Tetranuclear and trinuclear copper(I) pyrazolates as catalysts in copper mediated azide-alkyne cycloadditions (CuAAC)

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Abstract.

Homoleptic, tetranuclear copper(I) pyrazolates {[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$, {[3-(CF$_3$)-5-(*t*-Bu)Pz]Cu}$_4$, and {[4-Br-3,5-(*i*-Pr)$_2$Pz]Cu}$_4$ are excellent stand-alone catalysts for azide-alkyne cycloaddition reactions (CuAAC). This work demonstrates that a range of pyrazolates, including those with electron donating and electron-withdrawing groups to sterically demanding substituents on the pyrazolyl backbones, can serve as effective ligand supports on tetranuclear copper catalysts. However, in contrast to the tetramers and also highly fluorinated {[3,5-(CF$_3$)$_2$Pz]Cu}$_3$, trinuclear copper(I) complexes such as {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ and {[3-(CF$_3$)-5-(CH$_3$)Pz]Cu}$_3$ supported by relatively electron rich pyrazolates display poor catalytic activity in CuAAC. The behavior and degree of aggregation of several of these copper(I) pyrazolates in solution were examined using vapor pressure osmometry. Copper(I) complexes such as {[3,5-(CF$_3$)$_2$Pz]Cu}$_3$ and {[3-(CF$_3$)-5-(*t*-Bu)Pz]Cu}$_4$ with electron withdrawing pyrazolates were found to break up in solution to different degrees producing smaller aggregates while those such as {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ and {[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$ with electron rich pyrazolates remain intact. In addition, kinetic experiments were performed to understand the unusual activity of tetranuclear copper(I) pyrazolate systems.

Introduction

Triazoles represent an important class of heterocyclic ring structures due to their extensive biological and therapeutic applications.[1] Two possible isomers exist of triazoles, namely 1,2,3-triazoles and 1,2,4-triazoles. The 1,2,3-triazoles are of particular interest between these isomers because of their stability towards oxidative and reductive conditions and hydrolysis.[2, 3] They are also used as linkers in various bioconjugates as a replacement for canonical nucleobases, whose clinical use is often inhibited by toxicity and resistance issues.[4] Additionally, the 1,4-disubstituted version of 1,2,3-triazoles can serve as good models for bioactive amides due to its strong dipole moment, planarity, hydrogen bond donor/acceptor characters, and other features.

Due to the importance and wide utility, there has been much effort focused on the efficient synthesis of 1,2,3-triazoles. One of the earliest and most effective methods is the Huisgen cycloaddition where an azide and terminal alkyne are combined and heated.[5] However, this method yields a mixture of 1,4- and 1,5-disubstituted isomers, Figure 1. Furthermore, the need for elevated temperature and low yields makes Huisgen cycloaddition less than ideal for wider synthetic purposes.[6] Later, Sharpless and Meldal improved on this reaction and used a copper catalyst to obtain only the 1,4-substituted isomer, Figure 1.[7, 8] Using this copper-catalyzed azide–alkyne cycloaddition (CuAAC) route, many 1,4-disubstituted 1,2,3-triazoles could be synthesized in high yields, under milder conditions, and with easily removable solvents and byproducts.[7, 9-12] However, these reactions often require the use of a reducing agent such as sodium ascorbate to reduce

the copper source (e.g., commonly utilized copper(II) sulfate pentahydrate)[12] to the catalytically active copper(I) species.

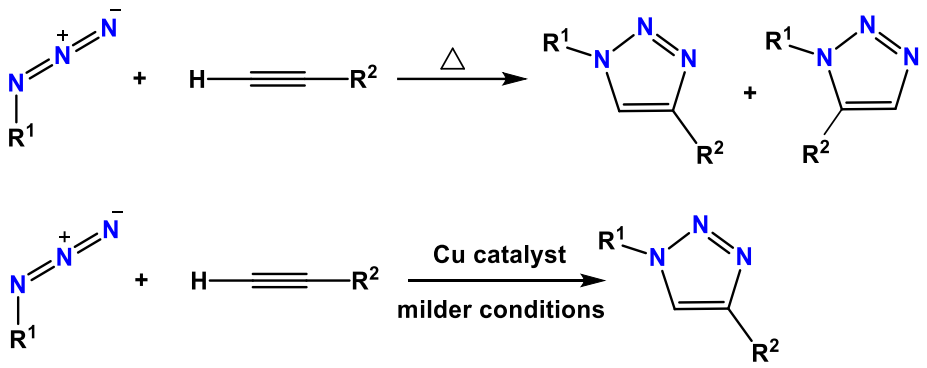

Figure 1. Huisgen cycloaddition (top) leading to the 1,4- and 1,5-regioisomers of 1,2,3-triazoles; Sharpless and Meldal, copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction affording the 1,4-regioisomer of 1,2,3-triazole (bottom)

More recently our group[13] and Titov, Larionov, and co-workers[14] found that the need for a reducing agent could be eliminated by using highly fluorinated, trinuclear copper(I) pyrazolates $\{[3,5\text{-}(CF_3)_2Pz]Cu\}_3$ (Figure 2, **1**)[15] and $\{[3,5\text{-}(3,5\text{-}(CF_3)_2Ph)_2Pz]Cu\}_3$ as catalysts.[16] These reactions are quite attractive as they are mediated by standalone copper pyrazolates, which serve as a bifunctional catalytic system providing the copper source and Bronsted base, operate at room temperature and afford only the 1,4-isomer in essentially quantitative yields.

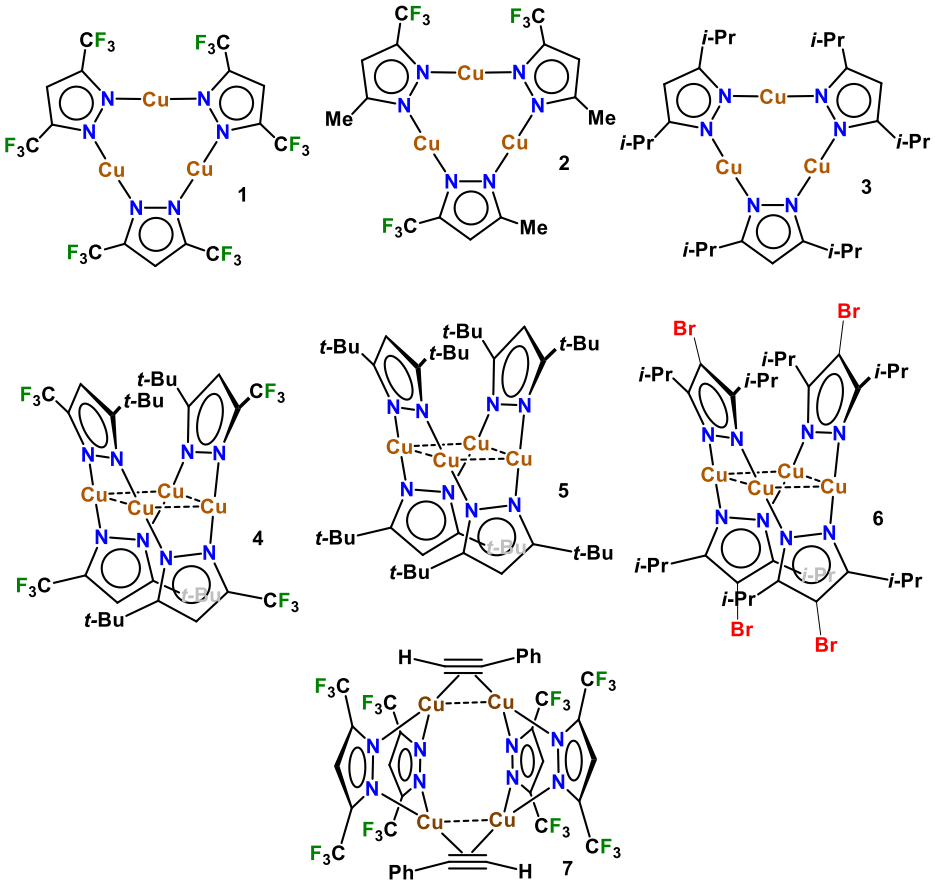

Figure 2. Structure of trinuclear and tetranuclear copper(I) pyrazolate complexes (**1** – **6**) and one of the proposed reaction intermediates (**7**) in copper pyrazolate mediated CuAAC reactions involving {[3,5-$(CF_3)_2$Pz]Cu}$_3$ (**1**).

There are a variety of copper(I) pyrazolates with different pyrazolyl ring substituents in the literature.[17-20] Among these, highly fluorinated copper(I) pyrazolates are relatively less common and under-utilized than their non-fluorinated analogs.[16, 21-28] Encouraged by the catalytic ability of these trinuclear copper(I) pyrazolates , we set out to investigate if other varieties such as copper trimers and tetramers supported by pyrazolates with less fluorine content were similarly effective in mediating the azide-alkyne cycloaddition chemistry.

Specifically, we investigated the catalytic ability of the trinuclear copper(I) pyrazolates {[3-(CF_3)-5-(CH_3)Pz]Cu}$_3$ (**2**) and {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**) relative to that of {[3,5-(CF_3)$_2$Pz]Cu}$_3$ (**1**), and the tetranuclear copper(I) pyrazolates {[3-(CF_3)-5-(*t*-Bu)Pz]Cu}$_4$ (**4**), {[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$ (**5**), and {[4-Br-3,5-(*i*-Pr)$_2$Pz]Cu}$_4$ (**6**), and uncovered some unique reactivity of tetranuclear species in CuAAC chemistry which does not depend much on the nature of substituents on the supporting pyrazolate (in contrast to the trinuclear analogs).[21, 29, 30]

Results and Discussion

Catalysis

As noted above, the highly fluorinated {[3,5-(CF_3)$_2$Pz]Cu}$_3$ (**1**) catalyzes azide-alkyne cycloadditions very effectively (Table 1, entries 1-4), affording ≥ 99% conversion at room temperature using only 1 mol percent of catalyst.[13, 16, 31] We found that the less fluorinated {[3-(CF_3)-5-(CH_3)Pz]Cu}$_3$ (**2**) and non-fluorinated {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**) catalyze the reaction between 1-octyne or phenylacetylene with *p*-tolylazide, under similar conditions, but only very sluggishly, giving disappointingly low conversion to product (entries 5-8). Although the percent conversion slightly improved when benzyl azide was used due to increased azide reactivity (entries 9-10),[32-34] they remained significantly lower than those observed with highly fluorinated catalysts. When using the sterically hindered 1-adamantyl azide, the percent conversion was zero at room temperature and only slightly increased when the reaction was heated in chloroform to 60°C.

Table 1. Azide-alkyne cycloadditions with trinuclear copper(I) catalysts. Reactions were performed at room temperature in dichloromethane using 1 mol% catalyst loading unless otherwise noted. *Reaction done in chloroform at 60℃.

Entry	Catalyst	Reaction Time	Alkyne	Azide	% Conversion	Ref
1	{[3,5-$(CF_3)_2$Pz]Cu}$_3$ (**1**)	12 hrs	1-octyne	*p*-tolylazide	99	[13]
2			phenylacetylene	*p*-tolylazide	99	[13]
3		4 hrs	1-octyne	benzylazide	> 99	[14]
4			phenylacetylene	benzylazide	> 99	[14]
5	{[3-(CF_3)-5-(CH_3)Pz]Cu}$_3$ (**2**)	12 hrs	1-octyne	*p*-tolylazide	12	This work
6			phenylacetylene	*p*-tolylazide	6	This work
7	{[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**)	12 hrs	1-octyne	*p*-tolylazide	13	This work
8			phenylacetylene	*p*-tolylazide	12	This work
9			1-octyne	benzylazide	15	This work
10			phenylacetylene	benzylazide	40	This work
11			phenylacetylene	1-adamantyl azide	0	This work
12			phenylacetylene	1-adamantyl azide	2*	This work
13		36 hrs	phenylacetylene	1-adamantyl azide	6*	This work

The {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**) and {[3,5-$(CF_3)_2$Pz]Cu}$_3$ (**1**) have sterically similar (the CF_3 group is considered as sterically similar to the *iso*-propyl group)[35, 36] but electronically very different[37] substituents. Therefore, the sluggish catalytic activity of {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**) may not be a simple result of steric effects. On the other hand, the pyrazolate ligands bearing *iso*-propyl and methyl groups are significantly better donors than weakly donating [3,5-$(CF_3)_2$Pz]$^-$. For example, copper(I) carbonyl complexes supported by tris(pyrazolyl)borates [HB(3,5-(*i*-Pr)$_2$Pz)$_3$]$^-$, [HB(3-(CF_3)-5-(Me)Pz)$_3$]$^-$, and [HB(3,5-$(CF_3)_2$Pz)$_3$]$^-$ show their CO stretching frequencies at 2056, 2107,

and 2137 cm^{-1}, respectively.[38-40] This could result in relatively strong Cu-N interactions and less electrophilic copper sites in {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**) and {[3-(CF_3)-5-(CH_3)Pz]Cu}$_3$ (**2**).

Recently, Larionov, Titov and coworkers reported a mechanism for the {[3,5-(CF_3)$_2$Pz]Cu}$_3$ (**1**) mediated CuAAC reaction in which tetranuclear copper(I) pyrazolate-alkyne complexes are believed to play a major role as intermediates in the catalytic cycle (see also ESI Figure S17).[31] They proposed that {[3,5-(CF_3)$_2$Pz]Cu}$_3$ (**1**) interacts with the triple bond of the alkyne via η^2-coordination to form the catalytically active "bis-butterfly" tetranuclear complex Cu$_4$(pyrazolate)$_4$(RC≡CH)$_2$ (Figure 2, **7**). Indeed, it is possible to break up the trinuclear {[3,5-(CF_3)$_2$Pz]Cu}$_3$ (**1**) with alkynes and form such tetranuclear intermediates, further supporting this proposed mechanism.[13, 41] This trimer can also form dimers with similar or even weaker donors such as CO.[42-44] Thus, it is likely that the poor catalytic ability of {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**) and {[3-(CF_3)-5-(CH_3)Pz]Cu}$_3$ (**2**) may be a result of stronger Cu-N bonds making the structure reorganization to access the tetranuclear intermediate[31] (or even a more common dinuclear copper intermediate complex)[45-49] formation more difficult through interactions with weak alkyne nucleophiles.

After observing disappointing outcomes from these less fluorinated and non-fluorinated copper(I) trimers, we turned our attention to the related tetranuclear species. Trinuclear copper(I) pyrazolates have a planar geometry (see **1**-**3**). Tetranuclear copper(I) pyrazolate complexes (e.g., **4-6**), in contrast, feature saddle-shaped structures.[19, 30, 50] Furthermore, trinuclear species tend to aggregate as a result of multiple inter-trimer cuprophilic Cu•••Cu interactions,[20, 21] whereas the tetramers usually remain as discrete

entities in the solid.[30, 50] Therefore, we anticipated we might observe different reactivity in tetranuclear copper(I) pyrazolates.

Table 2. Azide alkyne cycloaddition with copper(I) tetranuclear catalysts. Reactions were performed in dichloromethane, at room temperature, with 1 mol% catalyst loading unless otherwise noted. *Reaction done in chloroform at 60℃.

Entry	Catalyst	Reaction Time	Alkyne	Azide	% Conversion
14	{[3-(CF_3)-5-(*t*-Bu)Pz]Cu}$_4$ (**4**)	12 hrs	1-octyne	*p*-tolylazide	97
15			phenylacetylene	*p*-tolylazide	77
16			1-octyne	benzylazide	>99
17			phenylacetylene	benzylazide	>99
18	{[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$ (**5**)	12 hrs	1-octyne	*p*-tolylazide	98
19			phenylacetylene	*p*-tolylazide	63
20			1-octyne	benzylazide	>99
21			phenylacetylene	benzylazide	>99
22			phenylacetylene	1-adamantyl azide	4
23			phenylacetylene	1-adamantyl azide	28*
24		36 hrs	phenylacetylene	1-adamantyl azide	60*
25	{[4-Br-3,5-(*i*-Pr)$_2$Pz]Cu}$_4$ (**6**)	12 hrs	1-octyne	benzylazide	>99
26			phenylacetylene	benzylazide	>99

The activity of three different tetranuclear copper(I) pyrazolates, {[3-(CF_3)-5-(*t*-Bu)Pz]Cu}$_4$ (**4**), {[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$ (**5**), and {[4-Br-3,5-(*i*-Pr)$_2$Pz]Cu}$_4$ (**6**) in CuAAC were investigated (Figure 2). These catalysts were tested under identical conditions to previous trials using dichloromethane as the solvent at room temperature for 12 hours. Contrary to the trend found in trinuclear copper complexes, both electron deficient and electron rich tetranuclear copper pyrazolates were excellent catalysts (Table 2). It was observed

that the percent conversion improved to >99% (entries 16-17, 20-21, 25-26) when using the relatively more reactive benzylazide instead of *p*-tolylazide.[32-34] The percent conversion is somewhat lower when reacting phenylacetylene with *p*-tolylazide (entries 15, 19). This can be attributed to the increased steric bulk of the phenyl ring on the alkyne making coordination to the copper center of the catalysts more difficult. However, even with this increase in steric strain, the percent conversion remains much higher than those observed with electron rich copper(I) trimers. In contrast to trinuclear $\{[3,5\text{-}(i\text{-Pr})_2Pz]Cu\}_3$ (**3**), tetranuclear $\{[3,5\text{-}(t\text{-Bu})_2Pz]Cu\}_4$ (**5**) is also effective in the CuAAC involving highly sterically hindered 1-adamantyl azide, albeit at a higher temperature of 60°C, providing the desired triazole.

Vapor Pressure Osmometry

The excellent catalytic ability of all three tetranuclear copper(I) pyrazolates prompted a further investigation into the solution behavior of these complexes using Vapor Pressure Osmometry (VPO), Table 3. The electron rich complex $\{[3,5\text{-}(t\text{-Bu})_2Pz]Cu\}_4$ (**5**) was investigated at a concentration range of 4-12 mmol/kg and found to remain unchanged when dissolved in chloroform. For example, the experimentally observed molecular weight of 985 g/mol corresponded closely to the actual molecular weight of the complex, 970 g/mol indicating that this molecule exists as a tetramer in solution.

The solution behavior of $\{[3\text{-}(CF_3)\text{-}5\text{-}(t\text{-Bu})Pz]Cu\}_4$ (**4**) containing a relatively more electron deficient pyrazolate was also examined. In the concentration range 4-10 mmol/kg, the molecular weight was found to be 900 g/mol. Previous NMR studies of this

complex showed an equilibrium between two species, likely a trimer and tetramer in approximately a 1:1.52 ratio at low concentrations.[30] This corresponds to a calculated average weight of 917 g/mol and agrees well with VPO study results, indicating the presence of a mixture of trinuclear and tetranuclear copper pyrazolates at approximately the same ratio.

Table 3. Experimentally determined average molecular weights of the solution species of copper pyrazolate catalysts using Vapor Pressure Osmometry (VPO).

Catalyst	Concentration range (mmol/kg)	Actual MW (g/mol)	Observed MW (g/mol)
{[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$ (**5**)	4-12	971	985
{[3-(CF$_3$)-5-(*t*-Bu)Pz]Cu}$_4$ (**4**)	4-10	1019	900
{[4-Br-3,5-(*i*-Pr)$_2$Pz]Cu}$_4$ (**6**)	4-12	1174	1058
{[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**)	4-10	644	685
{[3,5-(CF$_3$)$_2$Pz]Cu}$_3$ (**1**)	4-10	800	529

The {[4-Br-3,5-(*i*-Pr)$_2$Pz]Cu}$_4$ (**6**) also displayed similar solution behavior at low concentrations. Within the concentration range 4-12 mmol/kg, the VPO gave a molecular weight of 1058 g/mol. NMR data indicated the presence of two species at approximately 1:1.5 ratio.[30] A mixture of trinuclear and tetranuclear species at that ratio indeed corresponds to a calculated average molecular weight of 1057 g/mol, which is in excellent agreement with the VPO results.

We have also examined the solution behavior of trinuclear copper complexes {[3,5-(CF$_3$)$_2$Pz]Cu}$_3$ (**1**) and {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**) (Table 3). The fluorinated, trinuclear copper catalyst {[3,5-(CF$_3$)$_2$Pz]Cu}$_3$ (**1**) at a concentration range of 4-10 mmol/kg, produced a VPO

based molecular weight of 529 g/mol. This weight closely corresponds to the molecular weight of a dinuclear copper complex, 533 g/mol. These results align well with work previously done by our group involving the silver(I) complexes.[51] For example, {[3,5-$(CF_3)_2$Pz]Ag}$_3$ displayed different degrees of aggregation, including dimers at different concentrations.

Finally, the solution behavior of {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**) was also investigated in a concentration range of 4-10 mmol/kg. The observed molecular weight of 685 g/mol closely corresponds to the actual molecular weight of a trinuclear species, 644 g/mol, indicating that it essentially exists as a trimer in solution. It is also interesting to note that {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ exists as a dimer of trimer with two short cuprophilic (Cu•••Cu) inter-trimer interactions in the solid state.[21] In fact, the observed molecular weight does match more closely to a mixture consisting of 13:1 trimer to dimer of trimer (which represent an average molecular weight of 689 g/mol). This work shows that the majority of inter-trimer Cu•••Cu contacts of this molecule do not survive in solution under the tested conditions. One could argue that tetramers in combination with trimers could also lead to similar average molecular weights (e.g., 8:2 mixture of {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ and "{[3,5-(*i*-Pr)$_2$Pz]Cu}$_4$"). Although that is a remote possibility, ^{1}H NMR data of {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**) (in contrast to **4** and **6**) do not show signs of such a mixture.

Overall, VPO data indicate that the fluorinated copper trimer {[3,5-$(CF_3)_2$Pz]Cu}$_3$ (**1**) and the relatively weakly donating pyrazolate supported tetramers {[3-(CF_3)-5-(*t*-Bu)Pz]Cu}$_4$ (**4**) and {[4-Br-3,5-(*i*-Pr)$_2$Pz]Cu}$_4$ (**6**) exist with their smaller aggregates in $CHCl_3$ solution. They have relatively weaker Cu-N interactions and more Lewis acidic copper sites relative

to {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**) and {[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$ (**5**), and could breakup more easily to smaller copper pyrazolate entities aided by solvents. Their ability to dissociate and structural flexibility in solution may contribute to the excellent catalytic ability displayed by these molecules in CuACC as the formation of reaction intermediates and establishment of equilibria with substrates, alkynes and organic azides, are easier. These observations also explain the notably low catalytic activity of {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**) since it does not break-up easily in $CHCl_3$, making the formation of catalytically active intermediates (e.g., copper acetylides or alkyne complexes) by interactions with CuACC substrates more difficult.

However, strong Cu-N interactions and the apparent structural integrity do not hinder the ability of {[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$ (**5**) to facilitate the azide–alkyne cycloaddition chemistry as evident from the catalytic data. Trinuclear copper(I) pyrazolate, {[3,5-(CF$_3$)$_2$Pz]Cu}$_3$ (**1**) mediated CuAAC believed to proceed via a key tetranuclear reaction intermediate.[31] Perhaps having preassembled tetranuclear species as in {[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$ (**5**) facilitate the formation of such catalytic intermediate quite easily, because, only minimum structural rearrangement is required (see **5** and **7**, Figure 2). Furthermore, analysis of solid state X-ray structural data show that tetramers like {[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$ (**5**), {[4-Br-3,5-(*i*-Pr)$_2$Pz]Cu}$_4$ (**6**) and {[3-(CF$_3$)-5-(*t*-Bu)Pz]Cu}$_4$ (**4**) have somewhat closer intra-trimer Cu•••Cu contacts (shortest Cu•••Cu separation of 2.96, 2.90 and 2.91 Å, respectively) than the corresponding separation observed in trimers like {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (3.19 Å).[52] In addition, Cu_4 framework in these molecules can adopt shapes ranging from nearly square to rhombus (e.g., Cu••Cu••Cu angles of {[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$ (**5**), {[4-Br-3,5-(*i*-

Pr)$_2$Pz]Cu}$_4$ (**6**) and {[3-(CF$_3$)-5-(*t*-Bu)Pz]Cu}$_4$ (**4**) span 69.5°- 109.3°, 66.1°-113.4°, and 79.8°-99.1°), while Cu$_3$ core in systems like {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**) is essentially equilateral triangles. Such flexible and closely held copper sites in Cu$_4$ systems could facilitate the CuAAC even if catalytic moiety involves two or more cooperating copper sites, such as the commonly reported bimetallic σ,π-alkynyl reaction intermediate and bridging acetylides.[12, 49, 53, 54]

Kinetics

Mechanistic and kinetic studies of copper catalyzed azide-alkyne cycloadditions have shown that alkyne (and to a lesser degree the organoazide)[55] coordination is an important earlier step in the catalytic cycle.[31, 56, 57] In addition, broken orders, as well as zero and first order rate dependance with respect to azide and alkyne under various conditions have been observed.[31, 46, 58] The catalytic intermediate based on copper could be mono, di, tri, tetra or poly-nuclear although most reports suggest that the catalytic process benefits from the participation of at least two copper centers.[31, 45, 49, 53, 58-61]

We also wanted to get additional insights to the mechanism by investigating the reaction kinetics mediated by copper(I) pyrazolates. The reactions of 1-octyne and benzylazide with tetranuclear catalysts {[3-(CF$_3$)-5-(*t*-Bu)Pz]Cu}$_4$ (**4**) and {[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$ (**5**), and trinuclear catalysts {[3,5-(CF$_3$)$_2$Pz]Cu}$_3$ (**1**) and {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**) were compared and monitored to investigate the rate of reaction of copper tetramers in comparison to copper trimers. An aliquot of each reaction mixture was analyzed via NMR and the percent conversion was calculated for each hour, Figure 3.

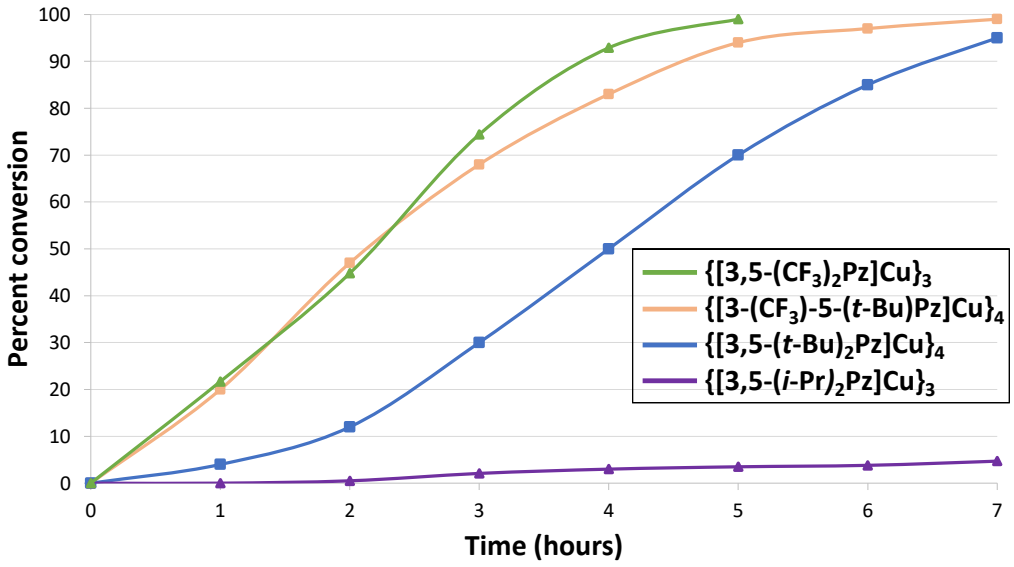

Figure 3. Percent conversion vs. time for copper(I) pyrazolate mediated CuAAC reaction at 20 °C with 1-octyne and benzylazide.

Results show that among the molecules tested at room temperature, **1** and **4** are the most active, closely followed by **5**, while **3** is essentially inactive. For example, the fluorinated trimer, $\{[3,5\text{-}(CF_3)_2Pz]Cu\}_3$ (**1**), afforded >99% conversion to product after five hours, while the non-fluorinated trimer, $\{[3,5\text{-}(i\text{-}Pr)_2Pz]Cu\}_3$ (**3**), gave only 5% conversion even after seven hours. This large difference in conversion may also be attributed to the ability to dissociate in solution, as indicated by vapor pressure osmometry data, and the facile formation of transition states. It is commonly accepted that the π–complex formation of copper(I) centers with alkyne substrate is a key initial step, in order to form the related σ-complex through deprotonation.[53] Generation of coordinatively unsaturated metal sites through ligand dissociation or disaggregation would facilitate

such reactions. Furthermore, recent work suggests that weaker Lewis base supporting ligands are beneficial for the rate of CuAAC reaction, perhaps through lowering of the activation barrier for the protonolysis triazolide of by the terminal alkyne.[58]

When comparing the rate of product formation with tetramer catalysts, it was found that the more electron rich tetramer, {[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$ (**5**) initially produced the desired 1,2,3-triazole somewhat slowly. However, in contrast to the electron-rich trinuclear species, {[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$ (**5**) catalyst still afforded the product in high (95%) conversion after 7 hours, suggesting the pyrazolate basicity plays a much smaller but clear role (see Figure 3) in tetranuclear copper complexes. Additionally, this shows again the apparent lack of dissociation in solution of this tetramer does not affect its catalytic efficacy.

Table 4. Overview of the conditions for the order determination of the various components of the reaction between 1-octyne and benzylazide using [{3,5-(*t*-Bu)$_2$Pz}Cu]$_4$ (**5**), {[3-(CF$_3$)-5-(*t*-Bu)Pz]Cu}$_4$ (**4**), or {[3,5-(CF$_3$)$_2$Pz]Cu}$_3$ (**1**).

Entry	Component	1-octyne (equiv)	Benzylazide (equiv)	Cu cat.	Cu complex (equiv)	Rate order
1	Cu$_4$ (**5**)	1	1	**5**	0.01 – 0.05	1.05
2	Cu$_4$ (**4**)	1	1	**4**	0.01 – 0.05	0.87
3	Cu$_3$ (**1**)	1	1	**1**	0.01 – 0.05	1.63
4	1-octyne	1 – 5	1	**5**	0.01	0.95
5	1-octyne	20 – 40	1	**5**	0.01	0.68
6	1-octyne	1-5	40	**5**	0.01	1.09
7	BnN$_3$	1	1 – 5	**5**	0.01	0.79
8	BnN$_3$	1	20 – 40	**5**	0.01	0.02
9	BnN$_3$	40	1-5	**5**	0.01	0.74

To further probe the kinetics of tetranuclear copper(I) pyrazolate catalysts, experiments were performed on the reaction of 1-octyne and benzylazide with {[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$ (**5**). Aliquots of the reaction mixture were taken at intervals and analyzed by ^{1}H NMR to calculate percent conversion to the desired 1,2,3-triazole. Reactions were carried out with different equivalents of each substrate while maintaining other components at constant concentration. An approximately first-order dependency on copper(I) tetramer concentration was observed, when it was maintained at catalytic levels (<5 mol%, Table 4, entry 1). The reaction order for another copper(I) tetramer, [{3-(CF$_3$)-5-(*t*-Bu)Pz}Cu]$_4$ (**4**), was also observed to be approximately first-order, see ESI for details. This may indicate that an undissociated copper(I) tetramers are involved in the rate determining step.[58] The observed first order dependency on copper tetramers also supports the hypothesis that a preassembled tetranuclear structure could contribute to the excellent catalytic ability of these copper(I) tetramers. When using the trinuclear copper(I) pyrazolate {[3,5-(CF$_3$)$_2$Pz]Cu}$_3$ (**1**) an approximately second order dependency is observed, see ESI for details. Based on the data from vapor pressure osmometry presented in this work, {[3,5-(CF$_3$)$_2$Pz]Cu}$_3$ (**1**) exists as a dinuclear species in solution. This second order dependency seen by our work and others[31] on this molecule could be attributed to two dimers involved in the rate determining step to form the required tetranuclear reaction intermediate. Most mechanistic studies on CuAAC imply the participation of two copper sites in the catalytically active intermediate,[45, 47] which is also possible from a Cu$_4$ system.

At lower equivalents, an approximately first order dependance with respect to 1-octyne was observed and a broken order of 0.75 was observed for benzylazide. This observed first order dependency suggests one alkyne is involved in the rate determining step. The observed broken order for azide likely indicates a pre-equilibrium before the rate determining step. At high equivalents a broken order of 0.68 is observed for 1-octyne and an approximately zero order dependance on benzylazide is observed. This may suggest that at higher equivalents other side reactions involving alkyne are more prevalent and a saturation of azide is reached.[56]

Conclusions

In summary, unlike the highly fluorinated, electron deficient trinuclear copper(I) pyrazolate complexes, the electron rich analogs such as {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$ (**3**) containing strongly donating pyrazolates, are less effective in CuAAC. This may be a consequence of stronger Cu-pyrazolate interactions making the breakup of planar nine-membered framework by alkynes, and the formation of catalytically active intermediates, more difficult. Tetranuclear copper(I) pyrazolates however, were found to be excellent catalysts even with electron donating and bulkier substituents on the pyrazolate ligands, which is probably due to the ease of attaining the possible tetranuclear reaction intermediates via the pre-formed tetranuclear catalyst precursors. Also, saddle-shaped tetramers have somewhat closely situated copper sites and a flexible Cu_4 framework relative to planar copper trimers, which may be an important feature that can facilitate reactions that involve multi-nuclear catalytic centers. The VPO data indicate the generation of smaller

copper pyrazolate aggregates in solutions relative to their solid-state versions, when supported by relatively weakly donating pyrazolates. The activity of the non-fluorinated tetranuclear {[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$ (**5**) complex is particularly noteworthy as it shows the ability to use more widely available, non-fluorinated pyrazolates in catalyst design for CuAAC chemistry.

Experimental

General Procedure for azide-alkyne cycloaddition

Benzyl azide, p-tolyl azide, 1-adamantyl azide, {[3,5-(*i*-Pr)$_2$Pz]Cu}$_3$, {[3-(CF$_3$)-5-(CH$_3$)Pz]Cu}$_3$, {[3,5-(*t*-Bu)$_2$Pz]Cu}$_4$, {[3-(CF$_3$)-5-(*t*-Bu)Pz]Cu}$_4$, and {[4-Br-3,5-(*i*-Pr)$_2$Pz]Cu}$_4$ were prepared via reported routes.[21, 29, 30, 62-64] All other reagents were obtained from commercial sources and used as received. For all reactions, 1 mol percent (0.0075 mmol) of the catalyst was added to a vial containing 100 mg (0.75 mmol) of azide, 0.75 mmol of alkyne, and 5 mL dried dichloromethane. The resulting solutions were stirred at room temperature, 20 °C, for 12 hours. Approximately 0.1 mL of the crude mixtures were taken in an NMR tube and $CDCl_3$ was added. Samples were analyzed using NMR and acquired at 25 °C on a JEOL Eclipse 500 spectrometer (^{1}H, 500.16 MHz; ^{13}C, 125.78 MHz), in $CDCl_3$, to check for the presence of the desired triazole. The percent conversion was calculated by comparing the peaks of the desired 1,2,3-triazole with the peaks of the starting azide. No by-products were observed.

Vapor Pressure Osmometry

Molecular weight data were obtained using a KNAUER Vapor Pressure Osmometer K-7000 with EuroOsmo 7000 software. Commercially available chloroform, without further purification, was used as the solvent and the instrument was operated at 30 °C, under air. Full experimental details for vapor pressure osmometry procedures and calculations can be found in the supplementary information.

General procedure for kinetic reactions

In an analogous method to the general procedure for azide-alkyne cycloaddition reactions the desired amount of azide (0.75, 1.5, 3.75, 15.0, or 30.0 mmol) and alkyne (0.75, 1.5, 3.75, 15.0, or 30.0 mmol) were combined and the appropriate volume of dried dichloromethane was added to reach a total volume of 5 mL. To this solution the desired mol percent of copper catalyst was added (1, 2, or 5 mol percent). The vials were closed, and the resulting solutions were stirred in a room temperature, 16 °C, water bath. Approximately 0.1 mL of dichloromethane solution was taken in an NMR tube at each time interval and $CDCl_3$ was added. Proton NMR (JEOL Eclipse 500 spectrometer (^1H, 500.16 MHz) was used to determine percent conversion by comparing product peak integration to peak integration of the reaction component kept constant.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

‡ Experimental details, additional figures and tables are provided in ESI.

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TOC figure and text

Tetranuclear copper complexes of widely available, electron-donating hydrocarbon group bearing pyrazolates are very competent catalysts for the azide-alkyne cycloadditions. Related trinuclear species supported by electron-rich pyrazolates are notably less effective mediators of this reaction under the same conditions.