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A Dicopper(I)-Dimesoionic Carbene Complex as a Click Catalyst: Mechanistic Implications.

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A dicopper(I) complex comprising a dimesoionic carbene and an acetate-bridge is synthesized and fully characterized. This complex is a potent pre-catalyst for the azide-alkyne cycloaddition reaction. A full kinetic investigation shows a first order in azide and a catalyst order smaller than one due to an equilibrated dimerization of the catalyst.

Introduction.

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Since its discovery in 2002, the copper(I) catalyzed azidealkyne cycloaddition (CuAAC) reaction has had an unprecedented influence in virtually all branches of chemistry.¹ This remains the best example of a Click reaction. Early investigations on improving the catalytic efficiency of the CuAAC reaction pointed to the positive influence of certain additive ligands that apparently stabilize the copper(I) catalyst and prevents its oxidation and decomposition.² In this regard, it was shown that N-heterocyclic carbenes (NHC) are well suited for the stabilization of copper(I) centers during CuAAC reactions, and several NHC-based catalysts for that reaction were reported and investigated (Figure 1).³ Very recently, it was shown that the catalytic cycle of the CuAAC reaction involves a dicopper center as a key intermediate.^{3e,4} NHC based copper complexes have played a vital role in the development and the understanding of that catalytic mechanism. Thus, it was shown early on by Straub and coworkers that a dicopper(I) complex based on a di-NHC ligand is a very active catalyst for the CuAAC reaction.^{3c} This investigation finally paved the way for the proposal of the aforementioned dicopper species as a key intermediate for the CuAAC reaction. Lately, Bertrand and coworkers have used cyclic alkyl amino carbenes (CAAC) as ligands for isolating several key intermediates of the CuAAC reaction and for further corroborating the importance of a dicopper(I) as a key intermediate in the catalytic cycle.^{3e} Apart from the importance of the NHC or CAAC ligands, the investigations of both Bertrand and co-workers as well as Straub and co-workers clearly showed that acetates (OAc) are the labile ligands of choice in such (pre)catalysts.^{3C,e,I-5}



Figure 1. Several reported copper-carbene (pre)catalysts for the CuAAC reaction.

We and others have recently pioneered the use of copper(I) complexes of mesoionic carbene (MIC) ligands as catalysts for the CuAAC reaction.^{3d,f,g} In a comparative study we showed that Cu-MIC complexes outperform their Cu-NHC counterparts as catalysts under identical reaction conditions.^{3d} In the following, we present a dicopper complex [1](OTf) that combines the methylene-bridged di-MIC ligand L, together with OAc as a labile ligand (Scheme 1). Furthermore, the labile OAc could serve as an internal base and the ligand platform which should favor the formation of the key dinuclear intermediates. Apart from the synthesis and the characterization of [1](OTf), we have tested the potency of [1](OTf) as a (pre)catalyst in the CuAAC reaction by using a variety of substrates. Most importantly, we present herein a thorough mechanistic picture with the help of a detailed kinetic investigation.

Results and discussion

The bis-triazolium salt $(H2L)(OTf)_2$, which is a precursor to the bis-MIC ligand L, was prepared from the corresponding 1,5-disubtituted-1,2,3-triazole following a route pioneered by

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 $^{^{+}}$ Electronic Supplementary Information (ESI) available: synthesis of [1](OTf), crystal structure (CCDC 1880094), $^{1}\mathrm{H}$ an $^{13}\mathrm{C}$ NMR spectra, procedure and calculations.. See DOI: 10.1039/x0xx00000x

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some of us.⁶ The complex [1](OTf) was synthesized through a deprotonation of $(H2L)(OTf)_2$ by acetate, followed by a reaction with copper(I) in CH_2Cl_2 (†ESI). Addition of THF to the reaction mixture led to a precipitation of a microcrystalline solid which was washed with THF to deliver [1](OTf) in the desired purity.



Scheme 1. Synthesis of [1](OTf).

Interestingly, [1](OTf) turned out to be air and moisture stable and hence all catalytic reactions could be performed in open vessels (see below). The absence of signals corresponding to the triazolium C-H protons in the ¹H NMR spectrum and the appearance of a signal at 183.4 ppm in the ¹³C NMR spectrum were indications of the formation of [1](OTf). The analysis of the complete ¹H and ¹³C NMR spectra, the detection of the molecular cationic peak in the ESI-MS and the elemental analysis data (+ESI) all pointed to the formation of pure [1](OTf). Single crystals of [1](OTf) as a dichloromethane and pentane solvates were obtained by layering a CH₂Cl₂ solution with pentane. In the molecular structure in the crystal (Figure 2) it is seen that each of the copper(I) centers is bound by one C-atom from the bis-MIC ligand L, and one O-atom from the OAc ligand. Slight distortions from linearity are observed in the coordination of both the two-coordinate copper centers, as seen from the C1-Cu1-O1 and C16-Cu2-O2 angles of slightly more than 172°. The Cu-C(MIC) and the Cu-O(OAc) distances are all in the expected range (†ESI, Table S7). The intramolecular Cu1-Cu2 distance is 2.7608(8) Å, a value that is lower than the sum of the van der Waals radius of two copper centers. While such a short distance can be taken as a first indication of copper-copper interaction in such systems, it should be borne in mind that the bridging nature of both L and OAc ligands does force the copper centers to a close proximity.



Figure 2. ORTEP view of complex [1]. Hydrogen atoms, anions and solvent molecules have been omitted for clarity.

The CuAAC reaction between phenyl acetylene_{/i}end_i benzyl azide in CDCl₃ serves as a model reaction Gold the Study of the catalysis displayed by [1](OTf).⁷ A first ¹H NMR experiment performed with equal concentrations of the two substrates ([Azide] = [Alkyne] = 0.2 mol.L⁻¹, [Cat] = 1.0 mol-%), revealed a rapid reaction that ends after approximately 30 minutes, Figure 3A. The isolated yield of the triazole product is 95%. The solutions stay limpid all along the reaction course and turns pale yellow only near the end, indicating the formation of copper acetylide polymers. The reaction is of overall first order as demonstrated by the plot of the logarithm of the concentrations in starting material versus time depicted in Figure 3B ($k_{obs.}$ = 0.101 min-1).



Figure 3. A: Completion versus time. **B:** $\ln[azide]$ versus time up to 80% completion (k_{obs} =0.101 min⁻¹, r² = 0.998).

Small excess experiments were applied to determine which of the reactants is involved in the rate determining step. The reaction profiles for equimolar and 1.2 equivalents of reactants are displayed in Figure 4. A clear overlay for equimolar quantities and small excess of alkyne is observed whereas a positive deviation for a small azide excess indicates that the azide participates in the slowest step but not the alkyne. For mono copper catalysts it was presumed that the cycloaddition step is the rate determining one,⁸ however, literature reports that the rate limiting step either involves the alkyne or the protonation of the triazolide.⁹



Figure 4. Completion versus time for different azide/alkyne ratio (\bullet : 1/1; \blacktriangle : 1/1.2 and \bullet 1.2/1 equivalent of azide/alkyne).

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Therefore, the rate law could be expressed as the following function of the observed rate constant:

$$[Azide]_{t} = [Azide]_{0.e} e^{-k_{obs} \cdot t}$$

with
$$k_{abs} = k_{abs} [cat]^{\alpha}$$
 Fq.2

The catalyst order was examined by varying the amount of [1](OTf) added in the reaction vessel at a fixed concentration (0.2M) of reactants (Figure 5A). Each of these curves corresponds to a first order kinetic (Figure 5B). It is emphasized that, a total conversion is observed with a catalyst loading of only 0.15 mol%. Indeed, 80% completion is reached in 110 minutes and, to the best of our knowledge such high efficiency is unprecedented in open flask solution (and not neat conditions) without reducing agent. The corresponding data are collected in Table 1.



Figure 5. A: [Triazole] versus time at [Aklyne]=[Azide]=0.2 mol.L⁻¹. B: In[Azide] versus time. ▲ : 1mol-%; ◆: 0.5 mol-%; ■: 0.31mol-%; ●: 0.15 mol-%.

Table 1. Apparent rate constant at different catalyst concentrations.								
[Cat](mol.L ⁻¹)	0.002	0.001	0.00062	0.0003				
<i>k_{obs}.</i> (min ⁻¹)	0.0912	0.0558	0.0325	0.018				
(R ²)	(0.997)	(0.998)	(0.999)	(0.999)				

The logarithm of Eq.2 affords the catalyst order and the rate constant (Eq.3, Figure 6):

$$ln(k_{obs.}) = \alpha.ln[Cat] + ln(k)$$
 Eq. 3



Figure 6. Ln(k_{obs.}) versus ln[Cat] (R²=0.994).

The catalyst order was estimated to 0.87 which is unexpected as a dinuclear complex should afford an order of one. A noninteger value below 1.0 is usually attributed to a fast and reversible formation of an inactive complex.¹⁰ Consequently we hypothesized the presence of an equilibrium based 1882a dimerization of the catalyst according to the mechanism described in Scheme 2. In step I the cationic binuclear catalyst [1] containing one equivalent of base reacts with the alkyne to form the complex [2] possessing a labile acetic acid ligand and a σ -alkyne bond. In step II, the acetic acid ligand is easily displaced to form the key $\sigma-\pi$ complex [3]. Noteworthy, this type of $\sigma-\pi$ complex has been isolated by Bertrand's group using non tethered Cu-CAAC.^{3e} We hypothesized that this complex equilibrates with a second equivalent of [3] to form an inactive dimer [4]. Although we were unable to isolate this complex, its presence is supported by the isolation of an octacopper(I) hexaacetylide cluster by Straub's group.¹¹ Importantly, this cluster is reversibly formed during the reaction of ethylenebis1,2,4-triazol-5-ylidene and ethyl propiolate. The rate determining step III, consists in the formation of the triazole. The last step (IV) is the protonation of the copper-triazolide probably helped by the carbonyl chelation of the acetic acid by the second copper followed by the protonation step.



Scheme 2. Proposed mechanism.

Overall, the accessible kinetics observations point to a first order transformation of the azide catalyzed by [3] which equilibrates with its dimer (scheme 3).



The corresponding rate law and the concentration versus time functions are given in equations 4-6 where k is the rate

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constant, C_0 the concentration of catalyst added in the reaction vessel and Ke the equilibrium constant (ESI):

$$v = -\frac{\partial v}{\partial t} = k.(-1 + \sqrt{1 + 8.K_e.C_0})/(4.K_e)$$
 Eq.4

 $[Azide]_{t} = [Azide]_{0.e}^{-\left(k \cdot \frac{-1 + \sqrt{1 + BK_{e}C_{0}}}{4K_{e}}\right)t}$ Eq.5

$$k_{\text{obs.}} = k \cdot \frac{-1 + \sqrt{1 + 8K_e C_0}}{4K_e}$$
 Eq.6

To determinate K_e and k, the curve of k_{obs} versus C_0 was fitted according to Equation 6 using gnuplot software (Figure 7A). Gratefully, the fit converged rapidly to k=68.5 min⁻¹ and K_e =160 mol.L⁻¹(†ESI for recalculation of the curves with computed values).¹²



Figure 7. A: k_{obs} . versus C_0 fitted according to Eq. 6.

A small substrate scope was screened using 1 mol-% catalyst to test the scope and limitations by means of ¹H NMR (Table 2).

		,	[1](OTf)	$N^{(N)} N R^1$	
R ^{1_N₃}	+	R ²	CDCl ₃ , 20-22 °C under air	$P_{\rm R}^{\rm N}$	

Table 2: substrate screening

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Entry	R1	R ²	Time	Conversion ^[a]	
1	Bn	CH₂OH	26h	39%	
2	Dipp	Ph	18h	27%	
3	Bn	^t Bu	20h	65%	
4	Ph	Ph	16h	92%	
5	Bn	CO ₂ Et	80 min	>99%	
6	Bn	N(CH ₂) ₃ -	85 min	>99%	
7	Bn	Ph	<80 min	>99%	

[a] Taken by ¹H NMR using 1,4-dimethoxybenzene as internal standard. [alkyne]=1/3 [azide], [1](OTf): 1 mol–% regarding the azide.

The catalyst not performs well for protic substrates (entry 1) corroborating the observation that coordinating protic solvents are also not suitable.⁷ This is probably due to the saturation of the catalyst or protonation of the triazolylidene carbene (pKa~24).¹³ Bulky substituents on the substrates lead to moderate yields (entries 2-3), probably due to the crowded nature of the catalyst. This is particularly important for the

azide partner for which its crowed environment redirectly interacts with the ligand (27%). On the other hand, terminal alkyne in which the steric matters are more distant affords better yield (65%). For neutral and non-bulky substrates, the catalyst performs excellently (entries 4-7). A triple Click reaction delivering the TBTA was complete within 85 minutes (entry 7).^{2a} For this reaction, the single double clicked products were observed at 25 and 35 min. It should be noted that all catalytic reactions were performed under air and in a solvent (not neat or 'on water'). Such conditions are highly unusual for such catalysis with isolated Cu(I) complexes.

Summarizing, we have presented a fully characterized dicopper(I) complex containing as ligands a robust di-MIC and a labile acetate. This air and moisture stable complex is a potent catalyst for the azide-alkyne cycloaddition. Detailed kinetic shows a reaction order of one with respect to the azide and a non-integer value for the catalyst points to an equilibrium with an inactive dimer. To the best of our knowledge, this is the first investigated catalytic system which shows this behavior.

Experimental

General remarks and instrumentation

Unless otherwise noted, all reactions were carried out using standard Schlenk-line techniques under an inert atmosphere of argon (Linde, HiQ Argon 5.0, purity ≥ 99.999%). Commercially available chemicals were used without further purification. THF and diethyl ether were dried and distilled from sodium/benzophenone. Other solvents were available from MBRAUN MB-SPS-800 solvent system. For the synthesis part, all solvents were degassed by standard techniques prior to use. For NMR, CDCl3 was passed through a small plug basic alumina. ¹H NMR and ¹³C {1H} spectra were recorded on JEOL ECS 400 spectrometer and JEOL ECZ 400R spectrometer at room temperature. Kinetic NMR spectra were recorded in Fourier transform mode with a Bruker AVANCE 500 spectrometer at 298 K. Chemical shifts are reported in ppm (relative to the TMS signal) with reference to the residual solvent peaks. Multiplets are reported as follows: singlet (s), doublet (d), triplet (t) quartet (q), quintet (quint), and combinations thereof. Internal standard for kinetic measurement is 1,4-dimethoxybenzene (1,4-DMB, Aldrich) recrystallized twice in cyclohexane. Its purity (99%) was determined using q-NMR sequence.¹⁴ Mass spectrometry was performed on an Agilent 6210 ESI-TOF. X-ray data were collected on a Bruker D8 Venture system at 100(2) K, using graphite-monochromated MoK α radiation ($\lambda \alpha$ = 0.71073 Å). The strategy for the data collection was evaluated by using the APEX3 software. The data were collected by $\omega + \phi$ scan techniques, and were scaled and reduced using Saint+ and SADABS software. The structures were solved by intrinsic phasing methods using SHELXT-2014/7. Structures were refined by full matrix least-squares using SHELXL-2014/7, refining on F2. Non-hydrogen atoms were refined anisotropically.

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Synthesis of the copper(I) complex [1](OTf).

The synthesis of complex [1]OTf was performed similar to a previously reported procedure.^{3c} In a 100 mL-Schlenk-flask the bi-triazolium salt (H2L)(OTf)2 (263 mg, 0.348 mmol, 1 equiv.) and sodium acetate (74.2 mg, 0.904 mmol, 2.6 equiv.) were stirred in dry and degassed CH₂Cl₂ for 5 h at 30 °C. Freshly prepared copper(I) acetate (158 mg, 1.29 mmol, 3.7 equiv.) was added.¹⁵ The suspension was stirred for 2 days at 30 °C. The resulting red suspension was filtered under inert atmosphere and the solvent was removed under reduced pressure. Addition of dry and degassed THF (5 mL) yielded microcrystalline precipitate after about half an hour. The solvent was decanted and the remaining solid was washed with dry, degassed THF twice. After drying under vacuum complex [1]OTf was obtained as an off-white solid with 0.6 entities of THF per complex molecule (38 %, 109 mg, 0.133 mmol). Single crystals suitable for X-ray diffraction were observed by crystallizing in dry and degassed CH₂Cl₂ layered with pentane.

¹H NMR (400 MHz, CD₂Cl₂) δ (ppm) = 7.75–7.28 (m, 22H, aryl-H + methylene-H), 2.09 (s, 3H, acetate-H) ppm. ¹³C NMR (101 MHz, CD₂Cl₂) δ (ppm) = 83.38 (C_{carbene}), 149.79, 135.15, 132.07, 130.93, 130.49, 130.10, 129.69, 127.22, 125.85, 70.50, 68.31 (THF), 31.17, 26.14 (THF), 22.63. Anal. Calcd. (%) for [C₃₂H₂₅N₆Cu₂O₅F₃S · 0.60 C₄H₈O] C 49.6, H 3.61, N 10.09; Found C 49.21, H 3.627, N 9.747. ESI-MS: m/z: [M–OTf]+ Calcd. 639.063, Found 639.062.

Catalysis.

All steps were carried out under air. In a vial the azide (0.4 mmol, 1 equiv.), alkyne (0.4 mmol, 1.0 equiv.) and 1,4dimethoxybenzene (6.9 mg, 0.05 mmol, 0.25 equiv.) as an internal standard were solved in CDCl₃ (2 mL), which was previously deactivated over basic aluminum oxide. A sample of the solution was taken to get a ¹H NMR control spectrum. A volume of 0.6 mL of the stock ($c_{azide} = c_{alkyne} = 0.2 \text{ mol/L}$) was added to the catalyst [1]OTf (0.0012 mmol, 1 mol%) in a vial. After solution of the complex, the sample was directly transferred into an NMR tube and ¹H NMR spectra were taken to monitor the reaction. All spectra were retreated by ACDNMR software using a house build macro. This macro integrates automatically the signals of the internal standard (1,4-DMB) at 6.9 ppm and two signals from the triazole: the benzylic CH₂ at 5.6 ppm and the CH₂OH at 3.75 ppm. Completions were calculated as the average of the two triazole integrations based on the constant amount of internal standard. As ACDNMR macro furnish a txt file for each spectrum, all these files were compiled in a single txt file and were include in an excel file for calculation.

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Conflicts of interest

There are no conflicts to declare.

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