Analysis of Substituent Effects on the Claisen Rearrangement with Ab Initio and Density Functional Theory

Viktorya Aviyente*

Chemistry Department, Bogaziçi University 80815, Bebek, Istanbul, Turkey

Hi Young Yoo and K. N. Houk*

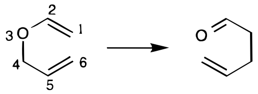
Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

Received January 27, 1997 (Revised Manuscript Received July 3, 1997[⊗]*)*

Transition structures for the Claisen rearrangements of 2- and (*E*)-6-substituted allyl vinyl ethers with CN, CH_3, and NH_2 groups were located with the Hartree−Fock method and the 6-31G* basis set. Energies were obtained using MP2 single points and B3LYP/6-31G* calculations. A Marcus theory type analysis was applied to separate the intrinsic and thermodynamic contributions to the activation energies. The calculations predict a decrease in the activation barrier for the 2-CN, 2-NH_2, and 6-NH_2 derivatives, while a large increase in the activation energy is predicted for the 6-CN derivative. The 2-CN and 6-NH_2 groups decrease the barrier height due to intrinsic contributions, while the rest are controlled by thermodynamic factors. To estimate solvent effects on rates, SCRF calculations for benzene and acetonitrile were performed.

Introduction

The Claisen rearrangement has been widely used in synthetic chemistry.[1] The chorismate−prephenate rearrangement is an enzyme-catalyzed Claisen rearrangement which has attracted much attention.[2] Because it is the only 3,3-sigmatropic shift reaction known to be catalyzed by an enzyme, attempts have been made to understand the factors responsible for the rearrangement by the study of rates of a variety of analogs of chorismate.[3,4] Solvent and isotope effects have also been studied.[4a,b] Models for the catalysis of this reaction by the enzyme chorismate mutase have been studied using Hartree−Fock (HF) and density functional theories; these studies reproduce the experimental patterns and provide insights into the origins of substituent effects.[4a,b]



In this paper, quantum mechanical methods have been used to elucidate the influence of substituents on this reaction. We have focused initially on substituent effects only at positions 2 and 6, in order to mimic the chorismate substrate and to provide insights into the substituent effects on the Claisen rearrangement of chorismate. Our calculations are in agreement with the results of Gao *et al.* for a variety of substituent effects on Claisen rearrangements.[4d] We provide a brief overview of the experimental kinetic results of monosubstituted allyl vinyl ethers, followed by a summary of the theoretical work carried out with various substituents, and an analysis of the origin of these effects.

The Arrhenius parameters for the isomerization of allyl vinyl ether (AVE) have been reported in the gas phase[5a] and in solution.[5b] Rearrangements with various types of substituents at all positions on AVE have been demonstrated, but quantitative information on substituent effects is limited.[6] Experimental relative rate factors for various substituents in comparison with the parent system are summarized in Scheme 1. Kinetic measurements of the influence of the cyano group on the Claisen rearrangement have been carried out by Carpenter. The cyano substituent was chosen as a small π acceptor.[5b] The rates on the Claisen rearrangement of the 1-CN and 6-CN derivatives are 0.90 and 0.11 times that of the unsubstituted system. Accelerations were observed for the cyano group at the other positions: the rate is 111 times faster for CN at C-2, 270 times faster for CN at C-4, and 15.6 times faster for CN at C-5. The effect of another electron-withdrawing group, carbomethoxy (CO_2CH_3), was investigated by Gajewski *et al.* The activation free energy for the rearrangement with the CO_2CH_3 group at C-2 is 3.0 kcal/mol less than that of AVE itself in dibutyl ether solvent, all extrapolated to

---

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1997.

[1] (a) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10,* 227. (b) Bartlett, P. A.; Johnson, C. R. *J. Am. Chem. Soc.* **1985**, *107*, 7792. (c) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (d) Pawlak, J. L.; Padykula, R. E.; Kronis, J. D.; Aleksejczyk, R. A.; Berchtold, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 3374.

[2] (a) Ganem, B. *Tetrahedron* **1978**, *34*, 3353. (b) Ganem, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 936.

[3] (a) Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R. Gande, M. E.; Ganem, B.; Carpenter; B. E. *J. Am. Chem. Soc.* **1987**, *109*, 1170. (b) Haslam, E. *Skimic Acid Metabolism and Metabolites*; Wiley & Sons: New York, 1993. (c) Chook, Y. M.; Gray, J. V.; Ke, H. M.; Lipscomb, W. N. *J. Mol. Biol.* **1994**, *240*, 476. (d) Lee, A. Y.; Karplus, P. A.; Ganem, B.; Clardy, J. *J. Am. Chem. Soc.* **1995**, *117*, 3627. (e) Lee, A. Y.; Stewart, J. D.; Clardy, J.; Ganem, B. *J. Chem. Biol.* **1995**, *2*, 195.

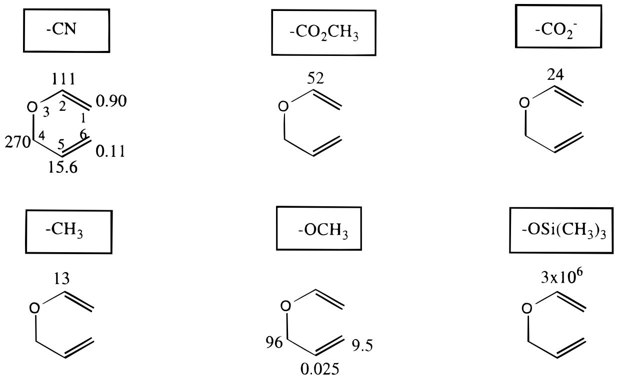
[4] (a) Wiest, O.; Houk, K. N. *J. Org. Chem.* **1994**, *59*, 7582. (b) Wiest, O.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, *117*, 11628. (c) Yoo, H. Y.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 2877. (d) Sehgal, A.; Shao, L.; Gao, J. *J. Am. Chem. Soc.* **1995**, *117*, 11337. (e) Lyne, P. D.; Mulholland, A. J.; Richards, W. G. *J. Am. Chem. Soc.* **1995**, *117*, 11345.

[5] (a) Schuler, F. W.; Murphy, G. W. *J. Am. Chem. Soc.* **1950**, *72*, 3155. (b) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983.

[6] (a) Koreeda, M.; Luengo, J. I. *J. Am. Chem. Soc.* **1985**, *107*, 5572. (b) Barluenga, J.; Aznar, F.; Liz, R.; Bayod, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1427. (c) Normant, J. F.; Reboul, O.; Sauvetre, R.; Deshays, H.; Masure, D.; Villieras. *J. Bull. Soc. Chim. Fr.* **1974**, 2072. (d) Welch, J. T.; Samartino, J. S. *J. Org. Chem.* **1985**, *50*, 3663. (e) Frey H. M.; Montague D. C. *Trans. Faraday Soc.* **1968**, 64, 2369. (f) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (g) Frey, H. M.; Pope, B. M. *J. Chem. Soc.* B, 1966, 209. (h) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972. (i) Denmark, S. E.; Harmata, M. A. *Tetrahedron Lett.* ***1984,*** *25*, 1543. (j) Curran, D. P.; Suh, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5002. (k) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160. (l) Wilcox, C. S.; Babston, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 6636.

S0022-3263(97)00143-6 CCC: $14.00

Scheme 1. Experimental Rate Factors for Various Substituents, Relative to the Parent Claisen Rearrangement



100 °C; no reaction was observed for the same group at C-6 under the same conditions.[3a] It was also found that the CO_2^- group at C-2 slows down the reaction 2.2 times with respect to the CO_2CH_3 group at the same position.[3a]

The effects of electron-donor groups on the rates of the Claisen rearrangement have been studied in various laboratories. The accelerating influence of substituents such as oxyanion,[6a] amino,[6b] fluoro,[6c,d] and methyl[6e] at C-1 has been experimentally established. Ireland has reported the activation free energy of 2-(trimethylsiloxy) substituted AVE to be 9 kcal/mol less than that of the parent molecule.[6f] In the gas phase, Frey observed a 1.5 kcal/mol lowering of the activation energy for 2-methyl-AVE as compared to the parent.[6g] Denmark and Harmata used a powerful electron donor, α-sulfonyl carbanion, to accelerate the Claisen rearrangement.[6h,i] The accelerating effects of donor substituents on the allyl group of the allyl vinyl ether have been thoroughly investigated by Curran *et al.*;[6j] CH_3 and OCH_3 groups at C-6 accelerate the rearrangement by 1.2 and 34.3 for 2-OTBS-AVE, respectively. Later, the same group reported the rearrangements of 4-, 5-, and 6-alkoxy AVEs. The 4- and 6-alkoxy derivatives react 96 and 9.5 times faster than the parent allyl vinyl ether, respectively, while 5-methoxy-AVE rearranges 40 times slower than AVE. In addition, a significant solvent effect is observed; the rate of rearrangement of the 4- and 6-alkoxy derivatives is increased upon changing from benzene to methanol, while the parent shows a much smaller effect.[6k] Wilcox and Babston measured the rearrangement rates for *O*-allyl-silylketene acetals and concluded that steric bulk at C-5 is rate accelerating, while electron-donation at C-5 is rate retarding.[6l]

In a study of substituent effects on pericyclic reactions, Gajewski *et al.* developed a nonlinear free-energy relationship for 3,3-sigmatropic shifts.[7a] They also measured kinetic isotope effects (KIEs) for rearrangements of allyl vinyl ether at isotopically labeled C-4 and C-6 and found that the transition state comes early and involves more C−O bond-breaking than C−C bond-making character; at 160.3°C, k_H/k_{D_2} at C-4 is 1.092 and the k_H/k_{D_2} at C-6 is 1/1.025.[7b] According to isotope effects measurements, 2-$OSi(CH_3)_3$ substitution resulted in a transition state with much more bond-breaking character than in the parent rearrangement.[7c]

The parent Claisen rearrangement is 15 times faster in 25% methanol versus *m*-xylene.[7d] KIEs measured in a mixture of these two solvents indicate that bond-breaking is not increased as the solvent polarity increases, evidence against an ionic transition state.

Carpenter and Burrows proposed a Hückel molecular orbital (HMO) model to correlate and predict substituent effects on the rates of Claisen rearrangements.[8] The model predicts that a donor group at positions 1, 2, or 4 will lower the energy of activation, while donor groups at positions 5 and 6 should have the opposite effect. According to Carpenter's model, acceptor substituents at C-1 and C-6 are expected to raise $\Delta H^{\ddagger}$, whereas the same substituents at C-2 and C-4 will lower $\Delta H^{\ddagger}$. MNDO calculations by Dewar predict that methoxy groups at positions 2 and 5 will lower the activation energy.[9]

Computational results for 2- and 6-substituted AVEs have been reported by Gao *et al.*[4d] and Wiest and Houk.[4a,b] The effects of the CO_2H and CO_2^- groups on the Claisen rearrangement have been analyzed; a lowering of the activation barrier has been determined for both substituents at C-2 and for CO_2^- at C-6; CO_2H at C-6 is found to increase slightly the activation barrier. Recently, Yoo and Houk have reported computed substituent effects for OH at all positions of AVE. They also reported a general method of analysis of hydroxy and alkoxy substituent effects on Claisen rearrangements of substituted substrates:[4c] an accelerating effect is predicted for hydroxyl substitution at all positions except for the C-5 position, in accordance with experiment. Gao *et al.* have used combined quantum mechanical and statistical mechanical calculations of solvation to assess the transition structure and substituent effects on the rates of Claisen rearrangements in aqueous solution; CN and F at C-2, and OCH_3 at C-6 accelerate the reaction.[4d] Their simulations show that the most dramatic substituent effect results from a combination of donor and acceptor substitution; the reaction rate of a 2-CN, 6-OCH_3 substituted AVE is estimated to be 1700 times as fast as that of AVE in water.

The chair transition structure for the Claisen rearrangements is more stable than the boat according to RHF calculations.[10] DFT[11a] and CASSCF/6-31G*[11b] calculations have confirmed these findings. The CASSCF/6-31G* level calculations have shown more oxallyl−allyl radical pair character, and the calculated isotope effects are in better agreement with experimental results than the RHF results, although the secondary deuterium isotope effect at C4 is overestimated. Among the activation barriers calculated for the Claisen rearrangement with various methods, the MP4/6-31G*//RHF/3-21G and B3LYP/6-31G* calculations show best agreement with experimental values.[12,13] The QM/MM study of the Claisen rearrangement of chorismic acid to prephenic acid has shown that the energy barrier relative to the gas phase is lowered in the enzyme by a combination of substrate strain and preferential hydrogen bonding in the transition state.[4e] A relatively flat potential energy

---

(7) (a) Gajewski, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 4394. (b) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**,*101*, 6693. (c) Gajewski, J. J.; Emrani, J. *J. Am. Chem. Soc.* **1984**, *106*, 5733. (d) Gajewski, J. J; Brichford, N. L. *J. Am. Chem. Soc.* **1994**, *116*, 3165.

(8) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6984.

(9) (a) Dewar, M. J. S.; Healy, E. F. *J. Am. Chem. Soc.* **1984**, *106*, 7127. (b) Dewar, M. J. S.; Jie, C. *J. Am. Chem. Soc.* **1989**, *111*, 511.

(10) Vance, R. L.; Rondan, N. G.; Houk, K. N.; Jensen, H. F.; Borden, W. T.; Komornicki, A.; Wimmer, E. *J. Am. Chem. Soc.* **1988**, *110*, 2314.

(11) (a) Wiest, O.; Black, K. A.; Houk, K. N. *J. Am. Chem. Soc.*. **1994**,*116*, 10336. (b) Yoo, H. Y.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 12047. (c) Hall, R. J.; Davidson, M. M.; Burton, N. A.; Hillier, I. H. *Phys. Chem.* **1995**, *99*, 921.

(12) (a) Yamabe, S.; Okumoto, S.; Hayashi, T. *J. Org. Chem.* **1996**, *61*, 6218. (b) Davidson, M. D.; Hillier, I. H.; Vincent, M. A. *Chem. Phys. Lett.* **1995**, *246*, 536.

(13) Borden, T. A.; Davidson, E. R. *Acc. Chem. Res.* **1996**, *29*, 67.

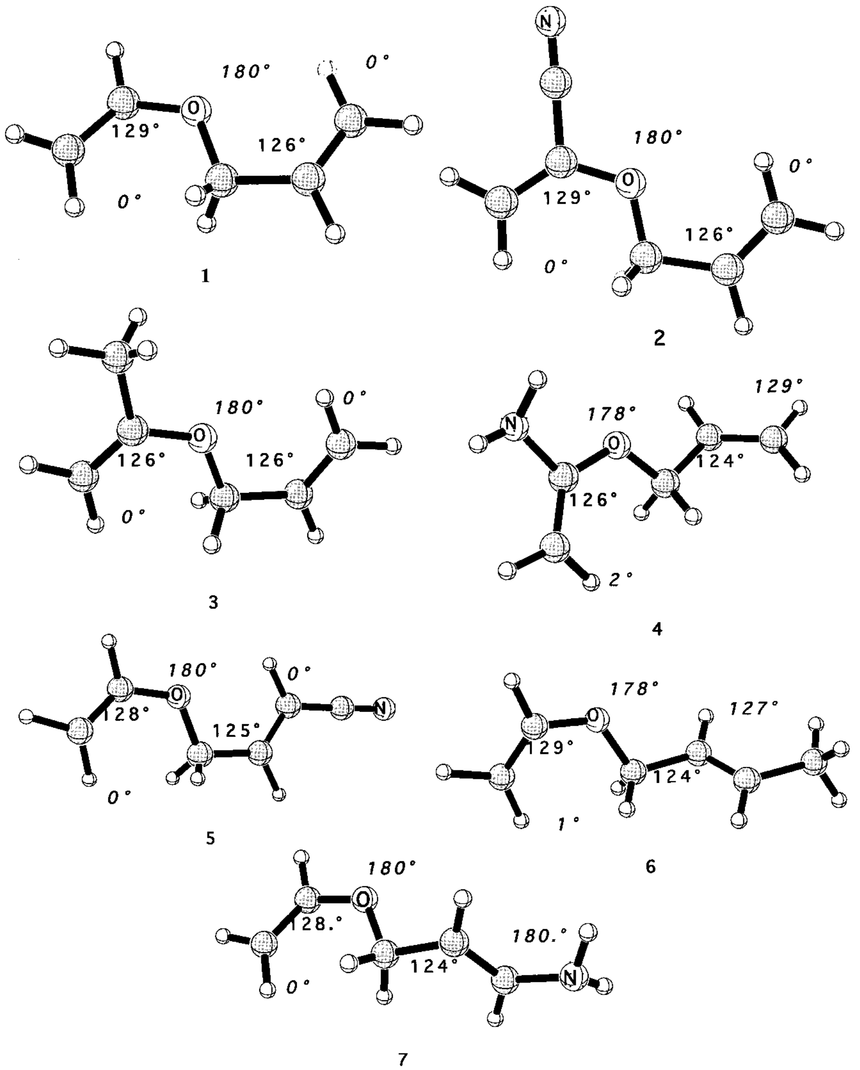


Figure 1. Optimized reactant structures of parent and substituted allyl vinyl ethers at the RHF/6-31G* level. Bond angles and dihedral angles (italics) are given.

surface has also been predicted for the 3-aza-Cope reaction at the MP2/6-31G*//RHF/6-31G* level.[14]

Satisfactory theoretical results for substituent effects have been obtained so far at the RHF/6-31G* level by Yoo[4c] and Gao[4d] at the RHF/6-31G*, RHF/6−31+G*, and BLYP/6-31G* levels by Wiest.[4a,b] Although the energetics for these systems are well-described with HF and the hybrid Becke3LYP methods, the prediction of the correct transition state geometry requires multiconfigurational wave functions plus correlation corrections, because of the relative flatness of the potential energy surface connecting the possible transition states such as bis-allyl, aromatic and 1,4-diyl structures.[11a] The possible role of cyclohexane-1,4-diyl intermediates for substituted cases of the Cope rearrangement has been discussed.[15] As pointed out by Borden for the Cope rearrangement, the global potential surfaces for pericyclic reactions contain regions where diradical structures exist, and calculations beyond the CASSCF level are necessary in order to obtain a qualitatively correct potential energy surface.[13] Nevertheless, the substituent effects may be calculated even at the RHF level, because the surface is very flat in the transition state region.

The aim of this work is to study the influence of a potent electron-donor group (NH_2), an electron-withdrawing group (CN), and an alkyl group (CH_3) on the transition state, geometries, and energies of Claisen rearrangements, when substituted at the 2 and 6 positions, for which experimental data are available. Marcus theory has been used to separate thermodynamic and intrinsic contributions to activation energies as proposed by Murdoch[16] and applied to the Claisen rearrangement previously by Yoo and Houk.[4c]

Computational Methods

Ab initio calculations were carried out with Gaussian 92[17] using the RHF/6-31G* basis set. The reactants (Figure 1), products (Figure 2) and transition structures (Figure 3) were fully optimized and characterized by frequency analyses. Relative energies are reported in Table 2. $\Delta H^{\ddagger}$ is calculated at 298.15K, and the zero point energies are scaled by 0.9135. Solvent effects were estimated using the self-consistent reac-

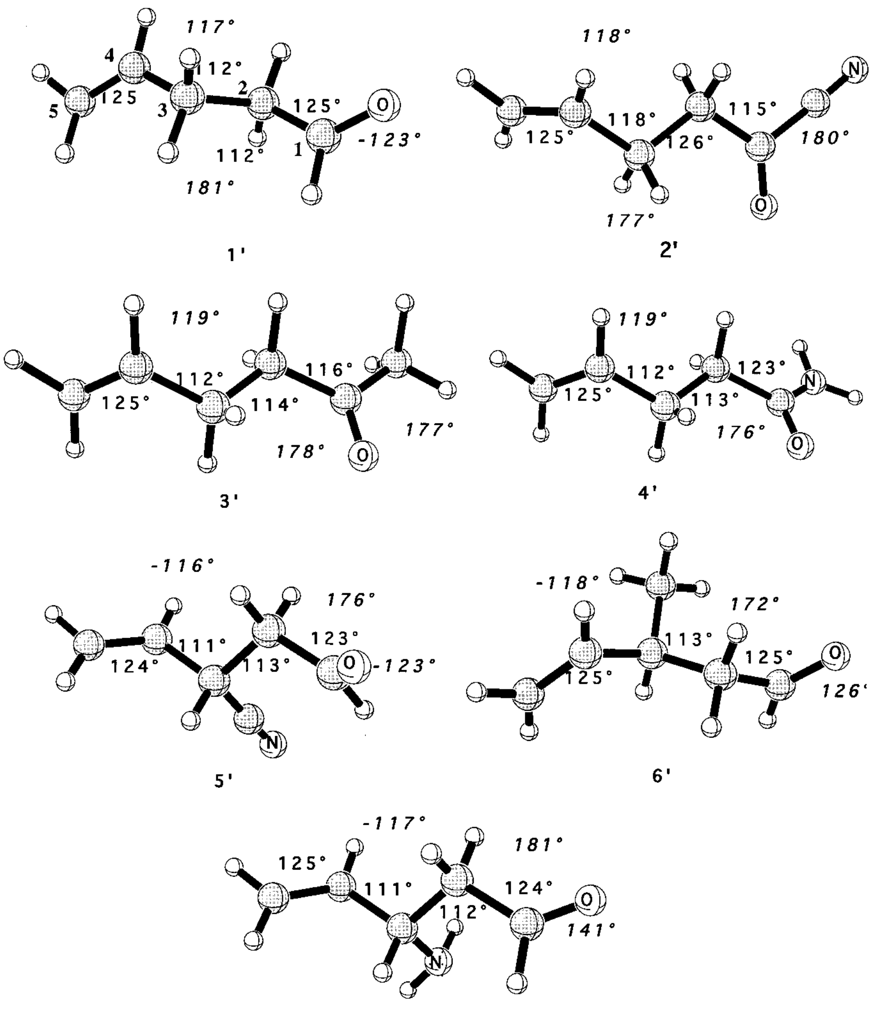
---

[14] (14) Walters, M. A. *J. Org. Chem.* **1996**, *61*, 978.

[15] (15) Wessel, T. E.; Berson, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 495.

[16] (16) (a) Chen, M. Y.; Murdoch, J. R. *J. Am. Chem. Soc.* **1984**,*106*, 4735 and references therein. (b) Murdoch, J. R. *J. Am. Chem. Soc.* **1983**,*105*, 2660. (c) Berry, M. S.; Murdoch, J. R. *Abstracts of Papers*; 184th National Meeting of the American Chemical Society, Kansas City, MO, Sept 1982; American Chemical Society: Washington, DC, 1982; PHYS 72.

[17] (17) Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W, Wong, M. W.; Foresman, J. W.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomberts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzales, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian 92, Revisions B and G.1; Gaussian Inc.: Pittsburgh, PA, 1992 and 1993.



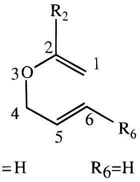
1′ 2′ 3′ 4′ 5′ 6′ 7′

Figure 2. Optimized product structures for the Claisen rearrangement of parent and substituted allyl vinyl ethers at the RHF/6-31G* level. Bond angles and dihedral angles (italics) are given.

tion field (SCRF) method.[18] B3LYP/6-31G* calculations[19] were carried out with Gaussian 94.[20] MP2 single point energy calculations were also performed on the RHF/6-31G* optimized structures.

Results and Discussion

We have investigated examples of a strong donor (NH_2), acceptor (CN), and an alkyl group (CH_3) at positions 2 and 6. The systems studied are shown below.



1. R_2=H	R_6=H
2. R_2=CN	R_6=H
3. R_2=CH_3	R_6=H
4. R_2=NH_2	R_6=H
5. R_2=H	R_6=CN
6. R_2=H	R_6=CH_3
7. R_2=H	R_6=NH_2

1. Reactant and Product Structures. Jorgensen has reported a thorough analysis of the conformations of allyl vinyl ether.[21] On the basis of the RHF/6-31G* calculation, the dihedral angle about the C2−O bond prefers to be near 0° to maintain conjugation of the oxygen with the vinyl fragment, while the staggered geometries about the C4−O bond yield preferred dihedral angles of 180°. All the possible conformations resulting from rotation around C2−O3, O3−C4, and C4−C5 have been explored for **1**−**7**. This dihedral is near 0° for **2**, **3**, and **5**, near 120° for **1**, **4** and **6**, and approximately 180° for **7**. The optimized geometries for the reactants are shown in Figure 1. A similar conformational search was examined for products. In all cases, the products (**1′**−**7′**) are nonplanar with the anti conformation about the C2−C3 bond, as shown in Figure 2.

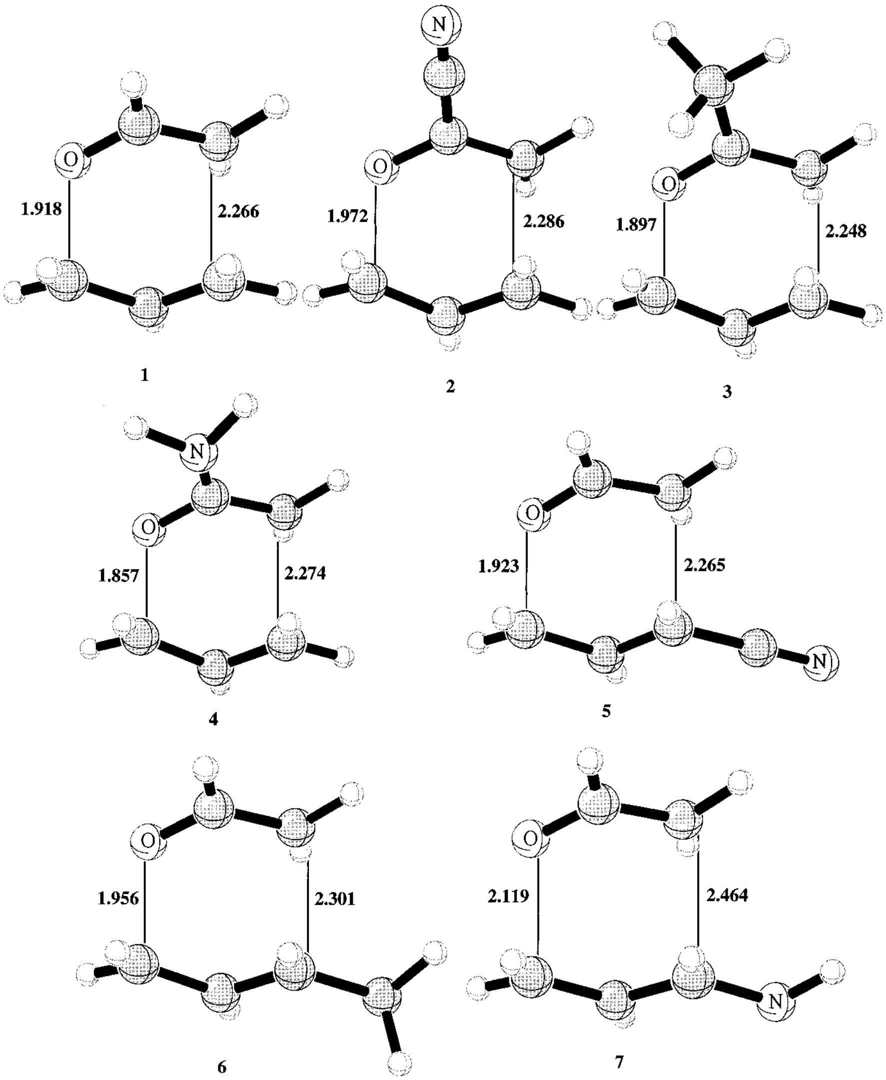
---

(18) (a) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, 113, 4776. (b) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Chem. Phys.* **1991**, 95, 8991.

(19) (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(20) Frisch, M. J. ; Trucks, G. W.; Schlegel, H. B .; Gill, P. M. W.; Johnson, B. G.; Robb.; M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.;Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Head-Gordon, M.; Gonzales, C.; Pople, J. A. Gaussian 94 Revisions B1; Gaussian Inc.: Pittsburgh, PA, 1995.

(21) (a) Severance, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1992**, *114*, 10966. (b) Severance, D. L.; Jorgensen, W. L. In *Claisen Rearrangement of Allyl Vinyl Ether. Computer Simulations of Effects of Hydration and Multiple-Reactant Conformers*; ACS Symposium Series 568; Cramer, C. J., Truhlar, D. G., Eds.; American Chemical Society: Washington, DC, 1994; Chapter 17.



1 2 3

4 5

6 7

Figure 3. Optimized transition structures for parent and substituted allyl vinyl ethers at the RHF/6-31G* level. Bond lengths are given in Å.

Table 1. Bond Lengths of Reactants and Transition Structures for the Claisen Rearrangement of Substituted Allyl Vinyl Ethers at the RHF/6-31G* Level

structure	R_2	R_6	C_1C_2	C_2O_3	O_3C_4	C_4C_5	C_5C_6	C_1C_6	C_2C_7	C_{7N}	C_2N	C_6C_7	C_6N
1. Reactant	H	H	1.320	1.342	1.399	1.500	1.317						
TS	H	H	1.374	1.262	1.918	1.390	1.376	2.266					
2. Reactant	CN	H	1.321	1.338	1.405	1.500	1.316		1.453	1.135			
TS	CN	H	1.374	1.254	1.972	1.386	1.376	2.286	1.476	1.136			
3. Reactant	CH_3	H	1.324	1.349	1.398	1.501	1.317		1.500				
TS	CH_3	H	1.378	1.268	1.897	1.391	1.377	2.248	1.512				
4. Reactant	NH_2	H	1.329	1.341	1.408	1.499	1.317			1.387			
TS	NH_2	H	1.379	1.268	1.857	1.398	1.374	2.274			1.376		
5. Reactant	H	CN	1.319	1.347	1.394	1.497	1.321			1.137		1.441	
TS	H	CN	1.378	1.258	1.923	1.388	1.381	2.265		1.136		1.447	
6. Reactant	H	CH_3	1.321	1.341	1.409	1.498	1.319					1.502	
TS	H	CH_3	1.374	1.259	1.956	1.384	1.382	2.301				1.506	
7. Reactant	H	NH_2	1.321	1.339	1.412	1.494	1.322						1.391
TS	H	NH_2	1.375	1.252	2.119	1.362	1.397	2.464					1.356

2. Transition Structures. Previous calculations on the transition state[11a,b] of AVE and substituted compounds[4c] have shown the chair conformation to be lower in energy than the boat. Only the chair conformation of each transition state has been considered here.

Table 1 lists the bond lengths of interest in the reactants and transition states. Bond lengths vary between 1.86 and 2.12 Å for the breaking C−O bonds and 2.23−2.46 Å for the forming C−C bonds. The CN group at C2 causes lengthening of the breaking C−O bond by ~0.06 Å and of the forming C−C bond by ~0.02Å. On the other hand, CH_3 and NH_2 groups at C2 reduce the breaking and forming bond lengths somewhat.

The NH_2 group at C6 influences the geometry of the transition state more than the other groups at this position: both the breaking and forming bonds are 0.20 Å longer than in the transition state for the parent system. The CO bond is stretched by 50% versus the reactant for 6-NH_2, by 38% for 6-CN, by 39% for 6-CH_3, and by 31% in the parent, AVE. Overall, the breaking C−O bond is much more sensitive to substitution than the forming C−C bond.

Table 2. Activation Energies for the Claisen Rearrangements of Substituted Allyl Vinyl Ethers at the RHF/6-31G*, B3LYP/6-31G*, and MP2/6-31G*//RHF/6-31G* Levels[a]

	RHF/6-31G*					
	ΔE_a		$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	B3LYP/6-31G*:ΔE_a	RMP2/6-31G*:ΔE_a
	($\epsilon = 1$)	($\epsilon = 37.5$)	($\epsilon = 1$)	($\epsilon = 1$)	($\epsilon = 1$)	(ϵ=1)
AVE	48.9 [25.4]^b [30.6]^c	48.2	47.0	−5.9 [−7.7]^b	27.9	26.5
2-CN-AVE	44.0(−4.9) [22.8]^c (−2.6)	43.9 (−4.3) 43.8^d	42.1 (−4.9)	−5.4 [−13.4]	24.8 (−3.1)	21.7 (−4.8)
2-CH_3-AVE	48.7 (−0.2) 29.1^e (−1.5)	48.2 (0.0)	46.8 (−0.2)	−5.1 [−10.2]^e	28.8 (0.9)	25.4 (−1.1)
2-NH_2 AVE	41.3 (−7.6)	41.1 (−7.1)	39.7 (−7.3)	−6.9	21.7 (−6.3)	18.9 (−7.6)
6-CN-AVE	53.2 (4.3) [28.7]^c (3.3)	55.1 (6.9)	51.1 (4.1)	−5.8 [−11.2]^c	31.7 (3.8)	27.3 (0.8)
6-CH_3-AVE	49.8 (0.9)	48.7 (0.5)	47.6 (0.6)	−6.3	30.1 (2.2)	27.3 (0.8)
6-NH_2-AVE	45.5 (−3.4)	42.8 (−5.4)	43.0 (−4.0)	−4.5	27.2 (−0.8)	28.8 (2.3)

[a] The relative energies between the parent and substituted allyl vinyl ether are given in parentheses. Experimental values are given in brackets. [b] Ref 5a. [c] Ref 5b. [d] Ref 4d. [e] Ref 6g.

3. Substituent Effects on Activation Energies. Table 2 lists calculated activation energies at various levels for the substituted cases and experimental activation parameters where available. For the Claisen rearrangement of AVE itself, nonlocal DFT calculations[11a,c] and MP4 calculations[12] predict activation energies in close agreement with the experimental value in the gas phase. Although the calculated activation energies for AVE vary considerably at different levels of theory, there is reasonable accord among the methods on the relative activation energies for substituted cases. The smallest differences between RHF and B3LYP involve the 6-CH_3 system, and the largest differences involve the 6-NH_2 case. Similar calculations with RHF and B3LYP methods were performed for the model compounds for chorismate, and the difference in relative activation energies was between 0.1 and 2.2 kcal/mol.[4b] All these methods predict ΔE_a values of −4, 0, and −7 (±1 kcal/mol) for 2-CN, 2-Me, and 2-NH_2, respectively. RHF and B3LYP are also in accord for substituents at the 6-position: thus, ΔE_a values of 4, 1, and −2 (±1 kcal/mol) are found for 6-CN, 6-Me, and 6-NH_2, respectively. However, the MP2 results for 6-CN and 6-NH_2 differ significantly, predicting ΔE_a values of 1 and 2 for these substituents. This may be due to the fact that these MP2 results come from single point calculations, and the location of stationary points with this method may change the relative energies. Furthermore, the RMP2 wavefunctions are unstable with respect to UMP2 wavefunctions. Where experimental values are available, RHF/6-31G* relative activation energies are within 1.0−2.3 kcal/mol, whereas with B3LYP/6-31G* values are within 0.5−2.4 kcal/mol of the experimental values. In general, B3LYP/6-31G* calculations reproduce energetics closer to experimental values than RHF/6-31G*, as mentioned in a previous work.[4b]

Carpenter's experimental findings on the cyano substituent (Scheme 1) are reproduced with both RHF/6−31G* and Becke3LYP/6-31G* calculations. Even though the substituent effects are overestimated, the trend is well-reproduced. Lowering of the activation energies by the 2-CN,[4d] 2-CO_2H,[4b] and 2-carbomethoxy groups[3a] have been observed or calculated. A CN group at C-6 raises the activation energy, because conjugation in the ground state is being lost in the transition state. The predicted trend is in agreement with Carpenter's observations[5b] and Gajewski's experimental result on 6-carbomethoxy allyl vinyl ether:[3a] this compound was stable over long periods of time at 100 °C, while the parent system rearranged at 80 °C. This provides evidence for the increase in the barrier height when a electron-withdrawing group is present at C6.

Table 3. Relative Activation Energies (kcal/mol) in Benzene and Acetonitrile as Compared to the Gas Phase Calculated at the RHF/6-31G* Level with the SCRF Model

structure	benzene ($\epsilon = 2.27$)	acetonitrile (ϵ=37.5)
AVE	−0.3	−0.7
2-CN-AVE	−0.1	−0.1
2-CH_3-AVE	−0.3	−0.5
2-NH_2-AVE	−0.1	−0.2
6-CN-AVE	0.8	1.9
6-CH_3-AVE	−0.1	−0.8
6-NH_2-AVE	−1.2	−2.7

CH_3 groups at C2 and C6 have only small effects on the energetics of the Claisen rearrangement. The 6-CH_3 group shows the smallest difference between RHF and B3LYP energies. No experimental values are available for comparison.

The NH_2 group is predicted to lower the activation energy by a large amount at C2 and a smaller amount at C6; similar effects were found in the computational results with other electron donor groups (OH, OMe, and F)[4b−d] as well as in experimental results (Me, OMe, OTBS, and OTMS).[6f,g,k]

4. Solvent Effects on Activation Energies. It has been observed experimentally that the Claisen rearrangement is influenced by the nature of the medium,[21] and theories have been advanced to explain these findings.[4d,e,22,23] In this study, activation energies in two solvents (benzene and acetonitrile) were calculated. The results from the SCRF approach, using a spherical cavity are listed in Table 3. The size of the solvent cavity of the substituted reactants and transition structures vary between 3.90 and 4.16 Å. Changes in polarity between the reactant and the transition state can lead to rate variations in different solvents.[24] Only the 6-CN and 6-NH_2 cases are influenced significantly here. This is in agreement with Curran's observations of rate acceleration by polar solvents for 6-OCH_3 AVE.[6k,l] Except for

---

(22) Davidson, M. D.; Hillier, I. H.; Vincent, M. A. *Chem. Phys. Lett.* **1995**, *246*, 536.

(23) (a) Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 8305. (b) Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 8794. (c) Cramer, C. J.; Truhlar, D. G. *J. Comput. Chem.* **1992**, *13*, 1089. (d) Cramer, C. J.; Truhlar, D. G. *Science* **1992**, *256*, 213.

(24) Reichardt, C., *Solvents and Solvent Effects in Organic Chemistry, 2nd ed.;* VCH; Weinheim, 1988.

Table 4. Activation Energy, $\Delta E^{\ddagger}$, Reaction Energy, $\Delta E_{\rm rxn}$, Intrinsic Barrier, $\Delta E_0^{\ddagger}$, and Relative Thermodynamic Contribution to the Activation Barrier (kcal/mol), $\Delta\Delta E^{\ddagger}_{\rm thermo}$, for the Parent and 2- and 6-Substituted Allyl Vinyl Ethers[a]

compound	$\Delta E^{\ddagger}$	$\Delta E_{\rm rxn}$	$\Delta E_0^{\ddagger}$	$E^{\ddagger}_{\rm thermo}$
AVE	48.9	−21.1	59.0	(0)
2-CN-AVE	44.0 (−4.9)	−19.5 (1.6)	53.3 (−5.7)	(0.8)
2-CH_3-AVE	48.7 (−0.2)	−23.4 (−2.3)	59.8 (0.8)	(−1.0)
2-NH_2-AVE	41.3 (−7.6)	−36.0 (−14.9)	57.9 (−1.1)	(−6.5)
6-CN-AVE	53.2 (4.3)	−13.9 (7.2)	60.0 (1.0)	(3.3)
6-CH_3-AVE	49.8 (0.9)	−16.7 (4.4)	57.9 (−1.1)	(2.0)
6-NH_2-AVE	45.5 (−3.3)	−15.4 (5.7)	52.9 (−6.1)	(2.7)

[a] RHF gas phase values are used in this table. Values relative to the parent are given in parentheses.

6-CN, SCRF calculations are consistent with transition states which are more polar than ground states. Polar solvents stabilize the transition states more than the ground states; therefore, the activation energies decrease in solution. For 6-CN, the ground state turns out to be more polar than the transition state so that the opposite result is observed.

5. Marcus Theory. As described earlier,[4c] in order to understand how substituents influence the reaction energetics, we have used a Marcus theory formalism[25] (eq 3) as proposed by Murdoch,[16] to separate intrinsic and thermodynamic contributions to the activation energy:

$$\Delta E^{\ddagger} = \Delta E_0^{\ddagger} + 1/2\Delta E_{\rm rxn} + (\Delta E_{\rm rxn})^2/16\Delta E_0^{\ddagger} \qquad (1)$$

$\Delta E^{\ddagger}$ is the activation barrier for the reaction, $\Delta E_{\rm rxn}$ is the energy of reaction, and the intrinsic barrier, $\Delta E_0^{\ddagger}$, is that of a hypothetical thermoneutral process. This permits an estimate of how much of the change in activation energy caused by the substituent is due to an alteration of the heat of reaction, based on the assumption that the extent of transition state lowering by a change in the reaction thermodynamics is a function of the position along the reaction coordinate. The remaining energy change is assumed to be due to an intrinsic effect specific to the method of calculation. The energy components for the parent and substituted allyl vinyl ethers from the RHF/6-31G* calculations are listed in Table 4.

For the 2-CN group, the main lowering of the activation energy comes from the intrinsic barrier (−5.7 kcal/mol). This arises from the stabilization of the developing partial negative charge on the enolate group in the transition state. The reaction is less exothermic than the parent reaction, and the small thermodynamic factor (0.8 kcal/mol) works against the intrinsic barrier lowering. For the 2-CH_3 AVE, there is a small decrease in activation energy which is also due to both factors. For the 2-NH_2 group, the lowering of the activation energy by 7.6 kcal/mol is mainly due to the thermodynamic factor, since there is only a lowering of 1.1 kcal/mol in intrinsic barrier, while the reaction energy is lowered by 14.9 kcal/mol. These effects are consistent with some charge separation in the transition state that can be stabilized by the cyano group, whereas the product carbonyl group is not stabilized by the cyano group, but is stabilized substantially by the amino group. Since NH_2 is an electron donor, there is a destabilizing interaction between the NH_2 group and a partial negative charge developed in the transition state, but it is thermodynamically very favorable due to very large amide resonance in the product.

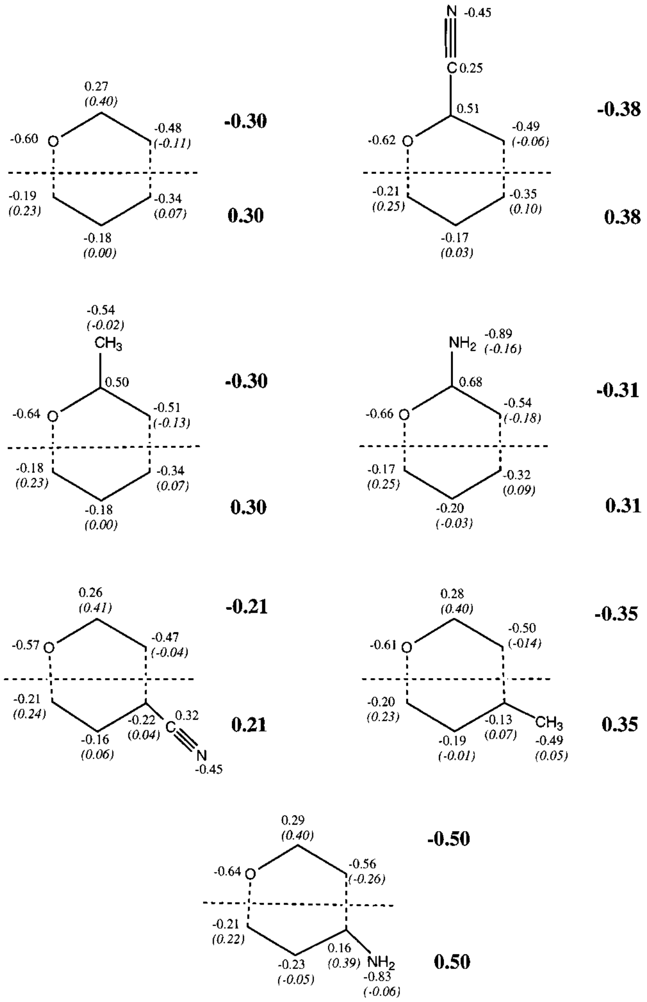


Figure 4. Charge distribution in the transition states of parent and substituted allyl vinyl ethers. The numbers in bold represent the charge on the moieties separated by the dashed line.

For the 6-CN system, the thermodynamic factor (3.3 kcal/mol) increases the activation barrier. A similar trend is observed for the 6-CH_3 group, even though the magnitude of the increase in activation is not as great as for the 6-CN case. For 6-NH_2, the decrease in activation energy is due to the intrinsic factor (6.1 kcal/mol). All three substituents at the 6-position make the reaction less exothermic; they stabilize the reactant by conjugation with the double bond, and this conjugation is removed in the product. The positive charge on the allyl moiety in the transition structure is better stabilized by an electron donor group at C6; hence, the intrinsic barrier lowering is substantial for NH_2.

It is also interesting to discuss how substituents influence the reaction thermodynamics and the transition state by considering the frontier molecular orbitals (FMO) of the reactant, the transition state, and the product. These are depicted in Figure 5. The high-lying filled orbitals of electron-donor groups interact in a destabilizing way with the filled orbitals of any of these species and in a stabilizing manner with the vacant orbitals. The low-lying vacant orbitals of electron-withdrawing groups give stabilization upon interaction with occupied orbitals and no effect upon interaction with vacant orbitals.

---

(25) (a) Marcus, R. A. *J. Chem. Phys.* **1956**, *24*, 966. (b) Marcus, R. A. *J. Chem. Phys.* **1968**, *72*, 891. (c) Shaik, S. S.; Schlegel, H. B.; Wolfe, S. In *Theoretical Aspects of Physical Organic Chemistry*; Wiley: New York, 1992; pp 33−44.

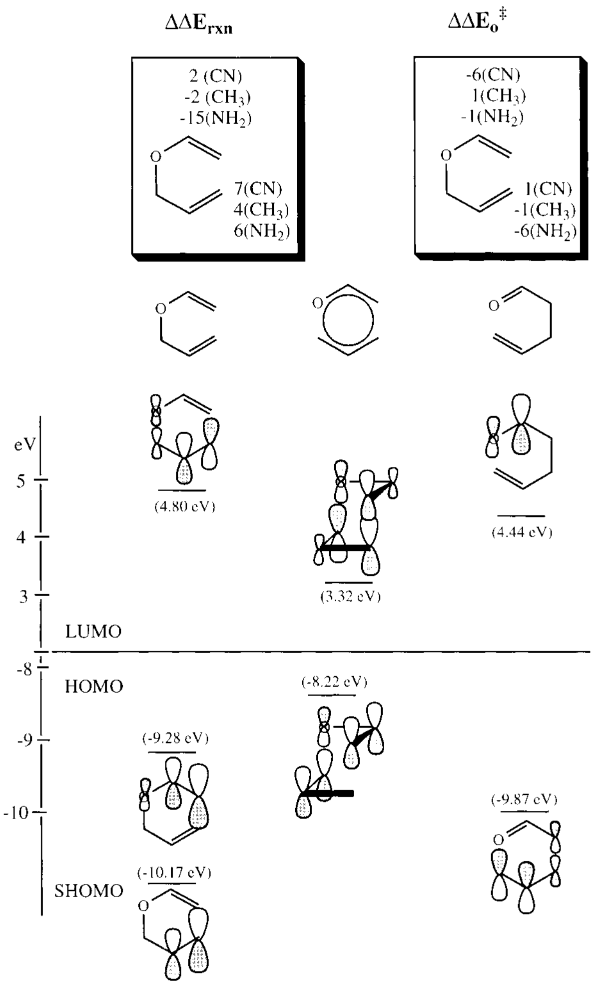


Figure 5. Representation of the SHOMO, HOMO, and LUMO of reactant; HOMO and LUMO of the transition state and product for Claisen rearrengment of allyl vinyl ether. Orbital energies are from RHF/6-31G* calculations. The numbers in boxes are the substituent reaction energy alteration (ΔE_{rxn}) and intrinsic contribution to the activation energies ($\Delta E^{\ddagger}$) at different positions.

A 2-CN substituent decreases the reaction exothermicity. The HOMO coefficient of the reactant is large at C2, and the stabilizing interaction with an acceptor at this position decreases the reaction exothermicity. The HOMO of the transition state at C2 is stabilized by CN; this explains the intrinsic contribution to the activation barrier. By contrast the 2-NH_2 group increases the exothermicity because of the large stabilizing interaction with the LUMO of the carbonyl group in the product. This is due to formation of a stable product, amide. The 2-CH_3 group behaves in the same way as the NH_2 group, but the effect is minor due to the weak electron-donor character of the methyl group.

A 6-CN substituent decreases the reaction exothermicity, because of stabilizing interactions with the SHOMO, which is absent in the product. The interaction of donors with the LUMO at C-6 stabilizes these compounds. This stabilizing interaction explains the decrease in the exothermicity of the NH_2 and CH_3 groups at this position. The dominant intrinsic factor for the 6-NH_2 system is also well-explained by the stabilizing interaction of the donor with the LUMO of the transition state. These results are in agreement with Houk and Yoo's findings,[4c] where the substituent effect of a donor substituent on the allyl group is found to be mainly intrinsic. The 6-NH_2 group lowers the intrinsic barrier the most, and the degree of bond-breaking in the transition state is a maximum. Lengthening of the CO bond is 0.20 Å, as compared to the parent.

The substituent effects on the 2-CN and 6-NH_2 systems are mainly intrinsic. Therefore, the transition structures are affected the most. This can be seen in the bond lengths of C1−C6 and O3−C4 in the transition structure (Table 1 and 4). These two systems have shown significant bond lengthening in the transition structure compared to the parent system, while those systems that are controlled thermodynamically have shown less bond lengthening in the transition structures.

Charges are also effective in rationalizing the substituent effects: Figure 4 depicts the charge distribution in the transition state for the compounds under investigation. In all of them a partial positive charge is on the allyl moiety and a partial negative charge is on the enolate. In the parent compound, the charge separation is 0.30 electron units.

For the 2-substituted systems, the differences in charge transfer from the allyl moiety to the enolate between the parent and the substituted compounds are 0.08, 0.00, and 0.01 electron for the CN, CH_3, and NH_2 groups, respectively, as indicated in Figure 4. According to these numbers, the electron-acceptor group, CN, can stabilize the partially negative oxallyl moiety of the transition state the most, as predicted above by the largest intrinsic contribution to the activation barrier.

For the 6-substituted compounds the changes in charge transfer from the allyl moiety to the enolate between the parent and the substituted compounds are −0.09, 0.05, and 0.20 electron for the CN, CH_3 and NH_2 groups, respectively. The lone pair of the electron-donor group, NH_2, at C6 can stabilize the positive charge present at the allyl part of the molecule. Previously, this fact has been qualitatively explained by referring to the LUMO of the allyl moiety which has positive charges at positions 4 and 6.[4c] An electron-withdrawing group like CN at position 6 is not expected to stabilize the allyl moiety.

Conclusion

Marcus theory is applied to separate the intrinsic and thermodynamic contributions of the substituents to the activation energy of the Claisen rearrangement. The transition states of the systems where the intrinsic factor is dominant have shown more bond-breaking character than bond-making. Weak dipolar character is observed in the transition states of the substituted allyl vinyl ethers. Frontier molecular orbital theory, charge distributions, and the geometrical features of the transition states elucidate the effects of substituents on rates of Claisen rearrangements.

Acknowledgment. We are grateful to the National Science Foundation for financial support of this research and to the Office of Academic Computing at UCLA for computer time. Dr. V. Aviyente is grateful to the Bogazici Üniversitesi Arastirma Fonu and Bogazici Üniversitesi Vakfi for partial support of travel expenses and to TUBITAK for support to the project TBAG-1319. NATO grant CRG 960407 is also gratefully acknowledged.

JO970143C