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Isotope effects and the experimental transition state for a prototypical thermal ene reaction

Daniel A. Singleton * and Chao Hang

Department of Chemistry, Texas A&M University, College Station, Texas 77843-3255, USA

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Abstract

A complete set of ^{2}H and ^{13}C kinetic isotope effects was determined for the ene reaction of allylbenzene with maleic anhydride. Both bond formation to C_1 and hydrogen transfer are implicated by the isotope effects for the rate-limiting step, and a concerted pericyclic transition state is concluded. The observed isotope effects correspond well with those predicted from Becke3LYP transition structures. These structures provide a good model for the steric interactions previously concluded to control selectivity in similar reactions. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: ene reactions; isotope effects; transition states; mechanism.

Ene reactions are additions of electrophilic double or triple bonds (enophiles) to alkenes with concomitant transfer of an allylic hydrogen (Eq. 1). Although ene reactions are allowed pericyclic processes, many have often been shown to involve multi-step mechanisms. This includes ene reactions of singlet oxygen,[1] nitroso compounds,[2] selenium dioxide,[3] triazolinediones,[4] and Lewis acid-catalyzed ene reactions.[5] In the absence of a Lewis acid, carbonyl and olefinic enophiles are considered most likely to undergo the concerted pericyclic mechanism. These reactions lack the complications seen with more reactive enophiles, such as the absence of a primary deuterium isotope effect or the trapping of intermediates. However, complex mechanisms have been suggested for even very simple ene reactions.[6] Numerous theoretical studies have found concerted transition structures for simple ene reactions,[7,8] and these structures have been used to design transition state analogs to obtain catalytic antibodies.[8b] However, few of these studies involve synthetically feasible reactions, and experimental evidence on the transition state geometry has been lacking.

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* Corresponding author. Tel: 409-845-9166; fax: 409-845-9452; e-mail: singleton@mail.chem.tamu.edu

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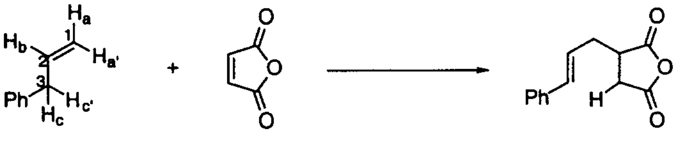
Recent studies have demonstrated that the comparison of a large set of high-precision experimental kinetic isotope effects (KIEs) with high-level transition structure/KIE calculations is a powerful tool for defining the mechanism and transition state geometry of organic reactions.[9] Here we apply this methodology to a prototypical uncatalyzed ene reaction of an olefinic enophile. The results establish a detailed experimental basis for the geometry of a concerted pericyclic transition state, and provide insight into the stereochemistry and selectivity of thermal ene reactions.

Isotope effects for the ene reaction of maleic anhydride with allylbenzene were determined at 175°C in the presence of BHT by previously reported methodology for the combinatorial measurement of isotope effects at natural abundance.[10] Under these conditions the ene product **1** is formed in >95% selectivity at low conversions (Scheme 1). At high conversions a small amount of decomposition of **1** occurs, but such product reactions should not impact the isotope effects measured by the methodology used.[10] Reactions of allylbenzene with limiting maleic anhydride were taken to 72±3% and 73±3% conversion, and the unreacted allylbenzene was recovered by vacuum distillation followed by fractional distillation. Analysis of the ^{13}C and ^{2}H composition of the recovered allylbenzene versus the original material was carried out by NMR using the *ortho* aromatic deuterium peak and the *para* aromatic carbon peak as internal standards, with the assumption that the isotopic composition does not change in composition. From the changes in isotopic composition the isotope effects were calculated as previously described.[10]



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Scheme 1.

The results are summarized in Table 1. The combination of the small but significant ^{13}C isotope effects at C_1 with the inverse deuterium KIE for $H_a/H_{a'}$ is indicative of bond formation to C_1 in the rate-limiting transition state. The $H_a/H_{a'}$ KIE of ≈0.97 is modest compared to a 'maximum' inverse isotope effect for bond formation to C_1 of ≈0.84.[11] This suggests an early transition state. The interpretation of the deuterium isotope effect at $H_c/H_{c'}$ is complicated by the nature of the natural-abundance experiment — the change in rate measured is that for *one* deuterium in $H_c/H_{c'}$ and represents a combination of primary and secondary isotope effects (referred to as $KIE_{1°}$ and $KIE_{2°}$, respectively). The observed isotope effect of 1.45–1.46 for $H_c/H_{c'}$ is $2/(1/KIE_{1°}+1/KIE_{2°})$. If the $KIE_{2°}$ is assumed to be in the range of 1.0–1.1,[12] then $KIE_{1°}$ is in the range of 2.13–2.70. This result, in combination with the C_3 isotope effect of 1.009–1.010, indicates that hydrogen transfer is also occurring in the rate-limiting transition state. Overall, an early concerted pericyclic transition state is qualitatively supported by the experimental isotope effects.

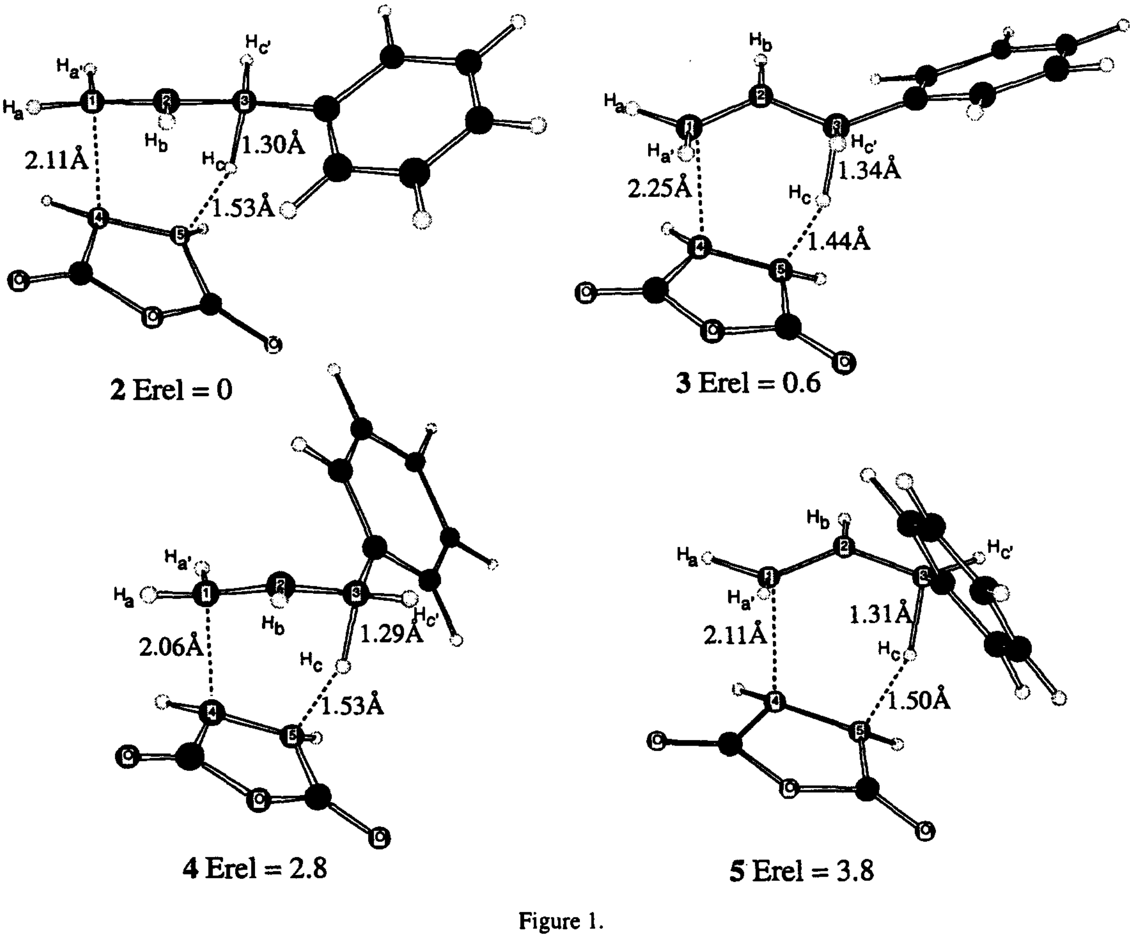
A more quantitative interpretation of the isotope effects and transition state geometry was obtained using theoretical calculations. The fully-optimized transition structures **2**–**5** for the ene reaction of allylbenzene with maleic anhydride (Fig. 1) were located in density functional calculations employing a Becke3LYP functional[13] and a 6-31G* basis set. The predicted activation barrier for this reaction is 24.0 kcal/mol (Becke3LYP+zpe), in reasonable agreement with the experimental barrier for reaction of maleic anhydride with other 1-alkenes of 21.5 kcal/mol.[14] The *endo* structure **2** is predicted to be favored over the *exo* structure **3** by 0.6 kcal/mol. Both **2** and **3**, which lead to the *trans* product, are predicted to be strongly favored over **4** and **5**, which form the *cis* product.

Theoretical isotope effects based on **2** and **3** (Table 1) were calculated by the method of Bigeleisen and Mayer[15] with the addition of a one-dimensional infinite parabolic tunneling correction.[16] Such

Table 1
Experimental and theoretically predicted isotope effects (k_H/k_D or $k_{^{12}C}/k_{^{13}C}$, 175°C) for ene reaction of allylbenzene with maleic anhydride

	Experimental[a]		Predicted	
	1	2	2	3
C_1	1.013(2)	1.014(2)	1.011	1.009
C_2	1.003(1)	1.003(2)	1.004	1.003
C_3	1.010(2)	1.009(1)	1.007	1.010
$H_a/H_{a'}$[b]	0.969(7)	0.970(8)	0.952	0.958
H_b	0.989(13)	0.981(13)	0.996	0.997
$H_c/H_{c'}$	1.46(2)	1.45(2)	1.50	1.55

[a] Experiments 1 and 2 were taken to 72±3% and 73±3% conversion, respectively.
[b] This value represents the geometric mean of the isotope effects at H_a and $H_{a'}$.
[c] This value represents $2/(1/KIE_{1°} + 1/KIE_{2°})$ (see text).



2 Erel = 0

3 Erel = 0.6

4 Erel = 2.8

5 Erel = 3.8

Figure 1.

predictions have been highly successful in a number of other reactions,[9] but the ene reaction here is a difficult case because of the involvement of hydrogen transfer in the transition state. Truhlar has found that a one-dimensional correction is inadequate for the prediction of even secondary KIEs in reactions involving hydrogen transfer, owing to multidimensional tunneling and variational transition state effects.[17] The expected underprediction of tunneling for atoms at reactive centers makes it unsurprising that the calculated KIEs at C_1, C_3 and $H_a/H_{a'}$ are low relative to experiment. Nonetheless, the errors in the predicted KIEs are small and the trend in experimental and calculated isotope effects is very similar. We therefore consider that the experimental isotope effects support the approximate accuracy of the theoretical transition structures.

The results here appear to rule out a transition state resembling a 2+2 cycloaddition or 2+2 charge complex as proposed by Kwart for the reaction of allylbenzene with diethyl mesoxalate.[6] In that reaction a substantially inverse H_b isotope effect had been observed, interpreted as indicating some degree of bonding to C_2 at the transition state.[18] The slight inverse isotope effect observed here for H_b is reminiscent of the nearly identical isotope effect observed for the deuterium on C_3 of isoprene in its Diels–Alder reaction with maleic anhydride.[9a] In both cases the small inverse effect is best attributed to inhibition of a C–H bending mode by the proximity of the maleic anhydride.

With some credibility given to the theoretically predicted structures, consideration may be given to the factors that should influence the selectivity of these reactions. Nahm and Cheng have reported a systematic study of the ene reaction of maleic anhydride with decene isomers, observing in each case the product distribution and stereochemistry.[19] They conclude that a pericyclic transition state is involved with interaction of both a hydrogen and the distal carbon of the ene with the olefinic carbons of maleic anhydride, and that the ene double bond in the *endo* transition state is tilted away from the maleic anhydride. This is a good description of **2**. Nahm and Cheng's analysis found that the *endo* structures were preferred but that the *exo* structures contributed substantially to the product mixture. This is in good accord with the predicted preference of only 0.6 kcal/mol for **2** over **3**. In **2** the interaction of the phenyl group with the anhydride ring is very slight; Nahm and Cheng found this to be the smallest of the steric interactions they considered in their quantitative prediction of product mixtures. In structures **4** and **5** there is a substantial steric interaction of $H_{a'}$ with the phenyl group, inhibiting formation of the *cis* product. If $H_{a'}$ is replaced by an alkyl group this steric interaction should be prohibitive. These are precisely the interactions found to be largest in Nahm and Cheng's quantitative analysis. These structures thus provide good intuitive models for the steric interactions found to control selectivity in ene reactions.

The multiplicity of mechanisms that have been demonstrated for ene reactions has hampered the understanding and prediction of selectivity in these reactions. We intend to use the combination of experimental isotope effects and theoretical calculations to explore a variety of ene reactions, with the goal of establishing a firm experimental basis for mechanism and transition state geometry in these synthetically important reactions.

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