

Theory of Substituent Effects on Pericyclic Reaction Rates: Alkoxy Substituents in the Claisen Rearrangement

Hi Young Yoo and K. N. Houk*

Contribution from the Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90095-1569

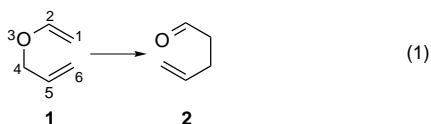
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Abstract: Transition structures, activation energies, and reaction energies were calculated by *ab initio* quantum mechanical methods for the Claisen rearrangements of five hydroxy-substituted allyl vinyl ethers. The RHF, DFT-(Becke3LYP), and CASSCF methods with the 6-31G* basis set were carried out. There is good agreement with activation energies measured for alkoxy-substituted compounds. The activation energies were separated into thermodynamic and intrinsic effects using Marcus theory as adapted by Murdoch for pericyclic reactions. Intrinsic effects were analyzed by frontier molecular orbital theory. The deuterium kinetic isotope effects calculated at the CASSCF/6-31G* level for the 2-OH allyl vinyl ether are in good agreement with the experimental results for the 2-OSiMe₃ derivative, and these calculated isotope effects show much more bond-breaking and less bond-making than those at both the RHF/6-31G* and Becke3LYP/6-31G* levels.

Introduction

Pericyclic reactions have relatively nonpolar transition states with considerable cyclic delocalization referred to as “aromatic character”.¹ Although the effects of substituents on rates are well understood for certain classes of pericyclic reactions, such as cycloadditions² and electrocyclic reactions,³ there is no general theory of rates of pericyclic reactions for all classes. We report an analysis of alkoxy substituent effects on Claisen rearrangements and a general method of analysis which should provide a framework for the development of a general theory.

Substituent effects on the rates of Claisen rearrangements (eq 1) have been experimentally investigated extensively.⁴ Dipolar



character in the transition state has been suggested by the studies of the origin of rate acceleration for these processes.^{4a–c} However, the degree of charge separation in the transition state has been debated.^{4a–c} Electron donor groups at C-1 and C-2

accelerate the rearrangement.^{4a,5} Methoxy groups at C-4 and C-6 accelerate the reaction, but a methoxy group at C-5 decelerates the reaction.^{4a}

Theoretical studies of rate effects have led to predictions which are not always consistent with the experimental results.^{4a,e,6} Carpenter's HMO model predicted rate deceleration by a donor group at C-6 rather than the rate acceleration observed.^{4a,e} Dewar's MNDO calculation predicted rate acceleration by a methoxy group at C-5 in contrast to the experimental result.^{4a,6}

Recently, Gao has reported RHF calculations on substituent effects and a QM/MM study of solvent effects on the rates of the Claisen rearrangement of substituted allyl vinyl ethers.⁷ His work has led to interesting predictions of solvent effects, some extremely large. Previously, various theoretical studies were investigated in order to understand the solvent rate effect for the Claisen rearrangement of allyl vinyl ether. The AM1-SM2 model study by Cramer and Truhlar⁸ and Monte Carlo simulations by Severance and Jorgensen⁹ show that the solute polarizability,⁸ as well as enhanced hydrogen bonding in the transition state,⁹ causes the rate effect. This polarization effect is also observed in Gao's QM/MM approach.¹⁰ The polarizable continuum models (PCM) combined with *ab initio* wave functions predict a solvation rate effect which is in good agreement with the experimental result.¹¹

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We have used *ab initio* calculations to investigate substituent effects on the rates of the Claisen rearrangements of substituted allyl vinyl ethers. Marcus theory has been used to separate thermodynamic and intrinsic contributions to activation energies, as proposed for pericyclic reactions by Murdoch.¹² Frontier molecular orbital theory has been used to understand substituent effects on intrinsic barriers. Understanding the origin of rate effects in the Claisen rearrangements of substituted allyl vinyl ethers provides a prototype for understanding substituent effects on other pericyclic reactions.

Computational Methods

Geometry optimizations and vibrational frequency calculations were carried out with the GAUSSIAN 92/DFT program¹³ using RHF and the Becke3LYP methods.¹⁴ The 6-31G* basis set was used for all calculations. A six electron/six orbital complete active space CASSCF calculation was performed with GAMESS¹⁵ and GAUSSIAN 94¹⁶ programs. All stationary points were characterized by vibrational frequency calculations. The self consistent reaction field (SCRFF)¹⁷ calculation was used to estimate solvent effects on rates. Previously, a continuum solvation model study (SM4-SRP) by Storer et al.¹⁸ showed reasonable solvation rate effects for the Claisen rearrangement of allyl vinyl ether in comparison with Gao's QM/MM calculation.⁷ The spherical cavity radius was determined by the method implemented in GAUSSIAN which involves computing the 0.001 au electron density envelope, scaling by 1.33, and adding 0.5 Å to the final cavity radius.¹³ A Monte Carlo conformational search was carried out for reactants and products using MacroModel version 4.5 with the MM3* force field to obtain information on relative energies of conformers.¹⁹ The force constants were used to calculate the theoretical isotope effects by using the program Quiver.²⁰ Frequencies from RHF/6-31G* calculations were scaled by 0.90, and frequencies from Becke3LYP/6-31G* and CASSCF/6-31G* calculations were not scaled.

Experimental Substituent Effects

The Claisen rearrangement of allyl vinyl ether has experimental activation enthalpies of 30.6 kcal/mol in the gas phase at 180 °C and

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Table 1. Experimental Activation Parameters (in Benzene) and Relative Rates in Various Solvents for the Claisen Rearrangements of Parent and Methoxy-Substituted Allyl Vinyl Ethers at 80 °C^a

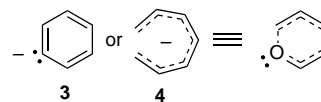
	ΔH^\ddagger (kcal/mol)	ΔS^\ddagger (eu)	k_{rel} (benzene- <i>d</i> ₆ , acetonitrile- <i>d</i> ₃ , methanol- <i>d</i> ₄)
parent	25.4 ± 0.7 ^b	-15.9 ± 1.5 ^b	1.0, 1.5, 1.7 at 134 °C
4-OMe	22.4 ± 0.4	-14.7 ± 1.0	1.0, 2.1, 18 at 65 °C
5-OMe	30.9 ± 0.9	-7.0 ± 2.0	1.0, 1.5, <i>c</i> at 139 °C
6-OMe	24.7 ± 0.3	-12.8 ± 0.7	1.0, 3.2, 68 at 80 °C

^a Reference 4a. ^b Activation parameters were measured in di-*n*-butyl ether and ref 4d. ^c The rate for the 5-methoxy allyl vinyl ether in methanol-*d*₄ was not reported.

25.4 kcal/mol in di-*n*-butyl ether at 113–173 °C.²¹ The effects of 2-(trialkylsiloxy) substituents on allyl vinyl ethers are well-known in the Ireland–Claisen rearrangement. The experimental ΔG^\ddagger of the 2-(trimethylsiloxy) allyl vinyl ether ($t_{1/2} = 210 \pm 30$ min) is about 8 kcal/mol less than that of the parent at 32 °C, using the experimental rate constants²² and the Eyring equation. Activation energies of the 4-, 5-, and 6-methoxy allyl vinyl ethers were measured in benzene-*d*₆ at 80 °C, and the rates of these three methoxy systems were also measured in acetonitrile-*d*₃ and methanol-*d*₄ at various temperatures.^{4a} As summarized in Table 1, methoxy groups at C4 and C6 lower the activation barriers by 3.0 and 0.7 kcal/mol, respectively. At the C5 position, the activation energy is raised by 5.5 kcal/mol. The solvent effects on rates are significant for the 4- and 6-methoxy-substituted allyl vinyl ethers, while the effect of solvent polarity on rates is small for parent and the 5-methoxy allyl vinyl ether.^{4a} Curran and Suh found ~10–20-fold rate increases for the Claisen rearrangement when a methoxy group is present at the C6 position.²³

Qualitative Theories of Substituent Effects

Carpenter proposed a simple Hückel molecular orbital theory (HMO) for substituent effects on pericyclic reactions.^{4e,24} The π energy of a molecule possessing a π system which is isoconjugate with the transition state was compared to the π energy of the reactant.²⁴ For the Claisen rearrangement, two transition state models were tested. Either a phenyl anion, **3**, or a heptatrienyl anion, **4**, yield the same substituent effects, except for an acceptor at C5.^{4e} HMO calculations predict that a donor group at C1, C2, or C4 would lower the activation energy, while a donor at C5 or C6 would raise the barrier of the Claisen rearrangement of allyl vinyl ether. Predictions made from HMO calculations for C1–C5 positions are in accord with the experimental studies.^{4a,c,22} However, methoxy groups at C6 accelerate the reaction.^{4a}



Dewar's MNDO calculations predicted that the Claisen rearrangement of allyl vinyl ether proceeds through biradicaloid transition state **5**.⁶ Later AM1 calculations indicated that the distinction between aromatic and biradicaloid transition states is not so apparent for the Claisen rearrangement of allyl vinyl ether.²⁵ The energy was 0.7 kcal/mol lower for the biradicaloid transition state than for the aromatic transition state. The CO and CC bond lengths for the biradicaloid transition state are

(21) The experimental ΔH^\ddagger is 30.6 kcal/mol in the gas phase (Schuler, F. W.; Murphy, G. W. *J. Am. Chem. Soc.* **1950**, *72*, 3155) and 25.4 kcal/mol in dibutyl ether solvent.^{4d}

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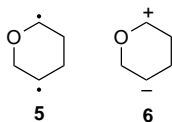
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Table 2. Calculated Activation Energies (kcal/mol) for the Claisen Rearrangement of Allyl Vinyl Ether

method	ΔE_a
RHF/6-31G* ^a	48.8
RMP2/6-31G* ^{a,b}	(24.3), ^c 26.1
RMP4/6-31G* ^c	[30.4], ^d 26.4 ^e
Becke3LYP/6-31G* ^f	26.8
Becke3LYP/6-311+G** ^f	26.1
CASSCF/6-31G* ^g	42.5
experiment, ΔH^\ddagger ^h	(30.6), ^h [34.1] ⁱ

^a Reference 26. ^b Reference 27. ^c The value in parentheses is enthalpy of activation, ΔH^\ddagger . ^d The reported values in brackets is the activation free energy from ref 11b. ^e Reference 32. ^f Reference 28. ^g Reference 29. ^h Reference 21. ⁱ The value in brackets is the activation free energy in the gas phase from ref 21.

1.577 and 1.843 Å, respectively, from the AM1 calculation.²⁵ Substituent effects on the rates at C2 and C5 of allyl vinyl ether were explained in terms of the polarizability of biradicaloids. Donor groups can stabilize a polarized species, **6**, more at C2 than C5. Both MNDO and AM1 calculations predicted rate acceleration by a methoxy group at C5.^{6,25} AM1 calculation predicted rate acceleration at C4 and rate deceleration at C6.²⁵ Experimental studies show instead a rate acceleration by methoxy groups at C4 and C6 and the rate deceleration at C5.^{4a}

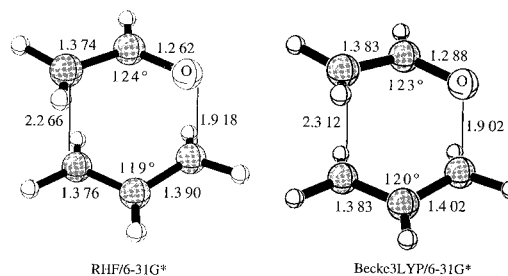


Neither the qualitative theory based on HMO calculations nor semiempirical calculations provide a general explanation of substituent effects.

Computational Results

Substituent Effects on Activation Energies. Calculated and experimental activation energies²¹ for the Claisen rearrangement of parent allyl vinyl ether are listed in Table 2. The MP2/6-31G* calculations lower the E_a by inclusion of electron correlation in comparison with the RHF calculation.^{26,27} The nonlocal DFT calculated activation energies^{27b,28} are 3–4 kcal/mol lower than the experimental result, but in better agreement with the experiment than RHF or CASSCF results.²⁹ Isotope effects from these DFT calculations are in best agreement with experiment.²⁸ A recent MP4 calculation predicts an activation free energy of 30.4 kcal/mol, which can be compared with the experimental value in the gas phase (34.1 kcal/mol).^{11b}

Calculations reported here involve RHF/6-31G* transition structures; this parent transition structure is compared to the DFT structure in Figure 1. Calculations were carried out with hydroxy groups to model donors like methoxy groups. In the course of our work, Gao reported calculations on methoxy-substituted cases.⁷ Calculated activation energies at the RHF/6-31G* level are listed in Table 3 along with available experimental results. As expected, the calculated activation energies at the RHF/6-31G* level are high compared to the experimental results.^{4a} However, the relative energies between

**Figure 1.** Optimized transition structures for the Claisen rearrangement of allyl vinyl ether at RHF/6-31G* and Becke3LYP/6-31G* levels. Bond lengths (Å) and angles are given.

parent and substituted systems which are shown in parentheses in Table 3 are in reasonable agreement with the experimental values.

Hydroxyl substitution at C1 or C2 accelerates the rearrangement. The activation energies for the 1- and 2-hydroxy allyl vinyl ethers are predicted to be lowered by 2.6 and 8.7 kcal/mol, respectively, with respect to the parent system. There is no experimental study done for a 1-methoxy substituent, but other donors at C1 accelerate the reaction.⁵ For example, the half-life for rearrangement of a morpholino-substituted compound at C1 is 29 h at 40 °C, while the estimated half-life for the parent at this temperature is around 5.3×10^4 h.⁵ⁱ Our calculation with a hydroxy substituent at the C2 position of allyl vinyl ether predicts a lowering of the activation barrier by 8.7 kcal/mol at the RHF/6-31G* level; a similar value is observed experimentally in the Ireland–Claisen rearrangement (Table 3).²² A hydroxy group at the C4 position of allyl vinyl ether lowers the activation energy by 1.0 kcal/mol. Experimentally, a 4-methoxy group lowers the activation energy by 3 kcal/mol. A hydroxy at C5 is predicted to raise the barrier by 4.8 kcal/mol, which is in good agreement with the experimental value for the 5-methoxy compound. The hydroxy group at C6 of allyl vinyl ether is predicted to lower the activation energy by 0.9 kcal/mol, similar to the 0.7 kcal/mol by a methoxy group observed experimentally. The 4- and 6-hydroxyl substituents accelerate the reaction, while the 5-hydroxyl decelerates it. The same rate trends are also observed in Gao's calculation at the RHF/6-31G* level using methoxy groups at C4–C6.⁷

SCRf calculations for the substituted cases at the RHF/6-31G* level were carried out to simulate solvation effects. Since most experimental data are in benzene solution, the dielectric constant of benzene, 2.284, was used for this calculation. Each reactant and transition structure was reoptimized with the SCRf solvent cavity at the RHF/6-31G* level. The resulting activation energies are listed in Table 3. There is very little difference between calculated energies of RHF gas-phase calculation and SCRf calculation for all the substituted cases.

Substituent Effects on Reaction Energies. The Claisen rearrangement of allyl vinyl ether is exothermic by ~ 17 kcal/mol.^{30,31} A recent calculation study by Yamabe et al. showed that the higher reactivities of allyl vinyl ethers and allyl aryl ethers in comparison with the other Claisen rearrangements containing hetero atoms (N, S, and P) are due to the thermodynamic factor which results from greater stability of forming the C=O bond in the product.³² The transition state is early and therefore resembles the reactant more than the product in

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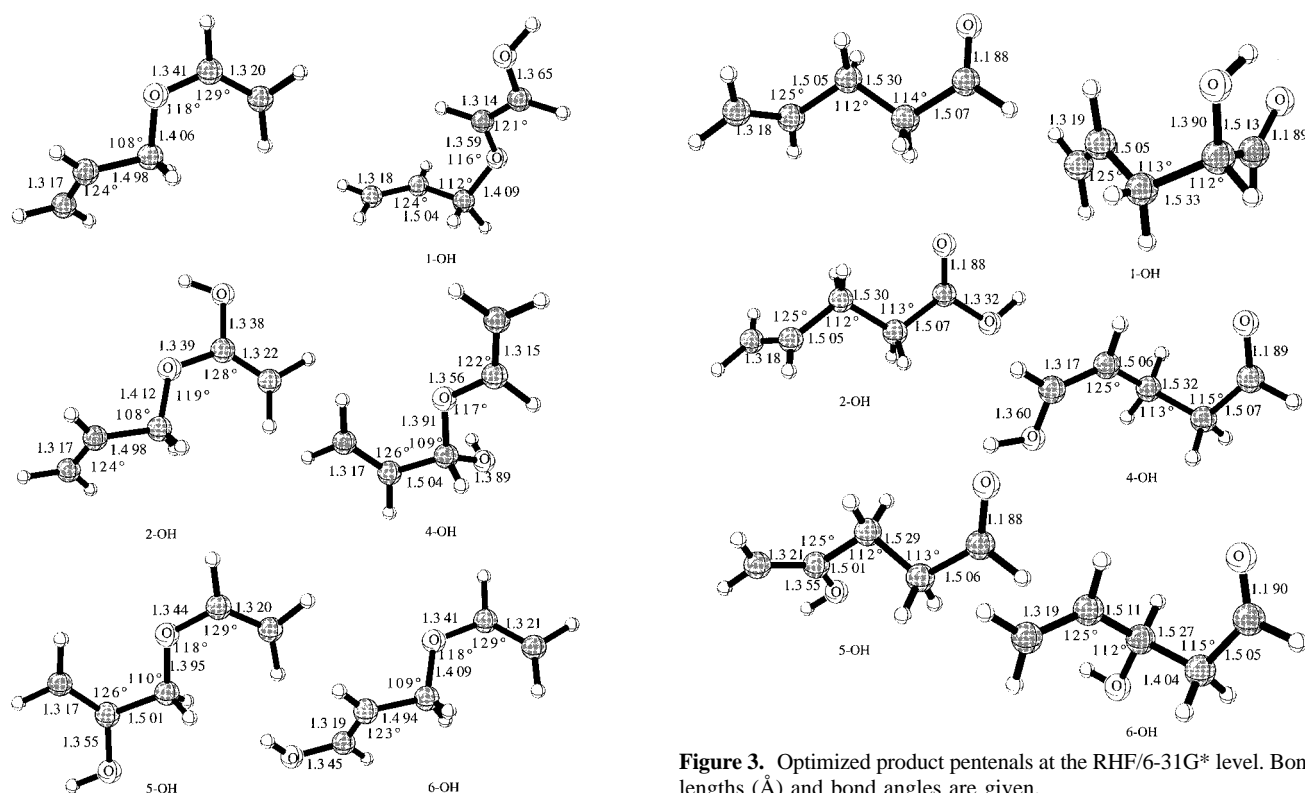
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Table 3. Activation Energies and Reaction Energies (kcal/mol) for the Claisen Rearrangements of Oxygen-Substituted Allyl Vinyl Ethers

	$\Delta H^\ddagger_{\text{expt}}^a$ exptl values	$\Delta H^\ddagger_{\text{theory}}$		ΔE_a^c RHF/6-31G*	ΔE_{rxn} RHF/6-31G*
		RHF/6-31G*	SCRF RHF/6-31G* ^b		
parent	30.6, ^d 25.4, ^e [31.3] ^f	46.9	46.6	48.8	-21.1
1-OH		44.3 (-2.6)	44.0 (-2.6)		-26.2 (-5.1)
2-OH	[23.8] ^g (-7.5)	38.2 (-8.7)	38.4 (-8.2)	39.7 (-9.1)	-39.2 (-18.1)
4-OH	22.4 (-3.0)	45.9 (-1.0)	45.5 (-1.1)	44.1 (-4.7)	-15.2 (+5.9)
5-OH	30.9 (+5.5)	51.7 (+4.8)	51.5 (+4.9)	52.8 (+4.0)	-22.3 (-1.2)
6-OH	24.7 (-0.7)	46.0 (-0.9)	45.5 (-1.1)	47.6 (-1.2)	-17.9 (+3.2)

^a The experimental activation enthalpies are obtained by using a trimethylsilyloxy group for the 2-substituted system and methoxy groups for the C4-C6 systems (ref 4a). ^b Thermal energy contributions from the gas phase RHF/6-31G* calculation were used to calculate the $\Delta H^\ddagger_{\text{theory}}$ for both gas phase and SCRF calculations. ^c Calculated activation energies of methoxy-substituted allyl vinyl ethers (ref 7). ^d In the gas phase (ref 21). ^e In dibutyl ether solvent (ref 4d). ^f Free energy of activation in dibutyl ether solvent at 100 °C. ^g For 2-(trimethylsilyloxy)allyl vinyl ether; calculated ΔG^\ddagger using Ireland's experimental value at 32 °C; see the explanation in the Experimental Substituent Effects section.

**Figure 2.** Optimized parent and hydroxy-substituted allyl vinyl ethers at the RHF/6-31G* level. Bond lengths (Å) and bond angles are given.

accord with the Hammond postulate.³³ The calculated energies of all the reactions studied here are summarized in Table 3. Reactant and product structures optimized at this level are shown in Figures 2 and 3, respectively. The reaction energy for the 2-hydroxy case is calculated to be -39.2 kcal/mol and is the most exothermic reaction, 18.1 kcal/mol more exothermic than the parent case. The product is a resonance-stabilized carboxylic acid. The rearrangements of the 4-hydroxy and 6-hydroxy cases are less exothermic than the unsubstituted case by 5.9 and 3.2 kcal/mol, respectively. The 4- and 6-hydroxy allyl vinyl ether reactants are stabilized more than products, since they are stabilized by the anomeric effect³⁴ and the vinylogous anomeric effect,^{23,35} respectively. The 1-OH reactant is destabilized due to the attachment of two electron donors to a common double

Figure 3. Optimized product pentenals at the RHF/6-31G* level. Bond lengths (Å) and bond angles are given.

bond; the rearrangement is more exothermic than the parent reaction. The 5-OH has a minor affect on the reaction energetics.

Ground State Conformation. The energetics reported are based upon the lowest energy reactant and product conformations. Severance and Jorgensen have previously studied the multiple conformations of allyl vinyl ether.³⁶ We explored the conformations of reactant and product using a Monte Carlo conformational search with the MM3* force field.¹⁹ Four torsion angles of substituted allyl vinyl ethers were varied: three

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Table 4. Dihedral Angles of Lowest Energy Reactant Structures Optimized at the RHF/6-31G* Level

	C2–O3	O3–C4	C4–C5
parent	0.8	178.0	130.0
1-OH	134.7	74.0	-128.5
2-OH	0.3	177.7	127.6
4-OH	-170.9	171.7	-3.2
5-OH	0.0	180.0	0.0
6-OH	1.3	177.8	118.4

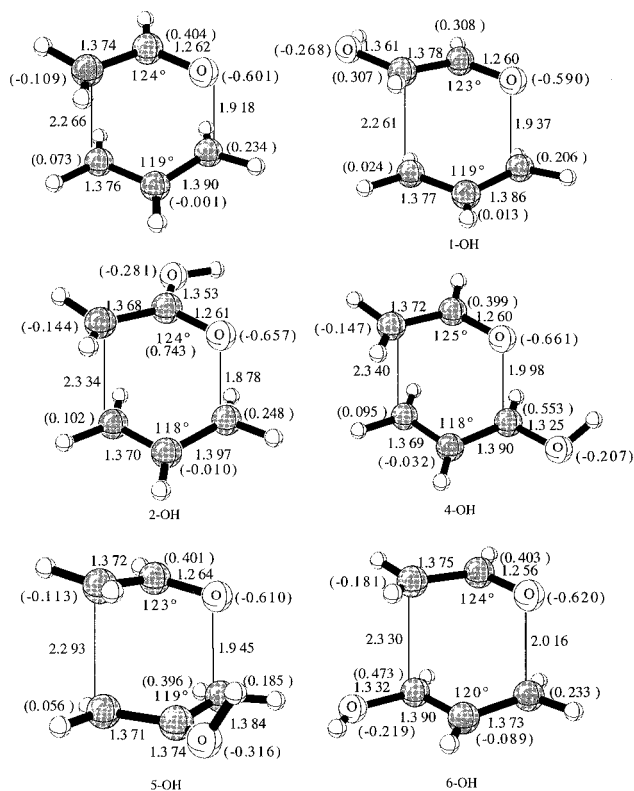
dihedral angles along the main chain of allyl vinyl ether and the dihedral angle around the CO single bond to the hydroxy substituent. The MM3* Monte Carlo conformational search yields between 14 and 30 minimum energy structures for each substrate. The energy of each structure was evaluated by a single point calculation at the RHF/6-31G* level. A smaller pool of minima (~10–15) was then chosen for each substrate by selecting those structures that were within +5 kcal/mol of the lowest energy structure. These low-energy structures were fully optimized at the RHF/6-31G* level. The resultant ordering of conformers after 6-31G* optimization is found to be substantially different from the MM3* ordering. The calculation was carried out with the 6-31G* basis set, since the relative energies of unsaturated oxygenated molecules are generally poor at the RHF/3-21G level.³⁷ The optimized allyl vinyl ethers are shown in Figure 2, and dihedral angles are listed in Table 4.

The dihedral angle about C4–C5 is 120° for the parent and 1-, 2-, and 6-OH-substituted allyl vinyl ethers. This dihedral angle is 0° for the 4- and 5-OH-substituted reactants. These dihedral angle preferences around C4–C5 as well as those around C2–O3 and O3–C4 and CO single bond to the hydroxy substituent are in good agreement with values found in Severance and Jorgensen's study of allyl vinyl ether.³⁶ The optimized pentenal products are shown in Figure 3.

RHF Transition Structures. The RHF/6-31G* optimized transition structures of substituted systems are shown in Figure 4. The chair transition structure was assumed for all the substituted systems, since this conformation is determined to be more favorable than the boat conformation experimentally³⁸ as well as theoretically.²⁶

The transition structure of the allyl vinyl ether reaction has a breaking CO bond distance of 1.92 Å and a forming C–C bond distance of 2.27 Å.²⁶ By comparison, the best DFT results predict that these bond lengths are 1.90 and 2.31 Å, respectively.²⁸ Hydroxyl substituents alter the geometry. A hydroxyl group at the C4 or C6 positions lengthens the CO bond by ~0.08–0.10 Å and the CC bond by ~0.06–0.07 Å. The CO and CC bond lengths for the 5-OH allyl vinyl ether are only 0.03 Å longer than in the parent system. The hydroxyl substituent at C1 and C2 causes fewer structural changes in the transition structures than does hydroxyl substitution on the allyl portion of the molecule. A hydroxy group at C1 only lengthens the CO bond by ~0.02 Å. A C2 hydroxyl causes a reduction of the CO bond length by 0.04 Å and lengthening of the CC bond by 0.07 Å, corresponding to an earlier transition state. CASSCF results reported later also predict an earlier transition state than for the parent system.

Secondary Kinetic Isotope Effects and Transition Structures with Correlation. The nature of the transition structure can be probed experimentally by secondary kinetic isotope

**Figure 4.** Optimized transition structures of the parent and the hydroxy-substituted allyl vinyl ethers at the RHF/6-31G* level. Mulliken charges are shown in parentheses.

effects (KIEs). The KIEs have been measured only for the parent and 2-(trimethylsiloxy) substituted allyl vinyl ethers. The experimental values for the 2-(trimethylsiloxy) allyl vinyl ether and theoretical KIEs for the 2-hydroxy allyl vinyl ether are compared to values for the parent system in Table 5. The KIEs are measured at different temperatures. The 2-OTMS substituent induces an increase in bond-breaking, indicated by the increase in isotope effect at C4, and a simultaneous increase in CC bond-making, indicated by the larger inverse isotope effect at C6. However, much of the difference in the KIEs of the parent and 2-OH derivative at 160 °C is actually due to the conformational change in the reactant which mainly involves the dihedral angle around the C4–C5 bond. The dihedral angles around C4–C5 for the parent and 2-OH systems are 0° and 120°, respectively. The KIEs calculated starting with a 120° dihedral angle for allyl vinyl ether at 160 °C at the RHF/6-31G* level are 1.073 at C4 and 0.918 at C6, nearly the same as for the 2-OH allyl vinyl ether. That is, the KIEs of the parent and 2-OH allyl vinyl ethers at the same temperature show no significant change in bond-breaking and bond-making upon hydroxyl substitution at the C2 position, according to isotope effect calculations. However, the secondary kinetic isotope effects calculated at the RHF/6-31G* level underestimate by 32% the isotope at C4 in comparison with the experiment on the 2-OTMS compound.³⁹ Since previous theoretical studies for the Cope and parent Claisen rearrangements have shown that DFT²⁸ and CASSCF²⁹ calculations reproduce experimental kinetic isotope effects better than RHF calculations, both methods were used to calculate kinetic isotope effects for the 2-OH case.

The optimized transition structures of the Claisen rearrangement of the 2-OH allyl vinyl ether at the RHF/6-31G*, Becke3LYP/6-31G*, and CASSCF/6-31G* levels are shown in

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Table 5. Secondary Deuterium Kinetic Isotope Effects for the Claisen Rearrangement of Allyl Vinyl Ether and the 2-OH (2-OTMS) Allyl Vinyl Ether

method	E_a	parent (160 °C)		E_a	2-OH (25 °C)		2-OH (160 °C)	
		4- k_H/k_{D_2}	6- k_H/k_{D_2}		4- k_H/k_{D_2}	6- k_H/k_{D_2}	4- k_H/k_{D_2}	6- k_H/k_{D_2}
RHF/6-31G* ^a	48.9	1.053	0.932	39.8	1.156	0.860	1.078	0.921
Becke3LYP/6-31G* ^b	26.8	1.058	0.953	20.1	1.120	0.898	1.057	0.946
CASSCF/6-31G* ^a	42.5	1.186	0.964	32.6	1.413	0.911	1.217	0.950
experimental	30.6 ^c [31.3] ^d	1.092 ± 0.005 ^e	0.976 ± 0.005 ^e	[23.8] ^f	1.48 ± 0.06 ^g	0.917 ± 0.03 ^g		

^a Reference 29. ^b Reference 28. ^c Reference 21. ^d Free energy of activation in dibutyl ether solvent at 100 °C. ^e Reference 30. ^f For the 2-(trimethylsiloxy) allyl vinyl ether; calculated ΔG^\ddagger using Ireland's experimental value at 32 °C in THF; see the explanation in the Experimental Substituent Effects section. ^g Reference 39; experimental kinetic isotope effects are obtained for the 2-(trimethylsiloxy) compound.

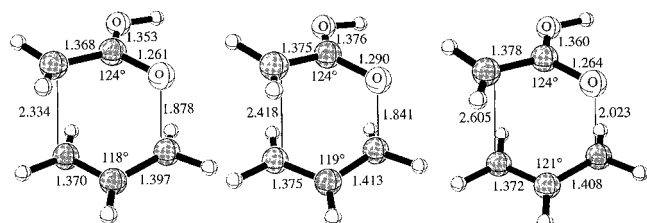


Figure 5. Optimized transition structures of the 2-hydroxy allyl vinyl ether at the RHF/6-31G* (left), Becke3LYP/6-31G* (middle), and MCSCF/6-31G* (right) levels. Bond lengths (Å) and bond angles are given.

Figure 5. The secondary deuterium kinetic isotope effects calculated at the CASSCF/6-31G* level are essentially within experimental error of the measured values. The O3–C4 and C1–C6 distances are 2.023 and 2.605 Å, respectively. The O3–C4 and C1–C6 distances of the CASSCF/6-31G* optimized transition structure of the parent allyl vinyl ether are 2.100 and 2.564 Å, respectively.²⁹ The KIEs at the CASSCF/6-31G* level agree reasonably well with the experiment, and are consistent with slightly more bond-breaking at C4 and bond-making at C6.

The force constants depend on the details of the transition structure geometry and determine the isotope effects.⁴⁰ Consequently, the calculated KIEs are sensitive to the level of theory. Previous theoretical studies for the Cope rearrangement of 1,5-hexadiene and the parent Claisen rearrangement of allyl vinyl ether have demonstrated this.^{28,29} Although various methods have a great impact on the kinetic isotope effects and detailed geometry of the transition structure, the activation barrier does not depend crucially on the exact geometry of the transition state. Theoretical studies of Cope rearrangements show how changing from a tight cyclohex-1,4-diyl geometry to a loosely coupled pair of allyl radicals causes little change in the energy.⁴¹ In spite of the necessity to use CASSCF for isotope effects, RHF and DFT should predict reasonable substituent effects. All three types of calculations show a similar lowering of activation energy by hydroxyl substitution at C2, similar to the experimental finding for the 2-(trimethylsiloxy) allyl vinyl ether.²² The relative activation energies of the parent and the 2-OH allyl vinyl ethers at the RHF/6-31G*, Becke3LYP/6-31G*, and CASSCF/6-31G* levels are 9.1, 6.7, and 9.9 kcal/mol, respectively. The magnitudes of relative activation energies from the RHF and CASSCF methods agree relatively well with the experimental value of 8 kcal/mol. This implies that the RHF calculations are sufficient level of theory to be used for understanding substituent effects in terms of energetic com-

parison between the parent and substituted allyl vinyl ether, even though only the CASSCF method can properly reproduce the geometry and isotope effects.

Charges. The Mulliken charge differences between reactant and transition structure at the RHF/6-31G* level are listed in Table 6. There is enolate/allyl cation character in the transition state; the charge separation calculated for the transition state of the parent system is 0.31 electron. Despite the significant rate acceleration for the 2-hydroxy allyl vinyl ether, there is only a 0.03 electron increase in charge separation in the transition state with respect to unsubstituted allyl vinyl ether. The CASSCF/6-31G* calculation also reports a 0.03 electron increase in charge separation for the 2-hydroxy system with respect to the parent allyl vinyl ether. The magnitude of the rate acceleration by the 4- and 6-OH allyl vinyl ethers is less, but these two systems show an increase of ~0.1 electron in the charge separation in the transition state. Storer et al.¹⁸ have shown that looser transition states result in greater acceleration and charge separation. This is also observed in Gao's QM/MM study on methoxy-substituted allyl vinyl ethers.⁷ The charge separation in the 5-OH transition state increases only by 0.01 electron with respect to that of the parent system. Charge separation for the 1-OH allyl vinyl ether is even less than the parent allyl vinyl ether by 0.06 electron. Accounting for solvation via SCRF calculations did not significantly change the charge separation in the transition states of any of the cases studied here.

Analysis of Thermodynamic and Transition State Effects on Rates. In order to analyze the substituent effects on these reactions, it is necessary to understand how substituents alter reaction energetics and influence transition state energies. Marcus theory is one of several approaches to analyze the activation energies of reaction pathways.¹² Although developed for electron transfers, it has been applied to various group-transfer reactions (e.g., proton, atom, and methyl transfer) and nucleophilic substitutions.⁴² The Marcus equation is given below (eq 2). The intrinsic barrier, ΔG_o^\ddagger , represents the barrier of a thermoneutral reaction. The free energy of activation, ΔG^\ddagger , of a nondegenerate reaction is equal to the sum of the intrinsic barrier and the thermodynamic contribution which depends on whether the reaction is endothermic or exothermic. The terms are defined in Figure 6.

$$\Delta G^\ddagger = \Delta G_o^\ddagger + \frac{1}{2}\Delta G_{\text{rxn}} + (\Delta G_{\text{rxn}})^2/16(\Delta G_o^\ddagger) \quad (2)$$

The $(\Delta G_{\text{rxn}})^2/16(\Delta G_o^\ddagger)$ term is a correction factor for nonadditivity of the intrinsic and thermodynamic effects.

Previously, the application of the Marcus equation to reactions that are intrinsically non-degenerate was limited. Murdoch suggested that the same formalism could be quite useful for

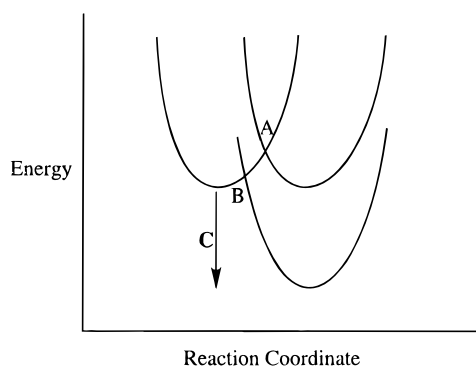
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Table 6. Changes in Mulliken Charges and Dipole Moments Calculated at the RHF/6-31G* Level

	Δ charges					
	parent ^a (TS-GS)	1-OH (TS-GS)	2-OH (TS-GS)	4-OH (TS-GS)	5-OH (TS-GS)	6-OH (TS-GS)
C1	0.033	0.053	0.075	-0.034	0.020	-0.034
C2	-0.007	0.000	-0.035	-0.010	-0.012	-0.006
O3	0.006	0.036	0.003	-0.030	0.006	-0.017
C4	-0.071	-0.121	-0.076	-0.070	-0.187	-0.065
C5	-0.070	-0.020	-0.073	-0.010	0.003	0.011
C6	0.108	0.050	0.123	0.069	0.197	0.076
O of a OH group		0.003	-0.017	0.085	-0.027	0.037
charge separation in TS	± 0.306	± 0.243	± 0.340	± 0.409	± 0.322	± 0.398
Δ dipole moment	1.60	1.99	-0.64	1.79	1.29	1.89

^a References 26 and 29.**Figure 6.** Marcus theory model for degenerate and exothermic reactions: (A) the intrinsic barrier of the thermoneutral reaction (ΔG_o^\ddagger); (B) the activation barrier of the exothermic reaction (ΔG^\ddagger); and (C) the reaction energy (ΔG_{rxn}).

pericyclic reactions. He advocated the general expression in eq 3 for arbitrary reaction coordinates. Murdoch has applied eq 3 to pericyclic reactions, and other chemical processes.⁴³ This is the same as Marcus theory if $h_2(x) = h_1(x)^2$, where h_1 and h_2 are odd and even functions of a given displacement (x) along the reaction coordinate.^{12,44} The Marcus equation (eq 4 below) is obtained from eq 3 when $h_1(\tau) = \tau = 1/4(\Delta E_{rxn})/\Delta E_o^\ddagger$ and $h_2(\tau) = \tau^2$.

$$\Delta E^\ddagger = \Delta E_o^\ddagger(1 - h_2(\tau)) + 1/2\Delta E_{rxn}(1 + h_1(\tau)) \quad (3)$$

$$\Delta E^\ddagger = \Delta E_o^\ddagger + 1/2\Delta E_{rxn} + (\Delta E_{rxn})^2/16(\Delta E_o^\ddagger) \quad (4)$$

Equation 4 has been applied to separate intrinsic and thermodynamic contribution of substituent effects on the rate of the five hydroxy-substituted Claisen rearrangements studied here. The intrinsic barrier, ΔE_o^\ddagger , is calculated by using eq 4 with the quantum mechanically calculated values of the activation energy, ΔE^\ddagger , and the reaction energy, ΔE_{rxn} .^{12,43}

The calculated intrinsic barriers for parent and hydroxy-substituted allyl vinyl ethers are listed in Table 7. These are RHF activation energies uncorrected with ZPE, and should be corrected by subtracting approximately 16 kcal/mol, the correlation error on activation barriers, to obtain values nearer the experimental values. The intrinsic activation energy of the parent reaction is 59.0 kcal/mol, which should be reduced to about 43 kcal/mol after correlation correction.

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Table 7. Activation Energy, Reaction Energy, Intrinsic Barrier, and Relative Thermodynamic Contribution to the Activation Barrier (kcal/mol) for the Parent and Hydroxy-Substituted Allyl Vinyl Ethers^a

	ΔE^\ddagger	ΔE_{rxn}	ΔE_o^\ddagger	$\Delta\Delta E_{thermo}^\ddagger$
parent	48.9	-21.1	59.0	(0)
1-OH	46.2 (-2.7)	-26.2 (-5.1)	58.6 (-0.4)	(-2.3)
2-OH	39.8 (-9.1)	-39.2 (-18.1)	57.7 (-1.3)	(-7.8)
4-OH	47.9 (-1.0)	-15.2 (+5.9)	55.2 (-3.8)	(+2.8)
5-OH	53.9 (+5.0)	-22.3 (-1.2)	64.8 (+5.8)	(-0.8)
6-OH	48.3 (-0.6)	-17.9 (+3.2)	56.9 (-2.1)	(+1.5)

^a Values relative to the parent are given in parentheses.

The lowering of the activation energy by 9.1 kcal/mol by a 2-hydroxyl group is mainly due to thermodynamic factors. There is only a 1.3 kcal/mol lowering of the intrinsic barrier, while 7.8 kcal/mol of the barrier lowering derives from the increase of exothermicity by 18.1 kcal/mol. The 1-hydroxy substituent increases the reaction exothermicity by 5.1 kcal/mol, and most of the activation energy lowering results from this effect. For both 4- and 6-hydroxy systems, the intrinsic contribution is dominant, and is even larger than the activation energy lowering, since the thermodynamic contribution raises the barrier. The large increase in activation energy caused by 5-OH is mainly an intrinsic factor, since there is a small increase in exothermicity caused by this group.

The Marcus formalism is equivalent to the assumption that the same factors which influence the reaction energy also influence the transition state by an amount proportional to the position of the transition state along the reaction coordinate. The way that substituents influence the reaction thermodynamics or directly influence the transition state (intrinsic barrier) can be analyzed by considering how substituents interact with the frontier molecular orbitals (FMO) of the reactant and transition state. These and the product FMOs are sketched in Figure 7. Alkoxy groups interact in a destabilizing four-electron fashion with the filled orbitals of the allyl vinyl ether system, and in a stabilizing two-electron fashion with the vacant orbitals of the molecule.

A 1-hydroxy substituent increases the reaction exothermicity. The HOMO of the reactant is large at C-1, and the destabilization upon interaction with a donor at this position disappears in the product. By contrast, a 2-hydroxy has smaller destabilizing interaction with the reactant HOMO, and this is replaced by a large stabilizing interaction with the LUMO, a carbonyl π^*_{CO} orbital, in the product. The substituent effects on rates are mainly thermodynamic for both of these groups.

Both 4-hydroxy and 6-hydroxy substituents decrease the reaction exothermicity. There is a small destabilizing interaction with the product HOMO at C4 and C6. However, both 4-hydroxy and 6-hydroxy cause considerable stabilization of the transition state. This arises from the stabilizing interaction

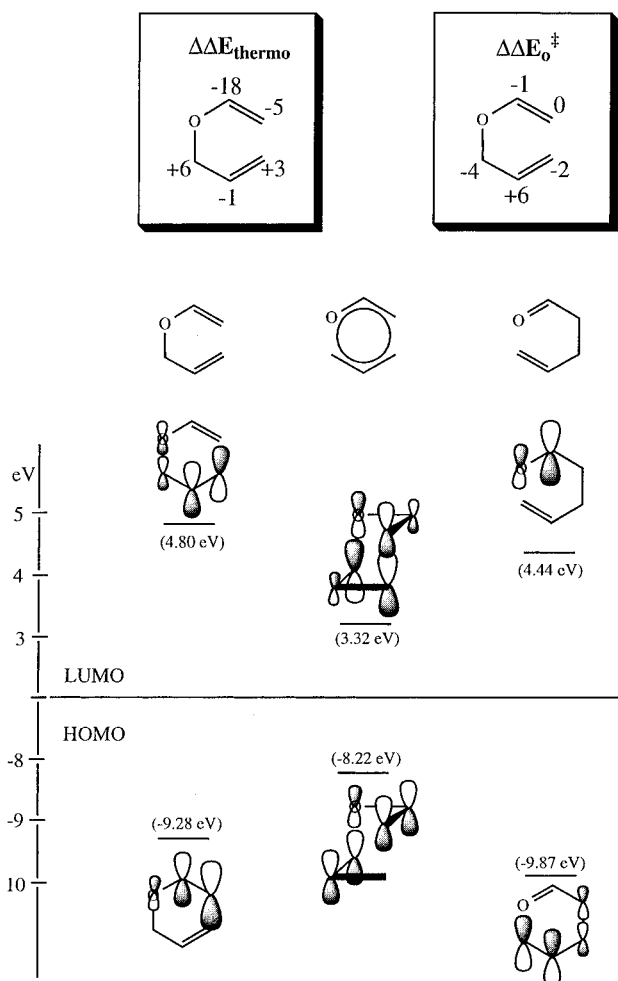


Figure 7. Representation of the HOMO and LUMO of reactant, transition state, and product for Claisen rearrangement of allyl vinyl ether. The numbers in the boxes are the substituent thermodynamic and intrinsic contribution to the reaction at different positions.

of the donors with the LUMO of the transition state. This stabilization is greater for 4-hydroxy than 6-hydroxy.

A 5-hydroxyl group increases the reaction exothermicity a small extent. This disagrees with the simple FMO analysis, which predicts a loss of a stabilizing interaction with π^* in the reactant and an increasing destabilizing interaction with the product HOMO. However, there is an additional factor which destabilizes the reactant. Whereas a $\sim 120^\circ$ conformer is favored about C4–C5 in the parent as well as the 1-, 2-, and 6-OH allyl vinyl ethers, this conformation is disfavored by the O–O repulsion that would arise in this conformation of the 5-OH compound. This is an extraneous factor in that it does not directly influence the strength of the breaking and forming bonds. The main transition state destabilizing interaction comes from a decrease of the stabilizing interaction of the donor orbital with the reactant LUMO, the π^*_{CC} orbital, in the transition state.

The substituent effects at the allyl group of the molecule are mainly intrinsic; hence the transition structures are altered. As shown in Figure 4, when a hydroxy substituent is present at the C4 and C6 positions, there is more noticeable bond breaking by lengthening the CO bond by ~ 0.08 – 0.10 Å compared to the parent system.

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The frontier orbital model gives a satisfactory account of the substituent effects. An alternative involves the charges in the transition state. How effective are these at rationalizing the substituent effects? The optimized transition structures and the charges indicate more polar character in the transition state of the substituted allyl vinyl ethers than that of the parent system. The maximum changes in charges are the 0.1 electron difference between the 4- and 6-hydroxy substituted allyl vinyl ethers and the parent allyl vinyl ether. The lone pair of an electron donor at the C4 and C6 positions can stabilize the partially developed positive charge. Coates et al. used this to explain the rate enhancement at C4 and C6 and suggested that the transition state resembles an enolate–oxonium ion pair.^{4a} There is only a 0.01 electron difference between the 5-hydroxyl and the parent system; the partially developed positive charge at C5 cannot be stabilized by a donor group. The transition state of the 1-hydroxy and 2-hydroxy systems where the intrinsic contribution is small shows little change in polar character with respect to that of the parent system: a 0.06 electron decrease and a 0.03 electron increase in the charge separation for the 1- and 2-OH allyl vinyl ethers, respectively.

Even though there is indication of more polar character in the transition state as compared to the parent system, this is not large enough for the transition state to be an enolate–oxonium ion pair. Gajewski's isotope effects suggested little ion-pair character in the transition state of allyl vinyl ether.⁴⁵ The transition state of the parent allyl vinyl ether reaction at the CASSCF/6-31G* level shows oxallyl–allyl radical pair character, which indicates less than half the ionic character exhibited by the RHF/6-31G* calculations, even though larger differences in charges are observed in going from ground state to transition state.²⁹ However, the CASSCF calculation on the parent system overestimates the extent of bond-breaking character, and the inclusion of dynamic correlation may lead to a little tighter transition state as it is observed in the Cope rearrangement.^{29,41b} Although the charge separation does not rise to the full unit charges, several solvation model studies have shown that rates are influenced by intramolecular charge transfer.^{7,8,18} Jorgensen proposed that the rate acceleration by water is not due to charge separation in the transition state, but to the accessibility of oxygen for hydrogen bonding,³⁶ and other solvation model studies showed the important factor of the solute polarization effect on solvent rate acceleration.^{8,18,46}

Conclusion

RHF/6-31G* calculations reproduce substituent effects found in experimental studies. Marcus theory^{12,43} combined with frontier molecular orbital theory can be used to rationalize the substituent effects on the rate for the Claisen rearrangement of allyl vinyl ether. The optimized transition structures and the charge separation in the transition state for the substituted allyl vinyl ethers show the weak dipolar character in the transition state.

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