Reinvestigation of the Isotope Effects for the Claisen and Aromatic Claisen Rearrangements: The Nature of the Claisen Transition States

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Received July 8, 1999

Abstract: The aliphatic Claisen rearrangement of allyl vinyl ether and the aromatic Claisen rearrangement of allyl phenyl ether are investigated in a combined experimental and calculational study. Theoretically predicted kinetic isotope effects (KIEs) at all levels disagree with about half of the literature experimental heavy-atom isotope effects. New experimental ^{13}C and ^{2}H isotope effects were determined by multisite NMR methodology at natural abundance, and ^{17}O isotope effects were determined by novel NMR methodology. These new experimental isotope effects are inconsistent with the literature values and agree well the high-level predicted KIEs, suggesting that the prior theory/experiment disagreement results from inaccuracy in the experimental KIEs. A one-dimensional tunneling correction is found to improve kinetic isotope effect predictions in a number of reactions and is found to be sufficient to provide differences between predicted and experimental heavy-atom isotope effects on the order of the experimental uncertainty in the reactions studied. The best agreement between experimental and predicted isotope effects is seen for the highest-level calculations. On the basis of the experimentally supported transition state geometries, the nature of the Claisen and aromatic Claisen transition states is discussed.

Introduction

The Claisen rearrangement of allyl vinyl and allyl aryl ethers is a synthetically and biosynthetically important reaction. The intramolecular and cyclic character of the rearrangement has long been established,[1] but considerable effort has gone into understanding the detailed nature and geometry of the transition state. Interest in the Claisen transition state has been spurred by its relation to the synthetically important substituent and stereochemical effects observed in these reactions,[2] as well as the observation of intriguing solvent effects[3−7] and the catalysis of a Claisen rearrangement by chorismate mutase and catalytic antibodies.[8] Theoretical predictions of transition structures for the Claisen rearrangement have been made at many levels.[9−12,14] The calculations uniformly agree that the rearrangement is concerted, and all correctly predict a chairlike transition state. However, there is considerable disagreement over the transition state geometry (Figure 1). CASSCF calculations predict a dissociative bis-allyl-like transition structure while the AM1 and MP2 structures are more toward the 1,4-diyl extreme, with the RHF and Becke3LYP structures between (along with a partially optimized MP4 structure).[10−13] The differing geometries engender significantly different predictions and understanding of substituent, solvent, and catalysis effects in these reactions.[15]

Several experimental studies have used kinetic isotope effects (KIEs) as a probe of the Claisen and aromatic Claisen transition state geometry.[6,16,17] Secondary deuterium KIEs have been interpreted qualitatively in terms of a fairly dissociative, early transition state for the aliphatic Claisen and a similarly dissociative but much later transition state for the aromatic Claisen.[17] However, the assumption in these interpretations of a linear relationship between bond order and isotope effect has been questioned.[18] Heavy-atom KIEs have been interpreted in terms of early transition states for both the aliphatic and aromatic

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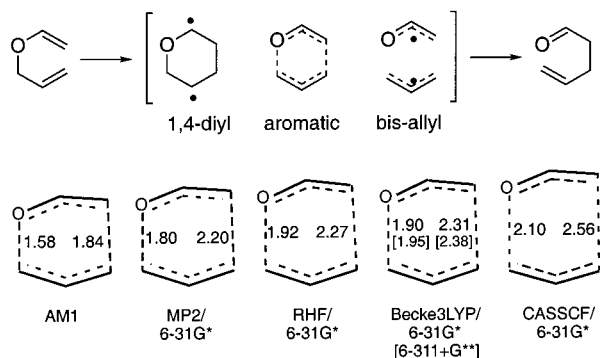
Figure 1. Idealized and calculated transition structures for the Claisen rearrangement. The calculated geometries are taken from refs 10−12.

Figure 2. Calculated transition structures for the aromatic Claisen rearrangement. The Becke3LYP/6-31G* and RHF/6-31G* geometries are taken from ref 14.

Claisen rearrangements. BEBOVIB modeling calculations on the heavy-atom KIEs find 50−60% breaking of the C−O bond and only 10−20% formation of the new C−C bond in the aromatic Claisen.[16] This does not fit well with recent RHF and Becke3LYP calculations on the aromatic Claisen rearrangement,[14] which are best described as predicting relatively late transition structures (vide infra). The BEBOVIB analyses also led to a number of conclusions on the dynamics of the rearrangements, including a surprising coupling of motion in the allyl and vinyloxy or phenoxy fragments at the transition state.[16]

A more quantitative approach to the use of isotope effects to establish transition state geometry involves the comparison of experimental and theoretically predicted KIEs.[10,12,19,17,18] Ideally, a close correspondence is found between the experimental and predicted isotope effects for a given transition structure. This is taken as evidence that the calculated transition structure is very similar to the actual transition state. Recently, tunneling-corrected KIE predictions based on Becke3LYP calculations were found to match exceptionally well with experimental values for the Diels−Alder reaction of isoprene with maleic anhydride,[20] peracid-mediated epoxidation of 1-pentene,[21] and the osmium tetroxide-mediated asymmetric dihydroxylation of *tert*-butylethylene.[22] In these cases the predicted KIEs are generally within the uncertainty of the experimental values, with root-mean-square (RMS) errors for the heavy-atom KIEs of 0.1−0.15%.

Prior to these examples, Houk and co-workers had compared semiclassical (without a tunneling correction) predicted KIEs with experimental values for the Claisen rearrangement of allyl vinyl ether.[10,12] The RMS errors in the predicted ^{14}C and ^{18}O isotope effects for the RHF, Becke3LYP, and CASSCF (all with a 6-31G* basis set) transition structures were 1.8, 2.3, and 0.9%, respectively.[10,12] This level of agreement of theoretical and experimental KIEs was characterized as very good at the time, but cannot be evaluated so favorably in light of the much greater
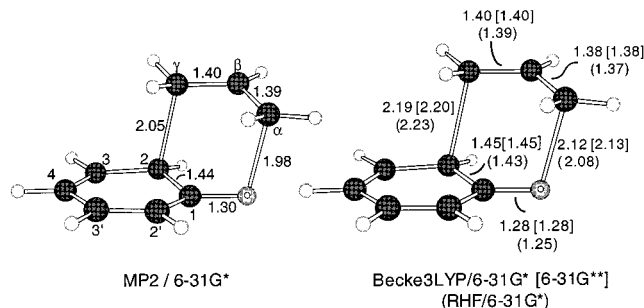
accuracy of recent KIE predictions.[7,20−22] Moreover, the observation of best agreement with the CASSCF calculations contrasts with poor predictions by these calculations in similar reactions.[23] In retrospect, the large error in the predicted KIEs appeared to suggest that some refinement was still required for either the Claisen transition structure geometries, or the methodology for predicting KIEs from these structures, or both. It should be noted that in a recent study of a polar decarboxylation reaction a wide array of calculational levels performed poorly in predicting the observed isotope effects.[24]

The observations above raise several important questions. First, which of the transition structures from Figure 1 is closest to the actual transition state for the Claisen rearrangement? Can any of the common theoretical methods reliably predict the transition state, say to the extent of predicting the lengths of the forming and breaking bonds to within 0.1 Å? Can isotope effects be predicted well for these simple pericyclic reactions? If so, how? Can the experimental isotope effects be used to distinguish between the diverse predicted structures?

We report here that there is a firm disagreement in about half the cases between the predicted and literature experimental heavy atom KIEs for both the aliphatic and aromatic Claisen rearrangements. However, new experimental KIEs can be predicted very well, suggesting that the prior theory/experiment disagreement results from inaccuracy in the experimental KIEs. On the basis of the new KIEs, we analyze the requirements for accurate KIE predictions, and see how well these predictions can delimit the physical transition state. The results have implications toward previous assessments of calculational methods for these reactions and toward both the detailed geometry and the general conception of the Claisen transition state.

Results

New Theoretical Structures. Transition structures obtained at the MP2/6-31G* and Becke3LYP/6-31G** levels for the aromatic Claisen rearrangement of allyl phenyl ether are shown in Figure 2, along with the Becke3LYP/6-31G* and RHF/6-31G* geometries previously reported by Yamabe.[14] The MP2 geometry is notably more 1,4-diyl-like than the RHF and Becke3LYP structures, as observed with the aliphatic Claisen. The Becke3LYP/6-31G** geometry differs very little from the 6-31G* but was investigated to see if the more balanced 6-31G** basis set would impact predictions of the deuterium KIEs.

Fully optimized transition structures for the aliphatic Claisen rearrangement obtained at the MP4(SDQ) and QCISD levels

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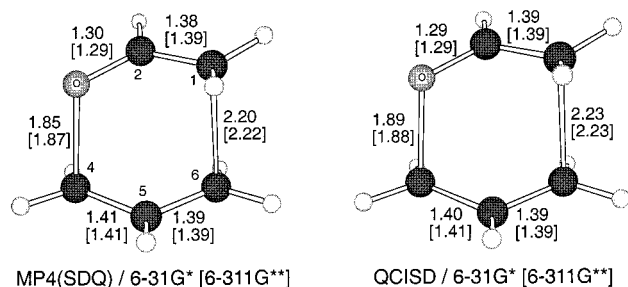(24) Czyryca, P.; Paneth, P. *J. Org. Chem.* **1997**, *62*, 7305.

Figure 3. Calculated transition structures for the aliphatic Claisen rearrangement.

with 6-31G* and 6-311G** basis sets are shown in Figure 3. All four structures are very similar, and the MP4(SDQ)/6-311G** and QCISD/6-311G** structures are nearly identical. (The numerical frequency calculation necessary for calculating isotope effects from these structures was only practical at the MP4(SDQ)/6-31G* level and was not carried out for the other structures.) The predicted activation barriers for these structures at the level of their geometry optimization are also very similar, ranging from 34.9 to 35.7 kcal/mol (see Supporting Information). The predicted activation barrier at the QCISD(T)/6311+G**// QCISD/6311G** level, including zero-point energy (ZPE) from the MP4(SDQ)/6-31G* calculation, is 29.8 kcal/mol, compared to an experimental $\Delta H^\ddagger$ of 29.5 kcal/mol.[25]

Calculated versus Literature Experimental KIEs. KIEs were predicted for each of the transition structures in Figures 1 and 2 and the MP4(SDQ)/6-31G* structure in Figure 3. The KIEs were calculated by the method of Bigeleisen and Mayer[26] from the scaled theoretical vibrational frequencies,[27] and tunneling corrections were applied using the one-dimensional infinite parabolic barrier model.[28] The tunneling correction (discussed below) has the effect of raising the calculated heavy-atom KIEs by 0.000—0.012 (see Supporting Information), with the largest corrections going to the largest KIEs. The effect on the predicted deuterium KIEs was much smaller, usually <0.002. To allow for a Boltzmann distribution of starting material conformations, complete conformational searches were carried out for the allyl vinyl ether and allyl phenyl ether. The KIE calculations were then based on a Boltzmann weighting of the isotope effects predicted for the lowest energy conformers (two for allyl vinyl ether and three for allyl phenyl ether, see Supporting Information), allowing for an entropy of mixing where appropriate. The predicted heavy-atom KIEs based on different starting material conformers differed by no more than 0.002. However, the calculated deuterium KIEs differed by as much as 2%.

The predicted KIEs at temperatures corresponding to literature experimental results are summarized in Tables 1 and 2, along with the literature experimental values.[16a,b,17a] Calculated KIEs for some of the aliphatic Claisen transition structures have been previously reported by Houk and co-workers,[10,12] although the
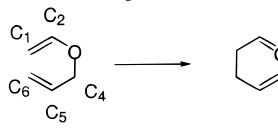
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(27) The calculations used the program QUIVER (Saunders, M.; Laidig, K. E.; Wolfsberg, M. *J. Am. Chem. Soc.* **1989**, *111*, 8989) with Becke3LYP, RHF, MP2, and AM1 frequencies scaled by 0.9614, 0.91, 0.943, and 0.953, respectively. (Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502). CASSCF and MP4(SDQ) scaling factors of 0.9015 and 0.951, respectively, were based on a least-squares fit with the scaled Becke3LYP frequencies for the starting allyl vinyl ether.

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Table 1. Calculated versus Literature Experimental KIEs for the Aromatic Claisen Rearrangement

	lit.	MP2 6-31G*	Becke3LYP 6-31G*	Becke3LYP 6-311G**	RHF 6-31G*
		$k_{^{12}C}/k_{^{14}C}$ or $k_{^{16}O}/k_{^{18}O}$ (220 °C)			
C_α	1.0306[a]	1.046	1.039	1.038	1.044
C_β	1.0119[a]	0.999	1.004	1.003	1.010
C_γ	1.0362[a]	1.030	1.037	1.037	1.036
C_1	1.0148[a]	0.998	1.000	1.000	0.997
C_2	1.0375[a]	1.020	1.028	1.028	1.027
O	1.0297[a]	1.028	1.023	1.022	1.025
RMS error		1.3%	0.9%	0.9%	1.0%
		k_H/k_D[b]			
γ-d_2	0.95 ± 0.02[c]	0.94	0.93	0.93	0.92
α-d_2	1.18 ± 0.02[c]	1.13	1.12	1.11	1.10

[a] See refs 16a,b. [b] The experimental deuterium KIEs were obtained in a temperature range of 170—195 °C, while the calculated values are for 180 °C. [c] See ref 17a.

predictions here differ due to the tunneling correction and the allowance for starting materials conformers.

None of the sets of calculated heavy-atom KIEs agree well with experiment, although cases of agreement with individual values are apparent. The RMS errors, ranging from 0.8 to 2.8%, are large, compared to the size of the isotope effects and the precision of the experimental values. This lack of agreement was not impacted significantly by the tunneling correction or the choice of frequency scaling factors (see Supporting Information).

The deuterium KIEs are considered separately because there is generally greater uncertainty in experimental values and because deuterium KIEs have been more difficult to correctly predict than heavy-atom KIEs. None of the calculations accurately predict the deuterium KIEs, but the disagreement appears systematic in nature—almost all of the calculated k_H/k_D values are lower than the experimental values. Only at the 1,4-diyl (AM1) and bis-allyl (CASSCF) extremes is there a clear correlation of the predicted deuterium KIE with the transition structure geometry, and these extremes make the poorest predictions of the experimental deuterium KIEs.

New Experimental KIEs. It seemed unusual that KIEs would be predicted very accurately for some pericyclic reactions and yet be predicted so poorly for Claisen rearrangements. For this reason, the isotope effects for these reactions were reinvestigated. The experimental ^{13}C KIEs for the rearrangement of allyl vinyl ether (at 120 °C in *p*-cymene) and the ^{13}C and ^{2}H KIEs for the rearrangement of allyl phenyl ether (either neat at 170 °C or in diphenyl ether at 220 °C to match literature conditions[16a]) were determined by recently reported methodology for the combinatorial high-precision determination of small KIEs at natural abundance.[29] Unreacted starting material from reactions taken to ~85—95% conversion was reisolated and analyzed by NMR compared to standard samples of the starting materials from the same commercial lots. The relative changes in ^{13}C composition for allyl vinyl ether were calculated using C_5 as an internal standard, and the changes in ^{13}C and ^{2}H composition for allyl phenyl ether were calculated using C_4 and the meta aromatic hydrogens as internal standards, respectively.[30] From

Table 2. Calculated versus Literature Experimental KIEs for the Aliphatic Claisen Rearrangement

	lit.	AM1	MP2 6-31G*	MP4(SDQ) 6-31G*	RHF 6-31G*	Becke3LYP 6-31G*	Becke3LYP 6-311+G**	CASSCF 6-31G*−6e/6o
d_{C_4-O}		1.58	1.80	1.85	1.92	1.90	1.95	2.10
$d_{C_1-C_6}$		1.84	2.20	2.20	2.27	2.31	2.38	2.56
				k_{12C}/k_{14C} or k_{16O}/k_{18O} (160 °C)				
C_2	1.027[a]	1.008	1.005	1.006	1.005	1.004	1.003	1.013
C_4	1.072[a]	1.050	1.058	1.066	1.065	1.055	1.053	1.073
C_6	1.0178[a]	1.059	1.030	1.033	1.036	1.030	1.028	1.021
O	1.050[a]	1.028	1.035	1.038	1.028	1.034	1.034	1.044
RMS error		2.8%	1.6%	1.5%	1.6%	1.7%	1.8%	0.8%
				k_H/k_D				
C_4-d_2:								
100 °C	1.119(19)[b]	0.996	1.080	1.087	1.097	1.065	1.086	1.255
160 °C	1.092(5)[c]	0.995	1.057	1.062	1.070	1.043	1.059	1.189
C_6-d_2:								
100 °C	0.953(15)[b]	0.867	0.939	0.910	0.901	0.935	0.949	0.963
160 °C	0.980(5)[c]	0.901	0.955	0.931	0.921	0.950	0.961	0.971

[a] See ref 16c. [b] See ref 6. [c] See ref 17b.

Table 3. Calculated versus New Experimental KIEs for the Aromatic Claisen rearrangement

k_{12C}/k_{13C}, k_{16O}/k_{17O}, or k_H/k_D at 170 °C

	expt 1[a]	expt. 2[a]	MP2 6-31G*	Becke3LYP 6-31G*	Becke3LYP 6-31G**	RHF 6-31G*
C_α	1.027(3)	1.025(2)	1.029	1.023	1.022	1.026
C_β	1.002(4)	1.002(2)	1.001	1.002	1.002	1.006
C_γ	1.020(5)	1.018(2)	1.018	1.020	1.020	1.020
C_1	1.001(3)	1.000(2)	1.000	1.000	1.000	0.998
$C_2 + C_{2'}$ [c]	1.008(3)	1.007(2)	1.006	1.009	1.009	1.008
$C_3 + C_{3'}$ [c]	1.003(3)	1.002(2)	1.000	1.001	1.001	1.000
C_4	1.0 (assumed)			1.000 (relative)		
O	1.012(4)	1.010(5)	1.017	1.013	1.013	1.015
RMS error[b]			0.18%	0.16%	0.16%	0.21%
α-d	1.071(10)	1.074(7)	1.067	1.061	1.057	1.053
β-d	0.985(13)	0.971(11)	0.981	0.986	0.984	0.991
γ_{cis}-d	0.978(7)	0.972(8)	0.972	0.967	0.970	0.961
		expt 3[a] (220 °C in diphenyl ether)				
C_α	1.020(5)		1.025	1.020	1.020	1.023
C_β	1.002(6)		1.001	1.002	1.001	1.005
C_γ	1.020(6)		1.017	1.019	1.019	1.019
$C_2 + C_{3'}$ [c]	1.006(4)		1.006	1.008	1.008	1.007
$C_3 + C_{3'}$ [c]	0.999(6)		1.000	1.001	1.001	1.000
C_4	1.0 (assumed)			1.000 (relative)		
RMS error[b]			0.24%	0.12%	0.12%	0.20%

[a] Experiments 1−3 were taken to 94.7 ± 0.4, 89.4 ± 1.0%, and 74.3 ± 2.0% completion, respectively. Standard deviations are given in parentheses. [b] Based on comparison of the predicted values with the complete set of experimental heavy-atom KIEs, not including the assumed C_4 KIE. [c] The observed KIE is the product of the KIEs for the two positions divided by their mean. [d] For comparison with the relative experimental values, the theoretical KIEs were made relative to the theoretical values at C_4. In each cast the absolute KIE predicted for C_4 was 1.000 ± 0.001.

the changes in isotopic composition, the KIEs were calculated as previously described.[29]

The [17]O KIEs were determined by a novel method[31] that is a variation on the above procedure. To both the recovered and standard samples of allyl vinyl ether or allyl phenyl ether was added ∼50 mol % acetone (from the same bottle). The ^{13}C NMR integrations of C_4 (allyl phenyl ether) or C_5 (allyl vinyl ether) versus the acetone carbons were then used to precisely determine the *relative* ratio of acetone in the two samples. The relative ratio of [17]O peaks could then be used to calculate the change in [17]O composition in the recovered material versus the standard, which was used to calculate the [17]O KIE.

The results are summarized in Tables 3 and 4, along with predicted KIEs for the experimental temperatures. In contrast

to the literature heavy-atom KIEs, the new heavy-atom KIEs closely correspond to some of the sets of predicted KIEs. All of the calculated transition structures result in reasonable predictions of the KIEs for the aromatic Claisen rearrangement, and predictions based on the Becke3LYP structure are particularly good. For the aliphatic Claisen the extreme transition structures resulting the AM1 and CASSCF calculations lead to poor predictions of the KIEs, but the other calculational levels are better and the MP4(SDQ)/6-31G* structure results in an excellent prediction of the aliphatic Claisen KIEs.

Allowing for experimental error and differences in conditions, the new deuterium KIEs for the aromatic Claisen rearrangement are consistent with the literature values.[17a] As above, the

Table 4. Calculated versus New Experimental KIEs for the Aliphatic Claisen Rearrangement

							Becke3LYP/		CASSCF
									$k_{^{12}C}/k_{^{13}C}$ or $k_{^{16}O}/k_{^{17}O}$ (120 °C)
	expt 1[a]	expt 2[a]	AM1	MP2 6-31G*	MP4(SDQ) 6-31G*	RHF 6-31G*	6-31G*	6-311+G**	6-31G*−6d 7a
C_1	1.014(2)	1.013(1)	1.030	1.013	1.012	1.011	1.012	1.012	1.007
C_2	1.000(2)	1.001(1)	1.000	1.002	1.000	0.996	0.999	1.000	1.003
O	1.017(5)	1.021(5)	1.013	1.019	1.019	1.015	1.017	1.018	1.020
C_4	1.035(2)	1.033(2)	1.026	1.033	1.035	1.032	1.029	1.029	1.037
C_5	1.0 (assumed)					1.000 (relative[c])			
C_6	1.015(1)	1.015(1)	1.030	1.016	1.015	1.014	1.014	1.014	1.007
RMS error[b]			1.1%	0.14%	0.13%	0.33%	0.28%	0.26%	0.51%

[a] Experiments 1 and 2 were taken to 86.5 ± 0.8 and $86.7 \pm 1.1\%$ completion, respectively. Standard deviations are given in parentheses. [b] Based on comparison of the predicted values with the complete set of experimental heavy-atom KIEs, not including the assumed C_5 KIE. [c] For comparison with the relative experimental values, the theoretical KIEs were made relative to the theoretical values at C_5. The absolute KIEs predicted for C_5 varied with theoretical level, and were 1.004, 1.001, 1.003, 1.007, 1.003, 1.002, and 1.005 for the AM1, MP2, MP4, RHF, Becke3LYP/6-31G*, Becke3LYP/6-31G**, and CASSCF calculations, respectively.

calculated KIEs tend to underpredict the experimental values. However, the MP2-predicted KIEs are notably very close to experiment.

Discussion

Theoretical Structures. The highest-level theoretical calculations of the aliphatic Claisen transition structure appear to converge in the similar geometries shown in Figure 3. The lack of triple excitations in these geometry optimizations is a weakness, and their inclusion was necessary for the highly accurate prediction of the activation barrier. However, the close similarity of these structures to the partially optimized MP4-(SDTQ) structure[12] previously reported suggests that including triples would not substantially impact the transition structure geometry.

In predicting isotope effects from these structures, it is worth considering how closely the geometry of the calculated transition *structure* can be expected to match the actual transition *state*, even if the calculation is "perfect". The transition structure is a saddle point on the potential energy surface, while the transition state is a saddle point on the free energy surface. The two may differ significantly if either the entropy or zero-point energy is changing rapidly in the area of the transition state, and this can substantially complicate the prediction of KIEs, even for secondary KIEs.[32] For the Claisen rearrangement the ZPE changes little between the starting material and transition state (only 0.97 kcal/mol at the MP4(SDQ)/6-31G* level), and the entropy is probably near a minimum at the transition state. For this reason entropy and ZPE effects on the transition state geometry should be minimal, and the Claisen rearrangement should be a relatively good case for the semiclassical isotope effect calculations used here.

For the aromatic Claisen rearrangement the higher-level calculations are not feasible and we are limited to Becke3LYP and MP2 predictions at best. The calculational results with aliphatic Claisen suggest that the two may err in opposite

directions with regard to the bis-allyl versus 1,4-diyl character of the transition structure. This conjecture will be discussed further with regard to the experimental KIEs. However, from theory alone, there is no basis for choosing between the discordant Becke3LYP and MP2 predictions of the transition structure geometry, nor have the calculations converged sufficiently for either to be reliable in their prediction of the lengths of the forming and breaking bonds to within 0.1 Å.

Literature versus New Experimental KIEs. A direct comparison of the literature heavy-atom KIEs with the new KIEs presented here is complicated by differing nuclei (^{14}C versus ^{13}C, [18]O versus [17]O), differing temperatures, and the *relative* nature of KIEs determined by NMR.[29] Nonetheless it is apparent that the literature and new KIEs are inconsistent at points. If we calculate the expected ^{14}C and [18]O KIEs as the new ^{13}C and [17]O KIEs taken to the 1.9th power and adjust for temperature, attributing all of the KIE to a difference in E_A,[33] the estimated KIEs for C_α, C_β, C_γ, and C_1 for the aromatic Claisen and C_2, O, C_4, and C_6 for the aliphatic Claisen are 1.038, 1.004, 1.038, 1.000, 1.012, 1.033, 1.059, and 1.026, respectively. This can be compared with 1.0306, 1.012, 1.036, 1.0148, 1.027, 1.050, 1.072, and 1.0178, respectively, from the literature KIEs in Tables 2 and 3. There is substantial agreement on only one of the values and the RMS difference is 1.2%.

There is no experimental basis for deciding which set of KIEs is correct. The literature sets of KIEs in Tables 1 and 2 are usually based on two completely independent sets of data with three KIE measurements in each set. Each set of the new KIEs in Tables 3 and 4 are based on six NMR KIE measurements. The measurement of ^{14}C KIEs is subject to a known danger from natural-abundance impurities.[34] On the other hand, the NMR-based measurement of KIEs here is a relatively new and unproven technique.

The agreement of the predicted KIEs with the new experimental KIEs is strikingly better, but the significance of this agreement is the critical question. The use of theory as the standard to decide between experimental results is intrinsically arguable. One way to analyze the question is by *reductio ad absurdum*, starting by assuming that the literature experimental KIEs are perfectly correct and that the RMS 1.2% disagreement between literature and new values is the result of a random error of ~0.6%[35] in the new KIEs. What then are the chances of a random agreement between the new experimental KIEs and the predicted values? Under the most favorable assumption that the

(30) The experimental KIEs obtained here are "relative" to the atom used as standard and are displaced from the actual KIEs by a factor equal to the KIE for the standard. Since the assumption of a negligible C_5 KIE for allyl vinyl ether is doubtful, we avoid the problem by normalizing the calculated KIEs to the standard atom. In this way, the experimental relative KIEs are compared with predicted *relative* KIEs. As a check on the assumption of a negligible ^{2}H KIE for the meta aromatic hydrogens of allyl phenyl ether, the KIEs were also determined for allyl *p*-tolyl ether using the para methyl group as standard. The k_H/k_D's observed were 1.081(6), 0.972(7), 0.975-(9), and 0.972(6) for the α, β, γ_{cis}, and γ_{trans} positions, respectively, which are within experimental error of the values found for allyl phenyl ether.

(31) This method was developed by S. R. Merrigan in this laboratory.

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Table 5. Effect of Tunneling Corrections on Prediction of Heavy-Atom KIEs

reaction	calculational method[a]	no. of values compared[b]	RMS error w/o tunneling (%)	RMS error with tunneling (%)
aromatic Claisen				
170 °C	Becke3LYP	14	0.21	0.16
	MP2	14	0.19	0.18
	RHF	14	0.25	0.21
220 °C	Becke3LYP	6	0.13	0.12
	MP2	6	0.25	0.24
		6	0.23	0.20
aliphatic Claisen				
	MP4(SDQ)	5	0.32	0.13
	MP2	5	0.46	0.14
	Becke3LYP	5	0.42	0.28
	RHF	5	0.73	0.33
epoxidation[c]	Becke3LYP	6	0.18	0.15
Diels−Alder[d]	Becke3LYP	4	0.27	0.10
Diels−Alder[e]	Becke3LYP	4	0.49	0.17
dihydroxylation[f]	Becke3LYP	4	0.37	0.15%

[a] The level of theory used to obtain the transition structure on which the predicted KIEs are based. [b] The number of experimental values. [c] The epoxidation of 1-pentene with m-CPBA, modeled theoretically as the epoxidation of propene with performic acid. See ref 21. [d] The reaction of maleic anhydride with isoprene. See ref 20. [e] The reaction of hexachlorocyclopentadiene with ethyl vinyl ether. See ref 37. [f] The asymmetric dihydroxylation of *tert*-butylethylene, modeled theoretically as the dihydroxylation of propene with $OsO_4 \cdot NH_3$. See ref 22.

"random" error in the new KIEs is identical for each of the separate experimental runs, an overall RMS error of only 0.15% for eight independent comparisons (C_α, C_β, C_γ, and C_1 for the aromatic Claisen versus Becke3LYP predicted values and C_2, O, C_4, and C_6 for the aliphatic Claisen versus the MP4 predicted values) would only occur 0.01% of the time (based on a Gaussian distribution at 4σ, since $0.6 = 4 \times 0.15$). This strongly suggests that the agreement of the predicted KIEs with the new experimental KIEs is not the result of random error, and we conclude that this agreement results from the mutual accuracy of the predicted and new experimental KIEs.

KIE Calculations and the Importance and Accuracy of a One-Dimensional Tunneling Correction. The semiclassical method for predicting isotope effects employed here is based on conventional transition state theory with an added one-dimensional tunneling correction that is calculated from the transition structure imaginary frequency. The advantage of a one-dimensional correction is its computational simplicity, but more advanced corrections would clearly be desirable. In reactions involving hydrogen transfer Truhlar has found that a one-dimensional correction is inadequate for the prediction of even secondary KIEs, owing to multidimensional tunneling and variational transition state effects. Truhlar concludes "Tunneling formulas based only on the imaginary frequency at the barrier are qualitatively incorrect."[32] Unfortunately, improved corrections are not readily applicable to large molecules.[36] On the other hand, the importance of using *any* tunneling correction for reactions not involving hydrogen transfer was not clear on initiating this work—for many reactions a one-dimensional tunneling correction on the KIE is very small.[19a,16b] It was

therefore important to answer the dual questions of whether a one-dimensional tunneling correction is necessary for these reactions, and whether it is sufficient.

Table 5 summarizes experimental heavy atom KIEs for the aromatic and aliphatic Claisen reactions, the Diels−Alder reaction of isoprene with maleic anhydride, epoxidation of 1-pentene with mCPBA, and the asymmetric dihydroxylation of *tert*-butylethylene, compared to predicted values with and without a tunneling correction. In every case the tunneling correction improves the prediction, sometimes substantially. Clearly a one-dimensional tunneling correction is an appropriate positive step in predicting KIEs. Moreover, considering the level of agreement between the predicted and experimental KIEs, the one-dimensional tunneling correction is for practical purposes *sufficient* in these reactions. Because the RMS differences between predicted and experimental values are on the order of the experimental uncertainty, more precise experimental KIEs would be required to evaluate any improved tunneling correction.

This conclusion has two important caveats. First, the simplistic tunneling correction would probably not suffice for predicting any isotope effect in hydrogen-transfer reactions. Second, accurate calculated KIEs cannot be expected if the calculated transition structure on which they are based is inaccurate. In this way the comparison of predicted and experimental KIEs can readily distinguish between qualitatively differing mechanisms.[21,22,37]

The result is different with deuterium KIEs. Secondary deuterium KIEs are often considered more structurally indicative than heavy-atom KIEs, based on their relation to the rehybridization of the reacting centers. However, the validity of many qualitative interpretations of secondary deuterium KIEs has been questioned by Jensen on the basis of calculations that show that such KIEs are not a simple function of the rehybridization.[38] Jensen's observations suggest the superiority of the structurally quantitative but interpretively empirical process of comparison of calculated and experimental deuterium KIEs. Unfortunately, two difficulties arise with deuterium KIEs. First, deuterium KIE measurements are generally less precise than with heavy atoms. Second, predictions of deuterium KIEs have generally been less accurate. In the present case the agreement between the calculated and experimental KIEs depends on the calculational level and whether literature (Tables 1 and 2) or new (Table 3) experimental KIEs are compared, but there is a definite trend toward underprediction of the k_H/k_D value. (Ignoring the AM1 and CASSCF predictions, the only exception is in Table 3 for the β-deuterium KIE, which is a small effect at a center not undergoing a change in hybridization.) This trend makes the definite suggestion that tunneling is being undercalculated, possibly due to some importance of multidimensional tunneling in the reaction. Although the error in the deuterium KIE predictions is not large, the inaccuracy makes it difficult to use comparisons of experimental and predicted deuterium KIEs to define in detail the transition state geometry. For this reason we focus on the results with heavy atom KIEs.

The Physical Transition State. The high level of accuracy associated with the best KIE predictions in Tables 3 and 4 has a significant structural implication: the calculated transition structures "approximate" the physical transition state. How close is this approximation, or to what extent do the experimental isotope effects delimit the detailed transition state geometry?

(35) Because the new heavy atom KIEs are ^{13}C or ^{17}O values and the literature KIEs are ^{14}C or ^{18}O values, a random error of 0.6% in the new KIEs would result in an error of $\sim 1.006^{1.9} - 1 = 1.2\%$ when expected values for the old KIEs are calculated from the new.

(36) For a dual-level calculational approach to advanced calculations of isotope effects in reactions involving multiple heavy atoms, see: Roberto-Neto, O.; Coitiño, E. L.; Truhlar, D. G. *J. Phys. Chem. A.* **1998**, *102*, 4568, and references therein.

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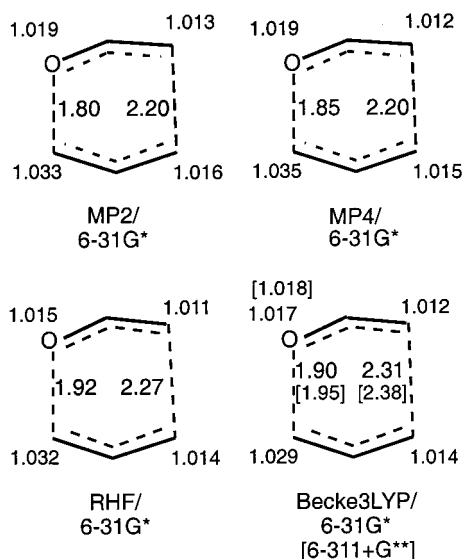
Figure 4. Variation in some predicted KIEs versus structure.

Figure 5. More O'Ferrall−Jencks diagram for the aliphatic Claisen rearrangement. Area A represents the range of transition state positions calculated from $O-C_4$ and C_1-C_6 bond orders for the MP2, MP4, RHF, and Becke3LYP calculated transition structures, using eq 1 with C = 0.3 to 0.6. Area B represents the transition state positions for these structures based on the C_1-C_2, C_2-O, C_4-C_5, and C_5-C_6 bond lengths compared to models of the 1,4-diyl and bis-allyl corners. (See Table 6.) Area C represents the expected transition state position based on the energetics of the four corners of the diagram and the transition state enthalpy.

From Table 4 the experimental isotope effects clearly exclude the extremes of the AM1 and CASSCF structures for the aliphatic Claisen. The agreement between the calculated and experimental KIEs is best with the MP4 structure, and without any consideration for the expected reliability of the differing calculations, the MP4 structure may be said to receive the most support from the experimental KIEs. The observation that the highest-level calculation leads to KIEs closest to experiment is certainly encouraging and supports the idea that isotope effects can be used as a sensitive measure of transition state geometry.

This conclusion, however, should be tempered by two observations. First, the experimental support for the MP4 structure from KIEs is not unequivocal. The MP2-calculated KIEs are virtually equivalent in accuracy to the MP4 values, and there is only moderately worse agreement with the KIEs based on the Becke3LYP structures. The experimental KIEs would therefore be consistent with a range of transition state geometries, and more precise values would be required to determine if the differing transition structures can be definitively resolved. Second, a simple relationship between the heavy-atom KIEs and transition structure geometry is lacking. This can be seen from Figure 4, which shows the forming C_1-C_6 and breaking $O-C_4$ bond distances alongside the predicted KIEs for C_1, C_4, C_6, and O for the various-level calculations. Within a range of 0.15 Å for the $O-C_4$ distance and 0.18 Å for the C_1-C_6 distance there is no noticeable trend in the predicted KIEs. Obviously, factors other than transition structure geometry affect the predicted KIEs, most particularly the quality of the frequency calculation at the various levels.

It should be noted here that the calculated KIEs are for the gas phase, while the experimental values are for solution chemistry. The agreement of the calculated and experimental values thus suggests some limit on the change in geometry on going from the gas phase to solution. This is not surprising, based on Gajewski's observation that secondary ^{2}H KIEs in aqueous media are within experimental error of those in nonpolar solvents.[6] However, a consideration of Figure 4 and the predicted ^{2}H KIEs for the various transition structure geometries in Table 2 suggests that either relatively large changes in the transition state geometry or extremely precise KIEs would be required to establish a solvent-effected change in transition state structure.
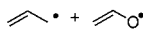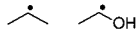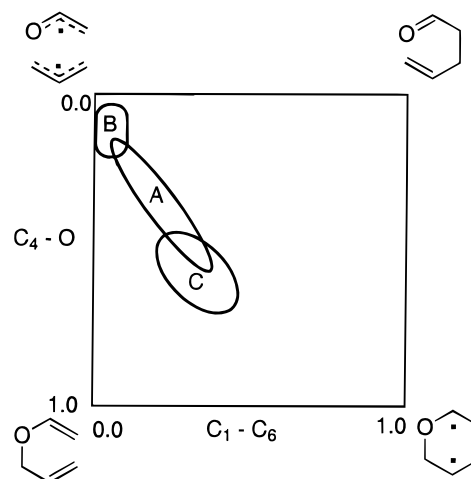
For the larger calculation of the aromatic Claisen the theoretical level is limited, and the two highest-level calculations (MP2 and Becke3LYP) differ substantially−0.14 Å for both the $C_\gamma-C_2$ and $C_\alpha-O$ distances. On the basis of the theoretical calculations alone, the normal process in this situation would be to assume that the error in a large calculation was analogous to that in a smaller calculation. Thus, assuming that the MP4 and QCISD structures of Figure 3 represent ∼true transition structures for the aliphatic Claisen, the MP2 and Becke3LYP structures err in opposite directions. Assuming the same direction of errors for the aromatic Claisen, the true transition structure would be hypothesized to be intermediate in geometry to the structures of Figure 2.

This qualitative hypothesis finds support from the kinetic isotope effects. From Table 3, the MP2, Becke3LYP, and RHF structures all result in excellent predictions of the experimental KIEs. Notably, the MP2 and Becke3LYP predictions bracket the experimental values at C_α and C_2. The Becke3LYP structure leads to a slightly better prediction of the less-precise ^{17}O KIE and 220 °C dataset, but overall the MP2 and Becke3LYP structures are best described as resulting in comparable-quality predictions of the KIEs. This is consistent with the physical transition state being somewhere between the two structures. However, as expected from the analysis with the aliphatic Claisen, the comparison of calculated and experimental KIEs is too limited in resolution for a more definitive geometrical interpretation.

The Nature of the Claisen Transition States. The approximate delimitation of the geometry of the Claisen transition states raises the question of how best to describe these structures. This is a necessarily qualitative and less well-defined topic than characterizing numerically the transition state geometry, but is important for *understanding* the Claisen rearrangements. This problem has usually been defined in terms of the early versus late character of the transition state, and the 1,4-diyl versus aromatic versus bis-allyl character. This is equivalent to the placement of the transition state on a More O'Ferrall−Jencks diagram[39] as in Figure 5, where one axis is the degree on bond

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Table 6. Comparison of Bond Lengths in Calculated Transition Structures with Bis-allyl and 1,4-Diyl Models

	MP2	MP4(SDQ)	HF	Becke3LYP
	6-31G*		6-31G*	6-31G*
C_1-C_2	1.383	1.383	1.374	1.383
C_2-O	1.307	1.295	1.262	1.288
C_4-C_5	1.408	1.405	1.389	1.402
C_5-C_6	1.386	1.387	1.376	1.383
total	5.484	5.470	5.401	5.456
total for bis-allyl model				
⟋⟍ • + ⟋⟍O•	5.414	5.427	5.430	5.437
total for 1,4-diyl model				
⟋⟍• ⟋⟍OH	5.852	5.865	5.856	5.851
% bis-allyl character	84%	90%	100%	95%
in transition structure				

Figure 6. FMO description of [3,3]-sigmatropic rearrangements.

Figure 7. Comparison of calculated bond distances in 1,4-diyl and bis-allyl models with bond distances in calculated transition structures for the aromatic Claisen rearrangement. All calculations used a 6-31G* basis set.

breaking of the O−C_4 bond and the other axis in the degree of bond making of the C_1−C_6 bond. As discussed below, we believe this description misses critical features of these reactions.

Indirectly defining from KIEs the progress of bond-breaking and bond-making along the axes in Figure 5 is difficult, even in qualitative terms. For example, secondary ^{2}H KIEs do not appear to be a simple function of the rehybridization of the reactive centers at the transition state.[38,18,29] However, a problem also arises in the direct description of bond orders from transition state geometries. Considering, for example, the Becke3LYP geometry of Figure 1, what bond order corresponds to a 2.31 Å C_1−C_6 distance? Using the Pauling relation of eq 1,

$$\frac{n_p}{n_0} = \exp\left[\frac{(R_0 - R)}{C}\right] \qquad (1)$$

the bond order would be 0.08 if 0.3 for the constant C is used,[40] but 0.28 if $C = 0.6$ as has been suggested for long bonds. For any value of C the O−C_4 bond breaking exceeds the C_1−C_6 bond making, and the transition state is ∼40% of the way from starting material to product. However, the placement of a transition state position in Figure 5 based on transition state O−C_4 and C_1−C_6 distances is arbitrary over a broad area.

Consideration of the 1,4-diyl versus bis-allyl character of the transition state from different perspectives raises a problem with the whole idea. Table 6 shows a comparison of the C_1−C_2, C_2−O, C_4−C_5, and C_5−C_6 bond lengths in the calculated transition structures compared to calculated bond lengths for models for the 1,4-diyl and bis-allyl extremes (isopropyl and 1-hydroxyethyl radicals for the 1,4-diyl, allyl, and oxallyl radicals for the bis-allyl). All of the relevant bonds in the 1,4-diyl models are longer than the corresponding bonds in the bis-allyl models. Assuming a linear relationship between the total of the C_1−C_2, C_2−O, C_4−C_5, and C_5−C_6 bond lengths in the calculated transition structures and the 1,4-diyl versus bis-allyl character in these
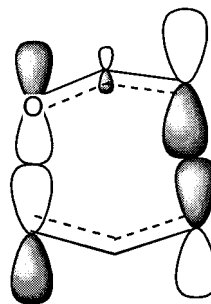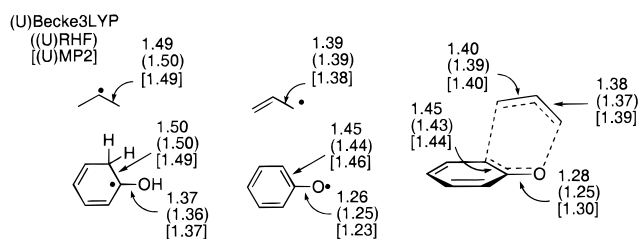
structures, the MP2, MP4, RHF, and Becke3LYP structures are all very near the bis-allyl extreme! On the other hand, an energetic analysis shows that the O−C_4 and C_1−C_6 bonds are nowhere near the dissociative limit. The heat of dissociation of allyl vinyl ether into allyl and oxallyl radicals is ∼48 kcal/mol, while the relative heat of formation of the 1,4-diyl is ∼49.5 kcal/mol.[41] At 29.5 kcal/mol,[25] the transition state for the aliphatic Claisen would not be expected to be near either corner of the More O'Ferrall−Jencks diagram.

This conflict in the description of the Claisen transition state arises from an erroneous implicit assumption in the two-dimensional More O'Ferrall−Jencks diagram that substantial bonding between the allyl and oxallyl fragments requires a compensatory decrease in C_1−C_2, C_2−O, C_4−C_5, and C_5−C_6 bonding. The Claisen transition state cannot be described as a tradeoff between the 1,4-diyl and allyl/oxallyl extremes—it has the structural properties of both. As pointed out previously by Carpenter,[42] the More O'Ferrall−Jencks diagram ignores the cyclically delocalized nature of the allowed pericyclic transition state. Another way of understanding the inaccuracy of this representation can be understood from the simple FMO description of [3,3]-sigmatropic rearrangements shown in Figure 6. Within FMO theory, one explanation for the allowed nature of the Claisen rearrangement is a bonding interaction between the HOMO of an oxallyl anion and the LUMO of allyl cation (or between the SOMO's of oxallyl and allyl radicals). This interaction can strongly stabilize the association of allyl and oxallyl groups without significant reorganization of the structure toward the 1,4-diyl. This allows a qualitative description of the Claisen transition state, consistent with both structural and energetic observations, as allyl/oxallyl fragments bound by cyclic delocalization. This is consistent with the Carpenter model of substituent effects in these reactions.

A similar analysis applies to the aromatic Claisen rearrangement. Figure 7 shows the calculated bond lengths in 2-propyl, allyl, 1-hydroxycyclohexadienyl, and phenoxy radicals compared

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Table 7. Average Integrations and R/R_0's for ^{13}C and ^{2}H Isotope Effects

	C_α	C_β	C_γ	C_1	C_2	C_3	C_4	n
			Allyl phenyl ether ^{13}C integrations and R/R_0's					
expt 1	997.2	1010.0	1068.6	957.9	2062.4	2018.9	1000.0	5
standard	923.4	1004.9	1009.8	955.3	2015.9	2002.2	1000.0	5
R/R_0	1.080	1.005	1.058	1.003	1.023	1.008	1.000	
$\Delta R/R_0$	0.009	0.012	0.016	0.006	0.008	0.010	-	
expt 2	973.0	1000.9	1046.6	952.0	2039.0	2001.8	1000	8
standard	921.6	997.3	1006.7	951.4	2006.8	1993.8	1000	8
R/R_0	1.056	1.004	1.040	1.001	1.016	1.004	1.000	
$\Delta R/R_0$	0.005	0.004	0.005	0.004	0.003	0.004	-	
expt 3	1020.8	995.5	1049.3	929.7	2040.3	1988.7	1000	7
standard	973.6	990.7	1001.4	928.9	2010.2	1991.5	1000	5
R/R_0	1.048	1.005	1.048	1.001	1.015	0.999	1.000	
$\Delta R/R_0$	0.012	0.015	0.015	0.011	0.011	0.015	- - - -	

	C_1	C_2	C_4	C_5	C_6	n
		allyl vinyl ether ^{13}C integrations and R/R_0's				
expt 1	1039.5	970.1	1057.2	1000	1039.4	6
standard	1011.8	969.3	988.6	1000	1009.1	4
R/R_0	1.027	1.001	1.069	1.000	1.030	
$\Delta R/R_0$	0.005	0.003	0.003	-	0.002	
expt 2	1037.9	972.0	1054.2	1000	1039.1	5
standard	1011.8	969.3	988.6	1000	1009.1	4
R/R_0	1.026	1.003	1.066	1.000	1.030	
$\Delta R/R_0$	0.003	0.002	0.004	-	0.002	

	H-γ_{cis}	H-γ_{trans}	H-β	H-α	H$_{meta}$	n
		allyl phenyl ether ^{2}H integrations and R/R_0's				
expt 1	517.4	540.7	523.9	1654.3	1000.00	6
standard	557.1	578.5	547.1	1360.9	1000.00	8
R/R_0	0.929	0.935	0.958	1.216	1000.00	
$\Delta R/R_0$	0.033	0.020	0.038	0.030	1000.00	
expt 2	486.3	486.8	480.2	1410.8	1000.00	5
standard	519.6	515.8	513.2	1208.5	1000.00	7
R/R_0	0.936	0.938	0.936	1.167	1000.00	
$\Delta R/R_0$	0.017	0.019	0.025	0.015	1000.00	

to the predicted bond lengths for the aromatic Claisen transition structures from Figure 2. The close agreement of the transition structure geometries with the allyl radical/phenoxy radical models is striking. Even with the relatively "1,4-diyl-like" MP2 transition structure, only the C—O distance is not very heavily weighted toward the bis-allyl extreme. Nonetheless, the C_2—C_γ and O—C_α distances of 2.05 and 1.98 Å are not so highly dissociative; they are much more bonding than expected if allyl radical/phenoxy radical character precluded the bonding between fragments associated with 1,4-diyl character.

Conclusions

It was recently concluded that "theory has been *modestly* [emphasis added] successful in reproducing the KIEs and energies of 3,3-shift transition states."[7] The results here demonstrate that theory can be highly successful at both, provided that the experimental KIEs are accurate and that appropriate methodology is used in predicting KIEs. There appear to be some limitations on the accuracy of deuterium KIE predictions using simple methodology, but a one-dimensional infinite parabolic barrier correction to tunneling suffices for heavy-atom KIE predictions in cases where no proton transfer occurs. The diversity of theoretical transition structures for the Claisen rearrangement can thus be sifted using comparisons of experimental and predicted KIEs as a guide. In both the aromatic and aliphatic Claisen, the transition state appears to be inter-mediate in nature between the B3LYP/6-31G* and the MP2/

6-31G* structures. In the case of the aliphatic Claisen, this is best represented by the MP4/6-31G* structure.

With some credibility given to some of the theoretically predicted transition structures for the Claisen and aromatic Claisen rearrangements, the difficulty of describing the nature of the transition states for these reactions in simple terms becomes apparent. The multidimensional bonding changes occurring along the reaction coordinate are not well described by two dimensions involving a simple tradeoff between 1,4-diyl and bis-allyl character. This does not mean that variation in the 1,4-diyl and bis-allyl character with substituents does not occur. However, other dimensions, particularly the aromaticity of the transition state, are necessary to describe the transition state geometry and should be important in substituent effects as well.

Experimental Section

Claisen Rearrangements of Allyl Phenyl Ether. As an example procedure (experiment 2 in Table 3), a mixture of 102.09 g (0.76 mol) of allyl phenyl ether, 0.07 g (0.88 mmol) of pyridine (to inhibit acid-catalyzed cyclization of the product), and 8.02 g of hexadecane (internal standard) was heated to 170 ± 5 °C under N_2 with stirring. Aliquots were periodically removed, and the progress of the reaction was analyzed by ^{1}H NMR based on the ratio of the allyl phenyl ether to the product 2-allylphenol, and by GC versus the hexadecane. (The two methods were found to agree on the absolute amount of allyl phenyl ether remaining to within the standard error of each measurement.) After 31 h the conversion was 89.4 ± 1.0%. After cooling to 25 °C, 100 mL of diethyl ether were added and the mixture was extracted

Table 8. Average Integrations and R/R_0's for ^{17}O Isotope Effects

	allyl phenyl ether		allyl vinyl ether	
	expt 1	expt 2	expt 1	expt 2
		^{13}C Spectra		
acetone in sample[a]	2058.3	570.1[b]	1965.7	2009.3
SD	8.5 ($n = 4$)	1.9 ($n = 4$)	5.6 ($n = 6$)	4.2 ($n = 6$)
acetone in standard[a]	1970.3	600.2[b]	1931.5	1931.5
SD	5.8 ($n = 4$)	2.4 ($n = 4$)	2.3 ($n = 6$)	2.3 ($n = 6$)
acetone in sample/ acetone in standard	1.045	0.949	1.018	1.040
SD[c]	0.005	0.005	0.003	0.002
		^{17}O Spectra		
sample[d]	879.0	1135.7	1066.3	1044.2
SD	4.5 ($n = 4$)	8.5 ($n = 4$)	3.1 ($n = 4$)	7.3 ($n = 4$)
standard[d]	887.3	1054.8	1057.6	1057.6
SD	7.9 ($n = 4$)	4.3 ($n = 4$)	3.8 ($n = 8$)	3.8 ($n = 8$)
R/R_0[e]	1.035	1.022	1.026	1.027
$\Delta R/R_0$[c]	0.012	0.010	0.006	0.008

[a] Average integration for the acetone methyl carbons, except as noted, relative to 1000 for C_4 of allyl phenyl ether or C_5 of allyl vinyl ether. [b] Average integration for the acetone carbonyl carbon. [c] Calculated as the square-root of the sum of the squares of the relative errors in the component values. [d] Average integration for the oxygen of allyl phenyl ether or allyl vinyl ether, relative to 1000 for acetone. [e] Ratio of ^{17}O integrations for the sample compared to standard, multiplied by the relative ratio of acetone in the sample versus standard.

with three 100-mL portions of 5.0 M aqueous NaOH. The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated on a rotary evaporator. The residue was subjected to two successive chromatographic purifications on 4 cm × 15 cm silica gel columns using 10% ethyl acetate/petroleum ether as eluent to afford the unreacted allyl phenyl ether in >99% purity (GC analysis).

An analogous reaction, experiment 1 in Table 3, was taken to 94.7 ± 0.4% conversion. In another reaction designed to approximate the conditions used to measure the ^{14}C and ^{18}O isotope effects for this reaction,[16a,b] (experiment 3 in Table 3) a mixture of 69.77 g (0.52 mol) allyl phenyl ether, 1651 g (0.018 mol) of diphenyl ether, and 4.31 g (0.018 mol) of hexadecane was heated to 220 ± 5 °C and taken to 91.3 ± 1.0% conversion. An extractive workup as above was followed by a series of recrystallizations from diethyl ether to remove the bulk of the diphenyl ether and chromatography on a 4 cm × 15 cm silica gel column using 4% dichloromethane /petroleum ether as eluent to afford 1.65 g of the unreacted allyl phenyl ether.

Claisen Rearrangements of Allyl Vinyl Ether. As an example procedure (experiment 1 in Table 4), a mixture of 75.25 g (0.895 mol) of allyl vinyl ether, 1500 mL of *p*-cymene, and 7.42 g of diglyme (internal standard) was heated to 120 ± 2 °C under N_2 with stirring. Aliquots were periodically removed, and the progress of the reaction was analyzed by GC. After 22 h the conversion was 86.5 ± 0.8%. Vacuum transfer of the cooled reaction mixture followed by fractional distillation on a glass-bead column afforded 4.025 g of allyl vinyl ether in >99% purity (GC). An analogous reaction was taken to 86.7 ± 1.1% conversion for experiment 2 in Table 4.

NMR Measurements. For each reaction the NMR spectra of the samples of recovered allyl phenyl ether or allyl vinyl ether were compared with standard material from the same synthetic lot as used in the reaction. The NMR samples of standard and recovered material were in each case prepared identically. ^{13}C NMR spectra were taken on ~3:1 mixtures of allyl vinyl ether or allyl phenyl ether with $CDCl_3$. ^2H NMR spectra were taken unlocked on neat samples. ^{17}O and ^{13}C NMR spectra for ^{17}O KIE measurements were taken ~1:1:1 mixtures of allyl vinyl ether or allyl phenyl ether, acetone, and $CDCl_3$. A T_1 determination by the inversion−recovery method was carried out on each NMR sample.

The ^{13}C spectra were recorded at 100.58 MHz on a Varian 400 NMR with inverse gated decoupling, using 134 s delays between calibrated 33° pulses for allyl phenyl ether and 130 s delays between calibrated 45° pulses for allyl vinyl ether. For allyl phenyl ether an acquisition time of 13.622 s was used and 489 984 points were collected, and for allyl vinyl ether an acquisition time of 5.014 s was used and 327 680 points were collected. The ^2H spectra for allyl phenyl ether were recorded at 61.395 MHz on a Varian 400 NMR at controlled temperature of 30 °C with calibrated 40° pulse widths, using an

acquisition time of 2.97 s and a 3.0 s delay between acquisitions. Integrations were determined numerically using a constant region for each peak that was ~5 times the peak width at half-height distance on either side of the peak. A zeroth order baseline correction was generally applied, but in no case was a first order (tilt) correction applied.

Results from All Reactions. For the ^{13}C and ^2H spectra, the integration of C_4 of allyl phenyl ether, C_5 of allyl vinyl ether, or the meta aromatic deuterium peak was set to 1000. The average integrations for the other carbons or deuteriums for each reaction, along with the standard results for the starting materials, are shown in Table 7. In each case *n* is the total number of spectra obtained. Table 7 also shows the values for R/R_0, calculated as the ratio of average integrations for recovered material relative to the standard. The standard deviations were calculated from eq 2.

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

The isotope effects and errors shown in Tables 3 and 4 were then calculated as previously described.[21]

^{17}O **Isotope Effects.** For the ^{13}C spectra of the acetone/sample or acetone/standard mixtures, the integration of C_4 of allyl phenyl ether or C_5 of allyl vinyl ether was set at 1000. The resulting average integrations for the acetone methyl carbons are shown in Table 8, along with calculated relative ratios of acetone in the sample. In one case an instrument problem led to incomplete decoupling of the acetone methyl group, and the carbonyl carbon was used instead. For the ^{17}O spectra the acetone oxygen integrations were set at 1000, and the resulting average integrations for the oxygens of allyl phenyl ether or allyl vinyl ether are given in Table 8. R/R_0's were then calculated as the ratio of ^{17}O integrations for the sample compared to standard, multiplied by the relative ratio of acetone in the sample versus standard. In each case errors were propagated in a standard fashion as the square root of the sum of the squares of the component errors. The $^{16}O/^{17}O$ isotope effects and errors shown in Tables 3 and 4 were then calculated as previously described.[29]

Supporting Information Available: Geometries and energies for new calculated structures and tables of calculated isotope effect without tunneling corrections. This material is available free of charge via the Internet at http://pubs.acs.org.

JA992372H