.; Wong, A.; Davies, I. W. *Org. Lett.* **2003**, *5*, 3975.

(5) Söderberg, B. C. G. *Curr. Org. Chem.* **2000**, *4*, 727.

(6) A significant study of the chemistry of biphenylnitrenes by laser flash photolysis, time-resolved IR, and by B3LYP and CASPT2 calculations has recently been published. The mechanism of cyclization proceeds via an open shell structure with essentially diradical character to form isocarbazole and a 1,5-hydrogen shift to form carbazole. Tsao, M.-L.; Gristan, N.; James, T. R.; Plattz, M. S.; Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **2003**, *125*, 9343.

(7) Sundberg, R. J. *J. Org. Chem.* **1965**, *30*, 3604.

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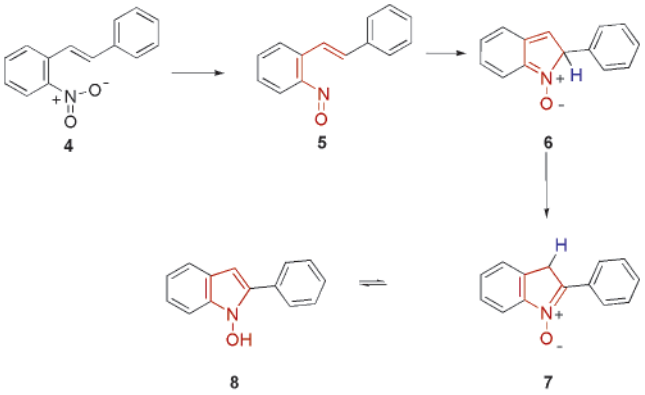
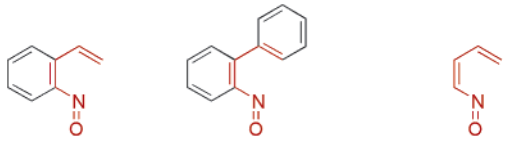
Scheme 2



predicting the intermediacy of *ortho*-nitrosostilbenes **5** and the formation of *N*-hydroxyindoles **8** (Scheme 2).[8,9] Triethyl phosphite is a rather indiscriminant reductant at 165 °C and is known to react with *ortho*-nitrosobenzenes at or below ambient temperature.[10] It remains to be established whether multiple reaction manifolds are in operation in the Cadogan reaction with the cyclization proceeding through both nitrene and partially deoxygenated intermediates.

Electrochemical studies on the redox[11] behavior of *ortho*-nitrostilbene **4** supports the intermediacy of a *ortho*-nitrosostilbene **5** en route to *N*-hydroxyindoles **8**. Recently, the chemical oxidation of *ortho*-hydroxylaminostyrenes to give *N*-hydroxyindoles has been reported to proceed at 0 °C.[12] Cyclization of the *ortho*-nitroso intermediate **5** to the nitronate **6** requires a subsequent 1,5-hydrogen shift to give 3*H*-indole 1-oxide **7** prior to the known isomerization to the *N*-hydroxyindole **8**.[13] We refer to this 1,2-process as a 1,5-shift since it also involves migration of the diene in the five-membered ring. This 1,5-shift is supported by the experimental observation of 1,5-alkyl and aryl shifts.[14] *ortho*-Nitroarylethanes have also been shown to react under basic conditions to give *N*-hydroxyindoles at 20 °C. The reaction was rationalized to proceed through an *ortho*-nitrosostyrene species that undergoes a 6π-electron 5-atom electrocyclic reaction.[15]

We have explored the 6π-electron 5-atom electrocyclic reaction and subsequent hydrogen shifts by computational methods to determine if these pathways are feasible under experimentally meaningful conditions. In this Letter, we describe our preliminary results for three prototypical systems: nitrosostilbene **5**, styrene **9** and biphenyl **10**.



The 6π-electron electrocyclization is common in hydrocarbons, and 1,3,5-hexatrienes undergo thermal electrocyclizations to form 1,3-cyclohexadienes. Bicyclo[3.1.0] hexenes are only rarely formed[16] but are observed photochemically depending on the conformation of the starting hexatrienes.[17] By contrast, for hetero-1,3,5-hexatrienes (heteroatom = O, N, S, Si) the 1,5-electrocyclization reactions are feasible and appear to be favored over 1,6-electrocyclizations.[18] For example, nitroso compounds produce nitrones in a reaction that can be formalized as a 1,5-electrocyclizations.[19,20]

To compare 1,5- and 1,6-electrocyclization pathways, 1-nitroso-1,3-butadiene **11** was our initial starting point. This system was studied computationally with B3LYP using the 6-31+G* basis set in Gaussian 98.[21] Computed activation enthalpies with B3LYP/6-31+G* are 9.8 and 8.8 kcal/mol for the 1,5- and 1,6-electrocyclization, respectively. As shown in Figure 1, the pyrrole product of 1,5-electrocyclization **12** is more stable by 4.3 kcal/mol than the oxazine **13**, which is the product of a slightly faster 1,6-electrocyclization.

In contrast to the parent system, *ortho*-nitrosostyrene **9** has a 17.9 kcal/mol activation energy for 1,5-electrocyclization and a 20.5 kcal/mol barrier for the 1,6-electrocyclization. The transition structure for the 1,5-electrocyclization is shown in Figure 2. The bond length between the terminal carbon and nitrogen atom is 2.027 Å. The vinyl group is nearly

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(13) Isomerization is solvent dependent. In DMF, the equilibrium is 100% **8**, whereas in MeOH, the equilibrium is 100% **7**. Nagayoshi, T.; Saeki, S.; Hamana, M. *Chem. Pharm. Bull.* **1981**, *29*, 1827.

(14) For 1,2-alkyl and -aryl shifts, see: Sundberg, R. J.; Yamazaki, Y. *J. Org. Chem.* **1967**, *32*, 290.

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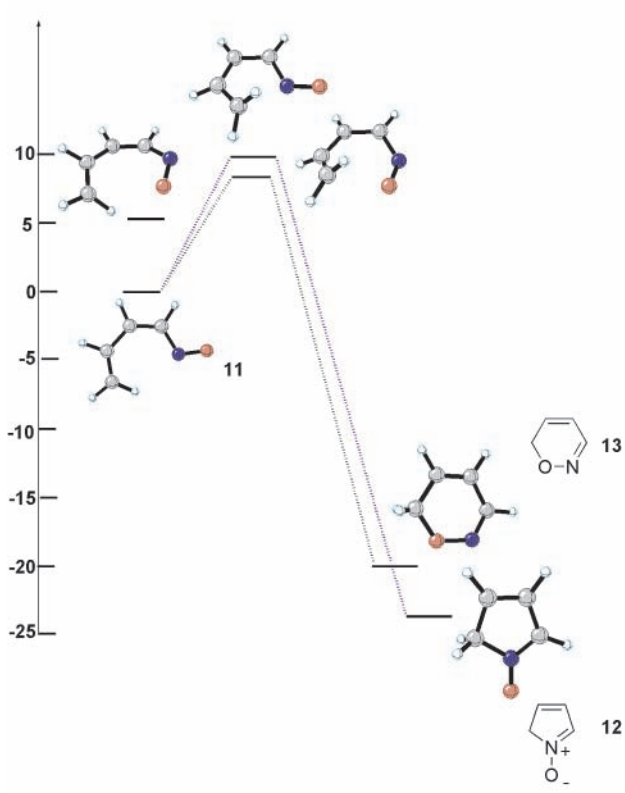

Figure 1. Energetics of the 1,5- and 1,6-electrocyclizations of 1-nitroso-1,3-butadiene.

coplanar with the benzene ring, deviating by 13° as compared to 26° in the transition structure of 1,6-electrocyclization. The double bond in the benzene ring is elongated in both cases from 1.40 to 1.43 and 1.45 Å for 1,5- and 1,6-

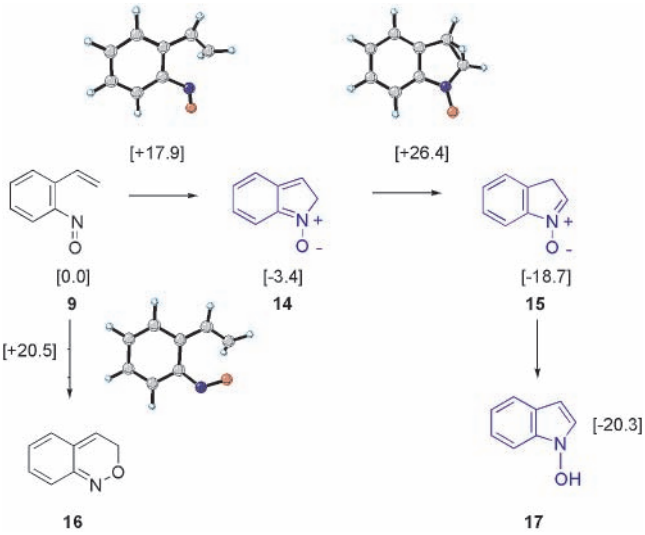

Figure 2. B3LYP/6-31+G*-optimized geometries and energetics for the 1,5- and 1,6-electrocyclization of **9**. Energies are given in kcal/mol relative to reactants.

Table 1. Computed Activation Enthalpies and Heats of Reaction for **9**, **5**, and **10** Leading to Hydroxylindoles at B3LYP/6-31+G* Level[a]

	reactant **9**	reactant **5**	reactant **10**
$\Delta H^{\ddagger}$(1,5-electro)	17.9	16.9	27.8
ΔH_{rxn}(1,5-electro)	−3.4	+3.7	+20.3
$\Delta H^{\ddagger}$(1,5-H)	26.4	20.7	23.3
ΔH_{rxn}(1,5-H)	−15.3	−25.4	−10.0
ΔH_{rxn}(isomer)	−1.6	+3.1	−29.3
$\Delta H_{overall}$	−20.3	−18.6	−19.3

[a] Energies are given in kcal/mol.

cyclizations, respectively. Interruption of aromaticity causes an increase in the activation barrier of 1,6-electrocyclization.

In the 1,5-electrocyclization of *ortho*-nitrosostyrene **9**, intermediate nitrone **14** is 3.4 kcal/mol more stable than the reactant. The 1,5-H shift providing **15** from **14** has a 23.0 kcal/mol activation barrier and gives the much more stable nitrone. Formation of *N*-hydroxyindoles via isomerizations, which we assume involves bases and/or metals present under the reaction conditions, is exothermic by 1.6 kcal/mol (Table 1). Overall, the exothermicity of reaction **9** to **17** is −20.3 kcal/mol.

In nitrosostilbene **5**, the second phenyl group decreases the cycloaddition activation barrier by 1 kcal/mol, but intermediate **6** is higher in energy by 3.7 kcal/mol than reactant **5**. The transition structure is shown in Figure 3.

The activation barrier for inward rotation of the phenyl group is 6.7 kcal/mol higher in energy. The forming nitrogen−carbon distance in the transition structure is 2.01

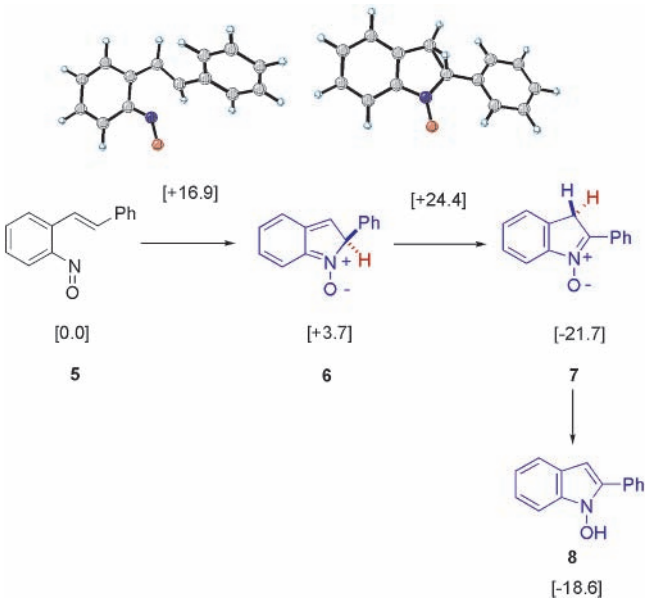

Figure 3. B3LYP/6-31+G*-optimized geometries and energetics for the 1,5-electrocyclization of **5**. Energies in kcal/mol relative to reactants.

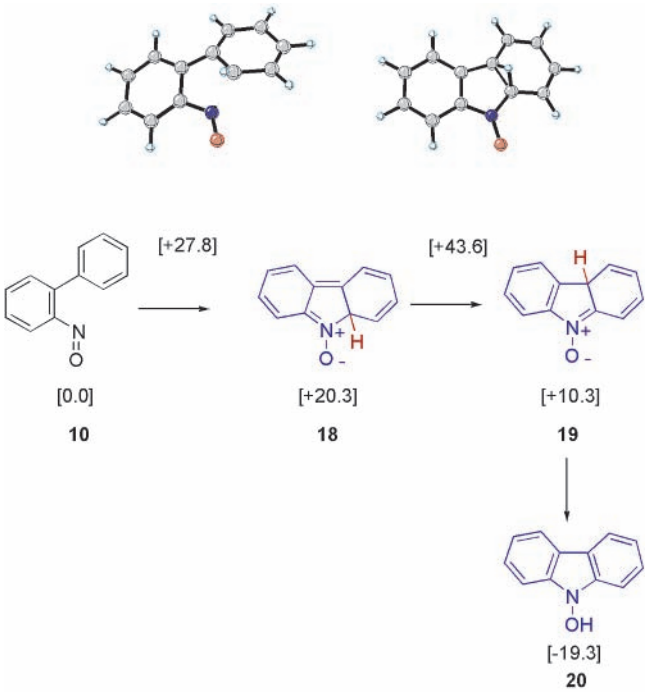

Figure 4. B3LYP/6-31+G*-optimized geometries and energies for the 1,5-electrocyclization of **10**. Energies are given in kcal/mol relative to reactants.

Å. The activation barrier for the 1,5-hydrogen shift is lower than that of nitrosostyrene **9** by 5.7 kcal/mol because, in intermediate **7**, the nitrone group is stabilized by conjugation with the adjacent phenyl group. This also decreases the heat of reaction by 10.1 kcal/mol. Overall, the reaction **5** to **8** is exothermic by −18.6 kcal/mol.

The cyclization of **10** (Figure 4) has the highest activation barrier of the 1,5-electrocyclizations studied, since the aromaticity of two benzenes is interrupted. The 1,5-hydrogen migration from **18** to **19** has a 27.8 kcal/mol activation barrier. Intermediate **19** is 10 kcal/mol above **10**, but the overall reaction is exothermic by 19 kcal/mol.

The 1,5-electrocyclization is favored over the 1,6-electrocyclization in all cases except nitrosobutadiene itself.

These computational studies clearly demonstrate that 1,5-electrocylization is a viable reaction pathway under the experimental reaction conditions and may even be competitive with nitrene formation. Given the theoretical evidence for the existence of oxygenated intermediates, additional experimental studies are underway to test this hypothesis.

Acknowledgment. We are grateful to the National Science Foundation for financial support. We also thank the San Diego Supercomputing Center and the UCLA Office of Academic Computing for computational resources. V.G. thanks the Scientific and Technical Research Council (TUBITAK) for a NATO Science Fellowship.

Supporting Information Available: B3LYP/6-31+G*-optimized Cartesian coordinates for reactants and transition structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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