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Intramolecular and Intermolecular Kinetic Isotope Effects (KIE) in the Nitrosoarene Ene Reaction: Experimental Evidence for Reversible Intermediate Formation

Waldemar Adam,[†] Oliver Krebs,*[,†] Michael Orfanopoulos,[‡] Manolis Stratakis,[‡] and Georgios C. Vougioukalakis[‡]

Institut für Organische Chemie, Universität Würzburg, Am Hubland D-97074 Würzburg, Germany, and Department of Chemistry, University of Crete, P.O. Box 1470, 71409 Iraklion, Crete, Greece

wadam@chemie.uni-wuerzburg.de

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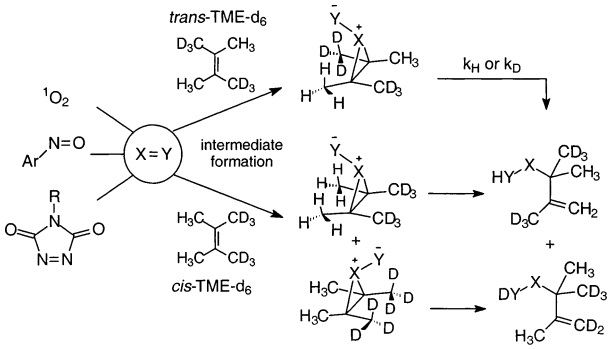
The intramolecular and intermolecular kinetic isotope effects (KIE) have been determined for the nitrosoarene ene reaction with deuterium-stereolabeled 2,3-dimethyl-2-butenes (TME). *trans*-TME-d_6 ($k_H/k_D = 3.0$) and *gem*-TME-d_6 ($k_H/k_D = 4.0$) show large intramolecular primary isotope effects. In contrast, the intramolecular competition in *cis*-TME-d_6 ($k_H/k_D = 1.5$) and the intermolecular competition for the TME-d_0/TME-d_{12} pair ($k_H/k_D = 1.98$) show considerably smaller, but mechanistically significant kinetic isotope effects. The latter fact is rationalized in terms of reversible formation of a three-membered-ring intermediate, namely the aziridine *N*-oxide, or a similar unsymmetrical, polarized diradical in the first step of the reaction. Such reversibility has also been implied earlier for triazolinedione (TAD) and singlet oxygen ($^1O_2$) with deuterium-stereolabeled 2-butenes, but of the three enophiles, ArNO is the most sensitive toward reversibility, which is due to its moderate reactivity and its high steric demand.

Introduction

The ene reaction of the heteroatom enophiles singlet oxygen ($^1O_2$),[1] nitrosoarene (ArNO),[2] and triazolinedione (TAD)[3] proceeds by a stepwise process through a three-membered-ring intermediate (Scheme 1). The mechanism of this complex pericyclic reaction has been extensively investigated by means of kinetic isotope effects,[1−3] which have provided the crucial experimental evidence for the intervention of the three-membered-ring intermediates for the three enophiles. The intramolecular isotopic competition in *cis*- and *trans*-2,3-dimethylbut-2-ene-d_6 (*cis*-TME-d_6 and *trans*-TME-d_6) has shown for these heteroatom enophiles small or even negligible kinetic isotope effects with *cis*-TME-d_6 ($k_H/k_D \approx 1$), but large ones for the *trans*-TME-d_6 ($k_H/k_D > 1$). Once the three-membered-ring intermediate has been formed from *cis*-TME-d_6 in the rate-determining step, the terminal atom of the enophile points either to the undeuterated or deuterated side of the alkene and there is no isotopic H/D competition (Scheme 1). In contrast, for the three-membered-ring intermediate derived from *trans*-TME-d_6, a primary isotope effect applies in the second product-forming step (H or D abstraction) and a large k_H/k_D value may be observed. Also in the intermolecular competition between TME-d_0 and TME-d_{12} only a small isotope effect operates, since the intermediate of the reaction with TAD and $^1O_2$ is formed irreversibly in the first rate-determining step; note that in such intermediates no differentiation between H and D abstraction is possible.

SCHEME 1. Formation of Three-Membered-Ring Intermediates and Hydrogen Abstraction in the Ene Reaction of $^1O_2$, ArNO, and TAD with Specifically Deuterium-Labeled Tetramethylethylenes (TME)



Recently, on the basis of computational results, a diradical intermediate was proposed as the hydrogen-abstracting entity in the ene reaction of ArNO[4a,b] and TAD.[4c] The observed kinetic isotope effects were rationalized in terms of hindered rotation around the C−N and the C−C bonds in the diradical, whereas the three-

[†] Universität Würzburg, http://www-organik.chemie.uni-wuerzburg.de/ak_adam.

[‡] University of Crete, http://www.chemistry.uoc.gr.

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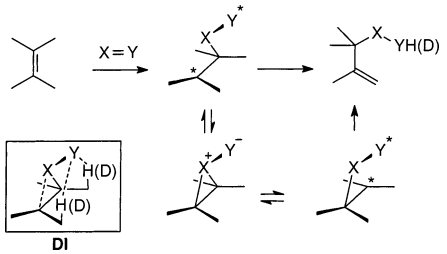
SCHEME 2. Diradical or Dipolar Intermediates (DI) in the Ene Reaction and the Three-Membered-Ring Species as Bystander



membered-ring intermediate was designated as the bystander responsible for the isomerization (necessary to rationalize the observed high k_H/k_D values for *gem*-TME-d_6), but not as the immediate precursor for the hydrogen abstraction process (Scheme 2). The hindered rotation (necessary to rationalize the observed small k_H/k_D values for *cis*-TME-d_6) was attributed to a bonding interaction between the sp^2 carbon and the enophile and coordination with the allylic hydrogen atoms, as shown for the structure **DI** (Scheme 2). Thus, such a **DI** species may also be viewed as an unsymmetrically bonded three-membered-ring intermediate. Furthermore, the diradical mechanism for TAD[4c,d] was recently challenged by stereochemical[4d] and stereoisotopic[4e] studies.

Kinetic isotope effects were investigated for ArNO by Seymour and Greene.[2] They used pentafluoronitrosobenzene as the nitroso enophile and found small k_H/k_D values for the reaction with *cis*-TME-d_6 and for the intermolecular competition with the TME-d_0/TME-d_{12} pair, whereas large k_H/k_D values were obtained for the reactions with *trans*-TME-d_6 and *gem*-TME-d_6. To accommodate these kinetic isotope effects, it was proposed that an aziridine *N*-oxide is formed irreversibly in the first, rate-determining step of the reaction. In this context, however, in our recent studies on the regioselectivity of the *p*-O_2N-C_6H_4-NO reaction[5] with the trisubstituted alkenes (*E*)- and (*Z*)-3-methyl-2-pentene (*E*-/*Z*-**1**), we observed that the *twix*/*twin* selectivity depended on the substitution pattern of the substrate (Figure 1).[5a] Notice that for the *Z*-**1** isomer, substantial *twin* abstraction has occurred, which is not the case for the *E*-**1** isomer. As rationalized in our communication,[5a] this fact points to reversible formation of the intermediate. In the hydrogen abstraction (second step!) 1,2-allylic strain ($^{1,2}A$) builds up for *Z*-**1**$_{twix}$, which is not the case for *E*-**1**$_{twix}$ (Figure 1); consequently, the *Z*-**1**$_{twix}$ intermediate reverts more readily.[5]

The mechanistically important new feature of the nitroso ene reaction, namely reversible formation of the aziridinium *N*-oxide intermediate in the first step as implicated by the product-based regioselectivity,[5] calls for

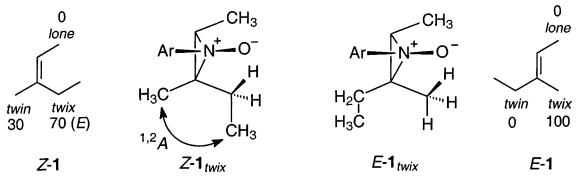


FIGURE 1. Dependence of the *twix*/*twin* regioselectivity on 1,2-allylic strain through hindered hydrogen abstraction.

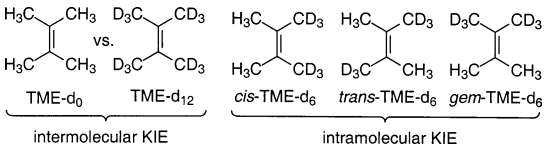


FIGURE 2. Deuterium-labeled tetramethylethylenes (TME) for the study of kinetic isotope effects (KIE).

rigorous experimental validation. Stephenson's kinetic isotope test,[1−3] for which the deuterium-labeled tetramethylethylenes (TME) in Figure 2 (or equivalently deuterium-labeled substrates) have been employed, provided conclusive mechanistic information on the reversibility issue in related pericyclic reactions.[6] Consequently, it was decided to use these TME derivatives in the ene reaction with 4-nitronitrosbenzene and to determine the intermolecular and intramolecular kinetic isotope effects (KIE). Should an appreciable KIE be observed for the TME-d_0/TME-d_{12} intermolecular pair and for the *cis*-TME-d_6 intramolecular substrate, reversibility in the nitroso ene reaction of tetrasubstituted alkenes would be validated.

Results

The ene reaction of *p*-nitronitrosobenzene (ArNO) with 2,3-dimethylbut-2-ene (TME) proceeds without side reactions and in high yield.[7] Intramolecular isotopic competition for the reaction of ArNO with *cis*-TME-d_6 and *trans*-TME-d_6 (Stephenson's isotope test)[1] and with *gem*-TME-d_6 was determined in terms of product ratios by means of ^{1}H NMR spectroscopy. The intermolecular isotope effect for the competition between TME-d_0 and TME-d_{12} was measured in terms of olefin consumption by GC analysis and confirmed by ^{1}H NMR spectroscopy of the ene products. The results are summarized in Table 1. For a composite overview, the reported kinetic isotope effects for $^1O_2$ and TAD are given in Table 1.[1−3,8]

As expected, the ene reactions of the nitrosoarene *p*-O_2N-C_6H_4-NO with *trans*-TME-d_6 (fourth column) and *gem*-TME-d_6 (last column) show high intramolecular primary isotope effects ($k_H/k_D \gg 1$). For *cis*-TME-d_6 (third column) and for the intermolecular competition between TME-d_0 and TME-d_{12} (second column), the isotope effects are substantially smaller, but still mechanistically significant.

The large difference between the reported[2] k_H/k_D value for C_6F_5-NO (1.03 ± 0.05) with TME-d_0 versus TME-d_{12} and our present value for *p*-O_2N-C_6H_4-NO (1.98 ± 0.05,

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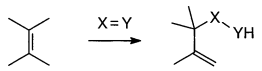
TABLE 1. Intermolecular and Intramolecular Kinetic Isotope Effects for the Ene Reaction of Tetramethylethylenes (TME) with Various Enophiles



	k_H/k_D values			
	intermolecular	intramolecular		
enophile	TME-d_0 vs. TME-d_{12}	*cis*-TME-d_6	*trans*-TME-d_6	*gem*-TME-d_6
p-O_2N-C_6H_4-NO[a,b]	1.98 (±0.05)[c] / 2.0 (±0.1)[d]	1.5 (±0.1)[d]	3.0 (±0.1)[d]	4.0 (±0.1)[d]
PTAD (refs 2, 3)	1.02	1.1	3.7	5.6
MTAD (refs 2, 3)	1.01	1.08	3.8	5.7
$^1O_2$ (refs 1, 8)	1.1	1.06	1.4	1.4

[a] The ene reaction of the nitrosoarene F_5C_6NO is discussed in the Supporting Information. [b] Full conversion of the enophile after 4 h at 0 °C. [c] In CH_2Cl_2, determined by GC analysis with cyclohexane as internal standard; calculated according to $k_H/k_D = \ln\{[A_H]/[A_H]_0\}/\ln\{[A_D]/[A_D]_0\}$; error ca. 3% of the stated value. [d] In $CDCl_3$, Determined by ^1H NMR spectroscopy; error ca. 5% of the stated value.

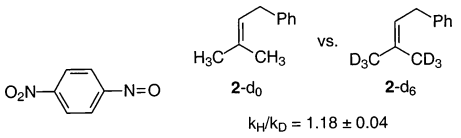


FIGURE 3. Intermolecular isotope effect in the ene reaction of *p*-nitronitrosobenzene with the 3-methyl-1-phenyl-2-butenes **2**-d_0 and **2**-d_6.

second entry) needed clarification. For this reason, the experiments with the C_6F_5-NO enophile were repeated (cf. Supporting Information). Our k_H/k_D values for the intermolecular competition with C_6F_5-NO scattered from 1.20 to 1.77 and depended strongly on the reaction conditions. Since for this enophile no reproducible k_H/k_D values could be obtained, the results for C_6F_5-NO have not been considered in our mechanistic analysis; the difficulties with this enophile are presented and discussed in the Supporting Information as a separate section.

For comparison purposes, the intermolecular kinetic isotope effect was also determined for the trisubstituted 3-methyl-1-phenyl-2-butene-d_0 (**2**-d_0) versus its geminally labeled analogue **2**-d_6 (Figure 3). The k_H/k_D value (1.18 ± 0.04) is much smaller than that for the tetrasubstituted TME-d_0/TME-d_{12} substrate pair (1.98 ± 0.05).

We shall now analyze mechanistically the kinetic isotope effects for the deuterium-labeled TME derivatives and interpret the novel features displayed by the nitrosoarene enophiles. Our present results demonstrate reversible formation of the three-membered-ring intermediate for the ArNO enophile. These findings shall also be compared with the TAD and $^1O_2$ enophiles, for which previously reversibility has been suspected in the case of *trans*-2-butene.[9]

Discussion

The inter- and intramolecular kinetic isotope effects for the ene reaction of the nitrosoarene enophile (ArNO), triazolinedione (TAD), and (to a less extent) singlet oxygen ($^1O_2$) in Table 1 are all large for *trans*-TME-d_6 and *gem*-TME-d_6 ($k_H/k_D \gg 1$; primary isotope effects). The effects are considerably smaller for *cis*-TME-d_6 and for the intermolecular competition between TME-d_0 and TME-d_{12} ($k_H/k_D < 2$). These differences in the intramolecular isotope effect between the cis-configured and trans-configured methyl groups, as well as the small intermolecular isotope effect for the competition between TME-d_0 and TME-d_{12}, have been previously rationalized in terms of the established two-step mechanism through an irreversibly formed three-membered-ring intermediate, namely the aziridine *N*-oxide intermediate (**AI**).[1−3] For the TME-d_0/TME-d_{12} pair and for *cis*-TME-d_6, once the enophile is fixed in the three-membered-ring intermediate, only one kind of isotope (either H or D) is available for abstraction at each side of the double bond and, thus, no primary kinetic isotope effect is to be expected for these substrates. However, in contrast to the hitherto accepted mechanism for the ArNO ene reaction, for which *irreversible* formation has been proposed for the aziridine *N*-oxide intermediate,[2] the presently observed kinetic isotope effects for *cis*-TME-d_6 and for the intermolecular competition between TME-d_0 and TME-d_{12} (Table 1) suggest *reversible* generation of the **AI** species. It should be mentioned again that instead of the symmetrical **AI**, also an unsymmetrical structure such as the **DI** in Scheme 2 may qualify to account for the experimentally observed reversibility (cf. Introduction).

Before we enter into the mechanistic analysis of the reversibility issue, it needs to be considered whether β-secondary or steric kinetic isotope effects account for the observed k_H/k_D values. For the intermolecular competition between TME-d_0 and TME-d_{12} a β-secondary KIE may apply, if it is assumed that the first reaction step is rate determining. However, the rehybridization of both olefinic carbon atoms from sp^2 to sp^3, as occurs in the formation of the proposed three-membered-ring intermediate, would lead to an *inverse* β-secondary isotope effect ($k_H/k_D < 1$) of 1−4% per D atom (a total of ca. 20% for the 12 allylic D atoms in TME-d_{12}). Such inverse secondary KIE already have been documented for the intermolecular competition in the ene reaction of TAD with β,β-dimethylstyrene-d_0/d_6[10] ($k_H/k_D = 0.76$) and phorone-d_0/d_6[11] ($k_H/k_D = 0.90$), for which the first step is rate limiting, but are in conflict with the present ene reaction of ArNO (Table 1), since here normal kinetic isotope effects ($k_H/k_D > 1$) were found. Moreover, for the *cis*-TME-d_6 substrate, a substantial primary intramolecular isotope effect was observed; however, in this case, a β-secondary isotope effect cannot operate in the first step due to the identical isotopic substitution at the allylic positions (each end of the double bond bears a CD_3 and a CH_3 group). A steric kinetic isotope effect (a CD_3 group is ca. 10% smaller than a CH_3 group)[12,13] cannot apply, since again $k_H/k_D < 1$ should have been obtained for the intermolecular competition (TME-d_{12} is sterically less hindered than TME-d_0).

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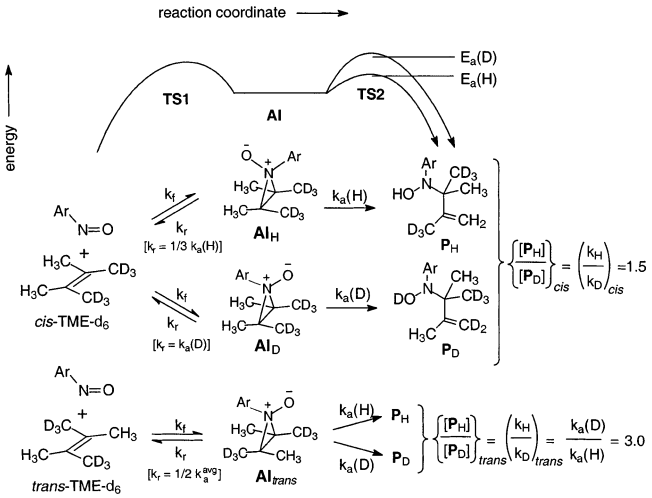

FIGURE 4. Reaction profile and mechanism for the ene reaction of ArNO with the *cis*-TME-d_6 and *trans*-TME-d_6 substrates and the kinetic analysis of the extent of reversibility (see Supporting Information).

The observed kinetic isotope effects for the intermolecular competition between TME-d_0 and TME-d_{12} and for the intramolecular competition in *cis*-TME-d_6 are rationalized mechanistically in terms of reversible formation of the aziridine *N*-oxide intermediates **AI** (Figure 4). To emphasize, the intermediates $\mathbf{AI}_H$ and $\mathbf{AI}_D$ may convert only to the corresponding products $\mathbf{P}_H$ and $\mathbf{P}_D$. Since the **TS1** and **TS2** transition states of the two reaction steps have similar activation energies,[5c] reversal competes with hydrogen or deuterium abstraction. For the latter process, a primary isotope effect may operate, which should perturb the product distribution for the intramolecular competition in the *cis*-TME-d_6 substrate and for the intermolecular competition in the TME-d_0/TME-d_{12} pair. Thus, since D abstraction is retarded compared to H abstraction, more of the intermediate $\mathbf{AI}_D$ reverts than $\mathbf{AI}_H$. Accordingly, more of the ene reaction is channeled along the H-abstracting path and $k_H/k_D > 1$ is expected.

From the observed isotope effects for the ene reaction of 4-nitronitrosobenzene with *cis*-TME-d_6 and *trans*-TME-d_6 (Table 1, entry 1), we shall now estimate the extent of reversibility. For this purpose, we shall apply the kinetic analysis employed recently to assess the reversibility in the related ene reaction of carbonyl enophiles.[6] On the basis of a steady-state treatment (see Supporting Information), eqs 1 and 2 may be derived, in which the terms are defined in Figure 4. The first

$$\frac{[\mathbf{AI}_H]}{[\mathbf{AI}_D]} = \left\{\frac{[\mathbf{P}_H]}{[\mathbf{P}_D]}\right\}_{cis} \times \frac{k_a(D)}{k_a(H)} \quad (1)$$

$$\frac{[\mathbf{AI}_H]}{[\mathbf{AI}_D]} = \frac{k_r + k_a(D)}{k_r + k_a(H)} \quad (2)$$

equation relates the quotient of the intermediates $\mathbf{AI}_H$ and $\mathbf{AI}_D$ to the product ratio $\{[\mathbf{P}_H]/[\mathbf{P}_D]\}_{cis}$, which constitutes the experimental kinetic isotope effect $[(k_H/k_D)_{cis} = 1.5$ (Table 1)] for the *cis*-TME-d_6 substrate, and the ratio of rate constants for hydrogen [k_a(H)] and deuterium [k_a(D)] abstractions. In the more complex eq 2, the same quotient $[\mathbf{AI}_H]/[\mathbf{AI}_D]$ provides the searched for information on the partitioning of these intermediates between reversal (k_r) and hydrogen [k_a(H)] versus deuterium [k_a(D)] abstractions. By equating both expressions, eq 3 is obtained from which the competition between reversal

$$\left\{\frac{[\mathbf{P}_H]}{[\mathbf{P}_D]}\right\}_{cis} \times \frac{k_a(D)}{k_a(H)} = \frac{k_r + k_a(D)}{k_r + k_a(H)} \quad (3)$$

(k_r) and abstraction (k_a) may be assessed, if the primary kinetic isotope effect [k_a(H)/k_a(D)] for the abstraction step (the product-forming second step) is known. This value is available from the *trans*-TME-d_6 substrate, for which the product ratio $\{[\mathbf{P}_H]/[\mathbf{P}_D]\}_{trans}$ is the experimental kinetic isotope effect $[(k_H/k_D)_{trans} = 3.0$ (Table 1)]. Since the steric kinetic isotope effect is negligible and β-secondary kinetic isotope effects do not apply in the first step for these substrates (same degree of deuteration at the allylic positions), the experimental kinetic isotope effect $(k_H/k_D)_{trans}$ represents the primary isotope effect for H versus D abstraction in the second product-forming step, i.e., $\{[\mathbf{P}_H]/[\mathbf{P}_D]\}_{trans} = k_a(H)/k_a(D) = 3.0$. It should be noted that the lack of steric and secondary isotope effects in the first step allows the rate constants for intermediate formation (k_f), reversal (k_r), and abstraction [k_a(H) and k_a(D)] to be considered the same for the *cis*-TME-d_6 and *trans*-TME-d_6 substrates, a necessary condition for the subsequent operation. Substitution for $k_a(H)/k_a(D)$ and for k_a(H) in eq 3 affords eq 4, in which now all terms are

$$\left\{\frac{[\mathbf{P}_H]}{[\mathbf{P}_D]}\right\}_{cis} \times \left\{\frac{[\mathbf{P}_D]}{[\mathbf{P}_H]}\right\}_{trans} = \frac{k_r + k_a(D)}{k_r + \left\{\frac{[\mathbf{P}_H]}{[\mathbf{P}_D]}\right\}_{trans} \times k_a(D)} \quad (4)$$

experimentally defined, to determine the relative k_r and k_a(D) values. For the experimental values $\{[\mathbf{P}_H]/[\mathbf{P}_D]\}_{cis} = 1.5$ and $\{[\mathbf{P}_H]/[\mathbf{P}_D]\}_{trans} = 3.0$ we obtain from eq 4 the simple relation $k_r = k_a(D) = {}^1/_3 k_a(H)$. Thus, whatever the absolute k_r and k_a values may be in the reaction with *cis*-TME-d_6, in relative terms, the $\mathbf{AI}_D$ intermediate reverts as much as it undergoes deuterium abstraction [$k_r = k_a(D)$], whereas the $\mathbf{AI}_H$ intermediate undergoes hydrogen abstraction three times more readily than it reverts [$k_r = {}^1/_3 k_a(H)$].

For the *trans*-TME-d_6 substrate, one intermediate, namely $\mathbf{AI}_{trans}$, partitions by hydrogen [k_a(H)] and by deuterium [k_a(D)] abstraction to the ene products (Figure 4) and, thus, two abstraction rate constants apply in the second step. Consequently, to assess the competition between reversal and abstraction, the average (k_a^{avg}) of k_a(H) and k_a(D) has been used for the *trans*-TME-d_6 substrate, which is $k_a^{avg} = [k_a(H) + k_a(D)]/2 = 2k_a(D)$. Since $k_r = k_a(D)$, it follows that $k_r = {}^1/_2 k_a^{avg}$ for *trans*-TME-d_6. Thus, for this substrate the intermediate $\mathbf{AI}_{trans}$ revert to the original olefin and the enophile half as much as it reacts to the ene products $\mathbf{P}_H$ and $\mathbf{P}_D$ (Figure 4).

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For the intermolecular competition between TME-d_0 and TME-d_{12} and the intramolecular competition for *gem*-TME-d_6, additionally secondary kinetic isotope effects may apply in the first and second reaction steps. Therefore, it is difficult to estimate the extent of reversibility for the respective **AI** intermediates as was done above for the *cis*-TME-d_6 substrate, but the extent of reversal should be in the same range.

Of mechanistic significance in regard to reversibility is the experimental fact that the k_H/k_D value for the intramolecular case of *cis*-TME-d_6 (1.5) is significantly smaller than that for the intermolecular case of the TME-d_0/TME-d_{12} pair (2.0). Evidently, secondary kinetic isotope effects participate in the product-forming second step in addition to the primary kinetic isotope effect. Of these, the α-secondary KIE is of no consequence since it runs in the same direction, whereas the β-secondary KIE exhibits contrary influences on the overall k_H/k_D values. Note that the carbon atom of the aziridine *N*-oxide intermediate, which bears the methyl group for hydrogen abstraction, must rehybridize from sp^3 to sp^2 and, thus, a *normal* β-secondary KIE must operate. Furthermore, also note that in the intramolecular *cis*-TME-d_6 case, for hydrogen abstraction in the second step always a CD_3 group is the neighbor, whereas for deuterium abstraction it is always a CH_3 group. In contrast, for the intermolecular pair TME-d_0/TME-d_{12}, a CH_3 group always is the neighbor for hydrogen abstraction in TME-d_0, but for deuterium abstraction in TME-d_{12} it is always a CD_3 group. For the *cis*-TME-d_6 case, different substituents (CH_3 versus CD_3) are involved, i.e., when a hydrogen atom is abstracted, a neighboring CD_3 hyperconjugates and vice versa. The overall KIE is given in eq 5, in which the subscript prim stands for the primary and the

$$\frac{k_H}{k_D}(cis\text{-TME-}d_6) \propto \left(\frac{k_{C-H}}{k_{C-D}}\right)_{prim} \times \left(\frac{k_{CD_3}}{k_{CH_3}}\right)_{\beta-sec} \quad (5)$$

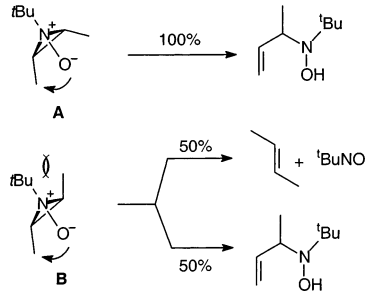
subscript β-sec for the secondary isotope effect. For the TME-d_0/TME-d_{12} case, the same substituents are involved, i.e., when H is abstracted, a CH_3 group hyperconjugates and vice versa; the overall KIE is given in eq 6. Since for the normal β-secondary KIE the ratio $k_{CH3}/k_{CD3} > 1$, it follows that the overall k_H/k_D(*cis*-TME-d_6) is smaller than k_H(TME-d_0)/k_D(TME-d_{12}), i.e., 1.5 versus 2.0. To observe, however, an overall k_H/k_D value experimentally, reversal of the three-membered-ring intermediate is necessary, since both KIE operate in the second step.

$$\frac{k_H(\text{TME-}d_0)}{k_D(\text{TME-}d_{12})} \propto \left(\frac{k_{C-H}}{k_{C-D}}\right)_{prim} \times \left(\frac{k_{CH_3}}{k_{CD_3}}\right)_{\beta-sec} \quad (6)$$

A similar difference in the overall k_H/k_D values is also displayed by the *trans*-TME-d_6 ($k_H/k_D = 3.0$) and *gem*-TME-d_6 ($k_H/k_D = 4.0$) substrate pair. In this case, however, the large primary kinetic isotope effect dominates in the product-forming second step, since there is a choice between hydrogen versus deuterium abstraction.

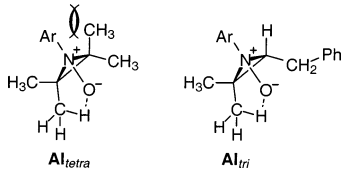
For additional support of reversibility, relevant work by Baldwin must be cited.[14] It was shown that heating

SCHEME 3. Steric Inhibition of Hydrogen Abstraction along the *skew* Trajectory in the Thermolysis of the Aziridine *N*-Oxides A and B



of authentic aziridine *N*-oxides (generated by oxidation of the corresponding aziridines with O_3 at −78 °C) above −30 °C resulted in ene products as well as fragmentation to the nitroso enophile and the alkene (Scheme 3). The latter was observed for the aziridine *N*-oxide **B**, in which the *skew* trajectory[5a] for hydrogen abstraction is sterically obstructed. As the oxygen atom of the *N*-oxide functionality in **B** aligns toward the allylic carbon atom for hydrogen abstraction, the *tert*-butyl group on the other side collides severely with the methyl substituent, such that hydrogen abstraction is encumbered and fragmentation into alkene and nitrosoalkane is promoted.[5a,b] This obstruction is absent in the aziridine *N*-oxide **A**, which leads exclusively to the ene product (Scheme 3).

Analogously, for the tetrasubstituted aziridine *N*-oxide intermediate $\mathbf{AI}_{tetra}$ derived from the nitrosoarene ene reaction with TME, such steric hindrance between the



aryl group and the allylic substituent results in a higher activation barrier for the second step and reversal is favored. This has been confirmed by the differences between the intermolecular competition of the tetrasubstituted substrates TME-d_0 and TME-d_{12} ($k_H/k_D = 1.98$, Table 1) versus the trisubstituted 3-methyl-1-phenyl-2-butenes **2**-d_0 and **2**-d_6 ($k_H/k_D = 1.18$, Figure 3). For the trisubstituted substrate, the kinetic isotope effect is much smaller than that for the tetrasubstituted TME. Clearly, in the case of the trisubstituted olefin, the hydrogen abstraction in $\mathbf{AI}_{tri}$ is sterically less hindered; thus, the activation barrier for the second step is smaller and reversal less likely. Nevertheless, some reversal also occurs, since the *skew* arrangement for hydrogen abstraction at the *twin* substituent is hindered, but this represents a minor pathway.[5a] In contrast, for the tetrasubstituted substrate, the barrier of the second step is increased through steric hindrance in the *skew* trajectory and, thus, reversal is more pronounced.

It remains to be considered whether the observed kinetic isotope effects may be rationalized in terms of rotational isomerization of an irreversibly formed diradical or zwitterionic intermediate, as has been mentioned already in the Introduction (Scheme 2).[4] For the *cis*-TME-d_6 and *trans*-TME-d_6 substrates, the k_H/k_D values should

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

be identical through isomerization of the acyclic intermediates by rotation about the C−N and C−C bonds. Hindered rotation around the C−N and C−C bonds in the acyclic zwitterionic or diradical intermediate, as displayed for the **DI** species (X = N and Y = O for ArNO) in Scheme 2, cannot explain the large $k_H/k_D = 1.98$ for the intermolecular competition between TME-d_0 and TME-d_{12} (Table 1). Here again, a β-secondary kinetic isotope effect needs to be considered, since it may apply in the first reaction step (the β-CD_3 group is less effective for hyperconjugation than CH_3).[13,15] For a zwitterionic or diradical intermediate, the sp^2 center is stabilized better by a CH_3 than a CD_3 group in the β position. Hence, for the partially bonded **DI** intermediate in Scheme 2 or an analogous zwitterionic species, a normal isotope effect of 5−15% per vicinal D (maximally about 90% for six D atoms) is possible.[16] However, also the change in hybridization from sp^2 to sp^3 for the newly formed C−N bond must be considered, which leads to an inverse kinetic isotope effect of ca. 10−20% for six D atoms.[10,11] Of these two opposing effects, the first (hyperconjugation) is expected to dominate and, thus, a normal isotope effect is expected ($k_H/k_D > 1$), but not as large as the observed value of 1.98. Moreover, it should be noted that for *cis*-TME-d_6 ($k_H/k_D = 1.5$), no β-secondary kinetic isotope effect is possible in the first step. Consequently, rotational isomerization of an irreversibly formed diradical or zwitterionic intermediate (Scheme 2) is unlikely for the observed kinetic isotope effects (Table 1), whereas reversible formation of a symmetrical aziridine *N*-oxide **AI** or of the corresponding unsymmetrical structure such as **DI** (Figure 4) provides a consistent mechanistic rationale for the present data.

Such reversible intermediate formation has been implied earlier for the $^1O_2$ and PTAD ene reactions with less nucleophilic, disubstituted substrates, namely the 2-butenes.[9] For example, the deuterium-labeled (*E*)-2-butene-d_3 displays a notable kinetic isotope effect for $^1O_2$ ($k_H/k_D = 1.25$) and PTAD ($k_H/k_D = 1.29$). It may be argued that these values are too small to provide definitive evidence for reversibility, but it should be kept in mind that $^1O_2$ displays generally small kinetic isotope effects (e.g., even for *trans*-TME-d_6 the k_H/k_D value is only 1.4)[17] and for PTAD a counteracting *inverse* secondary kinetic isotope effect[10,11] may play a role, which would mask the *normal* primary kinetic isotope effect in the product-forming second step. As in the *cis*-TME-d_6 case, for the (*E*)-2-butene-d_3 substrate, no isotopic H/D competition is possible once the three-membered-ring intermediate has been formed irreversibly. Thus, even the low k_H/k_D values for the ene reactions of (*E*)-2-butene-d_3 with $^1O_2$ and PTAD point to reversal of the respective three-membered-ring intermediates. Unfortunately, these k_H/k_D values for $^1O_2$ and PTAD cannot be compared directly with ArNO, because the latter enophile does not react with such disubstituted alkenes.

Alternatively, it may be argued that the kinetic isotope effects observed for the *trans*-configured CH_3 and CD_3 groups in (*E*)-2-butene-d_3 and *cis*-TME-d_6 and for the intermolecular competition in the TME-d_0/TME-d_{12} pair are due to the so-called *cis* effect,[18] in which the interaction of the enophile with the allylic hydrogen atoms of the alkene substrate stabilizes the first transition state.[19] Such an interaction weakens the C−H(D) bond, and the resulting decrease in the force constant lowers the zero-point energy, which is larger for the lighter H isotope and should give a normal isotope effect.[13] For ArNO, this rationale does not account for the experimental fact that the tetrasubstituted *cis*-TME-d_6 and the TME-d_0/d_{12} pair display such large k_H/k_D values (Table 1) compared to the trisubstituted **2**-d_0/d_6 pair (Figure 3). The reason for this is the enhanced reversibility for the ArNO enophile on account of increased steric hindrance in the *skew* geometry, as shown in the $\mathbf{AI}_{tetra}$ and $\mathbf{AI}_{tri}$ structures. Moreover, as discussed above, the difference in the kinetic isotope effect observed for *cis*-TME-d_6 (k_H/k_D 1.5) and TME-d_0/d_{12} (k_H/k_D 2.0) cannot be reconciled in terms of the *cis* effect, but relates to the secondary isotope effects in the product-forming second step through reversibility. In view of the mechanistic equivalence of the three enophiles ArNO, TAD, and $^1O_2$, we expect that reversible formation applies to all three-membered-ring intermediates; however, it depends on the substrate and the enophile whether reversibility may be experimentally detected by means of kinetic isotope effects.

From our present KIE results for the nitrosoarene ene reaction, we conclude that a stepwise mechanism with partial reversal of the intermediary aziridine *N*-oxide (or the related unsymmetrical structure **DI**) operates. The reversibility derives from a delicate balance of the activation barriers in the first and second steps of the ene reaction. This mechanistic feature is not unique for ArNO, but is also suspected to operate in the ene reaction of TAD and $^1O_2$. ArNO, due to its moderate reactivity and its steric demand, is the most sensitive enophile toward reversibility and, therefore, a very useful probe for the mechanistic elucidation of the subtleties of ene reactions.

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Supporting Information Available: Complete experimental procedures, the KIE data for F_5C_6NO, and the derivatives of eqs 1−4. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The small intermolecular KIE for the TME-d_0 and TME-d_{12} pair in the ene reaction with singlet oxygen [$k_H/k_D(^1O_2) = 1.1$, Table 1] was taken as evidence for reversible formation of the intermediates (ref 8).

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