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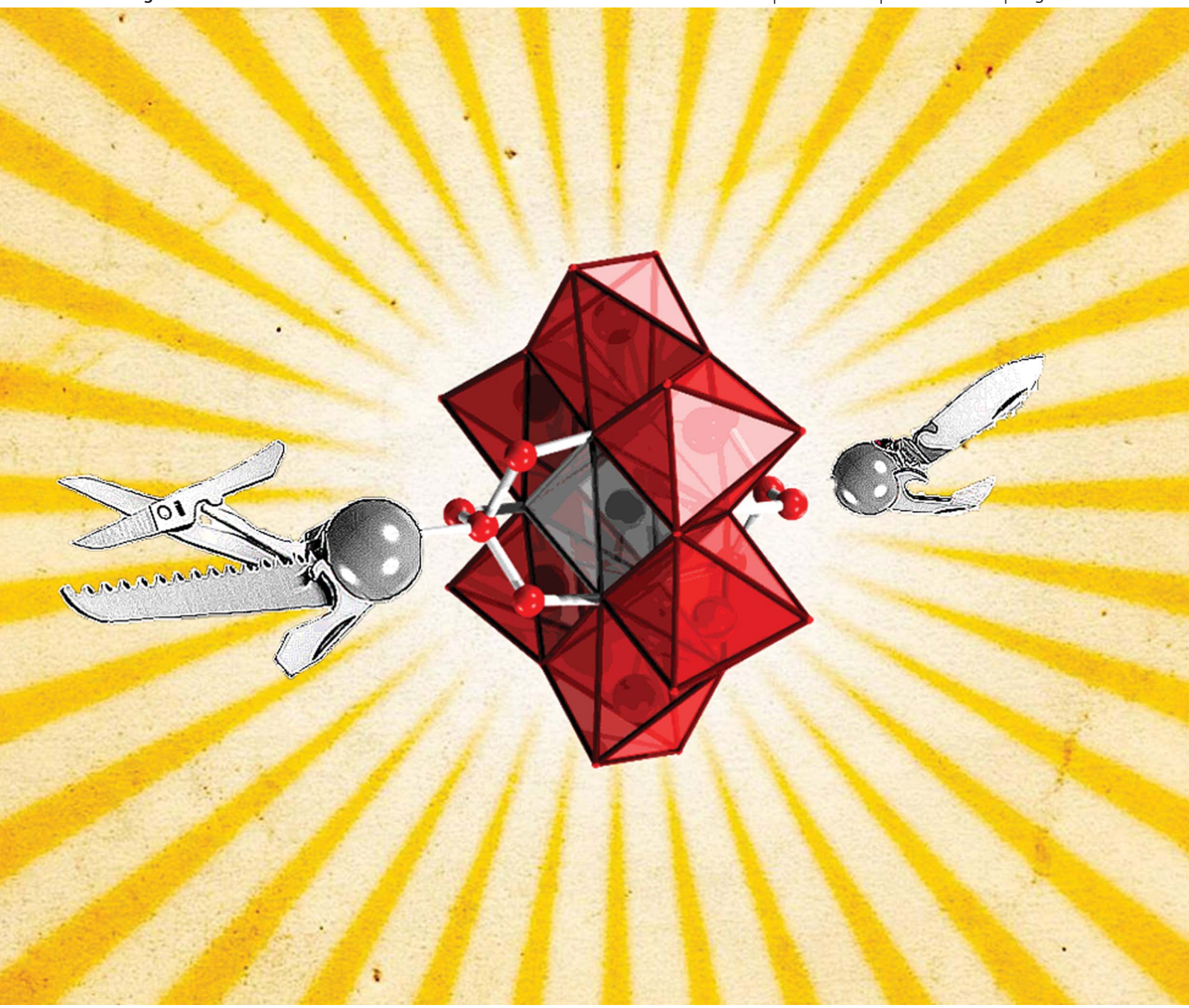

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A collection of robust methodologies for the preparation of asymmetric hybrid Mn–Anderson polyoxometalates for multifunctional materials†

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Here we report a suite of approaches for the isolation of asymmetrically grafted organic–inorganic hybrid Mn–Anderson polyoxometalate compounds $(TBA)_3[MnMo_6O_{18}((OCH_2)_3CNHR_1)((OCH_2)_3CNHR_2)]$ (where TBA = tetrabutylammonium). Both a "pre-functionalization" route (for compound **1** – $R_1 = -COC_{14}H_9$, $R_2 = -H$) using two different TRIS-based ligands ($(HOCH_2)_3CNHR$), and a "post-functionalization" of the preformed TRIS Mn–Anderson compound ($R_1 = R_2 = -H$) were demonstrated. Compounds **2** ($R_1 = -COC_{15}H_{31}$, $R_2 = -CO(CH_2)_2COOH$) and **3** ($R_1 = -COC_{15}H_{31}$, $R_2 = -H$) are some of the first reported examples of asymmetric Mn–Anderson compounds to have been synthesized by the latter route. The reliable and broadly applicable chromatographic method used to isolate these compounds relies on the difference in affinity of compounds' organic moieties for reverse phase (RP) media; the target asymmetric cluster will have an intermediate affinity, between that of the two symmetric by-products. For instances where this is not the case, we have prepared and isolated a "universal" asymmetric Mn–Anderson precursor **4** ($R_1 = -C(O)OC_{14}H_{11}$, $R_2 = -H$), which can be used as a precursor to synthesize practically any asymmetric Mn–Anderson system. The use of **4** as an "universal" precursor was successfully demonstrated in the synthesis and isolation of compound **5** ($R_1 = -COC_2H_5$, $R_2 = -H$), which would not be accessible by a simple 'one pot' approach. In addition to removing a significant barrier to the exploitation of asymmetric Mn–Anderson clusters as new functional materials, the methods presented here should be applicable to a range of other hybrid organic–inorganic clusters.

Introduction

Polyoxometalates (POMs), polyanions made up of high oxidation state transition metals linked by oxygen bridges, show great promise in a diverse range of fields such as electronics, catalysis and medicine,[1] but the challenges associated with their incorporation into devices remain a limiting factor in exploring their full potential. To overcome this, organic moieties can be attached to some metal-oxide frameworks to form organic–inorganic hybrid POM compounds, combining the versatility and well-established reactivity of organic ligands with the wide range of POM properties.[2] One method of forming these hybrid POM compounds is by incorporating alkoxide ligands into the POM framework, as demonstrated for the Lindqvist,[3] Dawson[4] and Anderson type architectures. Anderson-structure-based hybrids are commonly obtained for polyoxomolybdates incorporating Ni^{II}, Zn^{II}, Fe^{III} and Mn^{III} as a central heteroatom, by grafting two tris(alkoxo) groups (general formula: $(CH_2O)_3CR$) on either side of the planar metal-oxide arrangement characteristic of the Anderson structure.[5] Symmetrically functionalized Anderson clusters, bearing two identical ligands, have been widely studied,[6] primarily the Mn–Anderson cluster ($[MnMo_6O_{18}((CH_2O)_3CR)_2]^{3-}$). Pre-functionalization (organic ligands formed first then incorporated during the formation of the hybrid cluster),[7] post-functionalization (hybrid cluster formed first then modified by organic reactions)[8] and analytical techniques[9] have been developed to allow the grafting of increasingly intricate organic moieties and improve our understanding of the formation of hybrid POM architectures. Over the course of these studies, the use of organic ligands has proven to be a convenient means of introducing POMs into functional materials, such as vesicular self-assemblies,[8a] polymers[10] and directed surface assemblies.[7c] One such hybrid, the Anderson type structure, incorporates two ligands, with reports so far overwhelmingly concentrating on symmetric compounds where the two ligands are identical. However, it is also possible to use different ligands, giving "asymmetrically" capped hybrid systems. Only a few examples of these asymmetric compounds have been reported for the Mn–Anderson[11] along with the recent report of an

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Anderson-type compound functionalized on only one side[12] and a Lindvist-type polyoxovanadate with two different ligands.[13] This dearth may be explained by the fact that, as yet, no method exists to selectively form only the asymmetric product, nor is there a reliable technique for isolating this asymmetric compound from the symmetric by-products usually present in the reaction mixture. Fractional crystallization has been successful,[11a,c] but its success varies from one compound to another and it can be difficult to reproduce, precluding its routine use. Nevertheless, the few asymmetric Mn–Anderson clusters which have been successfully synthesized have proven their value as a mean of, for example, modulating the self-assembly behaviour of POMs on surfaces[11c] and allowing the covalent functionalization of surfaces to study selective cell adhesion.[11b]

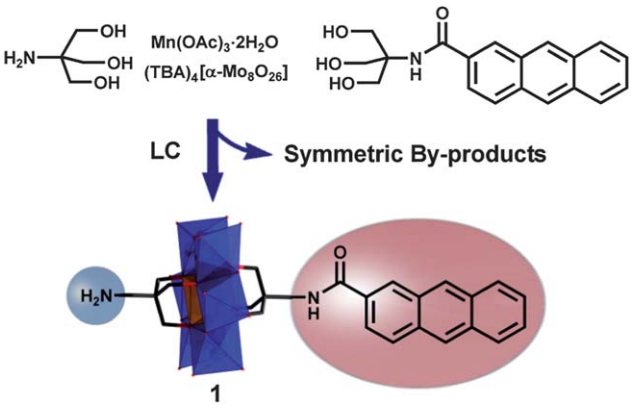
Liquid chromatography (LC) is a powerful technique which allows the analytical and preparative separation of materials from mixtures by exploiting the competitive interactions of the molecules with the stationary and mobile phases of a column. While extensively used in organic chemistry, LC is barely mentioned in hybrid POM chemistry. One attempt to purify a symmetrically grafted Mn–Anderson compound *via* normal phase chromatography was published by W. Wang *et al.*,[14] but lead to an undesired cation exchange (protonation of the cluster, which creates solubility issues) and poor yields. This inconvenience resulted in them later reporting a post-functionalization method which did not require further purification and writing: "the ability to circumvent chromatographic purification is extremely important […]".[8b]

As the purification of asymmetric hybrid compounds is the major obstacle limiting the exploration of their full potential, we began to investigate new methodologies to overcome it. An ideal method should be widely applicable, not only working for a narrow set of compounds but compatible with a diverse range of ligands and functionalities. Since reverse phase LC has been successfully applied to the resolution of various charged metal complexes,[15] we chose to investigate whether this could be used to resolve our hybrid Mn–Anderson POM mixtures.

Results and discussion

Proof of concept

In order to separate an asymmetric Mn–Anderson compound from the two corresponding unwanted symmetric by-products, the affinities of the two ligands for the stationary phase must be significantly different, yielding an asymmetric product of intermediate affinity – therefore, as a model compound, we chose a Anthracene–TRIS/TRIS Mn–Anderson compound ($(TBA)_3[MnMo_6O_{24}(C_{19}H_{16}NO)(C_4H_8N)]$, **1**). The fluorescent Anthracene–TRIS ligand, a very hydrophobic moiety (more strongly retained by RP media), could be used to form modular polymers[16] or be further functionalized by Diels–Alder reactions,[17] while the TRIS ligand ($((CH_2O)_3CNH_2)$), a far less hydrophobic moiety (less strongly retained by RP media), could be further modified by established post-functionalization techniques[8a,c] or used as an anchorage point for covalent surface functionalization.[11b] The asymmetric compound was formed in a one-pot pre-functionalization reaction (see Scheme 1) where



Scheme 1 Preparation of the Anthracene–TRIS/TRIS Mn–Anderson compound (**1**) (pre-functionalization approach). Color scheme: Mo (blue), Mn (orange), O (red), TBA cations are omitted for clarity.

the two tris(alkoxide) ligands are reacted with tetrabutylammonium octamolybdate $(TBA)_4[\alpha\text{-}Mo_8O_{26}]$ and manganese acetate ($Mn(OAc)_3$) in a refluxing solution of acetonitrile (MeCN).[6] This reaction leads to the formation of the asymmetric product (**1**) along with two unwanted symmetric by-products: TRIS Mn–Anderson and Anthracene Mn–Anderson $(TBA)_3[MnMo_6O_{24}(C_{19}H_{16}NO)_2]$. These products were all collected together as a mixture, from here on referred to as the crude mixture.

Test separation of the crude mixture was first performed on an analytical scale using standard C_{18} RP-HPLC columns eluted with a gradient of ammonium acetate buffer–MeCN (A–B) solvent mixture and revealed three peaks (Fig. 1a): the first one (0.85 minutes) is the least hydrophobic product, while the two

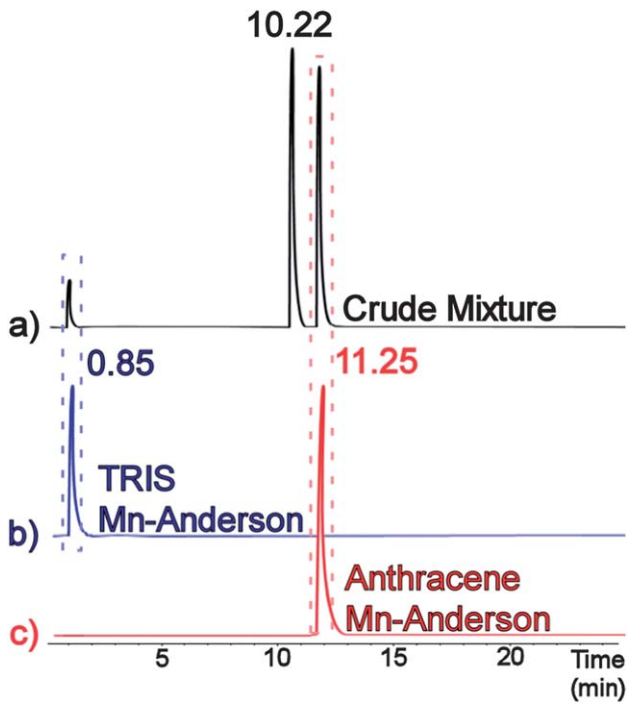


Fig. 1 RP-HPLC chromatograms of the crude mixture (a), the symmetrically pure TRIS Mn–Anderson (b) and the symmetrically pure Anthracene Mn–Anderson (c). Peaks assigned to the same compound are highlighted.

subsequent products (10.22 and 11.25 min) have higher affinities for the column, being correspondingly more hydrophobic. This was confirmed by correlation with analysis of pure samples of the symmetric by-products (synthesized by adaptation of a reported procedure)[6] under the same conditions. As expected, each pure compound produced a single peak, with TRIS Mn–Anderson barely retained on the column (matching the 0.85 min peak in the crude mixture; see Fig. 1b) and the Anthracene Mn–Anderson compound exhibiting a high affinity for RP media (matching the 11.25 min peak in the crude mixture, see Fig. 1c). The remaining peak could thus be reasonably assigned as the asymmetric product (**1**), which as expected manifested an intermediate affinity for the RP media.

This analytical RP-HPLC method was then adapted for preparative scale using standard commercially available C_{18} silica flash columns. Due to the poor solubility of the crude material in solvent A, it was introduced by a 'dry loading' method (adsorbed on celite, 20 wt%) and the fraction of solvent B at the beginning of the gradient was increased to ensure prompt transfer from the celite adsorbant onto the RP-silica column (ensuring separation by affinity, not solubility). Elution was detected by UV and an evaporative light scattering detector (ELSD), giving the chromatograms shown in Fig. 2a: the sharp peaks observed in RP-HPLC are very much broadened, but are still manifested as three distinct regions (I, II and III). Eluent corresponding to each region was collected (denoted as solution I, II and III) and analyzed by ESI-MS (spectra are shown in the ESI†) and RP-HPLC using the previously established conditions (chromatograms are given in Fig. 2b), allowing us to confirm the identity of the products eluted and their purity. The ESI-MS analysis of II confirmed the presence of the asymmetric Mn–Anderson product **1**, as several of the observed peaks can be assigned to fragments from the Anthracene–TRIS/TRIS Mn–Anderson cluster (Fig. S9 and Table S5†), while no peaks could be assigned to fragments of the symmetric by-products. RP-HPLC analysis of II confirm its purity: only one peak was observed (at 10.22 minutes, corroborating the assignment in the analytical separation), with both symmetric by-product peaks absent. Similarly, ESI-MS and RP-HPLC analyses of solutions I and III confirmed their identities as pure symmetric products (TRIS and Anthracene Mn–Anderson, respectively).

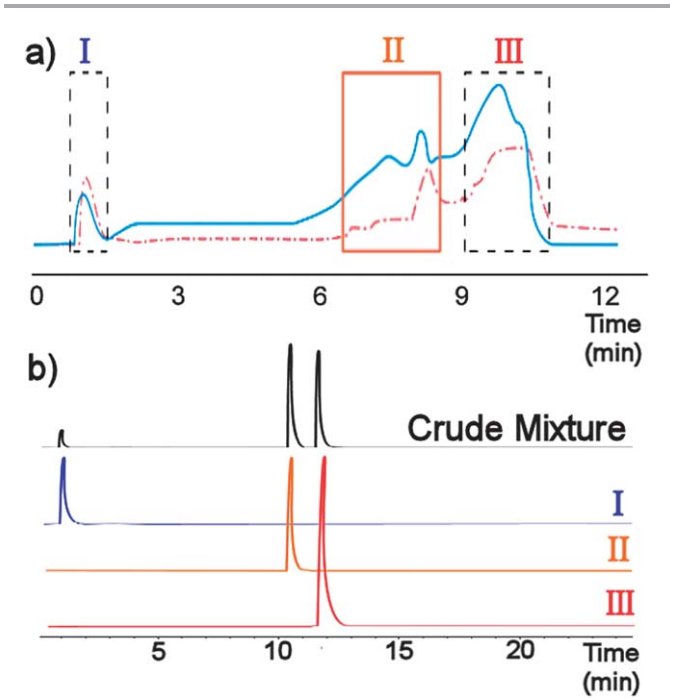


Fig. 2 (a) Chromatograms of the crude mixture separation on a preparative scale (UV at $\lambda = 254$ nm: solid blue line, ELSD: dashed pink line). Regions highlighted (I, II and III) correspond to the three products of reaction being eluted pure. In region II compound **1** is eluted pure. (b) RP-HPLC chromatograms of the solutions I, II and III confirming the identity and the purity of the product eluted in each region by comparison with the crude mixture.

To isolate **1**, solution II was collected and an excess of TBA bromide was added to ensure that **1** was isolated as a pure TBA salt (during ESI-MS analysis some protonated fragments were observed leading us to suspect that some minor cation exchange may occur in solution). The MeCN was evaporated leaving an aqueous solution from which an orange precipitate forms; this precipitate was crystallized from MeCN under slow ether diffusion (Et_2O) to yield pure compound **1**. The full characterization of **1** by elemental, NMR and X-ray crystallographic analyses proved that it was isolated as a pure TBA salt. The structure of **1**, based on X-ray crystallography, demonstrated the typical Mn–Anderson organization of the POM framework and the asymmetric feature of the compound with the TRIS ligand on one side of the metal-oxygen framework plane and the Anthracene–TRIS ligand on the other.

The separation by flash chromatography and the isolation of compound **1** is highly reproducible. Fig. S11† shows chromatograms for repetition of the same separation under the same conditions producing comparable yields and purity; this reproducibility is mirrored across the range of compounds. The efficiency of the separation, repeatability of the result, and the simplicity of the workup, make this chromatographic method suitable for the isolation of **1**. Nevertheless, a widely applicable method should be valid for a variety of pendant groups, so we started to study its applicability to other asymmetric Mn–Anderson clusters.

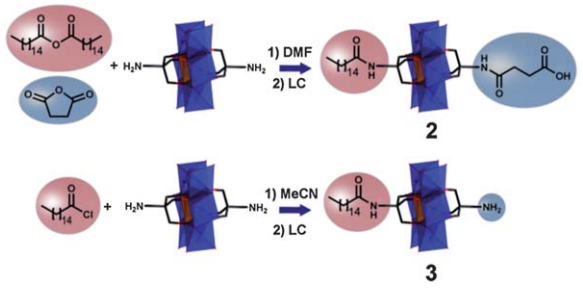
'Post-functionalization' approaches

To investigate whether the chromatographic methodology would be broadly applicable, two other ligand systems were studied under the same conditions as those established for compound **1**. Since **1** was synthesized *via* a pre-functionalization route adapted from a previous report, we wanted to investigate some new synthetic paths for the creation of asymmetric Mn–Anderson compounds, and so started to explore a variety of post-functionalization approaches. Here, the crude mixtures were synthesized by modification of the TRIS Mn–Anderson precursor using the reactive amine groups grafted on the POM as anchorage points to introduce more complex ligands. The use of a general precursor allows us to circumvent the ligand synthesis step and directly access certain functional groups which might make free ligands difficult to isolate (*e.g.* carboxylic acids).

The crude mixture of compound **2** was produced by reacting the preformed TRIS Mn–Anderson cluster with two different anhydrides: palmitic and succinic (Scheme 2). The reactivity of the TRIS Mn–Anderson compound with anhydrides was previously reported, and makes a large variety of pendant groups available.[8c] These ligands were selected firstly for their different hydrophobicities as well as other properties: clusters with the hydrophobic palmitic ligand have proven to be able to form self-assembled amphiphilic features,[8a] while the succinic anhydride introduces a carboxylic acid group on the cluster, which could subsequently be used as an anchorage point for further post-functionalization. The reaction conditions were briefly refined to give the asymmetric compound as the major product. We found that 4 equivalents of succinic anhydride and 2 equivalents of the palmitic anhydride (compared to the TRIS Mn–Anderson compound) lead to compound **2** ($(TBA)_3[MnMo_6O_{24}(C_{20}H_{38}NO)(C_8H_{12}NO_3)]$) as the major product (see ESI† for further details). The synthesis of the crude mixture of compound **3** was adapted from a reported procedure where palmitoyl chloride was used to react with both amines forming a symmetrically grafted Mn–Anderson amphiphile,[8a] and here the number of equivalents of palmitoyl chloride was reduced to obtain asymmetric compound **3** ($(TBA)_3[MnMo_6O_{24}(C_{20}H_{38}NO)(C_4H_8N)]$) as the major product (Scheme 2).

The mother liquors of both reactions were directly adsorbed on celite and purified using the chromatographic methodology. As for compound **1**, the chromatograms of compounds **2** and **3** consisted of three distinct regions with the middle one corresponding to the asymmetric product. Compounds **2** and **3** were both isolated as pure TBA salts using the same work up as that established for the isolation of compound **1**. The purity and identity of both compounds were checked by elemental, RP-HPLC and ESI-MS analyses (see ESI†).

The isolation of compound **2** and **3** following the same methodology as that established for compound **1**, without any alterations, demonstrates that this method can be reliably applied to purify a range of asymmetric hybrid Mn–Anderson clusters, so long as the ligands have sufficiently different affinities for RP media. However, to entirely eradicate the asymmetric isolation 'issue' allowing full focus on the design and study of the asymmetric compounds rather than their separation, resolution of Mn–Anderson clusters with different ligands of similar affinity for the RP media must also be addressed.



Scheme 2 Preparation of **2** and **3** using TRIS Mn–Anderson as a precursor (post-functionalization approach). Color scheme as in Fig. 1.

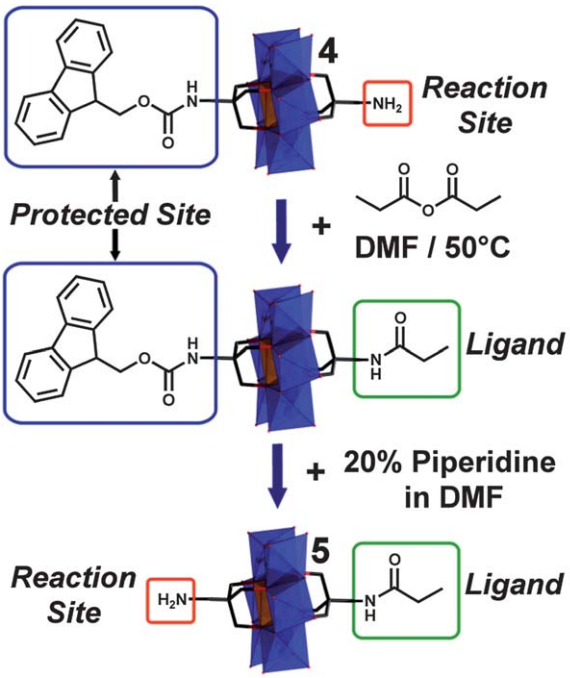
A "universal" asymmetric Mn–Anderson precursor

The chromatographic methodology presented here uses the differences of affinity for the RP stationary phase of the three compounds present in the crude mixture. Compounds **1** to **3** all have one hydrophilic and one hydrophobic ligand, hence the reaction mixtures are readily resolved. However, if two similarly-hydrophobic ligands were used, this method would not give sufficient resolution for a preparative separation (*i.e.* asymmetric products with two hydrophobic or two hydrophilic ligands would not be separated from their symmetric by-products). To overcome this issue, we set out to synthesize an asymmetric compound that could be isolated using the present chromatographic methodology and could then be used as a "universal" precursor for the synthesis of asymmetric Mn–Anderson compounds which could not be so readily separated, due to similar ligand affinities. Such a compound should have a reactive site which can be modified easily by post-functionalization techniques and a protected site that can be deprotected by simple reaction steps compatible with the metal-oxide core.

The 9-fluorenylmethyloxycarbonyl (Fmoc)[18] group used for the protection of amines, which can be removed under mild conditions compatible with the POM cluster (treatment with a solution of piperidine), is extremely hydrophobic, making it an appealing candidate for the protection of a "universal" precursor. Thus, an Fmoc protected TRIS ligand was synthesized following a reported procedure[19] and used to form an Fmoc–TRIS/TRIS Mn–Anderson compound (**4**, $(TBA)_3[MnMo_6O_{24}(C_{19}H_{18}NO_2)(C_4H_8N)]$), *via* a pre-functionalization approach. The pure asymmetric compound **4** was successfully isolated following the established chromatographic method and characterized by elemental, HPLC and ESI-MS analyses; the structure of **4** was obtained by single crystal X-ray crystallography, confirming the Fmoc protection of one amine of the TRIS Mn–Anderson cluster.

To illustrate the idea that compound **4** could be used as a "universal" asymmetric precursor to synthesize practically any asymmetric organic–inorganic Mn–Anderson cluster, it was used to synthesize **5** ($(TBA)_3[MnMo_6O_{24}(C_7H_{12}NO)(C_4H_8N)]$), an asymmetric propylamide/TRIS Mn–Anderson compound which could not previously be isolated using the chromatographic methodology, since neither the symmetric nor the asymmetric compounds are sufficiently hydrophobic to be retained on the column. **5** was synthesized in two steps (Scheme 3): **4** was first reacted with 10 equivalents of propionic anhydride and the intermediate product isolated by crystallization to remove the excess of acid. Subsequently, the intermediate product was treated with a 20% solution of piperidine in DMF to remove the Fmoc group and pure **5** was isolated by crystallization with Et_2O diffusion. All the analyses revealed that the amine was fully deprotected while the hybrid Mn–Anderson remained intact and as a pure TBA salt.

4 can therefore be considered a "universal" asymmetric Mn–Anderson precursor (barring unstable or reactive groups) since its structure allows for the formation and isolation of practically any other asymmetric Mn–Anderson compound by a succession of post-functionalization steps.



Scheme 3 Synthetic route for the synthesis of **5** by post-functionalization of the "universal" asymmetric Mn–Anderson precursor (**4**). Color scheme as in Fig. 1.

Conclusions and outlook

Here we report a reliable chromatographic methodology which drastically simplifies the isolation of asymmetric Mn–Anderson compounds, providing a difference in affinity for RP media between the two ligands. Where this condition is not met, we have shown that the difficulty can be overcome by post-functionalization of a "universal" asymmetric Mn–Anderson precursor. This suite of approaches should allow the routine isolation of practically any asymmetric Mn–Anderson compound, as illustrated by the diversity of the new compounds reported here, freeing researchers to concentrate on design and application of these materials (suggestions of which are given in Fig. 3) instead of incessant re-development of tedious purification techniques.

During our studies we have used a flash chromatography system with integrated detectors and standard C_{18} silica pre-packed columns (for practicality and safety). While convenient, elaborate equipment is not necessary for these separations: a standard 'manual' flash column could also be used (given means to safely apply enough pressure) and a whole range of alternative means (commercial and bespoke) exist to drive such a separation. Where a detector is not available, fractions may be characterized afterwards by other methods (*e.g.* RP-TLC, RP-HPLC, ESI-MS).

Furthermore, application of the chromatographic methodology presented here need not be limited to asymmetric Mn–Anderson clusters, and should be useful in a wide range of hybrid POMs. Indeed, RP-HPLC is already changing the way our group approaches hybrid POM synthesis, proving an invaluable tool to monitor reactions and confirm purity beyond this work.

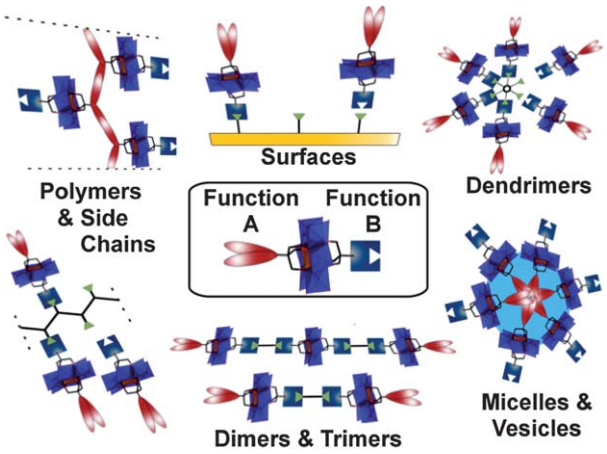


Fig. 3 Schematic representation of some of the potential applications of bi-functional asymmetric Mn–Anderson compounds in material and devices. In all of these cases, control of reactivity either side of the metal-oxide cluster is important to achieve the desired function.

Experimental

Instrumentation and materials

The instrumental operating conditions for the flash chromatography separations and the RP-HPLC analyses are given in Table 1 and further details on the instruments can be found in

Table 1 Instrumental operating conditions for RP-HPLC and flash chromatography

General			
Mobile phase	0.05 M ammonium acetate buffer (pH = 6.7–6.9) – solvent A MeCN – solvent B		
RP-HPLC			
Column	Phenomenex Luna® 3 μm C_{18}(2) 100 Å, 150 × 2 mm		
Gradient	Time (min)	A (%)	B (%)
	0.0	95	5
	3.0	95	5
	15.0	5	95
	17.0	5	95
Injection volume	5 μL		
Flow rate	0.5 mL min^{-1}		
Column temperature	25 °C		
Detector	UV (λ = 254 nm)		
Flash chromatography			
Column	Pre-packed Reveleris® C_{18} 4 g columns (two in series)[a]		
Gradient	Time (min)	A (%)	B (%)
	0.0	65	35
	2.2	65	35
	11.8	5	95
	12.9	5	95
Injection type	Adsorption on celite® 535 coarse (20 wt%, maximum total weight 1.8 g)		
Flow rate	18 mL min^{-1}		
Equilibration time	4 min		
Detector	UV (λ = 254 nm); ELSD		

[a] May be reused several times without loss of resolution.

the ESI.† 0.05 M ammonium acetate buffer at pH = 6.7–6.9 was obtained by dissolving 3.85 g of ammonium acetate (Fisher Scientific) in 1 L of deionized water. MeCN of HPLC grade was purchased from Fisher Scientific. Celite® 535 coarse purchased from Fluka was used for dry loading and is in the text referred to as "celite". Information on the instruments used for analyses can be found in the ESI.† When not specified, reagents were obtained from commercial sources.

Pre-functionalization approach

This synthetic path is suitable for clusters with one hydrophilic and one hydrophobic ligand when the ligands can be readily obtained *via* normal organic routes or when the post-functionalization approach would not succeed (*e.g.* reaction conditions not compatible with the metal-oxide core or solubility issues encountered with the TRIS Mn–Anderson compound). Compounds **1** and **4** were synthesized by a pre-functionalization approach based on previous reports,[11a,c] where the ligand is first synthesized by standard organic reactions and then grafted into the POM framework during the synthesis of the hybrid Mn–Anderson compound.

The synthesis of compound **4**, the "universal" asymmetric precursor, is presented here as an example of the pre-functionalization approach. The synthesis of compound **1** can be found in the ESI.†

Compound 4 – Fmoc–TRIS/TRIS Mn–Anderson compound $(C_{16}H_{36}N)_3[MnMo_6O_{24}(C_{19}H_{18}NO_2)(C_4H_8N)]$. A mixture of tetrabutlammonium octamolybdate[20] ($(TBA)_4[\alpha\text{-}Mo_8O_{26}]$, 1.53 g, 0.71 mmol), manganese acetate dihydrate ($Mn(OAc)_3\cdot 2H_2O$, 0.44 g, 1.62 mmol), tris(hydroxymethyl)aminomethane (TRIS, $((HOCH_2)_3CNH_2)$ 0.28 g; 1.87 mmol) and Fmoc–TRIS[19] ($(HOCH_2)_3CNH$–Fmoc, 0.64 g; 1.87 mmol) was refluxed in MeCN (45 mL) for 18 h. The resulting brown mixture was cooled down to room temperature and the precipitate removed by centrifugation to lead to a bright orange solution. The crude mixture was isolated by crystallization by Et_2O diffusion. After three days, orange crystals were formed and isolated (crude mixture yield: 1.40 g). 300 mg of the crude mixture adsorbed on celite (1.5 g) were purified *via* flash chromatography under the operating conditions summarized in Table 1. The purity of the fractions was established by RP-HPLC. The fractions composed exclusively of the asymmetric Fmoc–TRIS/TRIS Mn–Anderson cluster (retention time 10.26 min) were combined and a large excess of TBA bromide (0.5 g; 1.55 mmol) was added to the resulting solution. MeCN was evaporated under vacuum leading to the formation of an orange precipitate in the remaining aqueous solution. This precipitate was isolated by centrifugation and then dissolved in MeCN. The solution was centrifuged to remove any insoluble material and set up for crystallization with Et_2O diffusion. Within 3 days crystals of compound **4** were formed, dried and analyzed. Single crystals suitable for X-ray diffraction were grown from DMF by slow Et_2O diffusion (cubic crystal, 3 days). Yield: 588 mg, 0.28 mmol, 30% based on Mo (estimated from the purification of 300 mg of the crude material; equivalent to a 60% recovery of the asymmetric product); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 0.93 (m, 36H, CH_3 from TBA^+), 1.31 (m, 24H, CH_2 from TBA^+), 1.56 (m, 24H, CH_2 from TBA^+), 3.16 (m, 24H, CH_2 from TBA^+), 3.55 (s, br, 2H, NH_2), 4.23 (m, 3H, CH_2 + CH), 7.25–7.67 (m, 5H, 4 CH + NH), 7.75 (m, 2H, 2 CH), 7.88 (d, 2H, 2 CH, J = 7.4 Hz), 60.00–65.00 ppm (s, br, 6 CH_2); ^{13}C DEPTQ NMR (DMSO-d_6, 100 MHz): δ = 13.5 (CH_3), 19.2 (CH_2), 23.0 (CH_2), 46.7 (CH), 57.5 (CH_2), 65.7 (CH_2), 120.0 (CH), 125.6 (CH), 127.1 (CH), 127.6 (CH), 140.6 (C), 143.8 ppm (C); elemental analysis: calc. for $C_{71}H_{134}MnMo_6N_5O_{26}$ (2104.42 g mol^{-1}): C, 40.52; H, 6.42; N, 3.33; found: C, 40.52; H, 6.45; N, 3.41%.

Post-functionalization approach

This synthetic route, suitable for clusters with one hydrophilic and one hydrophobic ligand and reaction conditions compatible with the Mn–Anderson cluster, is usually faster than the pre-functionalization approach. A brief optimization of the reaction conditions to obtain the asymmetric as the major product might be needed (relative proportions of asymmetric and symmetric in the crude mixtures can be estimated by RP-HPLC or ESI-MS). Compounds **2** and **3** were synthesized by a post-functionalization approach, where the TRIS Mn–Anderson[6] is used as a common precursor and is modified by standard organic reactions. Other TRIS-based Mn–Anderson precursor could be used so long as reactive groups are available on the hybrid POM.

The synthesis of compound **2** is presented here as an example of the pre-functionalization approach. The synthesis of compound **3** is given in the ESI.†

Compound 2 – palmitic–TRIS/succinic-acid–TRIS Mn–Anderson compound $(C_{16}H_{36}N)_3[MnMo_6O_{24}(C_{20}H_{38}NO)(C_8H_{12}NO_3)]$. Succinic anhydride (72 mg, 0.64 mmol, 4 equiv.) and palmitic anhydride (180 mg, 0.32 mmol, 2 equiv.) were added to a solution of TRIS Mn–Anderson (300 mg, 0.16 mmol) in DMF (5 mL) and left to react overnight at 50 °C. The bright orange solution was then cooled to room temperature and, without any purification, celite (1.5 g) was added and the solvent evaporated under vacuum to obtain a powder ('dry loading'). The crude material adsorbed on celite was purified by flash chromatography (see Table 1 for further details). The pure fractions (purity checked by RP-HPLC, retention time of interest: 12.85 min) were combined and a large excess of TBA bromide (0.5 g, 1.55 mmol) was added to the resulting light orange solution. The MeCN was evaporated under vacuum leading to the formation of an orange precipitate in the remaining aqueous solution. This precipitate was isolated by centrifugation and then dissolved in MeCN. The solution was centrifuged to remove any insoluble material and left undisturbed for crystallization with Et_2O diffusion. Within 3 days, crystals of compound **2** were formed, dried and analyzed. Yield: 95 mg, 0.043 mmol, 27%; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 0.85 (m, 3H, CH_3), 0.94 (m, 36H, CH_3 from TBA^+), 1.15–1.70 (m, 74H, 13 CH_2 + 2× CH_2 from TBA^+), 2.24–2.45 (m, 4H, 2 CH_2), 2.66 (s, br, 2H, CH_2), 3.17 (m, 24H, CH_2 from TBA^+), 7.32 (s, br, 1H, NH), 7.90 (s, br, 1H, NH), 11.20 (s, br, 1H, OH), 62.00–66.00 ppm (s, br, 6 CH_2); ^{13}C DEPTQ NMR (DMSO-d_6, 100 MHz): δ = 13.5 (CH_3), 13.9 (CH_3), 19.2 (CH_2), 22.0 (CH_2), 23.1 (CH_2), 26.3 (CH_2), 28.7 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 31.2 (CH_2), 33.7 (CH_2), 57.5 ppm (CH_2); elemental analysis: calc. for $C_{76}H_{158}MnMo_6N_5O_{28}$ (2220.66 g mol^{-1}): C, 41.11; H, 7.17; N, 3.15; found: C, 41.09; H, 7.26; N, 3.26%.

"Universal" precursor (4) approach

This approach is suitable for the synthesis of asymmetric Mn–Anderson compounds with two ligands of similar affinity for RP media (whether the ligands are hydrophobic or hydrophilic). It can also be considered as an alternative to the post-functionalization approach if the two organic moieties will not react under the same reaction conditions.

Compound **5** was synthesized from the "universal" precursor **4** using a succession of post-functionalization steps.

Compound 5 – propylamide–TRIS/TRIS Mn–Anderson compound $(C_{16}H_{36}N)_3[MnMo_6O_{24}(C_7H_{12}NO)(C_8H_{12}NO_3)]$. Compound **4** (50 mg, 0.03 mmol) and propionic anhydride (33 mg, 0.25 mmol, 10 equiv.) were dissolved in DMF (1 mL) and heated overnight at 50 °C. The intermediate product was isolated from the bright orange solution by crystallization with slow Et_2O diffusion. A small sample of the product was analyzed by ESI-MS to check the presence of the intermediate product and the absence of the POM starting material (Fig. S37†). The crude material was then treated for 5 h at room temperature with a 20% piperidine solution by volume in DMF (1 mL). Solvent was evaporated under vacuum and the resulting orange powder washed twice with Et_2O. The orange product was dissolved in MeCN and diffusion of Et_2O into the MeCN solution resulted in the formation of crystals of pure compound **5** within 4 days. **5** was isolated, dried and analyzed. Crystals suitable for X-ray diffraction were grown from DMF with slow Et_2O diffusion. Yield: 43 mg, 0.02 mmol, 88%; ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 0.94$ (m, 39H, CH_3 + CH_3 from TBA^+), 1.31 (m, 24H, CH_2 from TBA^+), 1.57 (m, 24H, CH_2 from TBA^+), 2.40 (m, 2H, CH_2), 3.16 (m, 24H, CH_2 from TBA^+), 3.53 (s, br, 2H, NH_2), 7.37 (s, br, 1H, NH), 60.00–65.00 ppm (s, br, 12H, 6 CH_2); ^{13}C DEPTQ NMR (DMSO-d_6, 100 MHz): $\delta = 10.9$ (CH_3); 13.5 (CH_3), 19.2 (CH_2), 23.1 (CH_2), 27.0 (CH_2), 57.5 ppm (CH_2), elemental analysis: calc. for $C_{59}H_{128}MnMo_6N_5O_{25}$ (1938.24 g mol^{-1}): C, 36.56; H, 6.66; N, 3.61; found: C, 36.41; H, 6.69; N, 3.66%.

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