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A racemic *N,N*′-dioxide-iron(III) complex chemosensor for determination of enantiomeric excess, concentration and identity of hydroxy carboxylic acids with circular dichroism and fluorescence responses

Ruixue Peng [a], Lili Lin [a,*], Weidi Cao [a], Jing Guo [a], Xiaohua Liu [a], Xiaoming Feng [a,b,*]

[a] *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, PR China*
[b] *Collaborative Innovation Center of Chemical Science and Engineering, Tianjin 300171, PR China*

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ABSTRACT

A racemic *N,N*′-dioxide-iron(III) complex was first found to be an efficient chemosensor for simultaneous determination of the absolute configuration, concentration, and enantiomeric excess (ee) of hydroxy carboxylic acids in aqueous solution via circular dichroism (CD) and fluorescence. The accuracy of the ee measurement is very good, within 3%. And the analysis is fast, eliminating laborious derivatization and elaborating purification steps.

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Chiral compounds play an essential role in pharmaceutical and chemical sciences, and the enantioselective analysis of them has become one of the important aspects of academic and industrial research.[1] Analytic methods suitable for high-throughput screening (HTS),[2] which is widespread in the drug leads discovery in pharmaceutical firms, are quite required. Optical methods based on UV,[3] fluorescence,[4] and circular dichroism (CD)[5,6] spectroscopy are time-efficient, sensitive, and cost-effective. They are thought to be more suitable for HTS than chromatographic GC and HPLC techniques.[7] Optical sensing methods developed to date performed more than just recognition of the isomers of chiral compounds, they were desirable to determine the enantiomeric excess and the concentration of chiral compounds simultaneously. To achieve this goal, two sensors are usually used simultaneously or in tandem[8] by using fluorescence or UV except Pu[9] used one trifluoromethyl ketone-based fluorescent sensor to realize the enantioselective recognition of chiral diamines. By using CD spectroscopy, one chemosensor would usually be enough to reach the task. Up to now, one strategy is the combination of CD with multilayer perception artificial neural network analysis,[10] and the other is a dual sensing mode through CD determining the ee and UV/fluorescence determining the concentration. Through the latter strategy, Wolf applied racemic 1-(3′-formyl-4′-hydroxyphenyl)-8-(4′-pyridyl)-naphthalene *N*-oxide[11a,b]/palladium complexes[11c] to enantioselective determination of chiral diamines and amino alcohols while Jiang applied achiral perylenebisimide (PBI) dyes[11d] to realize the enantioselective determination of α-hydroxy carboxylates. Given the importance and requirement of simultaneous analysis, developing new efficient chemosensors which can determine both the ee values and concentration is still highly desirable.

On the other hand, *N,N*′-dioxide-metal complexes, which have been well developed by our group to catalyze various asymmetric reactions,[12] showed potential in enantioselective determination. Previously, we found *N,N*′-dioxide-Ni(II) complex exhibited fluorescent recognition of two isomers of chiral diamines, alcohols, and α-hydroxy carboxylic acids.[8f,13] Since a complete stereochemical analysis should reveal not only the absolute configuration but also the enantiomeric excess and the concentration of a chiral compound. Herein, we developed a racemic *N,N*′-dioxide-Fe(III) (*rac*-**PiMe**$_{\beta}$**Na**-Fe(III)) complex as a chemosensor to rapidly accomplish the comprehensive enantioselective recognition of hydroxy carboxylic acids with

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* Corresponding authors. Tel.: +86 28 85418249; fax: +86 28 85418249 (X.F.).
E-mail addresses: lililin@scu.edu.cn (L. Lin), xmfeng@scu.edu.cn (X. Feng).

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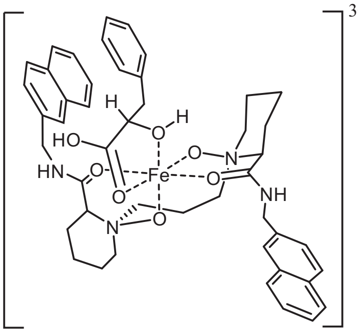

Figure 1. Proposed structure for the *rac*-**PiMe$_{\beta}$Na**-Fe(III) with **1**.

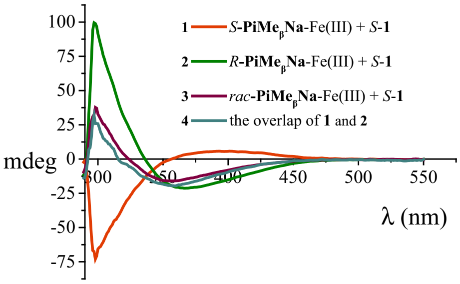

Figure 3. Comparison between the CD spectrum of *rac*-**PiMe$_{\beta}$Na**-Fe(III) with *S*-**1** (line 3) and the overlap spectrum (line 4) of *S*-**PiMe$_{\beta}$Na**-Fe(III) with *S*-**1** (line 1) and *R*-**PiMe$_{\beta}$Na**-Fe(III) with *S*-**1** (line 2).

high accuracy based on CD and fluorescent measurements in aqueous solvent.

According to our previous work,[14] the *N*-oxides and amide oxygens of *N,N′*-dioxide will coordinate with Fe in a tetradentate manner to form two six-membered chelate rings. After the addition of substrates, a rigid octahedral complex could be formed by the coordination of oxygen atoms of the substrate with the central metal of *N,N′*-dioxide-iron(III). We speculated that hydroxy carboxylic acid could also coordinate with *N,N′*-dioxide-iron(III) complex and form an octahedral complex (Fig. 1). What is more, a 1:1 coordination of metal complex with hydroxy carboxylic acid was confirmed by MS analysis. In MS spectrum, a peak at *m*/*z* 828.3 corresponding to [*rac*-**PiMe$_{\beta}$Na**-Fe(III)+**1**-2H$^+$]$^+$ was found.

We first differentiated chirality with *rac*-**PiMe$_{\beta}$Na**-Fe(III) as the sensor. With the addition of two enantiomers of 2-hydroxy-3-phenylpropionic acid **1** or tartaric acid **5** to *rac*-**PiMe$_{\beta}$Na**-Fe(III), the corresponding CD spectra showed a CD signal immediately. And the enantiomeric analytes gave opposite CD spectra (Fig. 2). Similar results were obtained with α-hydroxy carboxylic acids **2**–**4** and β-hydroxy carboxylic acid **6** (see the Supporting information). A titration was performed by adding each enantiomer of **1** into the solution of *rac*-**PiMe$_{\beta}$Na**-Fe(III) (see the Supporting information). The CD signal saturated when 0.5 equiv **1** was added. The binding constant of sensor with *S*-**1** and *R*-**1** was up to $4.877 \times 10^3\ \mathrm{M}^{-1}$ and $4.167 \times 10^3\ \mathrm{M}^{-1}$, respectively. A closer look at the sign of the maximum CD amplitudes around 300 nm allowed for enantiomer identification. The chemosensor generated a positive couplet below 350 nm when D-**5** was bounded and a negative couplet when L-**5** was bounded. α-Hydroxy carboxylic acids had a negative couplet for *S* enantiomer and a positive couplet CD responds for the *R* antipodes without exception. For β-hydroxyphenylpropionic acid, *S* enantiomer gave a positive couplet while *R* enantiomer gave a negative one. All measurements were taken within 5 min. We also tested other analytes bearing two –OH or –COOH groups, such as dibenzoyl tartaric acid and 1-phenyl-1,2-ethanedio. However, they were CD silent in the region of interest increment. The results confirmed that both –OH and –COOH were necessary for the recognition.

In order to understand the CD signal of *rac*-**PiMe$_{\beta}$Na**-Fe(III) with **1**, some control experiments were carried out (Fig. 3). *S*-pipecolic acid derived chiral *S*-**PiMe$_{\beta}$Na**-Fe(III) coordinating with *S*-**1** showed a positive signal around 390 nm and a negative signal around 300 nm, while *R*-pipecolic acid derived chiral *R*-**PiMe$_{\beta}$Na**-Fe(III) coordinating with *S*-**1** showed a negative signal around 370 nm and a positive signal around 300 nm. What is interesting, the sum of the two spectra was accordant with the spectrum of *rac*-**PiMe$_{\beta}$Na**-Fe(III) with *S*-**1**. So the signal of *rac*-**PiMe$_{\beta}$Na**-Fe(III) with *S*-**1** should be the result of the coordination of *S*-**PiMe$_{\beta}$Na**-Fe(III) with *S*-**1** and *R*-**PiMe$_{\beta}$Na**-Fe(III) with *S*-**1**.

The practicality of this chiral sensing was then examined for quantitative analysis of the enantiomeric composition of **1** and **5**. In both cases, a perfect linear relationship was found with R^2 over 0.997. Five scalemic samples of **5** covering a wide ee range were prepared and treated with the sensor *rac*-**PiMe$_{\beta}$Na**-Fe(III) at room temperature and gave the corresponding CD amplitudes at 392 nm (Fig. 4). Using the linear regression equation calculated from the calibration curve, the enantiomeric excess of these samples was determined (Table 1). Comparing the results of actual and

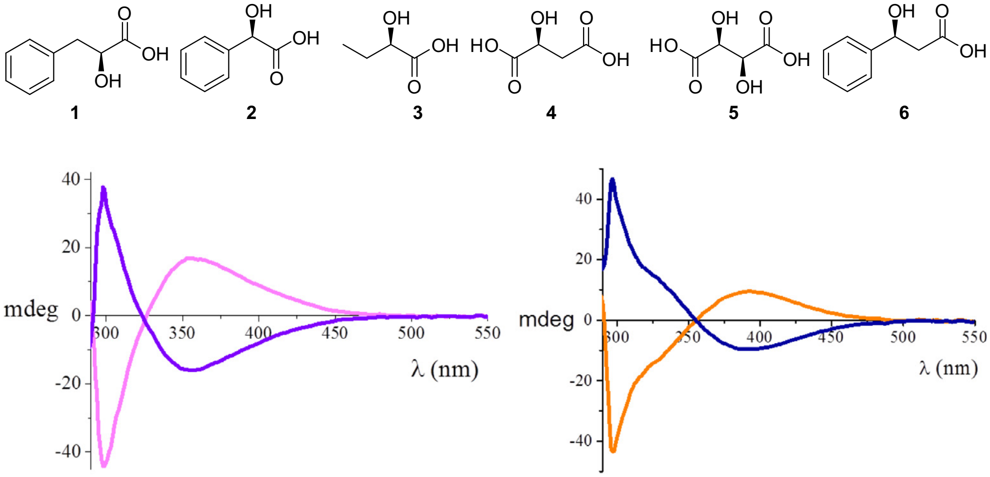

Figure 2. Top: Structures of substrates tested. Bottom: CD spectra of the Fe(III) complex derived from *rac*-**PiMe$_{\beta}$Na** (1.0×10^{-3} M in EtOH/H$_2$O = 3:1) and *R*-**1** (pink) or *S*-**1** (purple) (left) and D-**5** (blue) or L-**5** (orange) (right) at room temperature.

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