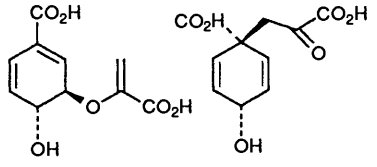
Claisen Rearrangement of Chorismic Acid and Related Analogues: an *Ab Initio* Molecular Orbital Study

Mark M. Davidson and Ian H. Hillier
Chemistry Department, University of Manchester, Manchester, UK M13 9PL

The structure and energies of the reactant and transition state for the Claisen rearrangement of chorismic acid and related analogues have been determined using *ab initio* molecular orbital methods. The rate acceleration found for chorismic acid compared to that of allyl vinyl ether is attributed to both reactant destabilisation and transition state stabilisation. The electronic effects responsible for the observed rate retardation associated with the ring carboxy and hydroxy groups have been identified.

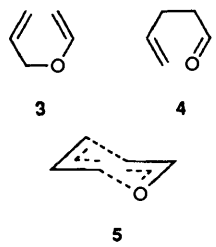
Chorismic acid (**1**) is of biochemical importance, being a key intermediate in the shikimate biosynthetic pathway used by bacteria and lower plants.[1] In this path to phenylalanine and tyrosine, chorismic acid undergoes a Claisen rearrangement to prephenic acid (**2**). This reaction is greatly accelerated (by a



1 **2**

factor of 2×10^6 at 37 °C)[2] by the enzyme chorismate mutase, which is the only enzyme catalysing a pericyclic reaction. However, the mechanism of the enzyme reaction remains obscure. A study of the pathway for the reaction **1**→**2** in the absence of the enzyme is of obvious value in understanding the catalytic effect of the enzyme and hence in designing potential inhibitors. In order to understand the relationship between structural features of **1** and its reaction rate, a number of analogues of the diester of **1** have been prepared and their rate of rearrangement studied.[3] Removal of the ring ester and hydroxy groups both result in a significant rate enhancement. These results led to suggestions as to the nature of the transition state and the effect of these substituents on it. Further experimental insight into the transition state is provided from secondary kinetic isotope effects[4] which can probe the extent of bond-breaking and -making in the transition state.

In this paper, we use *ab initio* electronic structure calculations to provide information on the structure and energetics of the reactants and transition state for the reaction **1**→**2** and for the corresponding reactions involving structures lacking the ring CO_2H and OH groups. Previous *ab initio* theoretical studies[5] have focused on the Claisen rearrangement of allyl vinyl ether (**3**) to pent-4-enal (**4**), which has been shown to proceed *via* a chair-like transition state (**5**).[6] Subsequent to these free-molecule calculations, the effect of solvent on the rate of the reaction has been studied using both simulation[7,8] and continuum methods.[9] As far as the Claisen rearrangement of chorismic acid is concerned, a theoretical MINDO/3 study[10] of the rearrangement of chorismate to prephenate has been reported.



3 **4**

5

Computational Details

NMR studies have shown that both the pseudo-diaxial (**6**) and pseudo-diequatorial (**7**) conformers of chorismic acid exist in aqueous solution,[11] structure **7** being the most stable. The non-enzymic[12] and enzymic[13] rearrangements of **1** have been shown to proceed *via* a transition state of chair-like structure (**8**) analogous to that (**5**) for the Claisen rearrangement of allyl vinyl ether (**3**). These rearrangements require a conformational change in which the pseudo-diequatorial conformer **7** which predominates in aqueous solution, is converted to the pseudo-diaxial conformer **6** on the way to the conformationally constrained transition state **8**.[14] In this paper, we study the pseudo-diaxial structure **6** of chorismic acid and the corresponding chair-like transition state structure **8**. In addition, we study the analogues of **6** and **8** that lack the ring CO_2H (**9**, **10**) and both the ring CO_2H and OH groups (**11**, **12**).

We present the results of calculations of isolated gas phase species which are a pre-requisite for the study of the reactions in condensed phases, both in solution and involving the enzyme chorismate mutase. Full geometry optimisation of the six structures (**6**, **8**–**12**) were carried out at the Hartree–Fock *ab initio* level using a 6-31G* basis. All structures were characterised by evaluation of the analytic second derivatives of the energy. Zero point energy and finite temperature corrections (at 298.15 K) were carried out within the rigid rotor, harmonic oscillator approximations.[15,16] All calculations were carried out using the GAUSSIAN 92[17] program on the Fujitsu VPX 240/10 of the Manchester Computing Centre.

Computational Results and Discussion

The calculations described herein are successful in predicting the change in transition state barrier for the Claisen rearrangement of chorismic acid and a number of analogues. In Table 1, we compare the calculated barriers with experimental values (at 75 °C in 2:1 v/v methanol–water).[3] These experimental data are for allyl vinyl ether (**3**), and for the corresponding esters of **6**, **9** and **11**. It can be seen that the absolute values of the calculated and experimental barriers differ considerably, due to neglect of correlation effects and, to a lesser extent, solvation effects. However, the relative barrier heights are in good agreement with the experimental values considering the complexity of the molecules studied.

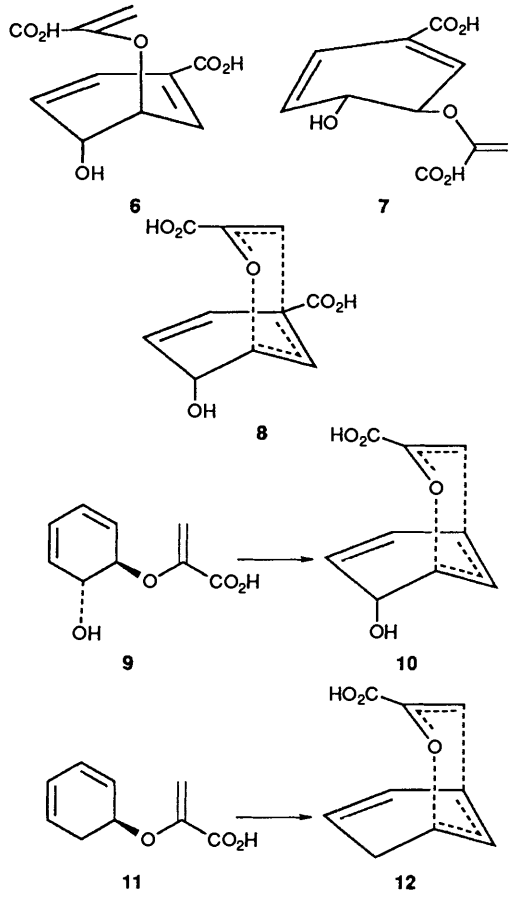


Table 1 Calculated energies (kcal mol^{-1})[a] of chair transition states, relative to reactants

Structure	ΔE	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$[b]
5	48.9	46.9	−5.9	48.7 (28.2)
8	43.2	41.3	−6.3	43.2 (26.2)[c]
10	40.3	38.5	−4.6	39.9 (24.5)[c]
12	39.6	37.6	−3.9	38.8 (20.2)[c]

[a] 1 cal = 4.18 J. [b] Experimental values[3] are in parentheses. [c] Experimental values[3] are for ester derivatives.

The optimised structures are shown in Table 2, where they are compared with the corresponding structures, **3** and **5**. A number of structural features are common to the reactions of chorismic acid (**6**) and the two analogues, **9** and **11**. Firstly, the structure of the transition state for the Claisen rearrangement is considerably more dissociative than for the rearrangement of ether **3** as witnessed by the longer C^4–O and C^1–C^6 lengths (see Table 2). A significant structural change in that part of the molecule not participating directly in the reaction is the reduction in the C^4–C^9 length on formation of the transition states. Thus, the more dissociative transition state in all three reactions is favoured by the accompanying increase in aromatic character of the cyclohexadiene ring as shown by the reduction in the C^9–C^4 bond length which accompanies the lengthening of the C^4–O bond in the transition state. Indeed, for all three molecules, our calculated transition state barrier (Table 1) is reduced from the value for allyl vinyl ether. In addition to structural changes in the transition state, there are also changes in the structure of the reactants (**6**, **9** and **11**) compared to that of ether **3**; of particular note is the longer C^4–O bond length in **6**, **9** and **11** compared to that in **3**. An associated lengthening of C^5–C^6 is also found, although this effect is smaller. These changes point to reactant destabilisation being an important effect contributing to the observed rate acceleration observed for chorismic acid and analogues. We now discuss in more detail each of the three molecules studied (**6**, **9** and **11**), starting with the Claisen rearrangement of **6**.

In the transition state for the reaction of ether **3**, there is substantial lengthening of the C^4–O bond (by 0.51 Å), and a long (2.27 Å) C^1–C^6 distance. Such an early transition state structure is reflected in the measured kinetic isotope effect (KIE) for reaction **3**→**4**.[18] Here, the normal KIE at the 4-position of **3** is roughly four times the inverse KIE at the 6-position. Our calculated structure for the transition state **8** for the rearrangement of **6** shows both longer C^4–O and C^1–C^6 lengths than those for the rearrangement of **3**. These findings are in line with the secondary tritium isotope effects used to probe the extent of bond-breaking and -making at the transition state for the rearrangement of chorismate to prephenate.[4] Although a substantial effect is found at the bond-breaking position, there was no detectable effect at the bond-making position suggesting a more dissociative transition state than for the reaction **3**→**4**, in agreement with our predicted transition state structures. From our calculated structures, we see that both the C^4–O and C^1–C^6 bonds are longer by ~0.13 Å in the transition state of **8** compared to those in the transition state of **3**. However, the effect of reactant destabilisation is seen by comparing the structure of the corresponding reactants, where the C^4–O bond at which bond-breaking occurs is 0.02 Å longer in **6** than in **3**. There is also an associated lengthening of the C^5–C^6 bond in **6** compared to **3**.

We now discuss the specific effect that the ring substituents, CO_2H and OH, have on the structure and energetics of the reactants (**9** and **11**) and the corresponding transition states (**10** and **12**). Turning first to the effect of the ring carboxylic acid group, the observed rate-retarding effect of this group has been attributed to its ground state conjugative stabilisation of the reacting double bond C^5=C^6.[3] This suggestion is in line with our predicted structures (Table 2) where removal of the carboxylic group leads to a slight shortening of the C^5=C^6 bond and lengthening of the C^4–O bond in the reactant acid, both observations pointing to reactant destabilisation. Apart from these changes, the structure of **6** and the analogue **9** are very similar. As far as the corresponding transition states are concerned, the two structures (**8** and **10**) are very similar. In particular, the C^4–O (bond-breaking) and C^1–C^6 (bond-making) lengths are essentially the same, so that no change in the degree of bond breakage or formation has taken place. Thus, our results suggest that the observed increase in the rate of reaction found on removal of the ring CO_2H group is predominantly due to reactant destabilisation.

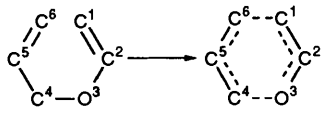
On the other hand, the further removal of the hydroxy group from the ring carbon atom, C^9, has a considerable structural effect on the transition state **12** (Table 2). There is significant lengthening of both the C^4–O and C^1–C^6 distances so that the transition state is more dissociative. Furthermore, in the transition state, the differences in the individual C–C distances of the ring are reduced upon removal of the OH group, as seen in the C–C bond lengths of structures **10** and **12** in Table 2. Thus, there is greater aromatic character in the cyclohexadiene ring of structure **12** than **10**.

Conclusions

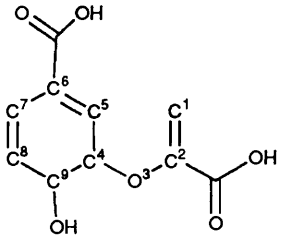
The *ab initio* calculations described herein predict that the transition states for the Claisen rearrangement of chorismic acid and analogues have appreciably stretched C–O bonds for bond-breaking and a long C–C length for the new bond formation. These findings are in contrast to a semiempirical MINDO/3 study of the rearrangement of chorismate to prephenate,[10]

Table 2 Bond lengths (Å) for reactants and chair transition state

Structure	C^1–C^2	C^1–C^6	C^2–O	C^4–O	C^4–C^5	C^5–C^6	C^6–C^7	C^7–C^8	C^8–C^9	C^9–C^4
3	1.320		1.341	1.406	1.498	1.317				
5	1.374	2.266	1.262	1.918	1.389	1.376				
6	1.318		1.359	1.426	1.508	1.328	1.478	1.324	1.508	1.535
8	1.379	2.389	1.252	2.052	1.382	1.382	1.477	1.323	1.503	1.512
9	1.318		1.356	1.431	1.507	1.324	1.476	1.325	1.510	1.536
10	1.374	2.389	1.254	2.053	1.380	1.381	1.473	1.324	1.505	1.513
11	1.319		1.355	1.435	1.508	1.325	1.472	1.324	1.506	1.531
12	1.372	2.466	1.252	2.137	1.376	1.381	1.466	1.326	1.499	1.498



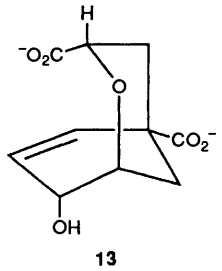
3 **5**



where the transition state had little C–O bond extension and considerable C–C bond formation. A similar discrepancy has been found in studies of the Claisen rearrangement of allyl vinyl ether by a semiempirical method.[19]

The observed acceleration in the rate of rearrangement of chorismic acid and derivatives compared to that of allyl vinyl ether is attributed to both transition state stabilisation associated with ring electron delocalisation and reactant destabilisation. The effect of the former is seen experimentally in the reduction in the rate found upon removal of unsaturation at C^7–C^8, when the barrier is found to increase by 5 kcal mol^{-1}.[3] We attribute the observed rate increase associated with removal of the ring CO_2H group to reactant destabilisation. In contrast to this, the observed rate enhancement accompanying the further removal of the ring OH group is attributed to increased transition state stabilisation due to increased aromatic character in the six-membered ring.

Finally, we note that recent crystal structures of a transition state analogue (**13**) with both chorismate mutase,[20] and a



13

catalytic antibody with chorismate mutase activity,[21] suggest that a similar pericyclic transition state occurs in both the catalysed and uncatalysed reactions.[20] The structural similarity of **13** and our transition states, **8**, **10** and **12**, is immediately apparent. Thus, the structure of the latter, determined herein, will probably be of value in understanding the origin of the large rate enhancement found in these catalysed reactions.

Acknowledgements

We thank SERC (UK) and Fujitsu Systems (Europe) Ltd. for support of this research, and Professor J. K. Sutherland for valuable discussions.

References

1 E. Haslam, *The Shikimate Pathway*, Halstead Press, Wiley, New York, 1974.
2 P. R. Andrews, G. D. Smith and I. G. Young, *Biochemistry*, 1973, **12**, 3492.
3 J. J. Gajewski, J. Jurayj, D. R. Kimbrough, M. E. Gande, B. Ganem and B. K. Carpenter, *J. Am. Chem. Soc.*, 1987, **109**, 1170.
4 L. Addadi, E. K. Jaffe and J. R. Knowles, *Biochemistry*, 1983, **22**, 4494.
5 R. L. Vance, N. G. Rondan, K. N. Houk, F. Jensen, W. T. Borden, A. Komornicki and E. Wimmer, *J. Am. Chem. Soc.*, 1988, **110**, 2314.
6 W. v. E. Doering and W. R. Roth, *Tetrahedron*, 1962, **18**, 67; P. Vittorelli, T. Winkler, H.-J. Hansen and H. Schmid, *Helv. Chim. Acta.*, 1968, **51**, 1457; H.-J. Hansen and H. Schmid, *Tetrahedron*, 1974, **30**, 1959.
7 D. L. Severance and W. L. Jorgensen, *J. Am. Chem. Soc.*, 1992, **114**, 10966.
8 J. Gao, *J. Am. Chem. Soc.*, 1994, **116**, 1563.
9 M. M. Davidson, I. H. Hillier, R. J. Hall and N. A. Burton, submitted for publication.
10 P. R. Andrews and R. C. Hadden, *Aust. J. Chem.*, 1979, **32**, 1921.
11 S. D. Copley and J. R. Knowles, *J. Am. Chem. Soc.*, 1987, **109**, 5008.
12 S. D. Copley and J. R. Knowles, *J. Am. Chem. Soc.*, 1985, **107**, 5306.
13 S. G. Sogo, T. S. Widlanski, J. H. Hoare, C. E. Grimshaw, G. A. Berchtold and J. R. Knowles, *J. Am. Chem. Soc.*, 1984, **106**, 2701.
14 A. P. Campbell, T. M. Tarasow, W. Massefski, P. E. Wright and D. Hilvert, *Proc. Natl. Acad. Sci. USA*, 1993, **90**, 8663.
15 J. E. Del Bene, H. D. Mettee, M. J. Frisch, B. T. Luke and J. A. Pople, *J. Phys. Chem.*, 1983, **87**, 3279.
16 W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, 1986.
17 M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart and J. A. Pople, GAUSSIAN 92, Gaussian, Inc., Pittsburgh, PA, 1992.
18 J. J. Gajewski and N. D. Conrad, *J. Am. Chem. Soc.*, 1979, **101**, 6693.
19 M. J. S. Dewar and E. F. Healy, *J. Am. Chem. Soc.*, 1984, **106**, 7127.
20 Y. M. Chook, H. Ke and W. N. Lipscomb, *Proc. Natl. Acad. Sci. USA*, 1993, **90**, 8600.
21 M. R. Haynes, E. A. Stura, D. Hilvert and I. A. Wilson, *Science*, 1994, **263**, 646.

Paper 4/01725K
Received 23rd *March* 1994
Accepted 21st *April* 1994