Functionalizing Polyoxotungstates

Highly Efficient Peptide Bond Formation to Functionalized Wells-Dawson-Type Polyoxotungstates**

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Polyoxometalates (POMs) are a large family of metal-oxygen clusters of the early transition metals in high oxidation states, most commonly V^{V}, Mo^{VI}, and W^{VI}.[1,2] Their diversity in structure and composition allows a wide versatility in terms of shape, polarity, redox potentials, surface charge distribution, and acidity. The last twenty years have witnessed a growing interest in the biological properties of POMs and their potential applications in medicine.[3] POMs exhibit antiviral—notably anti HIV[4,5]—as well as antitumor[6,7] and antibiotic[8,9] activities. Nonetheless, progress along these lines has been quite slow because of the low physiological stability of most POMs. Only a few POMs were reported with enhanced hydrolytic stability.[4,10,11] An original approach is the encapsulation of POMs in starch nanoparticles.[6]

The introduction of organic groups into the POM framework could greatly increase the number of compounds available for screening, together with a potential modulation of essential features, such as stability, bioavailability, and recognition.[3] While there is a significant amount of work on hybrid POMs,[12–14] there have been only scattered reports of the reactivity of the side chain of such functionalized POMs.[15–17] Many of these organically derivatized POMs are unstable in water. Starting from hydrolytically more stable cyclopentadienyltitanium substituted POMs,[11,18] Keana reported the preparation and reactivity of derivatives with various functional groups.[19–21] We decided to reexamine the heteropolytungstates $[\alpha_2\text{-}P_2W_{17}O_{61}(SnR)]^{7-}$ reported by Pope and co-workers,[22,23] with an alkyltin group in place of the more fragile CpTi-moiety. These heteropolytungstate compounds have promising antitumor activities,[24] but the organic groups that were introduced were very simple and did not allow further functionalization.[18,22,24]

It is important to have access to a wide variety of organic groups on the POM to meet specific requirements in biological applications. Different groups will enable the POM, for instance, to cross a membrane or to reach a specific receptor depending on their precise nature. We report herein our first findings on a flexible synthetic approach.

To obtain polyanions of the type $[\alpha_2\text{-}P_2W_{17}O_{61}(SnR)]^{7-}$ with different R groups, one can treat different $RSnCl_3$ with $[\alpha_2\text{-}P_2W_{17}O_{61}]^{10-}$.[22,24] This strategy suffers from the incompatibility of the trichlorotin moiety with most organic functions, and the scarce versatility it allows. To prepare a functionalized POM useful as a scaffold for many applications, we decided to graft a pendant carboxylic acid onto a POM (Scheme 1), because it would allow peptide or ester coupling reactions, which are compatible with most bioactive compounds.

The treatment of a buffered aqueous solution of $K_{10}[\alpha_2\text{-}P_2W_{17}O_{61}]$ **2**[25] with $Cl_3Sn(CH_2)_2CO_2H$ **7**[26] yielded a new anion which was precipitated by the addition of nBu$_4$NBr. The IR spectrum shows the vibrational bands arising from the Wells-Dawson structure without the typical splitting of the P–O stretching vibration in the lacunary compound,[27] thus indicating that the lacuna is filled. ^{31}P NMR analysis showed the presence of a single product with two nonequivalent phosphorous atoms ($\delta = -12.7$ and -9.65 ppm). The high-frequency resonance consists of a single line flanked by a pair of satellites arising from unresolved coupling with ^{117}Sn and ^{119}Sn ($J = 27.5$ Hz). Consequently, the tin atom is bound to the phosphate group. ^{1}H NMR confirms the presence of the side chain, thus showing unambiguously that we succeeded in preparing $[\alpha_2\text{-}P_2W_{17}O_{61}\{Sn(CH_2)_2CO_2H\}]^{7-}$ **3**, the starting compound for a new family of functionalized clusters.

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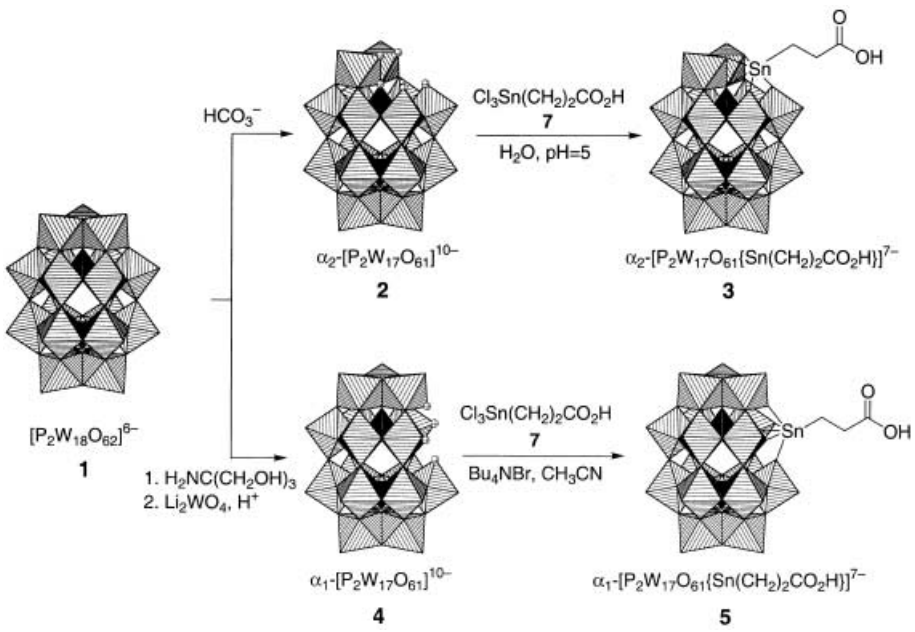


Scheme 1. Preparation of functionalized Wells-Dawson polyoxotungstates.

With this compound in hand, we endeavored to prepare the functionalized α_1-isomer **5**. Contrary to the α_2 isomer, the α_1 isomer is chiral and could be of great interest for the study of POM/receptor interactions.[4,28] The lacunary compound **4** isomerizes in aqueous solution.[29] For this reason, the reaction of **4** with **7** under the conditions established for the α_2 isomer gave low yields in **5**. We therefore developed a new synthesis in acetonitrile under phase transfer conditions to obtain **5** in 95% yield. To the best of our knowledge, this polyanion is the first example of a Wells-Dawson structure having an organic side chain in the α_1 position.

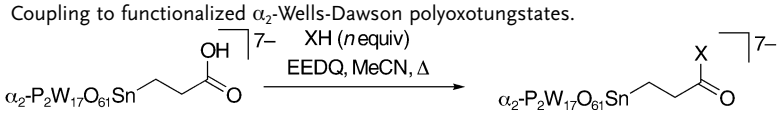
As our objective was to use the POM's "arm" as a linker, we sought conditions that would enable us to attach various molecules to the acid moiety. This task implies finding particularly efficient conditions—POMs with different side chains are almost impossible to separate—without creating cationic byproducts leading to scrambling of the counterions, which causes solubility and purity problems. Eventually, we were able to optimize the EEDQ-mediated coupling.[30] The only by-products are ethanol and quinoline, which can be easily removed (Table 1).

All reactions were carried out in refluxing acetonitrile. Primary and secondary amines led to the corresponding amides in high yields (Table 1, entries 1–3). Entry 3 shows that the reaction is sensitive to steric hindrance, as expected. With the intention of attaching POMs to the C terminus of peptides, it might become useful to have N-terminal scaffolds. Reactions of diamines, whether dialkyl or diaryl, proved surprisingly much more difficult (Table 1, entries 4–6) requiring longer reaction times to produce the aminoamides. However, no other POM was formed. When ethylenediamine was used (entry 6), the reaction never reached completion: at about 80% conversion, degradation occurred rapidly. Acid, ester and phenol functions were tolerated (Table 1, entries 7 and 8). It should be noted that simple α-aminoacids failed to give any amide (no conversion), while C protection of tyrosine triggered a nearly quantitative reaction (entry 8). This is probably due to the low solubility of the aminoacids under the reaction conditions. Lastly, esters could also be prepared. The reaction of **3** with benzyl alcohol (BnOH) gave **6h** in 86% yield. Coupling reactions with **5** proceeded similarly, but were accompanied by degradation. For instance, the reaction with benzylamine led to 50% of the desired amide accompanied by several derivatives of the α_2 isomer (among which 20% of **6a**).

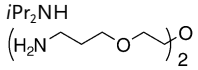
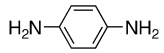
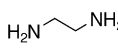
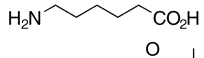
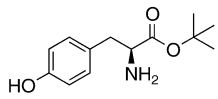
Finally, we had to show that the functionalization of the side chain did not affect the hydrolytic stability of the polyanion. For this purpose, we selected **6a**, which was made water soluble by the exchange of $n\mathrm{Bu_4N^+}$ with $\mathrm{Na^+}$. A saturated solution in physiological serum was monitored by ^{31}P NMR. No decomposition occurred at RT during ten days, and degradation did not exceed 12% at 37 °C after two days.

In conclusion, we have demonstrated that we could prepare both $[\alpha_1\text{-}P_2W_{17}O_{61}\{Sn(CH_2)_2CO_2H\}]^{7-}$ and $[\alpha_2\text{-}P_2W_{17}O_{61}\{Sn(CH_2)_2CO_2H\}]^{7-}$, and also further make derivatives of the α_2 series by attaching organic molecules to the

Table 1: Coupling to functionalized α_2-Wells-Dawson polyoxotungstates.



3 **6a-h**

Entry	XH	*n*	*t* [h]	Product, yield [%]
1	$BnNH_2$	3	4	**6a**, 86
2	Bn_2NH	2	8	**6b**, 90
3	iPr_2NH	3	12	**6c**, 80
4		6	140	**6d**, 70
5		6	120	**6e**, 66
6		7	120	–[a]
7		3	36	**6f**, 50
8		3	36	**6g**, 90
9	BnOH	2	12	**6h**, 86

[a] Maximum conversion was 80%. Rapid degradation followed. EEDQ = 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline.

arm. Work to determine the scope and limitation of our method is in progress. These results, as well as the behavior of POMs attached to bioactive compounds such as penicillin, will be reported in due course.

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