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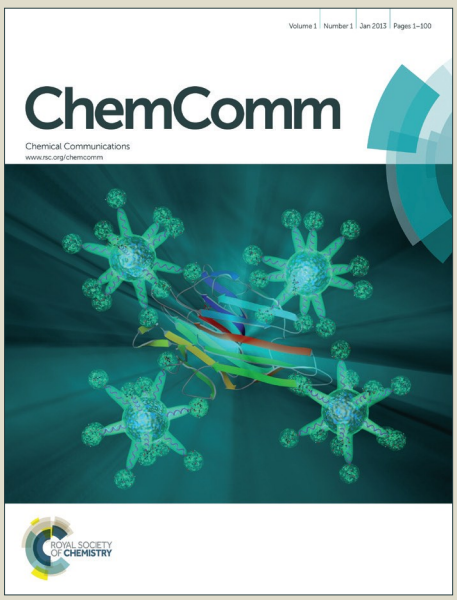

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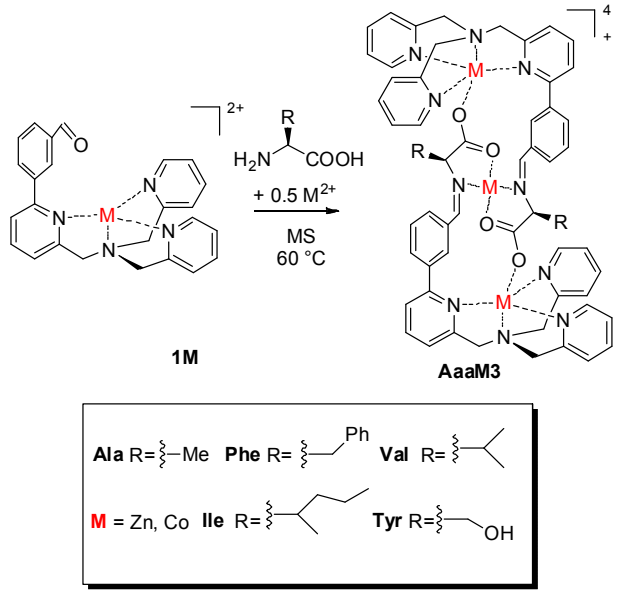
of the same configuration. This particular correlation between spectrum and absolute structure may be of limited interest *per se*, because there are several other methods to recognize the chirality of α-aminoacids. Nonetheless, this is the first example of a rational approach for exploiting VCD enhancement operated by Co^{2+}.

Mixing a modified tris-(pyridilmethyl)amine (**TPMA**) ligand, cobalt(II) or zinc(II) perchlorate and a series of natural α-aminoacids (**Aaa**), we obtain a self-assembling system where aminoacid chirality becomes embedded into a trinuclear Co^{2+} or Zn^{2+} complex, which can be isolated, crystallized and characterized (Scheme 1).[12, 18] We shall call these complexes by the 3-letter acronym of the α-aminoacid followed by Co3 or Zn3, to remind us the divalent cation, which was incorporated into the structure. Thus, the structure depicted in Figure 1 will be labeled **PheCo3** and in general we shall indicate these compounds as **AaaCo3** or **AaaZn3**. Unless expressly stated, all the aminoacids will belong to the L-series. We employed five widely different **Aaa**, which span a chemical space ranging from alkyl (**Ala**, **Val**, **Ile**) to aromatic (**Phe**) and polar (**Ser**) sidechains. In the case of **PheCo3** complex it has been possible to obtain crystals suitable for X-ray diffraction (Figure 1). The molecular structure has C_2 symmetry, with the two cobalt(II) ions at the two ends of the complex in trigonal bipiramydal geometry and with a typical propeller-shape of the three pyridine rings. The structure of the coordination sphere around the metal atoms and in particular the helicity of the propeller motif are dictated by the stereochemistry of the amino acid. The central cobalt(II) atom is octahedral and coordinates two imine nitrogens, two carboxylates and two water molecules.



Scheme 1. Synthetic scheme for the preparation of the self-assembly trinuclear **AaaM3** complexes starting from **1M** and the desired α-aminoacid. In all the structures, the counter anions are perchlorate. Water molecules bound to the central Co(II) are not shown for clarity.

The absence of specific interactions involving the aminoacid side-chain is well witnessed by ECD. This spectroscopy is primarily dictated by the relative orientation of the aromatic (pyridine and benzene) rings of the modified **TPMA**. As one can appreciate in Figure S1 (ESI), all the Co^{2+} complexes of widely different L-α-aminoacids display the same pattern and also very similar intensities (relative and absolute), notwithstanding the large differences in nature and even bulkiness of the **Aaa** side-chains. A similar geometry must occur also for **PheZn3**, whose ECD spectrum (Figure S1) follows a trend very similar to the cobalt(II) derivatives (although one may notice that the relative intensities of the two negative bands are different). We can conclude that we have practically identical conformations of the modified **TPMA** ligand in all **AaaCo3** and a rather similar structure for **PheZn3**.

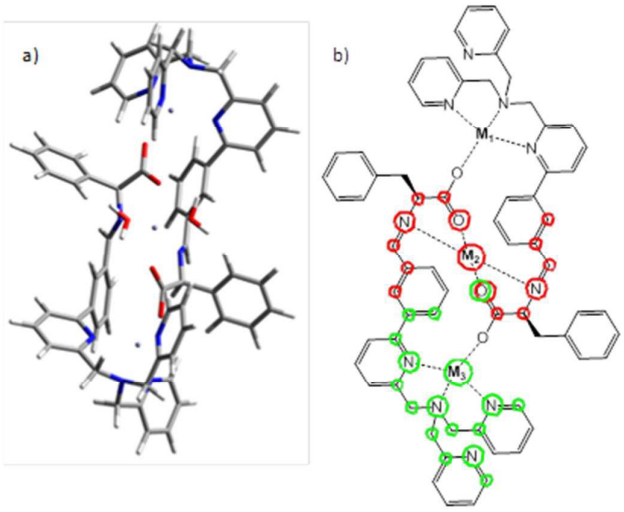


Figure 1. a) XRD structure of the trinuclear **PheCo3** complex obtained from L-phenylalanine as depicted in Scheme 1. b) Schematic representation of the complex structure in which the atoms within 4Å from each cobalt(II) metal ion are circled in red and green. Water molecules bound to the central Co(II) are not shown for clarity.

VCD spectra for compounds **PheCo3** and **PheZn3** are displayed in Figure 2. We may immediately observe the very large difference in the intensities of the VCD bands between Co(II) and Zn(II) complexes (notice that in Figure 2 different vertical scales are used for the two complexes). For **PheZn3**, we find at the best $\Delta\varepsilon = \pm 0.01\ M^{-1}cm^{-1}$, as it is customary for VCD spectra of organic molecules and most common metal complexes. In order to record this spectrum with sufficient signal-to-noise (S/N), we had to collect 8000 scans over about 90 minutes. The concentration of the sample was 66.22 mM and, because about 100 μL were required to fill the cell, we needed 11.69 mg of compound. This is in contrast with the (almost) isostructural **PheCo3,** which shows several absorption bands with $|\Delta\varepsilon| > 1\ M^{-1}cm^{-1}$, including a maximum around 1600 cm^{-1} with $\Delta\varepsilon = +3\ M^{-1}cm^{-1}$, i.e. two orders of magnitude stronger than **PheZn3** in the region between 1700 and 1500 cm^{-1}. To obtain more insight into these enhanced signals, we undertook a theoretical analysis of the normal modes. Unfortunately, the problem goes beyond the scope of the present communication: the complex giving rise to the spectum is large and open shell.

The S/N ratio of this cobalt(II) sample is so favorable that it is possible to drastically reduce its concentration for the VCD measurement and/or to shorten the acquisition time. As shown in Figure 3a, the decrease of the concentration from 40 mM down to 2.5 mM maintains practically unvaried the features of the VCD spectrum.

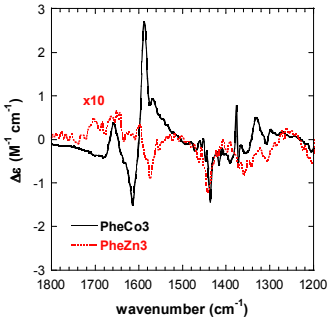


Figure 2. VCD spectra of **PheZn3**, multiplied by 10 (66.22 mM, path-length 0.1 mm; dotted red line) and **PheCo**3 (47.11 mM, path-length 0.1 mm solid black line).

It is noteworthy that at the lowest concentration only 0.43 mg of **PheCo3** complex were used. The signal enhancement is also reflected in the possibility to reduce the acquisition time to less than one minute as in the case of 50 scans (Figure 3b). This is beneficial not only for fast measurements, but also because it strongly limits baseline variations, which are largely determined by instrumental and temperature drifts, typically occurring on the timescale of hours.

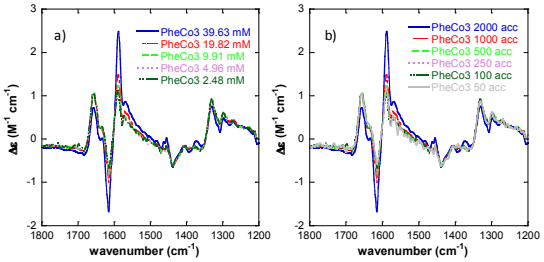


Figure 3. Invariance of the enhanced VCD features upon: (a) diluting the sample or (b) lowering the number of accumulations (acc). In the "dilution experiment", the number of scans was kept constant at 2000, while in the "accumulation variation" the sample concentration was 39.63 mM.

It is well known from previous literature in this field that there is no correlation between signs and relative intensities of the VCD bands between Zn and Co complexes, in spite of their structural similarity.[13, 14, 17] This is explained considering, in the case of **PheCo3**, the coupling of ligand-centered vibrational transitions with low-lying metal-centered electronic transitions of the d^7 system, which is impossible for the closed-shell d^{10} Zn(II). The interference between ligand-centered vibrational states and metal-centered electronic states is deemed responsible for strongly enhanced VCD.[14, 16] On the contrary, total VA is dominated only by the ligand-centered vibrational term, which makes it independent of the metal and indeed **PheCo3** and **PheZn3** have similar IR spectra as shown in Figure S2 (ESI).

We can now move from **PheCo3** to other **AaaCo3**, shown in Figure 4. We can appreciate that although there are some relevant differences (which would allow one to distinguish one Aaa from another) the signs sequence of the strong VCD bands in the region 1800-1500 cm^{-1} remains the same, it are easily recognizable and reproduced from one compound to another. This correspondence can therefore be used to determine the AC of α-aminoacids, by a simple visual correlation.

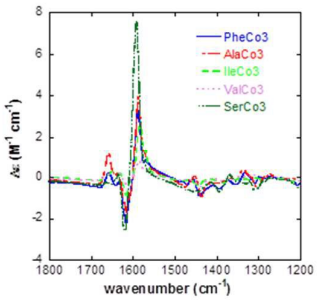


Figure 4. VCD spectra of PheCo3, AlaCo3, ValCo3, IleCo3 and SerCo3 complexes.

As it has been demonstrated, the enhancement of VCD signal intensity is mostly experienced by oscillators in the proximity of the metal center.[17, 19] In the present case, the Co(II) coordination spheres contain only atoms belonging to **TPMA** and to the main backbone of the **Aaa** (from carboxylate to the imine nitrogen), which remain identical irrespectively of the specific nature of the **Aaa**. Indeed, the **Aaa** side-chain, which differentiates one substrate from the next one, remains remote from the metal centers.

In order to further confirm our findings, we measured the spectra of **D-PheCo3** and of **GlyCo3**: the former should yield the mirror image of **PheCo3**, while the latter, based on an achiral aminoacid should provide a baseline spectrum. Both expectations are perfectly met, as demonstrated in Figure S5 (ESI).

Most current methods for α-aminoacid configuration determination require a pre-derivatization step, which requires time, but can be performed in parallel on a set of samples. It follows either spectrum recording (e.g. in ref. 12) or (usually) chromatographic separation (e.g. in ref. 20) which needs to be serially performed one sample at a time on costly instrumentation. With this work, we aimed at significantly reduce the instrumental acquisition time, moving a step in a yet unexplored field.

The protocol we presented above may be extended to develop new methods based on the dynamic formation of metal architectures. A similar approach is expected to be valid for other classes of compounds able to provide consistent/uniform self-assembled multinuclear architectures, in which specific metals would enhance the spectroscopic properties of the neighboring analytes.

Acknowledgements

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