

C. Rajalakshmi¹, S. S. Jibin¹, Rehin Sulay¹, Gopinathan Anilkumar², Vibin Ipe Thomas*¹

¹Department of Chemistry, CMS College Kottayam (Autonomous), Kottayam, Kerala, India

²School of Chemical Sciences, Mahatma Gandhi University, Kottayam , Kerala, India

ABSTRACT

Copper catalyzed Sonogashira coupling reactions are gaining importance owing to the low cost and less toxicity of copper as compared to the palladium catalyst. In the present work, a detailed computational study has been carried out on the Sonogashira coupling reaction between aryl halides and terminal alkynes catalyzed by Copper (I) species with *trans*-1,2- Diaminocyclohexane as ligand. All calculations are performed at Density Functional Theory (DFT) level, using the hybrid Becke3LYP functional. Cu and I atoms are described using an effective core potential (LANL2DZ) for the inner electrons and its associated double- ζ basis set for the outer electrons. For all other atoms, 6-311+G* basis set is used. The active catalytic species is a neutral 3-coordinate *trans*-1,2-diaminocyclohexane ligated Cu (I) alkyne complex. The reaction proceeds through a concerted oxidative addition and reductive elimination pathway involving one transition state. To traverse the effect of functional groups on the feasibility of reaction, substrates containing various functional groups are considered in our study. Substrates possessing electron withdrawing groups shows lower activation energies as compared to electron rich substrates. The theoretical results obtained are in good agreement with the experimental observation. Our study portrays the relevance of a combined theoretical and experimental approach for rationally improving the cross-coupling reaction mechanisms.

INTRODUCTION

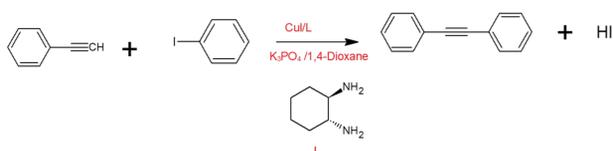
Transition metal catalyzed cross coupling reactions has become an inevitable tool in synthetic organic chemistry for the construction of C-C bonds. Among the variants, Sonogashira coupling has obtained a privileged status due to its role in the preparation of biaryl acetylenes, the precursor for many biologically active compounds like benzofuran. From the time of its discovery, there occur many variants in Sonogashira coupling. Among them, the cheaper and eco-friendly copper catalyzed Sonogashira coupling are gaining momentum in recent years. Understanding the mechanism of this reaction at the atomistic level will help to improve the reaction conditions further. We thereby employ a computational protocol using Density Functional Theory (DFT) method to investigate the mechanism of copper catalyzed Sonogashira coupling reaction employing *trans*-1, 2-diamino cyclohexane ligand.

METHODOLOGY

All molecular geometries were optimized without any structural constraints with Density Functional Level of Theory (DFT) using the hybrid Becke3LYP functional. For Cu and I effective core potentials of Hay and Wadt with double ζ valence basis set (LANL2DZ) were employed. For the atoms C, N and H 6-311+G (d) basis set was used. Transition state is confirmed by the intrinsic reaction coordinate calculation. To account the solvation effects, Conductor-like Polarizable Continuum Model (CPCM) solvation model was used with 1, 4-dioxane as solvent.

AIM OF THE WORK

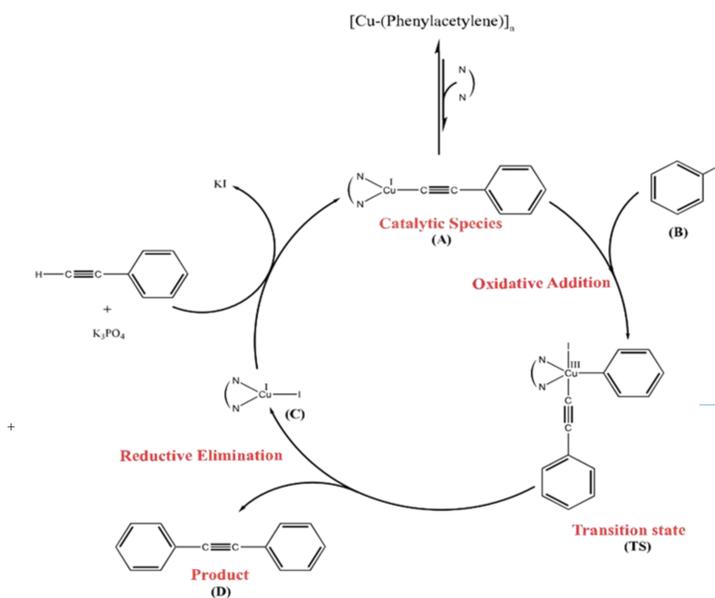
- To determine the most suitable mechanistic pathway for the copper catalyzed Sonogashira coupling using the *trans*-1,2-diaminocyclohexane ligand for the model system. (Scheme 1).
- To explore the effect of various functional groups in the substrate molecule on the feasibility of the cross coupling reaction.



Scheme 1

RESULTS AND DISCUSSIONS

On the grounds of theoretical calculation, a catalytic cycle for the reaction (scheme 1) has been proposed and shown in Scheme 2. The reaction initiates with the formation of a *trans*-1, 2-diaminocyclohexane ligated Cu (I) alkyne complex (A), which is proposed to be the active catalytic species in reaction. Further the Iodobenzene (B) attacks the catalytic species (A). The reaction proceeds thereafter by a concerted oxidative addition – reductive elimination pathway involving a transition state (TS) having an activation energy of 33.53 kcal/mol (Fig.1). A stable Cu (III) intermediate was absent in the reaction since every optimization attempt lead to the direct formation of cross coupled product from the transition state. The concerted mechanism could be attributed to the instability of Cu(III) metal and the ease of reductive elimination involving Csp²-Csp bond.



Scheme 2

Effect of Substituents on the Feasibility of Reaction

Our results show that the presence of electron withdrawing groups (COCH₃) on the substrate iodobenzene decrease the activation barrier of reaction (Fig.2) as compared to electron releasing groups(CH₃)(Fig. 3). This trend is attributed to the effect of substituents on the frontier molecular orbitals of the substrate molecules. The electron withdrawing group reduces the gap between HOMO of the copper acetylide complex and LUMO of the aryl halide thereby increasing the interaction between frontier molecular orbitals of reactants.

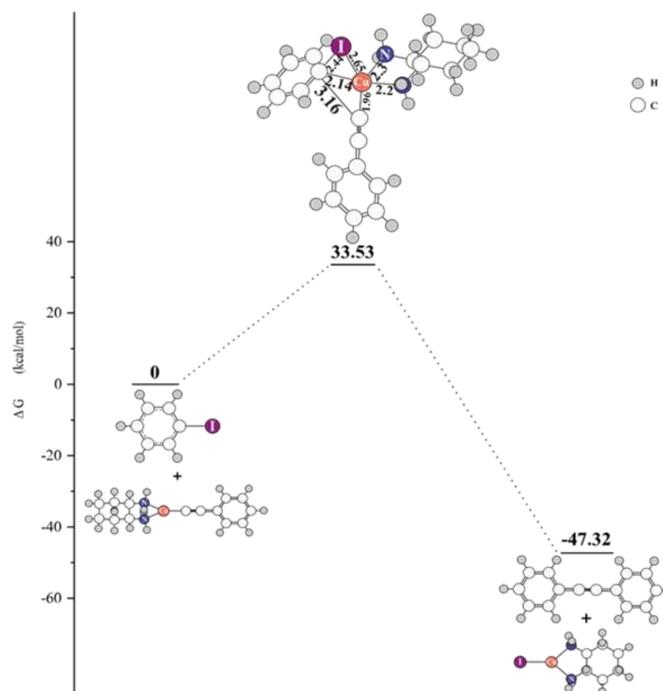


Fig. 1. Free energy profile diagram for catalytic pathway involving the model system

Alkyne	Arylhalide	E _{LUMO-E_{HOMO}} (eV)	ΔG [‡] kcal/mol	ΔG ^o kcal/mol
		3.98	33.53	-47.32
		4.04	33.47	-48.37
		2.95	30.98	-48.63

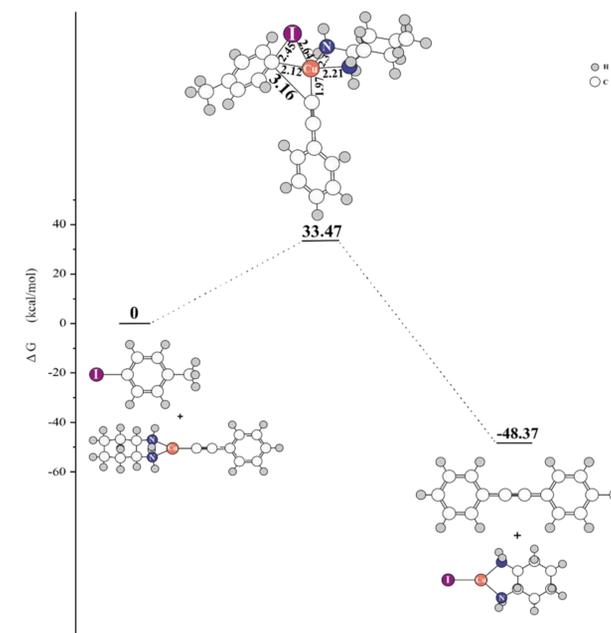


Fig 2 . Free energy profile (kcal/mol) for catalytic cycle involving electron releasing group (CH₃)

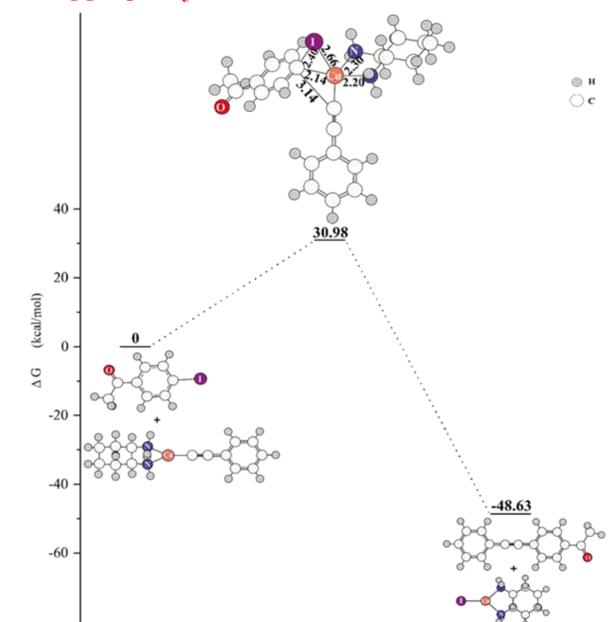


Fig. 3. Free energy profile (kcal/ mol) for catalytic cycle involving electron withdrawing group (COCH₃)

CONCLUSIONS

- The mechanism of copper catalyzed Sonogashira coupling reaction have been investigated with the aid of DFT method.
- Catalytic pathway involves a concerted oxidative addition-reductive elimination step.
- A Stable Cu (III) intermediate was absent in the catalytic pathway.
- Presence of electron-withdrawing groups on iodobenzene decreases the activation barrier of reaction.

REFERENCES

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