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Transition Structures for the Claisen Rearrangement

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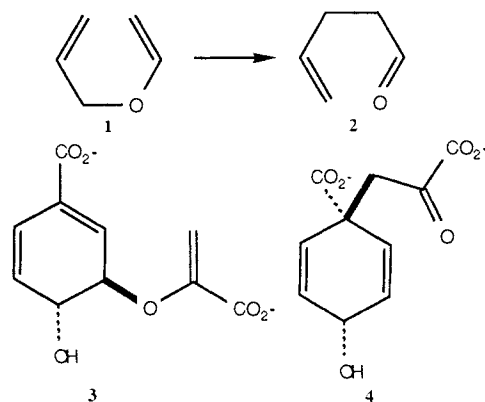
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The Claisen rearrangement of allyl enol ethers (**1** → **2**) is a [3,3]-sigmatropic shift that is extremely valuable in synthesis.¹ The enzyme-catalyzed rearrangement of chorismate, **3** to prephenate, **4**, has caused this reaction also to be of considerable interest in bioorganic circles.² Much effort has been invested in the creation of chorismate mutase inhibitors designed to be transition state analogues for the [3,3]-sigmatropic shift.³

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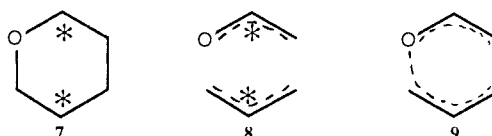
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The stereoselectivities observed for reactions of substituted molecules have led to the deduction that the transition structure for this transformation is chairlike, **5**, rather than boatlike, **6**.⁴



The same chair stereochemistry has been deduced for the enzymatic process.⁵ The extent of bond making and bond breaking has been controversial. At one extreme, the reaction might occur in two stages, via diradical or zwitterionic species, **7** or **8** (* denotes charge or an unpaired electron). Intermediate **7** is the result of CC bond making before CO bond breaking. This sequence of events is predicted by semiempirical quantum mechanical calculations.⁶ On the other hand, greater balance between CC bond making and CO bond breaking, to give the "aromatic transition state", **9**, has been deduced from secondary isotope effects⁷ and substituent effects on rates.⁸ Substituent effects also suggest that there is some charge separation in the transition states of reactions of substituted derivatives.⁸



We have performed ab initio quantum mechanical calculations to define the geometries and electronic characteristics of the chair and boat transition structures for the parent reaction. Our initial studies used the 3-21G, 4-31G, and 6-31G* basis sets.^{9,10} Geometries were optimized at the RHF level, and energies, including electron correlation, were calculated at the MP2/6-31G* level.¹⁰ MCSCF studies of the related Cope rearrangement have shown that RHF/3-21G geometries are similar to those obtained at adequate MCSCF levels.¹¹ Of course, a stable true diradical will

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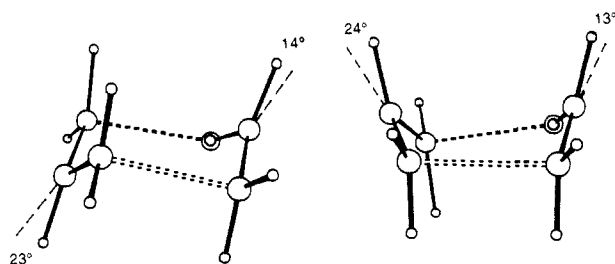


Figure 1. The HF 6-31G* chair and boat Claisen rearrangement transition structures. Angles are deviations of each CH bond from the plane of attached allyl or oxallyl fragment.

Table I. 6-31G* Bond Lengths for Allyl Vinyl Ether (1), Chair (5) and Boat (6) Claisen Rearrangement Transition Structures, and 4-Pentenal (2)

structure	C ₁ C ₂	C ₁ C ₆	C ₂ O	C ₄ O	C ₄ C ₅	C ₅ C ₆
1	1.320		1.342	1.399	1.500	1.317
5	1.374	2.264	1.261	1.917	1.390	1.376
6	1.373	2.362	1.257	1.980	1.385	1.375
2	1.507	1.539	1.188		1.319	1.505

not be found by RHF calculations. Similar conclusions have been reached for calculations on related pericyclic reactions such as the cyclobutene electrocyclic reaction¹² and the [1,5]-sigmatropic shift in 1,3-pentadiene.¹³ Since polarization functions have been shown to be important in some cases where carbonyl groups are involved, we also reoptimized the transition structures with the 6-31G* basis set. As shown below, only negligible changes in geometry occurred, although the reaction energetics are much more satisfactory.

The structures of the chair and boat transition structures are shown in Figure 1.¹⁴ Bond lengths for these and for 1 and 2 are given in Table I, and energies are summarized in Table II. The chair transition structure is more stable than the boat by 6.6 kcal/mol at the highest level investigated.

The surprisingly large difference between the energy of the chair and boat at the 3-21G level is likely related to the fact that the relative energies of conformations of unsaturated oxygen-containing molecules are very poor at the 3-21G level but reasonable at the 6-31G* level.^{9,12} The allyl fragment geometry is very similar to that of the two allyl moieties in the chair and boat Cope transition structures.^{11,16} Calculations on the Cope rearrangement with the 3-21G basis set give allyl CC bond lengths of 1.383–1.386 Å, compared to 1.381–1.388 Å here for the chair and boat Claisen and 1.389 Å for the allyl radical itself (UHF/3-21G).⁹ The oxallyl fragment geometry (CC = 1.374; CO = 1.290 Å) in the transition

Table II. Energies Relative to Allyl Vinyl Ether, 1 (kcal/mol)

level	ΔE (chair)	ΔE (boat)	ΔE (product)
RHF/3-21G	43.6	60.4	-0.8
RHF/4-31G	43.5		
RHF/6-31G* ^a	48.6	53.3	-21.9
RHF/6-31G*	48.8	53.3	-21.3
RMP2/6-31G* ^a	24.6	31.2	-23.2
$\Delta\Delta H^{b,c}$	-1.7	-1.8	
ΔH^*	22.9	29.4	
exptl ΔH^* ^d	29.8	32.8 ^e	-17.0 ^f
ΔS^* ^c	-7.7	-6.5	
exptl ΔS^* ^d	-7.7		+0.8 ^f

^a On RHF/3-21G optimized geometries. ^b ZPE and finite temperature correction at 455 K. ^c Calculated at $T = 455$ K using RHF/3-21G frequencies scaled by 0.89.⁹ ^d Gas-phase values from Schuler and Murphy (Schuler, F. W.; Murphy, G. W. *J. Am. Chem. Soc.* **1950**, *72*, 3155). Burrows and Carpenter (Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983) report $\Delta H^* = 25.4$, $\Delta S^* = -1.59$ in dibutyl ether solvent, while Gajewski et al.^{8b} report $\Delta H^* = 28.2$. ^e Heat and entropy of reaction were calculated from Benson's group equivalents; Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley-Interscience; New York, 1976.

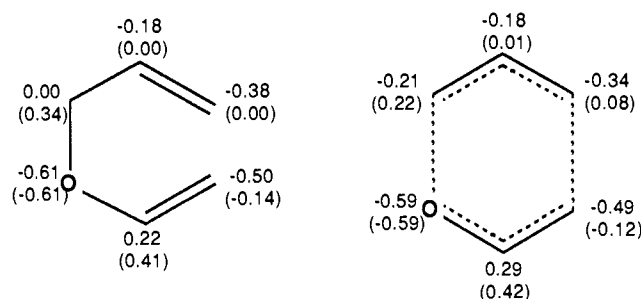


Figure 2. Mulliken charges (HF 6-31G*) for allyl vinyl ether and the chair transition structure. The numbers in parentheses are the sums of the charges on each heavy atom plus the attached hydrogens.

structure is similar to that of UHF/3-21G oxallyl radical (CC = 1.384; CO = 1.300 Å).⁹ The partially formed CC bond length is 2.1–2.2 Å, about the same as found for the Cope rearrangement¹¹ and other pericyclic reactions.^{12,17} The CO bond is stretched 33% from its reactant value, indicating appreciable CO bond breaking, which is qualitatively consistent with the isotope effect of 31% of the maximum possible observed by Gajewski and Conrad.⁷ On the other hand, the structure differs markedly from that obtained from semiempirical MNDO calculations,⁶ which predict essentially no stretching of the CO bond and considerable CC bond formation. This new geometry should provide a better model for the development of enzyme inhibitors.

As is typical for pericyclic reactions, the RHF activation energy (Table II) is too high, but correlation energy corrections at the MP2 level give a value reasonably close to the experimental values. After inclusion of correlation corrections, the calculated activation energy is too low, most likely due to the relatively small basis set used for these calculations.^{12,13}

The Mulliken charges at various positions in the reactant and chair transition structure are shown in Figure 2. The total group charge changes little, except at C₄, which becomes more negative, and C₆, which becomes more positive in the transition structures. There is no correlation of these charge changes with the observed effects of donor and acceptor substituents on rates of rearrangement.⁸

Transition structures for substituted Claisen rearrangements are under investigation.

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