Polyoxometalates (POMs) are discrete molecular forms of metal oxides, displaying a variety of electronic and catalytic properties and vastly increased solubility and structural variety compared to bulk metal oxides, but their synthesis involves complex self-assembly processes and can be hard to predict or design. Many POM structures are able to form organic−inorganic “hybrids”, where the metal−oxygen cores are directly connected to organic moieties. These organic components could provide a more predictable means of manipulating POM clusters than has been previously possible, allowing them to be incorporated into devices and materials, or shaped into specific function-driven architectures.

The Lindqvist $[\text{M}_6\text{O}_{19}]^{4−}$, Dawson $[\text{X}_2\text{M}_{18}\text{O}_{62}]$, and Anderson $[\text{XM}_n\text{O}_{24}]$ clusters ($X =$ heteroatoms, $M =$ transition metal “addenda”) can all be considered archetypal POM structures, and all three of them can be functionalized with the tris(hydroxymethyl)aminomethane (TRIS) linker (as the Mn or Fe Anderson, the $\{V_6\}$ Lindqvist, or the $\{P_5\text{W}_{12}\text{V}_3\}$ Dawson), replacing some of the terminal oxygen atoms of the POM structure with the hydroxyl groups of the TRIS moiety, providing a platform on which larger organic structures can be built, offering additional functionality, conferring new properties to the material, and providing new means by which the POM cores can bond to and interact with surfaces, metals, and other POMs.

The use of organic moieties to link POM cores together into large designed assemblies via both pre-functionalization approaches (where several POM cores are tethered to a single organic moiety during the formation of the hybrid) and post-functionalization approaches (where the POM hybrids are formed separately and subsequently linked together) has been observed for many different cluster types: up to four $\{\text{Mo}_6\}$ Lindqvists, the double, triple, quadruple, and dendrimeric $\text{TRIS}$-linked $\{P_5\text{V}_3\text{W}_{13}\}$ Dawson compounds; a TRIS−Mn Anderson cluster linked to two $\{\text{Mo}_5\}$ Lindqvist cores; and the photopolymerized coumarin-functionalized Mn Anderson cluster. Several POMs have also been incorporated into a variety of polymers. In all these examples, however, hybrid POMs either terminate an organic chain (if they have one active organic moiety) or undergo uncontrolled polymerization (if they have more than one), limiting the possibilities for variety and control of these multi-POM structures. No method has yet been published which allows the synthesis of monodisperse POM oligomers of controllable length and composition. This is principally due to the difficulty in producing POMs with two different functional sites, which may be sequentially functionalized, and the development of a suitable coupling methodology for AB coupling. A comparison of all possible couplings for mono- and bifunctional POMs using the Anderson cluster as an example is given in Scheme 1.

Herein we present solutions to these problems resulting in a powerful new synthetic methodology for the controlled synthesis of hybrid metal oxide oligomers with precisely controlled chain lengths. This is achieved by developing a coupling methodology that utilized our ability to produce asymmetric Mn Anderson hybrids with two different functional groups, resulting in a compound which behaves as a monofunctionalized hybrid until its second functional site is activated. To do this we designed and synthesized a collection of Mn Anderson hybrid-POM building blocks derived from azide- and alkyne-bearing TRIS groups (see Chart 1). These azide/alkyne groups form an AB coupling system which has been used to controllably link Mn Anderson clusters together, using both symmetric and asymmetric hybrids. Post-functionalization can then activate the asymmetric hybrids, allowing us to form oligomers ranging in size from two to five Mn Anderson units ranging 4−9 nm in size.

The target azide and alkyne TRIS ligands were chosen on the basis of the stability and availability of their carboxylic acid precursors: 4-azidobenzoic acid was chosen for the azido group and 4-bromostyrene was chosen for the alkyne group. The use of these TRIS-functionalized manganese Anderson clusters as "click" addenda allows us to form a monofunctionalized hybrid until its second functional site is activated. To do this we designed and synthesized a collection of Mn Anderson hybrid-POM building blocks derived from azide- and alkyne-bearing TRIS groups (see Chart 1). These azide/alkyne groups form an AB coupling system which has been used to controllably link Mn Anderson clusters together, using both symmetric and asymmetric hybrids. Post-functionalization can then activate the asymmetric hybrids, allowing us to form oligomers ranging in size from two to five Mn Anderson units ranging 4−9 nm in size.
Scheme 1. Combinations Possible with AA Couplings (between Two Identical Functional Groups) and AB Couplings (between Two Different Functional Groups) Shown for Anderson POMs

Two single-reactive-site compounds always give a dimer, and two double-reactive-site compounds always give a polymer. When a mixture of single- and double-reactive-site compounds is used, an AA system gives a mixture of all products, but an AB system gives a single trimer product (highlighted in blue).

Chart 1. The Six Basic Building Blocks Used To Form the Oligomers: Two TRIS ligands (1A and 1B), Two Symmetric Mn Anderson Clusters (2A and 2B), and Two Asymmetric Mn Anderson Clusters (3A and 3B)

and S-hexynoic acid for the alkyne group, with the corresponding TRIS linkers 1A and 1B being formed via reaction of TRIS with their carbonic anhydrides.20 1A and 1B were then used to form their respective Mn Anderson clusters, 2A and 2B. For the asymmetric compounds, 3A and 3B, two different techniques were employed: 3A was synthesized using a 1:1 mixture of TRIS ligand and 1A, with the asymmetric product separated using reverse-phase liquid chromatography (RPLC), while 3B was synthesized by coupling the S-hexynoic acid group directly to the previously reported FMOC-TRIS/TRIS asymmetric Mn Anderson cluster19 using N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) as a coupling agent21 and then deprotecting the FMOC group. 3A could not be readily synthesized in this manner—following the reaction by ESI-MS revealed incomplete conversion and undesirable side products when the post-functionalization reaction was attempted with 4-azidobenzoic acid. A representation of the building blocks is given in Chart 1.

Excellent work on Cu-catalyzed alkyne−azide cycloaddition (CuAAC, or “click”) reactions involving POM hybrids has already been performed by Micoine et al. using tin-substituted Dawson and Keggin clusters with azide and alkyne groups,22 showing that the two can be coupled together and to a number of other molecules. This method is used, in a paper by Hu et al., to incorporate a bifunctionalized silicon-substituted Dawson cluster into a polymer chain.23 However, this reaction is of limited use, as the reaction conditions used (sodium ascorbate and copper sulfate in water and acetonitrile) are not compatible with many more-easily reduced POM clusters, including the molybdenum-based Mn Anderson cluster, causing the rapid formation of a bright blue precipitate. To overcome this problem, our reactions used copper iodide as a source of CuI, with N,N-diisopropylethylamine (DIPEA) in degassed DMF under nitrogen at 40 °C.

If the CuAAC reaction were to be performed with the two symmetric ligands, 2A and 2B, we would expect to see uncontrolled polymerization of the POM hybrids and the formation of polydisperse chains. To avoid this, the reactions must always contain at least one asymmetric hybrid, 3A or 3B, which reacts on only one side and limits chain growth. Using both these asymmetric hybrids together we form a dimer, O-2, while a trimer, O-3, can be formed using a symmetric hybrid (2A or 3B) and its asymmetric partner (3A or 3B). In order to extend beyond this, the terminal amine groups of O-2 or O-3 can be activated using the same S-hexynoic acid/EEDQ protocol used to form 3B, then two further 3A asymmetric units can be added, growing the chain by two cores to give O-4 (starting with O-2) or O-5 (starting with O-3). This process could, in principle, be repeated to produce oligomers of any desired length. The four oligomers plus a monomer for comparison are shown in Chart 2.

Chart 2. Representation of the Mn Anderson Oligomers Synthesized from One Mn Anderson Core (2A) to Five (O-5)

The synthesis of O-2 and O-3 proceeded smoothly, and following the reactions by ESI-MS showed that the oligomers were present in solution, but also showed signals for both the Mn Anderson starting materials. Preliminary RP-HPLC analysis for 2A, 2B, 3A, 3B, and crude O-2 and O-3 showed a large gap in retention time between the asymmetric starting materials and the oligomers, with 3B having the lowest retention time. Based on this, 3B was chosen as the reagent to keep in excess in both
the oligomer syntheses (with 2A or 3A) to ensure that it would be the only Mn Anderson starting material left in solution, leaving a large gap in retention time between the starting material and the oligomers and avoiding the presence of partly reacted species. After this reaction was performed for O-3, the products were dried on silica and passed through an RP-LC column, giving clear separation between a quickly eluted product and one with a much longer retention time. The fraction with the longer retention time was tested by MS and showed peaks for O-3 but no peaks for 3B or 2A. Recrystallization from MeCN gave petal-shaped orange crystals which were dried and analyzed, giving MS and NMR results consistent with a pure product (none of the oligomers gave crystals of sufficient quality for X-ray diffraction). The same was observed when a similar technique was applied to the synthesis of O-2.

The synthesis of O-4 and O-5 required that the O-2 and O-3 oligomers first be activated with the 5-hexynoic acid/EEDQ protocol. However, with the same number of equivalents used to form 3B, an incomplete reaction was observed by MS. The number of equivalents had to be increased to 25 before the reaction could be driven to completion, giving the hexynoic-acid, a degree of protonation (TBA cation loss) was observed when a similar technique was applied to the synthesis of O-4, but no peaks for O-3 were then reacted with an excess of 3A to form O-4 and O-5, respectively, which were both then dried on silica and isolated from the residual 3A using the RPLC column. A representation of the full synthesis of O-4 is given in Scheme 2 as an example.

Scheme 2. Scheme Showing the Full Synthesis of O-4

Several standard analytical techniques were used to confirm the identity of the POM oligomers. 1H NMR analysis could be used to compare the relative integrations of the triazole peak (∼8.7 ppm) with the four peaks for the TBA cations, which are proportional to n/n-1 where n is the number of Mn Anderson cores, making the ratio unique for each oligomer. ESI-MS gives less decisive results, since the CuAAC coupling reactions are entirely atom efficient and there is theoretically no m/z difference between the peaks of the coupled products and those that could be observed for the clustering of uncoupled products produced by ionization. However, the progress of the reaction can be followed by observing the disappearance of peaks corresponding to the uncoupled products as they are converted to the oligomers over the course of the reaction.

A range of more novel experiments were performed to obtain information about the size and cross section of the oligomers in both the liquid and gas phase, and to assess their suitability for monitoring future reactions. First, size-exclusion HPLC was performed, with the TRIS–Mn Anderson hybrid being used as a monomer and compared to the four TRIS-terminated oligomers, using a Phenomenex PolySep GFP-P 2000 size-exclusion column, which has a nominal size range from 100 to 10 000 Da (the size range of the oligomers runs from ∼2000 to ∼10 000 Da). Each of the compounds gave a single peak and, as anticipated, the retention times, shown in the SI, decreased with increasing number of Mn Anderson cores, although the difference between oligomers reduces sharply as the size approaches the separation limit of the column (see SI). In addition to being a useful analytical method, on a larger scale SEC separation of these hybrid POM chain-growth reactions may be a reliable means of purification, since the smaller fragments being added are clearly resolved from the growing oligomers. To further assess the specific sizes of the oligomers, we performed ion mobility spectroscopy—mass spectroscopy (IMS-MS), which separates ions on the basis of their size and shape. Ions’ drift time in the IMS cell is observed, which may be converted into the collision cross section they present on collision with gas present—a representation of their size (cf. hydrodynamic radius in SEC).

The results of this analysis are shown in Figure 1: a clear, regular increase in cross-sectional area across the four oligomers. Two separate drift times are observed for the three peaks of O-4, suggesting that there may be two different conformations of this molecule present in the gas phase, each with a different cross-sectional area (as has been observed before for Mn Anderson hybrids).2 This is interesting since we expect long chain oligomers to start to fold into well-defined secondary structures. Indeed, these observations have allowed us to devise strategies for the design and modeling of hybrid metal oxide oligomer chains that could produce specific folded architectures.

Figure 1. IMS-MS arrival time distributions of selected hybrid Mn Anderson oligomers, labeled with collision cross section measurements obtained: dimer = O-2, trimer = O-3, tetramer = O-4, and pentamer = O-5.
In conclusion, we have presented a new synthetic methodology for the synthesis of precisely defined hybrid organic–inorganic metal oxide architectures. By developing the coupling chemistry, a library of symmetric and asymmetric azide and alkyne metal oxide synthons, we were able to develop a set of reaction conditions that allowed us to “click” the building blocks together in a modular fashion without decomposition of the hybrid metal oxide clusters. Compared to previous hybrid POM couplings, this method allows for greater control over the number of metal oxide POM cores, which can be increased sequentially. To demonstrate this, we synthesized four monodisperse oligomeric Mn Anderson hybrids, from a dimer to a pentamer, and looked at the relative and absolute sizes of the oligomers and how their identity can be confirmed. These synthetic advances will enable the investigation of properties emerging from the oligomerization of these Mn Anderson cores not observed in their monomer analogues. The modularity and mild conditions of this approach should also permit the incorporation of a range of other POM cores. For instance, any TRIS-based hybrid could take the part of the Mn Anderson cluster, such as the Fe or Cr Anderson structures, the \( \{V_3\} \) Lindqvist, or the \( \{P,W_{15}V_3\} \) Dawson, in addition to the wealth of “click”-based components already readily available. We believe this methodology may be extended, both in solution and in the solid state (via a supported reagent approach), to produce configurable metal oxide hybrid oligomers >10 nm in size, and we are currently working toward this goal in our laboratory.

**ASSOCIATED CONTENT**

**Supporting Information**

Full description of all synthetic procedures and detailed analysis for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

**AUTHOR INFORMATION**

*Corresponding Author*

*lee.cronin@glasgow.ac.uk*

**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

This work was supported by the EPSRC (grants EP/H0241107/1, EP/I033459/1, EP/J015156/1, and EP/L0236521/1), EU FP7Micreagents (318671), and the University of Glasgow.

**REFERENCES**