Bioorthogonal Cycloadditions of Isonitriles

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Isonitriles can react in a bioorthogonal ligation reaction with suited 1,3-dienes like 1,2,4,5-tetrazines in a (4+1) cycloaddition followed by a cycloreversion. In previous work we found an unusual high reactivity of sterically demanding tetrazines in the reaction with isonitriles, which could be traced back to attractive dispersion forces at the transition state [1].

Here we present an in-depth computational study on the isonitrile tetrazine ligation reaction of such sterically demanding and non-demanding tetrazines. Energy decomposition schemes are applied to trace reactivities back to their individual contributions, demonstrating the importance of dispersion and electrostatic attractions. Furthermore, dynamic effects due to shallow and entropic intermediates and low-barriers along an extended energy surface were investigated using quasi-classical reaction dynamics at the DFT level.

In addition, investigations of the reactivity of isonitriles with other 1,3-dienes such as cyclopentadienones are presented.

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[1] Julian Tu, Dennis Svatunek, Saba Parvez, Albert C Liu, Brian J Levandowski, Hannah J Eckvahl, Randall T Peterson, Kendall N Houk, Raphael Marcel Franzini; “Stable, Reactive and Orthogonal Tetrazines: Dispersion Forces Promote the Cycloaddition with Isonitriles”, Angewandte Chemie International Edition, **2019**, DOI: 10.1002/anie.201903877