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Summary:

Trans annular cyclization's of medium-ring amido alkenes – A computational study

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Trans annular cyclization reactions are an important method for transforming macrocyclic molecules into fused bicyclic structures. This type of reaction using amido alkenes as substrates has been reported, though the current scope is limited. The products formed through this type of trans annular cyclization (indolizidones and related fused heterocycles) are useful synthetic intermediates for many biologically active molecules. Therefore, a better understanding of the factors governing the stereochemical and regiochemical outcomes of this sub-class of trans annular cyclization's would be beneficial. As such, a computational study was undertaken to investigate the cyclization of amido alkene-derived bromonium ions. Both E and Z alkene geometries were modeled in an effort to determine their effect on the stereochemistry of the fused bicyclic products. Additionally, the spacing between the alkene and amide functionalities were varied to investigate the regioselectivity of cyclization. Initial conformational analysis calculations of halonium intermediates, transition state estimates, and bicyclic ammonium products using Merck molecular force field (MMFF) were performed in Spartan'18. Subsequent optimization and frequency calculations were performed in Gaussian16 using density functional theory (DFT) at the B3LYP 6-31G+ (d) level of theory. The results of this computational study will be described herein.