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The Glaser reaction mechanism. A DFT study

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Abstract—A detailed mechanism for the Hey modification of the Glaser oxidative coupling of terminal acetylenes has been formulated based on DFT calculations. The mechanism includes Cu(I)/Cu(III)/Cu(II)/Cu(I) catalytic cycle and explains the dioxygen molecule activation mechanism by Cu(I) species to give water molecule as final product of dioxygen reduction. The key step of the reaction mechanism is the oxidation of Cu acetylide by molecular oxygen to form dicopper-dioxo complex with $[Cu_2(\mu\text{-}O_2)]^{2+}$ core. Relatively low activation energies found for the reaction steps support the viability of the formulated mechanism. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The Glaser reaction was discovered more than 100 years ago by Glaser[1] when copper phenylacetylide was oxydized to diphenyl diacetylene by air in ethanol solution of ammonia (Fig. 1). Since then the Glaser reaction and its modifications have widely been used to synthesize various symmetrical and unsymmetrical diacetylenes, diacetylene-containing polymers, and macrocycles. A comprehensive review of the Glaser reaction scope, techniques and limitations can be found in Ref. 2. The Glaser oxidative coupling reaction is one of the few C–C bond forming reaction which takes place under very mild conditions in aqueous solutions and in the presence of oxygen, thus resembling enzymatic reactions. Many modifications and improvements have been introduced since the Glaser reaction was discovered in 1869. Hydrogen peroxide, potassium permanganate, potassium ferrocianyde, iodine or Cu(II) can be used instead of oxygen as oxidants.[2] The use of organic solvents (pyridine and cyclohexylamine) in the presence of catalytic amount of CuCl[3,4] allows one to avoid the isolation of copper acetylide during the reaction. On the other hand making use of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine–CuCl complex the Glaser reaction can be carried out in almost any organic solvent with high yield.[5,6]

In spite of the fact that the Glaser type reactions have widely been used in preparative chemistry, the mechanism of this reaction is not completely understood. The most recent mechanism postulated for the Glaser condensation is one considering Cu(II) acting as oxidant.[7] Although this mechanism takes into account such experimental observations as the second order reaction for alkynes and discards the radical mechanism, it is unable to describe the Glaser reaction involving molecular oxygen as oxidizing agent. Where the interplay between Cu complexes with different oxidation levels is of importance. When using molecular oxygen as oxidant for the Glaser condensation, Cu–O_2 intermediated should play an important role which is not reflected in the proposed mechanism. It has been recently shown that molecular oxygen forms adducts with Cu(I) supported by tertiary amines[8] which might be the intermediates in the Glaser reaction of this type (Scheme 1). From this point of view the Glaser condensation is one more example of binding and activation of dioxygen by copper ions which is important in numerous and diverse biological and catalytic processes.[9] The establishing of detailed mechanism of the Glaser condensation in the presence of molecular oxygen could be an important step toward the understanding of action of copper enzymes.

This paper describes a computational study of the Glaser oxidative coupling reaction trying to take into account the most important experimental observations.

1. The presence of amine is indispensable for the reaction to occur[2]
2. Copper acetylides produce diacetylenes when oxidized by molecular oxygen[2]
3. The reaction often takes place at room temperature that implies low activation energies for each step of condensation.

The oxidative coupling of acetylene in acetone media in the presence of catalytical amounts of *N*,*N*,*N*′*N*′-tetraethylenediamine (TMEDA)–Cu(I) complex and molecular oxygen as oxidant was chosen as model reaction. This modification of Glaser condensation is known as the Hay reaction.[5,6]

Keywords: Glaser reaction; density functional theory; dioxygen activation; diacetylene.

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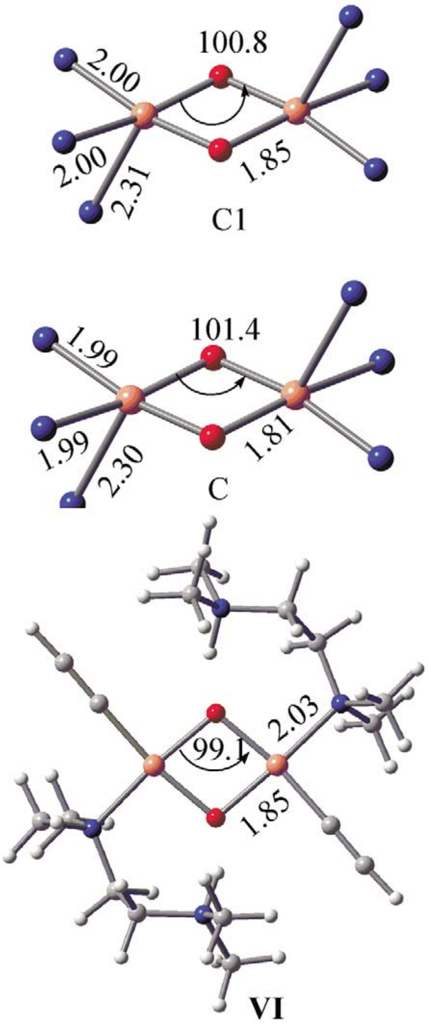
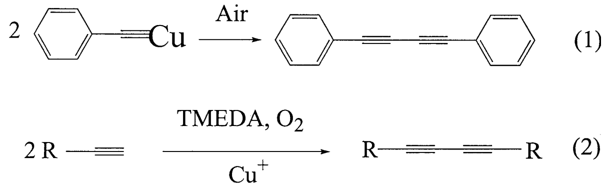


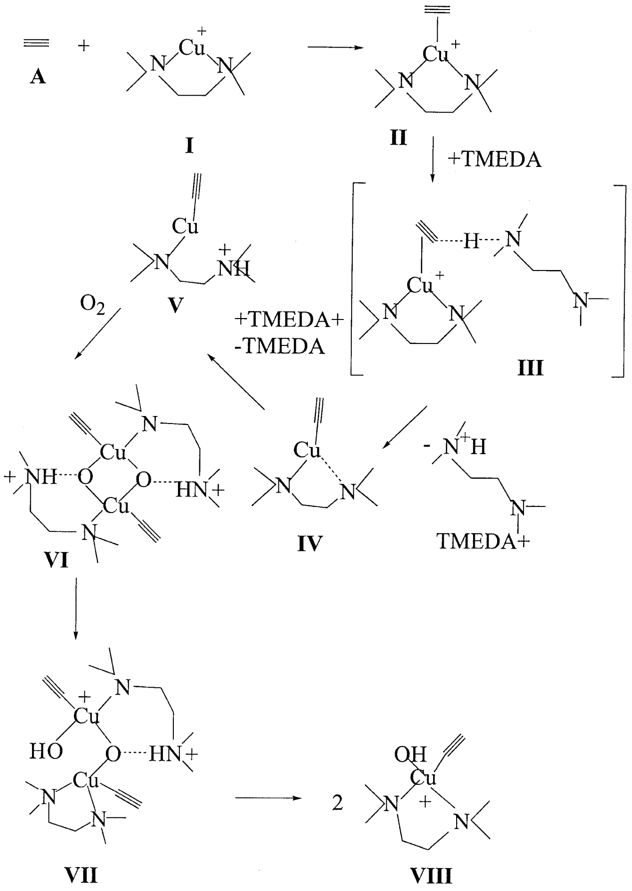
Figure 1. Experimental (**C**) and calculated at B3LYP/LACVP level (**C1**) geometries and selected distances and angles of copper coordination sphere for $[(L_3^{Bn}\text{-}d_{21}\text{-Cu})_2(\mu\text{-O})_2](SbF_6)_2$ $((L_3^{Bn})$=1,4,7-tribenzyl-1,4,7-triazacyclononane) complex. Geometry and selected distances of complex **VI** optimized at B3LYP/LACVP level.

2. Computational details

All calculation were carried out with Jaguar v 4.1 program.[10] The geometry optimizations were run at B3LYP/LACVP level of theory.[11–14] LACVP basis set uses standard 6-31G basis set for the fist and second row elements and LAC pseudopotential for core electrons of third row and heavier elements.[15] Restricted formalism was used to treat closed shell systems while for the open shell molecules unrestricted method was applied. The energy evaluation of each intermediate was carried out at B3LYP/LACVP(d,p) level of theory.



Scheme 1. The Glaser reaction (**1**) and the Hey modification of the Glaser reaction (**2**).



Scheme 2. Initial steps of the Glaser reaction mechanism.

Each stationary point was characterized by frequency calculations to ensure that a minimum (no imaginary modes) or a transition state (1 imaginary mode) is located. The Poisson–Boltzman solver[16,17] implemented in Jaguar v 4.1 was used to calculate the solvation effects on the studied molecules at B3LYP/LACVP(d,p) level of theory.

To estimate the applicability of B3LYP/LACVP level of theory to the modeling of the Glaser condensation the geometry of cationic portion of $[(L_3^{Bn}\text{-}d_{21}\text{-Cu})_2(\mu\text{-O})_2]$ $(SbF_6)_2$ $((L_3^{Bn})$=1,4,7-tribenzyl-1,4,7-triazacyclononane) was optimized and the obtained geometry was compared with X-ray data for this complex.[9] Fig. 1 shows a view of the copper coordination sphere for B3LYP/LACVP optimized structure (**C1**) and the structure obtained from X-ray diffraction data (**C**). As can be seen from the figure B3LYP/LACVP model reproduces bond lengths and bond angles within 0.04 Å and 1°, respectively. Therefore, all optimization were carried out at B3LYP/LACVP level. Additional tests have been implemented to verify the influence of solution reoptimization and the effect of the incorporation of d functions during the optimization on the reaction energies. Thus, complexes **II** and **IV** (Scheme 2) have been optimized at B3LYP/LACVP(d) level both in gas phase and in solution. The gas phase and solution reaction energies were found to be of 25.0 and 1.5 kcal/mol showing difference of 0.9 and 0.0 kcal/mol with B3LYP/LACVP(d,p)//B3LYP/LACVP model which is well within the error showed by B3LYP/6-31G(d) model (Table 1).

Table 1. Total electronic energies (E_e), solvation energies (E_s), NPA charges at selected atoms, Cu–O bond lengths, in studied reaction intermediates at B3LYP/LACVP(d,p)//B3LYP/LACVP level of theory, in Hartree

Molecule	E_e	E_s	Cu–O bond length (Å)	NPA charge		
				Cu	O	C(sp)[a]
A	−77.327794	−0.005788	–	–	–	–
I	−543.743326	−0.076955	–	0.83	–	–
II	−621.123153	−0.071090	–	0.91	–	–
III	−968.882403	−0.062260	–	0.77	–	−0.60
IV	−620.698562	−0.023399	–	0.63		−0.54
V	−621.089132	−0.087885	–	0.67		−0.67
VI	−1392.443246	−0.215396	1.85, 1.86	1.24, 1.24	−0.95, −0.95	−0.45, −0.45
O_2	−150.310525	0.000023	–	–	0.00	–
VII	−1392.442750	−0.219943	1.89, 1.89, 1.85	1.25, 1.25	−0.96, −0.95	−0.45, −0.39
VIII	−696.257142	−0.079500	1.81	1.22	−0.91	−0.43
IX	−1392.426766	−0.215788	1.86, 1.83	1.20	−0.99, −0.95	−0.36, −0.37
X	−619.560199	−0.081375	1.78	1.18	−1.11	–
DA	−153.480980	−0.005801	–	–	–	−0.11
XI	−696.898965	−0.079249	1.84	1.18	−1.14	–
XII	−696.879707	−0.0798471	1.97	1.22	−1.09	−0.58
XIII	−696.911060	−0.082678	2.10	1.18	−1.03	−0.56
XIV	−1393.755213	−0.217638	2.34, 2.34	1.05, 1.05	−1.03	−0.49, −0.48
XV	−620.209249	−0.076851	1.99	0.78	−1.05	–
H_2O	−76.417371	−0.013304	–	–	−1.02	–
TMDA	−347.756752	−0.006481	–	–	–	–
TMDA+	−348.142995	−0.090195	–	–	–	–

[a] Not linked to hydrogen.

3. Results and discussion

It is known that in the presence of ammonia CuCl forms $[Cu(NH_3)_2]^+$ ions in aqueous media.[18] Similar situation holds for TMEDA which is much more powerful complexation agent compared to ammonia forming Cu(TMEDA)$^+$ ions in organic solvents. According to the latest mechanism proposed for the Glaser condensation the first step of this reaction is complexation of acetylene (**A**) with complex **I** ion leading to the formation of complex **II** (Scheme 2). As can be seen from the Table 2 this process is exothermic both in gas phase and in solution and occurs with no activation energy. The complexation increases the acidity of acetylenic protons as can be jagged from the increase of NPA charge at acetylenic proton from 0.27 in acetylene to 0.31 in complex **II**. The complexation facilitates the acetylenic proton abstraction. This reaction can be either intra- or intermolecular. In the first case the proton is abstracted by dimethylamine group of complex **II**, while the second route involves the proton abstraction by another TMEDA molecule in solution. Both reaction routes have been studied and the intermolecular proton transfer was found to be more favorable kinetically and thermodynamically. As seen from Table 2 this reaction is only slightly endothermic. Solvation is an important factor favoring the formation of acetylide (**IV**) due to the energy gain occurring when TMEDA+ cation is solvated. The activation energy in solution was found to be only 8.0 kcal/mol, allowing for the reaction to occur at room temperature (Table 2). An alternative intramolecular proton transfer showed activation energy of 27.8 kcal/mol under the same conditions and has been discarded. Fig. 2 shows structures and selected bond lengths for the located transition states.

Table 2. Reaction energetics (in kcal/mol)

Reaction	Gas phase		Acetone	
	Δ*E*	E_a[a]	Δ*E*	E_a[a]
I+**A**=**II**	−32.7	–	−25.4	–
II+TMDA=**IV**+TMDA+	24.1	−1.6	1.5	8.0
IV+TMDA+=**V**+TMDA	−2.7	–	9.3	–
2**V**+O_2=**VI**	28.6	–	3.7	–
VI=**VII**	0.3	–	−2.6	–
VII=2**VIII**	−44.9	–	−6.7	–
2**VIII**=**DA**+2**X**	−54.6	54.9	−60.6	19.3
X+**A**=**XI**	−6.9	–	−1.9	–
XI=**XIII**	−7.6	12.1	−9.8	11.7
2**XIII**=2**XV**+**DA**	−48.5	42.0	−44.8	9.2
XV=**I**+H_2O	30.5	–	22.1	–

[a] Activation energies.

The next step postulated for the Glaser condensation is the formation of dicopper-dioxo complex with $[Cu_2(\mu\text{-}O_2)]^{2+}$ core from acetylide **IV** and molecular oxygen. Complexes with $[Cu_2(\mu\text{-}O_2)]^{2+}$ core, have recently been prepared and characterized.[8] They can be obtained by the reaction of molecular oxygen with Cu(I) supported by tertiary amines in organic solvents, conditions very similar to these used in the Hey modification of Glaser condensation. As the matter of fact, first Cu(II) $Cu_2(\mu\text{-}\eta^2\text{: }\eta^2\text{-}O_2)^{2+}$ type of complex is formed where O–O bond is only partially cleaved. However, as follows from high level theoretical calculations these two types of complexes are very nearly in energy and the energetic barrier to their interconversion, if one exists, small.[19] According to the modeling data the formation of dicopper-dioxo complex from acetylide **IV** and dioxygen is rather endothermic in solution (24.1 kcal/mol) which makes this reaction difficult to occur at room temperature. The calculations shows that the formation of dicopper-dioxo complex is much more favorable when protonated complex **V** and molecular oxygen are reacted to give complex **VI** due to additional stabilization coming from hydrogen bonding and solvation of charged species (Table 2). Protonated complex **V** can easily be formed by proton exchange

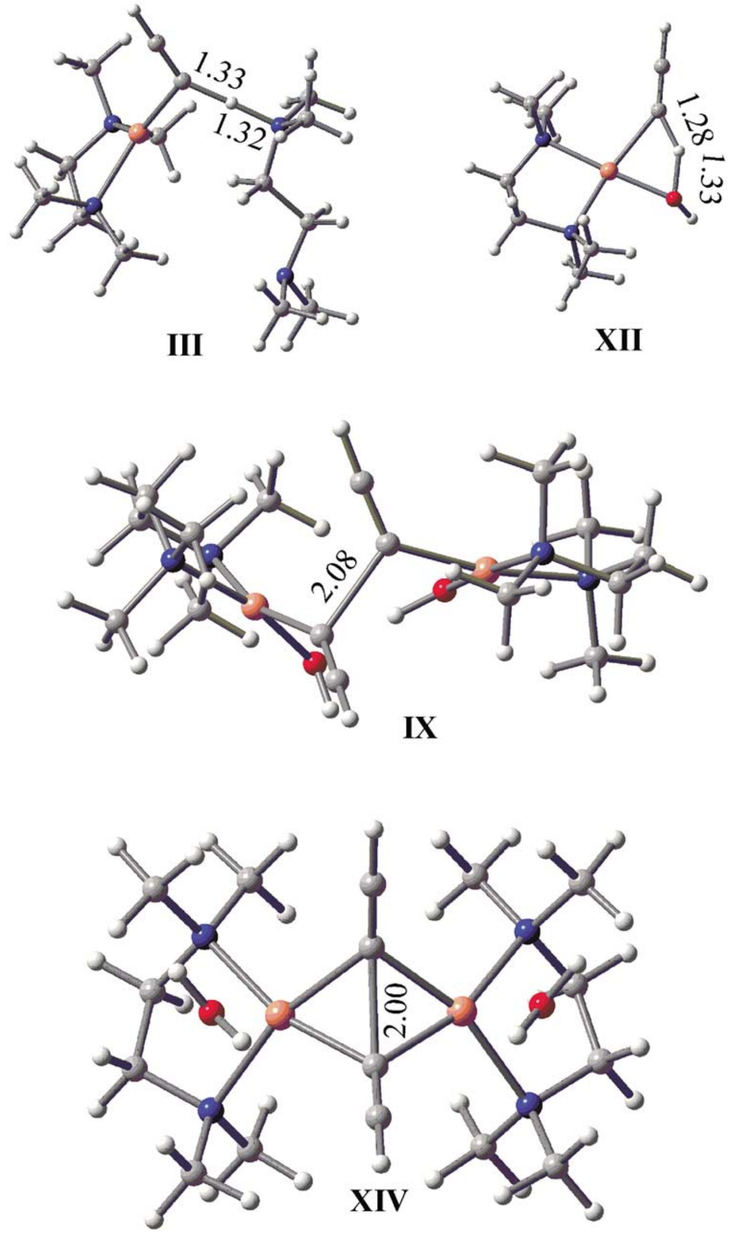
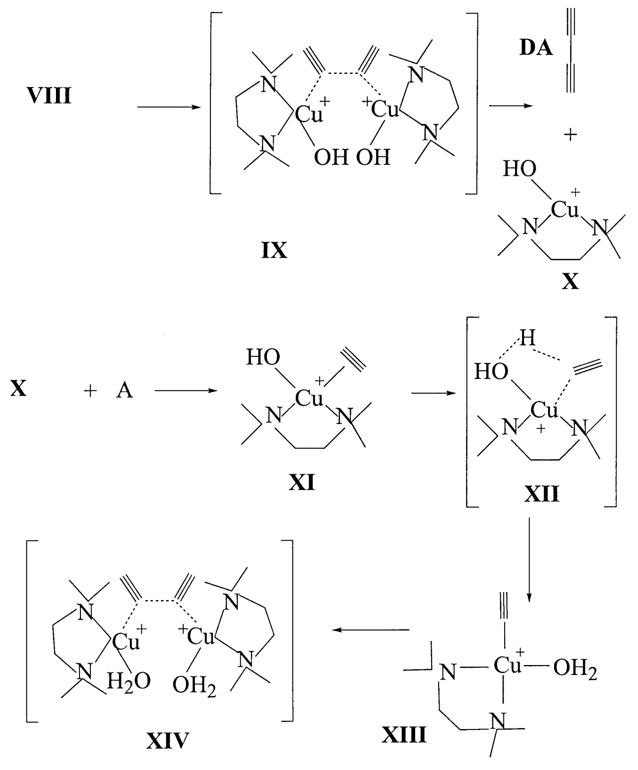


Figure 2. Geometry and selected distances of transition states located at B3LYP/LACVP level for the elemental steps of the Glaser reaction.

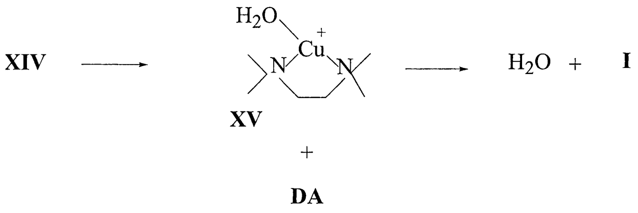
between TMEDA+ and **IV** (Scheme 2). The relaxed potential energy scan for this process carried out at B3LYP/LACVP level does not show any activation energy for this process. This reaction is slightly endothermic in solution (9.3 kcal/mol) not excessively, however, to make it impossible. Moreover, the viability of this step is supported by the fact of preparation and characterization of similar complexes.

The process of complex **VI** formation represents the oxidation of Cu(I). The valence state assigned to synthesized bis(oxo) complexes on the basis of structural characteristics and estimated through a bond valence sum (BVS) analysis is III.[20] When comparing the structural characteristics such as Cu–N and C–O bond lengths of complex **VI** with these found for **C1** (Fig. 1) one can see their similarity thus confirming the valence state III for this complex. The NPA analysis performed for the studied intermediates clearly shows that the formation of complex **VI** is a redox reaction where Cu is oxidized (NPA charge at Cu atom increases from 0.67 for **V** to 1.24 for **VI**) while dioxygen is reduced as can be seen from the NPA charges at oxygen atoms of −0.95. The O–O bond length increases to 2.40 Å showing that the formation of intermediate **VI** represents the activation of oxygen molecule. The hypothesis of valence variation Cu(I)/Cu(III) has already been formulated for a wide range of copper-catalysed reactions,[21] in particular, for acetylenic coupling.[22]

The transformations of **VI** to **VII** and **VII** to **VIII** are exothermic in solution showing ΔE of −2.6 and −‴ 6.7 kcal/mol, respectively. Reactions **VI=VII** and **VII=VIII** involve proton transfer to oxygen atom with simultaneous Cu–N bond formation and the cleavage of one of Cu–O bond. (Scheme 2). The proton transfer can be either intamolecular or TMEDA mediated intermolecular process similar to that postulated for **II–IV–V** transformation. Taking into account that there are intramolecular



Scheme 3. Intermediate steps of the Glaser reaction mechanism.



Scheme 4. Final steps of the Glaser reaction mechanism.

hydrogen bonding in complexes **VI** and **VII**, it is reasonably to suggest intramolecular proton transfer mechanism. Unfortunately, we were unable to locate transition states either for **VI**–**VII** or for **VII**–**VIII** reactions. It seems that each of the reactions is a complex one involving several separate steps such as proton transfer, Cu–O bond cleavage and N–Cu bond formation with different transition states for each of them.

The next step of the proposed mechanism is the transformation of two molecules of complex **VIII** to a molecule of diacetylene (**DA**) and two molecules of paramagnetic Cu(II) mononuclear complex (**X**) (Scheme 3). This reaction is highly exothermic (Table 2) and shows activation energy of 19.3 kcal/mol in solution. The driving force of this transformation is the oxidation of acetylene carbon from formal oxidation state −1 in **VII** to formal oxidation state 0 in **DA**, transforming Cu(III) to Cu(II). Once formed, the intermediate **X** reacts with another molecule of acetylene giving complex **XI**. This is an exothermic reaction both in the solution and the gas phase. Similar to **II** the complexation increases the acidity of acetylenic proton (NPA charges increases from 0.27 in acetylene to 0.31 in **XI**) facilitating the proton transfer to OH anion of **XI**. The transformation **XI**=**XIII** is thermodynamically more favorable compared to **II**=**IV**. This fact is certainly due to the difference in base strength of proton acceptor which is a tertiary amine in case of **II** and hydroxide ion in **XII**. According to the calculations the proton transfer is easy to occur since this reaction is exothermic with low activation energy (12.1 and 11.7 kcal/mol in gas phase and in solution, respectively). Two acetylide **XIII** molecules form another molecule of diacetylene and two molecules of Cu(I) complex **XV** (Scheme 4). Similarly to 2**VIII**=**DA**+2**X** reaction this reaction is highly exothermic (Table 2). The driving force of this reaction is the oxidation of acetylide carbon from −1 in acetylide to 0 in diacetylene by Cu(II) of complex **XIII** producing Cu(I) in complex **XV**. The activation energy of this transformation is high in gas phase (40.0 kcal/mol) but reduces greatly by in solution to 9.2 (kcal/mol). One can note the difference between two similar reactions 2**VIII**=**DA**+2**X** and 2**XIII**=**DA**+2**XV** (Table 2) leading to the formation of diacetylene molecules. The first one is significantly more exothermic than the second. Such a difference is due to the difference between standard potentials of Cu(III)+e=Cu(II) and Cu(II)+e=Cu(I) reactions. Cu(III) is much stronger oxidant compared to Cu(II). Depending on nature of the ligand the standard potential for Cu(III)+e=Cu(II) process is −0.45−(−1.02 V),[18] while for Cu(II)+e=Cu(I) one the standard potential is

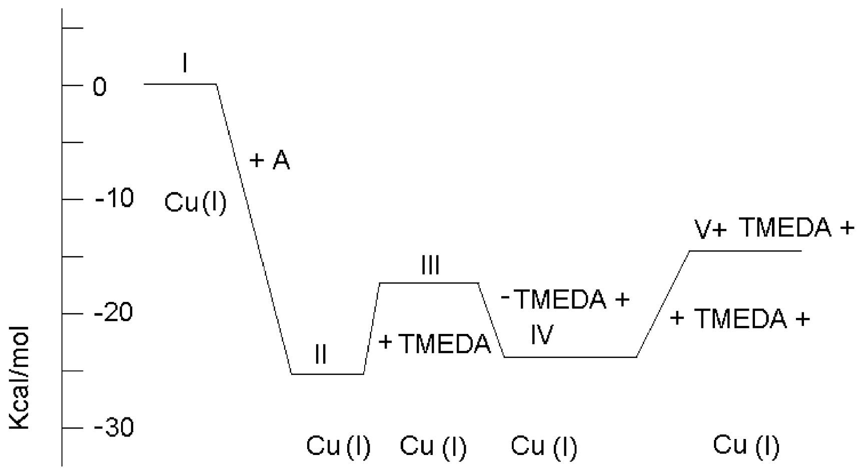


Figure 3. Energy profile for initial steps of Glaser reaction indicating valence states of copper atoms.

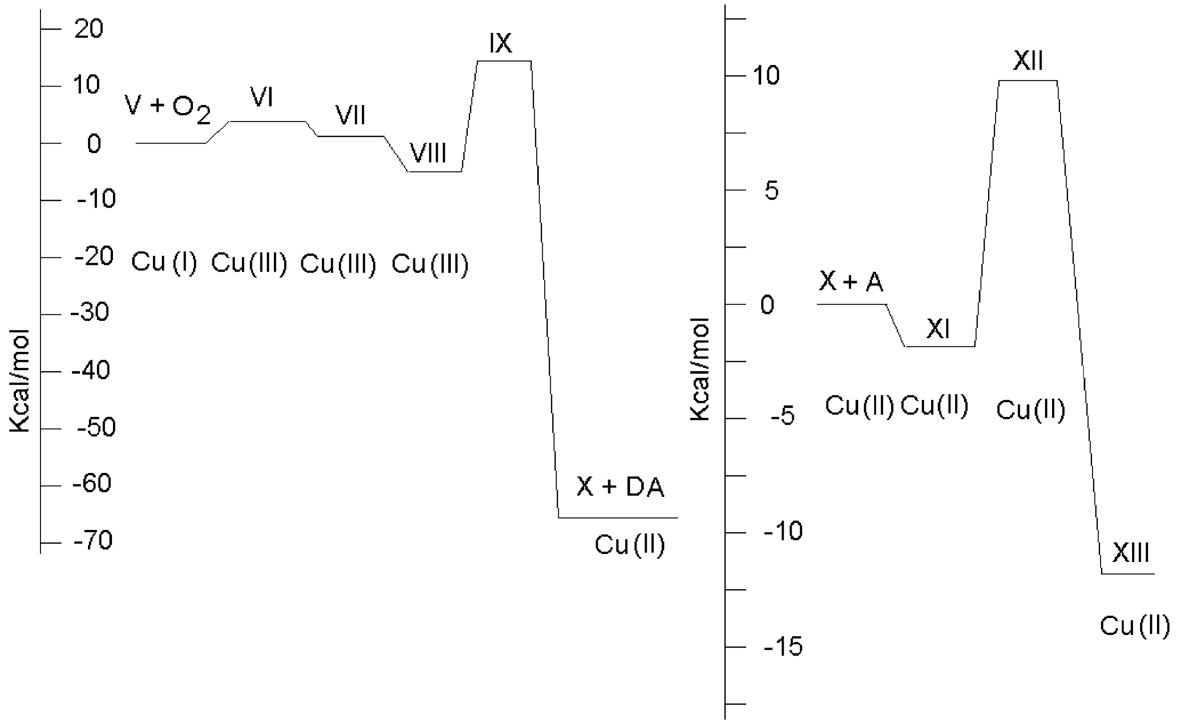


Figure 4. Energy profile for intermediate steps of Glaser reaction indicating valence states of copper atoms.

−0.153 V.[18] Since the reaction 2**VIII**=**DA**+2**X** represents the transformation of Cu(III) to Cu(II) and the reaction 2**XIII**=**DA**+**XV** is the transformation of Cu(II) to Cu(I) the first one is much more exothermic. Figs. 3–5 show energy profiles for different steps of Glaser reaction mechanism.

The dissociation of complex **XV** to water and complex **I** completes the catalytic cycle. This reaction requires according to the calculations 22.1 kcal/mol when solvation is taken into account.

4. Conclusions

A detailed mechanism for the Hay modification of the Glaser reaction has been formulated based on DFT study.

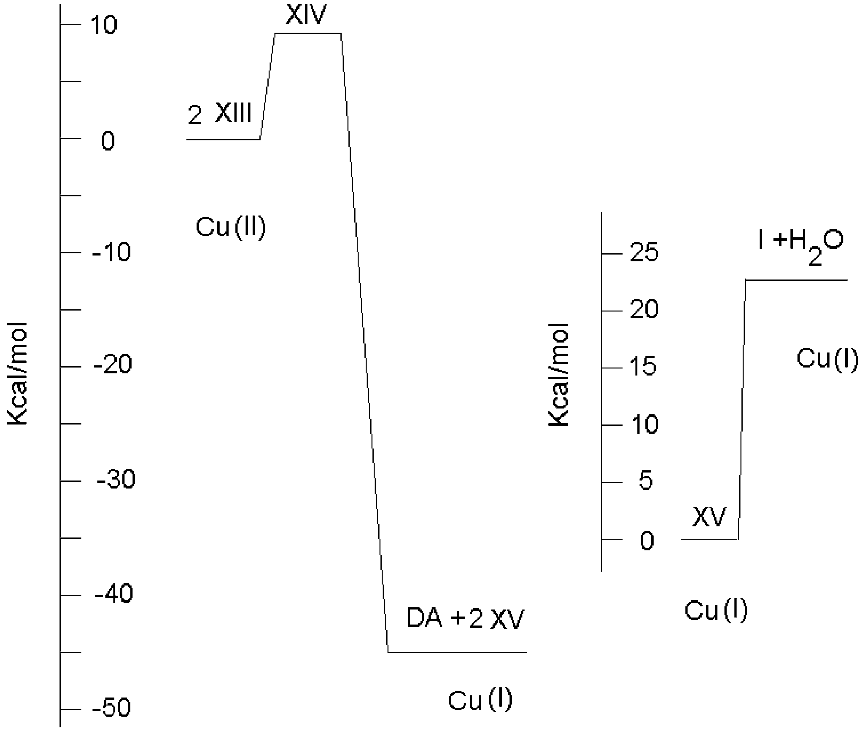


Figure 5. Energy profile for final steps of Glaser reaction indicating valence states of copper atoms.

The mechanism involves Cu(I)/Cu(III)/Cu(II)/Cu(I) catalytical cycle for this transformation. The key step for this reaction is the dioxygen activation occurring on the complexation of two molecules of acetylide **V** with molecular oxygen giving Cu(III) complex **VI**. The viability of this mechanism is supported by the fact of isolation and characterization of Cu(III) complexes similar to **VI** formed under the conditions of the Glaser coupling. The activation energies found for this mechanism are moderate, thus allowing for the reaction to occur at room temperature.

Acknowledgments

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