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Supplementary Material Available: Stereodrawing and tables of bond lengths and angles and of positional and thermal parameters (3 pages). Ordering information is given on any current masthead page.

Ketonization of 1,3-Cyclohexadienol, a Conjugated Enol

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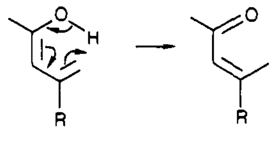
Although rates of enolization of aldehydes and ketones are fairly straightforward to measure,[1] determination of the rates of the reverse reaction has been hampered by the difficulty of obtaining solutions of the enols.[2] Recently, however, Kresge,[3] Capon,[4] and their collaborators have developed techniques to generate enols in greater than equilibrium concentrations, and they have been able to directly measure the rates of ketonization of a variety simple enols. In contrast to simple enols, however, the rates of ketonization of dienols remain largely unknown.[5] These compounds are of particular importance because they are intermediates in the conversion of β,γ-unsaturated ketones to their conjugated α,β-isomers.[6] Duhaime and Weedon[5d] have concluded, partly on the basis of the very rapid rates of uncatalyzed ketonization of **1a**,**b** (k = 40 s^{-1} for **1b** at 23 °C, $t_{1/2}$ = 17 ms), that dienols ketonize via a 1,5-sigmatropic hydrogen shift.



1a, R = Me
b, R = t-Bu

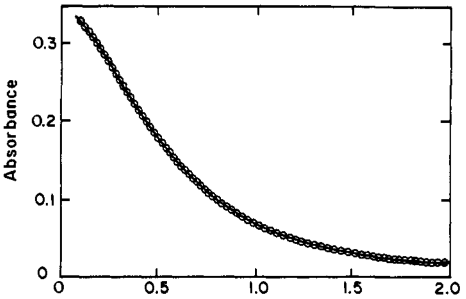
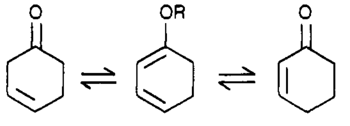


Figure 1. Plot of absorbance vs. time for the reaction of sweet potato acid phosphatase (0.0375 mg/mL) with 1,3-cyclohexadienol phosphate in D_2O solution (pD 4.70, [OAc$^-$] = 5 mM, 25.0 °C). The theoretical curve was calculated by using $k_1 = 7.26 \times 10^{-2}$ s^{-1} and $k_2 = 4.25 \times 10^{-2}$ s^{-1}. All experimental points are within ±0.0004 absorbance units of the theoretical line.

We have now examined the rate of water-catalyzed ketonization of 1,3-cyclohexadienol (**2a**), a dienol that is locked in a conformation such that a 1,5-sigmatropic rearrangement is impossible. In contrast to the rates of ketonization of **1a**,**b**, the uncatalyzed rate of ketonization of **2a** is relatively slow ($k_0 = 1.4 \times 10^{-2}$ s^{-1} in D_2O at 25 °C, $t_{1/2}$ = 48 s). In addition, this process leads exclusively to the β,γ-unsaturated isomer, rather than the α,β-unsaturated compound observed with **1a**,**b**. These results confirm the mechanism suggested by Duhaime and Weedon for **1a**,**b**.



3 **2a**, R = H **b**, R = PO_3H_2 **4**

The dienol **2a** was generated in situ by the action of sweet potato acid phosphatase on the corresponding enol phosphate **2b**.[7] When **2b** is treated with acid phosphatase in deuterium oxide at pD 4.7–5.6 and the reaction is monitored at 265 nm, a first-order decay with a significant induction period is observed (Figure 1). An ultraviolet scan of the product shows no significant absorbance above 220 nm, demonstrating that the final product is exclusively 3-cyclohexenone (**3**). We confirmed this conclusion by adding a small quantity of 10 N sodium hydroxide to the product solution and observing an increase in absorbance at 232 nm due to formation of **4**.

This variation of absorbance with time is characteristic of a series reaction (eq 1). For k_1 and k_2 both pseudo first order, the

$$\mathbf{2b} \xrightarrow{k_1} \mathbf{2a} \xrightarrow{k_2} \mathbf{3} \qquad (1)$$

change in absorbance may be analyzed by least-squares fitting of the data to a double exponential.[8] At relatively high concentrations of enzyme and low buffer concentration, the system is described quite well. At low enzyme concentrations, where $k_1 \lesssim k_2$, the data give only a fair fit (presumably because the k_1 process is not strictly first order). Alternatively, the reaction was run at high enzyme concentrations where the formation of the intermediate is rapid relative to its breakdown to products ($k_1 \gg k_2$). The data were then analyzed by ignoring the first part of the reaction and treating the system as a pseudo-first-order process. In cases where both methods were used, agreement was good (±15%).

Since in two-step reactions it is not generally true that the slower decay corresponds to the second step in the reaction,[8] it is necessary to demonstrate that the exponential decay that we attribute to ketonization (k_2) is due to that reaction and not some process

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[5] Dienols have been generated and observed, although their rates of ketonization have rarely been examined. See, for example: (a) Schmidt, E. A.; Hoffmann, H. M. R. *J. Am. Chem. Soc.* **1972**, *94*, 7832. (b) Noyori, R.; Inoue, H.; Katô, M. *J. Am. Chem. Soc.* **1970**, *92*, 6699. (c) Noyori, R.; Inoue, H.; Katô, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3673. (d) Duhaime, R. M.; Weedon, A. C. *J. Am. Chem. Soc.* **1985**, *107*, 6723. (e) Tureček, F.; Havlas, Z. *J. Org. Chem.* **1986**, *51*, 4066.

[6] (a) Ringold, H. J.; Malhotra, S. K. *Tetrahedron Lett.* **1962**, *15*, 699. (b) Malhotra, S. K.; Ringold, H. J. *J. Am. Chem. Soc.* **1963**, *85*, 1538. (c) *Ibid.* **1964**, *86*, 1997. (d) *Ibid.* **1965**, *87*, 3228. (e) Noyce, D. S.; Evett, M. *J. Org. Chem.* **1972**, *37*, 394. (f) *Ibid.* **1972**, *37*, 397. (g) Whalen, D. L.; Weimaster, J. F.; Ross, A. M.; Radhe, R. *J. Am. Chem. Soc.* **1976**, *98*, 7319.

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related to the enzyme-catalyzed hydrolysis of the phosphate. Two major lines of evidence are consistent with this conclusion. When the enzyme concentration is varied over a factor of 4, the rate constant changes only slightly (<20%), suggesting that the reaction is nonenzymatic. In addition, the observed general-base catalysis by acetate ion ($k_{\mathrm{OAc}^-} = 3.6\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$) is expected for ketonization but not for an enzymatic process.

In order to confirm that the k_2 process is not phosphatase-catalyzed hydrolysis of **2b**, the reaction was run at pD 4.70 and 1 mM acetate and quenched at various times by the addition of sodium hydroxide to give a pD >12. Addition of base inactivates the enzyme and causes both the product of ketonization, **3**, and the dienol intermediate **2a** to form 2-cyclohexenone (**4**) ($\lambda_{\max} = 232$ nm). Thus, monitoring the adsorbance at 232 nm as a function of time of quenching gives an estimate of the rate constant for phosphatase-catalyzed hydrolysis of **2b**. At 0.05 mg/mL of phosphatase, the rate constant is about 0.10 s^{-1}. This value is greater than 5-fold larger than the measured rate constant for ketonization (k_2) under these conditions.

Rate constants for ketonization were obtained at pD 4.70, 5.14, and 5.62 ($\mu = 0.1$, $NaClO_4$, acetate buffer, 25 °C). Extrapolation to zero acetate concentration gives values of $1.37 \times 10^{-2}\ \mathrm{s}^{-1}$ (pD 4.69), $1.58 \times 10^{-2}\ \mathrm{s}^{-1}$ (pD 5.14), and $1.40 \times 10^{-2}\ \mathrm{s}^{-1}$ (pD 5.62). Since these values are invariant with pD in this range they represent water-catalyzed ketonization (k_0). In order to compare the rate constants for ketonization of **1b** and **2a**, we multiply the rate constant of **2a** by an assumed solvent isotope effect of 5–10 to correct for the different solvents (D_2O vs. H_2O).[9] In addition, if we assume that we could have detected 5% of the conjugated isomer **4** in the product, the rate constant for protonation at the γ-carbon of **2a** can be calculated to be 10^3- to 10^4-fold slower than it is for **1b**. This large rate difference is probably due to the availability of a mechanism for **1b** which is unavailable to **2a**, presumably the 1,5-sigmatropic hydrogen shift, suggested by Duhaime and Weedon.[5d]

Acknowledgment. This work was supported by Grant GM 33059 from the National Institutes of Health.

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[9] The solvent isotope effect has been measured for the water-catalyzed ketonization of vinyl alcohol ($k_{H_2O}/k_{D_2O} = 12$).[4c]

Correlated Transition Structure for the 1,5-Sigmatropic Hydrogen Shift

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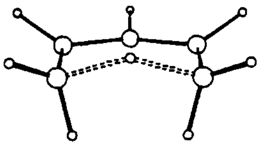
It was recently proposed that the 1,5-sigmatropic hydrogen shift in 1,3-pentadiene occurs via a "planar nonfacial" C_{2v} geometry.[1a] We wish to report extensive calculations that show that this claim is incorrect. We have also determined the influence of basis sets and electron correlation on the transition structure of this typical pericyclic reaction.

Ab initio transition structures obtained at the RHF level[2-5] for the 1,5-sigmatropic hydrogens shift of 1,3-pentadiene predict that the reaction occurs via a C_s suprafacial transition structure, **1**, consistent with experimental data.[6] MINDO/3 calculations also give a similar C_s transition structure,[7] but the activation energy is much higher than the experimentally observed value,[8] while the calculated isotope effects were too low. Vibrationally assisted tunneling was proposed for this reaction.



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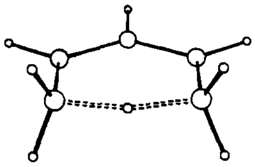

2

Dormans and Buck (DB) reported that a C_{2v} transition state, **2**, has a lower unrestricted Hartree–Fock (UHF) energy than the C_s transition state restricted Hartree–Fock (RHF) energy. They also propose that vibrationally assisted tunneling from this C_{2v} geometry is the mechanism for the 1,5-sigmatropic hydrogen shift.[1]

There are several clear lines of evidence that show that the C_{2v} geometry is not a transition structure. First, the experimental suprafacial stereochemistry of substituted cases[6] is not consistent with a planar transition structure. Second, the lower energy of the C_{2v} structure in the DB work is an artifact of the use of the UHF method for **2** and RHF for **1**. As shown in Tables I and II, when these two structures are reoptimized at the same computational level, the C_s structure is always lower in energy than the C_{2v}.[9] Third, the optimized UHF C_{2v} structure has two imaginary frequencies at the UHF/3-21G level; thus, it is not a transition state.[10] The second imaginary frequency (337i) corresponds to an distortion of the C_{2v} structure to the C_s structure. The C_s transition structure has only a single imaginary frequency.[3,4] In addition, the activation energies reported by DB are relative to the s-cis conformation of 1,3-pentadiene, instead of the more stable s-trans conformation.

We have carried out a systematic investigation of the influence of basis sets and electron correlation on the transition structure of the 1,5-sigmatropic shift. The large discrepancy between the calculated activation energy for the C_s structure and the experimental one is, indeed, due to neglect of correlation energy and not to location of an incorrect geometry. As seen in Table II, even including correlation energy only at the MP2/6-31G*//HF/3-21G level gives a calculated activation energy that is very close to the observed value of 36.1 kcal/mol.[8] At the single determinant level, the UHF energy is lower than the RHF energy. However, when electron correlation is included by the MP2 method, the restricted procedure gives a lower energy than the unrestricted. This is expected since the UHF wavefunction is heavily contaminated by higher spin states as seen from the $\langle S^2 \rangle$ value ($\langle S^2 \rangle = 0$ for a pure singlet).[11]

Table III shows additional results obtained for optimized reactant and C_s transition state calculations. There are only very small differences in geometries between RHF/3-21G and RMP2/6-31G* optimized structures. These structures are at most only 0.04 Å different in bond lengths and only a few degrees different in angles. Although there are not large changes in activation energies, improvements in the basis set at the RHF level result in an increase in the ΔE, which appear to be converging

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