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PAPER

Assessing the whole range of CuAAC mechanisms by DFT calculations—on the intermediacy of copper acetylides†‡

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The archetypal Cu(I)-catalyzed alkyne-azide click cycloaddition (CuAAC) has been explored thoroughly *via* density functional calculations, modeling copper nuclei with the LANL2DZ basis set and aqueous environments with CPCM solvation. All the mechanistic proposals, ranging from the intermediacy of copper acetylides to π-complexes and multinuclear clusters have been compared. The known features of the CuAAC reaction such as the observed second order kinetics for the Cu(I) species and the marked regioselectivity have been taken into account. The calculated energy barriers point to the intermediacy of copper(I) acetylides with two metal centers, in agreement with the observed kinetics, which exhibit barriers of 10.1 kcal mol^{-1} and 13.7 kcal mol^{-1} for the 1,4- and 1,5-regiochemistries, respectively, thus accounting for the marked regioselectivity of the copper catalyzed azide-alkyne cycloaddition. The copper acetylide *versus* π-complexes dilemma has also been experimentally addressed through the click reaction of benzyl azide and isotopically labeled phenylacetylene. The total proton/deuterium exchange in the afforded triazole demonstrates the formation of a copper acetylide intermediate during the transformation.

Introduction

The Cu(I)-catalyzed cycloaddition of alkynes and azides (CuAAC) constitutes the paradigm of the so-called click approaches enabling the expeditious and regiospecific preparation of triazoles,[1,2] a process that largely overcomes the minuses of the uncatalyzed classical Huisgen reaction.[3] Although other transformations exhibiting click characteristics have emerged recently,[4] the impressive biorthogonality,[5] general ease of execution, and smooth reaction conditions, including the possibility of using environmentally-friendly aqueous media, make the CuAAC an ideal choice to label biomolecules in their natural habitats. Extensive applications of this methodology to the preparation of highly functionalized and complex molecules have also transformed research areas such as materials and pharmaceuticals.[6]

Although copper-free triazole syntheses *via* cycloadditions of azides with cycloalkynes and cycloalkenes have been developed,[7] with computation revealing that the differences in reactivity are more related to differences in distortion energies than the strain released,[8] the metal-catalyzed reaction is still the favorite protocol to promote this synthetically important and selective chemical ligation. Unfortunately, the literature describes a variety of mechanisms in order to account for experimental observations, which cannot easily be reconciled. Clearly, the nature of the copper intermediates involved represents the misleading point. Thus, while numerous proposals suggest formation of copper acetylides, a fact consistent with the enhanced reactivity of terminal alkynes after proton abstraction; other studies point to the possibility of copper π-complexes as intermediates.

We now report a general computational investigation of reactivity and regioselectivity for CuAAC reactions dissecting the different conjectured mechanisms. In doing so, we have computed through DFT calculations all the proposed mechanisms for this important transformation. The present work first reassesses the initial theoretical study on the mechanism of the CuAAC reaction,[9] at our theoretical level, in order to allow direct comparisons of the energetics. This reinvestigation includes both the uncatalyzed alkyne-azide cycloaddition and the early suggested mononuclear copper-acetylide intermediacy.

All the other copper acetylide-type intermediates suggested up to now, along with the possibility of the intermediacy of copper π-complexes, which have been suggested by several authors, have also been analyzed through DFT calculations. To the best of our knowledge, this is the first study collecting all the proposals for the CuAAC transformation at the same level of theory, thereby enabling a direct comparison of the different energy barriers. Although our theoretical calculations point to the involvement of the two-metal center acetylides, as proposed recently, we could further confirm the unequivocal role of copper acetylides by carrying out the reaction of benzyl azide and isotopically labeled phenylacetylene in aqueous media. The complete lack of

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‡ Electronic supplementary information (ESI) available: complete Cartesian coordinates and energies for all calculated structures. See DOI: 10.1039/c0ob01001d

deuterium in the resulting triazole rules out the possibility of a direct participation of copper π-complexes as catalysts in CuAAC reactions.

Computational details

All geometries and energies, as well as frequency calculations, were computed using the B3LYP[10,11] density functional theory method as implemented in the Gaussian 03 package.[12] The LANL2DZ basis set[13] was employed for copper while the triple-ζ plus polarization basis set 6-311G(d,p) was used for the rest of atoms.

Solvation energies in water were added as single-point calculations using the conductor-like polarizable continuum model (CPCM).[14] Since for this method the choice of cavities plays an important role as both computed energies and properties depend significantly on the cavity size, the UAKS cavities were chosen, which have proven to be the most suitable cavities to reproduce solvation energies of charged organic species in water.[15] Zero-point vibrational energies and thermodynamic corrections at 298 K were calculated at the same level as geometry optimizations. Relative energies presented herein are free energies with respect to the most stable pre-reaction complex. Like in previous studies, the initial computational studies were performed on the Cu-catalyzed cycloaddition of methyl azide and propyne. For calculations involving a non-terminal alkyne, 2-butyne was selected as reactant.

Results and discussion

Uncatalyzed azide-alkyne cycloaddition

The uncatalyzed 1,3-dipolar cycloaddition of organic azides with alkynes was also studied by means of DFT calculations. The study found high energy barriers for both the 1,4- and 1,5-approaches.[9] We have also calculated the energy barriers for the coupling of methyl azide and propyne in order to properly compare its energetics with the catalytic pathways described through this paper.

Our calculations gave, as expected, analogous energy barriers for the 1,4- and 1,5-regiochemistries (Fig. 1), resulting in 36.1 and 35.6 kcal mol^{-1}, respectively. This energy difference explains the lack of regioselectivity when the cycloaddition is carried out in the absence of any catalyst as well as the slowness of the transformation. The formation of triazoles is highly exothermic by more than 48 kcal mol^{-1}.

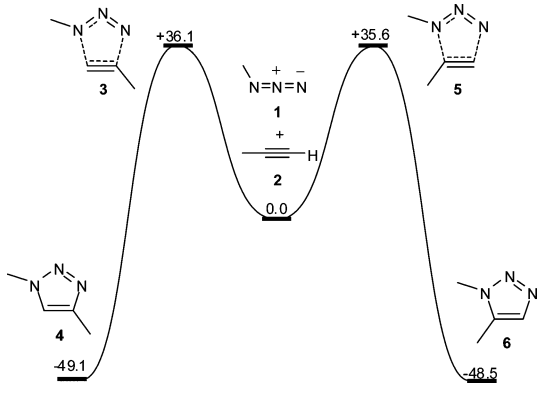


Fig. 1 Calculated energy barriers for the uncatalyzed azide-alkyne coupling in the absence of copper(I) species.

Mononuclear copper acetylide-based mechanisms

The first proposal for the mechanisms of the CuAAC reaction was provided by Sharpless and co-workers.[9] Based on this study, the high rate acceleration could be attributed to the stepwise formation of an unusual Cu(III)-metallacycle with a lower activation barrier. This mechanism has no precedents, though it agreed well with the experimental observations. The fact that the reactions proceed much faster in water can be explained by the ease in displacing a water ligand during the formation of the Cu(I) acetylide (exothermic path with ΔH = 11.7 kcal mol^{-1}) relative to an acetonitrile ligand.

At the present level of theory, we were able to locate both the transition structure **8** and the Cu(III)-metallacycle intermediate (**9**), whose formation constitutes the rate-determining step (Fig. 2). The putative initial complex between methyl azide and the Cu(I) acetylide (**7**) could not be observed, and the most stable complex binds to only one solvent ligand, such as in the cycloaddition conducted in pyridine (modelled at B3LYP/LACV3P+(d)).[16] The activation barrier for this step in water is 27.1 kcal mol^{-1}, substantially lower than the uncatalyzed reaction. The barrier for ring contraction leading to the triazole product is negligible,[9,16] and therefore this step is not usually computed.

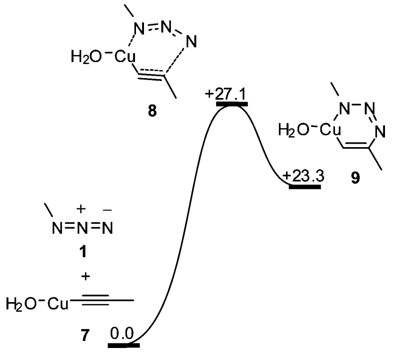
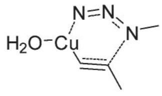


Fig. 2 Representation of the stepwise cycloaddition of **7** and methyl azide in water involving a mononuclear copper acetylide.

Since the CuAAC reaction occurs with a dramatic regioselectivity affording a single 1,4-disubstituted-1,2,3-triazole, it is generally assumed that the alternative cycloaddition involving the distal nitrogen of methyl azide would have an exceptionally high barrier. However, this key concern has not been addressed so far. To verify this surmise, the transition structure for such a cycloaddition (**10**) has been calculated and possesses a barrier of 40.1 kcal mol^{-1} (Fig. 3). This magnitude is much greater than that involving the proximal nitrogen of the azide and *even* higher than the uncatalyzed thermal process.

This sort of mechanism, invoking the intermediacy of transient copper acetylides, found support from the isolation of a Cu(I) triazolide (**11**), which comprised the stoichiometric reaction of a Cu(I) acetylide complex with a sterically demanding organoazide to afford **12** (Scheme 1).[17] A tris(triazolyl) methanol ligand has also been generated by a triple CuAAC and may serve as efficient catalyst of the Huisgen cycloaddition in combination with CuCl in water or neat conditions.[18]



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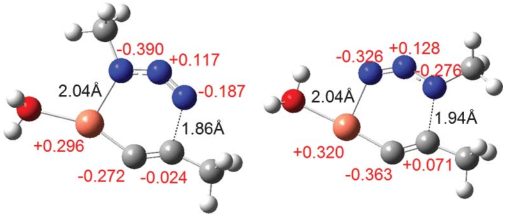
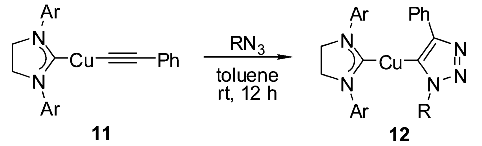


Fig. 3 Optimized structures for the transition structures **8** and **10** leading to regioisomeric triazoles.

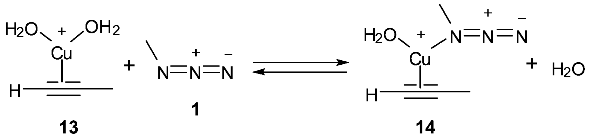


Scheme 1 Cycloaddition of copper acetylide **11** with a sterically demanding organoazide.

Intermediacy of π complexes

Some experimental findings on the copper-catalyzed azide-alkyne cycloaddition suggest that metal π-complexes could play a key role in accelerating the formation of triazoles. In a recent Pd-catalyzed heteroannulation of *o*-iodobenzyl azide with internal alkynes, triazoles fused with an isoindoline core were generated in the presence of Cu(I) as co-catalyst.[19] These results could be interpreted invoking coordination of Cu(I) with the π-electrons of the alkyne; in fact a mononuclear Cu-species was suggested. In a further and related study, 1,2,3-triazolo-[1,4]benzoxazines were equally obtained by reaction of 1-azido-2-(alkynyloxy)benzene with iodobenzene in the presence of Pd-Cu catalysts.[20] Again, the intramolecular cycloaddition of an azido group with an internal alkyne to give the 1,4-disubstituted triazole would require Cu-coordination to the triple bond. Since an unsubstituted triazole was also isolated as by-product, the latter could still be explained through the intermediacy of a copper acetylide. Thus, either two competing mechanisms may co-exist under certain conditions or π-complexes are most likely the actual species for the cycloaddition to occur.

Copper(I)-alkyne π-complexes such as **13** are known to exist in aqueous solutions. In the presence of an organic azide, which exhibits a significant nucleophilic character, especially at the proximal nitrogen atom, there should likely be an equilibrium like that depicted in Scheme 2. In this equilibrium the azide can exchange one of the water ligands to afford the metal complex **14**.



Scheme 2

These kind of π-coordinated structures would therefore be viable catalysts to promote triazole formation as long as the whole process exhibits relatively low activation barriers with respect to the uncatalyzed processes. Thus, the Cu-metallacycle **16** can be released from an initial π-complex (**14**) through a barrier of 29.1 kcal mol^{-1}, which is approximately 7 kcal mol^{-1} lower than the cycloaddition without the assistance of any catalyst. (Fig. 4). It should be noted that during the cycloaddition process, the metal center can host a second water molecule as ligand, which probably stabilizes still further the metallacycle **16** and its previous transition structure **15**.

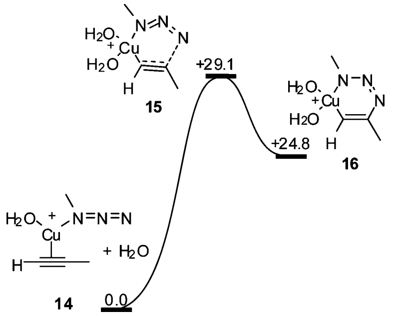


Fig. 4 Energy profile for the click cycloaddition of methyl azide and propyne starting from a π-complex.

Since no proton is involved in the steric outcome, it could be argued that this mechanistic proposal would neither account for the absolute regioselection nor the scarce reactivity of internal alkynes. To check out the first argument, we have computed the barrier for the cycloaddition leading to the other regioisomer through the transition state **17**. With an energy gap of 34.0 kcal mol^{-1}, the process will have an exclusive regiochemical preference in accord with experiments in solution. Moreover, the transition structure **18**, corresponding to the hypothetical CuAAC of methyl azide with 2-butyne, shows an activation barrier of 36.6 kcal mol^{-1} (Fig. 5). Therefore, such mononuclear metallocenes could explain much of the observed behavioral data, namely the effect of Cu(I) on rate acceleration, the regioselectivity, and the distinctive reactivity toward substituted alkynes.

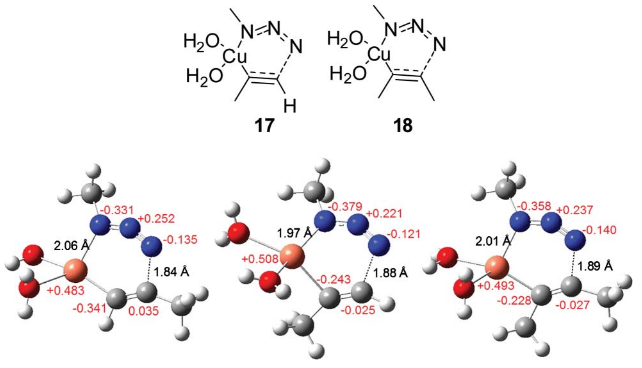
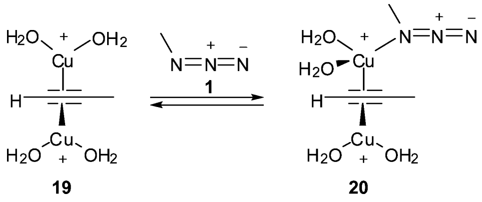


Fig. 5 Optimized transition states for the cycloadditions of propyne and methyl azide *via* mononuclear π-complexes (**15** and **17**) and of methyl azide with 2-butyne (**18**).

The above result fails to explain the second order kinetics with respect to Cu(I). In aqueous solutions of Cu(I) species, acetylenes may give rise to dinuclear π-complexes such as **19** in view of the orthogonal symmetry of their π-electrons.[21]

These complexes, in the presence of methyl azide, will form new complexes in which the proximal nitrogen coordinates with one Cu(I) center (Scheme 3). Fig. 6 depicts the optimized structures for both mono- and dinuclear π-complexes, and the latter coordinated with the azide. In this case, the copper atom adopts a quasi-tetrahedral arrangement. Such complexes could then be active catalysts leading to stable cupracycles in a similar way to the previous mechanism computed for the mono-copper complexes.



Scheme 3

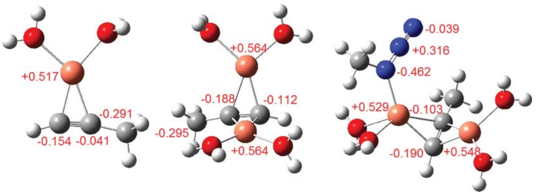


Fig. 6 Structures of mononuclear and dinuclear Cu-π-complexes (**13** and **19**). Coordination with methyl azide is shown on the right (**20**).

The results collected in Fig. 7 and 8 show the energy profiles and transition structures generating the Cu-triazolides **22**, **25** and **28**, which correspond to the two regiochemical approaches of methyl azide to propyne as well as to 2-butyne, respectively. The computed energetics are in agreement with the experimental observations, *i.e.* the marked regioselectivity and the unwilling participation of internal alkynes. Thus, the energy barrier for the 1,5-approach and the 2-butyne reaction are 27.6 and 28.2 kcal mol^{-1}, respectively, which are therefore analogous to those of the uncatalyzed transformations. In stark contrast the energy barrier for the 1,4-regiochemistry is 21.7 kcal mol^{-1}, more than 10 kcal mol^{-1} lower than the uncatalyzed cycloaddition, and becomes the favored pathway.

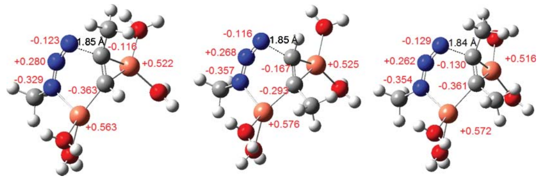


Fig. 8 Geometries for transition states **21**, **24** and **27**.

Tetranuclear copper acetylide complexes

Polynuclear complexes of Cu(I) halides and alkynes, involved apparently in catalytic conversions of these organic molecules, can be generated in solution and characterized in the crystalline state.[21] Accordingly, it may be suggested that formation of Cu-clusters cannot be discarded for clickable transformations. Moreover, the reaction partners, alkyne and azide, might not necessarily be coordinated to the same Cu center. Based on this assumption, Straub has recently performed gas-phase calculations (at the B3LYP/LACV3P++(d,p)//B3LYP/LACVP(d,p) level) for triazole formation *via* tetranuclear Cu(I) μ-acetylide and dinuclear Cu(I) phenanthroline complexes.[22] Such polynuclear bridging species (*e.g.* **29**) would show a higher thermodynamic stability toward organic azides than conventional Cu(I) acetylides. Straub points out, nevertheless, that the thermodynamic preference must be considered an approximation and the method itself may not reproduce cuprophilic interactions; *i.e.* they depend on the nature of the ligand and usually increase on increasing the σ-donor and π-acceptor ability of the ligand.[23]

Fig. 9 summarizes our quantum chemical calculations relative to tetrameric complex **29** following a mechanistic pathway similar to that of **23**. The transition state showing the observed regiochemistry is reached with a barrier of 28.5 kcal mol^{-1}. The alternative regioisomer, *via* the transition structure **33**, would be formed with a barrier of 38.7 kcal mol^{-1}; a fact accounting for the complete regioselectivity of the reaction. Fig. 10 shows the optimized geometries for both transition structures.[24]

Intermediacy of dinuclear copper acetylides

Further kinetic analysis by Fokin and associates on the reaction of benzyl azide and phenylacetylene revealed how a pseudo-first-order initial rate evolved, at intermediate concentrations, to second order both with respect to Cu(I) and alkyne.[25] Thus, such kinetic measurements indicated that the reaction should be at least second order with respect to the concentration of the L$_n$Cu(I) species.

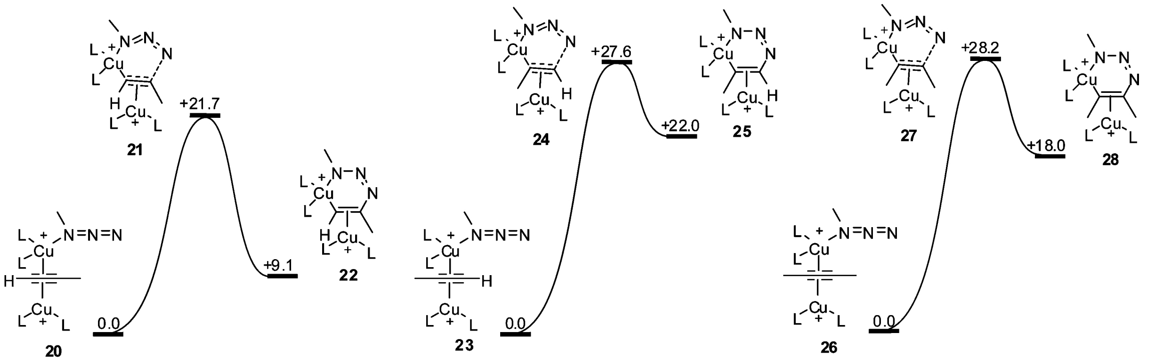


Fig. 7 Schematic representations of CuAAC reactions of methyl azide with propyne and 2-butyne involving dinuclear π-complexes (L = H_2O).

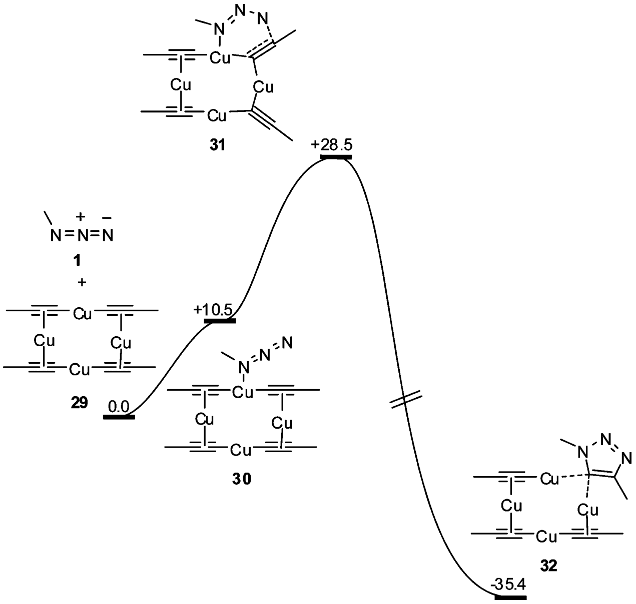
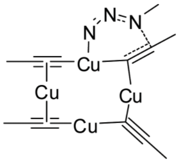


Fig. 9 Schematic mechanism for the formation of a polynuclear triazolide from methyl azide and one Cu-alkyne complex with π-electrons of the alkyne involved in the Cu(I) coordination.



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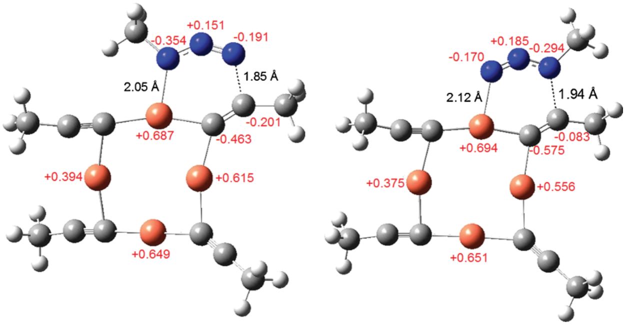


Fig. 10 Optimized ball-and-stick representations of transition structures **31** and **33**.

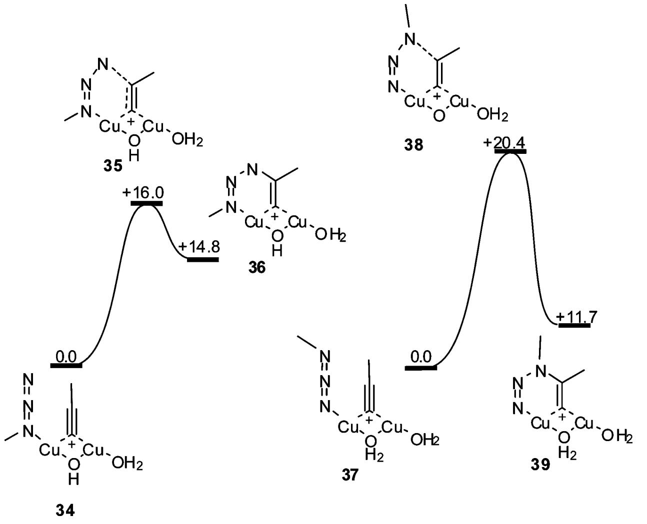


Fig. 11 Mechanistic profiles of the regioisomeric approaches of methyl azide and propyne through Cu-acetylides with two metal centers.

This observation along with the fact that commercially available copper acetylides failed to give the desired product, prompted them to re-assess the mechanistic proposal. That team proposed the intermediacy of σ-acetylide-Cu complexes, though with two Cu(I) atoms involved in the transition state. On computing such a proposal, one Cu(I) center binds to a nitrogen atom of methylazide to give rise to complex **34**, in which the other Cu center also activates the alkyne fragment. This initial dinuclear Cu-acetylide leads ultimately to the cupracycle **36** (Fig. 11). Proteolysis of the Cu–C bond both regenerates the catalyst and releases the triazole derivative.

As above, we did take into account the two possible approaches involving either the proximal or distal nitrogen of methyl azide, which gave Cu-acetylides **34** and **37**, respectively. The barrier leading to the 1,4-disubstituted triazole is 16.0 kcal mol^{-1}, significantly lower than all the above-described processes mediated by monomeric or tetrameric Cu-acetylides or π-complexes. Formation of the opposite regioisomer proceeds with a higher barrier, 20.4 kcal mol^{-1}, thus accounting for the observed regioselectivity. The corresponding geometries of transition states **35** and **38** are depicted in Fig. 12.

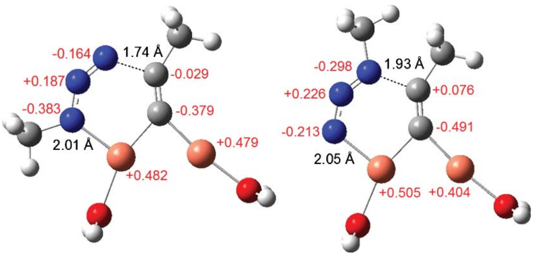


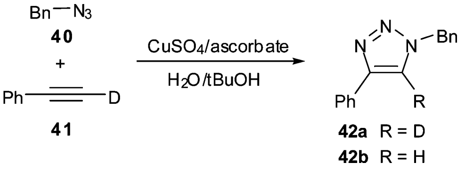
Fig. 12 Optimized transition structures **35** and **38**.

The mechanistic proposal by Fokin and co-workers clearly exhibits the lowest energy barrier of all the theoretically computed pathways in this thorough search. In addition, this mechanism succeeds in explaining the observed rate acceleration, regioselectivity, and second order kinetics for the copper species.

It is worth mentioning a recent publication about the CuAAC reaction,[26] which investigates the mechanism by means of real-time IR monitoring. Although the authors highlight the agreement between their experiments and those provided by Sharpless and associates,[9] that study does not rules out a dinuclear copper acetylide as intermediate. Thus, the initial azide-alkyne 1 : 1 complex observed by the authors, along with the rate-determining step (the triazole ring closure), is consistent with both the mononuclear and dinuclear mechanisms. However, the second-order kinetics observed for the copper reactant[25] supports the dinuclear copper acetylides as active species.

Isotopically labeled reactions

The preceding discussion reveals that copper acetylides should most likely be the intermediates that drive the CuAAC reaction to completion, even though such acetylides may not be a classical and conventional anion species, whose existence in water could be elusive. We realized that this puzzle between copper acetylides *versus* π-complexes when describing the mechanism for the CuAAC reactions could be unambiguously assessed by means of isotopically labeled alkynes in aqueous conditions. For this purpose, the model reaction involving benzyl azide and phenylacetylene was selected (Scheme 4).



Scheme 4 CuAAC reaction of benzyl azide and phenylacetylene-*d*.

Had the transformation taken place through π-complexes as the active catalyst, the resulting triazole would be **42a**, because the alkyne-deuterium bond is not dissociated in any step during the catalytic cycle. However, if the reaction occurs *via* copper acetylides, the deuterium atom would be released from the alkyne species during the formation of the catalyst. When the cycloaddition is over the copper-based catalyst will be recovered by hydrolysis of the resulting copper triazolide. Since the reaction is carried out in aqueous media, such a triazole will have the structure of **42b**, possessing a proton at the C-5 position of the triazole unit; a fact that can be easily monitored by ^{1}H NMR. Accordingly, we performed the reaction of benzyl azide with phenylacetylene or isotopically labeled phenylacetylene in equimolar amounts, using the $CuSO_4$/sodium ascorbate system as catalyst (for details see Experimental section).

Fig. 13 shows the ^{1}H NMR spectra of the triazoles obtained from both the unlabeled and deuterium-labeled alkynes. The signal at 7.67 ppm, corresponding to the proton on the heterocycle, could be detected in both experiments and further signal integration confirmed that such triazoles were completely protonated. Therefore, the above results are consistent with the intermediacy of copper acetylides in the reaction of benzyl azide and phenylacetylene employing copper sulfate and ascorbate as catalytic system under aqueous conditions.

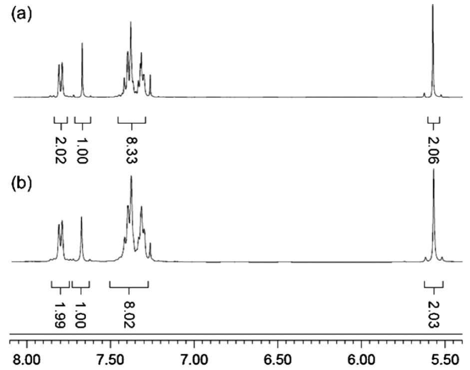


Fig. 13 ^{1}H NMR spectra of the triazoles obtained by reaction of benzyl azide with phenylacetylene (a) and phenylacetylene-*d* (b).

Conclusion

An in-depth analysis of all the mechanistic proposals for the Cu-catalyzed cycloadditions of azides and alkynes in aqueous media through DFT calculations showed that Cu-acetylides, in particular the two-metal center species proposed by previous kinetic studies,[25] are the most plausible intermediates in accelerating the formation of triazoles. The computed energy barriers for the catalytic pathways mediated by these species, 16.0 and 20.4 kcal mol^{-1} for the regioisomeric 1,4- and 1,5-approaches, respectively, explain the experimentally observed regioselection as well as the significant rate acceleration. In addition, the nature of the catalyst clarifies the observed second order kinetics for the copper species too.

The computed energy barriers for all the mechanistic proposals are the lowest estimates reported so far, ranging from the possibility of π-complexes as intermediates to transformations mediated by monocopper acetylides and copper clusters.

To unveil finally the controversy about the nature of the catalyst, the reaction of benzyl azide and isotopically labeled phenylacetylene in aqueous media has also been described. The total proton/deuterium exchange reaction fully agrees with the intermediacy of the copper acetylides proposed and rules out a direct role of π-complexes in accelerating the CuAAC reaction.

Experimental

Synthesis of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole

To a mixture of benzyl azide (1 mmol) and phenylacetylene (or phenylacetylene-*d*) (1 mmol) in 2 mL of *t*-BuOH/water (1 : 1), were added sequentially sodium ascorbate (19.8 mg, 10 mol%) and 50 μL of 1M aq. $CuSO_4 \cdot H_2O$ (5 mol%). The mixture was then stirred at 60 °C for 2–3 h until completion (TLC monitoring, hexane/ethyl acetate 2 : 1). The reaction mixture was further diluted with water (10 mL) and cooled in an ice bath. The resulting precipitate was filtered and dried under vacuum. Mp 128–129 °C, lit.[27] 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* 7.6 Hz, Ar), 7.67 (s, 1H, triazole), 7.42–7.26 (m, 8H, Ar), 5.57 (s, 2H, CH_2).

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