

# On the mechanism of CuCl mediated amine addition to diacetylenes

G. Huerta, L. Fomina \*

*Instituto de Investigaciones en Materiales, Universidad Nacional Autónoma de México, Apartado Postal 70-360, CU, Coyoacan, 04510, Mexico, DF, Mexico*

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## Abstract

A mechanism of CuCl mediated amine addition to diacetylenes resulting in pyrrole formation has been studied theoretically at B3LYP/6-31G\* level of theory. The reaction proceeds via formation of Cu-stabilized carbene intermediates and the formation of the first intermediate is the rate determining reaction step. The catalytic action of CuCl is due to the reduction of activation energy of the carbene intermediate formation from 75.0 to 50.1 kcal/mol. The decrease in activation energy is related to the reduction of HOMO–LUMO energy gap between nucleophile and electrophile due to complex formation allowing to catalogue this reaction as interaction between soft acid and base.

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*Keywords:* Copper chloride; Diacetylenes; Pyrroles

## 1. Introduction

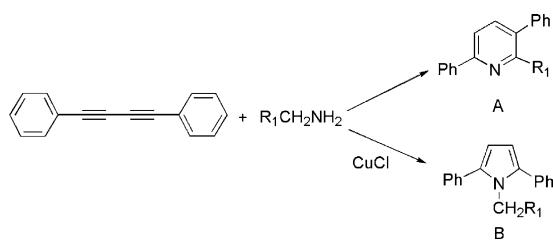
The addition of primary amines to a 1,3-diyne resulting in substituted pyrrole formation, which is catalyzed by Cu [1] and Ti [2] salts is one of the important routes to substituted pyrroles and has been widely used to prepare a number of no symmetrical and symmetrical 2,5-disubstituted pyrroles. The mechanism of pyrrole formation is not clear. Probably the reaction sequence consists of the hydroamination and subsequent 5-*endo* cyclization, however, no clear evidences for one mechanism or another have been documented yet. The need for the catalysis is evident since, when the addition of benzylamine to 1, 4-diphenyl-1, 3-butadiyne is carried out in the absence of the copper salts, the major product is the 2, 3, 6-triphenylpyridine, instead of the 1, 2, 5-triphenylpyrrole [3] (Scheme 1). Even using catalyst the reaction takes place at 160 °C–170 °C implying rather high activation energy [4, 5].

The aim of this paper is to obtain deeper insight into the mechanism of the reaction of diacetylene- amines using quantum chemistry tools to understand the effect of Cu(I) salts on the reaction mechanism.

## 2. Theoretical approach

As a model reaction the reaction between ammonia molecule and diacetylene (DA) has been selected. This model is the simplest possible yet maintaining all features of the real systems allowing complete and efficient potential energy scan to study all possible reaction routes and intermediates. All calculations were carried out with Jaguar v 6.0 program [6]. The geometry optimizations were run using hybrid B3LYP functional without any symmetry restrictions at B3LYP/6-31G\* level of theory which is successful for modeling of organic molecules [7]. LAC effective core potential [8] was used to describe Cu atom. Actually, B3LYP functional was successfully applied to model Cu-mediated reactions [9]. Frequency calculations were run for all structures to make sure that a transition state (one imaginary mode) or a minimum (zero imaginary modes) is located and to obtain free Gibbs energies of reaction intermediates. First, the potential energy scan of ammonia-DA system was carried out to locate all stationary points on the way from starting materials to product (pyrrole). Then, similar procedure was repeated with ammonia -DA-CuCl system to find out possible mechanisms of catalytic action of CuCl. Poisson–Boltzman solver [10,11] implemented in Jaguar v 6.0 was used to calculate the solvation effects on the studied molecules in dimethylformamide (DMF) at the same level of theory. In other words, the structures have not been reoptimized in the presence of solvent since it has been shown previously that reoptimization has very limited effect on the computed energies [12–16].

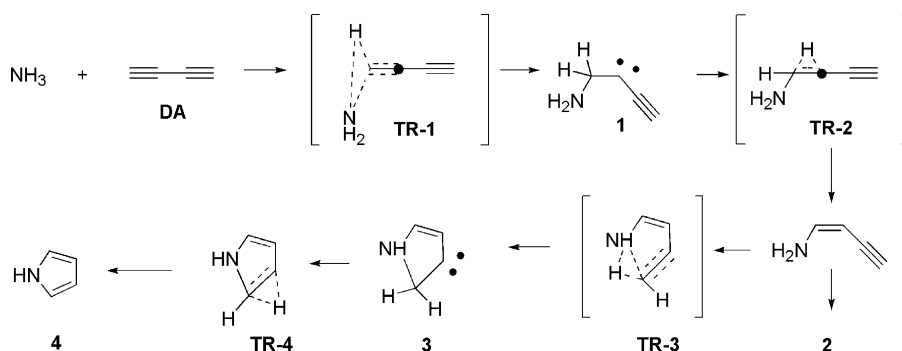
\* Corresponding author. Tel.: +52 55 5 622 47 27; fax: +52 55 5 616 12 01.  
E-mail address: lioud@servidor.unam.mx (L. Fomina).



Scheme 1. Reaction of diphenyldiacetylene with amines.

### 3. Results and Discussion

The first step of the reaction mechanism is a nucleophilic addition of ammonia molecule to the triple bond of DA molecule (Scheme 2). Potential energy scan along C–N distance shows that the first minimum on the way to pyrrole is intermediate **1** preceded by a transition state TR-1. As seen from the reaction energy profile (Fig. 1) this step is the rate limiting step of the reaction mechanism with the free



Scheme 2. Catalyst-free reaction mechanism of pyrrole formation.

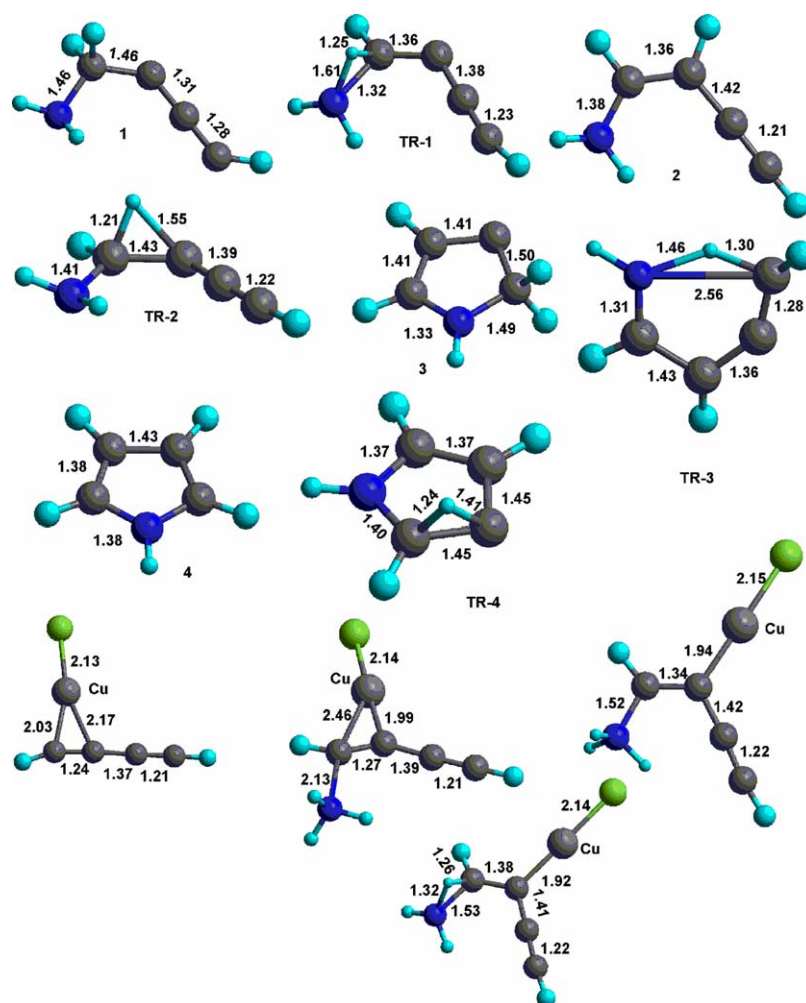


Fig. 1. B3LYP/6-31G\* optimized geometries of reaction intermediates for catalyst-free reaction mechanism of pyrrole formation.

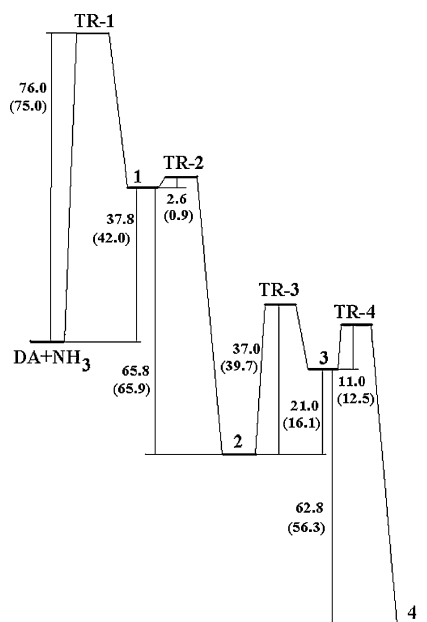
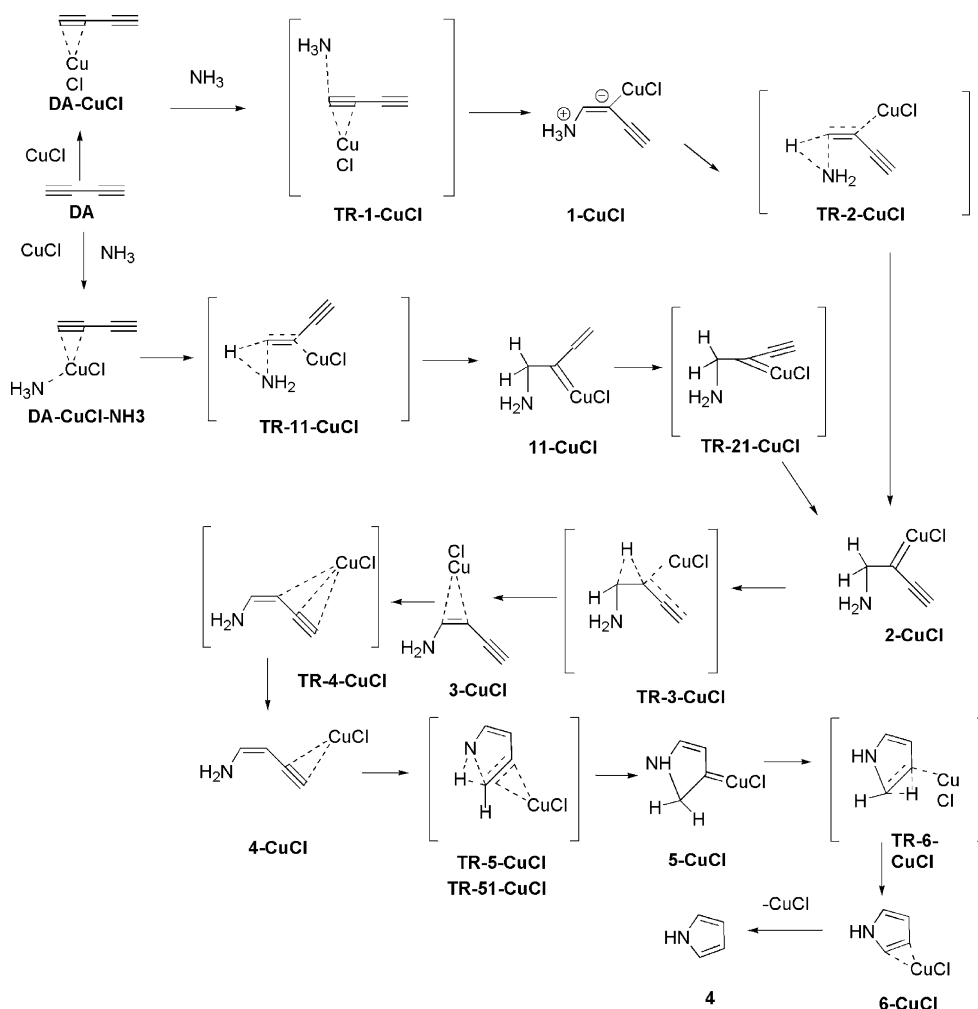


Fig. 2. Gas phase and solution phase (in brackets). Free Gibbs energy profile (kcal/mol) for catalyst-free reaction mechanism of pyrrole formation from DA and ammonia.

Gibbs activation energy of 76 kcal/mol. This step consists in simultaneous C–N bond formation and hydrogen transfer to produce intermediate **1**. Optimized geometries of the reaction intermediates are shown in the Fig.1. After second hydrogen transfer a much more stable intermediate **2** is formed. In this case the free Gibbs activation energy is only 2.6 kcal/mol. Intermediate **2** represents a result of the addition of ammonia to the one triple bond. Second addition occurs much easier than the first. As seen the free Gibbs activation energy of the next step (Fig. 2) is 37.0 kcal/mol in the gas phase, only a half compared to first addition step. This difference is due to favourable entropic factor. Thus, during the addition of ammonia to DA number of particles decreases, while in case of ring closure number of particles maintains. Formation of intermediate **3** is followed by the hydrogen transfer to give final pyrrole molecule with activation energy of 11.0 kcal/mol. As seen the rate limiting step of the proposed mechanism is the formation of intermediate **1** with free Gibbs activation energy of 76.0 kcal/mol. Since the formation of pyrrole from DA and ammonia is thermodynamically favourable ( $\Delta G = -69.8$  kcal/mol) the need for catalyst for reaction to



Scheme 3. CuCl mediated reaction mechanism of pyrrole formation.

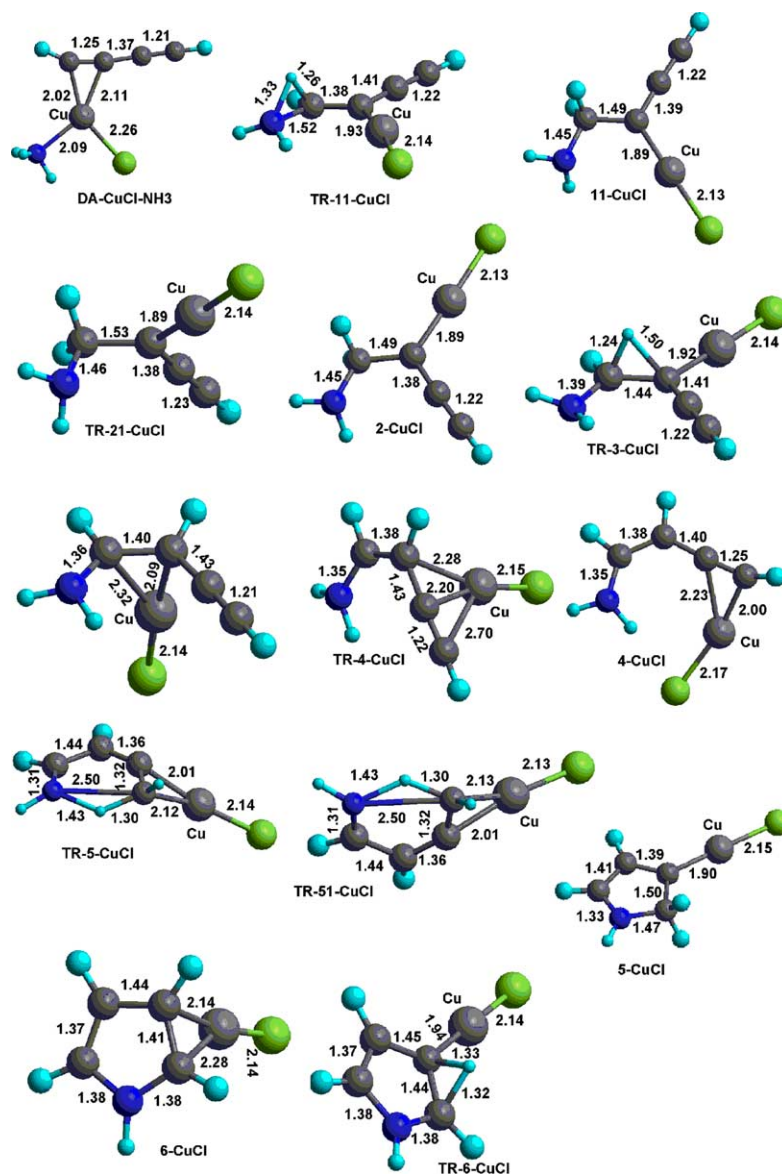


Fig. 3. B3LYP/6-31G\* optimized geometries of reaction intermediates for CuCl mediated reaction mechanism of pyrrole formation.

occur is the indication of kinetic control. Solvation barely affects the reaction energetics. Thus calculated free Gibbs activation energy for the rate determining step is 75.0 kcal/mol in DMF solution. The solvation corrected free Gibbs reaction energies are shown in Fig. 1 in brackets. As seen solvation does not change the conclusions made on the basis of gas phase reaction energies. The step of formation the intermediate **1** remains the rate determining step. Reaction intermediates **1** and **3** have carbene atoms in their structures as follows from Scheme 2 and Fig.1. A mechanism involving carbene intermediates was suggested [17,18] for Cu promoted cycloisomerization. However, neither experimental nor theoretical proofs have been provided to confirm the reaction pathway.

Cu<sup>+</sup> ions are known to form complexes with both amines and acetylenic bonds [19]. Two types of complexes were considered to be possible reaction intermediates; complexes DA-CuCl-NH<sub>3</sub> and CuCl-DA. First type of

complexes are able to reduce the free Gibbs activation energy due to entropic factor, second type of complexes are able to reduce the activation energy at the expense of electrophilicity increase of the triple bond after complexation. The exploration of potential energy surface in the presence of CuCl as a catalyst gives following reaction mechanism (Scheme 3). There are two different ways for the first reaction step to reach intermediate 2-CuCl representing first proton transfer (equivalent to intermediate **1** in CuCl free mechanism). One is starting from complex DA-CuCl-NH<sub>3</sub> where two reactive intermediate are pre-coordinated with Cu<sup>+</sup> center and another one where ammonia molecule attacks DA-CuCl complex. The energy profile of CuCl mediated mechanism is shown in Fig. 4. As seen each reaction path has two transition states on the way to intermediate 2-CuCl. In case of the first route the transition states corresponds to the simultaneous C–N bond formation, proton transfer and the rotation around C–C

Table 1.  
HOMO and LUMO energies of selected reaction intermediates in a.u. calculated at HF/6-31G\*\*/B3LYP/6-31G\*, NBO charges of selected atoms calculated at the same level of theory.

Molecule	HOMO	LUMO	NBO charge
NH <sub>3</sub>	-0.42368	-	-1.14 (N)
DA	-	0.12790	-0.14(C) <sup>a</sup>
DA-CuCl-NH <sub>3</sub>	-0.34191	0.06280	-0.39(C) <sup>a</sup> , -1.25(N)
DA-CuCl	-	0.03169	-0.34 (C) <sup>a</sup>
4-CuCl	-0.32907	0.05566	-0.87(N), -0.58(C) <sup>a</sup>
2	-0.29142	0.15131	-0.90(N), -0.27(C) <sup>a</sup>

<sup>a</sup>Terminal carbon atom.

bond. Second route involves the formation of C–N bond to give zwitterionic intermediate 1-CuCl followed by the proton transfer. The optimized geometries of the reaction intermediates are shown in Fig. 3. As seen from the energy profile the rate determining step in CuCl mediated mechanism remains the first proton transfer from ammonia to DA molecule. Therefore, this step is to determine the overall reaction rate. Compared to CuCl-free mechanism the activation energy of the rate determining step decreases greatly when CuCl molecule participates in the reaction cycle (from 76.0 to 41 kcal/mol in the gas phase) thus explaining the mechanism of catalytic action of CuCl which consists in decreasing of activation energy for the first proton transfer. Table 1 shows HOMO and LUMO energies of selected reaction intermediates calculated at HF/6-31G\*\*/B3LYP/6-31G\* and NBO charges of selected atoms calculated at the same level of theory to obtain deeper

insight into the action of catalytic mechanism of CuCl. The proton transfer and C–N bond formation are the reactions showing highest activation free Gibbs energies, therefore, they determine the overall reaction rate. Inspecting Table 1 one can see the reason of catalytic action of CuCl. As follows from the analysis of HOMO–LUMO energies and NBO charges, the nucleophilic attack of nitrogen atom at diacetylenic bond is orbital controlled reaction, characteristic of interaction between soft species. Contrary to what could be expected NBO charges at terminal carbon attacking by ammonia is more negative in DA-CuCl compared to DA. The free Gibbs activation energy correlates with HOMO–LUMO difference, not with charges. HOMO and LUMO of intermediates listed in Table 1 are shown in Fig. 5. As seen in all cases important contribution to HOMO for N-containing intermediates comes from  $P_z$  orbital of N which can be interpreted as N-lone pair. On the other hand, LUMO of electrophilic species has important contribution from  $\pi^*$  orbitals of DA unit. Therefore, addition reaction can be described in terms of HOMO–LUMO interactions. Thus, high activation energy of intermediate 1 formation is related with large energy difference between HOMO of ammonia and LUMO of DA (0.55158 a.u.). On the other hand the second addition to give intermediate 3 (Fig. 2) has much lower activation energy which is reflected in much lower HOMO–LUMO gap in molecule 2 (0.44273 a.u.). As seen from the Table 1 formation of complexes CuCl and DA leads to decrease in LUMO energy. Thus, LOMO in DA-CuCl is 0.09621 a.u.

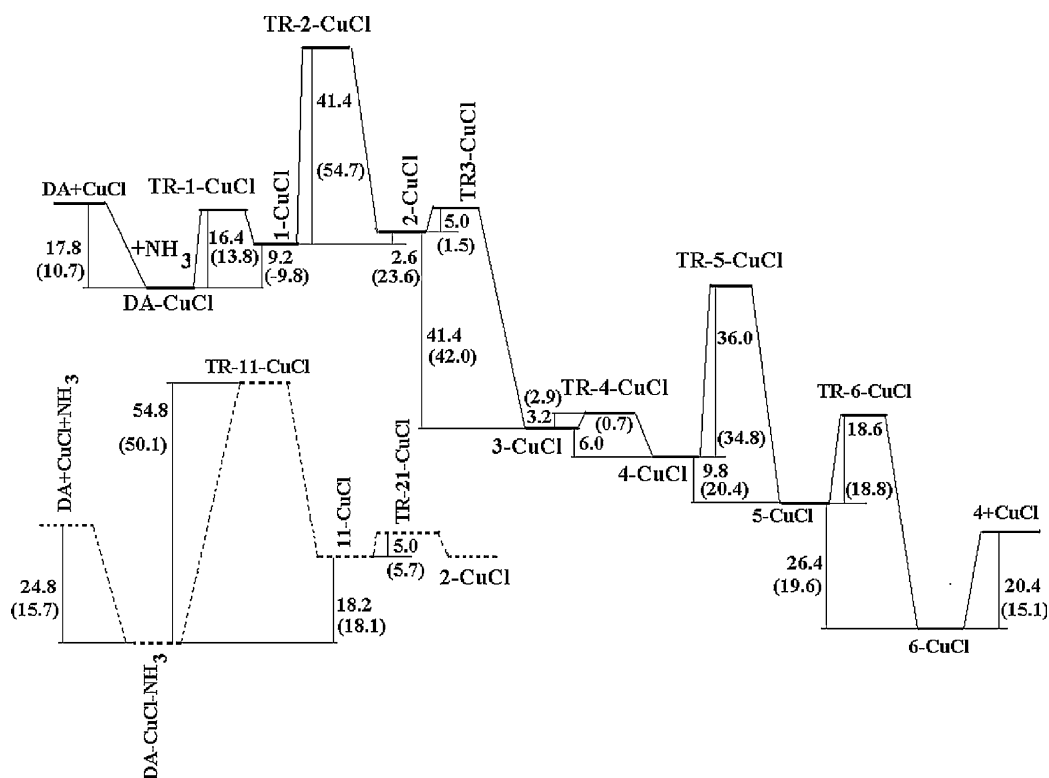


Fig. 4. Gas phase and solution phase (in brackets). Free Gibbs energy profile (kcal/mol) for CuCl mediated reaction mechanism of pyrrole formation from DA and ammonia.

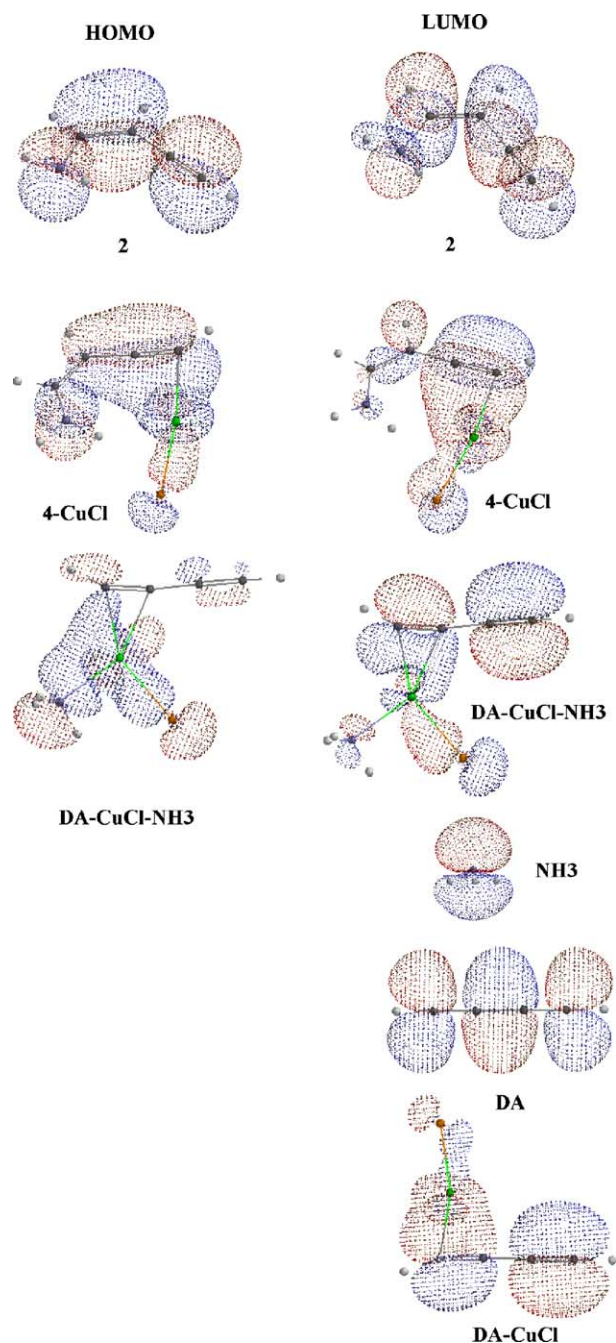


Fig. 5. HOMO and LUMO of selected reaction intermediates calculated at HF/6-31G\*\*/B3LYP/6-31G\* level.

lower compared to DA. Similar situation holds for DA-CuCl-NH<sub>3</sub> complex where HOMO–LUMO difference is reduced to 0.40471 a.u. compared to 0.55158 a.u. (difference between HOMO of ammonia and LUMO of DA).

Intermediate 2-CuCl is a stabilized carbene species as followed from its geometry (C–Cu distance is of 1.89 Å and C–C–C angle of 117.9°). After proton transfer 2-CuCl is transformed to 3-CuCl where Cu atom is coordinated with double C=C bond. The next addition step occurs after the migration of CuCl to triple bond to form intermediate 4-CuCl.

This step is easy to occur as seen from Fig. 4. The second addition step takes place similar to the first one generating Cu-stabilized carbene species 5-CuCl with C–Cu distance of 1.90 Å giving as a final product complex of pyrrole with CuCl (6-CuCl) where CuCl is linked to pyrrole double bond. The dissociation of complex 6-CuCl completes the catalytical cycle giving free pyrrole and CuCl. As seen from Fig. 4 solvation affects significantly the reaction energetics. Thus, in the gas phase the most favourable reaction path to 2-CuCl is the one involving the reaction between DA-CuCl and ammonia (Scheme 3, Fig. 4), while when solvation is taken into account the lowest energy profile involves the transformation of DA-CuCl–NH<sub>3</sub> complex.

#### 4. Conclusions

The rate determining step is the formation carbene intermediate 2-CuCl (simultaneous formation of C–N bond and proton transfer). The mechanism of catalytic action of CuCl involves the complexation of starting materials with CuCl reducing the HOMO–LUMO gap between nucleophile and electrophile thus, decreasing the activation energy of the rate determining step. The greater is the decrease in the HOMO–LUMO energy gap the more effective is the catalysts.

#### Acknowledgements

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#### References

- [1] J. Reisch, K.B. Schulte, *Angew. Chem.* 73 (1961) 241.
- [2] B. Ramanathan, A.J. Keith, D. Armstrong, A.L. Odom, *Org. Lett.* 6 (2004) 2957.
- [3] A.J. Chalk, *Tetrahedron Lett.* 33 (1972) 3487.
- [4] A. Stütz, H. Reinshagen, *Tetrahedron Lett.* 19 (1978) 2821.
- [5] K.E. Schulte, J. Reisch, H. Walker, *Arch. Pharm.* 299 (1966) 1.
- [6] Jaguar 6.0, Schrodinger, LLC, Portland, Oregon, 2005.
- [7] J.B. Foresman, A. Frisch, *Exploring Chemistry with Electronic Structure Methods*, Gaussian, Inc., Pittsburgh, PA, 1996.
- [8] P.J. Hay, W.R. Wadt, *J. Chem. Phys.* 82 (1985) 270.
- [9] L. Fomina, B. Vazquez, E. Tkatchouk, S. Fomine, *Tetrahedron* 58 (2002) 6741.
- [10] D.J. Tannor, B. Marten, R. Murphy, R.A. Friesner, D. Sitkoff, A. Nicholls, M. Ringnalda, W.A. Goddard III, B. Honig, *J. Am. Chem. Soc.* 116 (1994) 11875.
- [11] B. Marten, K. Kim, C. Cortis, R.A. Friesner, R.B. Murphy, M.N. Ringnalda, D. Sitkoff, B. Honig, *J. Phys. Chem.* 100 (1996) 11775.
- [12] V. Barone, M. Cossi, J. Tomasi, *J. Chem. Phys.* 107 (1997) 3210.
- [13] C.S. Pomeli, J. Tomasi, M. Sola, *Organometallics* 17 (1998) 3164.
- [14] I. Cacelli, A. Ferretti, *J. Chem. Phys.* 109 (1998) 8583.
- [15] S. Creve, H. Oevering, B.B. Coussens, *Organometallics* 18 (1999) 1907.
- [16] F. Bernardi, A. Bottoni, G.P. Miscone, *Organometallics* 17 (1998) 16.
- [17] M. Rubin, A.W. Sromek, V. Gevorgyan, *Synlett* 15 (2003) 2265.
- [18] S.M. Bachrach, J.C. Gilbert, *J. Org. Chem.* 69 (2004) 6357.
- [19] E.O. Fischer, H. Werner, M. Herberhold, (Eds.), *Metal-[pi] Komplexe Mit di- und Oligo-olefinischen Liganden*, vol. 1, Elsevier, Amsterdam, 1966.