Heterogeneous Catalysis

Triazolyl-Based Molecular Gels as Ligands for Autocatalytic 'Click' Reactions

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Abstract: The catalytic performance of triazolyl-based molecular gels was investigated in the Huisgen 1,3-dipolar cycloaddition of alkynes and azides. Low-molecular-weight gelators derived from L-valine were synthesized and functionalized with a triazole fragment. The resultant compounds formed gels either with or without copper, in a variety of

Introduction

The very useful and green concept that defines a click reaction involves the binding of two molecular building blocks in a facile, selective, high-yield reaction under mild, water-tolerant conditions with little or no generation of by-products.^[1,2] Of all the reactions that achieve a "click status", the Huisgen 1,3-dipolar cycloaddition of alkynes and azides is regarded as the premier example of a click reaction.^[3] However, due to the high activation energy, this cycloaddition is often very slow even at high temperatures, producing mixtures of regioisomers.^[4] The discovery that Cu^I catalysts could dramatically increase the reaction rate up to 107 times and improve regioselectivity, affording exclusively 1,4-regioisomers, underlined the importance of this reaction, enabling unique applications in synthesis, medicinal chemistry and materials science.^[5,6] The most common catalysts used in azide-alkyne cycloadditions are copper(II)/copper(I) salts, such as CuSO₄, CuI, CuBr, Cu(OAc), or copper(I) complexes such as [Cu(MeCN)₄]PF₆ or [Cu(MeCN)₄]OTf, in the presence of the reducing agent sodium ascorbate.^[7] Although these catalysts often provide reasonable reaction conditions, the thermodynamic instability of Cul, which usually results in easy oxidation to Cu^{II} and/or to disproportion to Cu(0) and Cu^{II}, drove research into copper ligands that are able to stabilize and modulate the catalytic activity of the Cu^I center.^[8] Recent investigations suggest that the complexes of polytriazole ligands coordinated to Cu¹ have the ability to catalyze the same reaction from which they are derived.^[9] The mild coordination ability of the triazole functionality allow the stabilization of Cu^I oxidation state and prevents the occurrence of disproportion reactions.^[10] Examples of efficient polysolvents of different polarity. The gelators coordinated Cu¹ and exhibited a high catalytic activity in the gel phase for the model reaction between phenylacetylene and benzylazide. Additionally, the gels were able to participate in autocatalytic synthesis and the influence of small structural changes on their performance was observed.

triazole ligands include the tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine (TBTA) or its analogue bearing bulky tert-butyl groups, 2-[4-{(bis[(1-tert-butyl-1H-1,2,3-triazol-4-yl)methyl]amino)methyl}-1H-1,2,3-triazol-1-yl]ethyl hydrogen sulfate (BTTES), which is described as one of the most efficient ligands for the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reported so far.^[11] TBTA has also been investigated as a heterogeneous catalyst for CuAAC after being anchored onto a NovaSyn® TG amino resin.^[9] Polymer solid supports containing Amberlist or terpyridine, silica-supported Cu¹ catalysts, metal organic frameworks (MOF), or copper on charcoal (Cu/C) are other examples tested in heterogeneous CuAAC.^[12] Although a wide range of organic and inorganic solid catalytic supports have been investigated, the application of supramolecular gels as heterogeneous catalytic media for the Huisgen 1,3-dipolar cycloaddition of alkynes and azides is scarce.

Supramolecular gels are nanostructured soft materials that result from the self-assembly of low-molecular-weight molecules, and are usually defined as gelators.^[13–16] After a primary self-organization of the gelator in one-dimensional aggregates by noncovalent interactions, these 1D objects further assemble into fibrilar architectures that, after physical crosslinking, form a 3D network that percolates the solvent. If the gelator is functionalized with a catalytic fragment, this assembly will result in an expanded supramolecular material with built-in catalytic sites. This organization of multiple catalytic features, such as multivalent interactions, neighboring effects and cooperativity.^[17–19]

Several studies mentioning supramolecular gels as active media for catalysis have been reported. Between them, the use of Pd^{II} metallogels containing pyridine-based ligands as catalysts for the aerobic oxidation of benzoyl alcohol to benzalde-hyde, as well as the application of bolaamphiphilic L-proline derived low-molecular-weight gelators as basic catalysts for the Henry nitro-aldol reaction, are two clear examples of success regarding the use of catalytic gels both in metallo- and or

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ganocatalysis, respectively.^[20,21] In the field of click reactions, Liu and co-workers have reported an hydrogelator that self-assembled into helical nanotubes in the presence of Cu^{II}, leading to a chiral catalyst that was active for a Diels–Alder reaction, whereas Gao and co-workers reported the application of chiral binaphthylbispyridine-based copper(I) metallogels as catalysts for the Huisgen 1,3-dipolar cycloaddition.^[22,23] Herein, we report the design, synthesis, and catalytic performance of lowmolecular-weight gelators derived from amino acid L-valine, functionalized with triazole fragments as a supramolecular mimic of the multivalent features of covalent polytriazole ligands such as TBTA. The catalytic activity of the synthesized compounds on the Huisgen 1,3-dipolar cycloaddition of alkynes and azides, as well as their application in their autocatalytic synthesis have also been investigated.

Results and Discussion

The L-valine phenyltriazolyl (PhTzVal_n) family of compounds have been synthesized from simple peptide coupling of the activated ester of bromobutyric acid to several alkylidendiamines,^[24] followed by substitution of the terminal Br with NaN₃, to give the bisazide derivatives, respectively (N₃Val_nN₃, see Figure S1). The final step consisted of a Huisgen 1,3-dipolar cycloaddition with commercially available phenylacetylene, leading to PhTzVal_n products (Figure 1).



Figure 1. Structure of two families of gelators: N₃Val_nN₃ and PhTzVal_n.

Self-assembly studies

The triazolyl functionalized compounds $PhTzVal_n$ were able to form self-sustainable gels in alcohols and water (Table 1). This ability is related to the amphiphilic character of the molecules.

Table 1. Gelation experiments with compounds $PhTzVal_n^{[a]}$						
Solvent	$PhTzVal_3$	$PhTzVal_6$	$PhTzVal_8$			
ethanol	G	G	G			
H₂O	G	I	G			
H ₂ O/tBuOH (1:1)	G	G	G			
2-propanol	G	SP	G			
methanol	G	G	G			
[a] I: Insoluble, G: Gel, SP: Swollen precipitate, c=11 mм.						

On the other hand, Cu^{I} -PhTzVal_n metallogels were prepared by heating the copper salt [$Cu(MeCN)_4$]PF₆ together with the PhTzVal_n gelators in a 1:2 ratio, until complete dissolution, followed by sonication (Figure 2).



Figure 2. Scheme of the Cu¹ coordination to the gel network and macroscopic image of the metallogel. The presence of dinuclear Cu¹ species cannot be discarded.^[25]

All the PhTzVal_n family of compounds were able to form strong gels in methanol either with or without the presence of copper, meaning that metal coordination was not the essential driving force for the self-assembly of the compounds. However, the presence of copper caused a slight decrease in the minimum gelation concentration (MGC) of the gelators PhTzVal₆ and PhTzVal₈, which means that it could positively contribute to the gelation of these compounds (Table 2). This fact suggests that there could be a difference within the family related to the length of the central alkylidene fragment.

Table 2. Minimum gelation concentrations of the native gelators and of the metallogels in methanol. ^[a]					
Gelator	Concentration [mM] Native	Concentration [mM] Native Metallogel			
PhTzVal ₃	4.7	4.9			
PhTzVal ₆	4.9	3.9			
PhTzVal ₈	7.4	6.5			

[a] Typical procedure: The gelator PhTzVal_n was heated in a 4 mL screwcapped vial in the presence of solvent (500 μ L), until complete dissolution. The resultant hot solution was then sonicated for 20 s, forming a gel which was subsequently allowed to age for 20 min at RT. The minimum gel concentration was defined as the minimum concentration of PhTzVal_n required to form a gel that withstands gravity when turned upside down.

To assess whether the metal–ligand interaction influenced the final structural arrangement of the hybrid metal-organic gel networks, wide angle X-ray powder diffraction (WAXD) was performed on the native and hybrid xerogels (Figure 3). The diffractograms revealed that the gelator PhTzVal₃ exhibits a completely amorphous pattern, whereas those having a longer carbon chain self-assembled in a more ordered structure, with low-angle peaks at 21.8 Å (PhTzVal₆) and 26.4 Å (PhTzVal₆) assignable to the length of partially extended molecules, as described before for related analogues.^[26] However, in the presence of the metal, sharp diffraction peaks appeared together with the broad signals of gelators that can be assigned



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Figure 3. XRD analysis of gels A) PhTzVal₃, B) PhTzVal₆, C) PhTzVal₈, and of D) Cu¹-PhTzVal₃, E) Cu¹-PhTzVal₆, and F) Cu¹-PhTzVal₈ metallogels.

to a periodic disposition of copper atoms coordinated to the network. It should be noted that these peaks do not correspond to free copper salt $Cu(MeCN)_4PF_6$ (see Figure S16). As mentioned before, the influence of the metal on the self-assembly of the gelator molecules was revealed for shorter carbon chain length gelator PhTzVal₃ (Figure 3 D).

Although the presence of the metal is not the main driving force for gelation, as observed for other reported metallogels,^[22-23, 27-30] the metal–ligand interactions have some influence on the self-assembly of the gelator. It has already been reported that metal–ligand interactions could influence the gelation, resulting in multifunctional metallogels with new interesting properties that could not be achieved in organogels, such as optical, catalytic or magnetic properties.^[31-33]

The native gels and the corresponding metallogels were also studied by circular dichroism spectroscopy to gain deeper insight into the structural arrangement of the resultant self-assembled materials (Figure 4). All the gels exhibited either a positive or negative dichroism signal, evidencing that the chiral information present at the molecular scale was transferred to gel-phase assemblies (Figure 4A). The spectra of the native gels having a longer carbon chain length PhTzVal₆ and PhTzVal₈ are characterized by the presence of two strong negative bands at 207 and 197 nm, respectively, suggesting similar supramolecular arrangement. The gel with the smallest carbon chain length, PhTzVal₃, seems to self-assemble in a different conformation, presenting two negative bands at 224 and 207 nm together with a positive lobe at 190 nm, which is characteristic of a helical type conformation.^[34] Such kind of helical arrangement has already been observed for L-valine derived bolaamphiphilic gelators functionalized with proline fragments and having a three-carbon spacer.^[35] These results suggest that the gelator with the shortest carbon chain self-assembles in a different supramolecular packaging structure in comparison to those having longer carbon chains, which is in accordance with the WAXD studies on the native gelators (Figure 3). This distinct supramolecular organization arises by the preferred formation of hydrogen bonds between different hydrogendonor and hydrogen-acceptor atoms on two consecutive column-packed molecules, leading to different energetically stable molecular packaging models depending on the carbon spacer length.^[36] Furthermore, the appearance of a negative band followed by a positive band in the CD spectrum of PhTzVal₃ may suggest that the molecule aggregates in an anticlockwise orientation.^[37]

The presence of the metal did not have a pronounced influence on the final conformation of the gels, except for the gelator PhTzVal₃, for which a blueshift of the band at 224 to 217 nm followed by a decrease in intensity was observed (Figure 4B). A change in the signal of the positive band at 195 nm was also detected. This suggests that the copper influences the supramolecular packing of the gelator, probably by interfering in the intermolecular interactions between the several nanobjects during the self-assembly process, providing a different orientation of the initial helical structure. In the metallogel Cu¹-PhTzVal₆, it seems that the addition of copper(I) induced a helical-type arrangement, suggested by the appearance of a positive band around 195 nm (Figure 4C), whereas for the metallogel Cu¹-PhTzVal₈ no significant differences were detected (Figure 4D).

The obtained metallogels were also analyzed by TEM, revealing some differences in the morphology of the fibers depending on the carbon chain length (Figure 5). Whereas it was possible to observe a highly crosslinked network of fibers having

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Figure 4. A) Superposition of the circular dichroism spectra of native gels with variable chain length [PhTzVal₃ (bottom line), PhTzVal₆ (middle line), PhTzVal₈ (top line)], and B) superposition of CD spectra of the native gels PhTzVal₃, C) PhTzVal₆, and D) PhTzVal₈ with the corresponding metallogels (thick lines).



Figure 5. TEM analysis of metallogels A) Cu¹-PhTzVal₃, B) Cu¹-PhTzVal₆, C) Cu¹-PhTzVal₈. D and E) STEM analysis of metallogels formed by the compound PhTzVal₆, and F) the corresponding EDS elemental analysis.

Chem. Eur. J. 2016, 22, 8676-8684

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10–12 nm width in the gel having the shortest carbon chain length (Figure 5 A), the metallogels with longer carbon chain length presented smaller fibers, suggesting some twists in the case of the gel Cu¹-PhTzVal₈ (Figure 5 C). The presence of copper in the gel network allowed us to characterize these structures by STEM without staining. The white contrast of the fibers (Figure 5 D–E) constitutes further evidence for the successful formation of a hybrid organic–inorganic network. Energy-dispersive X-ray spectroscopy (EDS) analysis performed on the fibers revealed the presence of Cu together with C and O, confirming the successful coordination of the copper to the gel (Figure 5 F). The distribution of copper along the fibers constitutes clear evidence of the proximity of the catalytic sites in self-assembled systems.

Catalysis

The fact that compounds PhTzVal_n were able to form hydrogels allowed the possibility of gelating them in a system of solvents in which the 'click' reaction generally occurs. This feature could also allow these gelators to be applied in click reactions occurring in biological environments. The catalytic activity of the hydrogel PhTzVal₃ in the model reaction between phenylacety-lene and benzylazide was first investigated (Figure 6).



Figure 6. Huisgen 1,3-dipolar cycloaddition between phenylacetylene and benzylazide.

The reaction was performed in a 1:1 $tBuOH/H_2O$ mixture in the presence of Cu^I-PhTzVal_n catalyst (1 mol%), in air and at room temperature, for periods of 3 to 8 h. The obtained results are summarized in Table 3.

The metallogels successfully catalyzed Huisgen 1,3-dipolar cycloaddition between phenylacetylene and benzylazide, achieving 50–60% conversion in the first 8 h, which is substan-

Table 3. Stud H ₂ O.	dy of the catalytic ad	ctivity of comp	oound PhTzVal₃	in <i>t</i> BuOH/	
Entry	Catalyst	Conversion [%] ^[a] 3 h 6 h 8 h			
1 2 3	Cu ^l -PhTzVal₃ Cu ^l -PhTzVal ₆ Cu ^l -PhTzVal ₈	21 24 19	44 55 43	63 62 53	

[a] Typical procedure: The reactants in stoichiometric proportion (0.24 mmol) were mixed and added directly at the top of the metallogel catalyst (1 mol%) composed of the gelator PhTzVal_n (4.8×10⁻² mmol) and the copper salt [Cu(MeCN)₄]PF₆ (2.4×10⁻² mmol). At the end of the experiment, the products were directly extracted with CDCl₃ (700 µL). The organic phase was dried over anhydrous MgSO₄ and the conversion was determined by ¹H NMR spectroscopic analysis.

tially higher than that reported for the copper salt [Cu-(MeCN)₄]PF₆ during 72 h (4% conversion).^[9,10] The successful coordination of the Cu¹ to the relatively labile triazole functionality of the gelators, allowing the formation of hemilabile copper complexes during the catalytic cycle, may be origin of this good catalytic activity. The presence of this kind of complex facilitates the cooperativity between the copper centers of the intermediate Cu¹-acetylide complex, leading to an acceleration of the reaction rate and preventing the formation of Cu¹-acetylide aggregates.^[18] The use of a metallogel as a heterogeneous catalyst facilitates the process of purification of the final product, allowing the separation of the catalyst simply by filtration, which could be attractive from an industrial point of view.

Although it is known that the presence of the triazole fragment positively influences the reaction rate, the 3D supramolecular arrangement of the hybrid metal-organic gel may also have an important role in its catalytic activity. The self-assembly of 1D aggregates in large fibers provides the formation of a network with a large surface area in contact with solution. Thus, the self-assembly of the gelators functionalized with the triazole fragment results in the formation of an expanded catalytic network in which the higher proximity of the catalytic sites favors the occurrence of cooperative interactions, providing enhanced catalytic properties. As a result, Cu^I ions are distributed along the surface of the fibers (Figure 5D), providing a high availability of the catalytic sites to the reactants. Additionally, the convergence of triazolyl ligands from different fibrils may also contribute to a better coordination of copper(I), which tends to adopt a tetrahedral coordination geometry (Figure 2).^[27]

Given that gelators PhTzVal_n are synthesized through a click reaction (see the Supporting Information) we envisioned the use of Cu^I-PhTzVal_n metallogels as catalysts for the ligand synthesis starting from the azide precursors (autocatalysis) (Figure 7). As observed for the PhTzVal_n family, the bis-azide precursors N₃Val_nN₃ (Figure 1) also form gels in methanol, either in the presence or absence of copper. The obtained N₃Val_nN₃ gels were transparent and colorless but acquired



Figure 7. Huisgen 1,3-dipolar cycloaddition between N_3 Val_n N_3 and phenylacetylene.

Chem. Eur. J. 2016, 22, 8676 – 8684

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Figure 8. Kinetics of the Huisgen 1,3-dipolar cycloaddition between $N_3Val_nN_3$ and phenylacetylene in the presence of 5 mol% [Cu(MeCN)₄]PF₆ (\blacklozenge), 10 mol% [Cu(MeCN)₄]PF₆ (\blacklozenge), and in the presence of 10 mol% metallogels (\blacktriangle) A) Cu^LPhTzVal₃, B) Cu^LPhTzVal₆, and C) Cu^LPhTzVal₈, during the first 6 h of reaction.

a green color when gelated in the presence of the copper salt $[{\rm Cu}({\rm MeCN})_4]{\rm PF}_6.$

Thus, the autocatalytic ability of the metallogels Cu^{I} -PhTzVal_n in the reaction represented in Figure 7 was investigated. For this experiment, the reactant N₃Val_nN₃, the gelator PhTzVal_n and the copper salt [Cu(MeCN)₄]PF₆ in a ratio of 10:1:1 were gelled together in a 4 mL screw-capped vial containing methanol as solvent, and phenylacetylene was subsequently added on the top of the two-component gel. In this case, a slight excess of copper salt was used, attending to the possibility that some of the N₃Val_nN₃ gel could also participate in the copper coordination. The aim of the autocatalysis experiment was to establish whether there was an increase in the rate of the reaction due to the continuous production of catalyst.

As shown in Figure 8, all the metallogels exhibited autocatalytic activity, being capable of catalyzing their own synthesis. In the absence of an initial amount of Cu^{l} -PhTzVal_n metallogel, an induction time with little or no conversion was observed, corresponding to the lapse required to obtain a minimum amount of active coordinated copper by slow catalysis of uncoordinated [Cu(MeCN)₄]PF₆. This effect is particularly evident in Figure 8 A.

It is remarkable that both reactant and catalyst are in the gel phase. Therefore, it could be proposed that initially the reaction could take place in those azide groups at the vicinity of the Cu-Triazole (Tz) catalytic sites. However, as the reaction continues, the number of azide groups near the catalytic centers would decrease and we could expect a decrease in the catalytic activity with time. This is not the case, and the reaction proceeds until completion; the time required to achieve quantitative conversion was 48 h for the gelator PhTzVal₃ and 14 h for gelators with longer carbon chain PhTzVal₆ and PhTzVal₈ (see Figure S18). These results are not surprising taking into consideration the well-known dynamic behavior of molecular gels that involve a reversible disassembly-reassembly process as well as the reported lability of Tz-Cu complexes, which could allow the translocation of Cu ions throughout the fibrillar network.^{5,10} These dynamic processes would be responsible for the relocation of reactive N₃Val_nN₃ components close to the catalytic centers and/or the translocation of metal ions towards PhTzVal_n molecules close to the azide analogues. A brief comparison between the results obtained in Figure 8 suggest a positive influence of the carbon chain length on the catalytic performance of the metallogelators, with the gels PhTzVal₆ and PhTzVal₈ exhibiting a higher catalytic activity than the corresponding analogue with a three-carbon chain, PhTzVal₃. Any direct relationship between the observed catalytic activity and the amount of copper coordinated to the PhTzVal_n gels or to the initial PhTzVal_n/N₃Val_nN₃ two-component gel mixtures was completely discarded, because the amount of copper coordinated to them was found by ICP-MS analysis to be more than 99% in all cases. Furthermore, the formation of the Cu^I-PhTzVal₈ complex was confirmed by mass spectrometry analysis, whereby a peak corresponding to the mass of the gelator coordinating one copper was observed $(m/z [M+H]^+)$ 831.4097) (see Figure S17). To better understand whether the difference observed in the catalytic performance of these materials is related to a different supramolecular arrangement of the gel network, the mixtures were analysed by WAXD at different stages of the reaction. For comparison, bisazide metallogels Cu^I-N₃Val_nN₃ were also studied (Figure 9). The obtained diffractograms suggest that the initial mixtures having a lower periodicity (low short-range order) have a better catalytic performance. These characteristics are readily observed in the initial hybrid mixtures Cu^I-PhTzVal₆-N₃Val₆N₃ (Figure 9F) and Cu^I-PhTzVal₈-N₃VaL₈N₃ (Figure 9J), resulting in a higher catalytic activity of these compounds. These results are quite reasonable when we consider that a high interplanar distance between the several gelator layers facilitates the formation of the phenyltriazole fragment at the end of the reactant N₃Val_nN₃ layers, because of reduced steric hindrance. The expansion of the structure resulting from the formation of the final product is clearly observed in the multicomponent gel Cul-PhTzVal3-N₃Val₃N₃ after 20 h (Figure 9C) and 48 h reaction (Figure 9D) and for Cu^I-PhTzVal₈–N₃Val₈N₃ after 20 h reaction (Figure 9L). In the multicomponent gel Cu^I-PhTzVal₆-N₃Val₆N₃, this expansion was observed to a lesser extent, because of the high similarity between the supramolecular arrangement of the initial mixture (Figure 9F) and that of the final product (Figure 8H), although the peak around 21 Å becomes more defined along the reac-

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Figure 9. WAXD performed for the metallogels A) $Cu^{L}N_{3}Val_{3}N_{3}$, E) $Cu^{L}N_{3}Val_{6}N_{3}$, I) $Cu^{L}N_{3}Val_{5}N_{3}$ and for the multicomponent metallogels B–D) Cu^{L} -PhTzVal₃–N $_{3}Val_{3}N_{3}$, F–H) $Cu^{L}PhTzVal_{6}-N_{3}Val_{6}N_{3}$, and J–L) $Cu^{L}PhTzVal_{8}-N_{3}Val_{8}N_{3}$ mixtures after 0 (B, F, J), 4 (G, K), 20 (C, H, L), and (D) 48 h of reaction.

tion time (Figure 9G and H). The lower catalytic activity of the gelator Cu^{l} -PhTzVal₃ may also be related to a possible coordination of Cu^{l} to $N_{3}Val_{3}N_{3}$. The most intense peak present in the diffractogram of Cu^{l} -N₃Val₃N₃ appears at 3.9 Å (Figure 9A), which is well in accordance with that belonging to the metallogelators Cu^{l} -PhTzVal_n (Figure 3D–F). On the other hand, this peak is absent in the diffractograms corresponding to Cu^{l} -N₃Val₆N₃ and Cu^{l} -N₃Val₈N₃ (Figure 9E and I, respectively). It is

well known that gelators having a central three-carbon spacer self-assemble in a different way to bolaamphiphilic gelators having a longer spacer.^[38] This particular self-assembly behavior may cause additional competition for the coordination of the copper when the gelators PhTzVal₃ and N₃Val₃N₃ are heated to-gether with the copper salt, causing a depletion in the catalytic performance of Cul-PhTzVal₃. In all the diffractograms, it is also important to highlight the appearance of a peak around



4.5 Å, which, according to previously reported xerogels, can be ascribed to the periodicity in the direction of the hydrogenbonding array, thus suggesting a self-assembly of the gelator molecules in a vertical direction (z-axis) both in the azides and in the final product.^[39] XRD analysis performed on the hybrid multicomponent metallogel mixtures at 50% conversion (Figure 9C, G, and K) revealed that the structural rearrangement of the system may lead to a slowdown of the reaction, achieving a kind of plateau at this stage (Figure 8). By looking at Figure 9C, G and K, it is observed that at this point of the reaction, the structure of the hybrid multicomponent gel mixtures resembles more that of the final product (Figure 9D, H, and L), although 50% of reactant is still present. This structural rearrangement acts as an inflection point on the catalytic activity of these compounds; after this plateau, the kinetics increases again towards the completion of the reaction (Figure S18).

The morphology of the hybrid multicomponent organic-inorganic gels was also analyzed at different stages of the reaction by TEM (Figure 10). Figure 10A shows that the gel net-



Figure 10. TEM analysis of A) Cu¹-N₃Val₆N₃, B) Cu¹-PhTzVal₆-N₃Val₆N₃, and C) Cu¹-PhTzVal₆-N₃Val₆N₃ after 4 h of reaction, and D) Cu¹-PhTzVal₆-N₃Val₆N₃ after 20 h of reaction.

work of $Cu^LN_3Val_6N_3$ is composed of long, thin fibers exhibiting a flower-like morphology. The presence of these fibers together with some smaller fibers belonging to the catalyst was observed in Figure 10B and C. In Figure 10C, some dark nuclei can also be observed that probably belong to the final product, considering their high similarity to the fibers present at the end of the reaction (Figure 10D), which, in turn, have similar dimensions to the fibers represented in Figure 5B, belonging to the pure metallogel. Although the synthesis of molecular gels using click chemistry is nowadays a common research interest, the uniqueness of the present study lies in the judicious utilization of click chemistry within a metallogel system for the autocatalytic synthesis of the gelator.

Conclusion

L-Valine-derived low-molecular-weight gelators functionalized with triazole units were successfully synthesized. The gelators coordinated copper, building hybrid organic-inorganic gels capable of catalyzing the Huisgen 1,3-dipolar cycloaddition of alkynes and azides. The obtained metallogelators exhibited a high copper loading capacity and can be regarded as efficient heterogeneous catalysts. It was also found that the supramolecular arrangement of these materials has a great influence on their catalytic performance. In contrast to other reported metallogels applied as catalysts for the same reaction, the metal was coordinated once the gel was formed, which allows for the loading of other metals with affinity to triazole ligands without disturbing their capacity for gelation.^[23] Furthermore, the formation of the metallogel in water or water/alcohol mixtures allow the study of the reaction under biological conditions. The fact that these gelators are derived from amino acids constitutes an additional advantage for the use of these compounds as catalytic systems for bioconjugation click reactions, regarding their biodegradability and biocompatibility.

Experimental Section

Structural and morphological characterization

¹H and ¹³C NMR spectra measurements were recorded with a Varian Mercury 300 MHz spectrometer at 30 °C. Powder X-ray diffraction (XRD) was performed at RT with a Bruker D4 Endeavor Xray powder diffractometer by using Cu-K α radiation. A sample of the dried gel was placed on a sample holder and data were collected for 2 θ values between 2 and 40° with a step size of 0.03° and a time step of 10 s. For transmission electron microscopy (TEM), a small portion of the gel was placed on a nickel grid coated with carbon and allowed to dry on air. Images were recorded with a JEOL 2100 microscope.

Synthesis

Detailed synthetic procedures and characterization are found in the Supporting Information.

Gelation procedure

The gelator PhTzVal_n (5.5×10^{-3} mmol) was heated in a 4 mL screwcapped vial in the presence of solvent (500 µL), until complete dissolution. The resultant hot solution was then sonicated for 20 s, forming a gel which was subsequently allowed to age for 20 min at RT. The formation of a gel was confirmed by the inversion tube test, whereby the resultant solid-like soft material did not flow upon inversion of the flask. The formation of metallogels was achieved by heating together the gelator and the copper salt Cu(MeCN)₄PF₆ in a 2:1 molar ratio.

For the formation of the two-component metallogels, $N_3 Val_n N_3$ (2.7×10⁻² mmol) was heated together with 10 mol% catalyst, composed of the gelator PhTzVal_n (2.7×10⁻³ mmol) and an equimolar amount of the copper salt [Cu(MeCN)₄]PF₆, in MeOH (300 µL) until complete dissolution. Gelation was achieved as described above. Yellow translucent materials that retained the solvent upon inversion of the vial were obtained.

Chem. Eur. J. 2016, 22, 8676–8684

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Catalysis experiments

Catalysis experiments were performed at RT without stirring. All the reactions were performed for periods of 3, 6, and 8 h by using a 1:1 H₂O/tBuOH mixture as solvent media. Briefly, the reactants in stoichiometric proportion were mixed and added directly at the top of the metallogel catalyst (1 mol%) composed of the gelator PhTzVal_n (4.8×10^{-2} mmol) and the copper salt [Cu(MeCN)₄]PF₆ (2.4×10^{-2} mmol). At the end of the experiment, the products were directly extracted with CDCl₃ (700 µL). The organic phase was dried over anhydrous MgSO₄ and the conversion was determined by ¹H NMR spectroscopic analysis.

Autocatalysis experiments

Catalysis experiments were performed at RT and without stirring. Phenylacetylene (3 equiv) dissolved in MeOH (158 μ L) was added on the top of the two-component catalytic metallogel, composed of N₃Val_nN₃ and 10 mol% Cu¹-PhTzVal_n, and the resultant mixture was allowed to react for 1 to 48 h. The reaction was stopped by adding 35wt% H₂O₂ (20 μ L) to promote the oxidation and consequent precipitation of copper. The resultant mixture was dried under nitrogen flow. For the control assays, the reactant was added on the top of N₃Val_nN₃ gelated in the presence of [Cu-(MeCN)₄]PF₆ (10 mol%), and allowed to react under similar conditions. The conversion was determined by ¹H NMR spectroscopic analysis in [D₆]DMSO.

Quantification of coordinated copper

The catalytic metallogel was broken up with a spatula and the surrounding solution was collected with a syringe and filtered through a 0.22 μ m filter. The metallogel was further washed with acetonitrile (2×100 μ L) to remove remaining uncoordinated copper and the obtained solution was evaporated. The resultant white solid was digested with 5% HNO₃ aq. solution and the amount of copper was quantified by ICP-MS analysis.

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CHEMISTRY A European Journal

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