ChemPubSoc Europe

DOI: 10.1002/chem.201402627

CHEMISTRY A European Journal Full Paper

Chirality Sensing

Induced Helical Chirality of Perylenebisimide Aggregates Allows for Enantiopurity Determination and Differentiation of α-Hydroxy Carboxylates by Using Circular Dichroism

Xin Wu,[a] Xuan-Xuan Chen,[a] Bing-Nan Song,[a] Yan-Jun Huang,[a] Zhao Li,[a] Zhan Chen,[a] Tony D. James,[b] and Yun-Bao Jiang*[a]

Abstract: We have developed a working strategy for accurate enantiomeric excess (*ee*) determination based on induced helical aggregation of achiral perylenebisimide (PBI) dyes. PBI dyes functionalized with boronic acid moieties were shown to be effective chirality sensors for α-hydroxy carboxylates. Seven α-hydroxy carboxylates tested showed strong induced Cotton effects in the perylene absorption region around $\lambda = 500$ nm, which were utilized for enantiomeric excess determination and chemo-discrimination of the analytes, with an average absolute error of 2% in *ee* determination and 100% correctness in analyte classification. Responses in the absorption spectra, which arise from the guest-enhanced aggregation, allow the determination of the sample concentration, thus enabling analysis of samples of unknown concentration and *ee*. The simplicity of the strategy, the ease of sample preparation, and the accuracy demonstrated, can potentially facilitate screening procedures in asymmetric synthesis.

Introduction

The discovery and production of most pharmaceutical agents requires asymmetric synthesis whose development is subject to the capacity of the available analytical tools for the determination of the enantio-composition of reaction products.[1] In addressing the disadvantages of common chromatographic techniques, optical sensors that show UV/Vis spectroscopic,[2] fluorescence,[3] NMR spectroscopic,[4] or circular dichroism (CD)[5] responses to the enantiomeric excess (*ee*) of chiral compounds have been developed, aiming to afford rapid and inexpensive protocols for high-throughput screening.[6] Given the potential of CD spectroscopy to differentiate between a pair of enantiomers without involvement of a chiral auxiliary, CD-based protocols represent a straightforward and efficient strategy to this end.[7] Most chiral compounds do not possess a chromophore, do not have a chromophore in close proximity to the stereocenter, or do not have a conformationally chiral chromophore, and therefore cannot be subject to direct electronic circular dichroism (ECD) analysis. This necessitates the attachment of a suitable chromophore to the chiral analyte, either by covalent derivatization,[5w–z] or by employing noncovalent[5a–c,h,i,q–s] or dynamic covalent[5d–g,j–m] interactions. The usual CD sensor strategy is to create conformational asymmetry from CD-silent chromophores that are achiral or dynamically racemic, but, become CD-active upon derivatization or interaction with the chiral analyte due to conformation restriction or preference to form a single conformer. Successful asymmetric induction by a chiral analyte that results in sufficiently intense CD signals from a chiral conformer, however, requires the preparation of elaborately designed sensor structures, such as arylacetylene frameworks[5j–l] and tripodal ligand-based metal complexes.[5e,h,y,z] The structural demand imposes limitations on the choice of the chromophores, for this reason many reported systems show induced CD at relatively short wavelengths that are susceptible to interference from impurities or chiral catalysts that absorb in the UV region.

Our approach in developing simple chirality sensing protocols for sensitive and interference-free *ee* determination used the supramolecular chirality of helical stacks generated from aggregation of π-conjugated dyes in solution rather than using conformational chirality from a single host–guest complex.[8] The phenomena of nonracemic chiral guest-directed formation of optically active aggregates from achiral building blocks[9] have been well documented, but their potential analytical applications remain largely unexplored,[10] most likely due to the time-consuming and cumbersome process of preparing aggregates. We herein report a simple and effective chirality sensing protocol by helical aggregates formed instantly after mixing achiral sensors and chiral analytes. We have envisioned that helical chirality from dye aggregates would allow

[a] X. Wu, X.-X. Chen, B.-N. Song, Dr. Y.-J. Huang, Prof. Dr. Z. Li, Z. Chen, Prof. Dr. Y.-B. Jiang
Department of Chemistry, College of Chemistry and Chemical Engineering
the MOE Key Laboratory of Spectrochemical Analysis and Instrumentation
and Collaborative Innovation Center of Chemistry
for Energy Materials (iChEM)
Xiamen University, Xiamen 361005 (P.R. China)
E-mail: ybjiang@xmu.edu.cn

[b] Prof. Dr. T. D. James
Department of Chemistry, University of Bath, Bath BA2 7AY (UK)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201402627.

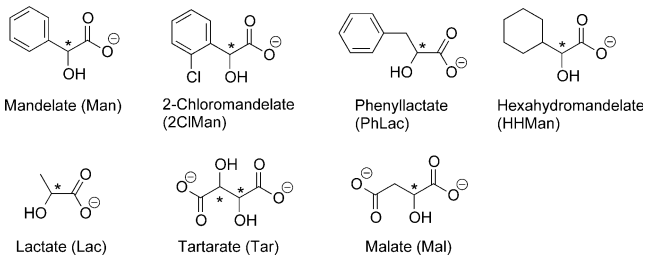
© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

chirality sensors to be designed as simply as attaching an analyte-binding site to an achiral dye capable of supramolecular polymerization. Perylenebismide dyes appear well suited as the dye component, by virtue of their capacity for efficient π stacking and formation of columnar aggregates with a rotational offset,[11] allowing easy generation of supramolecular chirality.[12] As a proof of principle investigation, we have chosen the boronic acid group[13] that rapidly and reversibly binds α-hydroxy carboxylates[14] (Scheme 1 a), which are of biomedical interest.[15] The sensors molecules we have designed, that is, compounds **1** and **2** (Scheme 1 b), feature a perylenebismide (PBI) core and boronic acid moieties attached to its periphery. The self-assembly involving aggregation of the PBI core and the binding of nonracemic α-hydroxy carboxylate guests to the periphery of the aggregates is expected to produce nonracemic helical PBI aggregates, showing induced CD signals in the PBI absorption. We herein report the use of compounds **1** and **2** for *ee* determination and differentiation of α-hydroxy carboxylates. Our protocol uses simple sensor molecules to achieve in-situ CD measurements of the chiral analyte irrespective of whether it contains a chromophore or not, and could be potentially applied to other classes of compounds by attaching other binding sites to the PBI framework.

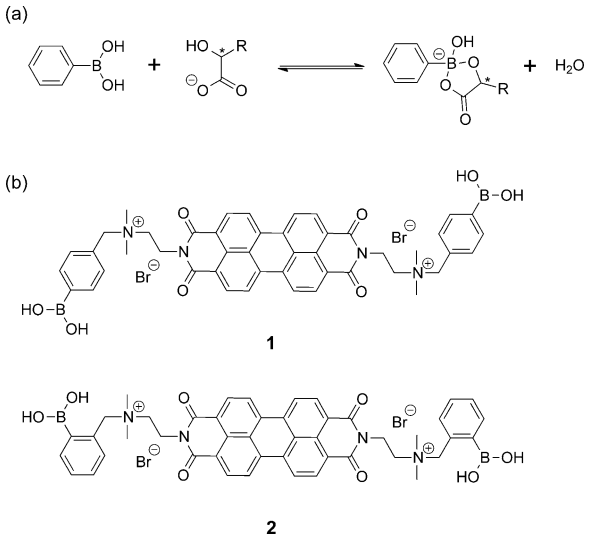
Results and Discussion

The achiral sensors **1** and **2** are structurally related compounds differing only at the position of the boronic acid group substituted at the terminal phenyl group (Scheme 1 b). They were readily obtained through imide coupling of *N*,*N*-dimethylethylenediamine with perylene tetracarboxylic dianhydride followed by treatment with bromomethylphenylboronic acids (Scheme S1 in the Supporting Information). Sensors **1** and **2** were found to exist dominantly as H-aggregates at 50 μM in water, as judged from the higher intensity of the 0–1 band ($\lambda = 500$ nm, $\varepsilon = 3.7\times10^4\ M^{-1}cm^{-2}$) compared to that of the 0–0 band ($\lambda = 542$ nm, $\varepsilon = 1.9\times10^4\ M^{-1}cm^{-2}$).[12] The dominant species are dimers because the shapes and molecular extinction coefficients of the absorption spectra were similar to the reported PBI dimers.[16] The aggregates were CD silent as expected due to the achiral character of the building blocks **1** and **2**. For a rapid chirality induction by a chiral analyte, the sensor–analyte aggregates were prepared by injecting a small volume of a solution of the sensor in methanol to an aqueous solution of chiral analyte. In the presence of Man, a typical α-hydroxy carboxylate (Scheme 2), the solution of compound **1** now exhibits a bisignate Cotton effect crossing zero at $\lambda =$ 500 nm, the maximum absorption wavelength of the aggregated perylene chromophore (Figure 1 b), clearly indicating exciton coupling of the rotationally displaced perylene chromophores.[17] These observations indicate a preferred helical arrangement of the aggregates of compound **1**. Mirror-image CD spectra were observed from solutions of sensor **1** with *R*- and *S*-Man (Figure 1 b). The CD signal reaches its maximum value at Man concentration of 1.0 mM and decreases at higher Man concentration (Figure 2), which is likely the result of variations in the size of the aggregates because the shape of the CD spectrum remains unchanged.

The hypothesis was confirmed by the absorption spectra and dynamic light scattering (DLS) data. Addition of Man led to a decrease in the absorption of compound **1**, suggesting



Scheme 2. Structures of the tested α-hydroxy carboxylate analytes.



Scheme 1. a) Interaction of boronic acid with α-hydroxy carboxylate at a pH value below the pK_a of boronic acid. b) Structures of the achiral sensors **1** and **2**.

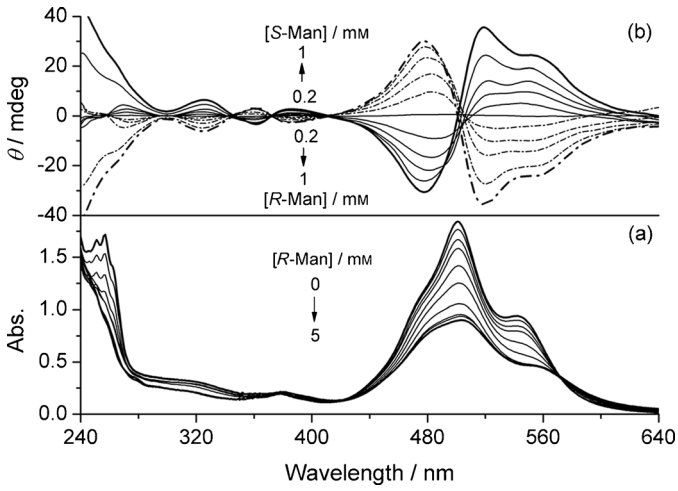


Figure 1. a) Absorption and b) CD spectra of compound **1** (50 μM) in the presence of *R*-Man (solid lines) or *S*-Man (dash lines) of increasing concentration in 50 mM pH 5.0 acetate buffer containing 2.5% MeOH.

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

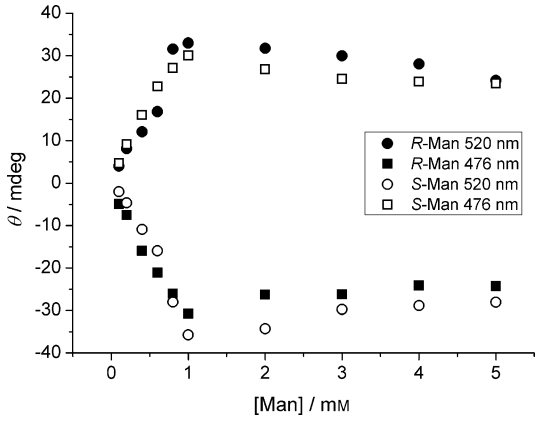


Figure 2. CD intensities of compound **1** at 520 and 476 nm against the concentration of *R*- or *S*-Man in pH 5.0 acetate buffer containing 2.5% MeOH.

a higher degree of aggregation.[18] In agreement with the absorption spectra, the DLS data show an increase of the average hydrodynamic diameter (D_h) from 204 to 2706 nm with concentrations of Man from 0.6 to 5 mM (Figure S5 in the Supporting Information), whereas the aggregate size with lower Man concentrations was too small to be accurately determined by DLS methods. The sigmoidal profile of the D_h dependence on the concentration of Man is likely due to the stepwise binding of Man, forming 1:1 and 1:2 (**1**/Man) complexes. The observed aggregation of compound **1** by Man can be rationalized as free biscationic **1** becoming monocationic and monozwitterionic (1:1 **1**/Man complex), or biszwitterionic (1:2 **1**/Man complex) upon binding of Man, reducing the intermolecular repulsions. It should be pointed out that the chiral induction process is indeed rapid. The injection of a solution of compound **1** in methanol into an aqueous solution of Man produces a stable CD spectrum instantly and remains unchanged for over a 1 h time period, except for a minor increase in the 1st Cotton effect (Figure S6 in the Supporting Information). The fact that 2-phenylpropionic acid, a structural analogue to Man with the hydroxy group replaced by a methyl group, failed in chirality induction and led to much weaker changes in the absorption spectra (Figure S7 in the Supporting Information) indicated that the successful chirality induction by Man is due to the boronic acid binding instead of binding of the quaternary ammonium group by ionic interactions. With the **2**/Man complex, similar absorption and CD titration profiles were observed (Figure S8 in the Supporting Information) and interestingly, an opposite helical sense was observed in the presence of the same Man enantiomer when the position of the boronic acid substitution in the building block is changed.

To test the scope for chirality sensing of α-hydroxy carboxylates, we examined the CD responses of compounds **1** and **2** toward six other analytes covering a wide structural diversity (Scheme 2). In all cases, mirror-imaged CD spectra were observed for the *R*- and *S*-enantiomers (Figures 1 and 2, and Figures S8–S22 in the Supporting Information), indicating the reliability of the CD signals. As shown in Figure 3, exciton-coupled CD spectra were observed for all analytes, with the exception of **1**/Mal where only a weak monosignate CD was observed at

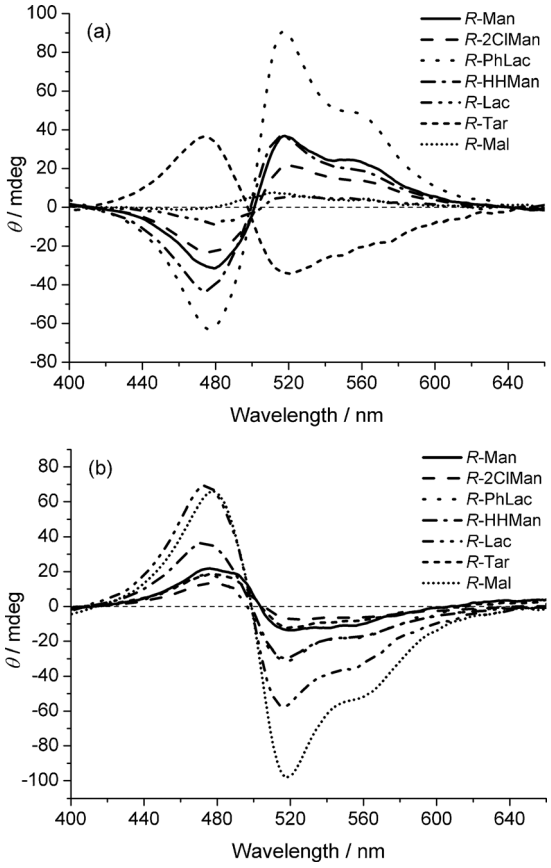


Figure 3. CD spectra of compound a) **1** (50 μM) and b) **2** (50 μM) in the presence of *R*-Man, *R*-2ClMan, *R*-PhLac, *R*-HHMan, *R*-Lac, *R*-Tar, and *R*-Mal in pH 5.0 acetate buffer containing 2.5% MeOH. Analyte concentrations are shown in Table S1 in the Supporting Information.

high Mal concentrations (Figure S20 in the Supporting Information). Although in some cases (e.g., compound **1** with Lac and Mal) the CD signal is not strong enough for an accurate *ee* determination, by employing two sensors **1** and **2**, all the analytes generate CD signals of sufficient strength with one of the two sensors (the weakest being 2-chloroMan with a $\Delta\varepsilon$ value of $\approx$15 mdeg). Small guest molecules have traditionally presented a challenge to both chiral discrimination and induction approaches; our protocol operates well with both large and small analytes.

The affinity of sensors **1** and **2** for α-hydroxyl carboxylate was evaluated by the concentration of the α-hydroxyl carboxylate unit at which the CD signal reaches a maximum value (Table S1 in the Supporting Information). Tar, which contains two α-hydroxyl carboxylate units, shows the highest affinity for both sensors, which allows for the stoichiometry to be determined by using a Job plot (Figures S22 and S23 in the Supporting Information), giving a sensor (**1** or **2**)-to-tartrate stoichiometry of 2:1, or a sensor-to-α-hydroxyl carboxylate unit stoichiometry of 1:1 (Scheme S2a in the Supporting Information). The highest affinity for Tar is the result of multivalent binding[19] between the divalent tartarate and the aggregate that can be regarded as a multivalent receptor for divalent tartarate.[20] With higher Tar concentrations, we observed an inter-

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

esting inversion of the sign of the CD signal for sensor **1** (Figure S18 in the Supporting Information). As the 2:1 **1**/Tar complex shows the opposite CD sign to that observed at high tartrate concentrations, as evidenced by the Job plot, the switch of the CD sign can be unambiguously ascribed to the binding of the other boronic acid group in compound **1** to Tar. Mal, which contains a carboxylate group in addition to the α-hydroxy carboxylate unit, shows a substantially higher affinity than other mono-α-hydroxy carboxylate analytes for sensor **2**, which can be ascribed to further stabilization by the electrostatic interaction between the anionic carboxylate group and the cationic perylene sensor (Scheme S2b in the Supporting Information), in addition to binding of the α-hydroxy carboxylate unit, as confirmed by the 3:2 stoichiometry (Figure S24 in the Supporting Information). For other monovalent analytes, whereas Man, 2-ClMan, PhLac, and HHMan show similar affinity for the sensors, with maximum CD observed at a guest concentration of 1–2 mM, much weaker binding was observed for lactate, which gave a maximum in the CD at 20 mM. We therefore propose that the binding of Man, 2-ClMan, PhLac, and HHMan is also driven by hydrophobic interactions between the large hydrocarbon units of the two bound analyte molecules within the same aggregate.

CD–*ee* curves were prepared for each analyte from the optimal sensor at the optimal analyte concentration (Figures S25–S31 in the Supporting Information). Because different analytes show different affinities for the sensors, the analyte concentrations we report for the CD–*ee* curves are therefore not the same for different analytes. The "majority rules" have been observed in supramolecular polymers,[21] in which a small *ee* produces a non-proportionally large CD signal. This effect was absent in our system. In most cases reported here, a linear CD response to the *ee* was observed, yet for PhLac with sensor **1** (Figure S27 in the Supporting Information) and for Mal with sensor **2** (Figure S31 in the Supporting Information) we observed an interesting CD–*ee* profile, which displays a steeper slope with high *ee*. This means that a small *ee* produces an even weaker CD signal than a linear response, which is opposite to the "majority rules". To account for this unusual observation, we first examined the absorption spectra of the sensors in the presence of analytes of the same concentration yet at varying *ee* for these two cases (Figures S32 and S33 in the Supporting Information). No significant *ee* dependence was observed, which precludes the possibility that the observed nonlinear relationship results from destabilization of the aggregates at low *ee*. We noticed that in these two cases, the dependence of the CD intensity on the analyte concentration displays sigmoidal characteristics (Figures S12 and S21 in the Supporting Information). Although the packing of two chiral-analyte-bound dye monomers is sufficient to generate an exciton-coupled CD spectra, the nonlinearly higher CD signal at higher analyte concentrations as shown in Figures S12 and S21 in the Supporting Information could possibly suggest that the consecutive packing of many enantiopure analyte-bound dye monomers produces a higher averaged CD signal than the packing of fewer chiral-analyte-bound dye monomers alone. Thus, random insertion of a dye monomer bound to the minor enantiomer would disrupt the consecutive packing of several dye monomers bound to the dominant enantiomer, thereby weakening the CD signal in a nonlinear manner, which would account for the observed counter majority rules. To provide further support for this hypothesis, the CD–*ee* relationship at lower analyte concentrations were examined. Because at lower analyte concentrations, there is less chance for consecutive packing of chiral-analyte-bound dye monomers, the "counter majority rules" effect should disappear or be weakened, according to our hypothesis. In both cases where "counter majority rules" were observed, decreasing the analyte concentration did restore the normal linear CD–*ee* relationship (Figures S34 and S35 in the Supporting Information). Although the "counter majority rules" effect has not yet been well understood, the nonlinear CD dependence on the *ee*, which displays a larger change in the high *ee* region is, however, preferred for sensing an *ee* close to 100%, which is of greater practical importance in asymmetric synthesis.

To examine the applicability of our system for the screening of organic reactions, when various species co-exist with the product and may interfere with the CD measurements, we recorded the CD spectra of **1**/Man in the presence of a variety of common chiral compounds, including a chiral amine, a chiral amino alcohol, a chiral carboxylate, and a chiral amino acid. The results indicate that, even when the potential interfering species is present at the same concentration as Man, the deviation is rather small ($<5.6\%$) (Figure S36 in the Supporting Information). Therefore, our protocol is selective for α-hydroxy carboxylates and any impurities present are unlikely to interfere with the *ee* sensing of α-hydroxy carboxylate products. However, when these interfering species co-exist with the chiral compound of interest even in trace amounts, the *ee* determination by optical rotation is not possible. Conventional optical rotation measurements require a large amount of sample and are highly susceptible to impurities,[22] and therefore are not suitable for screening reaction products. We also showed that the chirality induction is operational in methanol as well (Figure S37 in the Supporting Information), rendering our protocol suitable for water-insoluble chiral analytes.

A series of samples of "unknown" *ee* and known concentration were prepared and subject to analysis by the present protocol. In the cases of a linear CD–*ee* relationship, the *ee* of the "unknown" sample was calculated by comparing its CD intensity with that of a sample with 100% *ee*. In the cases where the CD signal varies nonlinearly with the *ee*, the "unknown" *ee* was calculated by linear interpolation from the CD–*ee* plot. The calculated *ee* values were compared to the actual values (Table 1), and an average absolute error of (± 2.0)% was found, which is within the range of acceptable error for high-throughput screening (HTS) in asymmetric synthesis.[6c]

The decrease of the CD signals at high analyte concentrations appears a limitation, making the knowledge of the analyte concentration necessary, because saturation of the CD spectra may not be reached (Figure 2). However, the analyte-induced absorption quenching of the peryleneboronic acid sensor due to an increased extents of aggregation (Figure 1a) allows the determination of the analyte concentration, over-

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 1. *Ee* determination of seven α-hydroxy carboxylate analytes of known concentration and comparison of the calculated *ee* values with the actual values.

Entry	Guest	Concentration [mM]	Sensor used	Actual *ee* [%]	Calcd *ee* [%]	Absolute error [%]
1	Tar	30[a]	**1**	10.0	11.6	1.6
2	Lac	20	**2**	−30.0	−33.7	−3.7
3	Man	1.0	**1**	50.0	46.5	−3.5
4	2ClMan	1.0	**1**	−70.0	−67.1	2.9
5	PhLac	1.0	**1**	80.0	79.4	0.6
6	Mal	0.3	**2**	−90.0	−90.6	−0.6
7	HHMan	2.0	**1**	96.0	95.0	−1.0

[a] The concentration was μM.

coming that limitation (Figure S38 in the Supporting Information). The results for simultaneous determination of the concentration and the *ee* are presented in Table 2, showing a satisfactory average absolute error of (±2.1)% for the *ee* determination.

Table 2. Comparison of the actual concentration and the *ee* of four Man samples with the concentrations and *ee* values calculated from respective absorption and CD spectral responses of compound **1** to Man.

Entry	Actual concentration [mM]	Actual *ee* [%]	Calcd concentration [mM]	Calcd *ee* [%]	Absolute error (*ee*) [%]
1	0.55	63.6	0.50	63.9	0.3
2	0.65	−69.2	0.61	−67.8	1.4
3	0.75	−84.6	0.73	−80.6	4.0
4	0.85	94.1	0.85	91.2	−2.9

Besides the *ee* and concentration determination, our protocol is also suitable for chemo-differentiation of α-hydroxy carboxylates by using linear discriminant analysis (LDA),[22] as different analytes generate different CD shapes (Figure 4). The ratio of the CD intensity at $\lambda = 475$ nm to the absolute value of CD intensity at $\lambda = 520$ nm was analyzed for a total of fourteen analytes, with each analyte tested at five concentrations (1, 2, 3, 4, and 5 mM). The two-dimensional LDA plot is shown in Figure 4. Similar to reported assignments,[5e,h] the greatest axis of differentiation *F*1 indicates the chirality of the analyte, whereas the second axis *F*2 arising from the shape of the CD spectrum (Figure 4) confirms that the data points for different analytes are well separated. A Jackknife analysis that classifies a data point based on functions created from the other four data points gives a 100% correct assignment, justifying the reliability of our protocol in chemo-differentiation of α-hydroxy carboxylates.

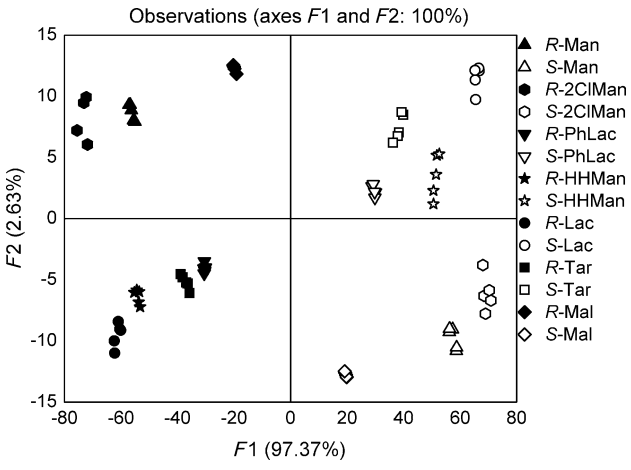


Figure 4. LDA plot created from the CD responses of sensors **1** and **2** to fourteen α-hydroxy carboxylates.

Conclusion

In summary, we have established a novel CD protocol for chirality sensing of chiral analytes bearing no chromophore, and which does not require the creation of conformational chirality in a single host–guest complex. Our approach employs analyte-directed chiral aggregation of achiral PBI dyes, which contain binding sites for the analyte. The analyte–sensor interaction can in principle be covalent or non-covalent. We successfully demonstrated a proof-of-principle assay with two structurally related boronic acid-conjugated achiral PBI sensors, capable of the *ee* determination of α-hydroxy carboxylates. Sufficiently strong CD signals can be observed at the perylene absorption region of around $\lambda = 500$ nm, immediately after mixing the sensor with solutions of seven structurally diverse α-hydroxy carboxylates. Diastereoselective aggregation of the sensor–analyte complex was shown to be responsible. Determination of a series of "unknown" *ee* produces average absolute errors of (±2.0) and (±2.1)% for samples of known and unknown concentrations, respectively. The different shapes of the CD spectra of the sensor molecules observed in the presence of different analytes allows the identification of the α-hydroxy carboxylates by using linear discriminant analysis. Compared with currently available chirality sensors, our protocol exhibits many advantages such as not requiring analyte derivation, simplicity of host design and synthesis, and applicability to structurally diverse analytes. The system is also environmentally benign by using water as a "green" solvent. It should be pointed out that the chiral induction works even though the stereocenter in the host–guest complex is twelve atoms away from the perylene chromophore. Such simple analyses are not possible with conventional chirality induction approaches by using conformationally chiral chromophores. We expect that our protocol will be generally applicable to chiral analytes that bear a stereocenter either close or remote to the binding site.

Experimental Section

Stock solutions of compounds **1** and **2** (2.0 mM) were prepared in MeOH. Stock solutions of α-hydroxyl carboxylic acids (1, 0.1, or 0.01 mM) were prepared in water. In the cases of Lac and Mal titrations where high guest concentrations were used, the guests were converted to the sodium salts before use. The guest solutions were diluted by using 100 mM acetate buffer and water to the de-

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

sired concentrations. To 1.95 mL of the guest solutions in 50 mM pH 5.0 acetate buffer was added 50 μL 2.0 mM MeOH sensor stock solutions and the resultant samples were instantly subject to CD and absorption spectra measurements.

Acknowledgements

This work was supported by the Ministry of Science and Technology of China through grant 2011CB910403 and by the National Science Foundation of China through grants 91127019, 21275121, and J1210014 to Y.B.J., and a NSFC-RS joint grant 21311130122 to Y.B.J. and T.D.J. The Catalysis and Sensing for our Environment (CASE) network is thanked for research exchange opportunities.

Keywords: chirality · circular dichroism · dyes/pigments · hydroxyl acid · polymers · supramolecular chemistry

[1] R. E. Gawley, J. Aube, *Principles of Asymmetric Synthesis*, 2ednd edElsevier Science, Oxford, **2012**.

[2] a) W. Xuan, M. Zhang, Y. Liu, Z. Chen, Y. Cui, *J. Am. Chem. Soc.* **2012**, *134*, 6904 – 6907; b) S. H. Shabbir, L. A. Joyce, G. M. da Cruz, V. M. Lynch, S. Sorey, E. V. Anslyn, *J. Am. Chem. Soc.* **2009**, *131*, 13125 – 13131; c) D. Leung, E. V. Anslyn, *J. Am. Chem. Soc.* **2008**, *130*, 12328 – 12333; d) D. Leung, J. F. Folmer-Andersen, V. M. Lynch, E. V. Anslyn, *J. Am. Chem. Soc.* **2008**, *130*, 12318 – 12327; e) X. Mei, C. Wolf, *J. Am. Chem. Soc.* **2006**, *128*, 13326 – 13327; f) J. F. Folmer-Andersen, V. M. Lynch, E. V. Anslyn, *J. Am. Chem. Soc.* **2005**, *127*, 7986 – 7987; g) L. Zhu, Z. Zhong, E. V. Anslyn, *J. Am. Chem. Soc.* **2005**, *127*, 4260 – 4269; h) L. Zhu, E. V. Anslyn, *J. Am. Chem. Soc.* **2004**, *126*, 3676 – 3677; i) Y. Kubo, S. Maeda, S. Tokita, M. Kubo, *Nature* **1996**, *382*, 522 – 524.

[3] a) M. M. Wanderley, C. Wang, C.-D. Wu, W. Lin, *J. Am. Chem. Soc.* **2012**, *134*, 9050 – 9053; b) F. Song, G. Wei, L. Wang, J. Jiao, Y. Cheng, C. Zhu, *J. Org. Chem.* **2012**, *77*, 4759 – 4764; c) H.-L. Liu, Q. Peng, Y.-D. Wu, D. Chen, X.-L. Hou, M. Sabat, L. Pu, *Angew. Chem.* **2010**, *122*, 612 – 616; *Angew. Chem. Int. Ed.* **2010**, *49*, 602 – 606; d) S. Yu, L. Pu, *J. Am. Chem. Soc.* **2010**, *132*, 17698 – 17700; e) J. Heo, C. A. Mirkin, *Angew. Chem.* **2006**, *118*, 955 – 958; *Angew. Chem. Int. Ed.* **2006**, *45*, 941 – 944; f) J. Zhao, T. D. James, *Chem. Commun.* **2005**, 1889 – 1891; g) J. Zhao, T. M. Fyles, T. D. James, *Angew. Chem.* **2004**, *116*, 3543 – 3546; *Angew. Chem. Int. Ed.* **2004**, *43*, 3461 – 3464; h) J. Zhao, M. G. Davidson, M. F. Mahon, G. Kociok-Köhn, T. D. James, *J. Am. Chem. Soc.* **2004**, *126*, 16179 – 16186; i) S. Pagliari, R. Corradini, G. Galaverna, S. Sforza, A. Dossena, M. Montalti, L. Prodi, N. Zaccheroni, R. Marchelli, *Chem. Eur. J.* **2004**, *10*, 2749 – 2758; j) X. Mei, C. Wolf, *J. Am. Chem. Soc.* **2004**, *126*, 14736 – 14737; k) T. D. James, K. R. A. Samankumara Sandanayake, S. Shinkai, *Nature* **1995**, *374*, 345 – 347; l) S. J. Lee, W. Lin, *J. Am. Chem. Soc.* **2002**, *124*, 4554 – 4555; m) M.-H. Xu, J. Lin, Q.-S. Hu, L. Pu, *J. Am. Chem. Soc.* **2002**, *124*, 14239 – 14246; n) J. Lin, Q.-S. Hu, M.-H. Xu, L. Pu, *J. Am. Chem. Soc.* **2002**, *124*, 2088 – 2089; o) V. J. Pugh, Q.-S. Hu, L. Pu, *Angew. Chem.* **2000**, *112*, 3784 – 3787; *Angew. Chem. Int. Ed.* **2000**, *39*, 3638 – 3641.

[4] a) J. Labuta, S. Ishihara, T. Šikorský, Z. Futera, A. Shundo, L. Hanyková, J. V. Burda, K. Ariga, J. P. Hill, *Nat. Commun.* **2013**, 4; b) Y. Pérez-Fuertes, A. M. Kelly, J. S. Fossey, M. E. Powell, S. D. Bull, T. D. James, *Nat. Prot.* **2008**, *3*, 210 – 214; c) A. M. Kelly, Y. Perez-Fuertes, J. S. Fossey, S. L. Yeste, S. D. Bull, T. D. James, *Nat. Prot.* **2008**, *3*, 215 – 219; d) T. J. Wenzel, *Discrimination of Chiral Compounds by using NMR Spectroscopy*, Wiley, New York, **2007**.

[5] a) K. W. Bentley, Y. G. Nam, J. M. Murphy, C. Wolf, *J. Am. Chem. Soc.* **2013**, *135*, 18052 – 18055; b) P. Zhang, C. Wolf, *Chem. Commun.* **2013**, *49*, 7010 – 7012; c) X. Li, C. E. Burrell, R. J. Staples, B. Borhan, *J. Am. Chem. Soc.* **2012**, *134*, 9026 – 9029; d) K. W. Bentley, C. Wolf, *J. Am. Chem. Soc.* **2013**, *135*, 12200 – 12203; e) L. You, G. Pescitelli, E. V. Anslyn, L. Di Bari, *J. Am. Chem. Soc.* **2012**, *134*, 7117 – 7125; f) L. You, J. S. Berman, E. V. Anslyn, *Nat. Chem.* **2011**, *3*, 943 – 948; g) J. M. Dragna, G. Pescitelli, L. Tran, V. M. Lynch, E. V. Anslyn, L. Di Bari, *J. Am. Chem. Soc.* **2012**, *134*, 4398 – 4407; h) L. A. Joyce, M. S. Maynor, J. M. Dragna, G. M. da Cruz, V. M. Lynch, J. W. Canary, E. V. Anslyn, *J. Am. Chem. Soc.* **2011**, *133*, 13746 – 13752; i) S. J. Wezenberg, G. Salassa, E. C. Escudero-Adán, J. Benet-Buchholz, A. W. Kleij, *Angew. Chem.* **2011**, *123*, 739 – 742; *Angew. Chem. Int. Ed.* **2011**, *50*, 713 – 716; j) D. P. Iwaniuk, C. Wolf, *Org. Lett.* **2011**, *13*, 2602 – 2605; k) D. P. Iwaniuk, C. Wolf, *J. Am. Chem. Soc.* **2011**, *133*, 2414 – 2417; l) M. W. Ghosn, C. Wolf, *J. Am. Chem. Soc.* **2009**, *131*, 16360 – 16361; m) S. Nieto, J. M. Dragna, E. V. Anslyn, *Chem. Eur. J.* **2010**, *16*, 227 – 232; n) S. Tartaglia, D. Padula, P. Scafato, L. Chiummiento, C. Rosini, *J. Org. Chem.* **2008**, *73*, 4865 – 4873; o) X. Li, M. Tanasova, C. Vasileiou, B. Borhan, *J. Am. Chem. Soc.* **2008**, *130*, 1885 – 1893; p) S. Nieto, V. M. Lynch, E. V. Anslyn, H. Kim, J. Chin, *J. Am. Chem. Soc.* **2008**, *130*, 9232 – 9233; q) X. Li, B. Borhan, *J. Am. Chem. Soc.* **2008**, *130*, 16126 – 16127; r) P. Bhyrappa, V. V. Borovkov, Y. Inoue, *Org. Lett.* **2007**, *9*, 433 – 435; s) J. M. Lintuluoto, K. Nakayama, J.-i. Setsune, *Chem. Commun.* **2006**, 3492 – 3494; t) X. Huang, N. Fujioka, G. Pescitelli, F. E. Koehn, R. T. Williamson, K. Nakanishi, N. Berova, *J. Am. Chem. Soc.* **2002**, *124*, 10320 – 10335; u) T. Kurtán, N. Nesnas, Y.-Q. Li, X. Huang, K. Nakanishi, N. Berova, *J. Am. Chem. Soc.* **2001**, *123*, 5962 – 5973; v) X. Huang, B. H. Rickman, B. Borhan, N. Berova, K. Nakanishi, *J. Am. Chem. Soc.* **1998**, *120*, 6185 – 6186; w) S. Superchi, R. Bisaccia, D. Casarini, A. Laurita, C. Rosini, *J. Am. Chem. Soc.* **2006**, *128*, 6893 – 6902; x) S. Superchi, D. Casarini, A. Laurita, A. Bavoso, C. Rosini, *Angew. Chem.* **2001**, *113*, 465 – 468; *Angew. Chem. Int. Ed.* **2001**, *40*, 451 – 454; y) A. E. Holmes, S. Zahn, J. W. Canary, *Chirality* **2002**, *14*, 471 – 477; z) S. Zahn, J. W. Canary, *Org. Lett.* **1999**, *1*, 861 – 864.

[6] a) J. F. Traverse, M. L. Snapper, *Drug Discovery Today* **2002**, *7*, 1002 – 1012; b) C. Wolf, K. W. Bentley, *Chem. Soc. Rev.* **2013**, *42*, 5408 – 5424; c) D. Leung, S. O. Kang, E. V. Anslyn, *Chem. Soc. Rev.* **2012**, *41*, 448.

[7] N. Berova, K. Nakanishi, R. W. Woody, *Circular Dichroism: Principles and Applications*, 2ednd edWiley-VCH, Weinheim, **2000**.

[8] a) J. H. K. K. Hirschberg, L. Brunsveld, A. Ramzi, J. A. J. M. Vekemans, R. P. Sijbesma, E. W. Meijer, *Nature* **2000**, *407*, 167 – 170; b) A. R. A. Palmans, J. A. J. M. Vekemans, E. E. Havinga, E. W. Meijer, *Angew. Chem.* **1997**, *109*, 2763 – 2765; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2648 – 2651.

[9] a) J.-S. Zhao, Y.-B. Ruan, R. Zhou, Y.-B. Jiang, *Chem. Sci.* **2011**, *2*, 937 – 944; b) L. Zhang, M. Liu, *J. Phys. Chem. B* **2009**, *113*, 14015 – 14020; c) S. J. George, Ž. Tomović, M. M. J. Smulders, T. F. A. de Greef, P. E. L. G. Leclère, E. W. Meijer, A. P. H. J. Schenning, *Angew. Chem.* **2007**, *119*, 8354 – 8359; *Angew. Chem. Int. Ed.* **2007**, *46*, 8206 – 8211; d) H. Fenniri, B.-L. Deng, A. E. Ribbe, *J. Am. Chem. Soc.* **2002**, *124*, 11064 – 11072; e) R. A. Garoff, E. A. Litzinger, R. E. Connor, I. Fishman, B. A. Armitage, *Langmuir* **2002**, *18*, 6330 – 6337.

[10] F. Riobé, A. P. H. J. Schenning, D. B. Amabilino, *Org. Biomol. Chem.* **2012**, *10*, 9152 – 9157.

[11] R. F. Fink, J. Seibt, V. Engel, M. Renz, M. Kaupp, S. Lochbrunner, H.-M. Zhao, J. Pfister, F. Würthner, B. Engels, *J. Am. Chem. Soc.* **2008**, *130*, 12858 – 12859.

[12] a) D. Görl, X. Zhang, F. Würthner, *Angew. Chem.* **2012**, *124*, 6434 – 6455; *Angew. Chem. Int. Ed.* **2012**, *51*, 6328 – 6348; b) F. Würthner, *Chem. Commun.* **2004**, 1564 – 1579.

[13] S. D. Bull, M. G. Davidson, J. M. H. van den Elsen, J. S. Fossey, A. T. A. Jenkins, Y.-B. Jiang, Y. Kubo, F. Marken, K. Sakurai, J. Zhao, T. D. James, *Acc. Chem. Res.* **2013**, *46*, 312 – 326.

[14] a) N. Katif, R. Harries, A. Kelly, J. Fossey, T. James, F. Marken, *J. Solid State Electrochem.* **2009**, *13*, 1475 – 1482; b) Y. Yang, P. T. Lewis, J. O. Escobedo, N. N. St. Luce, W. D. Trealeaven, R. L. Cooks, R. M. Strongin, *Collect. Czech. Chem. Commun.* **2004**, *69*, 1282; c) S. L. Wiskur, J. J. Lavigne, A. Metzger, S. L. Tobey, V. Lynch, E. V. Anslyn, *Chem. Eur. J.* **2004**, *10*, 3792 – 3804.

[15] a) G. M. Coppola, H. F. Schuster, *α-Hydroxyl Acids in Enantioselective Synthesis* Wiley-VCH, Weinheim, **1997**; b) L. Guo, X. Zhang, D. Zhou, A. L. Okunade, X. Su, *J. Lipid Res.* **2012**, *53*, 1327 – 1335; c) K. Djanashvili, L. Frullano, J. A. Peters, *Chem. Eur. J.* **2005**, *11*, 4010 – 4018.

[16] a) R. O. Marcon, J. G. dos Santos, K. M. Figueiredo, S. Brochsztain, *Langmuir* **2006**, *22*, 1680 – 1687; b) T. van der Boom, G. Evmenenko, P. Dutta, M. R. Wasielewski, *Chem. Mater.* **2003**, *15*, 4068 – 4074; c) H. Langhals, R. Ismael, *Eur. J. Org. Chem.* **1998**, 1915 – 1917; d) W. E. Ford, *J. Photochem.* **1987**, *37*, 189 – 204.

[17] M. Kasha, H. R. Rawls, M. A. El Bayoumi, *Pure Appl. Chem.* **1965**, *11*, 371.

 © 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[18] W. Wang, L.-S. Li, G. Helms, H.-H. Zhou, A. D. Q. Li, *J. Am. Chem. Soc.* **2003**, *125*, 1120 – 1121.
[19] C. Fasting, C. A. Schalley, M. Weber, O. Seitz, S. Hecht, B. Koksch, J. Dernedde, C. Graf, E.-W. Knapp, R. Haag, *Angew. Chem.* **2012**, *124*, 10622 – 10650; *Angew. Chem. Int. Ed.* **2012**, *51*, 10472 – 10498.
[20] X. Wu, Z. Li, X.-X. Chen, J. S. Fossey, T. D. James, Y.-B. Jiang, *Chem. Soc. Rev.* **2013**, *42*, 8032 – 8048.
[21] a) A. R. A. Palmans, E. W. Meijer, *Angew. Chem.* **2007**, *119*, 9106 – 9126; *Angew. Chem. Int. Ed.* **2007**, *46*, 8948 – 8968; b) J. van Gestel, A. R. A. Palmans, B. Titulaer, J. A. J. M. Vekemans, E. W. Meijer, *J. Am. Chem. Soc.* **2005**, *127*, 5490 – 5494; c) M. M. Green, B. A. Garetz, B. Munoz, H. Chang, S. Hoke, R. G. Cooks, *J. Am. Chem. Soc.* **1995**, *117*, 4181 – 4182.
[22] P. Schreier, A. Bernreuther, M. Huffer, *Analysis of Chiral Organic Molecules: Methodology and Applications*, De Gruyter, Würzburg, **1995**.

Received: March 16, 2014
Published online on July 30, 2014

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim