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Computational investigation of cyclic 8-membered enediyne chemistry

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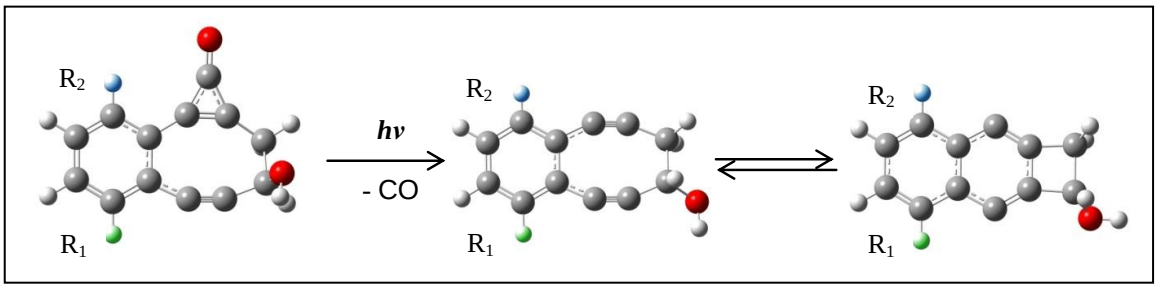
The extreme cytotoxicity of natural enediynes is attributed to the ability of the (Z)-3-ene-1,5-diyne fragment incorporated into a 10- or 9-membered ring cyclic system to undergo Bergman cyclo-aromatization and to produce DNA-damaging *p*-benzynediradical. The rate of this reaction strongly depends on the ring size. Thus 10-membered ring enediynes are stable, 9-membered ring analogs undergo slow cyclo-aromatization under ambient conditions or mild heating. Very little is known about reactivity of 8-membered ring enediynes due to their instability. Computational chemistry (Gaussian 09W; B3LYP hybrid function with the 3-21G basis set in a Linux operating system) was used as a tool to design and investigate the synthesis and reactivity of 8-membered cyclic enediynes that are structurally simple compared to the natural enediynes.



Computational studies revealed that the intra-molecular ring formation step (Nozaki cyclization) for the synthesis of 8-membered enediyne precursor is highly endothermic due to the presence of high ring strain. However, this reaction is more favorable in polar aqueous medium rather than in non-polar medium. The studies of substituent effect predict that increasing the steric hindrance at $\mathbf{R_2}$, favors the Nozaki cyclization reaction to minimize the steric properties between $\mathbf{R_2}$substituent and the acetyl protecting group.

According to theoretical results, “Bergman cyclo-aromatization” of 8-membered ring analogs is thermodynamically more feasible because ring strain is released in cyclo-aromatization. It is evident that when electron withdrawing groups are attached to the benzene ring (as $\mathbf{R_1}$ and $\mathbf{R_2}$), cyclo-aromatization process is accelerated by the field effect of electronegative substituents on *ortho*-positions that decrease the electron density at the acetylenic carbon atoms.

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