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Isotope Effects and the Mechanism of Allylic Hydroxylation of Alkenes with Selenium Dioxide

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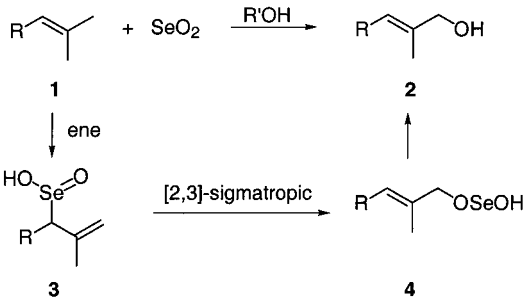
The mechanism of the allylic oxidation of 2-methyl-2-butene with selenium dioxide was explored by a combination of experimental and theoretical studies. A comparison of the experimental ^{13}C and ^{2}H kinetic isotope effects with predicted values shows that the observed isotope effects are consistent with an initial concerted ene step mediated by SeO_2. However, this comparison also does not rule out the involvement of a selenous ester in the ene reaction or a stepwise reaction involving reversible electrophilic addition of $HSeO_2^+$ followed by rate-limiting proton abstraction. Becke3LYP calculations strongly favor SeO_2 over a selenous ester as the active oxidant, with the predicted barrier for reaction of 2-methyl-2-butene with SeO_2 being 21−24 kcal/mol lower than that for reaction with H_2SeO_3. The possibility of a selenous ester being the active oxidant is also disfavored by the observation of oxidations in non-hydroxylic solvents. The involvement of $HSeO_2^+$ does not appear consistent with a lack of dependence of the reaction on the basicity of the reaction mixture. A concerted ene reaction with SeO_2 as the active oxidant appears to be the major mechanistic pathway operative in these reactions.

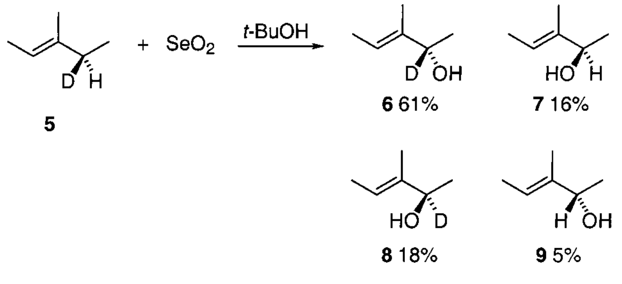
Introduction

Selenium dioxide mediates the unique allylic oxidation of alkenes with usual retention of position of the double bond.[1] The mechanism of this reaction baffled workers for many years until Sharpless and Lauer in 1972 were able to explain the selective oxidation as resulting from an initial ene reaction followed by a [2,3] sigmatropic shift that returns the double bond to its original location (Scheme 1).[2] With allowance for the possibility of conversion of either the product **2** or selenous ester **4** to more highly oxidized materials and ionization under some conditions of the intermediates **3** and **4**,[1a,3,4] this overall mechanism explains most of the diverse observations in the literature. However, some substantial mysteries remain regarding the first step in this mechanism.

Scheme 1



Although ene reactions are allowed pericyclic processes, many have been shown to occur by complex mechanisms. This includes ene reactions of singlet oxygen,[5] triazolinediones,[6] nitroso compounds,[7] acylium ions,[8] and Lewis acid-catalyzed ene reactions.[9] Allylic oxidations with selenium dioxide exhibit a significant primary deuterium kinetic isotope effect (KIE),[4,10] and this is usually considered indicative of a concerted ene reaction. However a primary KIE is also consistent with a reversible step followed by rate-limiting proton transfer, as has been recently established in Lewis acid-catalyzed ene reactions.[9] In an elegant experiment Stephenson and Speth found that the reaction of the optically active deuterated alkene **5** afforded the stereochemical "crossover" products **8** and **9** in addition to the expected products **6** and **7**. The crossover products are inconsistent with sequential concerted ene and [2,3]-sigmatropic steps. However, a stepwise ene mechanism could not simultaneously account for the observed primary KIE and the absence of isomerization of the starting alkene, and it was proposed that a mixture of concerted and stepwise ene mechanisms was operative.



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[1] (a) Wiberg, K. B.; Nielsen, S. D. *J. Org. Chem.* **1964**, *29*, 3353. (b) Dupont, G.; Zacharewicz, W. *Bull. Soc. Chim. Fr.* **1935**, *2*, 533. (c) Guillemonat, A. *Ann. Chem. (Warsaw)* **1939**, *11*, 143.

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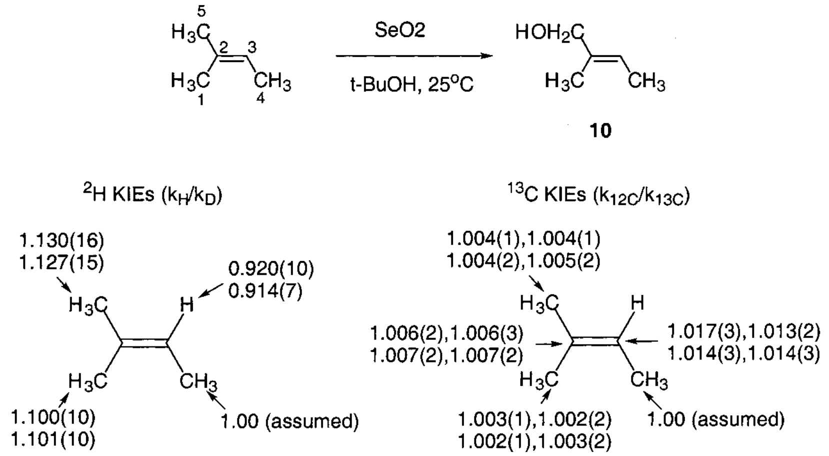
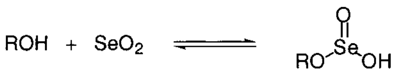


Figure 1. KIEs for the oxidation reaction of 2-methyl-2-butene with selenium dioxide.

A second unknown in these reactions is the nature of the active selenium oxidant. Selenium dioxide is hydrated by water to selenous acid with no detectable free selenium dioxide present at equilibrium,[11] and the analogous addition of the solvent alcohols or carboxylic acids used in these reactions is expected. However, the dehydration of selenous acid occurs readily so the formation of selenous esters in alcohols is likely reversible. Thus molecular selenium dioxide could still be the active oxidant if present in small amounts at equilibrium.



$$ROH + SeO_2 \rightleftharpoons RO-Se(=O)-OH$$

We describe here a combined experimental and theoretical study of selenium dioxide-mediated allylic oxidations. The results clarify the mechanism of the ene step and the identity of the actual selenium reactant, providing a detailed understanding of these reactions.

Results and Discussion

Isotope Effects. Our initial aim was to characterize the nature of the rate-limiting step in these reactions by determining ^{13}C and secondary deuterium isotope effects in addition to the usual primary deuterium effect. Toward that end, a complete set of ^{13}C and ^{2}H KIEs for the reaction of SeO_2 with 2-methyl-2-butene was determined combinatorially at natural abundance by our NMR methodology.[12] Reactions of 2-methyl-2-butene on a ≈1-mol scale with limiting SeO_2 were carried out in *tert*-butyl alcohol at 25 °C and were taken to 82(±3)% and 84(±2)% conversion. Under these conditions the initial product alcohol **10** is partially converted to more highly oxidized products—this should not affect the isotope effects determined from recovered starting material.[12] The unreacted 2-methyl-2-butene was recovered after an aqueous workup by fractional distillation. The resulting material was analyzed by ^{13}C and ^{2}H NMR compared to a standard sample of the original 2-methyl-2-butene. The changes in ^{13}C and ^{2}H isotopic composition were calculated by using the C4 methyl group as "internal standard" with the assumption that its isotopic composition does not change during the reaction.[13] From the changes in isotopic composition, the isotope effects were calculated as previously described.[12] The results from duplicate determinations of the ^{2}H KIEs (two independent reactions) and quadruplicate determinations of the ^{13}C KIEs (two independent reactions with two NMR samples for each run under slightly different conditions) are summarized in Figure 1 (see also Table 2).

Table 1. Comparison of Predicted and Experimental Isotope Effects ($^{12}C/^{13}C$ or H/D, 25 °C)[a]

	15−18						
	A[b]	B[c]	**19**	**20**	**21**[d]	**22**[d]	experimental
C1	1.003	1.004	1.000	0.998	1.002	1.001	1.002−1.003
C2	1.005	1.005	1.003	1.039	1.002	1.004	1.006−1.007
C3	1.015	1.015	1.015	1.028	1.008	1.014	1.013−1.017
C5	1.007	1.006	1.011	0.996	1.000	1.001	1.004−1.005
H_{vinyl}	0.956	0.953	0.982	0.988	0.994	0.944	0.914−0.920

[a] For comparison with the experimental values, the calculated KIEs given here are relative to ^{13}C and ^{2}H KIEs for the C4 methyl group of 1.000. [b] Weighted average based on a Boltzmann distribution of **15−18** using the Becke3LYP/6-311+G**//Becke3LYP/6-311+G** + ZPE energies. [c] Weighted average based on a 56:44 weighting of **15** and **17**. [d] Predicted equilibrium isotope effects for the formation of the intermediate.

A complication in interpreting the C1 and C5 methyl group ^{2}H KIEs when measured in this way is that they represent a combination of primary and secondary isotope effects for reaction of the monodeuterio alkene isotopomers **11** or **12** compared to the perprotio isotopomer **13.** The results also depend on the relative reactivity of the C5 and C1 methyl groups. If we define the relative reactivities of the C5 and C1 methyl groups as r: $(1 - r)$, the symmetry adjusted rate of reaction of **13** would then be $(r \times 3) + ((1 - r) \times 3)$, while the rate of reaction of **11** would be $(r \times 2)/KIE_{2°} + r/KIE_{1°} + ((1 - r) \times 3)/KIE_{2°'}$ and the rate of reaction of **12** would be $(r \times 3)/KIE_{2°'} + ((1 - r) \times 2)/KIE_{2°} + (1 - r)/KIE_{1°}$. ($KIE_{1°}$ is the primary isotope effect for abstraction of a proton versus a deuterium, while $KIE_{2°}$ and $KIE_{2°'}$ are secondary isotope effects when abstracting a proton, and the deuterium is either on the reactive carbon or in the other methyl group.) On the drastic assumptions that the secondary

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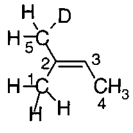
(13) Because of this assumption, the resulting KIEs are "relative" to the ^{13}C and ^{2}H isotope effects for the C4 methyl group. Small isotope effects in the C4 methyl group would not effect the qualitative interpretation of the KIEs. The theoretical calculations predict ^{13}C and ^{2}H isotope effects at C4 of ≈0.998 and ≈0.985, respectively, and quantitative comparisons of theoretical and experimental isotope effects were corrected for the C4 isotope effects.

isotope effects are negligible and KIE_{1° is the same for reaction at C1 and C5, the observed C5 and C1 isotope effects provide two equations in two unknowns with the solution $\mathrm{KIE}_{1^\circ} = 2.62$ and $r = 0.56$. A 56:44 relative reactivity for trans and cis methyl groups is very reasonable, being between the previously concluded values of 1:1[10] and 7:3.[14] The large primary isotope effect suggested by this analysis is in line with previous studies[4,10] and is consistent with a rate-limiting hydrogen transfer.



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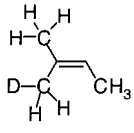

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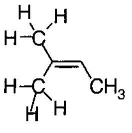

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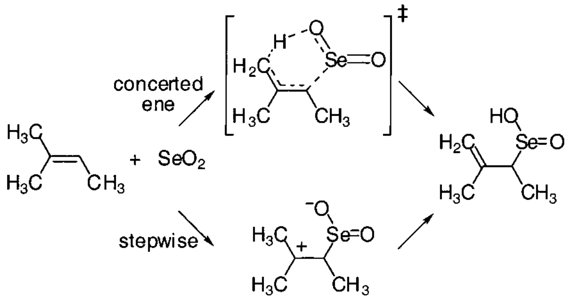
Qualitatively the ^{2}H KIE at C3 is indicative of rehybridization of C3 in the rate-limiting transition state, while the significant C3 ^{13}C KIE is characteristic of this carbon undergoing a substantial bonding change at the transition state. These two results are quite consistent with a rate-limiting concerted ene step as in the Sharpless/Lauer mechanism. However, there are some puzzling observations in the other isotope effects. The ^{13}C KIEs at C1 and C5 of 1.002–1.005 are surprisingly small for carbons undergoing a hydrogen abstraction, though it must be recognized that the observed KIEs for each carbon would reflect a weighted average of a primary ^{13}C KIE for abstraction and a negligible secondary ^{13}C KIE when the other methyl group reacts. The C2 KIE at 1.006–1.007, on the other hand, is slightly larger than might have been expected for an ene step, as the bonding change at this carbon is minor. For comparison, in the ene reaction of allylbenzene with maleic anhydride the ^{13}C KIE at the analogous carbon is 1.003.



14

An alternative mechanism is an electrophilic attack of SeO_2 on the alkene to form the intermediate zwitterion **14.** The intermediacy of a zwitterion of this type or a protonated analogue was proposed by Stephenson to account for the stereochemical crossover products formed from **5**.[10] Rate-limiting formation of the zwitterion would account for the ^{2}H and ^{13}C KIEs at C2 but would not explain the observation of substantial primary ^{2}H KIEs. A better alternative is reversible formation of the zwitterion followed by rate-limiting proton transfer. This would be consistent with the primary ^{2}H KIEs at C1 and C5, but would offer no advantage over the concerted mechanism in explaining the C1, C2, and C5 ^{13}C KIEs. Overall, the isotope effects do not qualitatively distinguish between concerted and stepwise mechanisms. A more quantitative interpretation of the isotope effects was therefore pursued using theoretical calculations.

Calculated Structures. Transition structures for the ene reaction of 2-methyl-2- butene with SeO_2 or selenous acid (H_2SeO_3) were located in Becke3LYP calculations using a 6-311+G** basis set for selenium and 6-31G* for all other atoms. For the calculation of isotope effects *(*vide infra*)* the SeO_2 transition structures were also optimized using a 6-311+G** basis set on all atoms. A total of four structures were found with SeO_2 (**15**–**18**, Figure 2), depending on the direction of orientation of the unreactive oxygen and whether the hydrogen is abstracted from the Cl or C5 methyl group. For the reaction with selenous acid, only the abstraction from the C5 methyl group was studied, and four transition structures were located. (The lowest-energy structure was **19**, and the others are given in Supporting Information.) Transition structures for the [2 + 2] cycloaddition (**20**) and for the formation of an episelenone (Supporting Information) were also located. The formation of an episelenone was predicted to be 47.1 kcal/mol above the starting materials, and it was not considered further.

The activation energies for the SeO_2 transition structures **15**–**18** (including ZPE, calculated versus alkene + SeO_2) are predicted to be ≈21–24 kcal/mol below the best selenous acid transition structure **19** (calculated versus alkene + H_2SeO_3). However this difference is complicated by the greater stability of the selenous acid—in water the SeO_2 is hydrated,[11] and reaction via SeO_2 would require an initial uphill dissociation of the H_2SeO_3. Estimating ΔG as $\Delta E - T\Delta S$ where the ΔE and ΔS are taken from the gas-phase calculations, formation of the selenous acid is exergonic by 3.1 kcal/mol at 25 °C. In 55 M water, $[H_2SeO_3]/[SeO_2]$ would be ≈10500. Under our typical synthetic conditions in *tert*-butyl alcohol, the preference for the *tert*-butyl selenous ester (t-$BuOSeO_2H$) over SeO_2 + *tert*-butyl alcohol is decreased—estimating ΔG in the same way the formation of the *tert*-butyl selenous ester is endergonic by 1.4 kcal/mol. In support of this prediction, SeO_2 is highly soluble in water but is only sparingly soluble in *tert*-butyl alcohol. In 10.5 M *tert*-butyl alcohol, $[t\text{-}BuOSeO_2H]/[SeO_2]$ would be ≈1. It should be noted that the predicted relative energy of SeO_2 versus H_2SeO_3 or t-$BuOSeO_2H$ could easily be off by a few kcal/mol, corresponding to errors in the predicted equilibrium constants above of orders of magnitude. However, this does not affect the conclusion that molecular SeO_2 should be accessible in alcoholic solution. One other calculational prediction is relevant to the question of SeO_2 versus selenous ester mediated mechanisms—the ene reaction with SeO_2 is predicted to be exothermic by 6.0 kcal/mol while the ene reaction of H_2SeO_3 is *uphill* by 14.7 kcal/mol. Overall, the calculational results strongly favor SeO_2 over a selenous ester (such as t-$BuOSeO_2H$) as the actual oxidant in the reaction.

The possibility of an initial [2 + 2] cycloaddition had been previously proposed.[15] The calculations predict that the [2 + 2] cycloaddition of neutral SeO_2 via transition structure **20** would be disfavored by 16.6 kcal/mol compared to the best direct ene transition structure. A [2 + 2] cycloaddition with a protonated $HSeO_2^+$ as the addend was assumed in the previous proposal. With H_2SO_4

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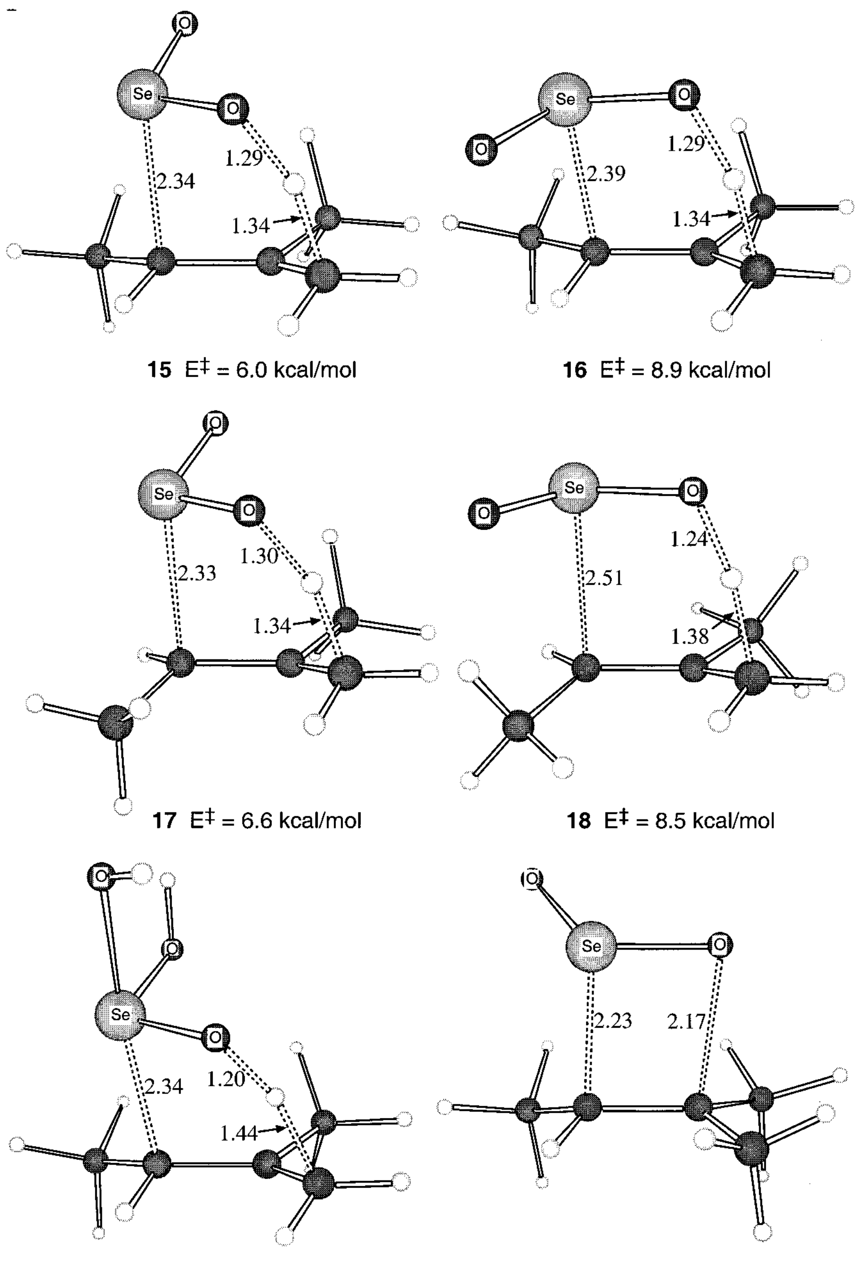
[14] Woggon, W.-D.; Ruther, F.; Egli, H. *J. Chem. Soc., Chem. Commun.* **1980**, 706.

[15] Trachtenberg, E. N.; Nelson, C. H.; Carver, J. R. *J. Org. Chem.* **1970**, *35*, 1653.



15 E‡ = 6.0 kcal/mol **16** E‡ = 8.9 kcal/mol

17 E‡ = 6.6 kcal/mol **18** E‡ = 8.5 kcal/mol

19 E‡ = 29.8 kcal/mol **20** E‡ = 22.6 kcal/mol

Figure 2. Transition structures and energies (Becke3LYP + ZPE, versus starting materials) for the reaction of 2-methyl-2-butene with SeO_2 or H_2SeO_3.

present, this protonation may be facile, but such conditions result in addition products instead of the normal allylic oxidation.[16] We were unable to locate a transition structure for a [2 + 2] cycloaddition with $HSeO_2^+$.

Several attempts to locate the possible zwitterionic intermediate **14** in gas-phase calculations failed, unsurprisingly. Another attempt to locate **14** used an Onsager solvent model[17] assuming a solute radius of 3.5 Å and the dielectric constant ($\epsilon = 78.38$, to maximally stabilize the zwitterion.) This also failed, with the zwitterionic species spontaneously reverting to starting materials. However, we were able to locate **14** using four explicit water molecules to stabilize the zwitterionic species by hydrogen bonding to the anionic oxygens as in **21.** This solvated zwitterion was optimized in Becke3LYP calculations with a 6-311+G* basis set on Se and a 6-31+G** basis set for the other atoms. The resulting structure has the formal bonding pattern of a zwitterion, but the C−Se bond is very long (2.60 Å) and only 0.27 e^- is transferred from the alkene to the SeO_2 in a natural orbital charge analysis. The alkene appears to retain substantial double bond character with a C_2−C_3 distance of 1.38 Å. Because of this, the barrier for rotation about the original C=C in intermediate **21** would be expected to be considerable. This makes it unlikely that the zwitterion could account for the stereochemical crossover products observed by Stephenson with **5.**[10] It should be noted that the limited viability of the zwitterion in water would be exacerbated in the decreased polarity of *tert*-butyl alcohol ($\epsilon = 10.9$)

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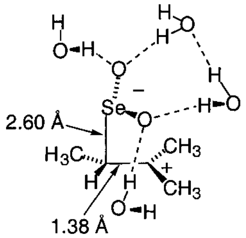
(16) Javaid, K. A.; Sonoda, N.; Tsutsumi, S. *Tetrahedron Lett.* **1969**, 4439.

(17) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 4776.

or nonpolar benzene ($\epsilon = 2.28$).



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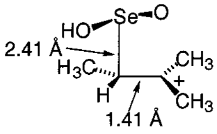

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The alternative possible structure suggested by Stephenson to explain stereochemical crossover is the cation **22,** as might be formed by an electrophilic attack of $HSeO_2^+$ on the alkene. As with **21**, **22** has a long C−Se distance [2.41 Å versus 2.33 Å for the transition state **17** and 2.05 Å for the ene product (see Supporting Information for the full structure of **21**, **22**, and the ene product)], and it appears to retain a significant portion of the double bond character with a C_2-C_3 distance of 1.41 Å.

Calculated versus Experimental Isotope Effects. The comparison of experimental and calculated KIEs has been found to provide a sensitive measure of the transition state geometry and the accuracy of calculated transition structures. Toward that end, KIEs were predicted for each of the transition structures **15**−**20** by the method of Bigeleisen and Mayer[18] from the scaled theoretical vibrational frequencies,[19] and tunneling corrections were applied using semiclassical Wigner correction.[20,21] In addition, equilibrium isotope effects were predicted for the formation of **21** and **22.** Table 1 shows weighted-average KIE predictions for **15**−**18,** weighting in two different ways. One weighting is based on a Boltzmann distribution using the Becke3LYP/6-311+G**//Becke3LYP/6-311+G** + ZPE energies. Because this weighting is sensitive to small changes in the relative energies of 15−**18** (beyond the reliable accuracy of the calculations), we also calculated a 56:44 weighting of the two best stereoisomeric transition structures **15** and **17** based on the relative reactivity for trans and cis methyl groups arrived at above. (The predicted KIEs for the individual transition structures for each calculation are shown in Supporting Information.)

The agreement of the experimental ^{13}C KIEs with the calculated values based on the SeO_2 transition structures **15**−**18** is excellent—most of the calculated KIEs with either weighting method are within the uncertainty range of the experimental values and the difference between calculated and experimental values never exceeds 0.003. The predicted ^2H KIE for the vinylic position agrees less well with the experimental value. However, predictions for ^2H KIEs have often been less accurate and the heavy-atom KIE predictions are more reliabl.[22] Altogether, the comparison of experimental KIEs and those predicted for **15**−**18** would appear to support the accuracy of the SeO_2 transition structures.

However, the isotope effect data for this reaction does not by itself exclude two other possible mechanisms. For reaction via a selenous ester, the H_2SeO_3 transition structure **19** leads to predicted KIEs that are also in reasonable agreement with experiment. Although the predicted KIEs based on **19** are not as good as those based on **15**−**18**, allowance for the KIEs for the eight possible H_2SeO_3 transition structures (only four of which were calculated) would be likely to improve the agreement with experiment. The intermediacy of **22** also appears consistent with the observed KIEs. If the cation **22** were formed in a rapid equilibrium followed by rate-limiting proton transfer to form the ene product, the observed kinetic isotope effects at the C3, C2, and H_{vinyl} nonreacting positions might be expected to resemble the equilibrium isotope effects for formation of **22.** The predicted isotope effects at C3, C2, and H_{vinyl} for **22** agree very reasonably with the experimentally observed KIEs.

The results here do exclude a rate-limiting [2 + 2] cycloaddition as in **20**, as the isotope effects predicted for this process diverge greatly from the experimental values. The argument against **21** is weakened by the fact that we are comparing predicted equilibrium isotope effects with observed kinetic isotope effects. However, in contrast with observations for a very similar intermediate proposed for Lewis acid-catalyzed ene reactions,[9] the results here notably provide no support for the zwitterionic intermediate.

Resolution of the Mechanism. The comparison of predicted and experimental KIEs leaves open multiple possible mechanisms, and we consider here other observations that bear on the possibilities.

The calculational results strongly disfavor a selenous ester (such as *t*-$BuOSeO_2H$) as the active oxidant. This is based on the 21−24 kcal/mol lower predicted barrier for reaction of SeO_2 as well as the predicted endothermicity of the H_2SeO_3 ene reaction by 14.7 kcal/mol. The calculational results are backed up by the experimental observation that the reaction of 2-methyl-2-butene with SeO_2 proceeds in benzene. This reaction is slow, probably due to the low solubility of SeO_2 in benzene, but a reaction of SeO_2 with excess 2-methyl-2-butene at 25 °C produced 43% of **10** in 1 day. SeO_2 allylic oxidations have also been carried out in neat pyridine.[10] It is difficult to exclude as a possibility the mediation of these reactions by trace amounts of water. However, H_2SeO_3 ($pK_a = 2.46$) would be largely deprotonated in pyridine and $HSeO_3^-$ is unlikely to be electrophilic. On the whole, the calculational and experimental results would appear to exclude a selenous ester or H_2SeO_3 as the reactive species in these reactions.

The formation of the cation **22** by electrophilic attack of $HSeO_2^+$ requires an initial protonation of SeO_2. The pK_a of $HSeO_2^+$ is unknown but it seems highly unlikely that SeO_2 can deprotonate *tert*-butyl alcohol. However, selenous half esters (such as *t*-$BuOSeO_2H$ in *tert*-butyl alcohol) would likely be present under any reaction conditions and could serve as an acid catalyst. The observation that the reactions can be carried out in the

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[19] The calculations used the program QUIVER (Saunders, M.; Laidig, K. E.; Wolfsberg, M. *J. Am. Chem. Soc.* **1989**, *111*, 8989) with Becke3LYP frequencies scaled by 0.9614. (Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502).

[20] Wigner, E. P. *Z. Phys. Chem.* **1932**, *B19*, 203.

[21] In previous papers we have used a one-dimensional infinite parabolic barrier model for the tunneling correction (Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman & Hall: London, 1980; pp 60−63) but this model becomes qualitatively incorrect when the transition structure imaginary frequency is large, as is the case for the ene transition structures here and for most hydrogen-transfer reactions. The two models make similar predictions in other reactions.

[22] Meyer, M. P.; DelMonte, A. J.; Singleton, D. A. *J. Am. Chem. Soc.* **1999**, *121*, 10865.

presence of pyridine or in pyridine solvent argues against such acid catalysis. Nonetheless, it might be argued that pyridine is not basic enough and that pyridinium ions ($pK_a = 5.25$) could serve as the acid catalyst. To minimize the possibility of acid catalysis, we explored the allylic oxidation in the presence of the more strongly basic Proton-Sponge (1,8-bis(dimethylamino)naphthalene, **23**). The **23** reacts with SeO_2 as it dissolves in *tert*-butyl alcohol. This is apparently by formation of $t\text{-BuOSeO}_2^-$ $\mathbf{23}\cdot H^+$ because the **23** disappears from solution but is recovered unchanged after treatment with base. Addition of 13 mol % **23** to an allylic oxidation resulted in an induction period as the SeO_2 dissolved, but then the reaction proceeded at approximately the same rate as in the absence of **23** (based on periodic NMR observations of the % conversion in aliquots taken from similar reactions). The lack of a significant decrease in rate in the presence of the basifying $t\text{-BuOSeO}_2^-$ $\mathbf{23}\cdot H^+$ is evidence against a specific acid-catalyzed reaction via $HSeO_2^+$.[23]

Conclusion

While the comparison of predicted and experimental KIEs has been used effectively to distinguish between mechanistic possibilities in other reactions, it is a dull tool in allylic oxidations with selenium dioxide. There is a close correspondence of the experimental KIEs with those predicted for the concerted ene reaction of SeO_2 with 2-methyl-2-butene, but the observed KIEs could also be consistent with an ene reaction of a selenous ester or with reversible electrophilic attack by $HSeO_2^+$ followed by rate-limiting proton transfer in the zwitterion. Luckily the latter two mechanisms appear to be excludable based on other factors. Calculational results strongly disfavor a selenous ester being the active oxidant, and this is supported by the observation that a hydroxylic solvent is unnecessary for these reactions. The involvement of $HSeO_2^+$ does not appear consistent with a lack of dependence of the reaction on the basicity of the reaction mixture.

Because the isotope effects observed in a reaction reflect a weighted average of the operative mechanistic pathways, we cannot exclude the presence of a minor mechanistic pathway involving a stepwise ene reaction, as would account for the crossover products observed by Stephenson.[24] Overall, however, a concerted ene reaction with SeO_2 as the active oxidant would appear to be the major mechanistic pathway operative in these reactions.

Table 2. Average ^{13}C and ^{2}H Integrations and R/R_0's for Allylic Hydroxylations

^{13}C Results

	C1	C2	C3	C4	C5
exp la[a]	1030.47	1019.39	1101.29	1000.0	1067.03
standard	1025.16	1008.24	1070.39	1000.0	1060.50
R/R_0	1.005	1.011	1.029		1.006
$\Delta R/R_0$	0.002	0.004	0.004		0.001
exp 2a[a]	1029.24	1018.63	1095.48	1000.0	1067.42
standard	1025.16	1008.24	1070.39	1000.0	1060.50
R/R_0	1.004	1.010	1.023		1.007
$\Delta R/R_0$	0.003	0.006	0.004		0.002
exp 1b[b]	1019.57	1009.65	1076.91	1000.0	1043.99
standard	1016.31	997.758	1052.53	1000.0	1037.68
R/R_0	1.003	1.012	1.023		1.006
$\Delta R/R_0$	0.002	0.004	0.005		0.003
exp 2b[b]	1021.41	1010.65	1079.9	1000.0	1046.25
standard	1016.31	997.758	1052.53	1000.0	1037.68
R/R_0	1.005	1.013	1.026		1.008
$\Delta R/R_0$	0.004	0.004	0.004		0.004

^{2}H Results

	H_{vinyl}	$C1H_2D$	$C4H_2D$	$C5H_2D$
exp 1	1096.59	3455.32	3000.0	3614.46
standard	1272.7	2955.1	3000.0	2966.65
R/R_0	0.862	1.169		1.218
$\Delta R/R_0$	0.017	0.025		0.015
exp 2	1068.14	3504.58	3000.0	3655.09
standard	1272.7	2955.1	3000.0	2966.65
R/R_0	0.839	1.186		1.232
$\Delta R/R_0$	0.013	0.026		0.016

[a] Data collected using 175 s delays and an acquisition time of 7.999 s collecting 287232 points. [b] Data collected using 150 s delays and an acquisition time of 5.501 s collecting 220032 points.

Experimental Section

Theoretical Calculations. All calculated structures were obtained using Gaussian 98.[25] Vibrational frequency analyses were carried out on all stationary points, and all transition structures exhibited one imaginary frequency.

Allylic Hydroxylations. As an example procedure, a mixture of 104.3 g (1.49 mol) of 2-methyl-2-butene, 92.3 g (0.832 mol) of selenium dioxide, and 9.42 g (0.12 mol) of benzene (used as NMR internal standard) in 580 mL of *tert*-butyl alcohol was stirred for 24 h at 25 °C. By NMR analysis of an aliquot the reaction was found to be 82 ± 3% complete. The reaction was quenched by addition of 2500 mL of ice−water, and the resulting mixture was extracted with three 250-mL portions of toluene. The combined organic layers were dried over $MgSO_4$ and distilled using a 30 cm Vigreaux column until the head temperature reached 80 °C. The distillate was then redistilled fractionally to afford 12.4 g of the unreacted 2-methyl-2-butene in >99% purity by GC analysis. An analogous reaction using 94.6 g of 2-methyl-2-butene was taken to 84 ± 2% conversion, and 10.8 g of unreacted 2-methyl-2-butene was recovered.

NMR Measurements. NMR measurements were taken on neat samples of 2- methyl-2-butene in 10 mm NMR tubes filled to a constant height of 5 cm. A T1 determination by the inversion−recovery method was carried out for each NMR

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(23) A general acid-catalyzed ene reaction involving a concerted SeO_2 protonation/ene reaction is not excluded by the observations here. However, such reactions are only expected when the proton transfer becomes significantly exothermic as the reaction proceeds. (Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 4731.) This is unlikely as the intermediate seleninic acid **22** should be highly acidic. [The pK_a's of other seleninic acids are around 4.5 (McCullough, J. D.; Gould, E. S. *J. Am. Chem. Soc.* **1949**, *71*, 674) and **22** would be made more acidic by the carbocation substituent.]

(24) Theoretical structures **21** and **22** suggest that rotation about the C2−C3 bond would not be facile in intermediates for the stepwise ene reaction, and this makes these intermediates a less attractive explanation of Stephenson's crossover products than when originally proposed. It should be noted that a small amount of racemization by ionization of the initial selenous ester product (e.g., **4**) could account for the observation of crossover products if 1,3-allylic transposition of the selenous ester is slow. (See: Gassman, P. G.; Singleton, D. A.; Kagechika, H. *J. Am. Chem. Soc.* **1991**, *113*, 6271.)

(25) 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.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98, Revision A. 6*; Gaussian, Inc.: Pittsburgh, PA, 1998.

sample, and the T1 for each NMR signal remained constant within experimental error from sample to sample.

The ^{13}C spectra were recorded at 100.58 MHz with inverse gated decoupling. One set of spectra was collected using 150 s delays between calibrated 45° pulses and an acquisition time of 5.501 s collecting 220032 points, and a second set of spectra for each sample was collected using 175 s delays between calibrated 45° pulses and an acquisition time of 7.999 s collecting 287232 points. The ^{2}H spectra were recorded at 61.395 MHz with calibrated 45° pulse widths, using an acquisition time of 17.066 s collecting 16384 points. Integrations were determined numerically using a constant region for each peak that was ≈5 times the peak width at half-height on either side of the peak, and using only a zeroth order baseline correction.

Results for All Reactions. The relative integration of the C4 methyl group was set to 1000 for ^{13}C spectra and 3000 for ^{2}H spectra. The average integrations for the other carbons or deuteriums for each reaction are shown in Table 2, along with the standard results for the starting materials. In each case the averages are based on six spectra. Table 2 also shows the relative isotopic enhancements (R/R_0), calculated as the ratio of integrations for the recovered versus standard materials. The standard deviations ($\Delta R/R_0$) were calculated from eq 1, where IntSample is the average integration for each sample peak (listed in the table), IntStandard is the average integration for the corresponding peak in the standard (listed in the table), and ΔIntSample and ΔIntStandard are the standard deviations in the sample and standard peaks, respectively. From the R/R_0's, $\Delta R/R_0$'s, and uncertainties in the % conversion, the KIEs and errors were calculated as previously described.[12]

$$\Delta R/R_0 = R/R_0{*}\,((\Delta \mathrm{IntSample}/\mathrm{IntSample})^2 + (\Delta \mathrm{lntStandard}/\mathrm{IntStandard})^2)^{1/2} \quad (1)$$

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Supporting Information Available: Energies and full geometries of all calculated structures and isotope effect predictions for structures **15**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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