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Can the Nitroso Ene Reaction Proceed Concertedly?

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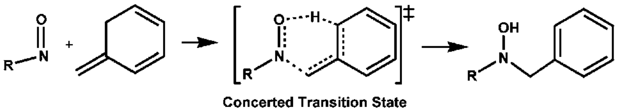
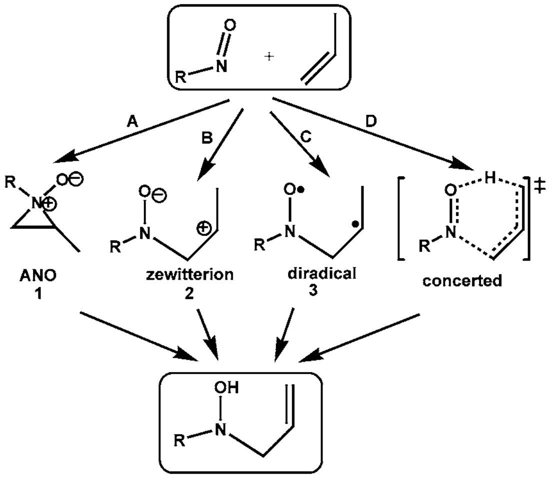
ABSTRACT



All nitroso ene reactions so far reported follow exclusively stepwise reaction paths. Herein, we report the first concerted nitroso ene reaction that occurs between *o*-isotoluene (or its naphthalenic analogues) and nitroso compounds (e.g., nitrosomethane and 4-nitronitrosobenzene).

Scheme 1



Since its discovery in 1965,[1] the nitroso *ene* reaction has become one of the most versatile approaches to the direct regioselective and stereoselective allylic functionalization of alkenes.[2,3] However, the mechanism of the nitroso ene reaction is complicated by the high and diverse reactivity of nitroso compounds and, hence, is a debatable subject.[2,4] A total of four distinct mechanisms (Scheme 1) have been proposed to date, including three stepwise paths (A, B, and C) and a concerted pericyclic path D. While the stepwise path A was supported by the observed kinetic isotope effect,[4a−d] ab initio calculations,[4d] and the independent synthesis of aziridine *N*-oxide (ANO, **1**),[5] path C involving a polarized diradical intermediate **3** was proposed recently based on the results of more elaborate ab initio calculations.[4e] So far, neither experimental nor theoretical evidence is available to show that the nitroso ene reaction adopts the concerted path D. Herein, we show, by means of density functional calculations, that the ene reaction between nitrosomethane (MeNO) and *o*-isotoluene (OIT)[6] adopts a concerted pericyclic path exclusively (Scheme 2).

The ene reaction between MeNO and OIT was studied at the (U)B3LYP/6-31G* theoretical level.[7,8] It has been shown by Houk et al.[4e] that for normal nitroso ene reactions this

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[1] Banks, R. E.; Barlow, M. G.; Haszeldine, R. N. *J. Chem. Soc.* **1965**, 4714.

[2] For a leading review on the nitroso ene reaction, see: Adam, W.; Krebs, O. *Chem. Rev.* **2003**, *103*, 4131.

[3] (a) Braun, H.; Felber, H.; Kresse, G.; Ritter, A.; Schmidtchen, F. P.; Schenider, A. *Tetrahedron* **1991**, *47*, 3313. (b) Adam, W.; Bottke, N.; Krebs, O.; Saha-Möller, C. R. *Eur. J. Org. Chem.* **1999**, 1963.

[4] (a) Seymour, C. A.; Greene, F. D. *J. Org. Chem.* **1982**, *47*, 5226. (b) Adam, W.; Bottke, N.; Krebs, O. *J. Am. Chem. Soc.* **2000**, *122*, 6791. (c) Adam, W.; Bottke, N.; Krebs, O. *Org. Lett.* **2000**, *2*, 3293. (d) Adam, W.; Bottke, N.; Engels, B.; Krebs, O. *J. Am. Chem. Soc.* **2001**, *123*, 5542. (e) Leach, A. G.; Houck, K. N. *J. Am. Chem. Soc.* **2002**, *124*, 14820.

[5] Baldwin, J. E.; Bhantnagar, A. K.; Choi, S. C.; Shortridge, T. J. *J. Am. Chem. Soc.* **1971**, *93*, 4082.

[6] *O*-Isotoluene has substantial stability and can be handled at room temperature for up to 1 h. For references on the synthesis and stability of *o*-isotoluene, see: (a) Gajewski, J. J.; Gortva, A. M. *J. Am. Chem. Soc.* **1982**, *104*, 334. (b) Gajewski, J. J.; Gortva, A. M. *J. Org. Chem.* **1989**, *54*, 373. (c) Bartmess, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 335. (d) Bartmess, J. E.; Griffith, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 2931.

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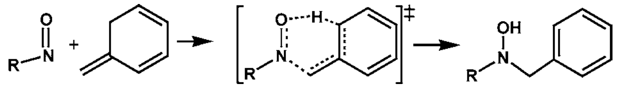
Scheme 2



method predicted reasonable energetics that are comparable to those obtained by UCCSD(T)[9] and CASPT2[10] single-point calculations.[4e] Detailed potential energy surface scans for the (MeNO + OIT) ene reaction showed the presence of neither diradical nor zwitterionic intermediate, i.e., the reaction does not adopt the stepwise paths at all. Instead, the calculations clearly indicate that this reaction itself is an elemental step and proceeds concertedly. The optimized structures for the transition states and products (all close-shell singlets) of this reaction are depicted in Figure 1. The predicted enthalpies, free energies, and entropies for the transition states and products are listed in Table 1.

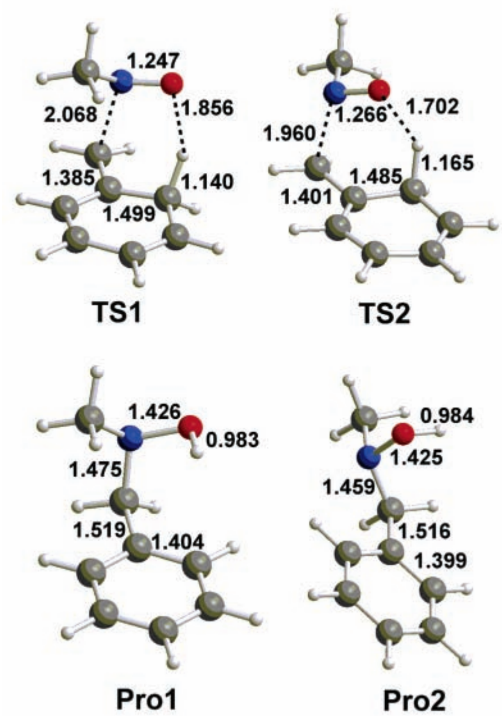


Figure 1. Optimized geometries for the transition states (**TS1** and **TS2**) and products (**Pro1** and **Pro2**) of the ene reaction between MeNO and *o*-isotoluene (OIT).

There are two distinct concerted paths predicted for this reaction, involving two diastereomeric TSs (Figure 1), *endo* **TS1** and *exo* **TS2**, respectively. The corresponding products are **Pro1** and **Pro2** (Figure 1). The *endo* transition state **TS1** is 2.3 kcal/mol higher in enthalpy than the total enthalpy of the reactants. This *endo*-mode path is highly exothermic with a predicted reaction enthalpy of −44.4 kcal/mol. The *exo*-mode path is also highly exothermic ($\Delta H = -43.8$ kcal/mol), but its transition state **TS2** is 6 kcal/mol (in enthalpy) higher than the *endo*-mode **TS1**. Thus, the ene reaction of MeNO with OIT would adopt predominantly the *endo*-mode concerted path with a small activation enthalpy of 2.3 kcal/mol.

Table 1. Computed (B3LYP/6-31G*) Enthalpies ΔH (kcal/mol), Free Energies ΔG (kcal/mol), and Entropies ΔS (cal/mol·K) for the Transitions States (**TS1** and **TS2**) and Products (**Pro1** and **Pro2**) of the Ene Reaction between MeNO and *o*-Isotoluene

	TS1	Pro1	TS2	Pro2
ΔH	2.3	−44.4	8.3	−43.8
ΔG	16.1	−30.5	22.3	−30.6
ΔS	−46.3	−46.5	−47.1	−44.5

It should be noted that the concerted ene reaction of (MeNO + OIT) considered here is both kinetically and thermodynamically favorable over the stepwise ene reaction of (MeNO + propene) concerned previously.[4e] At the same theoretical level, the overall activation and reaction enthalpies for the stepwise (MeNO + propene) ene reaction were predicted to be 14.3 and −10.3 kcal/mol,[4e] respectively. This is reasonable because the concerted (MeNO + OIT) ene reaction apparently benefits from aromatic stabilization in its product, as indicated by its much higher exothermicity than that of the (MeNO + propene) ene reaction. Hence, the concerted (MeNO + OIT) ene reaction has a much smaller activation enthalpy than the stepwise (MeNO + propene) ene reaction, in faithful agreement with the Hammond postulate.[11] Accordingly, the concerted (MeNO + OIT) ene reaction has a rather early transition state (Figure 1).

The controlling effects of aromatic stabilization on the kinetics and thermodynamics have been previously demonstrated in many pericyclic reactions such as the Diels−Alder reaction[12] and 1,5-sigmatropic hydrogen shift.[13] For example, the Diels−Alder reaction of *o*-quinodimethane (as enophile)

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(7) All structures were optimized at the B3LYP/6-31G* level using Gaussian98: 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.; 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.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*; Gaussian, Inc.: Pittsburgh, PA, 1998.

(8) For references on the hybrid density functional B3LYP method, see: (a) Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(9) Pople, J. A.; Head-Gordon, M.; Raghavachari, K. *J. Chem. Phys.* **1987**, *87*, 5968.

(10) Andersson, K.; Malmqvist, P.-Å.; Roos, B. O. *J. Chem. Phys.* **1992**, *96*, 1218.

(11) Hammond, G. S. *J. Am. Chem. Soc*. **1954**, *77*, 334.

(12) (a) Manoharan, M.; DeProft, F.; Geerlings, P. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1767. (b) Manoharan, M.; De Proft, F.; Geerlings, P. *J. Org. Chem*. **2000**, *65*, 7371.

(13) Alabugin, I. V.; Manoharan, M.; Breiner, B.; Lewis, F. D. *J. Am. Chem. Soc*. **2003**, *125,* 9329.

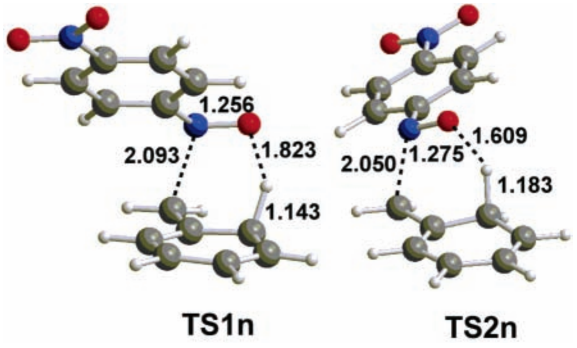
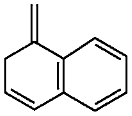


Figure 2. B3LYP/6-31G*-optimized geometries for the transition states (**TS1n** and **TS2n**) of the ene reaction between NO_2PhNO and *o*-isotoluene (OIT).

was found to be both kinetically and thermodynamically more favored than that of the prototypic diene, 1,3-butadiene, because of the much larger aromatic stabilization in the transition state and product of the Diels−Alder reaction of *o*-quinodimethane.[12] It is worth noting that in these chemical precedents the reaction pathways are similar for both the aromatic and nonaromatic reactions, though they differ largely in activation energy and reaction heat. Thus, our work represents an ultimate case that aromatization can alter even the reaction mechanism.

In addition, the ene reaction of OIT with another widely employed nitroso compound, 4-nitronitrosobenzene (NO_2-PhNO), also proceeds concertedly. Figure 2 depicts the two optimized transition states (**TS1n** and **TS2n**) of the concerted ene reaction of OIT with NO_2PhNO. The predicted activation enthalpies are 1.0 and 5.6 kcal/mol for the *endo*-mode path (via **TS1n**) and the *exo*-mode path (via **TS2n**), respectively.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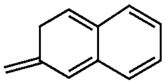
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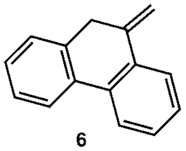
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Finally, we believe the nitroso ene reactions involving 1-methylene-1,2-dihydronaphthalene **4**,[14] 2-methylene-1,2-dihydronaphthalene **5**,[14] or methylenedihydrophenanthrene **6**[14] would all be highly exothermic due to aromatic stabilization in their reaction products, and would all proceed concertedly.

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Supporting Information Available: Cartesian coordinates, electronic energies, and number of imaginary frequencies for each structure. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For references on the synthesis and kinetic stability of these compounds, see: (a) Scott, L. T.; Brunsvold, W. R. *J. Org. Chem.* **1979**, *44*, 461. (b) Murata, I.; Nakazawa, T.; Kato, M.; Tatsuoka, T.; Sugihara, Y. *Tetrahedron Lett.* **1975**, 1647. (c) Sugimoto, A.; Yoneda, S. *J. Chem. Soc., Chem. Commun.* **1982**, 376.