# On the Transition State of the Chorismate–Prephenate Rearrangement

Olaf Wiest and K. N. Houk*

*Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024*

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*Summary:* The ground state and transition structures of the Claisen rearrangement of chorismic acid and chorismate have been calculated using ab initio theory.

The conversion of chorismate to prephenate (Figure 1) is a unique pericyclic process. It not only occurs thermally under mild conditions,[1] but is also the only [3,3]-sigmatropic rearrangement for which an enzyme, chorismate mutase, is known.[2] The reaction can also be catalyzed by catalytic antibodies, two of which have been thoroughly characterized.[3] Inhibitors of chorismate mutase, which is involved in the shikimic acid pathway to aromatic amino acids in bacteria, fungi, and higher plants,[4] are of interest as potential herbicides and antibiotics. The most potent inhibitor known so far, **1**,[5] has also been used as hapten to elicit the antibody catalysts. Although much work has been devoted to the catalyzed[6] and uncatalyzed[7] reaction, the precise nature of catalysis is not well understood.

The key to insight into enzyme catalysis is a detailed knowledge of the geometry and electronic structure of the transition state.[8] Therefore, we have undertaken a theoretical investigation of the chorismate–prephenate transformation using ab initio theory. As a part of our ongoing studies of the details of catalysis by enzymes and antibodies, we report here the location and characterization of the transition structure of this reaction using the RHF/6-31G* method.[9] This represents a major improvement over previously reported EHT[1] and MINDO/3[10] calculations and provides the geometric and electronic features which will lead to an understanding of how catalysts accelerate this reaction.

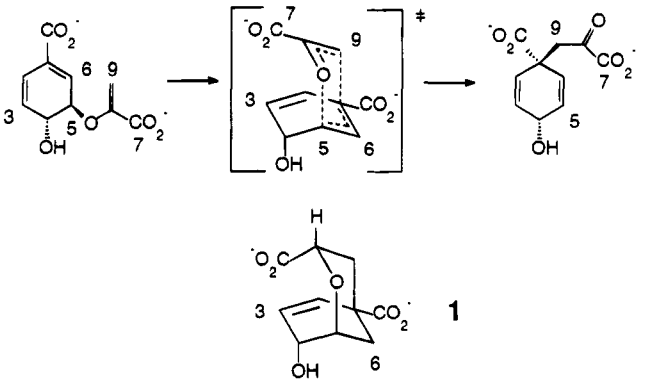

**Figure 1.** Claisen rearrangement of chorismate to prephenate and transition state analog **1**.

Calculations were carried out with the GAUSSIAN series of programs.[11] All structures reported were fully optimized and characterized by harmonic frequency analysis. The reported energies include zero point energies. Kinetic isotope effects were calculated using the program QUIVER.[12] Frequencies from RHF calculations have been scaled by 0.9.

Both the diacid **2a**[13] and the dianion **2b** have been studied. Both can adopt several conformations. We could localize the two minima for **2b** shown in Figure 2, corresponding to the diequatorial and the diaxial conformations, but no minimum similar to the transition structure could be located at the RHF/6-31G* level. The results calculated for **2a,b** are summarized in Table 1. The diequatorial conformation is the more stable one, with energy differences of 5.7 kcal/mol for the diacid and 15.8 kcal/mol for the dianion. The large difference in energy for the two conformations of chorismate **2b** is due to a strong intramolecular hydrogen bond between the hydroxy function and the side chain carboxylate ($R_{HO}$ = 1.63 Å), as shown in Figure 2. In solution, the hydrogen bond is presumably bridged by solvent molecules (as it

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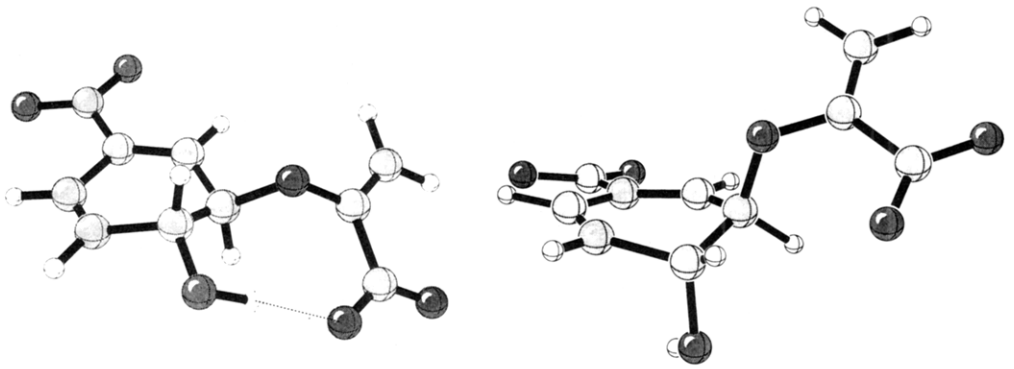

**Figure 2.** Diequatorial (left) and the diaxial (right) ground state conformations of **2b**.

**Table 1. Energies and Geometry Data for the Claisen Rearrangements of 2a,b (RHF/6-31G*)**

| | $GS_{dieq}$ | $GS_{diax}$ | transition structure | | | |
|---|---|---|---|---|---|---|
| compd | $E$ (hartree) | $\Delta E$ (kcal/mol) | $\Delta E_a$ (kcal/mol) | $\Delta E_a^{rel\,a}$ (kcal/mol) | $R_{CO}$ (Å) | $R_{CC}$ (Å) |
| **2a** | −833.437 51 | 5.7 | 50.4 | 3.0 | 2.076 | 2.408 |
| **2b** | −832.454 91 | 15.8 | 67.8 | 20.4 | 2.032 | 2.446 |

[a] Relative to the allyl vinyl ether at the RHF/6-31G* level: $\Delta E_a$ = 47.4 kcal/mol.

is in the solid state),[14] thus lowering the energy difference between the conformers. From NMR experiments, a energy difference of ~1.4 kcal/mol has been deduced.[7b] It has already been noted[7b] that this hydrogen bond is an important factor for the conformational equilibrium of **2b** and is in part responsible for the large solvent dependence of the reaction.

Because of the neglect of correlation energy, calculated activation energies for the Claisen and related reactions are too high by about 15−25 kcal/mol.[15] Substitutent effects on activation energies are much more accurate. With the 17 kcal/mol correction calculated for the parent Claisen rearrangement, the gas phase activation energies of **2a** and **2b** are predicted as 34 and 51 kcal/mol, respectively. In aqueous methanol, the activation energy of the rearrangement of the dimethyl ester of **2a** is 26.2 kcal/mol[7a] which is 8 kcal/mol less than the calculated value for the diacid in the gas phase. This difference is approximately equal to the 2−3 kcal/mol lowering of the activation energy of the parent Claisen reaction in aqueous methanol,[16] plus the replacement of the 5−6 kcal/mol intramolecular hydrogen bond by intermolecular hydrogen bonding. The activation energy of the chorismate rearrangement is 20.7 kcal/mol in aqueous solution.[1] The gas phase estimate of 51 kcal/mol is 30 kcal/mol higher. In the gas phase, there is high electrostatic repulsion between the two carboxylates in the transition state, and very strong hydrogen bonding of the carboxylate and hydroxyl group in the diequatorial ground state. Both of these factors will be eliminated in aqueous solution, reducing the activation energy by 30 kcal/mol. Both enzyme and antibody catalysis involve strong hydrogen bonding of both carboxylates,[2d,e,3f] which is necessary in the absence of solvation by water. The structures and charge distributions of the transition structure **2b** itself and of the stable transition state analog, Bartlett's inhibitor **1**, are shown in Figure 3. The bond lengths for the forming and breaking bonds in the transition state of **2b** (2.446 and 2.032 Å, respectively) are considerably longer than those calculated for the parent compound (2.264 and 1.917 Å, respectively)[15a] at the same level of theory and in sharp contrast to the transition state obtained by semiempirical methods.[1,9] This looser transition state is due to the stabilization of the positive partial charge by the cyclohexadienyl moiety.

It has been shown that secondary kinetic isotope effects (SKIE) are sensitive probes for the geometries of transition states.[15,17] The tritium secondary kinetic isotope effects calculated for **2b** are given in Table 2. The calculated SKIE at position 5, related to the CO distance, is within experimental error of the measured value;[18] thus, the bond breaking is described well by these calculations. The 8% inverse value calculated at position 9 is rather far from the 1% inverse experimental value. This indicates that $R_{7-9}$ is even longer than the large calculated value of 2.446 Å.

Comparison of the calculated transition structure for **2b** with Bartlett's inhibitor, **1**, reveals some characteristics which explain some of the properties of the inhibitor and the antibodies elicited against it. The positions of the two carboxylate functions, which are known to be crucial for molecular rcognition,[6a] are very similar in both. The cyclohexene ring in **1** is not as flat as in the cyclohexadienyl part of the calculated transition structure. The overall charge pattern is similar for both except for the positions 3 and 6. The dipole moment, which provides a measure of the stabilization which can be afforded by a polar environment along the reaction path,[19] is considerably higher for the calculated transition structure. The charge transfer of 0.35 electrons between the cyclohexadienyl and the enolpyruvyl moiety as well as the negative partial charge on the ether oxygen might also be the targets for more specific interactions in the active sites of the enzyme and the antibodies. The differences between the transition state analog **1** and the actual transition structure **2b** are mirrored in the active sites of the catalytic antibody and the enzyme, respec-

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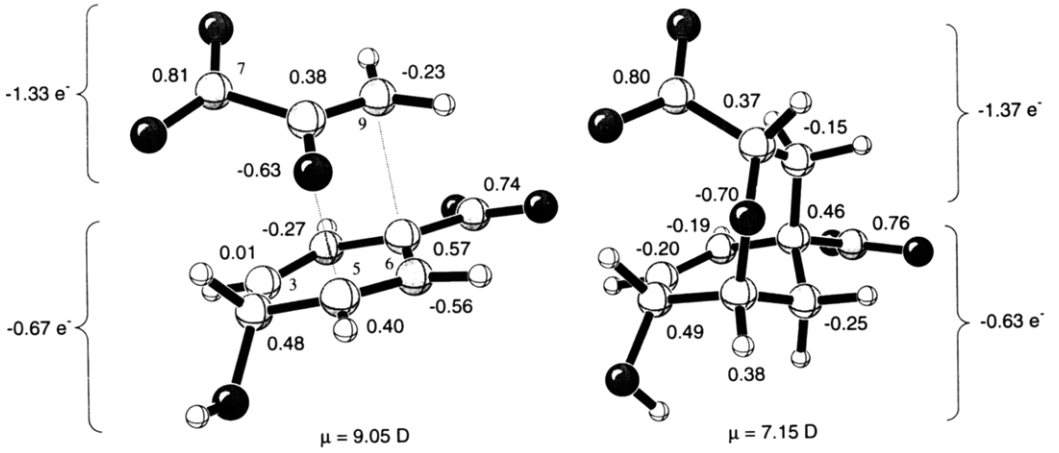


**Figure 3.** Structures, charge distributions (CHELPG/RHF 6-31G*, with hydrogen atoms summed into heavy atoms), and dipole moments for the transition structure of **2b** (left) and the enzyme inhibitor **1** (right).

**Table 2. Calculated Tritium Secondary Kinetic Isotope Effects (SKIE) for 2b**

| SKIE | expt[a] | calcd (RHF/6-31G*) |
|---|---|---|
| 5-$^1$H/5-$^3$H | 1.149 ± 0.012 | 1.140 |
| 9-$^1$H/9-$^3$H | 0.992 ± 0.012 | 0.922 |

[a] From ref 18.

tively, which are complementary to these structures. Since the reaction studied is the first one where the three dimensional structures of a catalytic antibody[3f] as well as of a native enzyme[2d] are known, an analysis of the stabilizing interactions provides a unique opportunity to compare the mechanisms of catalysis by enzymes and antibodies. A quantitative study of the stabilizing interactions is in progress.

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**Supplementary Material Available:** Energies, zero point energies, and Cartesian coordinates of all structures reported (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm edition of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.