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The New *skew* and the Established *cis* and *gem* Regioselectivities in the Ene Reaction of Trisubstituted Olefins: Comparison of the Singlet Oxygen, Triazolinedione, and Nitrosoarene Enophiles

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Experimental work on the enophilic regioselectivity of $^1O_2$ and TAD with trisubstituted olefins shows that $^1O_2$ prefers side-on hydrogen abstraction at the more crowded side (*cis* effect)[1] and TAD end-on at the more crowded end (*gem* effect),[2] as displayed in Figure 1. For nitroso compounds, however, no data appear to be available as to whether *cis* or *gem* regioselectivity applies. Greene examined the ene reaction of pentafluoronitrosobenzene on deuterium-stereolabeled alkenes, and concluded that the same mechanism operates as established for singlet oxygen and triazolinedione, i.e., an irreversibly formed aziridine *N*-oxide[3] intermediate intervenes, analogous to the perepoxide[4] for $^1O_2$ and the aziridine *N*-imide[5] for TAD. Very recent experimental and computational results by Singleton[6] for the ene reaction of TAD have provided cogent arguments in favor of a diradical intermediate. Irrespective of the electronic and structural nature of the actual transition states and/or intermediates involved, the following product data (regioselectivities) are clear-cut about the enophilic hydrogen abstraction from the olefin: $^1O_2$ abstracts side-on (*cis* effect) and TAD end-on (*gem* effect). Be this as it may, the following pertinent questions must be asked:

(a) Does the nitrosoarene enophile follow *cis* or *gem* regioselectivity? (b) What structural factors in the enophilic hydrogen abstraction are responsible for the dichotomy in the regioselectivities of $^1O_2$ (*cis*) and TAD (*gem*)? Our present experimental data disclose that the regiochemical behavior of nitrosoarenes is a hybrid between that of $^1O_2$ and TAD, i.e., ArNO abstracts the hydrogen atom from the alkyl group at the more crowded side (*cis*) as well as more crowded end (*gem*). This novel result is rationalized in terms of a *skew* orientation for ArNO, dictated by steric interactions, and sheds light on the control of the *cis* versus *gem* regioselectivities in the $^1O_2$ and TAD ene reactions.

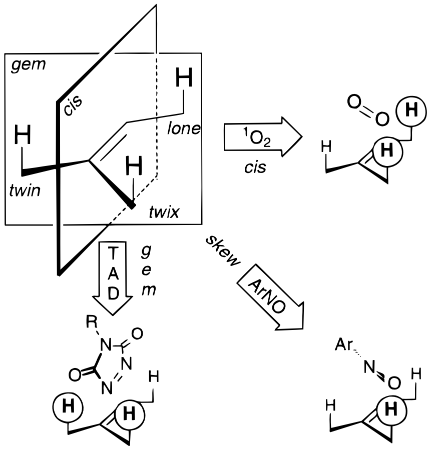
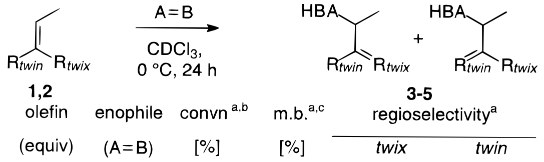


Figure 1. Regioselectivities in the ene reaction of trisubstituted olefins for the enophiles singlet oxygen ($^1O_2$), triazolinedione (TAD) and nitrosoarene (ArNO); the respective *cis*, *gem*, and *skew* hydrogen abstractions are shown, no intermediates are implied.

Table 1: Regioselectivities in the Ene Reaction of 4-Nitronitrosobenzene (ArNO) and Phenyltriazolinedione (PTAD) with (*E*/*Z*)-3-Methyl-2-pentene (*E*/*Z*-**1**) and (*E*/*Z*)-2-Methyl-1,1,1-trideuterio-2-butene (*E*/*Z*-**2**)



	olefin (equiv)	enophile (A = B)	convn[a,b] (%)	m.b.[a,c] (%)	regioselectivity[a]	
					twix	twin
1	*E*-**1** (2.0)	ArNO	69	80	>95 (**3a**)	<5 (**3b**)
2	*Z*-**1** (2.0)	ArNO	43	87	70 (*E*-**3b**)[d]	30 (**3a**)
3	*E*-**2** (1.5)	ArNO	71	83	88 (**4a**)	12 (**4b**)
4	*Z*-**2** (1.5)	ArNO	72	77	81 (**4b**)	19 (**4a**)
5	*E*-**2** (1.0)	PTAD	>95	88	54 (**5a**)	46 (**5b**)
6	*Z*-**2** (1.0)	PTAD	>95	98	53 (**5b**)	47 (**5a**)

[a] Determined by ^1H NMR spectroscopy, error ±5% of the stated value. [b] Based on 100% conversion of olefin. [c] Mass balance. [d] The *E* configuration was determined by NOE spectroscopy.

The ene reaction of 4-nitronitrosobenzene (ArNO) with *E*- and *Z*-3-methyl-2-pentenes (***E*/*Z*-1**) and with *E*- and *Z*-2-methyl-1,1,1-trideuterio-2-butenes (*E*/*Z*-**2**) gave the expected ene products, which were identified and quantified by means of ^1H NMR (600 MHz) spectroscopy and isolated as well as fully characterized (cf. Supporting Information). Furthermore, since the regioselectivity data for the ene reaction of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) with the *E*/*Z*-**2** substrates were not known, they were also determined (Table 1).

The results in Table 1 reveal unequivocally that the nitrosoarene preferably abstracts a hydrogen atom from trisubstituted olefins at the more crowded end (*gem*) and more substituted side (*cis*) of the double bond, that is, the combined characteristics of the *gem* and *cis* effects are evident; but compared to $^1O_2$ and PTAD, the ArNO enophile possesses the higher extent of regioselectivity (Scheme 1). Unlike $^1O_2$ but like PTAD, the ArNO abstracts predominantly a hydrogen atom from the *gem* alkyl group on the more substituted side (defined as the *twix* group)[7] of the alkenes **1** and **2**, yet much more pronounced than PTAD. For the latter, as much as ca. 50% ene reaction takes places at the *twin* alkyl group[7] in all substrates, while for ArNO, abstraction from this

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(7) The regiochemical differentiation of the three alkyl groups in trisubstituted olefins has to date not been well defined. For this reason and the ease of referral in the text, we suggest the following codification (see Figure 1): Attention is focused on the central alkyl substituent, which is defined as the *twixt* group (R_{twix}, for simplification the last “t” has been dropped); “twixt” comes from old English and means “between”, i.e., R_{twix} is between a geminal and vicinal alkyl group. The other geminal substituent is then designated as the *twin* group (R_{twin}), and the remaining vicinal substituent as the *lone* one (R_{lone}).

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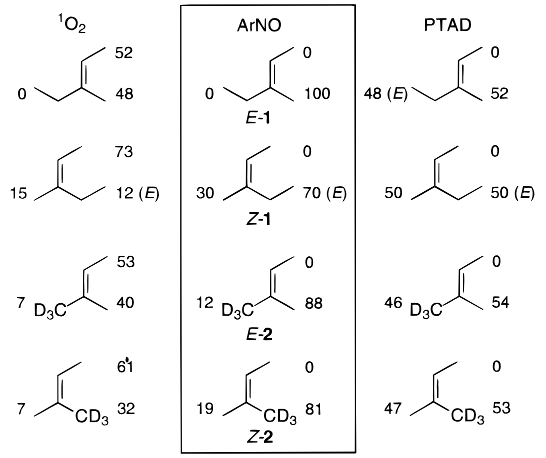
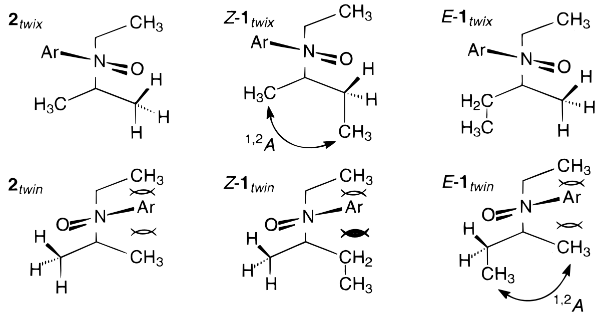
Scheme 1



site ranges only between 0 and 30%. Impressive is the *E*-**1** substrate, since ArNO reacts exclusively (>95%) at the *twix* position, whereas it is only ca. 50% for both $^1O_2$ and PTAD. What all three enophiles have in common is that the regioselectivity for hydrogen abstraction at the *twix* methylene substituent in the *Z*-**1** substrate is lower (only nominally for PTAD); mechanistically significant, the *E*-diastereomer is preferentially formed for all three enophiles. These remarkable regioselectivities of the enophiles ArNO (*skew*, R_{twix}), $^1O_2$ (*cis*, R_{twix}/R_{lone}) and PTAD (*gem*, R_{twix}/R_{twin}) signify distinct abstraction modes and call for rationalization.

In the ene reaction of the nitrosoarene, the two configurations $\mathbf{2}_{twix}$ and $\mathbf{2}_{twin}$ may be envisaged for an enophile/substrate encounter complex, in which the pertinent steric repulsions are shown (this model applies irrespective of possible intermediates). For clarity, in the $\mathbf{2}_{twix}$ arrangement, the *N*-oxide functionality points to the *twix* alkyl (R_{twix}) substituent, while in $\mathbf{2}_{twin}$ it points of the *twin* (R_{twin}) one. A large steric effect becomes evident on closer inspection: In the $\mathbf{2}_{twin}$ geometry, the aryl substitutent of the nitroso compound is located between the flanking R_{twix} and R_{lone} alkyl groups of the more crowded and sterically congested side of the double bond. In contrast, in the $\mathbf{2}_{twix}$ configuration this repulsion is less because the aryl group interacts only with the R_{twin} substitutent. The latter pushes the aryl group of ArNO toward the unsubstituted corner of the double bond and results in a *skew* line arrangement to afford the major product by hydrogen abstraction from the R_{twix} group. Thus, the combined steric repulsions of the aryl group with the R_{twix} and R_{lone} substitutents, and additionally with the R_{twin} group, forces the ArNO to follow along the *skew* geometry in the favored $\mathbf{2}_{twix}$ arrangement and hydrogen abstraction takes place almost exclusively from the R_{twix} group, as displayed in the Figure 1.

Structures $\mathbf{2}_{twix}$, $\mathbf{2}_{twin}$, *Z*-$\mathbf{1}_{twix}$, *Z*-$\mathbf{1}_{twin}$, *E*-$\mathbf{1}_{twix}$, E-$\mathbf{1}_{twin}$



Notable is also the significantly lower *skew* regioselectivity for the *Z*-**1** (70:30) versus the *E*-**1** (100:0) diastereomer (Scheme 1; Table 1, entries 1 and 2). This is not in accord with an irreversibly formed intermediate, as proposed for all three ene reactions ($^1O_2$, PTAD and ArNO)![3b] Were that the case for the present substrates *Z*-**1** and *E*-**1**, it becomes difficult to rationalize, why the sterically less encumbered *E*-$\mathbf{1}_{twin}$ versus the *Z*-$\mathbf{1}_{twin}$ leads to lower (actually none!) hydrogen abstraction from the *twin* position of substrate *E*-**1**. As revealed by *Z*-$\mathbf{1}_{twix}$, during the abstraction of the coplanar allylic hydrogen atom from its *twix* alkyl group, unfavorable 1,2-allylic strain ($^{1,2}A$) builds up.[8] It is a question of the balance between this 1,2-allylic strain and the steric interaction between the aryl group of the ArNO enophile and the R_{twix} and R_{lone} substituents. For the *Z*-**1** diastereomer, these two effects are counteracting, while for *E*-**1** they are reinforcing. Thus, for the *Z*-**1** substrate proportionally more *Z*-$\mathbf{1}_{twin}$ is populated than for *E*-**1** and, consequently, more *twin* abstraction is observed for *Z*-**1** (entries 1 and 2). This is not compatible with an irreversible formation of an aziridine *N*-oxide.

Is the newly discovered *skew* abstraction unique for nitroso enophiles? Since steric effects are responsible for this enophilic reactivity, one would expect that $^1O_2$ (the smallest of all enophiles) should be the least prone to engage in this course of action. Nevertheless, if sufficiently obliged,[9] even $^1O_2$ exhibits steric sensitivity, as manifested in the so-called "nonbonding large group effect" for the neopentyl substrate **6**.[10] Comparison of its $^1O_2$ regioselectivity with that of the substrates **1** and **2** (Scheme 1) unmistakably reveals preference for hydrogen abstraction from the R_{twix} group in the neopentyl case **6** ($^1O_2$). Thus, with the large *tert*-butyl group at the *twin* site, the $^1O_2$ molecule abstracts preferentially through the *skew* geometry rather than the usual *cis* one. Similar nonbonding interactions operate also for the PTAD enophile,[11] but more effectively because of the larger size. Therefore, although the usual *gem* regioselectivity applies, again a strong *skew* preference is promoted and exclusive hydrogen abstraction from the R_{twix} group results (compare the regioselectivities for **6** with those in Scheme 1).

Structures 6 ($^1O_2$) and 6 (PTAD)

In conclusion, from the present exercise in regiochemistry we have learned that the enophilic regioselectivity may be rationalized in terms of the well established *cis* ($^1O_2$) and *gem* (TAD) and the newly recognized *skew* (ArNO) effects. For all three enophiles steric interactions are important, but they appear to be more pronounced for ArNO. It should be mechanistically instructive to probe this new concept experimentally and theoretically in further depth.

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Supporting Information Available: Experimental section (PDF). This material is available via the Internet at http://pubs.acs.org.

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