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Concentration-Independent Stereodynamic *g*-Probe for Chiroptical Enantiomeric Excess Determination

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Supporting Information

ABSTRACT: Enantiomeric excess (ee) determination is crucial in many aspects of science, from synthesis to materials. Within this subject, coupling molecular sensors with chiroptical techniques is a straightforward approach to the stereochemical analysis of chiral molecules, especially in terms of process immediacy and labor. Stereodynamic probes typically consist of racemic mixtures of rapidly interconverting enantiomeric conformers able to recognize a chiral analyte and greatly amplify its chiroptical readout. A great number of sensors have been developed, but their activity is generally restricted to one or a few classes of chemicals, and the analysis outcome relies on precise knowledge of the probe and analyte concentrations. This aspect in particular limits the potential practical applications. Here we report an oxo-vanadium(V) aminotriphenolate complex that was found to act as a concentration-independent stereodynamic sensor for a wide range of compounds. The bare complex is CD-silent, but coordination of an enantioenriched substrate immediately gives rise to intense Cotton effects in the visible region. Furthermore, a geometry change during the substrate−complex interaction leads to a marked optical response, as witnessed by a strong red-shift of the probe absorption bands, thus allowing the generation of dichroic signals in an "interference-free" area of the spectrum. This peculiarity allows for a linear correlation at high wavelengths between the ee of the analyte and anisotropy *g*-factor. This parameter derives from the differential circularly polarized light absorption of the sample but is independent of concentration. The newly developed sensor based on a simple coordination process has an unprecedented general character in terms of substrate scope and employment.

Quantitative chirality assessment is fundamental due to the broad effect that stereochemistry has in many different scientific fields. Within this subject, there is a strong urge to develop fast and effective methods to perform enantiomeric excess (ee) analysis to couple with high-throughput screening synthesis.[1] Besides the strong efforts to improve efficiency of chromatographic,[2] mass spectroscopy,[3] and fluorimetric[4] methods, chiroptical spectroscopies represent a fast and reliable tool to reduce the cost and time of stereochemical analysis. Among the available techniques, circular dichroism (CD) is highly preferred because of its widespread diffusion and low cost per analysis. Nevertheless, an accurate CD analysis requires the presence within the analyte of a strong chromophore absorbing in a spectral region where no interference from other molecules can be present. To achieve these results, the focus has recently been on supramolecular approaches that involve the use of stereodynamic probes.[5] In this case, the employed chemosensor carries a chromophore unit and a labile stereogenic element in a fast racemization equilibrium. Through the interaction with a chiral analyte, this equilibrium is shifted to a preferential stereoisomer of the probe that is responsible for the chiroptical readout. A large number of stereodynamic CD probes capable of rapid and sensitive detection of absolute configuration and ee of chiral analytes have been found by exploiting many different systems ranging from small molecular probes to self-assembled supramolecular structures.[5,6] One widely used approach is based on the use of metal complexes of tetradentate ligands which assume a propeller-like rearrangement around the metal center whose *P* or *M* configuration is controlled through the incorporation of a chiral analyte.[7] Some examples of these systems, based on tris(2-pyridylmethyl)amine (TPMA) metal complexes, were initially developed by Canary and Anslyn and more recently by us for determining the absolute configuration and ee of carboxylic acids, amino acids, and alcohols.[8] While these probes have shown a good linear relationship between the ee and the dichroic signal, it is essential to know the exact composition of the analyzed sample in order to obtain accurate stereochemical information. To overcome this issue, strong efforts have been directed toward the development of probes able to gather ee without knowing the concentrations of the different species in solution.[9] In this Communication, we report a vanadium(V) complex of a tetradentate ligand that is able to perform (i) stereochemical analysis in the presence of a plethora of different chiral compounds and (ii) in a region of the UV/vis spectrum that is less prone to display absorption of other organic molecules; more importantly, (iii) the chromophoric switch that follows substrate binding allows readout of the ee independently from the concentration of the probe and/or the analyte.

In recent years, we have been studying the catalytic activity of aminotriphenolate (TPA) complexes.[10] Similar to TPMA, TPA ligands are characterized by a propeller-like arrangement of the ligand around the metal center when viewed along the metal−nitrogen axis. As a consequence, C_3-symmetric trigonal bipyramidal (TBP) complexes are obtained in the two helical arrangements, which interconvert at room temperature, yielding

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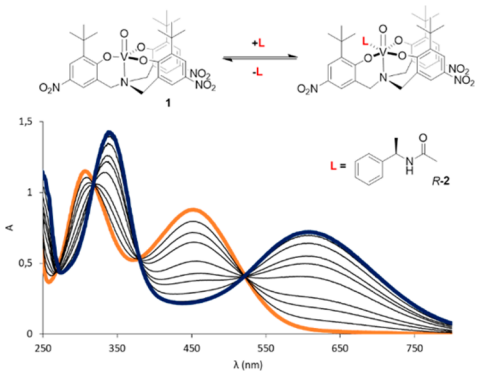

Figure 1. UV titration of a 5.0×10^{-5} M $CHCl_3$ solution of **1** with compound *R*-**2**. The spectrum of pure **1** (bold orange line) and that in the presence of 20 equiv of *R*-**2** (bold blue line) are highlighted.

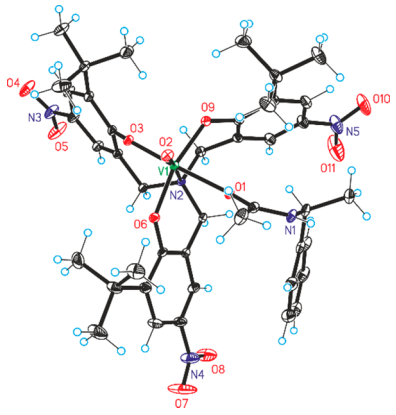

Figure 2. ORTEP representation of the adduct between complex **1** and amide *S*-**2**.

a racemic mixture of enantiomeric complexes. We have focused on d^0 metals, with particular attention to vanadium(V) complexes. Besides the interesting properties of these systems as Lewis acids for hydrogen peroxide[10e] and carbon dioxide activation,[10d] oxo-vanadium TPA complexes revealed the tendency to coordinate an additional monodentate ligand, shifting toward an octahedral geometry.[11,12] Since our first report on these vanadium TPA complexes,[10e] we noticed that this transformation is accompanied by a color shift. This peculiar feature inspired us to synthesize the novel oxo-vanadium TPA complex **1**. In more detail, we decided to decorate the upper part of the complex with a bulky *tert*-butyl group to prevent the formation of metal aggregates and to add nitro groups on the ligand framework with the double intention of enhancing the electrophilicity of the metal center and generating a strong chromophore. The complex is easily prepared by mixing the opportune triphenolamine ligand and an equimolar amount of vanadium(V) oxytriisopropoxide. ^{1}H and ^{51}V NMR analyses (Supporting Informatin (SI) Figure S1) confirm the formation of **1** and the TBP C_3-symmetrical displacement of the ligand around the metal.

As usually occurs when the vanadyl moiety is bound to phenolic units,[13] **1** shows strong absorptions in the UV/vis spectrum, and two bands are observed at 308 and 450 nm (Figure 1). This is due to ligand-to-metal charge transfer (LMCT) from the phenolate oxygen to the vanadium(V) empty d orbitals. When **1** is dissolved in common coordinating solvents or in the presence of a donor species, its UV/vis spectrum exhibits red-shifts of both bands. Specifically, the second band moves significantly up from 450 to 600 nm, reflected in a marked color change of the solution from orange to deep blue (SI Figure S2). As an example, UV titrations of a chloroform solution of **1** with *N*-[(*R*)-1-phenylethyl]acetamide (*R*-**2**) result in the clear formation of isosbestic points, suggesting a 1:1 stoichiometry between the complex and the substrates (Figure 1). The titration points show that the association process has a high binding constant ($K = 5 \times 10^4$ M^{-1}), similar to those for other Lewis bases such as sulfoxides (see SI). The interaction can also be witnessed through ^{51}V and ^{1}H NMR. A novel resonance in the ^{51}V NMR is observed after substoichiometric addition of (*R*)-methyl *p*-tolyl sulfoxide (*R*-**3**) corresponding to the newly formed 1:1 adduct. On the other hand, in ^{1}H NMR the same addition results in a broadening and a resonance shift of the signals of **1** (SI Figures S9 and S10).

Further confirmation of the binding was achieved also in the solid state through X-ray analysis of suitable crystals obtained from a toluene solution of **1** in the presence of the enantiopure amide *S*-**2** (Figure 2). The refined structure presents the twisted TPA ligand only in a *M* (Λ) conformation, with the amide binds to the vanadium center through its carbonyl switching the system to octahedral. The steric hindrance of the phenyl ring is responsible for the handedness of the ligand around the metal center. Interestingly, even moving to the octahedral geometry, the system maintains the propeller-like arrangement of the phenolate rings.

The crystal structure data supporting effective stereochemical induction of complex **1** through interaction with a chiral analyte, together with its high affinity toward generic donor species and its chromophore properties, prompted us to investigate the CD activity of **1** in the presence of chiral Lewis bases. As expected from preliminary information, the CD spectrum of a chloroform solution of **1** in the presence of amide *R*-**2** shows strong Cotton effects in the visible region between 600 and 350 nm (Figure 3a). The registered CD signals appeared immediately after the reagents were mixed, along with the characteristic color change of the solution in the presence of donor species. No dichroic signal was observed in the same region when CD analysis was performed on either pure complex **1** or amide guest *R*-**2**. A mirror image spectrum was obtained when *S*-**2** was used instead of *R*-**2** in the presence of **1**. The same CD pattern was also observed with chiral primary amines **4**–**6** (Figure 3c–e). The sign of CD bands for primary amines revealed a common trend since in every case negative signals were observed with *R* compounds and vice versa. The activity of **1** as a stereodynamic probe was evaluated also with other classes of Lewis bases (Figure 3b,f–i).

Intense dichroic signals were obtained by employing enantiopure amino-alcohols, cinchona alkaloids, sulfoxides, and *N*-oxide species. Especially for the latter two groups, only a few examples of chemosensors capable of chirality sensing have been reported.[6c] A weak or negligible CD response was obtained with substrates with poor donor capabilities, such as chiral alcohols and carboxylic acids. However, by adding the non-coordinating base *N*,*N*-diisopropylethylamine (DIPEA) in an equimolar amount with respect to the analyte, it became possible to record a CD spectrum for some chiral Brønsted acidic compounds (see Figure 4 and SI). This strategy allowed us to detect dichroic signals in the visible region employing enantiopure carboxylic acids, *N*-Boc-protected amino acids, α-hydroxy esters, and phosphoric acids. To our knowledge, no other examples of a stereodynamic probe with a similar widespread activity have been reported so far.

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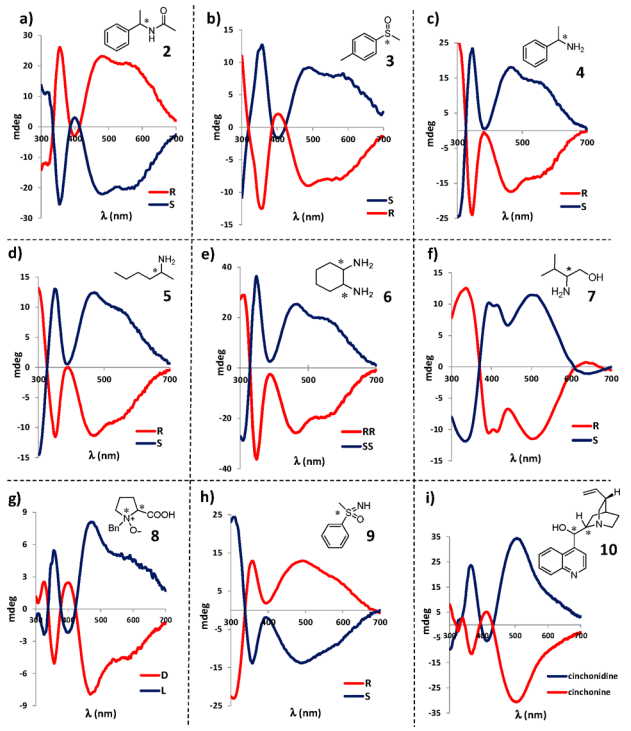

Figure 3. CD spectra recorded between 700 and 300 nm for chloroform solutions of complex **1** (10^{-4} M) in the presence of different chiral compounds: (a) [**2**] = 2×10^{-4} M, (b) [**3**] = 2×10^{-4} M, (c) [**4**] = 2×10^{-3} M, (d) [**5**] = 5×10^{-4} M, (e) [**6**] = 2×10^{-4} M, (f) [**7**] = 2.5×10^{-4} M, (g) [**8**] = 2×10^{-4} M, (h) [**9**] = 2×10^{-3} M, and (i) [**10**] = 5×10^{-4} M. The amount of the latter was that required for a full color switch of the sample, which is qualitative evidence of a predominance of the octahedral species in the solution.

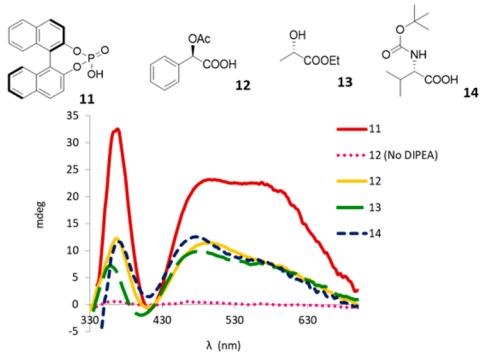

Figure 4. Examples of CD spectra of chloroform solutions containing complex **1** (10^{-4} M), a Brønsted acidic compound ([**11**, **12**, **14**] = 2×10^{-4} M; [**13**] = 4×10^{-4} M), and DIPEA. Analyses employing **12** are reported both in the presence (bold yellow line) and in the absence (dashed pink line) of DIPEA.

In order to test whether **1** could be exploited for ee determination, we measured the CD ellipticity values (θ) for a series of samples containing **1** and *R*- or *S*-**2** at known enantiopurity. A straight linear relationship was observed between the CD response and the ee of **2** (SI Figure S30). However, while by knowing analyte and probe concentrations it is possible to know with a good accuracy the ee, we reckoned that the probe theoretically has the possibility to identify the ee independently of the concentrations of the two partners, due to the unique properties of the vanadium TPA complex to change absorbance upon coordination of the analyte. In particular, in the wavelength region >600 nm, only the octahedral adduct is responsible for light absorption (see Figure 1), and, taking advantage of the CD detector's ability to record simultaneously both dichroic signal ($\Delta\varepsilon$) and absorbance (ε), we can directly find the anisotropic *g*-factor ($g = \Delta\varepsilon/\varepsilon$).[14] This parameter is independent of the concentration of the octahedral species but proportional to the ee. Although the *g*-factor has been successfully employed for stereochemical analyses with chromatographic methods,[15] until now it has not been applied for ee determination with stereodynamic probes. This is due to the difficulty in locating a spectral region where only the CD-active diastereomeric adduct absorbs. In the case of the TPA vanadium system **1**, only the octahedral species is responsible for the light absorption at wavelengths >600 nm, thus permitting the use of the anisotropic *g*-factor.

To check whether the probe was able to perform "concentration-independent" ee measurements, we varied either the concentration of the probe or of the analyte while keeping the ee of the analyte constant. As expected, CD spectra of six different solutions are highly affected by these variations (SI Figure S31b); thus, it is not straightforward to calculate ee from the ellipticity values. Conversely, the *g*-factors of all the samples are practically identical above 600 nm, confirming their predicted independence of concentration at high wavelengths (Figure 5). It

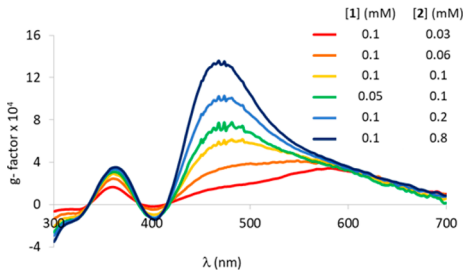

Figure 5. Anisotropy *g*-factor spectra of six chloroform solutions containing complex **1** and amide *R*-**2** in different ratios.

is worth underlining that in this way a full conversion of complex **1** to the octahedral species is not necessary for an accurate measurement. However, the presence of the probe–analyte adduct as the major species, as well witnessed by the sample's color shift, reduces the error. Hence, we then studied the correlation between the ee of the analyte and the *g*-factor by building a calibration curve based on 18 solutions with different contents of **1** and **2** and different ee's (Figure 6 and SI Table S2). An excellent linear correlation was found by plotting the *g*-factor values against the ee of the analyte, thus establishing a very simple function to determine the ee of the amide species **2** in the presence of our stereodynamic probe.

Here we have presented a novel concentration-independent stereodynamic probe able to amplify the chiroptical signal for a large variety of substrates. A general Lewis acid–base interaction is responsible for binding the analyte to the metal center, which allows for a wide substrate scope. Moreover, since a chromophoric switch occurs, in a specific region of the spectrum, the absorbance is ascribable only to the probe–analyte aggregate. This particular feature allows use of the concentration-independent anisotropic *g*-factor to find the ee of the analyte. This innovative methodology for ee measurement will pave the way for a novel generation of chiroptical probes and the implementation of high-throughput screening techniques in modern CD spectrometers.

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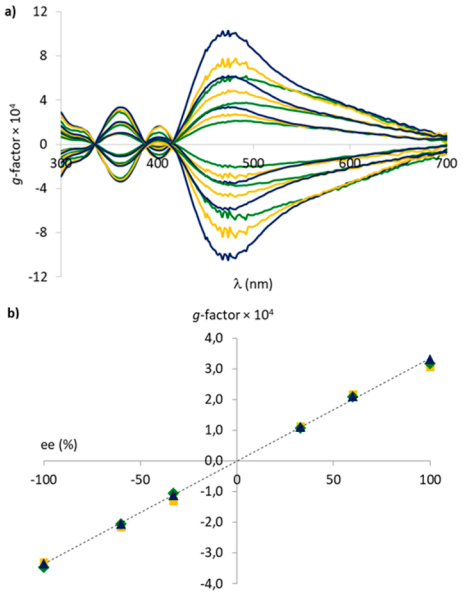

Figure 6. (a) Anisotropy *g*-factor spectra of the 18 samples analyzed. The color of each curve corresponds to different concentrations of complex **1** and amide **2** concentrations in the sample: [**1**] = 1×10^{-4} M, [**2**] = 1×10^{-4} M, yellow curves; [**1**] = 5×10^{-5} M, [**2**] = 1×10^{-4} M, green curves; [**1**] = 1×10^{-4} M, [**2**] = 2×10^{-4} M, blue curves. For each sample composition, six measurements were performed by changing the ee of amide **2** (−100, −60, −33, +33, +60, +100). (b) Calibration curve of *g*-factor values between 590 and 620 nm against the ee of the analyte. A point was plotted for each sample, fitting the equation $y = 3.346 \times 10^{-6}x$, $R^2 = 0.9984$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b09469. Crystallographic data for the adduct between complex **1** and amide *S*-**2** have been deposited at the Cambridge Crystallographic Data Center under accession number CCDC 1568016.

Experimental procedures for UV/NMR titrations and chirality sensing, synthesis of complex **1**, and characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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