Understanding the mechanism and regioselectivity of the copper and Ruthenium catalyzed 1,3-dipolar cycladdition of azido ribose derivative with alkyne. A DFT study

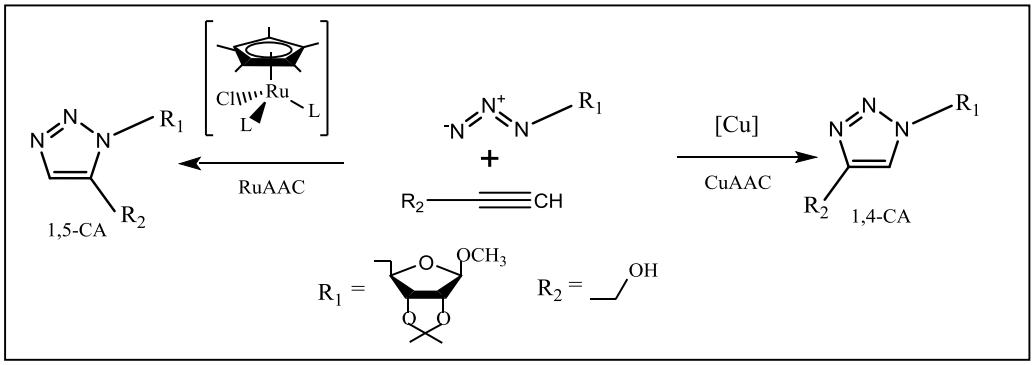
Y. Yousfi*, W. Bencchouk* and S. M. Mekelleche

Laboratoire de Thermodynamique Appliquée et Modélisation Moléculaire
Département de Chimie, Faculté des Sciences, Université A. Belkaïd, B.P. 119, Tlemcen, 13000. Algeria
*E-mails: youcef.yousfi@student.univ-tlemcen.dz ; benchouk_wafaa@mail.univ-tlemcen.dz

1,2,3 Triazoles constitute a family of compounds known for their momentous and valued biological activities. Their biomedical applications include the treatment of tumors, diabetes, microbial and fungal infections and inhibition of HIV protease.

Experimentally, the uncatalyzed cycloaddition of azido derivative of ribose with alkyne provides a mixture of 1,4- and 1,5-triazole regioisomers at higher temperature. Whereas, the Copper-catalyzed Azide−Alkyne Cycloaddition (CuAAC) gives only the 1,4-disubstituted triazole. Another discovery in the field of *click chemistry* reveals that the Ruthenium-Catalyzed Azide−Alkyne Cycloaddition (RuAAC) yields, exclusively, the 1,5-disubstituted triazole.

In the present work, both the uncatalyzed and the CuAAC and RuAAC reactions (***Scheme 1***) were modeled and discussed in terms of relative energies obtained from quantum-mechanical calculations performed at the B3LYP/6-31G(d) level of theory. For Cu(I), Ru(II) and Cl atoms, the LANL2DZ effective core potential has been used. In the absence of Cu(I) and Ru(II) catalysts, two regioisomeric reaction pathways were studied, indicating that the AAC reaction takes place through an asynchronous one-step mechanism. Coordination of Cu(I) to alkyne produces relevant changes in this AAC reaction as a consequence of the large enhancement in the nucleophilicity of the corresponding dinuclear Cu(I)-acetylide complex with formation of the experimentally observed 1,4-tiazole. Formation of the 1,5-tiazole via the RuAAC appears to proceed via oxidative coupling of the azide and alkyne reactants to give a six-membered ruthenacycle intermediate. The first carbon-nitrogen sigma bond is formed between the more electronegative carbon of the alkyne and the electrophilic terminal nitrogen of the azide. This step is followed by a reductive elimination yielding the formation of the final 1,5-triazole product.



Scheme 1

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