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Steric and Conformational Control of the Regioselectivities in the Ene Reaction with Trisubstituted Cycloalkenes: Comparison of the Enophiles Singlet Oxygen, Triazolinedione, and Nitrosoarene

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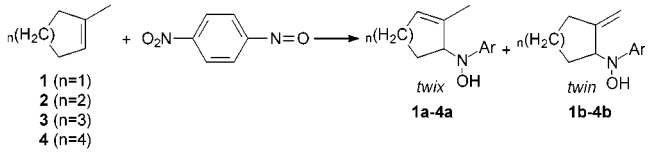
ABSTRACT



The nitrosoarene ene reaction with the cycloalkenes 1–3 and *E*-4 proceeds in high *twix* regioselectivity to afford the hydroxylamine ene products 1a–4a (*twix*) and 1b–4b (twin, except far *E*-4 *twix*). Steric interactions in the enophile attack are responsible for the *skew* trajectory of the nitrosoarene enophile. For *Z*-1-methylcyclooctene (*Z*-4), *twin* abstraction dominates, caused by conformational constraints (transannular interactions) in the hydrgogen-atom abstraction. The balance between these steric and conformational factors dictates the regioselectivity in the ene reaction

The study of regioselectivity has provided important information on the mechanism of chemical reactions; in the case of ene reactions,[1] it has become established as a valuable experimental tool to assess the trajectory of the enophile attack (Figure 1). Thus, while $^1O_2$ favors hydrogen abstraction on the more crowded side of the olefin (*cis* effect)[2] and triazolinedione (TAD) prefers to react at the more crowded end (*gem* effect),[3] the enophile 4-nitronitrosobenzene (ArNO) undergoes the recently discovered highly regioselective ene reaction at the *twix* position of the olefin (*skew* effect).[4]

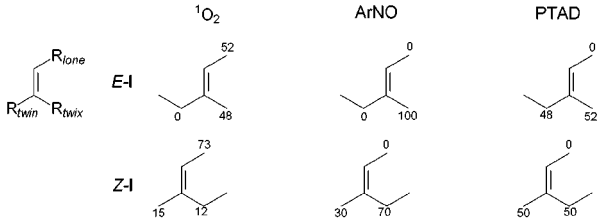


Figure 1. Regioselectivities in the ene reaction for the enophiles $^1O_2$, ArNO, and PTAD with the diastereomeric pair of the acyclic trisubstituted olefins *E*-**I** and *Z*-**I**.

(1) (a) Stratakis, M.; Orfanopoulos, M. *Tetrahedron* **2000**, *56*, 1595−1615. (b) Orfanopoulos, M.; Foote, C. S.; Smonou, I. *Tetrahedron Lett.* **1987**, *28*, 15−18. (c) Stephenson, L. M.; Grdina, M. J.; Orfanopoulos, M. *Acc. Chem. Res.* **1980**, *13*, 419−425.

(2) (a) Orfanopoulos, M.; Grdina, M. B.; Stephenson, L. M. *J. Am. Chem. Soc.* **1979**, *101*, 1, 275−276. (b) Schulte-Elte, K. H.; Muller, B. L.; Rautenstrauch, V. *Helv. Chim. Acta* **1978**, *61*, 2777−2783. (c) Stratakis, M.; Orfanopoulos, M.; Chen, J. S.; Foote, C. S. *Tetrahedron Lett.* **1996**, *37*, 4105−4108.

(3) (a) Ohashi, S.; Leong, K.; Matyjaszewski, K.; Butler, G. B. *J. Org. Chem.* **1980**, *45*, 3467−3471. (b) Adam, W.; Schwarm, M. *J. Org. Chem.* **1988**, *53*, 3129−3130.

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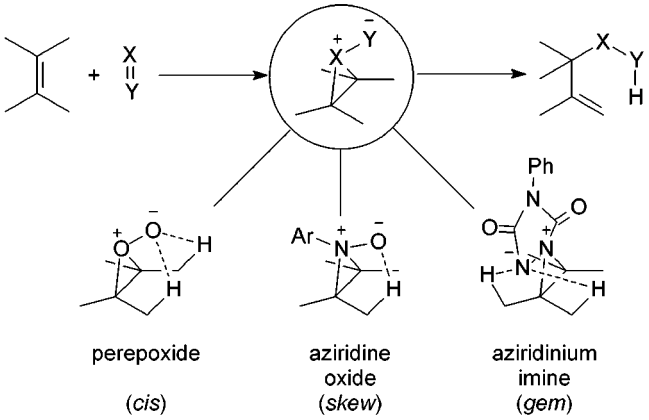
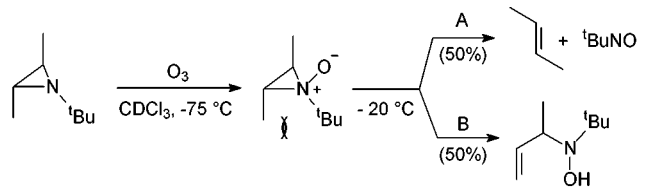
The profound differences in the trajectories of attack for these three isoelectronic enophiles is the more puzzling if it is realized that the same two-step mechanism with irreversible formation of a three-membered-ring intermediate has been proposed on the basis of deuterium kinetic isotope and stereolabeling studies with tetramethylethylene as ene substrate (Scheme 1).[5] In contrast, with *trans*-disubstituted

Scheme 1. Intermediates of the Ene Reaction of $^1O_2$, ArNO, and PTAD with Tetramethylethylene



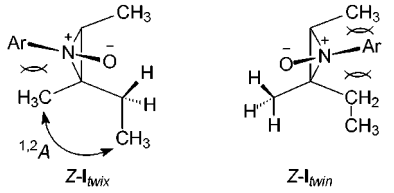
alkenes, for the singlet oxygen[6] and nitroso enophiles[7] the three-membered-ring intermediates are supposedly formed reversibly; in this case the hydrogen abstraction (second step) determines the rate and the first step is fast. In particular, for nitroso enophiles, it was demonstrated that an independently generated aziridine *N*-oxide affords either the ene product or dissociates to the olefin and nitroso compound (Scheme 2).[7] The driving force for the retro cleavage is the

Scheme 2. Rearrangement of a Preformed Aziridine *N*-Oxide to the Ene Product and Fragmentation into Olefin and *tert*-Nitrosobutane



steric interaction between the *cis*-configured methyl and *tert*-butyl substituents and thereby fragmentation competes with hydrogen abstraction.

With trisubstituted olefins, which have been instrumental in disclosing the novel *skew* trajectory for the nitrosoarene ene reaction,[4] the diastereomeric olefin pair *E*/*Z*-**I** (Figure 1) suggests also reversible generation of the aziridine *N*-oxide intermediates *Z*-$\mathbf{I}_{twix}$ and *Z*-$\mathbf{I}_{twin}$. Although the *skew* trajectory



is sterically favored for structure *Z*-$\mathbf{I}_{twix}$, unfavorable 1,2-allylic strain builds up during hydrogen abstraction through conformational effects and this aziridine *N*-oxide reverts. Therefore, the *twin* abstraction becomes more competitive through the *Z*-$\mathbf{I}_{twin}$ intermediate, despite the fact that this *skew* trajectory is sterically more obstructed due to the interactions of the nitroso aryl group with the *cis*-configured methyl and ethyl substituents of the *Z*-**I** substrate. Evidently, the reversibility of the aziridine *N*-oxide intermediate is conditioned by a delicate balance of steric effects in the *skew* approach of the enophile (first step) and conformational constraints in the hydrogen abstraction (second step). This study seeks to probe and elucidate this mechanistic dichotomy.

We have chosen the 1-methylcycloalkenes **1**−**4** as suitable olefinic substrates for this purpose. For the *Z* isomers, the *twix* group is part of the ring system and, therefore, the hydrogen abstraction should be subject to conformational effects (cf. *Z*-$\mathbf{I}_{twix}$). For *twin* abstraction, steric interaction between the aryl group of the nitrosoarene enophile and the bulky ring skeleton is expected (cf. *Z*-$\mathbf{I}_{twin}$). Both effects may be readily varied by successive ring enlargement. Of the *E* isomers, only the *E*-1-methylcyclooctene is available; the lower rings are too strained and do not persist for isolation. The unusual feature of the *E*-1-methylcyclooctene compared to its *Z* isomer is that the *twix* group is not part of the ring system. Moreover, all substituents in the *E* isomer are bent backward due to the strained ring system,[8] such that the steric effects in the approach of the enophile and the conformational influence on the hydrogen abstraction are expected to be quite different from the *Z* isomer. It was, therefore, of mechanistic importance in regard to enophilic reactivity to assess the *twix*:*twin* regioselectivity as a function of ring size for the *Z*-configured cycloalkenes **1**−**4**, while for the diastereomeric cyclooctene pair *E*,*Z*-**4** the influence of ring strain was to be probed. Herein we present and compare the results (Figure 2) of the three isoelectronic enophiles $^1O_2$, PTAD, and ArNO. The ene products were identified and quantified by means of ^{1}H NMR (600 MHz) spectroscopy, isolated, and fully characterized (cf. Supporting Information).

(4) Adam, W.; Bottke, N.; Krebs, O. *J. Am. Chem. Soc.* **2000**, *122*, 6791−6792.

(5) (a) Grdina, B.; Orfanopoulos, M.; Stephenson, L. M. *J. Am. Chem. Soc.* **1979**, *101*, 3111−3112. (b) Cheng, C. C.; Seymour, C. A.; Petty, M. A.; Greene, F. D.; Blount, J. F. *J. Org. Chem.* **1984**, *49*, 2910−2916. (c) Seymour, C. A.; Greene F. D. *J. Org. Chem.* **1982**, *47*, 5226−5227. (d) Greene, F. D. In *Stereochemistry and Reactivity of Systems Containing π-Electrons*; Watson W. H., Ed.; Verlag Chemie Int.: Deersfield Beach, FL, 1983; pp 197−240.

(6) (a) Orfanopoulos, M.; Foote, C. S. *Free Rad. Res. Commun.* **1987**, *2*, 321−326. (b) Orfanopolous, M.; Smonou, I.; Foote, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 3607−3614.

(7) Baldwin, J. E.; Bhantnagar, A. K.; Choi, S. C.; Shortridge, T. J. *J. Am. Chem. Soc.* **1971**, *93*, 4082−4084.

(8) (a) Poon, T. H. W.; Pringle, K.; Foote, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 7611−7618. (b) Poon, T. H. W.; Park, S. H.; Elemes, Y.; Foote, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 10468−10473.

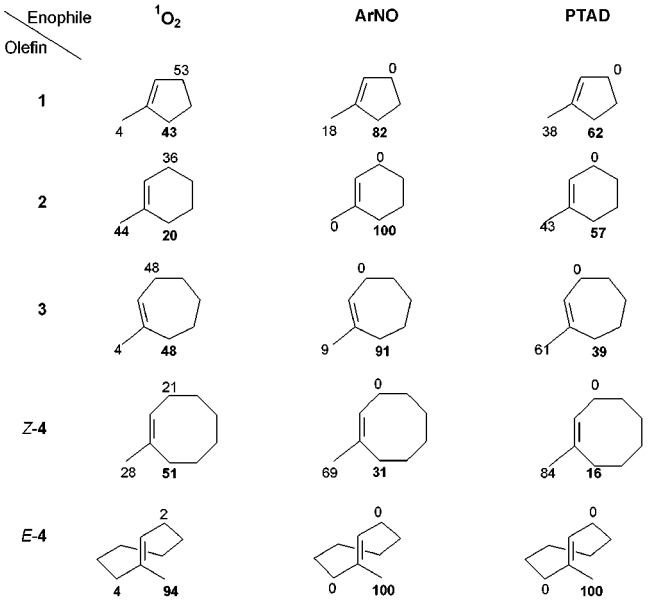


Figure 2. Dependence of the ene regioselectivities on the ring size of trisubstituted cycloalkenes with the enophiles $^1O_2$, PTAD, and ArNO; the *twix* regioselectivities are emphasized in boldface.

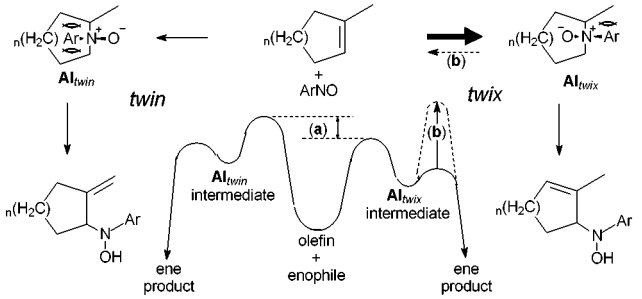
For the cycloalkenes **1**−**3**, the nitrosoarene ene reaction shows a high *twix* preference; as expected, no *lone* abstraction was observed. The *twix*/*twin* ratios are 82:18 for the cyclopentene **1**, >95:5 for the cyclohexene **2**, and 91:9 for the cycloheptene **3**. Comparison of the nitrosoarene regioselectivities with those of singlet oxygen and PTAD (cf. Figure 2) underlines the individual character of these three enophiles: Singlet oxygen abstracts predominantly the *lone* and *twix* hydrogen atoms from the more substituted side of the double bond (*cis* effect)[9] and PTAD abstracts the *twin*- and *twix*-hydrogen atoms of the more substituted end of the double bond (*gem* effect),[10] while the nitrosoarene abstracts with high preference the *twix*-hydrogen atom (*skew* effect).

The above established regioselectivity pattern does not apply to the diastereomeric cyclooctene pair *Z*/*E*-**4**. For *Z*-1-methylcyclooctene (*Z*-**4**), the *twin* abstraction is not only competitive but it is the major pathway for the nitrosoarene ene reaction (*twix*/*twin* ratio 31:69). The *twix* hydrogen atom is part of the cyclooctene ring, and its abstraction is diminished by conformational effects. Therefore, the *twin*-hydrogen abstraction, which is hindered by steric repulsion between the aryl group of the nitrosoarene enophile and the ring skeleton, becomes the major pathway. Also for PTAD and singlet oxygen an enhanced *twin* selectivity applies in their ene reaction with *Z*-1-methylcyclooctene (*Z*-**4**). Thus, for PTAD *twin* selectivity dominates (*twix*/*twin* ratio 16:84), although usually the *twin*- and *twix*-hydrogen atoms are abstracted in comparable amounts.[3] Noteworthy is the increasing amount of *twin* abstraction for the PTAD enophile with the increasing ring size, i.e., cyclopentene (38%), cyclohexene (43%), cycloheptene (61%), and cyclooctene (86%); indeed, for the latter two substrates *twin* selectivity prevails (cf. Figure 2).

For *E*-1-methylcyclooctene (*E*-**4**), all three enophiles show strong preference to abstract the hydrogen atom from the *twix* position. This may be accounted for in terms of the unusual geometry for the strained *E*-**4** molecule, in which the *twin* and *lone* methylene groups of the partially pyramidalized double bond are bent backward and these hydrogen atoms are not as readily available for ene reaction due to conformational reasons. Nevertheless, the approach of the enophile onto this olefin is not sterically hindered and hydrogen abstraction from the *twix* position is conformationally unencumbered. This is the first case in which all three enophiles display essentially exclusive *twix* regioselectivity.

The high *twix* selectivity in the nitrosoarene ene reaction with the *Z* olefins (except *Z*-**4**) may be rationalized in terms of the steric interactions (ease of enophile attack) between the ring skeleton of the cycloalkene with the aryl group of the nitrosoarene enophile and the conformational accessibility (proper alignment) of the allylic hydrogen atom. We shall argue in terms of the two-step mechanism with the intermediacy of an aziridine *N*-oxide, as established by Greene in the early 1980s (Scheme 3).[5] The formation of the aziridine

Scheme 3. Formation of the Aziridine *N*-Oxides AI_{twix} and AI_{twin} in the Nitrosoarene Ene Reaction with Cycloalkenes; Regioselectivity Controlled through Steric Interactions in the Enophile Attack (a) and by Conformational Constraints in the H Abstraction (b)

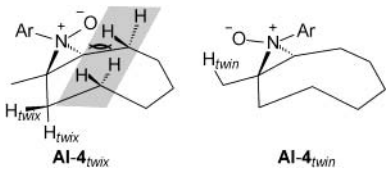


N-oxide intermediate $\mathbf{AI}_{twix}$ (first step) is favored for the *Z*-substrates **1**−**3** since the enophilic attack (*skew* trajectory) is sterically less hindered than that for $\mathbf{AI}_{twin}$. Furthermore, no serious conformational constraint exists on the hydrogen abstraction (second step) at the *twix* site; therefore, *twix* regioselectivity dominates. In this *skew* trajectory of the ArNO enophile, presumably the first step is rate-determining and the second one fast, which constitutes a case of irreversible aziridine *N*-oxide formation, as originally proposed by Greene.[5]

The exception is *Z*-1-methylcyclooctene (*Z*-**4**), for which even a moderate *twin* selectivity is observed (*twix*/*twin* ratio 31:69). Analogous to the smaller cycloalkenes **1**−**3**, for steric reasons the aziridine *N*-oxide $\mathbf{AI}_{twix}$ is also favored over

(9) Jefford, C. W.; Rimbault, C. G. *Tetrahedron Lett.* **1981**, *22*, 91−94.
(10) Cheng, C.-C.; Seymour, C. A.; Petti, M. A.; Greene, F. D.; Blount, J. F. *J. Org. Chem.* **1984**, *49*, 2910−2916.

AI$_{twin}$; thus, conformational effects must again be at work for the cyclooctene *Z*-**4**. Indeed, inspection of models reveals that 1,5-transannular strain builds up during the hydrogen-atom abstraction at the *twix* position (see structures **AI-4**$_{twix}$ and **AI-4**$_{twin}$). Such 1,5-transannular effects are well docu-



mented for eight-membered rings.[11] Although sterically the *twix* attack with formation of the **AI-4**$_{twix}$ intermediate is favored compared to *twin* attack to afford **AI-4**$_{twin}$, through transannular effects (conformational constraints) a higher barrier to hydrogen abstraction at the *twix* position is encountered; thus, the **AI-4**$_{twix}$ intermediate reverts to the starting materials. Again, this constitutes a case of reversible aziridine *N*-oxide, i.e., a reaction profile in which the first step is fast (easier enophile attack) and the second step slow (encumbered hydrogen abstraction); consequently, *twin* attack competes more effectively. Once the aryl group of the nitroso enophile has pushed itself across the cyclooctene ring and the aziridine *N*-oxide is formed (slow first step), the latter rushes on to the ene product by hydrogen abstraction (fast step) since no transannular impediments apply. The *skew* trajectory for the *twix* attack by ArNO on the cyclooctene *Z*-**4** conforms to the reversible formation of the aziridine *N*-oxide intermediate.

(11) (a) Glenn, M. P.; Penman, K. G.; Kitching W. *Chem. Commun.* **2000**, 309−310. (b) Nordlander, J. E.; Kotian, K. D.; Raff, D. E.; Njoroge, F. G.; Winemiller, J. J. *J. Am. Chem. Soc.* **1984**, *106*, 1427−1432. (c) Traynham, J. G.; Couvillon, T. M. *J. Am. Chem. Soc.* **1967**, *89*, 3205−3211.

The above regioselectivity results and their mechanistic rationalization make it evident that a complex reaction profile underlies enophilic reactivity. Although the gross mechanism is similar (two-step process with the intervention of a three-membered-ring intermediate), the individualistic traits are conspicuous for the three isoelectronic enophiles in that $^1O_2$ displays the *cis*, PTAD the *gem*, and ArNO the *skew* effect. Moreover, the olefin structure plays a decisive role as to which of the two steps, i.e., enophilic attack (first step) or hydrogen abstraction (second step), determines the rate and thereby whether the intermediate is generated reversibly or irreversibly. For the nitroso enophile, which we have examined in detail herein, the aziridine *N*-oxide is the key intermediate. Its irreversible generation (slow first step) is favored by low steric effects between the enophile and the substrate in the *skew* trajectory (*twix* regioselecivity), while its reversilbe formation (slow second step) applies when hydrogen abstraction is obstructed through conformationally conditioned misalignment and/or strain. The balance between these two steric and conformational factors dictates the regioselectivity in the ene reaction. Unquestionablely, trisubstituted olefins (previously[4] acyclic and presently cyclic ones) provide valuable mechanistic information on enophilic reactivity.

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Supporting Information Available: Experimental section. This material is available free of charge via the Internet at http://pubs.acs.org.

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