



Co(II)-Induced Giant Vibrational CD Provides a New Design of Methods for Rapid and Sensitive Chirality Recognition

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We designed a stereodynamic system, where the chirality of the analyte templates the helicity of the first coordination sphere of Co(II). Giant VCD bands induced by low-lying electronic states of Co(II) allow one to measure a completely significant and conclusive VCD spectrum in only a few seconds and/or on minute quantities of the analyte. This paves the way to the development of similar protocols, overcoming the limitations due to weak VCD signals for the assignment of absolute configurations.

Vibrational Circular Dichroism (VCD) is currently one of the best methods to assign the absolute configuration (AC) of organic molecules: the VCD spectrum can be considered a chiral fingerprint, reporting molecular stereochemistry, through a manifold of transitions occurring in the mid-IR.¹ VCD is generally applicable, because all molecules display a vibrational spectrum, in contrast to Electronic CD (ECD), which depends on the existence of chromophores.² The main limitations of VCD stem from weak signals (compared to total vibrational absorption, VA), which calls for concentrated samples, long acquisition times, keen choice of blank, which is ideally represented by the racemate, and special care in recording reference baseline. A typical protocol for AC assignment includes: 1) baseline and sample spectra collection, in close sequence to minimize instrumental drift, which generally takes from a few to several hours acquisition; 2) a thorough conformational search; 3) DFT geometry optimization; 4) VCD calculation for each conformer; 5) Boltzmann averaging these computed spectra using the energies calculated in point 3; 6) comparison between computed and experimental spectra. The

whole process is time consuming and every assignment of AC has to be considered as a separate problem. There are few cases, where one can transfer VCD information from structurally correlated systems.^{3,4} Moreover, any error in each of these passages may have consequences in the correct interpretation of the VCD spectrum and ultimately in the assignment of AC of the target molecule.⁵

On the other hand, ECD gained large popularity among organic and natural products chemists, thanks not only to its sensitivity, but also to simple structure/spectrum correlations.⁶ In many such cases, one takes advantage of a chirality transfer from the analyte onto a reporter system. The reporter is usually intrinsically achiral and has suitable spectroscopic features, i.e. has characteristic absorption bands, which can be easily recognized and are separated from contributions of the analyte. Because of the analyte-reporter interaction, the latter becomes itself chiral and displays ECD on its own transitions. Insofar, as all chiral analytes bearing the same functional group impart the same geometrical features to the reporter, its ECD spectrum allows the determination the AC of the analyte.⁷⁻¹²

Inspired by these works, we wanted to follow the same line of thought with VCD but, as we just said, to do so we needed a “reporter, which is by itself achiral but has suitable spectroscopic properties”. We decided to take advantage of a property, which is unique of VCD: certain transition metal complexes, notably containing Ni²⁺ and Co²⁺,^{13,14} and to a lesser extent several Ln³⁺ ions,¹⁵ display strongly enhanced VCD spectra.¹⁶ Very recently, Buma and Woutersen further demonstrated such extraordinary behavior by directly mixing aminoacids and a Co²⁺ or a Ni²⁺ salts.¹⁷ As expected, they did record strong VCD spectra, which are however not correlated with each other and, for this reason, they would not help one for AC assignment.

We developed a stereodynamic self-assembling structure incorporating Co²⁺ (or Zn²⁺, taken as a negative control) and an α -aminoacid. The chirality of the aminoacid dictates the helicity of the assembly, which is reflected in a series of very large VCD bands. The sequence of signs of these giant VCD signals is

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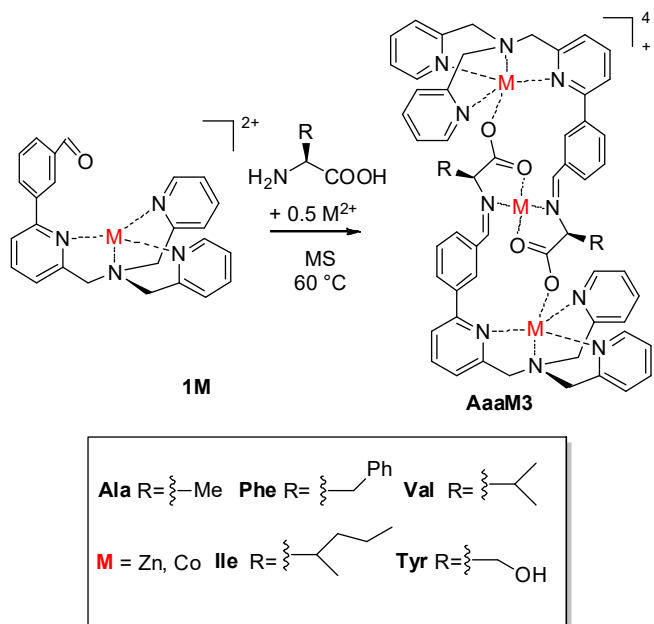
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Electronic Supplementary Information (ESI) available: Experimental details (Spectral acquisition procedure and parameters; synthesis and characterization of complexes), ECD spectra, IR absorption spectra and “error” or “noise” channel of VCD measurements, VCD for the enantiomers of **PheCo3** and for **GlyCo3**.

perfectly recognized from one to another amino acid 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 -amino acids. Nonetheless, this is the first example of a rational approach for exploiting VCD enhancement operated by Co^{2+} .

Mixing a modified tris-(pyridylmethyl)amine (TPMA) ligand, cobalt(II) or zinc(II) perchlorate and a series of natural α -amino acids (Aaa), we obtain a self-assembling system where amino acid 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 -amino acid 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 amino acids 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 bipyramidal 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 -amino acid. In all the structures, the counter anions are perchlorate. Water molecules bound to the central $\text{Co}(\text{II})$ are not shown for clarity.

The absence of specific interactions involving the amino acid 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 -amino acids 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**.

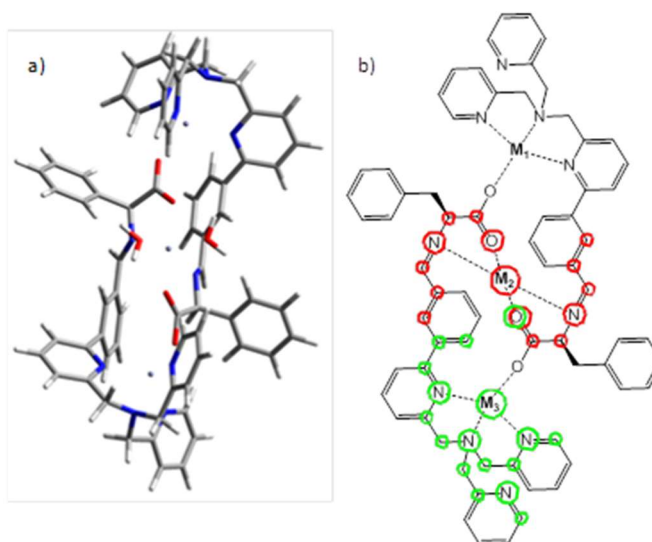


Figure 1. a) XRD structure of the trinuclear **PheCo3** complex obtained from L-phenylalanine as depicted in Scheme 1. b) Schematic representation of the complex structure in which the atoms within 4 Å from each cobalt(II) metal ion are circled in red and green. Water molecules bound to the central $\text{Co}(\text{II})$ 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 $\text{Co}(\text{II})$ and $\text{Zn}(\text{II})$ complexes (notice that in Figure 2 different vertical scales are used for the two complexes). For **PheZn3**, we find at the best $\Delta\epsilon = \pm 0.01 \text{ M}^{-1}\text{cm}^{-1}$, 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 $|\Delta\epsilon| > 1 \text{ M}^{-1}\text{cm}^{-1}$, including a maximum around 1600 cm^{-1} with $\Delta\epsilon = +3 \text{ M}^{-1}\text{cm}^{-1}$, 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 spectrum 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.

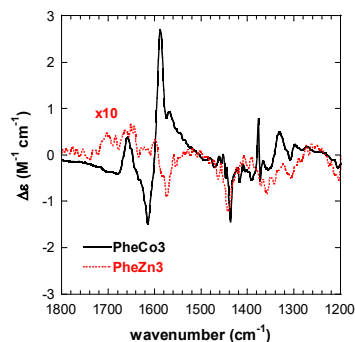


Figure 2. VCD spectra of **PheZn3**, multiplied by 10 (66.22 mM, path-length 0.1 mm; dotted red line) and **PheCo3** (47.11 mM, path-length 0.1 mm solid black line).

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.

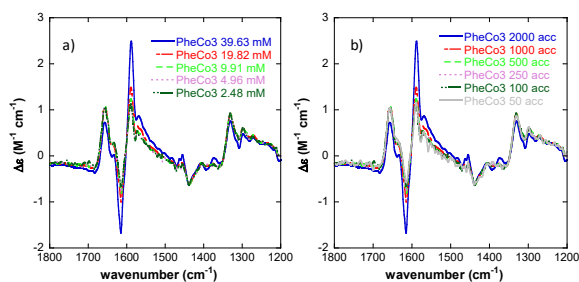
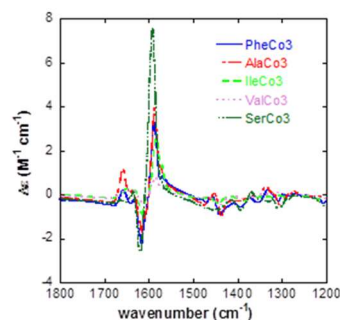


Figure 3. Invariance of the enhanced VCD features upon: (a) diluting the sample or (b) lowering the number of accumulations (acc). In the “dilution experiment”, the number of scans was kept constant at 2000, while in the “accumulation variation” the sample concentration was 39.63 mM.

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 **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.

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