Controlling IEDDA Reaction with Macrocyclic Tetrazine

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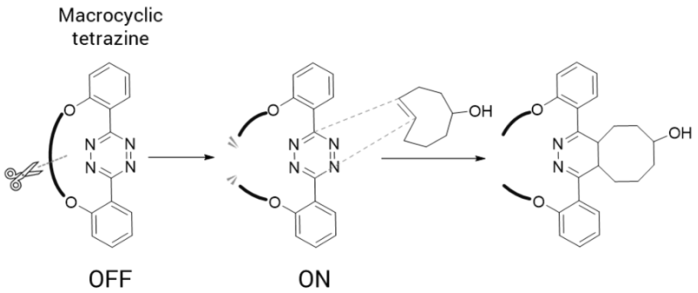
Tetrazine cycloaddition refers to the reactions between tetrazines and dienophiles via inverse electron-demand Diels-Alder (IEDDA). Owing to its exceptionally fast kinetics and excellent biocompatibility, this bioorthogonal reaction has been applied in various fields spanning from material sciences to biomedicine and has been utilized for therapeutic in humans[1,2]. This otherwise spontaneous reaction can be controlled by developing activatable tetrazines or activatable dienophiles. However, all activatable tetrazines have only been based on the oxidation of dihydrotetrazine into tetrazine[3,4], while tetrazine activation that relies on controlling tetrazine reactivity has yet to be developed.

Here we showed that connecting the two phenyl substituents of 3,6-diphenyltetrazine by a chemical bridge (macrocyclic tetrazine) can make it unreactive towards one of the most reactive dienophiles, *trans*-cyclooctene (TCO). Our theoretical study revealed that the suppressed reactivity was mainly attributed to the high distortion energy of the macrocyclic tetrazine that was originated from the rigid conformation. Furthermore, we also demonstrated the first example of tetrazine activation based on the cleavage reaction of the chemical bridge in macrocyclic tetrazine.



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