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The Endocyclic Restriction Test: Oxygen Transfer from *N*-Sulfonyl Oxaziridines to Alkenes

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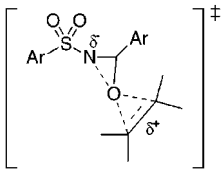
ABSTRACT

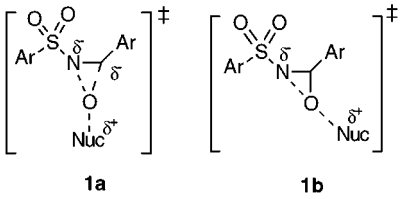


The transition state for the transfer of oxygen from *N*-sulfonyl oxaziridines to alkenes has been investigated experimentally using the endocyclic restriction test. Molecules containing oxaziridines and alkenes were prepared and the ability of each system to intramolecularly transfer oxygen was evaluated. The results are consistent with a transition state in which N–O bond cleavage is more advanced than C–O bond cleavage.

N-Sulfonyl oxaziridines are often the oxidants of choice for transfers of oxygen to carbanions, sulfides, disulfides, enolates, selenides, and alkenes.[1] Seminal work by Davis and co-workers has led to the development and wide application of these compounds as "Davis reagents".[1] The mechanism of oxygen transfer has been the subject of experimental[2] and theoretical[3] investigations. When neutral nucleophiles are used, the transfer of oxygen is suggested to be a concerted process with simultaneous breaking of the N−O and C−O bonds of the oxaziridine in the transtion state.[2b] However, Evans, Davis, and Dmitrienko have reported reactions which they interpret as being consistent with the N−O bond of the oxaziridine breaking before the C−O bond when carbanions[2a,4] and enamines[5] are oxidized.

We report determination of the location of atoms in the transition state for transfer of oxygen from *N*-sulfonyl oxaziridines to a carbon−carbon double bond through use of the endocyclic restriction test. [6]

The transition-state structures proposed for concerted oxygen transfer from the oxaziridine to a nucleophile are depicted in Figure 1. In **1a**, the nucleophile is represented as attacking the oxygen atom with symmetrical C−O and N−O bond breakage. An alternative transition-state model, where the N−O bond breaking is more advanced than the



1a **1b**

Figure 1. Hypothetical transition states for oxygen transfer of *N*-sulfonyl oxaziridines to nucleophiles.

(1) For a reviews of *N*-sulfonyl oxaziridines, see: Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703. Davis, F. A.; Chen, B.-C. *Chem Rev.* **1992**, *92*, 919.

(2) (a) Davis, F. A.; Wei, J.; Sheppard, A. C.; Gubernick, S. *Tetrahedron Lett.* **1987**, *28*, 5115. (b) Davis, F. A.; Billmers, J. M.; Gosinak, D. J.; Towson, J. C.; Bach R. D. *J. Org. Chem.* **1986**, *45*, 4240. (c) Knipe, A. C.; McAuley, I. E.; Khandelwal, Y.; Kansal, V. K. *Tetrahedron Lett.* **1984**, *25*, 1411.

(3) (a) Bach, R. D.; Andres, J. L.; Davis, F. A. *J. Org. Chem.* **1992**, *57*, 613. (b) Bach, R. D.; Coddens, B. A.; McDouall, J. J. W.; Schlegel, H. B.; Davis, F. A. *J. Org. Chem.* **1990**, *55*, 3325. (c) Bach, R. D.; Wolber, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1410.

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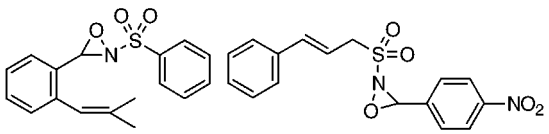
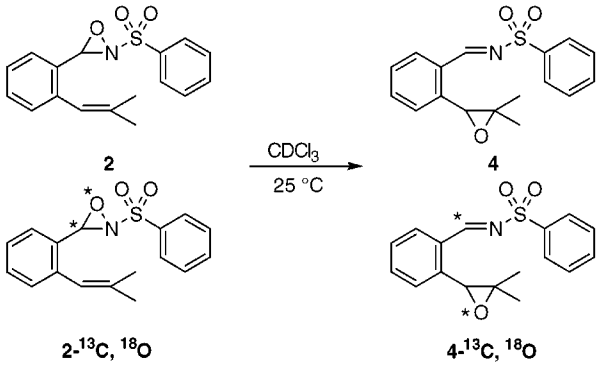
C−O bond cleavage, is shown in **1b**. In this alternative model, the nucleophile attacks the oxygen atom of the oxaziridine on the backside of the N−O bond similar to an S_N2 displacement at oxygen.

Alkenes are among the least reactive species that are oxidized by *N*-sulfonyl oxaziridines and are therefore expected to be more sensitive to perturbations from the ideal transition-state geometries than less selective, more reactive nucleophilic species. Compounds **2** and **3** were prepared and their reactivities examined. Analyses of molecular models suggest that **2** is capable of intramolecularly transferring oxygen from the oxaziridine to the alkene through a transition state analogous to **1b**. Oxaziridine **3** cannot intramolecularly achieve a transition-state geometry similar to **1b**, but could intramolecularly rearrange through a transition state analogous to **1a**. If the transition state for oxygen transfer to give an epoxide cannot be achieved, the reaction may take place intermolecularly. Observation of an intermolecular reaction at high dilution is taken as evidence that a system cannot achieve the proper orientation of atoms in transition state intramolecularly due to the tether linking the reactive functionalities.



2 **3**

Oxaziridine **2** isomerized to **4** in 0.05 M chloroform solutions. The molecularity of this transformation was established by a double-labeling experiment. Doubly labeled **1-^{13}C,^{18}O** was prepared and a ~1:1 mixture of **1** and **1-^{13}C,^{18}O** was allowed to react at a concentration of 0.05 M in $CDCl_3$ at 60 °C. The results of that experiment are summarized in Table 1. These data demonstrate that **2** undergoes oxygen transfer intramolecularly.

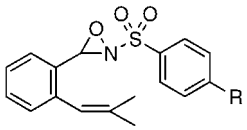


2 **4**

2-^{13}C, ^{18}O **4-^{13}C, ^{18}O**

The rate of isomerization of **2** was measured by ^{1}H NMR integration of the oxaziridine, alkene, and methyl groups of **2** as a function of time. The reaction was first order at a concentration of 0.03 M with a rate constant of $(1.6 \pm 0.3) \times 10^{-4}$ (s^{-1}), corresponding to a half-life of 72 min at 25 °C.

The fact that **2** intramolecularly isomerizes implies that reaction via a transition state analogous to **1b** is a viable pathway for this compound. To demonstrate that the reaction of **2** is not atypical of *N*-sulfonyl oxaziridine oxidations, a linear free-energy study was carried out. The rates of isomerization of **5**, **6**, and **7** were measured. In each case first-order kinetics were observed. The rate constants and relative rates are given in Table 2. The presence of a *p*-NO_2 group accelerates the rate of reaction while the electron-donating *p*-CH_3 group retards the rate of reaction. A plot of these data against σ_p gave a line with a slope (ρ) of 0.95 ± 0.2. ($r = 0.990$).



2: R=H
5: R=CH_3
6: R=Cl
7: R=NO_2

Table 1. Results of Double Label Experiment on **2**

label	reactant 1[a]	intra.[b]	inter.[c]	**4**[d]
^{12}C,^{16}O	50 ± 3	50 ± 3	27 ± 2	50 ± 3
^{13}C,^{16}O	5 ± 2	5 ± 2	27 ± 3	5 ± 2
^{12}C,^{18}O	0	0	22 ± 3	0
^{13}C,^{18}O	45 ± 5	45 ± 5	22 ± 3	44 ± 3

[a] All isotope ratios were measured by FI/MS. [b] Calculated intramolecular result based on the isotopic enrichment of the starting materials. [c] Calculated Intermolecular result assumes complete scrambling of the isotopic labels and negligible heavy atom isotope effects. [d] Experimentally determined isotope ratio for a derivative of product **4**. Refer to the supplementary information for details.

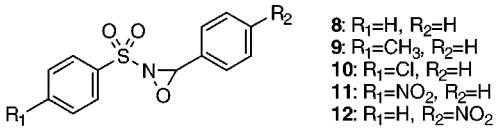
Table 2. First-Order Rate Constants for the Isomerization of **2**

reactant	k_{obs} (s^{-1})	relative rate
2	$(1.6 \pm 0.3) \times 10^{-4}$	1.00
5	$(1.25 \pm 0.05) \times 10^{-4}$	0.93
6	$(2.5 \pm 0.3) \times 10^{-4}$	1.84
7	$(9 \pm 2) \times 10^{-4}$	6.75

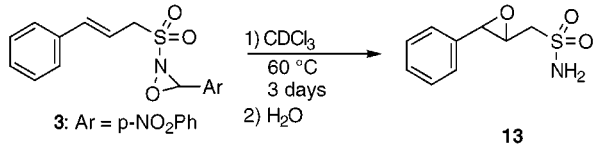
Davis and co-workers reported $\rho = 1.07 \pm 0.15$ ($r = 0.981$)[2b] for the reaction of **8**−**11** with 1-methylcyclohexene. Within the error of the measurements, the ρ values correspond, and we conclude that the intramolecular rearrangement of **1** takes place through a transition state which is electronically similar to the intermolecular reaction of **8**−**11**. If transition state **1b** were operative only for **2**, and **5**−**7** and **1a** were operative for **8**−**11**, different values for ρ would

(4) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.
(5) Mithani, S.; Drew, D. M.; Rydberg, E. H.; Taylor, N. J.; Mooibroek, S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **1997**, *119*, 1159.
(6) Beak, P. *Acc. Chem. Res.* **1992**, *25*, 215.

be expected. The former would be expected to be more sensitive to electronic substitution on the aromatic ring as there is more negative charge is on the nitrogen in **1b** than **1a**.



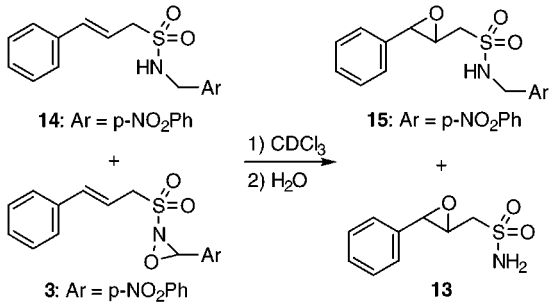
These results do not exclude the possibility that reaction pathways through transition states similar to **1a** could also be viable. To assess this transition-state geometry, oxaziridine **3** was investigated. At higher concentrations (0.1 M in $CDCl_3$), **3** was found to produce a small amount of **13** after several days at 56 °C. Hydrolysis of the sulfonimine apparently follows oxygen transfer. In addition, a large number of unidentified decomposition products were formed. At lower concentrations (0.005 M in $CDCl_3$), **3** completely decomposed over 7 days at 56 °C without producing a detectable amount of **13**. These observations imply that the reaction of **3** to ultimately produce epoxide **13** intermolecular.



Attempts to execute double-label experiments were hampered by our inability both to obtain isotopic distribution data for **13** and to derivitize **13** to a more suitable compound for analysis without loss of the oxygen label.

To further explore the reactivity of **3**, an intermolecular reporter **14**, was employed. Equimolar amounts of **3** and **14** were sealed in an NMR tube and allowed to react in $CDCl_3$ at 56 °C. At higher concentrations (0.1 M total concentration of alkene), both **13** and **15** were detected in the mixture after hydrolysis along with a number of decomposition products. At lower concentrations (0.01 M total concentration of alkene), a trace amount of **15** was detected after 82 h. At very low concentrations (0.005 M total concentration of alkene), **3** completely decomposed after 7 days at 56 °C while producing neither **13** nor **15**. Reporter **14** was found to react with **12** to produce **15** at higher concentrations (0.05 M with respect to each species), but not at lower concentrations (0.005 M with respect to each species).

The fact that intermolecular epoxidation of **14** by **12** was only observed at higher concentrations and that **3** only produces epoxides from either itself or from **14** at the same concentrations support the conclusion that **3** does not transfer oxygen intramolecularly. Epoxide **13** is formed by an intermolecular reaction. These experiments also demonstrate that the oxaziridine of **3** is of similar reactivity to the oxaziridine of **12**. We therefore conclude that reaction of **3** through a transition state analogous to **1a** is disfavored.[7]



In summary, we have shown that the transition-state structures for the reaction of *N*-sulfonyl oxaziridines with olefins are best represented by Figure **1b** and that reaction via transition states analogous to **1a** is not favorable.[8] Transition state **1b** may lead to hemiaminal intermediates that have been observed spectroscopically for the reaction of *N*-sulfonyl oxaziridines with organomagnesium reagents[2a] and have been suggested as intermediates in other transformations.[4,5] We suggest that anionic and neutral nucleophiles react with *N*-sulfonyl oxaziridines through similar transition states. The preferred trajectory for substitution at the oxygen atom of the oxaziridine places the entering and leaving groups in apical positions with respect to the transferred oxygen. This transition state is similar to that of substitution at the oxygen atom of a peroxide and is analogous to an S_N2 displacement at oxygen.[9]

Acknowledgment. This work was supported by a grant from the National Science Foundation (98-19422).

Supporting Information Available: Experimental procedures for the preparation of all compounds and intermediates and sample kinetic data for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The observation that at 0.01 M a trace of epoxide **10** can be detected is best understood in terms of competitive reaction pathways. As **2** decomposes, its relative concentration decreases and the velocity of the epoxidation **9** increases relative to the epoxidation of **2** (or products derived from **2**). Alternatively, the reactivity of the alkene of **9** could be slightly different than the reactivity of the alkene of **2** or products that result from the reaction of **2**.

(8) Our experiments do not distinguish between planar and spiro transition states. Molecular models suggest that either transition state may be available to **2** and **3**.

(9) Woods, K. W.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 6281. Bach, R. D.; Winter, J. D.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1995**, *117*, 8586. Yamabe, S.; Kondou, C.; Minato, T. *J. Org. Chem.* **1996**, *61*, 616. Singleton, D. A.; Merrigan, S. R.; Liu, J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 3385.