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# Copper(I)-Catalyzed Cycloaddition of Azides to Multiple Alkynes: A Selectivity Study Using a Calixarene Framework

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**Abstract:** Copper(I)-catalyzed addition of limited amounts of azides to multiple alkynes, which led to statistical mixtures of triazole/acetylene derivatives or, in other cases, resulted in preferred formation of multiple triazoles, was studied at pre-organizable calixarene platforms bearing up to four propargyl groups. Depending on calixarene structures and reaction conditions, the unprecedented specific or selective formation of exhaustively triazolated calixarenes or a complete loss of the selectivity were observed. Both autocatalytic copper activation and a local copper(I) concentration increase due to copper–triazole complexation were thoroughly studied as the most expected reasons for the selectivity and both were disproved. Mixed triazolated/propargylated calixarenes and their copper(I) complexes proved not to be involved in the cascade-like process that was modeled to be driven by an intramolecular transfer of two copper(I) ions from a just-formed binuclear copper intermediate to the adjacent acetylene unit.

## Introduction

Copper-catalyzed azide–alkyne cycloaddition (CuAAC) has rapidly become widely used in organic chemistry and related disciplines since the long-known Huisgen reaction has been shown to be efficiently catalyzed by copper(I) salts and complexes.[1] The $Cu^{I}$ catalysis provided both rate enhancement and regioselectivity of the cycloaddition under mild conditions with wide range of copper sources and solvents, which has allowed application of CuAAC for various molecular systems including multifunctional or/and very sensitive ones.[2] First established for conformationally constrained small bis(azides),[3a] CuAAC between multiple azides and alkynes has been shown to be clearly selective towards multiple triazoles in cases of oligoazide derivatives of cyclodextrins,[3b] calixarenes,[3c] silsesquioxane,[3d] etc. In contrast, 'inverted' CuAAC reactions of multiple alkynes and azides have proceeded with a far less predictable outcome. Preferred formation of bis(triazoles)[3e–h] or complete loss of the selectivity resulted in statistical mixtures of mono- and bis(adducts),[3a] both have been published for bis(alkynes), including structurally related ones. The only example of clear selectivity towards adjacent multiple triazoles has been recently published for poly(propargyl metacrylate) which has been converted into a polymer with a definite multitriazole–multipropragyl blocks sequence under CuAAC with a limited amount of benzyl azide.[3i]

Though tentative rationalizations for the selectivity[3i] or for its absence[3a] have been provided, they could not be cross-correlated even for the known cases and, thus, gave no general understanding of the mechanism of $Cu^{I}$-catalyzed addition of azides to multiple alkynes. Herein we studied equimolar reactions between azides and two, three, and four propargyl groups grafted at narrow rims of calixarenes known for their power in the tunable pre-organization of multiple functional units.[4] The reactions gave the full range of CuAAC outcomes (from completely nonselective reactions to specific formation of multitriazoles) that allowed the investigation of the selectivity in detail to provide a fully consistent explanation for it.[5]

## Results and Discussion

Within the first set of reactions that initiated all further study, equimolar mixtures of cone tetrakis(propargyloxy)calix[4]arene **1** and azides were subjected to CuAAC with several well-known copper(I) catalysts (Scheme 1, Table 1). No reaction occurred at room temperature, but, surprisingly, upon heating, azides were spent nearly exclusively on exhaustive modification of starting calixarene to form tetrakis(triazoles) **2**–**4**, ~75 mol% of unreacted **1** returned, and no partially triazolated calixarenes were detected in the samples after removal of Cu-salts (for representative $^{1}H$ NMR spectra, see Figure 1, traces of byproducts due to acetylene homocoupling or triazole iodination were detected in several cases). Kinetic measurements of CuAAC between **1** and benzylazide showed no traces of partially triazolated calixarenes even in early samples (see the Supporting Information).

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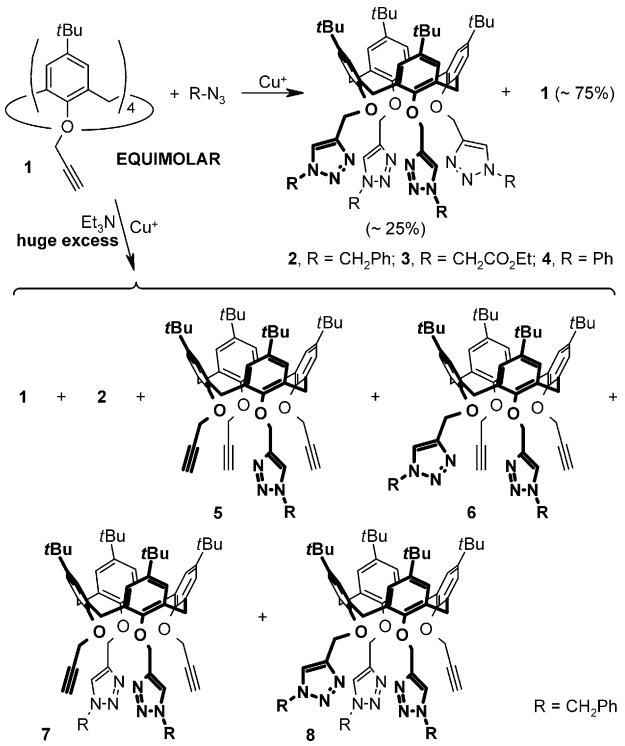



**Scheme 1.** Selective (top) and nonselective (bottom) routes of equimolar CuAAC reactions between **1** and azides.

**Table 1.** Reaction conditions for selective conversion of **1** into **2**–**4** under equimolar CuAAC.[a]

| Entry | Azide | Catalyst | Solvent | $T$ [°C] |
|---|---|---|---|---|
| 1 | $PhCH_2N_3$ | CuI·$P(OEt)_3$ | toluene | 110 |
| 2 | $PhCH_2N_3$ | $CuSO_4$/sodium ascorbate[b] | $THF/H_2O$ | 65 |
| 3 | $PhCH_2N_3$ | $[Cu(CH_3CN)_4]PF_6$ | toluene[c] | 110 |
| 4 | $PhCH_2N_3$ | CuCl | toluene[d] | 110 |
| 5 | $EtOC(O)CH_2N_3$ | CuI·$P(OEt)_3$ | toluene | 110 |
| 6 | $EtOC(O)CH_2N_3$ | CuI[b] | toluene | 110 |
| 7 | $EtOC(O)CH_2N_3$ | CuI/DIPEA (20 equiv per $Cu^+$) | toluene | 110 |
| 8 | $PhN_3$ | CuI·$P(OEt)_3$ | toluene | 60[e] |

[a] 15 mol% of catalyst, reaction time 5–7 h, $c$(calixarene) = $c$(azide) = 0.01 M. [b] Longer heating needed to complete the reaction. [c] No reaction in boiling $CH_3CN$ even with excess of azide. [d] Wet toluene needed to be used with this catalyst. [e] Lower temperature needed to prevent side reactions of $PhN_3$.

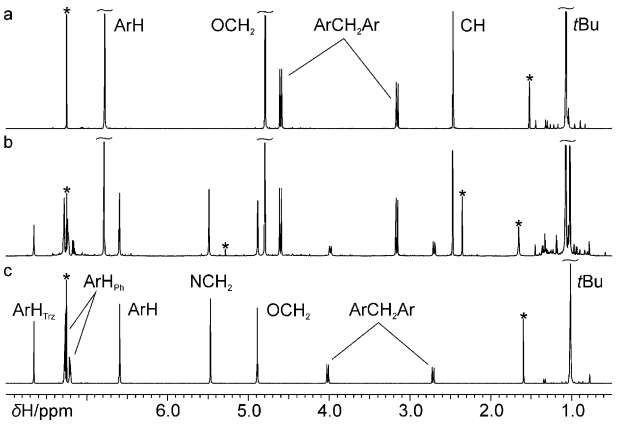



**Figure 1.** $^1H$ NMR spectra of a) pure **1**, b) the mixture obtained in equimolar reaction of **1** with $PhCH_2N_3$ (Table 1, entry 4) after removal of Cu-salts, c) pure **2**; $CDCl_3$, 600 MHz; * = residual solvent signals.

**Table 2.** Major products content in equimolar CuAAC reaction of partially propargylated calixarenes with azides.

| Reaction/conditions[a] | Major product | Major product content [mol.%] Exp.[b] | Stat.[c] | Max.[d] |
|---|---|---|---|---|
| **10** + $PhCH_2N_3$/A | **15** | 50 | 31.8 | 50 |
| **10** + $EtOC(O)CH_2N_3$/A | **16** | 47 | 31.8 | 50 |
| **11** + $PhCH_2N_3$/A | **17** | 35 | 31.8 | 50 |
| **11** + $EtOC(O)CH_2N_3$/A | **18** | 37 | 31.8 | 50 |
| **12** + $PhCH_2N_3$/A | **19** | 30 | 8.5 | 33 |
| **12** + $EtOC(O)CH_2N_3$/A | **20** | 25 | 8.5 | 33 |
| **21** + $EtOC(O)CH_2N_3$/A | **23** | 18 | 6.2 | 33 |
| **24** + $PhCH_2N_3$/A | –[e] | | | |
| **24** + $PhCH_2N_3$/B | **26** | 50 | 31.8 | 50 |
| **25** + $PhCH_2N_3$/A | –[e] | | | |
| **25** + $PhCH_2N_3$/B | **27** | 27 | 8.5 | 33 |
| **28** + $PhCH_2N_3$/A | **29** | 15 | 8.5 | 33 |
| **28** + $EtOC(O)CH_2N_3$/A | **30** | 14 | 8.5 | 33 |

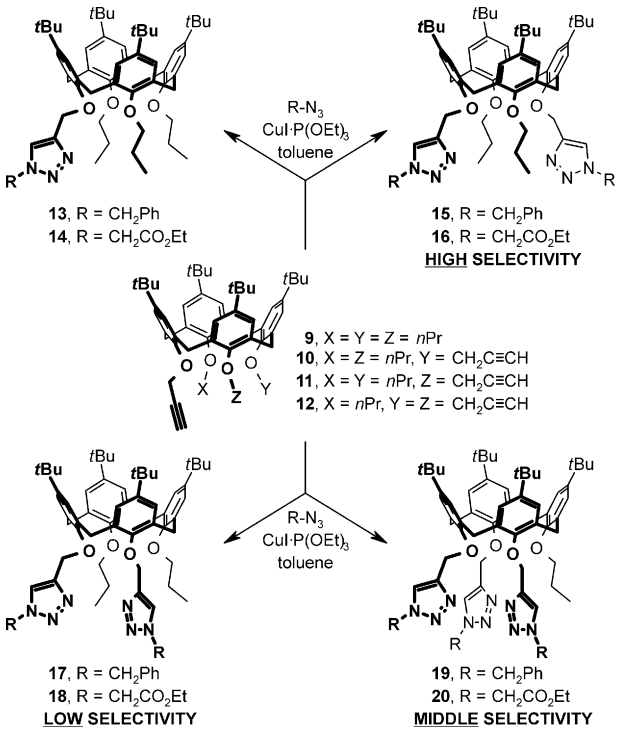
[a] Conditions A: CuI·$P(OEt)_3$ (15%), toluene, reflux, 7 h. B: $CuSO_4 \cdot 5H_2O$ (20%)/sodium ascorbate, $THF/H_2O$, reflux, 7 h. $c$(calixarene) = $c$(azide) = 0.01 M. [b] Measured by integration of calixarene aromatic signals in $^1H$ NMR spectra of reaction mixtures after removal of Cu-salts. [c] Calculated from formal kinetic equations assuming equal rate constants for every step. [d] Theoretical yield for the reaction furnishing the major product specifically. [e] Complex mixture, no major product was detected.

The CuAAC reactions of **1** retained selectivity towards tetrakis(triazoles) in solvents of different polarity and in the presence of limited amounts of Cu-competitive ligand (Table 1, entry 7), but turned to the nonselective route with a huge amount of $Et_3N$ (240 equiv per $Cu^+$) giving all possible mixed propargylated/triazolated calixarenes **5**–**8**.

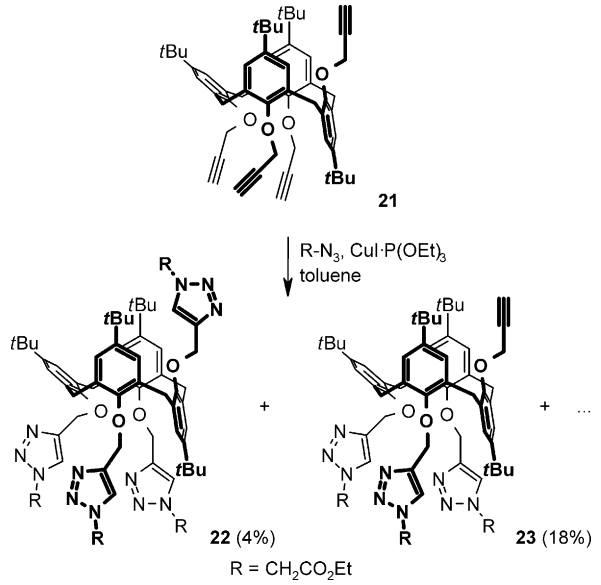
Partially propargylated calixarenes were also studied in equimolar CuAACs (see Table 2 for numerical data). Propargylated/propylated calixarenes **10**–**12** pre-organized (but not fixed) in cone conformations converted into multiple triazoles with a selectively governed by mutual arrangement of acetylene units in the substrate: CuAAC reactions of proximal bis(alkyne) **11** were nearly nonselective, whereas those of its distal isomer **10** showed a high selectivity or even specificity towards bis(triazoles) **15** and **16** (Scheme 2). As a perfect example, equimolar CuAAC reaction of partial cone (paco) calixarene **21** gave predominantly tris(triazole) **23** with co-directed adjacent propargyl groups involved in the reaction (but not the alternating one as approved by ROESY), and just a limited amount of tetrakis(triazole) **22** (Scheme 3).

In apolar toluene, when residual conformational motions in bis- and tris(propargylated) calixarenes **24** and **25** were suppressed by OH···OR bonding, extremely low yields of bis- and tris(triazoles) **26** and **27** were observed in CuAAC, even with an excess of benzylazide (Scheme 4).

In contrast, in an H-bond competitive $THF/H_2O$ mixture, calixarenes **26** and **27** turned out to be major or even exclusive products of equimolar CuAACs that resembled nicely the selec-

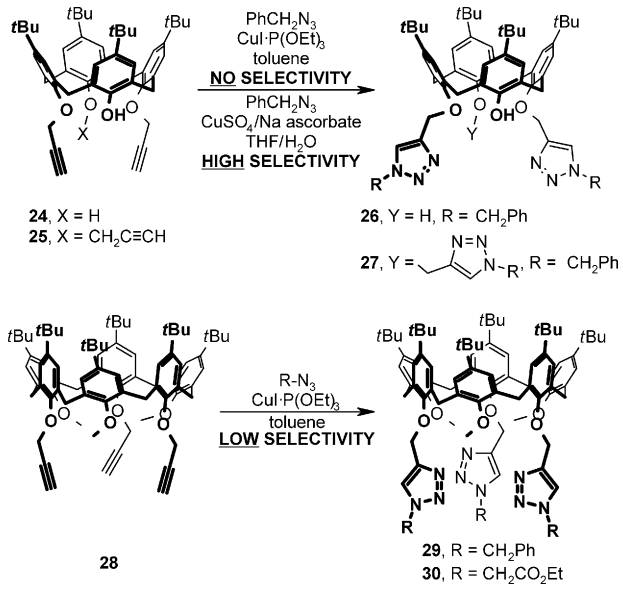



**Scheme 2.** CuAAC reactions of cone calixarenes **9**–**12** with nonsuppressed residual conformational mobility.




**Scheme 3.** Equimolar CuAAC reaction between **21** (paco) and ethyl-2-azidoacetate.

tive formation of related propylated/triazolated calixarenes **15** and **19** (Scheme 4) from **10** and **12**, respectively. Tris(propargylated) calix[6]arene **28** reacted well with an excess of azides but showed limited selectivity towards tris(triazoles) in equimolar CuAACs, which could arise from conformational restrictions due to through-cavity $CH_3\cdots\pi$-interactions,[6] and could not be avoided by changing the catalytic system.




**Scheme 4.** CuAAC reactions of cone calixarenes **24**, **25**, and **28** with suppressed residual conformational mobility.

The data presented cover all possible outcomes for $Cu^I$-catalyzed addition of limited equivalents of azides to multiple alkynes. Selectivity of the reaction towards multiple triazoles did appear or did not for structurally related, or even isomeric, multiple alkynes (e.g. **10** and **11**), and was not governed by simply the number of acetylene units within a substrate (e.g. tris(acetylene) **12** reacted less selectively than tetrakis(acetylene) **1** and bis(acetylene) **10**), but also by their mutual arrangement and flexibility.

Looking for a general rationalization for our results, we first explored theoretically an autocatalytic reason for the selectivity of CuAAC. The idea of intramolecular triazole-promoted lowering the activation barrier of CuAAC[7] (Figure 2) at additions of second and further azide molecules to multiple alkynes seemed attractive because of known rate-enhancing effects of tris(benzyltriazolylmethyl)amine (TBTA) and related compounds.[8]

Calculations applied for a TBTA-stabilized simple CuAAC reaction showed the activation profit of ~6 kcal mol$^{-1}$ provided by the ligand. Nevertheless, analogous intramolecular stabilization probed for diverse combinations of triazole and propargyl

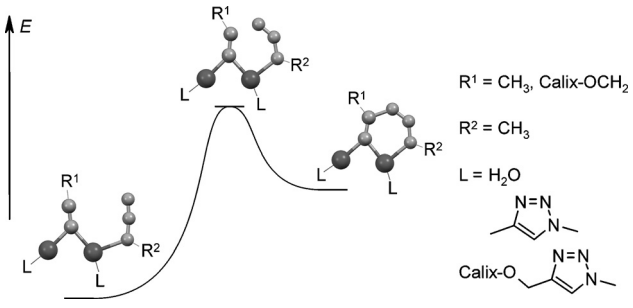



**Figure 2.** Rate-determining step of CuAAC and formation of a six-membered metallacycle.

units at the calixarene backbone gave the maximum profit of 1.5 kcal mol$^{-1}$ (see the Supporting Information for details). So the activation of this type could not drive the CuAAC selectivity towards multiple triazoles (though might contribute to it), and also gave no explanation for the differences in selectivity of isomeric substrates.

An efficient entrapment of copper ion(s) by a substrate or/and semiproducts might prevent the ions from leaving the reacting calixarene molecule unless all its triple bonds have been converted to triazoles. In such a case, the local concentration of $Cu^+$ might be increased and this, in turn, may lead to a rate enhancement for second and further CuAAC conversions of multiple alkynes, which could thus explain the observed selectivity. To check this proposal, equimolar reactions between **1** and azides were run at 1, 5, 10, 15, 20, 50, 100, 200 (two $Cu^+$ per calixarene molecule), 400, 800 (two $Cu^+$ per triple bond), and 1000 mol% of loaded catalyst (CuI·P(OEt)$_3$, toluene, 100 °C, identical calixarene and azide concentrations in all runs). In all the cases, the highly selective formation of tetra(triazoles) **2** and **3** was observed, so the reaction outcome (but not rates which were not monitored) was not dependent on $Cu^+$ concentration, and a strong copper binding by reacting components could not be responsible for the selective formation of multitriazoles.

Still, a direct study of copper complexation and reactivity of calixarenes **5**–**8**, which were supposed to be semiproducts at conversion of tetra(acetylene) **1** into tetra(triazole) **2**, gave interesting and unexpected results. While tetrakis(propargylated) calixarene **1** formed no complexes when treated with CuI·P(OEt)$_3$[9] at room temperature or at heating (no complexation-induced shifts were observed in $^1$H NMR spectra of [D$_8$]toluene solutions), all four mixed triazolated/propargylated calixarenes **5**–**8** formed internal copper complexes in which both the triazole and acetylene unit took part in the ion stabilization (as follows from complexation-induced shift values in $^1$H NMR spectra of 1:2 mixtures of the calixarenes and CuI·P(OEt)$_3$ in [D$_8$]toluene, see the Supporting Information). Notably, mono- and bis(triazolated) calixarenes **5**–**7** did form the complexes rapidly at room temperature (5–10 min), whereas much more time (up to 72 h) was needed to equilibrate the mixture of **8** and CuI·P(OEt)$_3$. The equilibrium was reached much faster ($<$ 2 h) at 100 °C, but resulted in a different spectral pattern that reflected a different structure of **8**·$(Cu^+)_n$.[10]

Calixarenes **5**–**8** were studied in equimolar CuAACs with benzylazide either with direct catalyst loading or with preliminary copper(I)-complex preparation (Table 3). The presence of several triazole units in a substrate did not stimulate the CuAAC reactivity of neighboring propargyl groups within the same molecule at room temperature with 15% $Cu^+$ loading. Even more unexpectedly, at elevated temperature and 15% $Cu^+$, compounds **5** and **6** with one or two adjacent triazole groups reacted significantly slower than respective propargylated/propylated calixarenes **9** and **11**, and showed no selectivity towards exhaustively triazolated adduct **2**. Notably, calixarene **5** was converted in low yield into proximal bis(triazole) **6**, but not to its distal isomer **7**. The latter was not detected in any reaction mixture that might result from its nonselective

**Table 3.** Calixarene products of equimolar CuAAC reactions between compounds **5**–**8** and benzylazide in toluene.[a]

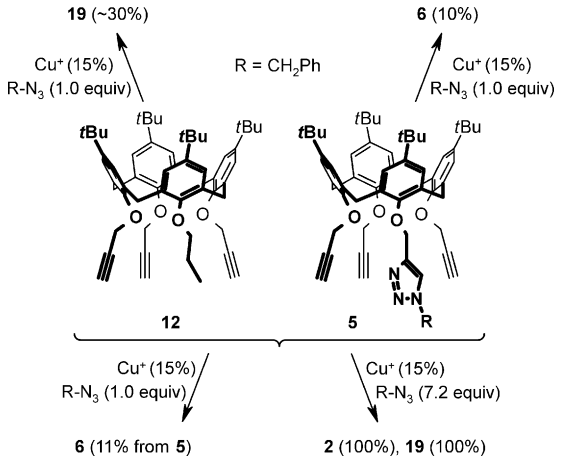
| Conditions | Substrate **5** | **6** | **7** | **8** |
|---|---|---|---|---|
| $Cu^+$ (15%), R-N$_3$, 24 h, rt | –[b] | –[b] | –[b] | –[b] |
| $Cu^+$ (15%), R-N$_3$, 7 h, 100 °C | **6** (10%) | **8** (12%)<br>**2** (6%) | **8** (26%)<br>**2** (37%) | **2** (100%) |
| 1) $Cu^+$ (200%), 2 h, 100 °C or 72 h, RT<br>2) R-N$_3$, 24 h, RT | –[b] | –[b] | –[b] | **2** (100%) |
| 1) $Cu^+$ (200%), 2 h, 100 °C<br>2) R-N$_3$, 8 h, 100 °C | **6** (20%)<br>**2** (25%) | **8** (29%)<br>**2** (34%) | | |

[a] CuI·P(OEt)$_3$ was used as the $Cu^+$ source, $c$(calixarene) = $c$(azide) = 0.01 M. [b] No calixarene products were detected by $^1$H NMR spectroscopy.

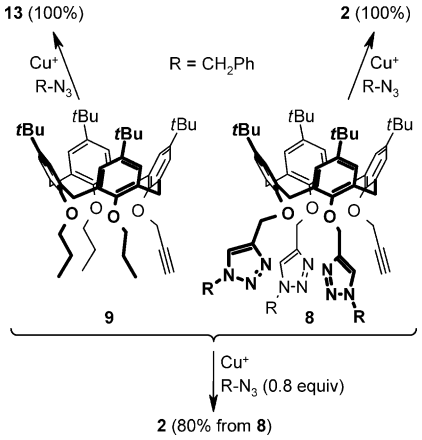
(compare with **10**) but complete conversion into calixarenes **8** and **2** under the CuAAC conditions. When copper complexes of **5** and **6** were first prepared using 200 mol% of CuI·P(OEt)$_3$, the room-temperature equimolar reactions with benzylazide failed, while heating resulted in complete conversion of the substrates into mixtures of **2** and calixarenes with a single reacted triple bond adjacent to a triazole unit (**5**→**6**, **6**→**8**). Similar behavior was observed for distally propargylated/triazolated calixarene **7** already with 15% of $Cu^+$. One could conclude tentatively, that tris(triazolated) calixarene **8** often observed in the reaction mixtures was less reactive in CuAAC than its formal precursors **5**–**7**, and even **1**. But that was not the case, as calixarene **8** reacted completely under CuAAC with one equivalent of $PhCH_2N_3$ at 15% of $Cu^+$ and was the only triazolated calixarene reactive at room temperature after preliminary copper complexation.

Several competitive reactions were run to analyze directly the difference in CuAAC reactivity of partially propargylated calixarenes containing and not containing triazole groups within the molecules. Surprisingly, from an equimolar mixture of tripropargylated calixarenes **5** and **12** the only triazolated one was involved in CuAAC reaction with one equivalent of $PhCH_2N_3$ and converted in low yield into calixarene **6**, whereas **12** returned unchanged, though was reactive under similar conditions in the absence of **5** (Scheme 5). This showed that copper complexation by **5** efficiently inactivated the metal ion for catalysis of both intramolecular and intermolecular CuAACs. When excess of the azide (weak copper-coordinating ligand) was added, the complex lability was increased and both **5** and **12** were completely converted into the corresponding exhaustively triazolated calixarenes **2** and **19**.

For the 'opposed' pair of compounds (**8** and **9**) each containing a single acetylene unit, a quite different reactivity in competitive CuAACs was observed (Scheme 6). With 15 or 200% of CuI·P(OEt)$_3$ loaded (including precursive copper complexation), limited $PhCH_2N_3$ did always react with triazolated/propargylated calixarene **8** but not with propylated analogue




**Scheme 5.** Independent (top) and competitive (bottom) CuAAC reactions of tripropargylated calixarenes **12** and **5**.




**Scheme 6.** Independent (top) and competitive (bottom) CuAAC reactions of monopropargylated calixarenes **9** and **8**.

**9**, and no traces of calixarene **13** were detected in reaction mixtures.

Though the outstanding behavior of **8** was not yet rationalized, the data on reactivity of calixarenes **5**–**7** showed clearly that (at least) one and two triazole units located near by a reacting triple bond within the same molecule did not assist the selective conversion of multiple acetylenes into multiple triazoles, and calixarenes **5**–**7** themselves and their copper complexes did not intermediate the CuAAC-transformation of **1** into **2**.

These observations proved that neither copper(I) activation nor its strong binding by triazole units within reacting molecules were responsible for the selectivity of CuAAC towards multiple triazoles.[11] Thus, an efficient copper-ion(s) transfer within the multifunctional substrate that moved the reacting center to a neighboring triple bond intramolecularly rather than intermolecularly, remained to be proposed as a main driving force for the observed CuAAC selectivity.[12]

To meet the experimental data on the invariance of multiple CuAAC outcomes from outer copper concentration, both copper(I) ions had to be transferred from an intramolecular source to the reacting triple bond. As a copper(I) triazolide[13] could release just a single copper ion, another intramolecular source for the second $Cu^+$ was required to exclude undesired copper recruitment from bulk solution. Within the catalytic cycle of CuAAC, formation of a dicopper triazolyl intermediate might be proposed at a six-membered metallacycle contraction step (a cheap step with ~1.6 kcal mol$^{-1}$ barrier as modeled for the simplest CuAAC between propyne and methylazide) before its fast conversion into copper triazolide at $Cu^+$ release (Figure 3).

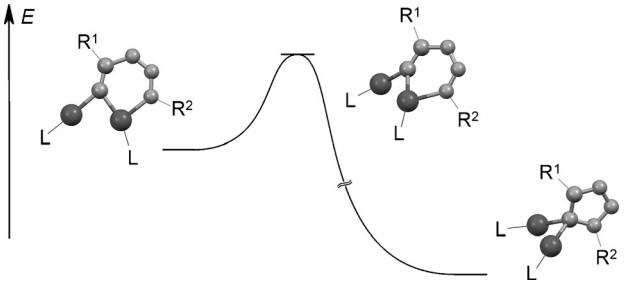



**Figure 3.** Ring-contraction step of CuAAC. Formation of proposed transfer-ready dicopper intermediate.

As no direct evidence for the formation and reactivity of dicopper intermediates of this type could be obtained, we applied quantum-chemical calculations to model possible intramolecular copper-transfer complexes to get an explanation for all the experimental data on the selectivity of CuAAC towards multiple triazoles.

First, dicopper triazolyl intermediates were modeled for prefinal CuAAC cycles at conversion of calixarene-based bis- and tris(alkynes) **10**–**12** into multiple triazoles ($CH_3N_3$ was used as the simplest azide, water molecules were used to complete the environment of copper ions where appropriate). Next, the yet nonreacted acetylene groups were forced to π-coordinate intramolecularly to one of two copper atoms of the dicopper triazolyl intermediates, and the resultant structures were subjected to full geometry optimization with no constraints.[14]

Though the starting geometries were created manually, in the energy-minimized complexes the triple-bond-to-copper π-coordination retained and, less expected, the second copper atoms were also 'moved' to a close proximity to alkyne units. Thereby, the dinuclear complexes presented in Figure 4 might be regarded as Cu-transfer ones. At the same time, the distance between the acetylene terminal carbon and the non-π-bound copper atom in the complex of **10** (shown in dot-lines in Figure 4a) was nearly 1.5 times shorter than that of **11** (Figure 4b). Reasonably, the distances reflected the different efficiency of dicopper transfer in the two complexes as far as they correlated well with the experimentally observed CuAAC behavior of **10** (showed perfect selectivity towards bis(triazoles)) and **11** (showed nearly no selectivity towards bis(triazoles)).

In general, the two structural features of starting oligoacetylene substrates seemed crucial for the formation of good CuAAC-transfer complexes in which the transfer of both copper atoms to a next reacting triple bond would not be interfered by an intermolecular copper exchange. First, the

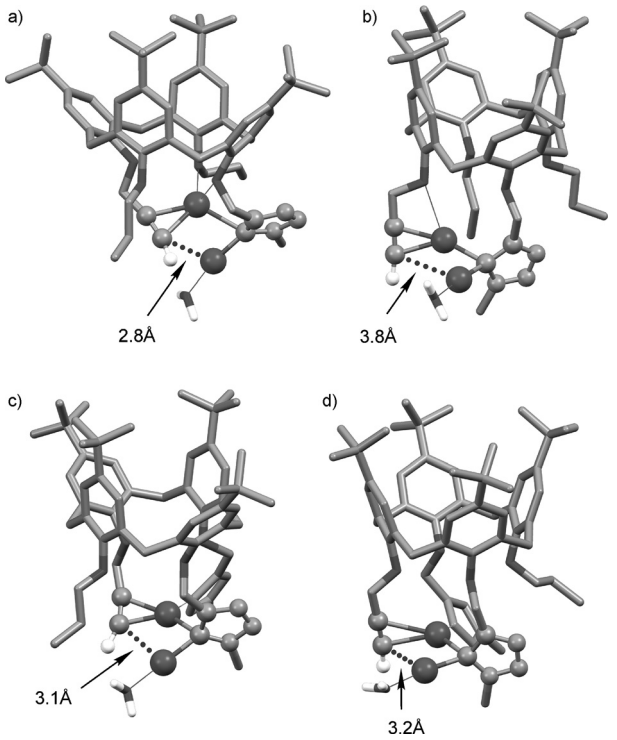



**Figure 4.** Energy-minimized structures and key Cu–C interatomic distances of dicopper transfer complexes at final CuAAC additions of methylazide to calixarenes a) **10**, b) **11**, c,d) **12** (at different order of triple-bonds reactions).

mutual arrangement and flexibility of the reacting acetylene units must allow the proper orientation of the dicopper triazolyl unit and the next reacting acetylene unit (e.g., H-bonds in **24**, **25**, unless broken, and $CH_3\cdots\pi$-interactions in **28** restricted the acetylene units' motions and allowed no efficient Cu-transfer to be developed). Second, additional donor atoms or/and groups must be presented (or formed) within the substrate molecule to assist the formation of tightened dicopper transfer complexes through additional Cu stabilization. For instance, in the complex of **11** (Figure 4b) the only ether oxygen atom of the reacting propargyl group provided an additional stabilization of the $\pi$-bound copper atom that gave no tightening of the overall structure and left the second copper atom at 3.8 Å distance from the targeted acetylene terminal carbon atom. In contrast, in modeled complexes of **10** and **12** (Figure 4a,c,d), the $\pi$-bound copper atom was additionally stabilized by several ether oxygen atoms from reacting and nonreacting calixarene units as well as by triazole groups (for **12**); such a multidentate copper coordination resulted in tightened transfer complexes with much shorter key Cu–acetylene distances of 2.8–3.2 Å, which allowed the intramolecular transfer of both copper atoms rather than an intermolecular one.[15]

The presented simple (and relatively fast) modeling and analysis of dicopper transfer complexes gave the desired explanation for all the experimental data on the highly selective (for **1**, **10**, **12**, **24**, **25**), and poorly or nonselective (for **11**, **21**, **28**) conversions of multipropargylated calixarenes into the corresponding multiple triazoles in equimolar reaction with azides under copper catalysis. It explained also the complete loss of the selectivity provided by the addition of a huge amount of a copper-targeted ligand (e.g., triethylamine); at lower concentration such an additional ligand could not easily reach the well-packed copper atom(s) within the transfer complexes or their precursors to compete even with weak Cu–O bonding, whereas at much higher concentrations (compared to that of the solvent) it could solvate all the components and turn the intermolecular copper exchange to prevail over the intramolecular copper transfer.

To verify the proposed methodology at a noncalixarene molecule, the copper-transfer complex of 1,6-heptadiyne **31** was modeled (Figure 5). This bis(alkyne) has been published to con-

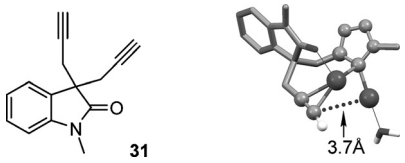



**Figure 5.** Energy-minimized structure and key Cu–C interatomic distance of dicopper transfer complexes at addition of second methylazide molecule to 1,6-heptadiyne **31**.

vert into bis(triazoles) in equimolar CuAAC with benzylazide predominantly (but not highly selectively) unless the reaction medium has been changed from $CH_2Cl_2$ to ketones or, better, to 2,5-hexandione.[3e] In the calculated structure, the key Cu–C distance of 3.7 Å was not very short but still could allow a moderately efficient intramolecular copper transfer in the complex tightened by a solvent-breakable coordination bond between the $\pi$-bound copper atom and amide oxygen atom.[16]

Though easily checkable (in the proposed simple version), the dicopper transfer must not be regarded as the only key process through all the cascade of CuAAC reactions, and other processes might contribute significantly to rates of deeper steps of multiple CuAACs. From them, the autocatalysis discussed above seemed the most plausible to rationalize the outstandingly high CuAAC reactivity of calixarene **8** containing a single triple bond surrounded by three adjacent triazole units.

## Conclusion

Being intrigued by the observed selective and condition-independent (except for certain reasonable cases) copper(I)-catalyzed conversion of cone tetrakis(propargyloxy)calix[4]arene into tetrakis(triazoles) when reacted with one equivalent of an azide, we performed a detailed study of equimolar CuAAC reactions between azides and a series of calixarenes with different number, mutual arrangement, and flexibility of propargyl groups attached to narrow rims. From the series of experiments we got a full range of multiple CuAAC outcomes including highly selective conversions of multiple acetylenes into multiple triazoles as well as those resulting in nearly statistical mixtures of triazolated/propargylated calixarenes. As reasons for the drastically different reactivity of the quite similar oligoacetylene molecules were not easily formulated, we studied ex-

perimentally and theoretically several most attractive rationalizations for the selectivity and its absence.

Neither autocatalytic rate enhancement of CuAAC nor one provided by $Cu^{+}$-entrapment were proved to control the selectivity of the multiple reactions. Still, the consistent rationalization for all the experimental data came from the modeling of an intramolecular transfer that moved not a single but both copper atoms from a just-formed triazole unit to an adjacent triple bond within the same oligoacetylene molecule. The model assumed the dicopper triazolyl intermediate as the copper source, and Cu–C-distance and the metal atoms hindrance as indicators for the efficiency of the dicopper intramolecular transfer process. Though the simplified modeling gave no exact parameters for a 'perfect' dicopper-transfer coordination environment, it worked fine at the comparative level and allowed us to arrange the oligoalkynes according to their ability to form the corresponding multiple triazoles in a cascade of CuAAC reactions.

The results presented are easily applicable for the analysis of the CuAAC reactivity of nearly all known types of multipropargylated calixarenes and related macrocycles widely used nowadays for constructing various molecular receptors/sensors. It is expected also that the experimental treatment of CuAAC activation through copper-to-multitriazole complexations along with the theoretical modeling of the intramolecular dicopper transfer made in this work will allow the analysis and, more importantly, the prediction of the selectivity of multiple CuAAC reactions of diverse oligoalkynes.

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**Keywords:** calixarenes · click chemistry · copper complexes · multiple alkynes · reaction mechanism

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[11] Still, these effects might assist deeper steps of multiple CuAAC (addition of the fourth azide in the case of **1**), which followed both from activation energy calculations and extended reactivity of **8**.

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