Molecular Sensing of Chiral Carboxylic Acid Enantiomers Using CD Inductions in the Visible Light Region

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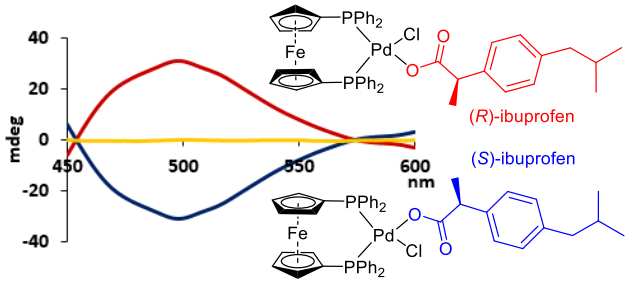


ABSTRACT: The reaction between a chiral carboxylic acid molecule and 1,1′-bis(diphenylphosphino)ferrocenepalladium dichloride in the presence of a mild base generates a chiroptically active metal complex displaying strong CD signals in the visible light region, a highly sought-after goal in the optical sensing realm. The molecular recognition process is complete within a few minutes and can be used for fast chiroptical determination of the enantiomeric composition and concentration of carboxylic acid samples. This method is operationally simple and broadly applicable to a large variety of structures including important drugs, natural products, amino acids and hydroxy acids. All components needed are commercially available and this optical sensing assay can be readily adapted by any laboratory interested in chirality analysis and high-throughput experimentation.

Introduction

Chiral carboxylic acids exist widely in nature where they play fundamental roles in a fascinating blend of chemical processes and complex biological systems. They are also in high demand as versatile synthetic building blocks or invaluable precursors of multifunctional natural products and are frequently encountered moieties in important biologically active compounds including ibuprofen, naproxen, tiagabine, abietic acid, isosteviol, and dihydroartemisinic acid. The general significance, structural variety and broad application scope of chiral carboxylic acids are truly remarkable and continue to attract widespread attention across the chemical and health sciences. As the pharmacological activity or utility is often closely connected with the chirality of carboxylic acids, many laboratories regularly face the task to determine or monitor their enantiomeric composition, preferably by processing a large number of samples in automated high-throughput fashion. Chiral chromatography and NMR spectroscopic methods with chiral derivatizing reagents or solvating agents are the current gold standard but often cause a bottleneck in compound development projects because they are intrinsically serial techniques and cannot match high-throughput screening (HTS) expectations. Accordingly, methods based on mass spectrometry,[1] UV,[2] fluorescence,[3-5] gas-phase rotational resonance,[6] IR,[7] electronic circular dichroism (ECD),[8-11] fluorescence-detected CD spectroscopy,[12] and biochemical assays[13] have been introduced. During recent years, several groups have demonstrated that chiroptical sensing methods are particularly useful.[14-16] A variety of chromophoric sensors that undergo stoichiometric interactions with a chiral acid molecule, e.g. formation of a supramolecular assembly,[17,18] hydrogen bonding[19-21] or salt bridges,[22] to generate a strong circular dichroism (CD) signal for accurate determination of the sample enantiomeric ratio (*er*) have been introduced. The use of achiral sensors is particularly attractive because it avoids the formation of diastereomers and takes full advantage of the inherently enantiodifferentiating nature of CD spectroscopy. In some cases, concomitant induction of nonenantioselective UV or fluorescence signals allows quantification of the total amount of both enantiomers in addition to the *er* value.

Unsurprisingly, the large majority of chiroptical assays that have been developed to date target α-amino acids[23-38] and α-hydroxy acids[39-48] which are privileged bidentate structures favoring effective CD signal inductions. Despite the introduction of sensing systems that can differentiate between enantiomers of monofunctional analytes,[17-22,49-53] a widely applicable optical method that is complete within a few minutes, based on a simple mixing protocol with readily available assay components, and allows combined concentration and *er* determination solely from far red-shifted CD inductions with maxima appearing in the visible light region has not been reported. To this end, an achiral probe generating a strong CD maximum beyond 450 nm upon binding of a chiral carboxylic acid would be most useful because this simplifies the analytical task as diastereomer formation can be ruled out, decreases the risk of possible interferences from chiral impurities that may have intrinsic CD signatures at shorter wavelengths, and is more amenable to the use in automated CD plate readers that have technical issues with measurements around 400 nm.[54]

Results and Discussion

During our search for a molecular sensor that would fulfill all these expectations we considered the potential of metal coordination chemistry using the sensors **1**-**6** and 2-phenylpropanoic acid, **7**, as test analyte. Indeed, we found that formation of a palladium(II) complex by mixing (*R*)-**7** and $Pd(OAc)_2$ in the presence of a tertiary amine generates a respectable CD maximum around 320 nm (SI). With this encouraging proof-of-concept in hand we sought to include chromophoric phosphine ligands to favor stoichiometric carboxylate binding, which we expected would facilitate quantitative sensing applications, and concomitant induction of a strong CD signal at significantly longer wavelengths. While we had limited success with $(PPh_3)_2PdCl_2$, we observed CD inductions above 400 nm with [bis(2-(diphenylphosphino)phenyl)ether]$PdCl_2$, **3**, and its 1,1′-bis(diphenylphosphino)ferrocene analogue, **4**. The strong, red-shifted chiroptical response obtained with **4** is particularly impressive and a rare example of ligand-enhanced CD induction occurring in the visible light region. We were delighted to record an induced CD (ICD) maximum of approximately 40 mdeg appearing around 475 nm at 2.65 mM in tetrahydrofuran (Figure 1). Moreover, the palladium complex **4** is commercially available and soluble in common organic solvents. These noteworthy features underscore the practicality of this chiroptical sensing method which only requires mixing of the sensor, base and carboxylic acid, and can be easily adapted by any laboratory interested in chirality analysis. Interestingly, a similar ICD effect was observed with the corresponding nickel complex **5** but not with the cobalt analogue **6**.

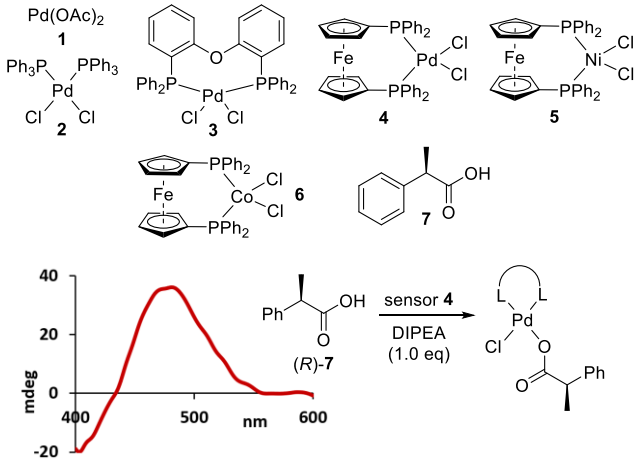


Figure 1. Structures of the sensors investigated and CD induction obtained by coordination of (*R*)-2-phenylpropanoic acid to the Pd complex **4**.

We continued with investigating the mechanistic underpinnings and experimental parameters of the molecular sensing assay. ^{1}H NMR spectroscopic analysis with ibuprofen, **8**, showed that the carboxylate binding is fast and complete within 15 minutes as indicated by the characteristic upfield shifts of the methyl and methine protons in **8** (Figure 2).

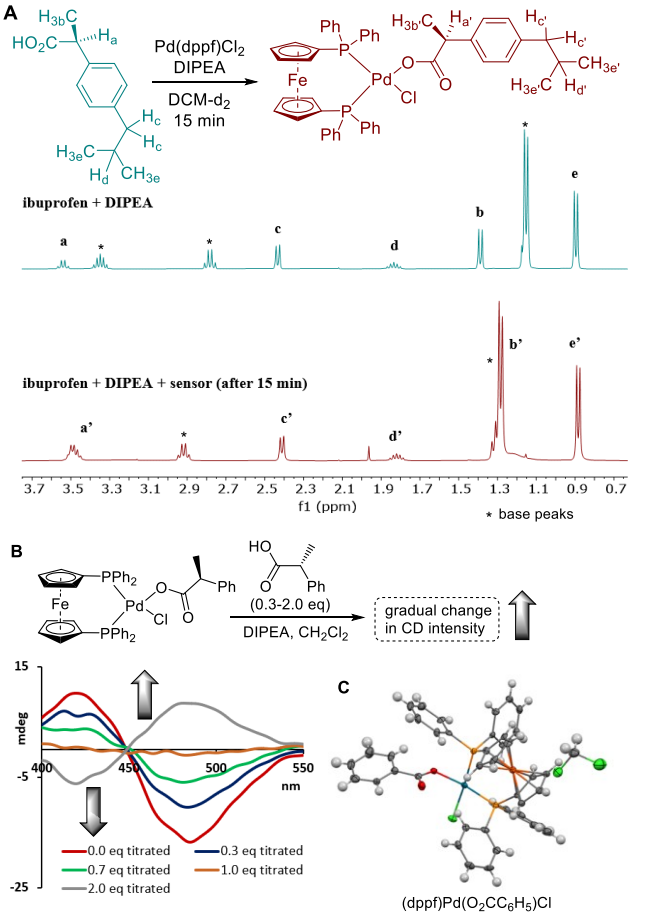


Figure 2. Mechanistic studies. ^{1}H NMR reaction monitoring with ibuprofen (A), CD titration experiments with both enantiomers of 2-phenylpropanoic acid (B), and X-ray analysis (ellipsoid contour 50% probability) of a benzoate complex obtained from **4** (C).

Titration experiments then revealed that excess of the chiral acid doesn't change the ICD signal intensity indicating that the chiroptical sensing is a result of stoichiometric analyte coordination which was further corroborated by ESI-MS analysis (SI). To exclude the possibility of carboxylate- or chloride-bridged dimers or higher supramolecular aggregates that would also consist of equimolar sensor and analyte amounts, we decided to pursue crystallographic analysis. Unfortunately, all attempts to form single crystals with coordination complexes derived from ibuprofen or other analytes and sensor **4** were unsuccessful, presumably because of the high rotational freedom of these acids which impedes efficient packing into a crystal lattice. We therefore resorted to using silver benzoate to abstract one chloride, which was thus easily removed as AgCl prior to the crystal growth experimentation, and to introduce a rather rigid acid scaffold instead. This approach proved successful and we were able to grow a single crystal suitable for X-ray crystallography which is in agreement with our MS analysis and CD titration experiments.[55] Altogether, these studies suggest that only one chloride is replaced from **4** and that the CD induction originates from the formation of a mononuclear 1:1 coordination complex.

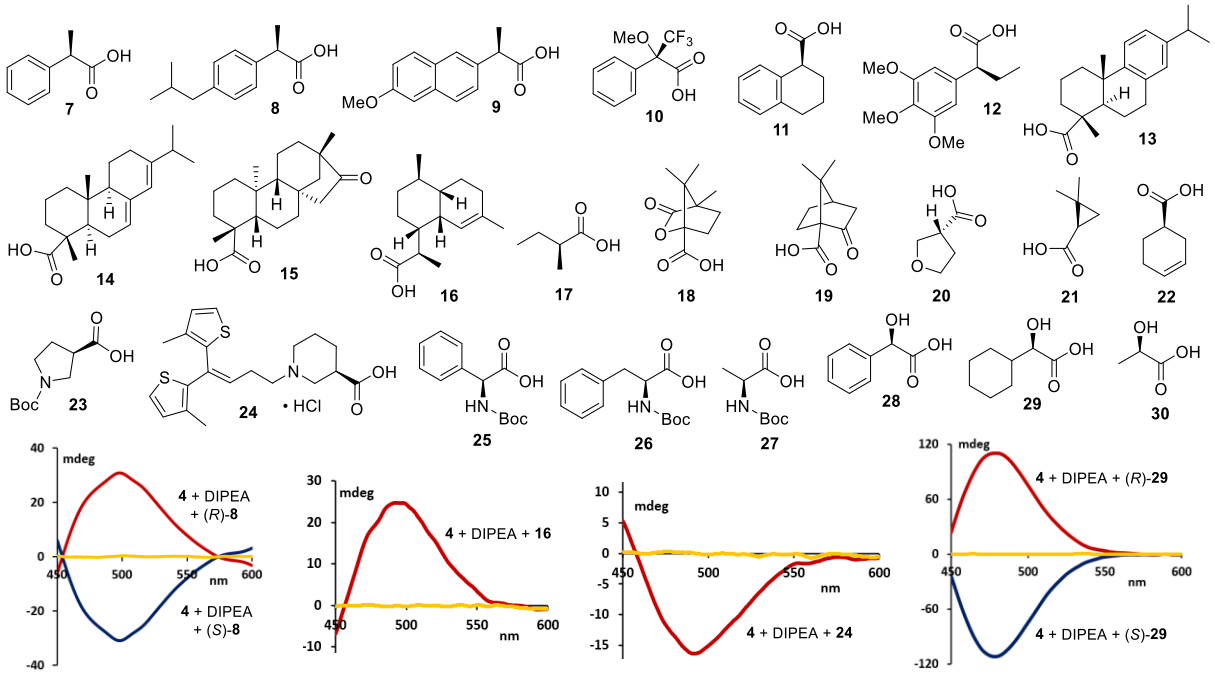


Figure 3. Structures of carboxylic acids tested in this study and selected ICD spectra obtained with **4** (red or blue) or in the absence of **4** (yellow). See SI for details.

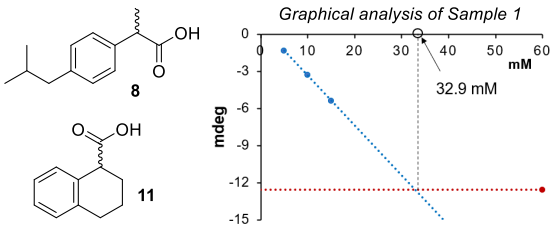
As expected, no CD effect was observed in the absence of base which is required for carboxylate formation and subsequent metal coordination. Finally, we set out to determine if the analyte binding to the palladium(II) center is reversible. Titration of increasing amounts of (*R*)-2-phenylpropanoic acid into a solution of the palladium complex originally formed from the (*S*)-enantiomer and **4** showed that the ICD maximum continuously decreases and even reverses when the former is added in excess. Having established that the carboxylate coordination is a dynamic process we considered the possibility of using a chiral Pd complex for NMR spectroscopic enantioselective analysis. However, efforts with ((*R*)-BINAP)$PdCl_2$ as chiral NMR solvating agent under similar conditions did not show any sign of carboxylic acid enantiodifferentiation.

The chiroptical induction obtained with (*S*)-ibuprofen and **4** was then further optimized by screening bases and solvents (SI). We found that Et_3N, diisopropylethylamine and sodium *tert*-butoxide give the same ICD signals albeit with varying intensity while K_2CO_3, 2,6-lutidine and pyridine were ineffective. Diisopropylethylamine was chosen for all following experiments because it favors strong signal induction under relatively mild conditions. The testing of various combinations of CH_2Cl_2, THF, ACN or MeOH as reaction and diluting solvents showed that the strongest chiroptical responses can be obtained when the assay components are first mixed in CH_2Cl_2 and then diluted with MeOH to the desired CD analysis concentration. With this protocol in hand, we were able to evaluate the sensing scope of our assay. For this task, we chose a large selection of chiral carboxylic acids **7**-**30** ranging from the purely aliphatic scaffolds **17** and **21** to analytes carrying aromatic groups, *e.g.* **10** and **11**, as well as drugs such as naproxen, **9**, and tiagabine, **24**, and natural products like dehydroabietic acid, **13**, abietic acid, **14**, isosteviol, **15**, and dihydroartemisinic acid, **16** (Figure 3). The sensor was also successfully applied to several amino acids **23**-**27**, hydroxy acids **28**-**30**, and other multifunctional compounds such as **12**, **18** and **19**. Without exception, we observed far-red shifted CD maxima appearing between 450 and 500 nm while the chiral carboxylic acids remained CD-silent in this area in absence of the sensor (SI). As is typically the case with small molecule sensors like the palladium complex **4**, the sign and intensity of the CD signal induced upon binding of an analyte is strongly determined by the proximity of its chirality center to the binding site. Enantioselective sensing of compounds exhibiting more distant stereocenters is often not possible or gives significantly decreased CD effects. This trend is apparent by comparison of the decreasing ICD effects obtained by chiroptical sensing of (*R*)-2-phenylbutanoic acid and (*R*)-3-phenylbutanoic acid (see SI). To this end, the ICDs measured upon binding of **20**-**24** to **4** are quite remarkable and demonstrate the sensitivity of this assay as these compounds represent some of the most challenging targets by exhibiting remote chirality. However, a comparison of the ICDs obtained with **13**-**15** carrying multiple stereocenters reveals that chiroptical effects originating from the most proximate chirality center dominate over those from more distant asymmetric carbon atoms. These three rigid scaffolds share the same absolute configuration at the chirality center adjacent to the acid group but the stereochemistry at the more remote carbons in compound **15** differs from **13** and **14**. Nevertheless, they all generate a negative CD response upon coordination to **4** which reveals a somewhat intuitive distance-dependent priority rule, indicating that sensing of diastereomeric scaffolds may be outside the scope of this assay as the more remote stereocenters play significantly diminished roles and can therefore not be effectively differentiated.

To demonstrate the utility of our CD sensing method we prepared ten samples containing ibuprofen or 1,2,3,4-tetrahydronaphthalene-1-carboxylic acid in various enantiomeric ratios ([*R*]:[*S*]) and overall concentrations ([*R*]+[*S*]). These were then subjected to our chiroptical assay with sensor **4** following a simple protocol that allows determination of both *er* and total acid concentration solely by a series of four CD measurements, *i.e.* without additional UV or fluorescence sensing, and without

a calibration curve as previously reported from our laboratory.[38] This method is only briefly described herein using the first sample containing enantioenriched (*S*)-ibuprofen with an enantiomeric composition of 65 (*S*):35 (*R*) at 35.0 mM as an example. To four 100.0 μL aliquots of this sample were added varying amounts of **4** and amine base, and the reaction volumes were adjusted to 2.5 mL using CH_2Cl_2. These solutions were stirred for 15 minutes and CD analysis was performed after diluting 250.0 μL aliquots with 2.0 mL of MeOH. The experimentally obtained CD amplitudes at 490 nm were plotted against the concentrations that **4** would have been at in the original sample without the two dilution steps. Linear regression analysis using the CD amplitudes determined in the region of excess of the analyte over **4** showed a linear increase (blue line). A horizontal line parallel to the x-axis representing the range where the CD amplitude is stagnant because the sensor is in excess of the carboxylic acid analyte was also obtained (red line). Importantly, this line shows the maximum ICD signal obtainable with this sample and the same value would always be measured as long as **4** is present in excess.

Table 1. Chirality sensing of carboxylic acid samples with 4.



Sample #	Actual Composition		CD Sensing Results	
	Conc (mM)	*er* (*S*:*R*)	Conc (mM)	*er* (*S*:*R*)
1	35.0	65.0:35.0	32.9	65.5:34.5
2	40.0	70.0:30.0	40.3	71.0:29.0
3	45.0	60.0:40.0	43.7	67.0:33.0
4	30.0	95.0:5.0	33.0	90.5:9.5
5	38.0	80.0:20.0	33.0	84.0:16.0
6	35.0	20.0:80.0	36.7	21.0:79.0
7	25.0	65.0:35.0	20.0	72.5:27.5
8	30.0	70.0:30.0	32.0	75.0:25.0
9	28.0	10.0:90.0	26.0	5.5:94.5
10	25.0	25.0:75.0	28.9	22.5:77.5

Samples 1-5 contained **8**; 6-10 contained **11**. See SI for details.

The x-value at the intersection of these two lines reveals the original concentration of the carboxylic acid in Sample #1 (keeping the sample dilution protocol described above in mind) as 32.9 mM. With the concentration of the analyte in hand, the enantiomeric composition was then calculated by comparing the y-axis value (in mdeg) with the ICD value that an enantiopure reference would produce at that concentration. This gave an enantiomeric ratio of 65.5:34.5. The absolute configuration of the major ibuprofen enantiomer was determined from the sign of the observed CD signals. We like to point out that this requires comparison with a reference sample of known absolute configuration when using **4** as sensor. The determination of absolute configuration based on induced CD effects is not a trivial task. If a reference sample is not available, it should be conducted either with additional computational analysis or in conjunction with another experimental technique unless the relationship between the sign of the induced Cotton effect and the three-dimensional analyte structure can be generally rationalized based on exciton-coupled CD effects.[56]

This graphical analysis method was applied to all ten samples and the results are shown in Table 1. To determine the error margins of the concentration and *er* determinations originating from the maximum CD induction deviations observed, the mdeg values were varied by 0.5 mdeg for all four measurements of Sample #1. An averaged (maximum) deviation of 2.08 mM, 6.3% (3.8 mM, 11.6%) was calculated by this analysis. The *er* value on the other hand changed only slightly. The averaged (maximum) *er* deviation calculated was 66.1:33.9 which corresponds to 2.7% (67.0:33.0 or 6.5%). Generally, the comprehensive concentration and *er* sensing analysis occurs with good accuracy and error margins that are similar to previously reported methods.[16]

Conclusion

In summary, we have developed a practical chiroptical carboxylic acid sensing method that generates strong CD signals in the visible light region. The molecular recognition is based on the formation of a well-defined equimolar metal complex obtained by coordination of a carboxylate molecule to 1,1′-bis(diphenylphosphino)ferrocenepalladium dichloride in the presence of a mild base. This ligand substitution process is complete within a few minutes and coincides with the induction of quantifiable CD maxima that occur between 450 and 500 nm. The usefulness of this approach, which is operationally simple and broadly applicable to a variety of acids, including important drugs, natural products, amino acids and hydroxy acids, was demonstrated with the chiroptical determination of the enantiomeric composition and concentration of ten samples. In addition to the broad application scope and long-wavelength CD inductions, perhaps the most noteworthy advantage over previously reported methods is that this assay allows concentration and *er* analysis solely based on CD measurements. All components needed are commercially available and this chiroptical sensing method can be readily adapted by any laboratory interested in chirality analysis. The mixing protocol can be executed under air and it is compatible with generally available high-throughput experimentation equipment and multiwell CD plate readers if parallel analysis of hundreds of samples is desirable.

ASSOCIATED CONTENT

The Supporting Information is available free of charge at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

Assay development, optimization, mechanistic studies and analytical details. NMR and CD and MS spectra, crystallographic information.

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