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Graphical abstract

The full reaction mechanism for the copper catalyzed oxidative coupling of two terminal alkynes is computationally characterized with DFT methods.
Toward a mechanistic understanding of oxidative homocoupling: the Glaser–Hay reaction

Jesús Jover,*a Philipp Spuhler,*b Ligang Zhao,*b Ciarán McArdleb and Feliu Maseras*bc

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The copper-catalyzed oxidative homocoupling of terminal alkynes has been studied with DFT methods. The role of Cu(I) or Cu(II) as initial oxidation state, as well as the effect of changes in the substrate and the base have been examined. Oxidants responsible for outer- and inner-sphere electron transfer processes have been also investigated. The Cu/O2 interactions, which arise when dioxygen is employed as oxidant, have been treated explicitly to fully describe the 4-electron reduction process, providing a plausible mechanism that could serve as a model for other aerobic oxidative couplings. The obtained results completely agree with the reported experimental data, the computed free energy barriers are low enough for the reactions to proceed at room temperature, and electron-poor alkynes and stronger bases lead to faster reactions.

Introduction

Metal-mediated coupling reactions have become one of the main tools to carry out the formation of C–C bonds.1 The importance of cross-coupling, between an R–X (X = halide) and R’–Y (Y = electropositive group) was recognized by Nobel Prize in 2010.2 Not all systems are however amenable to cross-coupling, and as a result, homocoupling, where the reaction occurs between two identical partners, is also a subject of interest. In homocoupling, an external reducing or oxidating agent is often necessary to bring the metal back to its initial oxidation state. The use of dioxygen in oxidative homocoupling is particularly appealing because only water is formed as byproduct of the oxidation.3

One of the earliest and most simple examples of oxidative homocoupling is the Glaser reaction, reported originally in 1869.4 Glaser observed that a mixture of phenylacetylene, copper (I) chloride and ammonium hydroxide in ethanol, when exposed to air, smoothly formed diphenylacetylene (Scheme 1). The scope of the reaction was later expanded, as it was stated that O2 can be replaced by many other oxidants.5,6 A crucial modification of the reaction, reported by Hay in the 1960s,5 indicated that the addition of nitrogen ligands such as TMEDA (N,N,N’,N’–tetramethylthelylenediamine) allowed the reaction to be carried out under mild conditions using copper (I) chloride as catalyst. Since then a variety of copper (I) and (II) salts and nitrogen ligands, i.e. tertiary amines or pyridines, have been used to perform the oxidative coupling of acetylenes providing good results.9,10–12 In most experiments, a ligand excess or an external base is added because it has been demonstrated that the reaction is faster under basic conditions. Different bases, ranging from ammonium hydroxide employed by Glaser to organic amines (e.g. piperidine, NEt3, etc.) or inorganic salts such as sodium carbonate or acetate have been employed.14,15 Another piece of relevant experimental information states that acidic acetylenes produce the fastest reaction rates,16 indicating that the terminal proton abstraction plays a crucial role on the mechanism.

The Glaser-Hay reaction is technologically relevant, as the 1,3-diyne products obtained have a wide range of interesting applications in optical materials, organic conductors and molecular devices as well as antifungal activity,18 conducting polymers and liquid crystals.19 On the other hand, the study of simple Glaser coupling reactions can serve as a benchmark for other, more complicated, oxidative coupling reactions where dioxygen is employed as oxidant. Even more, improving our knowledge of these reactions can be used to better understand more complicated systems such as copper oxyspecies20 and oxygenases e.g. superoxide dismutase or tyrosinase, or even oxygen evolution systems.21

The detailed mechanism of the Glaser-Hay reaction remains to be determined. One of the most elaborate proposals was made by Bohlmann and co-workers in 1964,18 summarized in Scheme 2. According to their scheme, the reaction starts with the π–coordination of the triple bond to a copper (I) species that facilitates the activation of the terminal C–H bond by an external base. It was also proposed that the 1,3-diyne is formed by reductive elimination from a dinuclear copper (II) acetylide species (Scheme 2b). The Bohlmann mechanism neglects however the crucial oxidation step required to close the cycle, as part b) starts with copper (II) but ends up with copper (I).

An alternative proposal was made more recently based on B3LYP DFT calculations.23 A lot of emphasis was placed in this
case in the interaction between copper and dioxygen, but the results had serious shortcomings. A detailed analysis of the computed thermodynamics reveals that although the reported potential energy barrier for the catalytic cycle is around 22 kcal/mol, the value increases above 50 kcal/mol when free energy corrections are introduced. In addition, the proposed mechanism is completely specific for the employed reactants and it cannot explain why the reaction proceeds with different copper sources and oxidants. The appropriateness of the B3LYP functional for dioxygen systems in homogeneous catalysis are scarce and focused on very specific cases. Computational studies in the role of copper involving copper, little is known about its detailed reaction mechanisms. 12,15,25-29  

Computational Methods

All the structures have been fully optimized in acetone using the Gaussian09 package, with the PBE density functional. The standard 6-31G(d) basis set was used for all H, C, N, F and O atoms; the Stuttgart triple zeta basis set (SDD), along with the associated ECP to describe the 10 core electron, was employed for Cu and Fe. In addition, an extra dispersion function was employed in the optimization of the negatively charged iron complexes. Solvation free energies are computed with the (IEF-PCM) continuum dielectric solvation model using the radii and non-electrostatic terms for Truhlar and coworkers’ SMD solvation model. In all cases frequency calculations were carried out to ensure the nature of stationary points and transition states, and allowing the calculation of Gibbs free energies at 25°C and 1 atm for all the species involved in the catalytic cycles.

Additional single point calculations on the previously optimized geometries were carried out with a larger basis set. The 6-311+G** all-electron basis set was used for all H, C, N, F and O atoms while the aug-cc-pVTZ-PP basis set including polarization and the associated electron core potential was employed for Cu. In the case of Fe atoms, the all-electron aug-cc-pVTZ basis set was used. The empirical dispersion terms were computed for the optimized geometries using the DFT-D3 package by Grimme using the corresponding PBE-D34 functional. Unless otherwise stated, all the reported energy values correspond to the Gibbs free energies obtained with the large basis sets including solvation in acetone and the dispersion corrections.

As the mechanisms involve copper (I), copper (II) and copper (III) complexes with different multiplicities, different spin states are involved. Although we computed the triplet state in a number of cases, it was always found higher in energy than the corresponding singlets, and because of that they are discussed in the text only in selected points.

Along the reaction pathways mononuclear and dinuclear species coexist, it is not easy to assign a unique origin of energies for both species at the same time. In order to get a better numeric interpretation of the catalytic cycles a colour code has been allocated to the computed free energy values; the black numbers correspond to the unique energy origin corresponding to a copper monomer, which means that the energies for the dimers have been halved. In contrast, blue numbers correspond to energies calculated in a “dinuclear” scale, where two copper monomers are considered as the origin of energies. This colour coding is useful when trying to compare energy differences along the reaction pathways; thus, when comparing a mononuclear and a dinuclear species the black number will be used whereas a comparison between two dinucleurs will be computed with the blue values.

We present in this article a computational study on the mechanism of the Glaser–Hay reaction. Computational applications to aerobic oxidative coupling have been limited, but they have a long story of success in cross-coupling and other processes involving electron transfer in copper complexes. As a first approach, a general mechanism, valid for most outer sphere oxidants along with copper (I) reagents will be studied. At this stage K,[Fe(CN)₆] will be employed as the benchmark oxidant, representative of those that can be found in the literature. Then, the mechanism of the catalytic reaction starting from copper (II) will be evaluated with the same kind of oxidants. Afterwards, the full Glaser–Hay reaction mechanism will be studied to model the explicit interaction between the metal species and O₂ when the latter is used as oxidant; this will show how the dioxygen works in aerobic oxidative copper-coupling catalyzed reactions.

**Scheme 2** Bohmann proposal for Glaser coupling of acetylenes (B = N ligand).

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**Table 1**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Equilibrium Constant</th>
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<td>Cu₂(C≡C)₂ + O₂ → Cu₂O₂ + C≡C</td>
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**Table 2**

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**Table 3**

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**Table 4**

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**Table 5**

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<td>50 kcal/mol</td>
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Results and Discussion

Outer sphere mechanisms for Glaser-Hay couplings

In this section, we describe the calculations used to explore the general mechanism for Glaser-Hay couplings where \( K_3[Fe(CN)_6] \) is employed as an outer sphere oxidant. Since there is no direct interaction between copper complexes and the oxidant, the latter has been treated merely as an electron source in these mechanisms; the corresponding reduction semireaction has been computed as shown in Equation 1.

\[
[Fe(CN)_6]^{3-} + 1e^{-} \rightarrow [Fe(CN)_6]^{4-} \quad \text{(Eq. 1)}
\]

First we describe the catalytic cycle for the phenylacetylene homocoupling reaction catalyzed by \([Cu(TMEDA)]^+\). Additional TMEDA units are used as base, which is consistent with the excess of ligand usually introduced in the Glaser-Hay conditions. A detailed description of this catalytic cycle is shown in Scheme 3, all the species along this pathway have been named as \( GX \) since they are related to this general catalytic cycle. In all the schemes the copper atoms have been colour-coded to indicate the oxidation state of the metal, copper (I) is black, copper (II) is red and copper (III) is purple; additionally, in most schemes the oxidation state of the copper atom has been included between brackets. The catalytic cycle can be divided in three main steps: (i) alkyne deprotonation (from \( G_1 \) to \( G_3 \)), (ii) copper oxidation (from \( G_3 \) to \( G_5 \)), and (iii) reductive elimination (from \( G_5 \) to \( G_1 \)).

The catalytic cycle starts with the \( \pi \)-coordination of phenylacetylene to the copper (I)–TMEDA complex (\( G_1 \)) to form the \( \pi \)-acetylene complex (\( G_2 \)). This latter compound is more stable than the starting materials (\(-24.3 \text{ kcal/mol}\)), and it seems plausible that the alkyne coordination to \( G_1 \) may be barrierless. G2 presents the expected trigonal geometry, with the metal coordinating both \( \text{Csp} \) atoms. Next, the alkyne C–H terminal bond is activated by the base, a free TMEDA ligand, to yield the copper (I)–\( \sigma \)-acetylide complex (\( G_3 \)); this process is mediated by the corresponding transition state for the deprotonation (\( DP\_TS \)) which lies 17.5 kcal/mol higher than \( G_2 \). The alternative intramolecular deprotonation pathway, where TMEDA is bound to the metal before the proton transfer, has been also calculated, affording a very similar barrier (see ESI). The relative energy of \( G_3 \) is around 4 kcal/mol above than that of \( G_2 \), indicating that the deprotonation process is slightly endergonic. Detailed structures of \( G_2 \), \( DP\_TS \) and \( G_3 \) are provided in Figure 1.

The dimerization of \( G_3 \) yields the corresponding copper (I) dinuclear species \( G_4 \); in this intermediate both copper atoms adopt tetrahedral geometries, with the TMEDA ligands perpendicular to the Cu2–C(sp)2 planar core. This process is practically thermoneutral, as less than 2 kcal/mol are required. Dicopper (I) complex \( G_4 \) is oxidized by the iron complexes to the dicopper (II) analog \( G_5 \), just four kcal/mol are required for this process. \( G_5 \) complex corresponds to the closed-shell singlet structure; with a bonding orbital delocalized in the two copper centers, the related triplet had a slightly higher energy. G5 presents the expected tetrahedral geometry, with the metal coordinating both \( \text{Csp} \) atoms. Next, the alkyne C–H terminal bond is activated by the base, a free TMEDA ligand, to yield the copper (I)–\( \pi \)-acetylide complex (\( G_7 \)). This latter compound is more stable than the starting materials (\(-24.3 \text{ kcal/mol}\)), and it seems plausible that the alkyne coordination to \( G_1 \) may be barrierless.

Fig. 1 Detailed structures of \( G_2 \), \( DP\_TS \) and \( G_3 \).
attempts to locate the open-shell singlet analogue, with one unpaired electron on each copper (II) center i.e. the antiferromagnetic solution, were unsuccessful. Nevertheless it is expected that the energy difference between these three electronic states is small. G5 is quite symmetrical: both copper atoms adopt almost square-planar geometries where the Cu–Cp distances are 1.96 and 1.99 Å. Interestingly, the Cu–Cp core is not planar; the angle between both copper planes takes a value of 127º and both acetylide substituents lie quite close (Csp–Csp distance is 2.49 Å). A detailed structural representation of intermediates G4 and G5 can be found in Figure 2. An alternative pathway associated to the alkynyl metathesis that would yield G1 and a bisalkynyl copper (III) complex was studied and discarded because it was not possible to correctly optimize the latter structure.

The transition state for the bimetallic reductive elimination (RedEl_TS) has been found to be only 6.6 kcal/mol higher than G5, making this stage a very easy process. The geometry of this transition state, which looks very similar to G5, shows that the distance between the acetylide groups has been shortened to 1.88 Å. The release of the coupled dihydridacycletene takes the catalytic cycle back to the starting point. The overall energetics indicate that the reaction is exergonic by 23.8 kcal/mol. The computed Gibbs free energies allow the calculation of the apparent activation energy for the reaction, which can be related to the turnover frequency. This can be easily done by means of the energetic span model developed by Koszuch and Shaik. This methodology states that the apparent activation barrier corresponds to the energy difference between the highest and the lowest species when the latter appears first in the catalytic cycle, as in our case of study. In this case the activation barrier is 17.5 kcal/mol and corresponds to the deprotonation process of the coordinated alkyn (from G2 to DP_Ts). The magnitude of this barrier indicates that the reaction could be easily carried out at room temperature; moreover, the barrier is independent of the oxidant nature in agreement with the fact that any other oxidant (even slightly weaker) than K2[Fe(CN)6] (+0.36 V) can be used to carry out this reaction. Our mechanism is also consistent with the rate acceleration by stronger bases and more acidic alkynes, as both participate in the deprotonation step. This was further confirmed by the additional calculations summarized in Table 1.

In the computed catalytic cycle, all intermediates contain copper (I), except G5, that has copper (II). G5 is generated in the oxidation step, and yields immediately a lower barrier reductive elimination. Attempts to compute alternative catalytic cycles, with an earlier oxidation step and more copper (II) intermediates produced higher energy barriers. The mechanism is nevertheless consistent with the experimental efficiency of systems where the catalyst is introduced as a copper (II) complex (e.g. CuCl2).

**Table 1 Rate limiting step dependence on base and substrate (kcal/mol).**

<table>
<thead>
<tr>
<th>Base Influence</th>
<th>Base</th>
<th>G2</th>
<th>DP_Ts</th>
<th>Barrier</th>
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<tbody>
<tr>
<td>NH3</td>
<td>-24.3</td>
<td>-1.8</td>
<td>22.5</td>
<td></td>
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<tr>
<td>TMEDA</td>
<td>-24.3</td>
<td>-6.8</td>
<td>17.5</td>
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<tr>
<td>OH</td>
<td>-24.3</td>
<td>-20.8</td>
<td>3.5</td>
<td></td>
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</tbody>
</table>

Substrate influence (R–PhC≡CH)

<table>
<thead>
<tr>
<th>R</th>
<th>G2</th>
<th>DP_Ts</th>
<th>Barrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-F</td>
<td>-24.1</td>
<td>-7.2</td>
<td>16.9</td>
</tr>
<tr>
<td>p-H</td>
<td>-24.3</td>
<td>-6.8</td>
<td>17.5</td>
</tr>
<tr>
<td>p-Me</td>
<td>-25.7</td>
<td>-7.3</td>
<td>18.4</td>
</tr>
</tbody>
</table>

Cu(OAc)2 or Cu(NO3)2 in the reaction media. This requires a simple “precatalytic” cycle where copper (II) is converted into copper (I) by means of a preliminary alkynie homocoupling as described in the literature. This precatalytic stage, depicted in Scheme 4, starts with the coordination of a free phenylacetylene to G1’ to yield the π-acetylene complex G2’. The deprotonation, using a free TMEDA ligand, is an almost barrierless process since only 0.6 kcal/mol are required. Once G3’ is obtained the copper (II) dimer G5 is formed, then the reductive elimination takes place and the product is released, generating the copper (I) catalyst that may continue the catalytic reaction. The computed Gibbs free energies indicate that for this precatalytic stage the barrier is just 6.6 kcal/mol, corresponding to the bimetallic reductive elimination process (computed as the free energy difference between G5 and RedEl_TS). Nevertheless, since the catalytic reaction corresponds to the one described in Scheme 3, the overall barrier for the whole reaction would be, as stated above, the alkyn deprotonation (17.5 kcal/mol). Scheme 4 provides a low energy pathway to reduce Cu(II) precursors to Cu(I) material to enter the catalytic cycle, though other mechanisms could also be envisaged involving participation of external base or ligand metathesis. This is in any case a side question, as none of these steps participate in the main catalytic cycle.

A distinct alternative would be that the process described in Scheme 4 were the main catalytic cycle, which could then be closed by the oxidation of G1 to G1’ by the external oxidant. This oxidation step would have a similar barrier to that of the deprotonation in the main cycle reported above. However, we discarded this alternative mechanism, because in this case the rate would depend on the oxidant, and not on the nature of the base, contrary to experimental observation.

**Inner sphere mechanism for the Glaser–Hay coupling: Modeling the Cu–O2 interactions**

In this section the complete mechanism of the Glaser–Hay coupling using dioxygen as oxidising agent is described. Although O2 and some Cu–O2 species are recognized as good outer sphere oxidants it should be expected that this kind of systems reacted following an inner sphere pathway. In fact, the studied Cu(I)/TMEDA/O2 system has been reported to act as such in C–H activation processes. The explicit use of dioxygen introduces a lot of additional steps in the catalytic cycle, and...
because of this we start by presenting a simplified picture of the overall mechanism in Scheme 5, where only the most significant species are shown. The three main steps described above (Scheme 3) for the reaction with the external oxidant are conserved: (i) alkyne deprotonation (from $G_1$ to $G_3$), (ii) copper oxidation (from $G_3$ to $G_5$), and (iii) reductive elimination (from $G_5$ to $G_1$). Steps (i) and (iii) are identical, and will therefore not be further discussed. However, step (ii), the copper oxidation, is much more complicated, and can be divided in three additional substeps: (iia) dioxygen cleavage (from $G_3$ to $O_5$), (iib) first oxygen protonation (from $O_5$ to $O_{13}$), (iic) second oxygen

Scheme 4 Proposed precatalytic cycle for the Cu(II)-catalyzed Glaser coupling of phenylacetylene including the computed free energy values in kcal/mol (Cu(I), Cu(II); phenylacetylene is depicted as ≡).

Scheme 5 Simplified mechanism for the full catalytic cycle of the Glaser Hay coupling of phenylacetylene using dioxygen as oxidant (Cu(I), Cu(II), Cu(III); phenylacetylene is depicted as ≡). The dotted box highlights the intermediates involved in the oxidation step.
protonation and water extrusion (from O13 to G5). In all cases species containing incoming oxygen atoms are noted as OX while species that have appeared before maintain the GX notation. All the free energy values presented in these schemes and subsequent tables are computed using the same energy reference (G1).

The oxygen cleavage takes part in two steps (Scheme 6). Intermediate G3, resulting from alkyne deprotonation, reacts with O2 (in the triplet state) and, after a 2–electron transfer, the σ–acetylide–copper (III)-η1–peroxo complex O4 is obtained. It was not possible to find any copper (I)–O2 species, or copper (II)-superoxo complex, which may be formed prior to the electron transfer. The step from G3 to O4 involves a spin-crossing from triplet to singlet, likely through a low barrier minimum energy crossing point (MECP). In O4 the copper atom adopts a slightly distorted square pyramidal structure, with the peroxo occupying two coordination sites and one nitrogen atom of the TMEDA ligand lying far in an axial position at 2.43 Å of the metal. The peroxide moiety is bound to the copper in a side-on manner, with both Cu–O distances close to 1.89 Å. This first oxidation process is endergonic, as O4 is 10.3 kcal/mol above the previous intermediate. The coordination of a second G3 complex to O4, implies the second two–electron transfer, and yields the bis(μ-oxo)–dicopper (III) complex O5 (Figure 3) which at -9.5 kcal/mol is well below the energy of the preceding transition step for alkyne deprotonation. After the oxygen cleavage, comes substep (iiib) the first proton transfer to the oxygen. The best pathway we have found for this process is shown in Scheme 7 where the TMEDA ligands act as proton shuttles that allow the cleavage of the Cu2O2 core. Of course, alternative pathways are plausible, see Supporting Information, and it would not be unexpected that the reaction could proceed by one of those to give rise to the same product formation with energy requirements not very different to the ones shown here. In the pathway proposed in Scheme 7, the reaction proceeds from O5 by the cleavage of the C–N$_\text{calc}$ bond for one of the copper atoms; a step that requires less than 2 kcal/mol. Once O6 is formed, a proton transfer between the nitrogen and one of the free protonated TMEDA ligands (obtained in the acetylene deprotonation step) happens. This process, which is endergonic by another 7.2 kcal/mol, yields the complex O7. Then the proton transfer occurs between the TMEDA and the oxygen atom and O9, with a protonated bridge oxygen, is obtained. The second bridge protonation follows the same reaction sequence until complex O12, with the two bridging oxygen atoms protonated. After the proton transfer to the oxygen atom the dimeric species are no longer stable and two monomeric O13 species are formed; this copper (III) intermediate adopts the expected square planar geometry and constitutes the lowest free energy point in the catalytic cycle so far. Process (iib) involves minor energy changes in most steps, and does not change the identity of the previously determined rate-limiting steps. The metal remains as copper (III) through all these steps.

The reaction follows then the pathway shown in Scheme 8 where a water molecule is removed from the system. O13 reacts with the copper (I) intermediate G3 formed in the first steps of the reaction; the formation of the dimeric species O14 involves a concomitant one-electron transfer from one copper center to the other one through the bridging alkynyl and hydroxyl groups. In this point, our mechanistic proposal diverges from that of Fomina and co-workers, as they proposed the formation of dimeric species from the equivalent of two O13 units. This complex would be a copper(III) dimer, and have a completely different behaviour, and substantially higher energy than the copper(II) dimer we are proposing. The conversion from O13 plus G3 to O14 is almost thermoneutral (only 1.5 kcal/mol are required) and
yields a structure where the bridging groups lie practically at the same distance from both copper atoms. A small rearrangement of ligands in O14, where the hydroxo bridging group is replaced by the second alkyne, provides the bis-μ-alkynyl dimer O15.

Scheme 7 Proposed mechanism for the bis-oxo bridge protonation in the Glaser Hay coupling of phenylacetylene including the computed free energy values in kcal/mol (Cu(III); phenylacetylene is depicted as ≡).

The protonation of the hydroxyl group by TMEDA-H⁺ produces one molecule of water and the dinuclear species G5 that is ready for the reductive elimination step described above in the outer-sphere mechanism. This second protonation and extrusion process is a downhill sequence that does not bring any significant barrier to the overall catalytic cycle.

The reaction energy, computed as the formation of a diphenyldiacetylene from two phenylacetlenes and one half of dioxygen, is exergonic by 56.9 kcal/mol, in agreement with the strong oxidizing power of O₂ to H₂O. Although the mechanism for this inner sphere mechanism looks more complicated than the one for outer sphere oxidants, the apparent reaction barrier remains the same (17.5 kcal/mol) corresponding to the deprotonation of the coordinated alkyne, confirming that the reaction rate is independent of the nature of the oxidant and indicating that it should work smoothly at room temperature.

Scheme 8 Proposed mechanism for the second oxygen protonation and water extrusion in the Glaser-Hay coupling of phenylacetylene including the computed free energy values in kcal/mol (Cu(II), Cu(III); phenylacetylene is depicted as ≡).
or a η²-peroxocopper (III) could act as oxidants. This alternative pathway has also been computed and can be found in the Supporting Information. The barriers found are quite low, but still higher than those of the inner sphere mechanism here described. Moreover, an outer sphere mechanism would not comply with what is observed experimentally for similar systems i.e. whenever TMEDA is used along copper in presence of dioxygen the dinuclear bis(μ-oxo)–dicopper (III) complexes are observed. This result favoring the inner sphere may seem to be in contrast with the fact that most experimental evidence on copper-dioxygen interactions focuses on the intermediates of outer sphere electron transfers. A more careful analysis of experimental literature shows however that the observation of these intermediates requires the use of specific, usually bulky ligands, in the understanding that in the absence of those an inner sphere mechanism would operate.

Conclusions

The mechanism of the Glaser-Hay oxidative coupling of terminal alkynes has been characterized by DFT means. In the case of copper (I) couplings where an outer sphere oxidant is employed, the mechanism resembles the classical Bohlmann proposal: first the alkyne coordinates to copper, enhancing the acidity of the terminal proton that can be abstracted by an external base. After deprotonation the copper (I)–σ-acetylide dimerizes and can be oxidized by most outer-sphere oxidants to yield the corresponding copper (II) dimers; finally, a fast bimetallic reductive elimination yields the product. If copper (II) is used as starting material, there is a minor nuance in the form of low barrier precatalytic cycle where the first 1,3-diyne unit is produced, the mechanism then reverting to that for copper (I) catalysts.

In the case where dioxygen is employed as an inner-sphere oxidant, the mechanism follows a pathway similar to that of natural oxidases. Bis(μ-oxo)–dicopper (III) complexes are formed in first instance, after the protonation of the bridge a reaction between copper (I) and copper (III) yields the same copper (II) dimers as in the outer-sphere mechanism and, from those, the C≡C coupling reaction is quite easy. The rate-limiting step for all the studied reactions corresponds to the Cu-coordinated alkyne deprotonation, demonstrating why more acidic acetylenes and stronger bases provide higher reaction rates. In addition, the calculated barrier is low enough (17.5 kcal/mol) to allow the reaction to proceed at room temperature, as observed experimentally.

Notes and references

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† Electronic Supplementary Information (ESI) available: Includes all computed potential energies, enthalpies, free energies, dispersion corrections, energy profiles and optimized structures, along alternative Glaser-Hay pathways. See DOI: 10.1039/b000000x/


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