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A General Strategy for Ligation of Organic and Biological Molecules to Dawson and Keggin Polyoxotungstates

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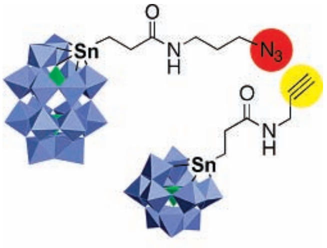
ABSTRACT



water-compatible ligation

The copper-catalyzed azide/alkyne cycloaddition (click chemistry) is used for the first time in polyoxometalate chemistry to graft any kind of organics (lipophilic, water-soluble, biologically relevant) to polyoxotungstates to generate hybrids. The method is not limited by solvent matching between the polyoxometallic platforms and the organic substrates.

The applications of organic-functionalized inorganic nanoparticles have soared these past few years. Those hybrid objects mix organic and inorganic fragments and require a specific chemistry. In particular, the traditional organic toolbox often needs to be remodeled to be compatible with the inorganic components of the nanoparticles.

Our interest is focused on the functionalization of polyoxometalates (POMs) as a specific class of stable and stoichiometrically well-defined nanoparticles. POMs are molecular inorganic clusters with tremendous potential as catalysts, biomedical tools, molecular magnets, and building blocks for new materials.[1] Inclusion of organic moieties would generate many new structures.[2] Yet, the conditions for the connection of the organic partners to *lacunary* POMs − no strong basic conditions, no cations, use of water, etc. − often limit the number of organic molecules that can be introduced.

We[3] and others recognized that it would be helpful to perform organic chemistry on simply functionalized *non-lacunary* hybrid POMs to prepare more complex molecules[4] or polymers.[5] Nonetheless, once their cations are fixed, POMs generally have very narrow solubilities, which led the

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existing methodologies to often fail for reagents with mismatched solubilities. For example, despite the importance of water-soluble molecules for chemical biology applications of POMs, our previous approach was limited to the coupling of organosoluble amines.[3] It does not work with water-soluble molecules because the POM platforms suitable for this particular organic chemistry are only soluble in MeCN. It also does not lead to designed POM oligomers, in which polyoxometallic subunits are bridged by an organic spacer.

Peng's methodology[6] is a very useful way to access polyoxomolybdate dimers in the imido Lindqvist series introduced by Maatta.[7] However, it has not been extended to Keggin and Dawson polyoxotungstates that are stable at physiological pH and thus biologically more relevant. Hill's[14c] and Pope's[4f] approaches work with the latter platforms but only afford oligomers with identical polyoxometallic frameworks. Thus, formation of dissymmetrical structures and — more generally — a truly easy and general way to graft organics to Dawson and Keggin heteropolyanions are still challenging tasks.

The copper-catalyzed 1,3-dipolar cycloaddition of azides and alkynes has emerged as a unique way for modular assembly of diversely functionalized subunits.[8] As a consequence, it has been used in chemical biology,[9] material science,[10] and nanotechnology.[11] Coated metal oxide nanoparticles were shown to survive the click conditions.[12] However, to the best of our knowledge, there is no precedent for the development of such chemistry to polyoxometalates.

Indeed, the standard protocol for click chemistry did not look compatible with the intrinsic properties of POMs, which are oxidants that could be reduced by either the copper(I) salt used to catalyze the reaction or the stoichiometric reductant generally used to ensure turnover. In addition, copper ions might combine with the polyanionic moieties and lead to unwanted precipitations triggered by solubility changes via cation exchange and/or loss of catalytic activity. In this communication, we show that these difficulties can be overcome.

Because they are only weak oxidants, polyoxotungstates are better candidates for click chemistry than polyoxomolybdates. Functionalization through organotin groups is a powerful strategy to obtain organic derivatives.[3,13] We thus synthesized the six new hybrid heteropolyphosphotungstates **1**−**6** as representatives of the Keggin (TBA$_4$[PW$_{11}$O$_{39}$SnR′]) and Dawson (TBA$_7$[P$_2$W$_{17}$O$_{61}$SnR′]) series (α_1 and α_2, Figure 1). In that way, we could gather data on the role of both charge and the intrinsic chirality of the polyanions. In all cases, we prepared the acetylenic and azido terminal POMs following our established amide-forming method.

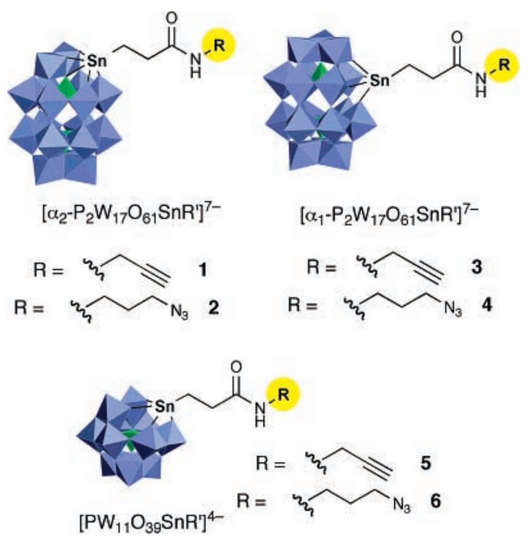

Figure 1. Polyoxotungstic platforms chosen for ligation.

Compounds **1**−**6** are insoluble in the commonly used water−alcohol mixture. We therefore had to switch to aqueous acetonitrile as solvent for the coupling reactions and to decrease the concentration of all reactants to ensure solubility. The initial reactions were carried out following this modified CuSO$_4$/ascorbate procedure,[8] with α_2-Dawson POM **1** and benzyl azide in a 1:2 MeCN/water mixture. Only traces of the desired triazole (identified through its aromatic proton) were obtained after workup, and the starting material

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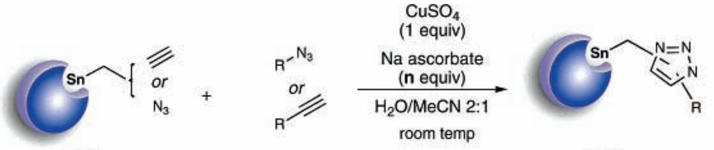
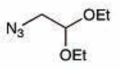
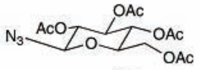
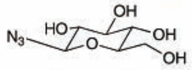
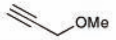
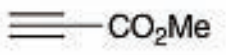
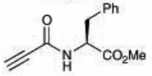
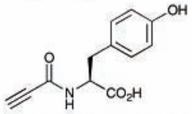
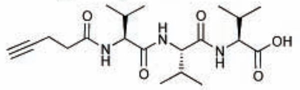
Table 1. Grafting of Organic Molecules to Polyoxotungstates through Copper-Catalyzed Dipolar Cycloaddition



1-6 → 7-19

entry	S. M.[a]	reagent	n	P[b].	yield (%)
1	**1**	BnN_3	10	**7**	92
2	**1**		10	**8**	90
3	**1**		10	**9**	93
4	**1**		10	**10**	85
5	**1**		30	**11**	85
6	**2**		10	**12**	81
7	**2**		10	**13**	87
8	**2**		10	**14**	77
9	**2**		30	**15**	70
10	**2**		40	**16**	68
11	**3**	BnN_3	10	**17**	81
12	**4**		10	**18**	72
13	**5**	BnN_3	40	**19**	71
14	**6**		40	**20**	63

[a] S.M. = starting material. [b] P. = product

was recovered. Encouragingly, though, no blue color appeared, suggesting that no reduction occurred. We surmised that the lack of reactivity originated from the anticipated ion pairing of the POM with the copper cations. Because the latter were presumably randomly arranged around the polyoxometallic structure and tightly bound to the polyoxometallic surface, the copper concentration near the reacting centers was presumably too low for catalytic activity. To overcome this problem, we increased the copper and reducing agent loadings. Upon working with one full equivalent of $CuSO_4$ and excess sodium ascorbate, full conversion of the starting material **1** was observed.

In a typical experiment (Table 1, entry 1), hybrid POM **1** was treated with benzyl azide in the presence of $CuSO_4$ (1 equiv) and sodium ascorbate (10 equiv) in aqueous acetonitrile ($H_2O/MeCN$ 2:1) and delivered the desired hybrid **7** in 92% yield after 24 h and purification by ion exchange (see Supporting Information for experimental details). FTIR and ^{31}P NMR spectra indicated an intact POM framework. Signals in ^{1}H NMR at 8.19 ppm and ^{13}C NMR at 124 and 147 ppm proved unambiguously the formation of the triazole ring. The identity of the compound was further confirmed by ESI-MS. The reaction proved quite general. It worked with all the POM platforms **1**−**6**, regardless of the charge, size, or terminus on the initial POM. Aliphatic (entries 1, 11 and 13) or polar side chains could be installed. Coupling to the propargylic ester (entry 7) was an essential achievement because it provides an entry toward peptide ligation. Gratifyingly, *N*-propargylamide phenylalanine (entry 8), unprotected tyrosine (entry 9), and a longer peptide (entry 10) could be grafted to POM **2**. The tyrosine side-chain modification was not possible using our previous methodology because of the mismatched solubility of the partners.

Carbohydrates could also be conjugated, in both their protected (entry 4) and free (entry 5) forms. This could equally not be done with our previous methodology. Products **10** and **11** are the first examples of POM glycoconjugates.[15] The ability to form water-stable conjugates in which the hydroxyl groups are not bound to the metals and thus can potentially be recognized by biological receptors is an important step for examining their chemical biology. That the reaction does not require protecting groups is good news for those applications.

The couplings of the Keggin polyanions required more sodium ascorbate (Table 1, entries 13 and 14). These POMs were insoluble in $H_2O/MeCN$ 2:1 in the presence of only 10 equiv of sodium ascorbate, but they dissolved in the presence of 40 equiv.

Interestingly, when the amount of water was decreased, the conversion rate dropped for all types of POMs. We think these observations − as well as the excess sodium ascorbate and copper sulfate needed−are further confirmations that the polyanionic nature of the POM does impact the reactivity

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(15) Mannose has been used recently to attach Dawson phosphotungstovanadates to dendrimers (see ref 14). Given their nature, those compounds are not fully characterized from a molecular point of view. In addition, use of the hybrid dendrimers for biochemical purposes would be impossible because the biologically relevant carbohydrate hydroxyls are employed for the anchoring of the inorganic part to the organic dendrimers.

of the copper-catalyzed Huisgen cycloaddition. Indeed, we believe that the ion pairing between the POM and the Cu^{2+} plays a crucial role. The high water content in the solvent and the presence of a high concentration in sodium ascorbate favor the dissociation of those water-soluble ion pairs and make the copper available for the catalytic reaction. Less-charged Keggin polyanions with mixed cationic surroundings are less soluble in water and thus require more sodium to go into the water phase.

The extremely high versatility of the click methodology let us consider a modular approach for assembly of POM oligomers. As a proof of concept, we decided to prepare a mixed α_2-Dawson/Keggin phosphotungstate dimer (Scheme 1). Synthesis of such a dimer would demonstrate both that hybrid dendrimers can be synthesized and that this can be done in a dissymmetric way.

Scheme 1. Preparation of a Dissymmetric Mixed Polyoxometallic Dimer

Dimer **21** was smoothly prepared in 59% yield from POMs **2** and **5**. The reaction required more $CuSO_4$ and ascorbate. This was not too surprising because two POMs consume the cations present in solution. The identity of the new POM **21** was unambiguously established by ^{1}H, ^{13}C, and ^{31}P NMR and negative-mode ESI-MS (see Supporting Information). Because of the value of POM dendrimers,[4,14] we will extend this methodology to the preparation of other dimers and higher-order oligomers.

In conclusion, we have introduced an efficient and general method to couple very different kinds of molecules (lipophilic and hydrophilic) to inorganic polyoxometalates, which opens the way to varied applications which will be reported in due course.

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Supporting Information Available: All new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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