J|A|C|S
COMMUNICATIONS

The Ene Reactions of Nitroso Compounds Involve Polarized Diradical Intermediates

Andrew G. Leach and K. N. Houk*

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

Received December 24, 2001; Revised Manuscript Received October 11, 2002

The timing of bond-formation processes and the nature of intermediates in ene reactions of singlet oxygen, triazolinediones, and nitroso compounds are lingering enigmas in mechanistic chemistry. The ene reactions of singlet oxygen[1] and triazolinediones[2] involve mechanisms that are delicately balanced between stepwise pathways involving diradical or three-membered ring intermediates and concerted processes. Triazolinediones favor the diradical path.[3] Singlet oxygen follows a novel two-step mechanism involving a valley-ridge inflection, but no intermediate.[4] Adam et al. recently reported B3LYP studies of the ene reaction of nitroso compounds and proposed a two-step mechanism through an aziridine *N*-oxide (ANO) intermediate.[5] We have explored the potential surfaces of several ene reactions of nitroso compounds with theoretical methods appropriate for open-shell systems; we find that polarized diradicals are obligatory intermediates in these reactions.

Many mechanisms have been proposed for ene reactions (Scheme 1). These include the concerted pericyclic path and three stepwise paths, involving a diradical **1**, a zwitterion, **2** (the extreme of a closed shell, polar structure), or an ANO, **3**. The diradical and zwitterion, once formed, may go directly to products or cyclize reversibly to yield an ANO. It is usually expected that a diradical will undergo rapid rotation about single bonds.

We have studied these reactions using B3LYP/6-31G*.[6] Since concerns have been raised concerning the ability of this method to correctly describe the reactions of heteroatomic radicals,[7] we have also computed the energetics with higher-level single-point calculations (UCCSD(T) and CASPT2).[8]

Potential energy surface scans for the reaction of HNO with propene showed that there is no direct path linking the ANO to either reactants or products. Both of these steps could only be achieved by passing through a local minimum, the polarized diradical intermediate (PD) shown in Figure 1 as **4a**. Such intermediates are found for all of the cases studied here, including NO_2PhNO with propene and MeNO with TME (**4c** and **4d** in Figure 1). We were unable to locate a concerted transition state for the ene reaction. The transition states of Adam et al. actually connect with the PD, not the ANO.[5]

Spin-restricted B3LYP optimization of the diradical, **4a**, gave a polar, open-chain structure, with the same conformation as the diradical, but with a more pronounced CH−O interaction, and only 1.6 kcal/mol higher in energy. A structurally similar triplet diradical is 5.2 kcal/mol above the singlet. The diradical itself has polar character, evidenced by the partial charge transfer from the alkene to HNO of 0.2 electron, calculated by the NBO method. This would suggest that the energy and structure should be sensitive to changes in solvent polarity. Indeed, optimizations with polar solvents (modeled with the PCM method) show a decrease in energy of the PD accompanied by a decrease in the $\langle S^2\rangle$ value and a reduction in the energy gap between restricted and unrestricted structures, indicating an increase in polar character. The gas-phase diradical has a value of $\langle S^2\rangle$ of 0.64, suggesting a degree of spin contamination lower than is usually observed for pure singlet diradicals with UB3LYP.[9]

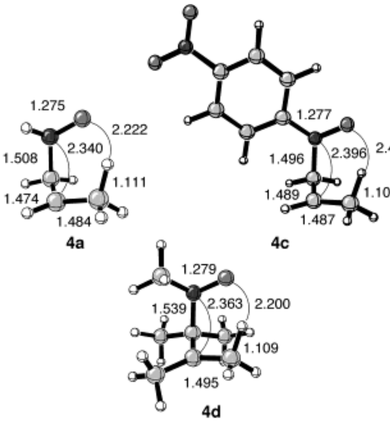
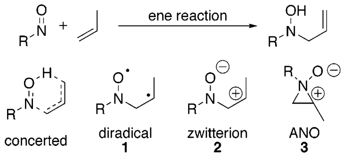
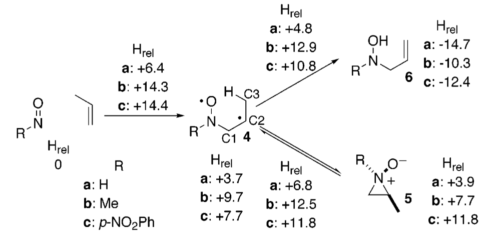


Figure 1. The polarized diradicals involved in the reaction between HNO and propene, NO_2PhNO and propene, and MeNO and TME.

Scheme 1



Scheme 2 [a]



[a] Enthalpies relative to reactants in kcal/mol are indicated.

The reactions and energetics shown in Scheme 2 were obtained with (U)B3LYP/6-31G*. The rate-determining formation of PD **4a** is endothermic, and the PD preferentially proceeds to product **6a** with a second barrier of only 1.1 kcal/mol. The PD can form ANO, **5a**, with a barrier of 3.1 kcal/mol. With the exception of the PD, each species has $\langle S^2\rangle = 0$, and restricted and unrestricted methods yield identical structures and energies. One representation of the PD is as a bond-stretch isomer of the ANO; however, the ground state of the PD is essentially an oxyradical, while the ANO involves cyclization of an aminyl radical, corresponding to the ${}^2A'$ excited state of a nitroxyl radical.[10] That is, the apparent "bond-stretch isomers" actually have different electronic configurations.

Due to uncertainty about the reliability of UB3LYP and of the existence of the PD, we wished to verify that the mechanism

10.1021/ja012757b CCC: $22.00

Table 1. Enthalpies for the Reaction of HNO with Propene (kcal/mol) Calculated with a Range of Single-Point Energy Evaluations Using the B3LYP/6-31G* Geometry and Vibrational Corrections

method	TS1[a]	PD	TS2[b]	product	TS3[c]	ANO
B3LYP/6-31G*	6.4	3.7	4.8	−14.7	6.8	3.9
UCCSD(T)/6-311+G**	17.0	13.1	13.8	−17.2	14.2	6.3
CASPT2(10,8)/6-31G*	6.7	0.1	2.3	−18.9	4.6	3.3

[a] Transition state linking reactants to the PD intermediate. [b] Transition state linking PD to products. [c] Transition state linking PD to ANO.

Table 2. Enthalpies of the Transition States and Minima for the Reaction of MeNO with **7** in kcal/mol Relative to Reactants

regioisomer	TS1	diradical	TS2	product	TS3	ANO
twix	12.7	9.2	12.0	−7.0	11.9	6.9
twin	13.3	10.4	13.0	−9.0	13.6	10.4
lone	14.1	12.3	14.5	−4.5	12.9	6.9

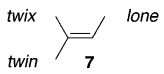
remains unchanged with higher-level calculations. CCSD(T) and CASPT2 single point-calculations on each B3LYP structure, detailed in Table 1, reveal that the PD remains a minimum, in a well of depth less than 2.2 kcal/mol, and the relative positioning of each of the transition states is approximately constant. The ANO remains a minimum with a barrier of less than 8 kcal/mol to ring opening. The methods differ in the size of the rate-limiting barrier that they predict.

HNO and propene unequivocally involve a PD in their ene reaction. We also performed analogous studies on the reactions of both MeNO and *p*-nitronitrosobenzene with propene. The energetics of these reactions (**b** and **c** in Scheme 2) are comparable. The exception to this is that the ANO for the nitrosoarene, **5c**, is identical in enthalpy to the transition state leading to it from the diradical. Here, the ANO is destabilized because the resonance involving the nitrogen lone pair of the NO grouping and the aromatic ring is lost in the ANO; for such a reaction, the ANO is a higher energy distorted geometry of the PD intermediate.

Calculations on CC and CN rotation in the diradical formed between MeNO and propene showed that the PD has properties normally attributed to the ANO. There are two barriers for rotation about the C_1−N bond of 4.5−4.6 kcal/mol. For rotation about the C_1−C_2 bond, barriers of 4.4−4.6 kcal/mol were found. The rotation transition states are all higher in energy than those linking the diradical to products or to the ANO. Two effects are responsible for this high barrier—CH−O hydrogen bonding to the rather negatively charged oxygen atom and a favorable interaction between the 2p orbital of C_2 and the π^* orbital of the NO bond. This interaction leads to two nearly degenerate orbitals which accommodate two electrons, either paired (a polar configuration) or unpaired (a diradical configuration). It is these orbitals which are responsible for the polarized diradical character of this species.

Experimental kinetic isotope effects for the reaction between pentafluoronitrosobenzene and tetramethylethylene (TME), measured by Seymour and Greene require that if a diradical is to be involved, rotation about CC and CN single bonds of the PD must be slow, as calculated, and that the RNO moiety can interchange between the ends of the olefin.[11] We predict that this may happen via the ANO. We used the B3LYP transition states for the reaction between MeNO and TME to predict KIEs. These calculations mirror the published values if it is assumed that the reaction involves rate-limiting diradical formation followed by competition between H abstraction and reversible cyclization to an ANO. However, recent experimental studies revised the value of the intermolecular KIE.[12] The revised value of k_H/k_D of 1.77 was rationalized by reversible formation of an ANO. The reversible formation of a PD suggested by the calculated energetics (see Supporting Information) can also accommodate this value.

Initial computations, summarized in Table 2, suggest that B3LYP calculations reproduce the experimentally observed regioselectivity of reactions with 2-methylbut-2-ene, **7**—twix is favored over twin, and lone is least preferred.[13] The calculations used MeNO as a model for the experimentally employed NO_2PhNO.



7

As the data in Table 2 indicate, the regioselectivity is determined in the first step of the reaction, leading to PD formation. The diradical corresponding to the *twin* reaction can only go on to yield the *twin* product. The diradicals corresponding to the *twix* isomer may cyclize to an ANO. On subsequent reopening, it will not yield significant amounts of the *lone* product because the transition state for H abstraction from the *lone* position is 2.5 kcal/mol higher in energy than that for abstraction from the *twix* position. The reaction outcome depends only on the relative amounts of *twin* and *twix* diradical formed, which is governed by TS1—the difference in energy of the two relevant transition states is 0.6 kcal/mol, corresponding to a regioselectivity of 75:25 (*twix*:*twin* at 0°C), in close agreement with the ratio of 81:19 found experimentally using isotopically labeled 2-methylbut-2-ene.

We conclude that the ene reaction of nitroso compounds is stepwise and involves the intermediacy of a polarized diradical. This PD has the unusual property of having rotational barriers that are higher than the barriers to product formation. An ANO may also be involved, but it is an innocent bystander on the pathway in the same manner proposed by Singleton for the ene reactions of triazolinediones.[4b] This mechanism can explain kinetic isotope effects and regioselectivities observed for these reactions.

Acknowledgment. We thank the UK Fulbright Commission and AstraZeneca (fellowship to A.G.L.), the National Science Foundation (CHE-9986344) and the NCSA (MCA93S015N) for financial support, and Dr. M. D. Bartberger and Professors D. A. Singleton and C. S. Foote for helpful discussions.

Supporting Information Available: Full citations for Gaussian98 and MOLCAS; Cartesian coordinates for each structure (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Prein, M.; Adam, W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 477−494. (b) Stratakis, M.; Orfanopolous, M. *Tetrahedron* **2000**, *56*, 1595−1615.
(2) (a) Vassilikogiannakis, G.; Stratakis, M.; Orfanopolous, M. *Org. Lett.* **2000**, *2*, 2245−2248. (b) Poon, T. H. W.; Park, S. H.; Elemes, Y.; Foote, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 10468−10473 and references therein.
(3) (a) Chen, J. S.; Houk, K. N.; Foote, C. S. *J. Am. Chem. Soc.* **1997**, *119*, 9852−9855. (b) Singleton, D. A.; Hang, C. *J. Am. Chem. Soc.* **1999**, *121*, 11885−11893.
(4) Singleton, D. A.; Hang, C.; Szymanski, M. J.; Kuwata, K. T.; Chen, J. S.; Leach, A. G.; Greer, A.; Foote, C. S.; Houk, K. N. Manuscript submitted.
(5) Adam, W.; Bottke, N.; Engels, B.; Krebs, O. *J. Am. Chem. Soc.* **2001**, *123*, 5542−5548.
(6) Calculations were performed with Frisch, M. J. et al. *Gaussian98*, revision A.7; Gaussian Inc.: Pittsburgh, PA, 1998 and K. Andersson, M. et al. *MOLCAS*, Version 5; Lund University, Sweden 2000. Full author citations are provided in Supporting Information.
(7) Bottoni, A.; Casa, P. D.; Poggi, G. *J. Mol. Struct. (THEOCHEM)* **2001**, *542*, 123−137.
(8) See Supporting Information.
(9) Leach, A. G.; Catak, S.; Houk, K. N. *Chem. Eur. J.* **2002**, *8*, 1290−1299.
(10) Ricca, A.; Weber, J.; Hanus, M.; Ellinger, Y. *J. Chem. Phys.* **1995**, *103*, 274−280.
(11) Seymour, C. A.; Greene, F. D. *J. Org. Chem.* **1982**, *47*, 5227−5229.
(12) Adam, W. Personal communication.
(13) Adam, W.; Bottke, N.; Krebs, O. *J. Am. Chem. Soc.* **2000**, *122*, 6791−6792.

JA012757B