

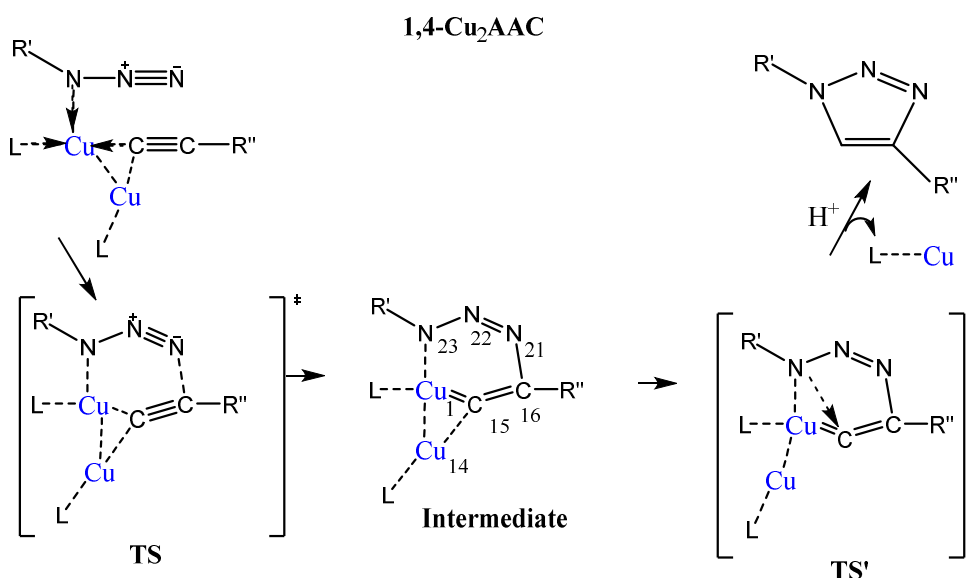
Exploring the regioselectivity for the cycloaddition of azides to alkynes catalyzed by dinuclear copper clusters (Cu_2AAC) with the topology of $\nabla^2(\rho)$ and $\nabla\nabla^2(\rho)$

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This study constitutes an extension of a previous research on the regioselectivity of the copper catalyzed cycloaddition of azides to alkynes¹ (CuAAC) by Quantum Chemical Topological methods. In particular, by following the evolution the topology of the laplacian of the electronic charge density, $\nabla^2\rho(r)$, and its gradient vector field, $\nabla\nabla^2\rho(r)$ along the reaction coordinates, computed with different Density Functionals (B3LYP, LCwPBE, M06-L, wB97XD, and M06-2X) and 6-311++G(d,p) basis set. For the mononuclear process, we found that a H-type interaction conditions the attack of the azide in the 1,5- CuAAC .¹

In addition, given that experimental evidences² seem to suggest the participation of a second Cu atom in the reaction coordinate, we have explored very recently³ the mechanism involving a dinuclear copper cluster at the LCwPBE/6-311++G(d,p) level (see Scheme). Interestingly, the catalyst modifies the uncatalyzed Huisgen mechanism, by inducing sequentially first the terminal N-C bond and the internal afterwards in a concerted fashion for the 1,4- CuAAC and stepwise for the 1,4- Cu_2AAC . Furthermore, as seen in the topology of $\nabla^2(\rho)$ the catalyst provoked that a carbon acts as a nucleophile and turned pericyclic mechanism into pseudopericyclic.³



[1] Calvo-Losada S., Pino M.S. and Quirante J.J., *J. Mol. Model.*, **20**, 2187 (2014)

[2] Worrell B. T., Malik J. A. and Fokin V.V., *Science*, **340**, 457 (2013)

[3] Calvo-Losada S., Pino M.S. and Quirante J.J., *J. Phys. Chem. B*, **119**, 1243 (2015)