

Application of Molecular Dynamics and Quantum Calculations to Determine Reaction Pathway

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Abstract

Theoretical applications of chemistry provide insights into chemical reactions that experimentation cannot always provide. Molecular modeling was used to investigate the synthesis of a cyclopenta[c]pyridine product from a 1,8-enedial substrate, a synthesis completed by the Hofferberth lab.¹ Our research was designed to determine the most likely mechanism for this important reaction. The lowest energy pathway was discovered for a part of the overall reaction.

Introduction

Derivatives of the cyclopenta[c]pyridine product are found in numerous biological applications: endothelial cell suppression and testosterone-responsive carcinoma SC115 inhibition are included among other uses.² Computational techniques were used to investigate this reaction, allowing for a closer inspection of the reaction pathway.

We investigated this reaction in two broad parts, the initial "isomer reaction" and the subsequent "funnel reaction" (Figure 1). The reactant, the 1,8-enedial substrate, proceeds first through four possible isomers and then through two possible transition states towards the final product.

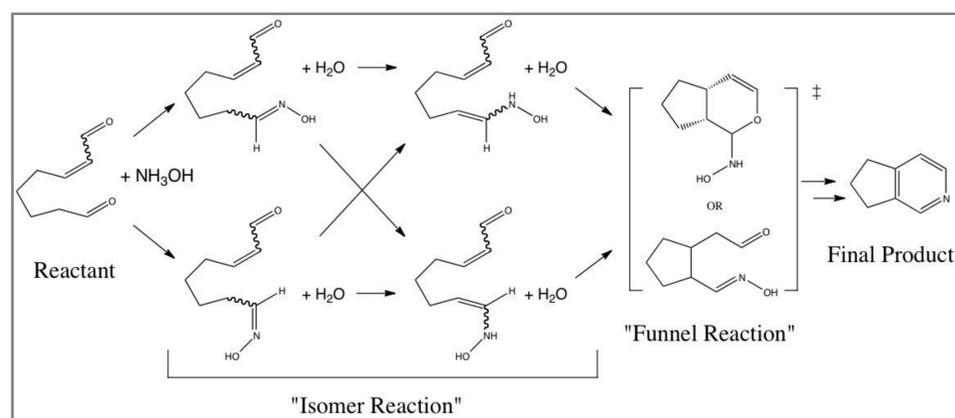


Figure 1. The progression of the studied reaction from the 1,8-enedial reactant to the cyclopenta[c]pyridine product. The two principally studied stages of the reaction included the "isomer reaction," including four possible diastereomers, and the "funnel reaction," involving two possible mechanisms that will yield the product.

Methods

Using the assumption that a reaction moves from reactants to products by following the path of lowest energy conformational changes, quantum mechanical calculations were formed that allow for the prediction of the associated energies for each structural change on the expected path.

The intermediate structures were constructed and minimized (Figure 2). Modeling was accomplished by initially using the Ohio State supercomputer with Monte Carlo simulations, followed by minimizations in Gaussian, a suite of molecular programs. By examining the results from the calculations, we predicted the likely path the reaction takes from reactant to product.

Isomer Reaction

The reactant, which has various derivatives and several conformations, was first examined in two of its most basic forms (Figure 2A and 2B). After reacting with hydroxylamine, a total of four different stereoisomers could be formed, with two isomers being possible at each step. Determining the path through these isomers is at the heart of our investigation of the "isomer reaction."

Overall, the energy calculations do not suggest a distinct path through the isomer reaction, as the paths do not agree among the two examined reactants. However, in all cases the structure that precedes entry into the "funnel reaction" is predicted to take on a folded, almost cyclical, conformation. This conformation would be very favorable considering that the next segment of the reaction, the "funnel reaction," requires the molecule to form cyclic intermediates.

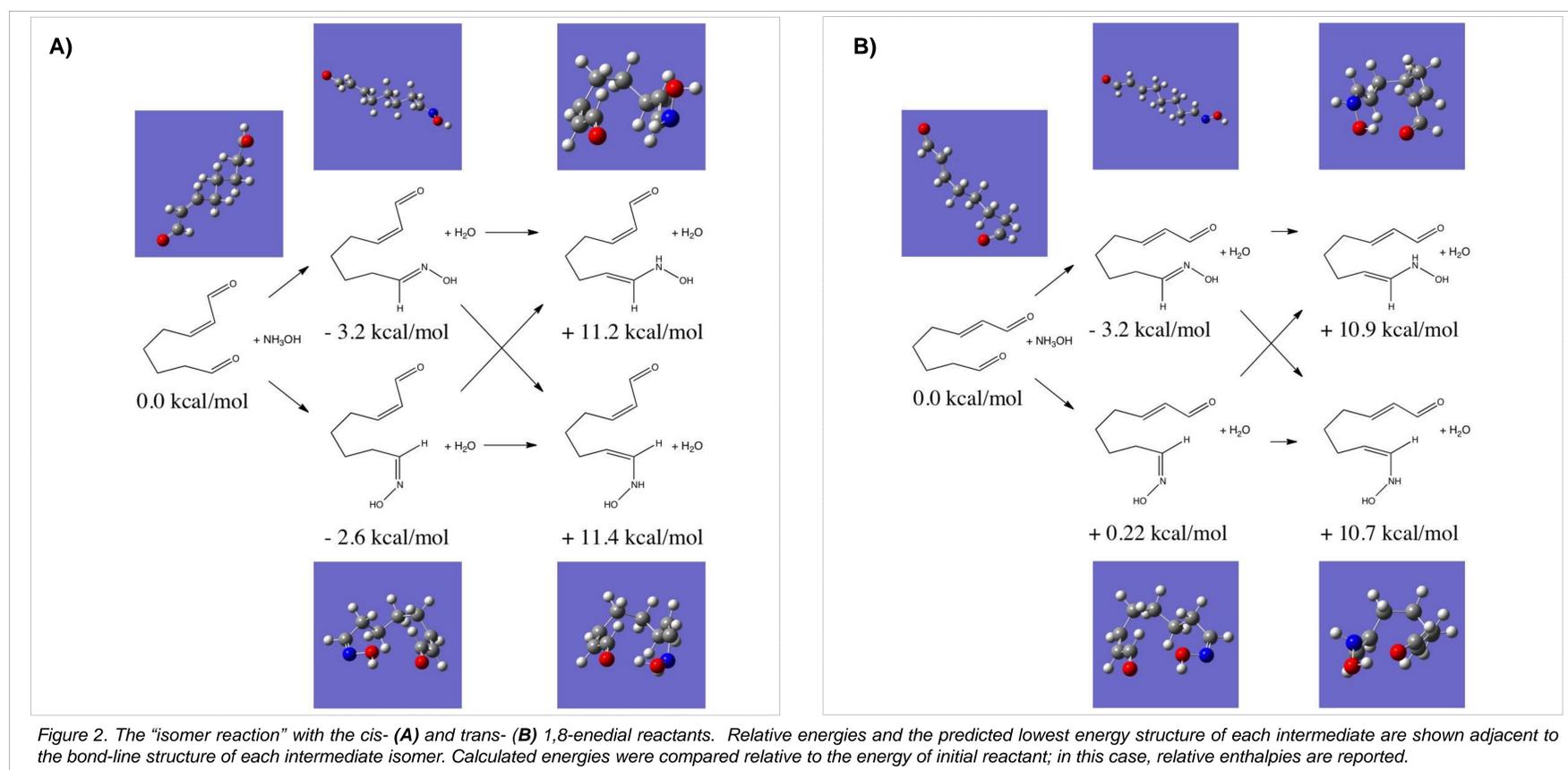


Figure 2. The "isomer reaction" with the cis- (A) and trans- (B) 1,8-enedial reactants. Relative energies and the predicted lowest energy structure of each intermediate are shown adjacent to the bond-line structure of each intermediate isomer. Calculated energies were compared relative to the energy of initial reactant; in this case, relative enthalpies are reported.

Ongoing Research

To further refine our knowledge of the route through the "funnel reaction," the activated complexes of the "funnel reaction" are being modeled. Activated complexes are found at the transition state of each successive transformation. Once completed, each potential complex will be tested to determine if an energy maximum was reached, and if the complex both allows a return to its precursor and can proceed to the next stage in the reaction.

Once plausible activated complexes are found, the energy of each complex will be determined. Nature favors the least energetic pathway, so the less energetic of the two proposed complexes will be favored. Other substituted reactants are being examined to better develop our knowledge of this reaction.

References

1. Beckett, J. S.; Beckett, J. D.; Hofferberth, J. E. *Org. Lett.* **2010**, *12*, 1408.
2. Catozzi, N.; Edwards, M. G.; Raw, S. A.; Wasnaire, P.; Taylor, R. J. *J. Org. Chem* **2009**, *74*, 8343-8354.

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