Determination of the Dehydration Mechanism of a Secondary Alcohol Using Thermodynamic Simulations.

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Mechanism, Dehydration, Thermodynamics

ABSTRACT

The mechanism of the dehydration of a secondary alcohol was determined by way of electronic calculations using Gaussian 161. Calculations on Gaussian were carried out by a Hartree-Fock optimization followed by multiple DFT energy scans using B3LYP2. This was done for every molecule to calculate stepwise and overall changes in thermodynamics. The results disproved the assumption that a secondary alcohol dehydrates by an E1 mechanism as the free energy barrier of the E2 mechanism was shown to be lower.



INTRODUCTION

Many chemical reactions have multiple pathways to bridge reactants to products. These are most commonly observed in reactions involving organic substances and their chemical mechanisms. While there are multiple pathways, they will not be thermodynamically equal and favor one mechanism over the others. A secondary alcohol can be dehydrated by one of two mechanisms; a two-step or a one-step dehydration. The most probable mechanism can be determined by looking at the thermodynamics of each one.

THEORY

The dehydration of an organic compound in water can follow an E1 or an E2 mechanism as shown in Schemes 1 and 2.

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| --- | --- |
|  |  |

**Schemes 1 & 2.** The E1 and E2 reaction schemes of the dehydration of a secondary alcohol.

It is predicted that the E1 mechanism is the most probable reaction pathway because water is not a strong enough base to deprotonate a hydrogen β to the alcohol. This claim will be tested by using Gaussian 161 to model and calculate the thermodynamics of each molecule at every step of both mechanisms. The changes in thermodynamics for each step will be calculated according to

(1)

(2)

(3)

(4)

The LUMOs and HOMOs of each molecule will be observed to understand the role of electronic energies in the reactions. The energy of the HOMO-LUMO gap will be calculated using the following

(5)

The stereochemistry will also be altered to investigate its effect on the thermodynamics of the reaction. Because there are three stereocenters in molecule A, there will be eight different stereoisomers which will be referred to according to Figure 1.



**Figure 1.** Molecule A with numbered stereocenters.

Because the stereocenters are located on cyclohexane rings, each constituent can be categorized as orientated up or down. The naming convention that will be used is in the form 123.

For example, UUU is the stereoisomer with the alcohol and both methyl groups in the “up” position whether it be axial or equatorial.

COMPUTATIONAL DETAILS

Building of molecular models and calculations were done using Gaussian 161. Each molecule was optimized for their minimum energies using the Hartee-Fock (HF) method with the 3-21G basis set. Once optimized, energy scans were taken using the DFT method with the B3LYP correlation functional and the following basis sets: 3-21G, 6-31G, 6-311G, 6-311G(2d), and 6-311G(2d,2p). Each basis set scan was based on the previous scan to produce more accurate results. The final scan was an optimization and frequency scan using DFT – B3LYP – 6-311G(2d,2p). This process was repeated for water, hydronium ion, intermediates, and every stereoisomer.

RESULTS AND DISCUSSIONS

**General Thermodynamics** **and Mechanism Stability.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Δ*H* (kcal/mol)** | | | | **Δ*S* (kcal/mol∙K)** | | | | **Δ*G* (kcal/mol)** | | | | **Δ*U* (kcal/mol)** | | | |
| **E1** | B1-A | C1-B1 | D1-C1 | D1-A | B1-A | C1-B1 | D1-C1 | D1-A | B1-A | C1-B1 | D1-C1 | D1-A | B1-A | C1-B1 | D1-C1 | D1-A |
|  | -26.85 | -7.50 | 38.17 | 3.82 | 0.0026 | 0.0407 | -0.0057 | 0.0376 | -27.62 | -19.65 | 39.87 | -7.39 | -26.59 | -20.95 | 37.91 | -9.62 |
| **E2** | B2-A | D2-B2 |  | D2-A | B2-A | D2-B2 |  | D2-A | B2-A | D2-B2 |  | D2-A | B2-A | D2-B2 |  | D2-A |
|  | -26.85 | 30.67 |  | 3.82 | 0.0026 | 0.0350 |  | 0.0376 | -27.62 | 20.23 |  | -7.39 | -26.59 | 16.97 |  | -9.62 |

**Table 1.** Changes in thermodynamics for each step and for the overall reaction in both E1 and E2 mechanisms.

The changes in enthalpy, entropy, free energy, and internal energy of each step and overall for both reaction schemes are shown in Table 1 by using Equations 1-4. Both mechanisms share the same deltas for the first step as molecule A is protonated by a hydronium ion as seen both in Schemes 1 and 2. In addition, both mechanisms have the same deltas for the overall reactions as the only difference between the two are the pathways that they proceed.

|  |  |  |  |
| --- | --- | --- | --- |
| **E1** | **Δ*H* (kcal/mol)** | ***T*Δ*S* (kcal/mol)** | **Enthalpic/Entropic** |
| B1-A | -26.85 | 0.7713 | Entropic |
| C1-B1 | -7.50 | 12.1436 | Entropic |
| D1-C1 | 38.17 | -1.6992 | Enthalpic |
| D1-A | 3.82 | 11.2158 | Entropic |
| **E2** |  |  |  |
| B2-A | -26.85 | 0.7713 | Entropic |
| D2-B2 | 30.67 | 10.4445 | Enthalpic |
| D2-A | 3.82 | 11.2158 | Entropic |

**Table 2.** Values of Δ*H* and *T*Δ*S* when *T* = 298.15*K*.

The data in Table 2 compares the energy values of Δ*H* and *T*Δ*S* for each step and overall in both mechanisms. By comparing these values, the driving force of the mechanism can be determined, whether it be enthalpically driven or entropically driven. Overall, the dehydration of molecule A is an entropically driven reaction. The only step that is enthalpically driven, which is the same in both mechanisms, is the step where a double bond is formed because energy is required in the formation of a bond.

**HOMO and LUMO Analysis.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | E1 | | | | E2 | | |
|  | A | B | C | D | A | B | D |
| LUMO (hartrees) | -0.01849 | -0.20403 | -0.29002 | -0.05235 | -0.01849 | -0.20403 | -0.05235 |
| HOMO (hartrees) | -0.24326 | -0.39347 | -0.38397 | -0.23983 | -0.24326 | -0.39347 | -0.23983 |
| Gap (hartrees) | 0.22477 | 0.18944 | 0.09395 | 0.18748 | 0.22477 | 0.18944 | 0.18748 |

**Table 3.** HOMO-LUMO energy gaps for molecule A, intermediates,

and products in both mechanisms.

Inspection of the HOMO and LUMO energy gaps in Table 3 shows a large drop in the gap in intermediate C in the E1 mechanism. This is explained by the formation of a reactive carbocation that has a small HOMO-LUMO gap. Rather than forming a more reactive species in the E1 mechanism, the reaction would follow the E2 mechanism to avoid the less electronically stable intermediate.

**Effect of Chirality on Thermodynamics.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Δ*H* (kcal/mol)** | | | | **Δ*S* (kcal/mol∙K)** | | | | **Δ*G* (kcal/mol)** | | | |
| **E1** | B1-A | C1-B1 | D1-C1 | D1-A | B1-A | C1-B1 | D1-C1 | D1-A | B1-A | C1-B1 | D1-C1 | D1-A |
| **UUU** | -32.70 | -2.41 | 38.17 | 3.06 | -0.0043 | 0.0481 | -0.0057 | 0.0382 | -31.40 | -16.77 | 39.87 | -8.30 |
| **UUD** | -27.15 | -6.36 | 39.38 | 5.87 | 0.0036 | 0.0396 | -0.0050 | 0.0381 | -28.22 | -18.17 | 40.88 | -5.50 |
| **UDU** | -28.19 | -3.62 | 36.61 | 4.81 | -0.0002 | 0.0444 | -0.0058 | 0.0383 | -28.13 | -16.84 | 38.35 | -6.61 |
| **UDD** | -32.14 | 9.75 | 19.46 | -2.92 | -0.0044 | 0.0459 | -0.0036 | 0.0379 | -30.84 | -3.94 | 20.55 | -14.23 |
| **DUU** | -26.85 | -7.50 | 38.17 | 3.82 | 0.0026 | 0.0407 | -0.0057 | 0.0376 | -27.62 | -19.65 | 39.87 | -7.39 |
| **DUD** | -29.07 | -6.42 | 39.38 | 3.89 | -0.0035 | 0.0466 | -0.0050 | 0.0381 | -28.03 | -20.31 | 40.88 | -7.45 |
| **DDU** | -26.94 | -3.16 | 36.61 | 6.52 | 0.0032 | 0.0406 | -0.0058 | 0.0379 | -27.89 | -15.25 | 38.35 | -4.78 |
| **DDD** | -26.14 | 4.08 | 19.46 | -2.59 | 0.0025 | 0.0392 | -0.0036 | 0.0381 | -26.89 | -7.60 | 20.55 | -13.94 |
| **E2** | B2-A | D2-B2 |  | D2-A | B2-A | D2-B2 |  | D2-A | B2-A | D2-B2 |  | D2-A |
| **UUU** | -32.70 | 35.76 |  | 3.06 | -0.0043 | 0.0425 |  | 0.0382 | -31.40 | 23.10 |  | -8.30 |
| **UUD** | -27.15 | 33.02 |  | 5.87 | 0.0036 | 0.0346 |  | 0.0381 | -28.22 | 22.72 |  | -5.50 |
| **UDU** | -28.19 | 32.99 |  | 4.81 | -0.0002 | 0.0385 |  | 0.0383 | -28.13 | 21.51 |  | -6.61 |
| **UDD** | -32.14 | 29.21 |  | -2.92 | -0.0044 | 0.0423 |  | 0.0379 | -30.84 | 16.61 |  | -14.23 |
| **DUU** | -26.85 | 30.67 |  | 3.82 | 0.0026 | 0.0350 |  | 0.0376 | -27.62 | 20.23 |  | -7.39 |
| **DUD** | -29.07 | 32.96 |  | 3.89 | -0.0035 | 0.0416 |  | 0.0381 | -28.03 | 20.57 |  | -7.45 |
| **DDU** | -26.94 | 33.45 |  | 6.52 | 0.0032 | 0.0347 |  | 0.0379 | -27.89 | 23.10 |  | -4.78 |
| **DDD** | -26.14 | 23.55 |  | -2.59 | 0.0025 | 0.0355 |  | 0.0381 | -26.89 | 12.95 |  | -13.94 |

**Table 4.** Thermodynamic values of eight stereoisomers of molecule A

following the naming convention in Figure 1.

The previous sections used the DUU stereoisomer for analysis. According to Table 4, stereochemistry plays a role in the thermodynamics of the dehydration of molecule A. Steric hinderance influences the thermodynamics as shown by comparing the thermodynamics of DDD and UDD. Because both methyl groups are pointed away from the alcohol in UDD, it can be protonated by a hydronium ion with minimal interference. In addition, the axial-equatorial orientation of the alcohol affects the thermodynamics. The up position for the alcohol is equatorial, which is preferred because of its steric bulk. As a result, the thermodynamics of UUU is more stable than that of DUU.

CONCLUSION

Based on thermodynamics, the more probable reaction pathway is the E2 mechanism. This was concluded from the data in Table 1 by comparing the free energies of the final step, D­1-C1 and D2-B2, which is the formation of a double bond. The E2 mechanism has a lower activation energy than the E1 as the change in free energy of a reaction is directly related to its activation energy. In addition, the Arrhenius Law relates the free energy to the equilibrium constant and a lower free energy corresponds to more formation of products. The

HOMO-LUMO gaps of intermediate molecules can provide extra insight into their relative reactivities and stabilities. Finally, although the chirality of a reactant will not change the dominating mechanism, it will affect the thermodynamics of a mechanism overall.

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