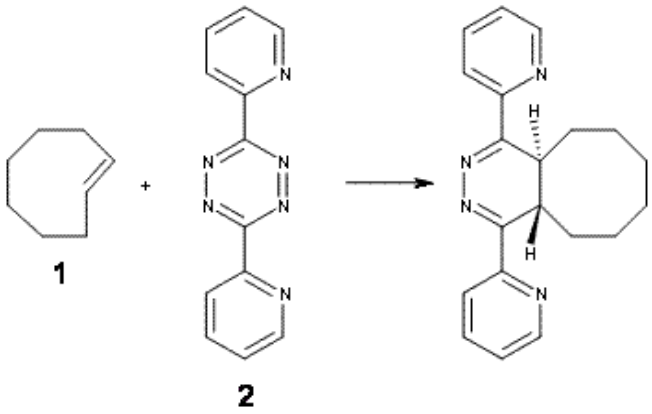
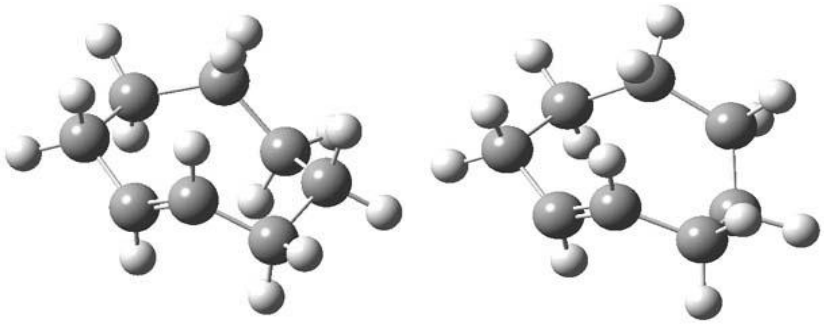
TRANS-CYCLOOCTENE AS A CLICK ALTERNATIVE

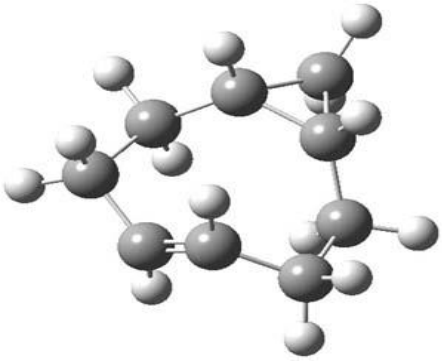
The click reaction, the copper-assisted cycloaddition of an azide with an alkyne, has been extended to biological systems by use of a strained alkyne (cyclooctyne) thereby eliminating the need of the toxic copper agent.[1] Fox has extended this analogy with the reaction of strained *trans*-cyclooctene**1** with tetrazine **2**.[2]



The interesting new twist here is to add more strain to *trans*-cyclooctene to perhaps make the cycloaddition even faster. Bach[3] had pointed out that the half chair conformation of **1** is almost 6 kcal mol^{-1} higher in energy than the ground state (Figure 1). Fox suggests that fusing a cyclopropyl ring to the eight-member ring would create a ring in the half chair **3**. Since **3** would be even more strained than **1**, it should undergo a faster cycloaddition reaction.



1 **1 (half chair)**



3

Figure 1. M06L/6-311+G(d,p) optimized structures of **1** and **3**.

Though Fox did not estimate the strain of **3**, I have computed the structure of **1** constrained to the geometry of **3**, with the two hydrogens that replace the bonds to the cyclopropyl carbon allowed to optimize. This restricted geometry is in fact 6.1 kcal mol^{-1} (M06L/6-311+G(d,p)) higher in energy than **1** – so the fusion of the 3-member ring does net the strain increase expected by Bach.

Fox reports estimates of the free energy of activation (at M06L/6-311+G(d,p)) for the reaction of**1**or **3** with **2**. The barrier for the raction with *trans*-cyclooctene **1** is 8.92 kcal mol^{-1}, while the barrier for the reaction with **3** is 6.95 kcal mol^{-1}. A methylenehydroxyl derivative of **3** was synthesized and it does react 180 times faster than the reaction with **1**. Furthermore, the differences in the experimental free energies of activation is 3.0 kcal mol^{-1}, in excellent agreement with the computed difference.

Source: http://comporgchem.com/blog/?p=1709