Revisiting the mechanism of the mono nuclear copper-catalyzed cycloaddition of azide and alkynes (CuAAC) by the topology of $\nabla^2\rho(r)$ and $\nabla\nabla^2\rho(r)$.

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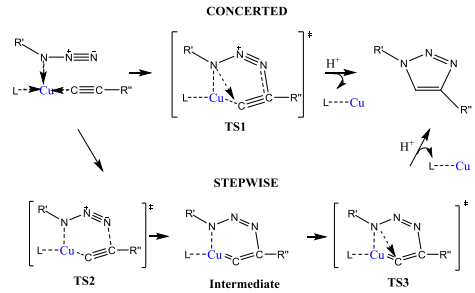
The Copper-catalyzed azide–alkyne cycloaddition (CuAAC) was the beginning of a new branch in organic chemistry called "click chemistry".[1] A term coined by Sharpless to describe a set of bond-forming reactions useful for direct assembly of molecules with a specific function.

The CuAAC reaction exhibits a high regioselectivity combined with excellent yields for the overall reaction and also an efficient catalyst effect. The first mechanistic proposal set up by the Sharpless et al. (outlined in Scheme 1) was confirmed afterwards by B3LYP theoretical calculations. Nonetheless, new accumulated experimental facts have pointed out the convenience of clarifying many others aspects concerning this mechanism that are not yet well known, such as the role of the solvent, the influence of chelating azides, the oxidation state and the number of Cu atoms involved in the catalysis or the influence of ligands attached to Cu. But, most importantly, the role of copper in the mechanism, as opposed to other metals such as Ruthenium without the same catalytic activity, that is far from being well understood yet.

In this work, we first address the suitability of the B3LYP density functional to describe this process and secondly, the regioselectivity of the process rationalized by the topology of the laplacian of the charge density, and the associated gradient vector field, $\nabla\nabla^2\rho(r)$. Our DFT calculations with others functionals (M06-2X or LC-wPBE) show that the nature of the mechanism (stepwise or concerted) for the simplest CuAAC reaction depends on the ligands attached to Cu(I). On the other hand, the topological evolution of the charge density, $\rho(r)$, and of the laplacian of the charge density, $\nabla^2\rho(r)$, shed light on the regioselectivity of the process and the catalytic activity of Cu(I).



1. J. E. Hein and V. V. Fokin *Chem. Soc. Rev*. **2010**, 39, 1302–1315 and references therein.

2. For example, J. E. Hein, J. C. Tripo, L. B. Krasnova, K. B. Sharpless and V. V. Fokin, *Angew. Chem. Int. Ed.* **2009**, 48, 8018-8021.