Chiral Polyoxometalates

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Chiral Recognition of Hybrid Metal Oxide by Peptides**

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Over the past decade, the importance of nanosized inorganic clusters in fields as diverse as catalysis and biotechnologies has soared.[1] However, whereas preparation of enantiopure organic molecules has become a routine task, that of chiral nanoclusters remains very challenging, despite their great potential for asymmetric catalysis or biological molecular recognition.[2]

Polyoxometalates (POMs) are a diverse family of metal oxide clusters, with defined architectures and variable, but controlled, sizes in the nanometer range. They can be selectively further derivatized with organic molecules.[3] This structural diversity allows tuning of the metal oxide's physical and chemical properties (such as, redox, electronic, bioactivity), and thus offers significant opportunities in catalysis, drug discovery, imaging, and materials research.[4] Access to chiral enantiopure POMs would offer wide new perspectives, for example, in asymmetric catalysis, selective targeting of chiral biomolecules, the control of crystal polymorphism, molecular electronics.

Chirality in POM chemistry[5] can derive from stereogenic arrangement of achiral subunits in the solid state or in supramolecular assemblies.[6] Intrinsically chiral POM frameworks can be synthesized, in a racemic[7] or enantiopure[8] form. Achiral POM structures can be made chiral by the removal of one metal atom (formation of a lacunary POM), or by its substitution with a heterometal or other atom. This approach does not modify much the overall shape of the cluster, so the resulting chirality is extremely subtle. Thus, no chiral POM of this type has to date been resolved. We present herein the first example of such a resolution.

We decided to approach the α_1-substituted Dawson polyoxotungstate $[\alpha_1\text{-}MP_2W_{17}O_{61}]^{n-}$ (Figure 1 a). The exterior of this POM is mostly an oxide surface, with no marked steric differences that an approaching molecule could take advantage of to discriminate between enantiomers (Figure 1 b).

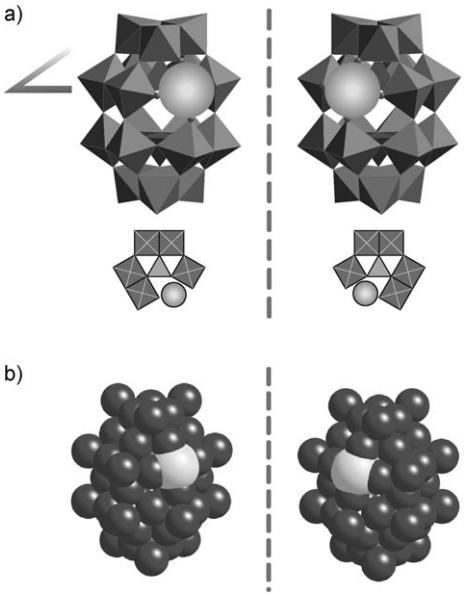

Figure 1. Chirality of the Dawson moiety $\{\alpha_1\text{-}SnP_2W_{17}O_{61}\}$: a) polyhedral representation and representation of the horizontal plane indicated by the shaded angle; b) Space-filling model (Sn in light gray).

In a seminal article, Pope and co-workers showed that complexation of $[\alpha_1\text{-}CeP_2W_{17}O_{61}]^{7-}$ with amino acids gave diastereomeric arrangements, differentiated in the ^{31}P NMR spectrum.[9] Based on our observation that a strong bond to the organic ligand coupled to additional hydrogen bonds allowed better chiral sensing of $[\alpha_1\text{-}YbP_2W_{17}O_{61}]^{7-}$,[10] we surmised that multiple hydrogen-bonding interactions with organic molecules could provide the key to directed chiral recognition and resolution.

We felt that our recently reported oxo-acyl platform $(TBA)_6[\alpha_1\text{-}P_2W_{17}O_{61}\{SnCH_2CH_2C(=O)\}]$ (**1**)[11] (TBA = tetra-*n*-butyl ammonium) should be a good target for kinetic resolution since it has a reactive, activated carboxyl moiety directly attached to the stereogenic POM framework. We have shown that **1** exists as a single regioisomer, most likely with the acyl group attached to the Sn-O-W oxo ligand of the edge-sharing Sn,W diad in the belt.[11] In addition, and contrary to the case with the other chiral POMs reported to date, **1** can be further functionalized and would thus provide us with an entry to a great variety of hybrid chiral POMs.

Oligopeptides appeared to be good candidates to establish hydrogen bonds with the polyanionic nanocluster. They are easily available in both enantiomeric forms. To accommodate the size of the POM, and thus to increase the odds to achieve

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chiral recognition of the metal-oxo framework, we selected tripeptides as the organic partners.[12]

In a typical experiment, racemic **1** was treated with 0.5 equivalents of the peptide H_2N-Trp-Ala-Leu-CO_2Me at room temperature for one day (Table 1). The desired adduct (**2a**) was isolated together with residual **1**. One of the diastereomers of the POM conjugate **2a** was formed in slight excess (59/41, as determined by ^1H NMR spectroscopy, entry 1). As expected, lower temperatures led to better selectivity (Table 1; entries 2 and 3), with −40 °C allowing the best compromise between selectivity and conversion, as the reactions became extremely slow at lower temperatures. The selectivity factor[13] was estimated at 6.

Variation of the amino acids resulted in slight modifications in the selectivity (Table 1; entries 4–7). The use of a simple chiral amine led to low selectivity (Table 1; entry 8). This result validates our initial hypothesis that extended chains should better wrap around the nanosized POM, and that this predominantly takes place via hydrogen bonding of the peptide to the negatively charged cluster.

From our initial screening it appeared that H_2N-Trp-Ala-Leu-CO_2Me was the most promising tripeptide. We thus used it to optimize the kinetic resolution. Carrying out the reaction between racemic **1** and 1 equivalent of the tripeptide at −40 °C for 48 h delivered about 78 % converted POM **2a** in approximately 65/35 diastereomeric ratio, along with 20 % recovered **1** (Scheme 1). Separation of the two POMs was challenging. We optimized a mixed-solvent system to take full advantage of slight solubility differences. Thus, **1** selectively precipitated out of an acetone/EtOH (1:1) solution of **1** and **2a** upon addition of diethyl ether (see Experimental Section for additional details).

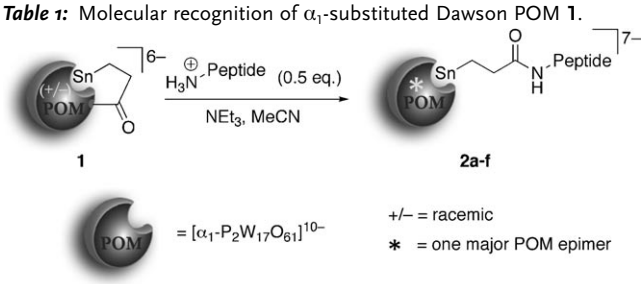
NMR spectroscopic analysis (^1H, ^{31}P, ^{13}C) showed that single diastereomers were obtained from reaction of the recovered **1** with any chiral nucleophile (see Supporting Information for spectra). This demonstrated that **1** recovered from the kinetic resolution was already 99 % enantiopure and we determined it to be the dextrogyre enantiomer ($[\alpha]_D^{20} = +5.5$, *c* 1, acetone). The kinetic resolution was repeated to ensure enantiopurity of **1**.

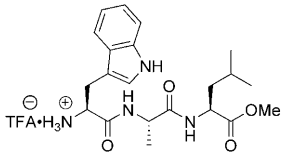
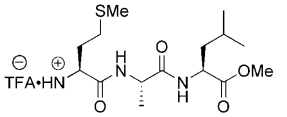
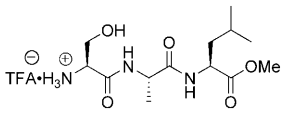
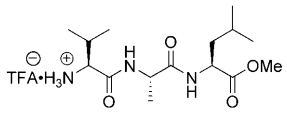
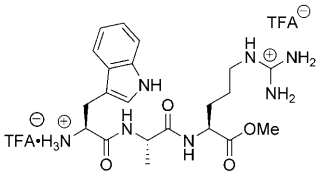
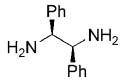
Starting from the all-D peptide, we could prepare (−)-**1** ($[\alpha]_D^{20} = -5.3$, *c* 1, acetone, Scheme 1). Circular dichroism (CD) analysis further confirmed that we had achieved complete resolution of the enantiomers of **1** (Figure 2). The spectra of (+)-**1** and (−)-**1** are mirror images. Note that Cotton effects are observed for bands over the total width of the absorption spectrum of **1**.

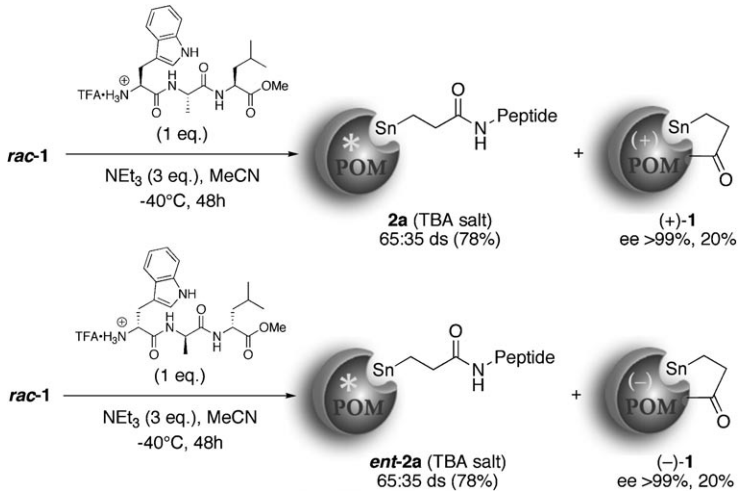
A rapid assessment of the configurational stability of the chiral α_1-substituted Dawson POMs showed neither racemization nor degradation. Indeed, no variation of the optical rotation of an acetone solution of (+)-**1** was observed after one month. In addition, an acetonitrile solution (80 °C) of enantiopure **2b**—prepared by derivatization of (+)-**1**—proved to be configurationally stable. Neither epimerization nor decomposition was detected.

In conclusion, molecular recognition of the chiral metal oxide surface of an α_1-substituted

Table 1: Molecular recognition of α_1-substituted Dawson POM **1**.



Entry	Peptide	*T* [°C]	Conv. (%), *t*	Prod., d.r.	k_{rel}
1		RT	50, 24 h	**2a**, 59/41	1.7
2		−20	46, 24 h	**2a**, 72/28	4
3		−40	44, 48 h	**2a**, 77/23	6
4		−40	50, 24 h	**2b**, 70/30	3
5		−40	50, 24 h	**2c**, 60/40	1.8
6		−40	42, 24 h	**2d**, 66/34	2.5
7		−40	30, 24 h	**2e**, 66/34	2
8		−40	35, 24 h	**2f**, 60/40	1.7



Scheme 1. Kinetic resolution of the enantiomers of α_1-Dawson POM **1**.

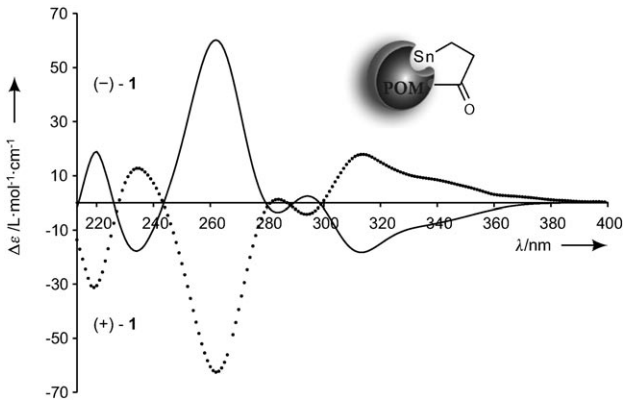


Figure 2. CD Spectra of enantiopure **1** (MeCN, $c = 200\ \mu M$).

Dawson polyoxotungstate enabled its kinetic resolution—a tool from organic chemistry—, which has been made possible by the unique properties of organic hybrids of POMs. In the immediate future, a determination of the absolute configuration of the enantiomers will be sought, as well as a deeper understanding of the folding of the organic side chain of the hybrids (not limited to peptides), since prediction of their 3D shape is a prerequisite for understanding their interaction with both small molecules and biomolecules. Open questions aside, the opportunities created are numerous, since the enantiopure hybrid can be derivatized at will using our established method.[11] Applications of designed chiral hybrids in catalysis (chiral anions), medicinal chemistry (POMs have numerous biological properties), and materials science will follow.

Experimental Section

Kinetic resolution of α_1-Dawson derivative 1. To a solution of racemic $(TBA)_6[\alpha_1\text{-}P_2W_{17}O_{61}\{SnCH_2CH_2C(=O)\}]$ (**1**, 0.26 mmol, 1.5 g), in acetonitrile (25 mL) at −40 °C was added the peptide $TFA{\cdot}H_3N^+$-Trp-Ala-Leu-OMe (0.26 mmol, 1 equiv) and triethylamine (0.78 mmol, 3 equiv). The mixture was stirred at −40 °C for 48 h, and the reaction was allowed to warm to room temperature. A cation-exchange resin (Amberlyst 15, 16–50 mesh, TBA^+ form) was then added, followed by acetone (25 mL) and the mixture was stirred at room temperature for 15 min. The resin was removed by filtration and the filtrate was concentrated in vacuo. The oily residue was dissolved in acetone/EtOH (40 mL/40 mL), and enantioenriched **1** was precipitated upon addition of Et_2O (120 mL). The white precipitate was collected by filtration and the solid could be redissolved in acetone/EtOH (8 mL/8 mL). Upon addition of Et_2O (20 mL), enantioenriched **1** (99 % *ee*) precipitated as a white solid (300 mg, 20 %). The kinetic resolution was repeated to ensure enantiopurity of **1** (see Supporting Information).

Optical rotation of enantiopure **(+)-1** was measured: $[\alpha]_D^{20} = +5.5$ (*c* 1, acetone). Optical rotation of enantiopure **(−)-1**: $[\alpha]_D^{20} = -5.3$ (*c* 1, acetone). Full characterization is included in the Supporting Information.

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